(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 April 2020 (30.04.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/086732 A1

(51) International Patent Classification:

C07D 207/333 (2006.01)	*A61P 21/00* (2006.01)
C07D 231/18 (2006.01)	*A61P 25/00* (2006.01)
C07D 277/36 (2006.01)	*A61P 27/02* (2006.01)
C07D 277/60 (2006.01)	*A61P 31/12* (2006.01)
C07D 307/64 (2006.01)	*A61P 35/00* (2006.01)
C07D 333/50 (2006.01)	*A61P 37/00* (2006.01)
C07D 401/04 (2006.01)	*A61K 31/381* (2006.01)
C07D 405/04 (2006.01)	*A61K 31/407* (2006.01)
C07D 471/04 (2006.01)	*A61K 31/4365* (2006.01)
C07D 487/04 (2006.01)	*A61K 31/4162* (2006.01)
C07D 495/04 (2006.01)	*A61K 31/519* (2006.01)
C07D 498/04 (2006.01)	*A61K 31/437* (2006.01)
C07D 498/20 (2006.01)	*A61K 31/4985* (2006.01)
C07D 513/04 (2006.01)	*A61K 31/428* (2006.01)
A61P 1/00 (2006.01)	*A61K 31/429* (2006.01)
A61P 1/16 (2006.01)	*A61K 31/426* (2006.01)
A61P 1/18 (2006.01)	*A61K 31/341* (2006.01)
A61P 3/00 (2006.01)	*A61K 31/4025* (2006.01)
A61P 9/00 (2006.01)	*A61K 31/4155* (2006.01)
A61P 11/00 (2006.01)	*A61K 31/435* (2006.01)
A61P 13/00 (2006.01)	*A61K 31/415* (2006.01)
A61P 17/00 (2006.01)	*A61K 31/40* (2006.01)
A61P 19/00 (2006.01)	

(21) International Application Number:
PCT/US2019/057682

(22) International Filing Date:
23 October 2019 (23.10.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/749,730	24 October 2018 (24.10.2018)	US
62/749,712	24 October 2018 (24.10.2018)	US
62/749,725	24 October 2018 (24.10.2018)	US
62/751,386	26 October 2018 (26.10.2018)	US
62/751,380	26 October 2018 (26.10.2018)	US
62/751,301	26 October 2018 (26.10.2018)	US
62/801,930	06 February 2019 (06.02.2019)	US
62/802,637	07 February 2019 (07.02.2019)	US
62/802,654	07 February 2019 (07.02.2019)	US
62/812,813	01 March 2019 (01.03.2019)	US
62/812,794	01 March 2019 (01.03.2019)	US
62/812,517	01 March 2019 (01.03.2019)	US

(71) Applicant: **NOVARTIS INFLAMMASOME RESEARCH, INC.** [US/US]; 251 Little Falls Drive, Country of New Castle, Wilmington, DE 19808 (US).

(72) Inventors: **ROUSH, William**; IFM Management, Inc., 855 Boylston Street, Suite 1103, Boston, MA 02116 (US). **VENKATRAMAN, Shankar**; IFM Management, Inc., 855 Boylston Street, Suite 1103, Boston, MA 02116 (US). **GHOSH, Shomir**; IFM Management, Inc., 855 Boylston Street, Suite 1103, Boston, MA 02116 (US). **SHEN, Dong-Ming**; IFM Management, Inc., 855 Boylston Street, Suite 1103, Boston, MA 02116 (US). **KATZ, Jason**; IFM Management, Inc., 855 Boylston Street, Suite 1103, Boston, MA 02116 (US). **SEIDEL, Hans, Martin**; IfM Management, Inc., 855 Boylston Street, Suite 1103, Boston, MA 02116 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

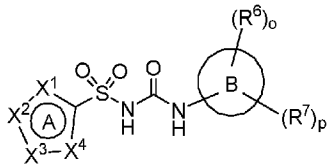
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

WO 2020/086732 A1

(54) Title: COMPOUNDS AND COMPOSITIONS FOR TREATING CONDITIONS ASSOCIATED WITH NLRP ACTIVITY



(AA)

(57) Abstract: In one aspect, compounds of Formula AA, or a pharmaceutically acceptable salt thereof, are featured or a pharmaceutically acceptable salt thereof, wherein the variables shown in Formula A can be as defined anywhere herein.

[Continued on next page]

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

COMPOUNDS AND COMPOSITIONS FOR TREATING CONDITIONS ASSOCIATED WITH NLRP ACTIVITY

TECHNICAL FIELD

This disclosure features chemical entities (e.g., a compound that modulates (e.g., antagonizes) NLRP3, or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that are useful, e.g., for treating a condition, disease or disorder in which a decrease or increase in NLRP3 activity (e.g., an increase, e.g., a condition, disease or disorder associated with NLRP3 signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder in a subject (e.g., a human). This disclosure also features compositions as well as other methods of using and making the same.

The present disclosure also relates to, in part, methods and compositions for treating anti-TNFα resistance in a subject with an NLRP3 antagonist. The present disclosure also relates, in part, to methods, combinations and compositions for treating TFNα related diseases and anti-TNFα resistance in a subject that include administration of an NLRP3 antagonist, an NLRP3 antagonist and an anti-TNFα agent, or a composition encompassing an NLRP3 antagonist and an anti-TNFα agent.

BACKGROUND

The NLRP3 inflammasome is a component of the inflammatory process and its aberrant activation is pathogenic in inherited disorders such as the cryopyrin associated periodic syndromes (CAPS). The inherited CAPS Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) and neonatal onset multi-system inflammatory disease (NOMID) are examples of indications that have been reported to be associated with gain of function mutations in NLRP3.

NLRP3 can form a complex and has been implicated in the pathogenesis of a number of complex diseases, including but not limited to metabolic disorders such as type 2 diabetes, atherosclerosis, obesity and gout, as well as diseases of the central nervous system, such as Alzheimer's disease and multiple sclerosis and Amyotrophic Lateral Sclerosis and Parkinson disease, lung disease, such as asthma and COPD and pulmonary idiopathic fibrosis, liver disease,

such as NASH syndrome, viral hepatitis and cirrhosis, pancreatic disease, such as acute and chronic pancreatitis, kidney disease, such as acute and chronic kidney injury, intestinal disease such as Crohn's disease and Ulcerative Colitis, skin disease such as psoriasis, musculoskeletal disease such as scleroderma, vessel disorders, such as giant cell arteritis, disorders of the bones, such as Osteoarthritis , osteoporosis and osteopetrosis disorders eye disease, such as glaucoma and macular degeneration, diseased caused by viral infection such as HIV and AIDS, autoimmune disease such as Rheumatoid Arthritis, Systemic Lupus Erythematosus, Autoimmune Thyroiditis, Addison's disease, pernicious anemia, cancer and aging.

In light of the above, it would be desirable to provide compounds that modulate (e.g., antagonize) NLRP3.

Several patients having inflammatory or autoimmune diseases are treated with anti-TNFα agents. A subpopulation of such patients develop resistance to treatment with the anti-TNFα agents. It is desirable to develop methods for reducing a patient's resistance to anti-TNFα agents. In light of the this, it would also be desirable to provide alternative therapies for treating inflammatory or autoimmune diseases (for example NLRP3 inflammasome inhibitors) to avoid or minimise the use of anti-TNFα agents.

Intestinal bowel disease (IBD), encompassing Ulcerative Colitis (UC) and Crohn's disease (CD), are chronic diseases characterized by barrier dysfunction and uncontrolled inflammation and mucosal immune reactions in the gut. A number of inflammatory pathways have been implicated in the progression of IBD, and anti-inflammatory therapy such as tumor necrosis factor-alpha (TNF-a) blockade has shown efficacy in the clinic (*Rutgeerts P et al N Engl J Med 2005; 353:2462-76*). Anti-TNFa therapies, however, do not show complete efficacy, however, other cytokines such as IL-1b, IL-6, IL-12, IL-18, IL-21, and IL-23 have been shown to drive inflammatory disease pathology in IBD (*Neurath MF Nat Rev Immunol 2014;14;329-42*). IL-1b and IL-18 are produced by the NLRP3 inflammasome in response to pathogenic danger signals, and have been shown to play a role in IBD. Anti-IL-1b therapy is efficacious in patients with IBD driven by genetic mutations in CARD8 or IL-10R (*Mao L et al, J Clin Invest 2018;238:1793-1806, Shouval DS et al, Gastroenterology 2016;151:1100-1104*), IL-18 genetic polymorphisms have been linked to UC (*Kanai T et al, Curr Drug Targets 2013;14:1392-9*), and NLRP3 inflammasome inhibitors have been shown to be efficacious in murine models of IBD (*Perera AP et al, Sci Rep 2018;8:8618*). Resident gut immune cells isolated from the lamina

propria of IBD patients can produce IL-1b, either spontaneously or when stimulated by LPS, and this IL-1b production can be blocked by the ex vivo addition of a NLRP3 antagonist. Based on strong clinical and preclinical evidence showing that inflammasome-driven IL-1b and IL-18 play a role in IBD pathology, it is clear that NLRP3 inflammasome inhibitors could be an efficacious treatment option for UC, Crohn's disease, or subsets of IBD patients. These subsets of patients could be defined by their peripheral or gut levels of inflammasome related cytokines including IL-1b, IL-6, and IL-18, by genetic factors that pre-dispose IBD patients to having NLRP3 inflammasome activation such as mutations in genes including ATG16L1, CARD8, IL-10R, or PTPN2 (*Saitoh T et al, Nature 2008;456:264, Spalinger MR, Cell Rep 2018;22:1835*), or by other clinical rationale such as non-response to TNF therapy.

Though anti-TNF therapy is an effective treatment option for Crohn's disease, 40% of patients fail to respond. One-third of non-responsive CD patients fail to respond to anti-TNF therapy at the onset of treatment, while another third lose response to treatment over time (secondary non-response). Secondary non-response can be due to the generation of anti-drug antibodies, or a change in the immune compartment that desensitizes the patient to anti-TNF (*Ben-Horin S et al, Autoimmun Rev 2014;13:24-30, Steenholdt C et al Gut 2014;63:919-27*). Anti-TNF reduces inflammation in IBD by causing pathogenic T cell apoptosis in the intestine, therefore eliminating the T cell mediated inflammatory response (*Van den Brande et al Gut 2007:56:509-17*). There is increased NLRP3 expression and increased production of IL-1b in the gut of TNF-non-responsive CD patients (Leal RF et al Gut 2015;64:233-42) compared to TNF-responsive patients, suggesting NLRP3 inflammasome pathway activation. Furthermore, there is increased expression of TNF-receptor 2 (TNF-R2), which allows for TNF-mediated proliferation of T cells (*Schmitt H et al Gut 2018;0:1-15*). IL-1b signaling in the gut promotes T cell differentiation toward Th1/17 cells which can escape anti-TNF-a mediated apoptosis. It is therefore likely that NLRP3 inflammasome activation can cause non-responsiveness in CD patients to anti-TNF-a therapy by sensitizing pathogenic T cells in the gut to anti-TNF-a mediated apoptosis. Experimental data from immune cells isolated from the gut of TNF-resistant Crohn's patients show that these cells spontaneously release IL-1b, which can be inhibited by the addition of an NLRP3 antagonist. NLRP3 inflammasome antagonists - in part by blocking IL-1b secretion - would be expected to inhibit the mechanism leading to anti-TNF non-responsiveness, re-sensitizing the patient to anti-TNF therapy. In IBD patients who are naive to

anti-TNF therapy, treatment with an NLRP3 antagonist would be expected to prevent primary- and secondary-non responsiveness by blocking the mechanism leading to non-response.

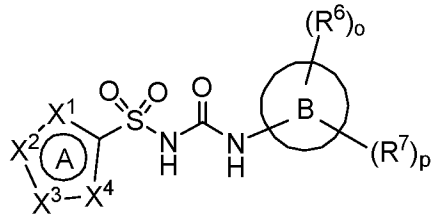
NLRP3 antagonists that are efficacious locally in the gut can be efficacious drugs to treat IBD; in particular in the treatment of TNF-resistant CD alone or in combination with anti-TNF therapy. Systemic inhibition of both IL-1b and TNF-a has been shown to increase the risk of opportunistic infections (Genovese MC et al, Arthritis Rheum 2004;50:1412), therefore, only blocking the NLRP3 inflammasome at the site of inflammation would reduce the infection risk inherent in neutralizing both IL-1 and TNF-a. NLRP3 antagonists that are potent in NLRP3-inflammasome driven cytokine secretion assays in cells, but have low permeability in vitro in a permeability assay such as an MDCK assay, have poor systemic bioavailability in a rat or mouse pharmacokinetic experiment, but high levels of compound in the colon and/or small intestine could be a useful therapeutic option for gut restricted purposes.

The present invention also provides alternative therapies for the treatment of inflammatory or autoimmune diseases, including IBD, that solves the above problems associated with anti-TNFα agents.

SUMMARY

This disclosure features chemical entities (e.g., a compound that modulates (e.g., antagonizes) NLRP3, or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that are useful, e.g., for treating a condition, disease or disorder in which a decrease or increase in NLRP3 activity (e.g., an increase, e.g., a condition, disease or disorder associated with NLRP3 signaling).

In some embodiments, provided herein is a compound of Formula AA



Formula AA

or a pharmaceutically acceptable salt thereof, wherein the variables in Formula AA can be as defined anywhere herein.

This disclosure also features compositions as well as other methods of using and making the same.

The present invention is also relates to the Applicant's discovery that inhibition of NLRP3 inflammasomes can increase a subject's sensitivity to an anti-TNFα agent or can overcome resistance to an anti-TNFα agent in a subject, or indeed provide an alternative therapy to anti-TNFα agents.

Provided herein are methods of treating a subject that include: (a) identifying a subject having a cell that has an elevated level of NLRP3 inflammasome activity and/or expression as compared to a reference level; and (b) administering to the identified subject a therapeutically effective amount of an compound of Formula I or a pharmaceutically acceptable salt, solvate, or co-crystal thereof.

Provided herein are methods for the treatment of inflammatory or autoimmune disease including IBD, such as UC and CD in a subject in need thereof, comprising administering to said subject a therapeutically effective amount a compound for Formula I or a pharmaceutically acceptable salt, solvate, or co-crystal thereof, wherein the NLRP3 antagonist is a gut-targeted NLRP3 antagonist.

Provided herein are methods of treating a subject in need thereof, that include: (a) identifying a subject having resistance to an anti-TNFα agent; and (b) administering a treatment comprising a therapeutically effective amount of a compound for Formula I, or a pharmaceutically acceptable salt, solvate, or co-crystal thereof to the identified subject.

Provided herein are methods of treating a subject in need thereof, that include: administering a treatment comprising a therapeutically effective amount of a compound for Formula I or a pharmaceutically acceptable salt, solvate, or co-crystal thereof to a subject identified as having resistance to an anti-TNFα agent.

Provided herein are methods of selecting a treatment for a subject in need thereof, that include: (a) identifying a subject having resistance to an anti-TNFα agent; and (b) selecting for the identified subject a treatment comprising a therapeutically effective amount of a compound for Formula I or a pharmaceutically acceptable salt, solvate, or co-crystal thereof.

Provided herein are methods of selecting a treatment for a subject in need thereof, that include selecting a treatment comprising a therapeutically effective amount of a compound for Formula I or a pharmaceutically acceptable salt, solvate, or co-crystal thereof for a subject identified as having resistance to an anti-TNFα agent.

In some embodiments of any of the methods described herein, the treatment further includes a therapeutically effective amount of an anti-TNFα agent, in addition to the NLRP3 antagonist.

An "antagonist" of NLRP3 includes compounds that inhibit the ability of NLRP3 to induce the production of IL-1β and/or IL-18 by directly binding to NLRP3, or by inactivating, destabilizing, altering distribution, of NLRP3 or otherwise.

In one aspect, pharmaceutical compositions are featured that include a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients.

In one aspect, methods for modulating (e.g., agonizing, partially agonizing, antagonizing) NLRP3 activity are featured that include contacting NLRP3 with a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). Methods include *in vitro* methods, e.g., contacting a sample that includes one or more cells comprising NLRP3, as well as *in vivo* methods.

In a further aspect, methods of treatment of a disease in which NLRP3 signaling contributes to the pathology and/or symptoms and/or progression of the disease are featured that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In a further aspect, methods of treatment are featured that include administering to a subject a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same), wherein the chemical entity is administered in an amount effective to treat a disease in which NLRP3 signaling contributes to the pathology and/or symptoms and/or progression of the disease, thereby treating the disease.

Embodiments can include one or more of the following features.

The chemical entity can be administered in combination with one or more additional therapies with one or more agents suitable for the treatment of the condition, disease or disorder.

Examples of the indications that may be treated by the compounds disclosed herein include but are not limited to metabolic disorders such as type 2 diabetes, atherosclerosis, obesity and gout, as well as diseases of the central nervous system, such as Alzheimer's disease and multiple sclerosis and Amyotrophic Lateral Sclerosis and Parkinson disease, lung disease, such as asthma and COPD and pulmonary idiopathic fibrosis, liver disease, such as NASH syndrome, viral hepatitis and cirrhosis, pancreatic disease, such as acute and chronic pancreatitis, kidney disease, such as acute and chronic kidney injury, intestinal disease such as Crohn's disease and Ulcerative Colitis, skin disease such as psoriasis, musculoskeletal disease such as scleroderma, vessel disorders, such as giant cell arteritis, disorders of the bones, such as osteoarthritis , osteoporosis and osteopetrosis disorders, eye disease, such as glaucoma and macular degeneration, diseases caused by viral infection such as HIV and AIDS, autoimmune disease such as rheumatoid arthritis, systemic Lupus erythematosus, autoimmune thyroiditis; Addison's disease, pernicious anemia, cancer and aging.

The methods can further include identifying the subject.

Other embodiments include those described in the Detailed Description and/or in the claims.

Additional Definitions

To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

As used herein, the term "NLRP3" is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous NLRP3 molecules,

isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

"API" refers to an active pharmaceutical ingredient.

The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a chemical entity (e.g., a compound exhibiting activity as a modulator of NLRP3, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof;) being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study.

The term "excipient" or "pharmaceutically acceptable excipient" means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each component is " pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term "pharmaceutically acceptable salt" may refer to pharmaceutically acceptable addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and

organic acids. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. The term "pharmaceutically acceptable salt" may also refer to pharmaceutically acceptable addition salts prepared by reacting a compound having an acidic group with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt s not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described hereinform with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid:organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

The term "pharmaceutical composition" refers to a mixture of a compound described herein with other chemical components (referred to collectively herein as "excipients"), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

The term "subject" refers to an animal, including, but not limited to, a primate (*e.g.*, human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

The terms “treat,” “treating,” and “treatment,” in the context of treating a disease or disorder, are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or to slowing the progression, spread or worsening of a disease, disorder or condition or of one or more symptoms thereof.

The terms “hydrogen” and “H” are used interchangeably herein.

The term "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, saturated or unsaturated, containing the indicated number of carbon atoms. For example, $C_{1\text{-}10}$ indicates that the group may have from 1 to 10 (inclusive) carbon atoms in it. Non-limiting examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl.

The term "haloalkyl" refers to an alkyl, in which one or more hydrogen atoms is/are replaced with an independently selected halo.

The term "alkoxy" refers to an -O-alkyl radical (e.g., $-OCH_3$).

The term "carbocyclic ring" as used herein includes an aromatic or nonaromatic cyclic hydrocarbon group having 3 to 10 carbons unless otherwise noted, such as 3 to 8 carbons, such as 3 to 7 carbons, which may be optionally substituted. Carbocyclic rings may be monocyclic or bicyclic, and when bicyclic, can be fused bicyclic, bridged bicyclic, or spirocyclic. Examples of carbocyclic rings include five-membered, six-membered, and seven-membered carbocyclic rings.

The term “heterocyclic ring” refers to an aromatic or nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, or 3 atoms of each ring may be substituted by a substituent. When heterocyclic rings are bicyclic or tricyclic, any two connected rings of the bicycle or tricycle may be fused bicyclic, bridged bicyclic, or spirocyclic. Examples of heterocyclic rings include five-membered, six-membered, and seven-membered heterocyclic rings.

The term "cycloalkyl" as used herein includes an nonaromatic cyclic, bicylic, fused, or spiro hydrocarbon radical having 3 to 10 carbons, such as 3 to 8 carbons, such as 3 to 7 carbons, wherein the cycloalkyl group which may be optionally substituted. Examples of cycloalkyls

include five-membered, six-membered, and seven-membered rings. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

The term “heterocycloalkyl” refers to an nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring, fused, or spiro system radical having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, or 3 atoms of each ring may be substituted by a substituent. Examples of heterocycloalkyls include five-membered, six-membered, and seven-membered heterocycloalkyl rings. Examples include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and the like.

The term "aryl" is intended to mean an aromatic ring radical containing 6 to 10 ring carbons. Examples include phenyl and naphthyl.

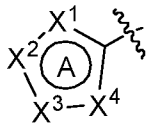
The term "heteroaryl" is intended to mean an aromatic ring system containing 5 to 14 aromatic ring atoms that may be a single ring, two fused rings or three fused rings wherein at least one aromatic ring atom is a heteroatom selected from, but not limited to, the group consisting of O, S and N. Examples include furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like. Examples also include carbazolyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, triazinyl, indolyl, isoindolyl, indazolyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl. phenazinyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl, 1H-benzimidazolyl, imidazopyridinyl, benzothienyl, benzofuranyl, isobenzofuran and the like.

The term “hydroxy” refers to an OH group.

The term “amino” refers to an NH_2 group.

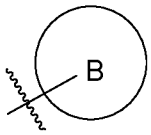
The term “oxo” refers to O. By way of example, substitution of a CH_2 a group with oxo gives a C=O group.

As used herein, the terms "the ring A" or "A" are used interchangeably to denote



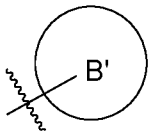
in formulas AA and AA-1, wherein the bond that is shown as being broken by the wavy line connects A to the $S(O_2)NHC(O)NH$ moiety of Formula AA.

As used herein, the terms "the ring B" or "B" are used interchangeably to denote



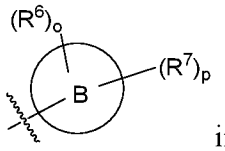
in formula AA wherein the bond that is shown as being broken by the wavy line connects B to the NHC(O) group of Formula AA.

As used herein, the terms "the ring B'" or "B'" are used interchangeably to denote

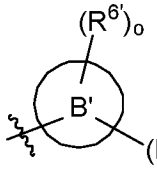


in formula AA-4 wherein the bond that is shown as being broken by the wavy line connects B' to the NHC(O) group of Formula AA-1.

As used herein, the term "the substituted ring B" or "the optionally substituted ring B" is used to denote

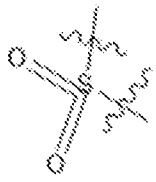


in formula AA and



in formula AA-1, wherein the bond that is shown as being broken by the wavy line connects B to the NHC(O) group of Formula AA and Formula AA-1.

As used herein, the recitation "$S(O_2)$", alone or as part of a larger recitation, refers to the group

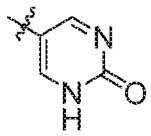


.

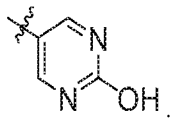
In addition, atoms making up the compounds of the present embodiments are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without

limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C.

The scope of the compounds disclosed herein includes tautomeric form of the compounds. Thus, by way of example, a compound that is represented as containing the moiety



is also intended to include the tautomeric form containing the moiety



The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features and advantages of the invention will be apparent from the description and drawings, and from the claims.

As used herein, the terms “patient” or “subject” refer to a mammalian organism, preferably a human being, who is diseased with the condition (i.e. disease or disorder) of interest and who would benefit from the treatment.

As used herein, the term “prevent”, “preventing” or "prevention" in connection to a disease or disorder refers to the prophylactic treatment of a subject who is at risk of developing a condition (e.g., specific disease or disorder or clinical symptom thereof) resulting in a decrease in the probability that the subject will develop the condition.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment to ameliorating the disease or disorder (i.e. slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms or pathological features thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter or pathological features of the disease, e.g. including those, which may not be discernible by the subject. In yet another embodiment, “treat”, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g. stabilization of at least one discernible or non-discernible symptom), physiologically (e.g.

stabilization of a physical parameter) or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder, or of at least one symptoms or pathological features associated thereof. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying progression of the disease to a more advanced stage or a more serious condition.

As used herein, the term "therapeutically effective amount" refers to an amount of the compound of the invention, e.g. tropifexor (as herein defined, e.g. in free form or as a stereoisomer, an enantiomer, a pharmaceutically acceptable salt, solvate, prodrug, ester thereof and/or an amino acid conjugate thereof), or cenicriviroc (in free form or as a pharmaceutically acceptable salt, solvate, prodrug, and/or ester thereof, e.g. in free form or as a pharmaceutically acceptable salt thereof), which is sufficient to achieve the stated effect. Accordingly, a therapeutically effective amount used for the treatment or prevention of a liver disease or disorder as hereinabove defined is an amount sufficient for the treatment or prevention of such a disease or disorder.

DESCRIPTION OF THE DRAWINGS

Figures 1: Expression levels of RNA encoding NLRP3 in Crohn’s Disease patients who are responsive and non-responsive to infliximab.

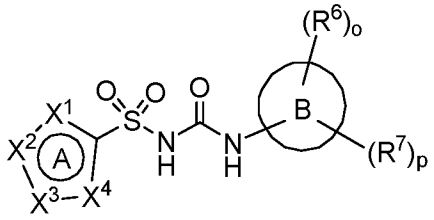
Figures 2: Expression levels of RNA encoding IL-1β in Crohn’s Disease patients who are responsive and non-responsive to infliximab.

Figures 3: Expression levels of RNA encoding NLRP3 in Ulcerative Colitis (UC) patients who are responsive and non-responsive to infliximab.

Figures 4: Expression levels of RNA encoding IL-1β in Ulcerative Colitis (UC) patients who are responsive and non-responsive to infliximab.

DETAILED DESCRIPTION

In one aspect, provided herein is a compound of Formula AA



Formula AA

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;

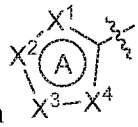
X^3 is O, S, N, CR^3, or NR^3;

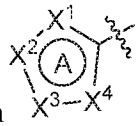
X^4 is O, S, N, CR^4, NR^4, or $–X^5\text{-}X^6\text{-}$;

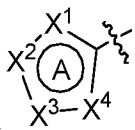
X^5 is N or CR^5;

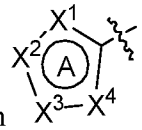
X^6 is N or CR^6;

when X^4 is $-X^5\text{-}X^6$, then: X^1 is N or CR^1, X^2 is N or CR^2, and X^3 is N or CR^3;

when X^4 is other than $-X^5\text{-}X^6\text{-}$, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is $-X^5\text{-}X^6\text{-}$, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

when X^4 is other than $-X^5\text{-}X^6\text{-}$, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is $-X^5-X^6-$, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

from two to four of R^1, R^2, R^3, and R^4 are present or from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and

wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least two of the two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20};

R^{20} is selected from the group consisting of: hydroxy, halo, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{21}, C_2-C_6 alkenyl optionally substituted with one or more R^{21}, C_2-C_6 alkynyl optionally substituted with one or more R^{21}, C_1-C_6 alkoxy optionally substituted with one or more R^{21}, OC_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{21}, $S(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, $OS(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, C_6-C_{10} aryl optionally substituted with one or more R^{21}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{21}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{21}, and $CONR^8R^9$; or

at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

R^{21} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

wherein any of R^1, R^2, R^3, R^4, R^5, and R^6 that are not taken together with the atoms connecting them to form a ring, when present, are each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more

R^{22}, NH-(C=NR^{13})$NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, =NR^{10}, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;

R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

B is a 5-10-membered heteroaryl or C_6-C_{10} aryl ring;
o = 1 or 2;
p = 0, 1, 2, or 3;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally

substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;

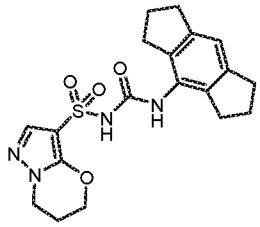
R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and

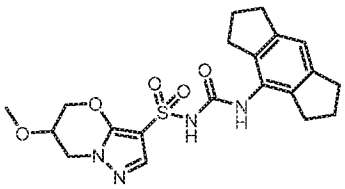
each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

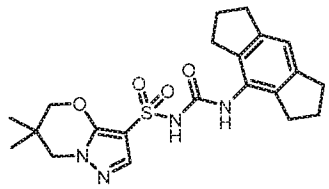
provided that when B is 5-10-membered heteroaryl including from 2-3 ring nitrogen atoms, at least one R^6 is attached to B at a position *ortho* to the $–HNC(=O)NHS(O)_2$- moiety of Formula AA;

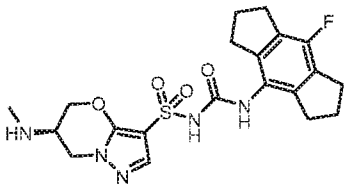
when B is 2-pyridyl, pyrimidin-6-yl, or pyrimidin-4-yl, B is not substituted with a cyano group at a position *ortho* to the $–HNC(=O)NHS(O)_2$- moiety of Formula AA;

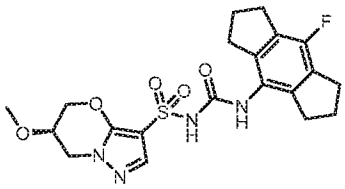
and

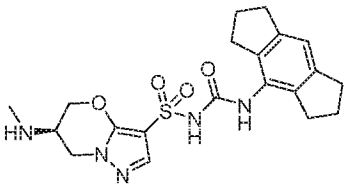


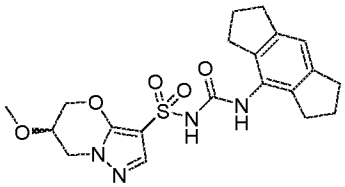


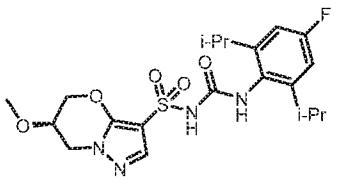


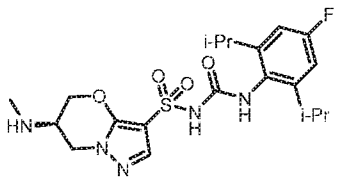


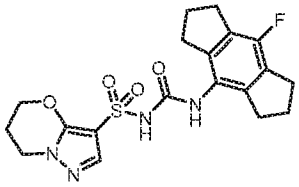


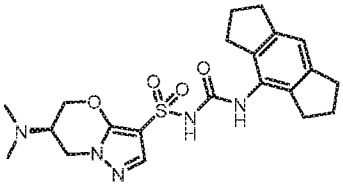


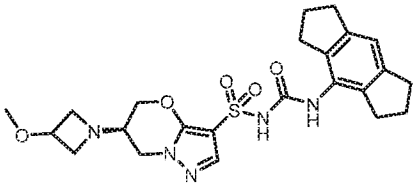


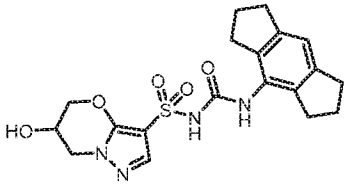


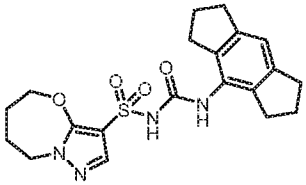


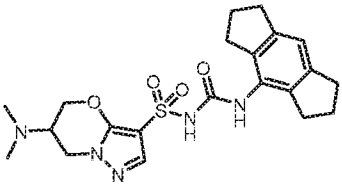


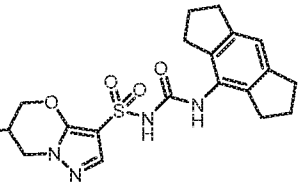


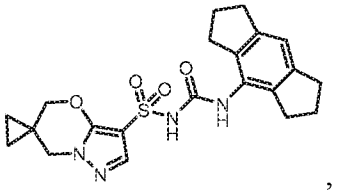


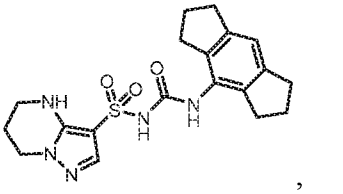


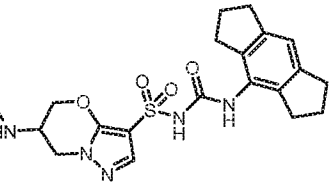












with the proviso that the compound of Formula AA is not a compound selected from the group consisting of:

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

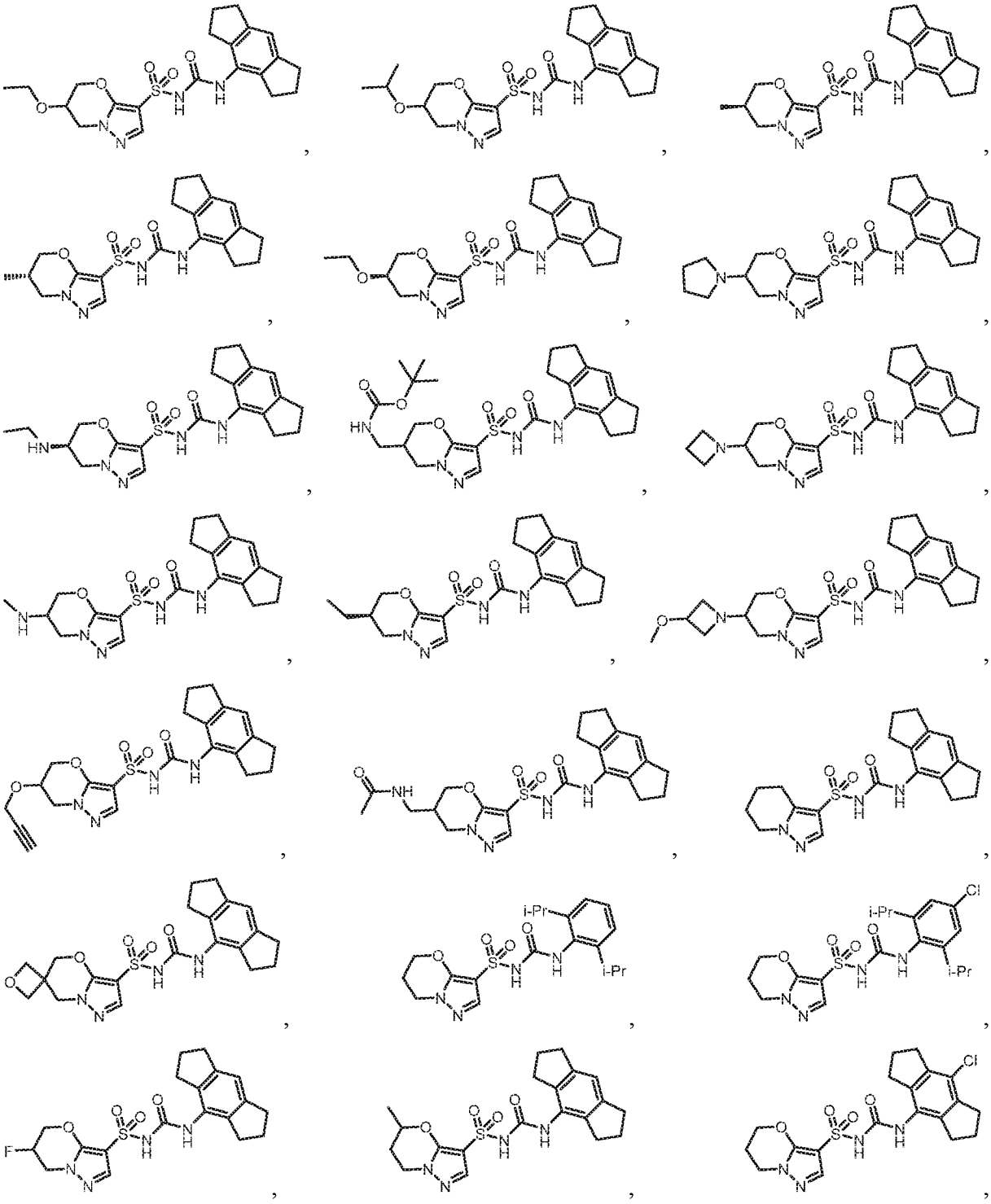
,

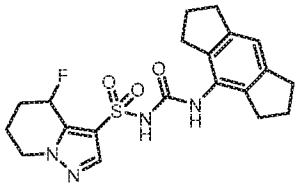
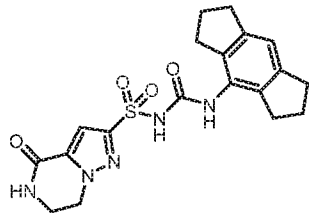
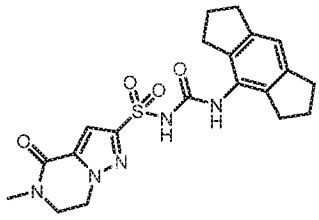
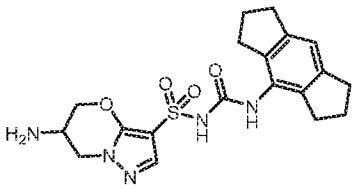
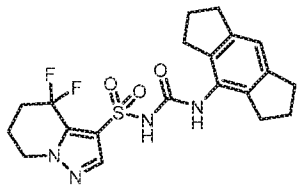
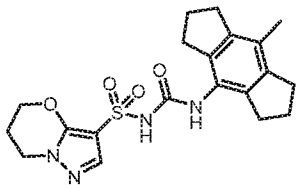
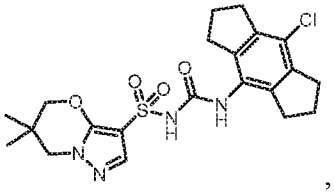
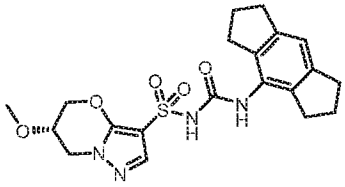
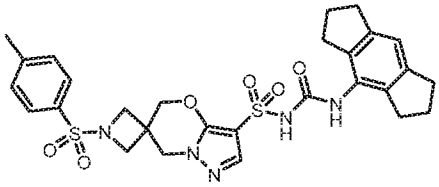
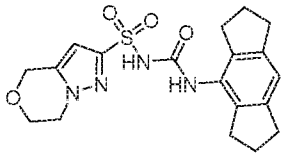
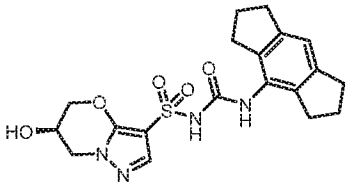
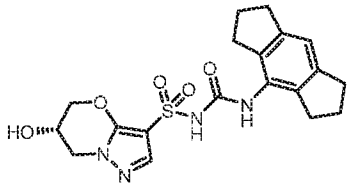
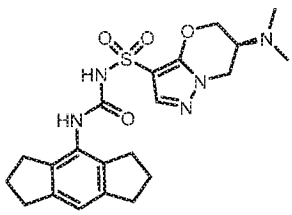
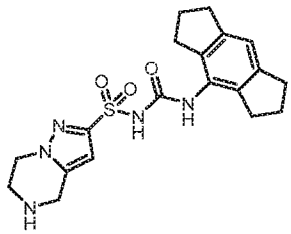
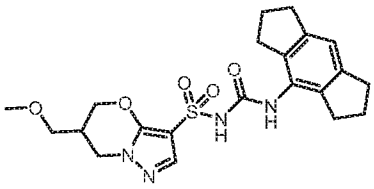
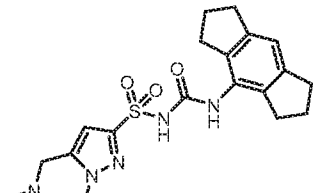
,

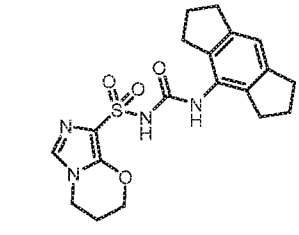
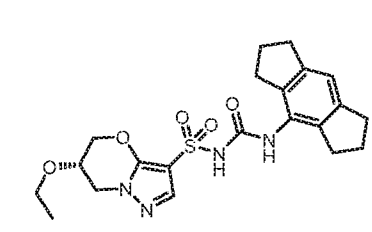
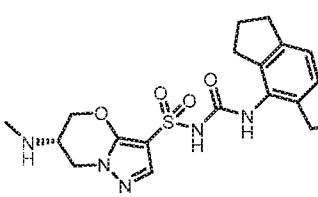
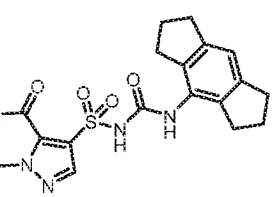
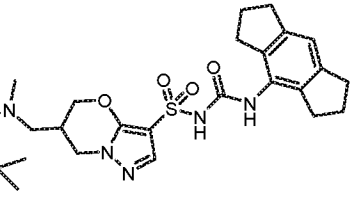
,

,

,



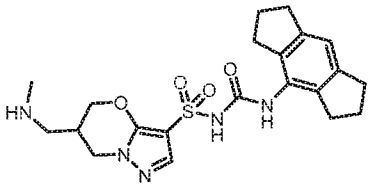
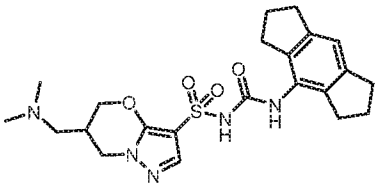
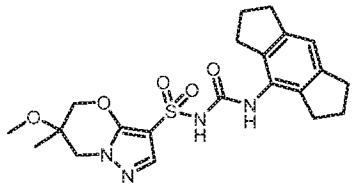
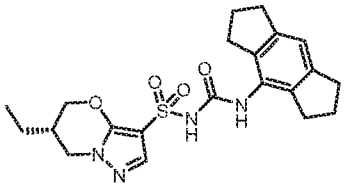
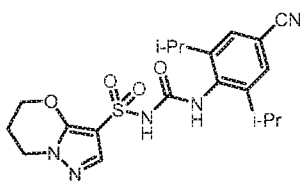
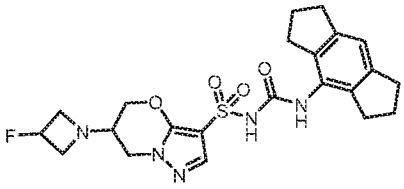
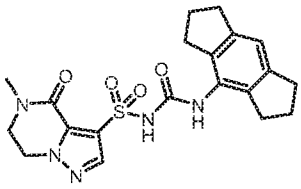
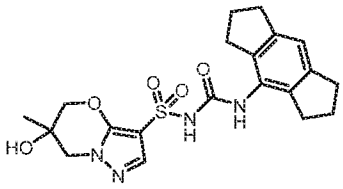
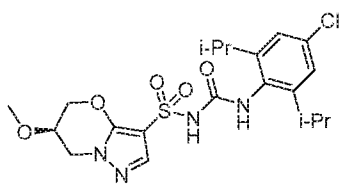
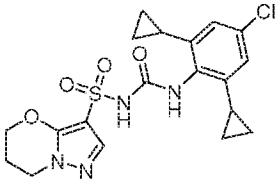
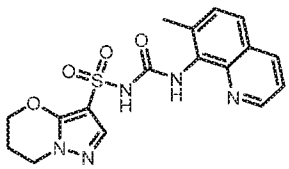
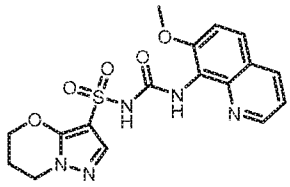
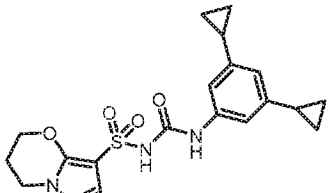
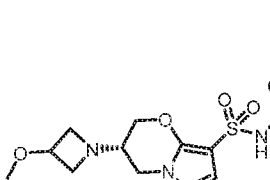

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

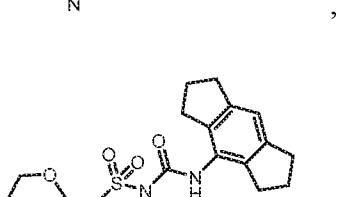
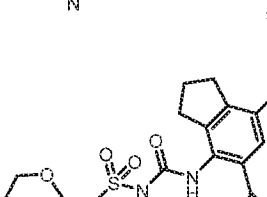
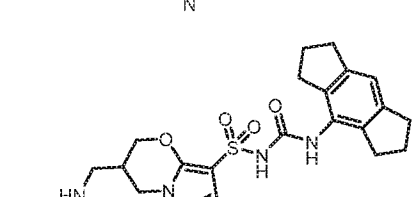
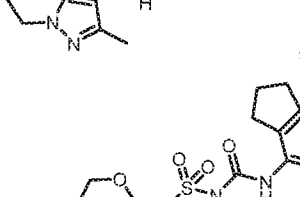
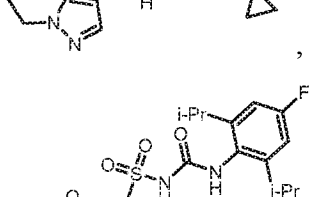
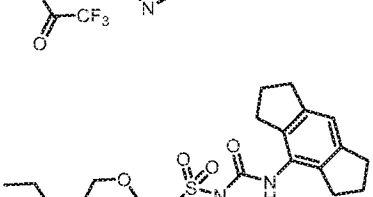
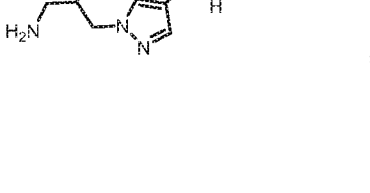
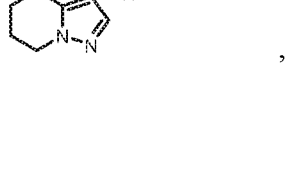
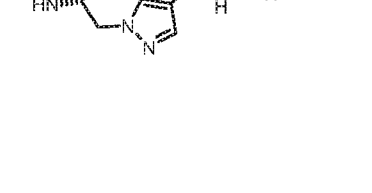
,

,

,

,

,

,

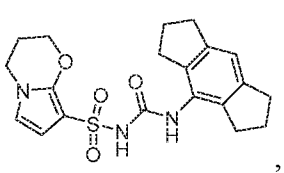
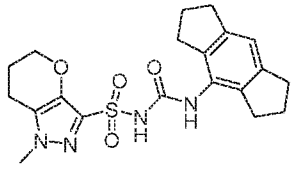
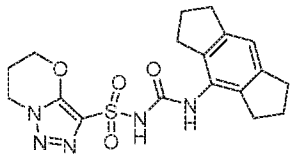
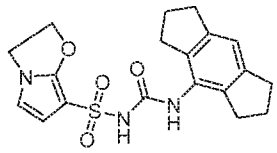
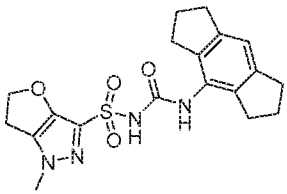
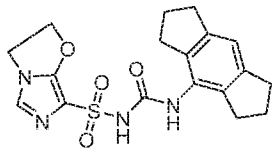
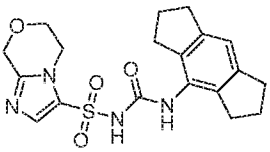
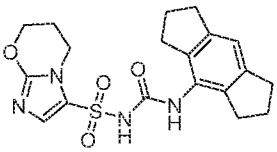
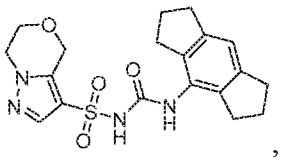
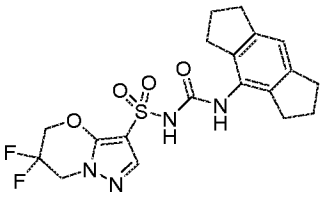
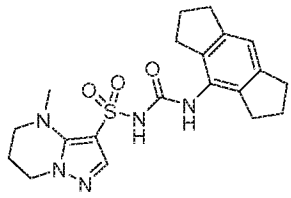
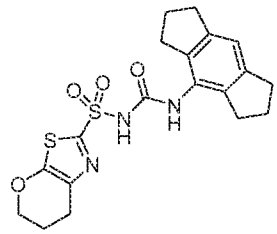
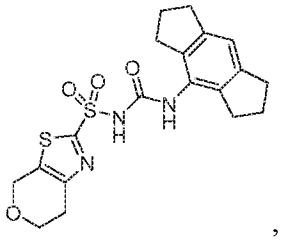
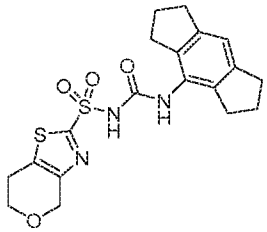
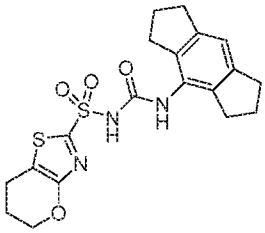
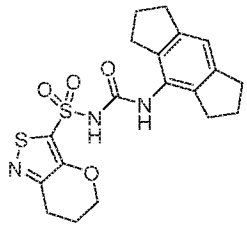
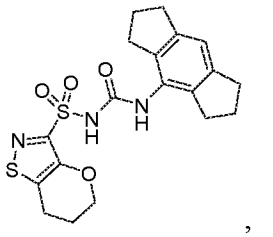
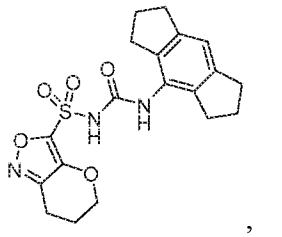
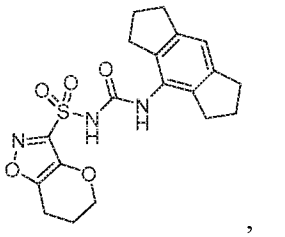
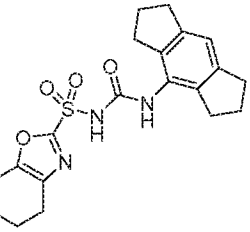
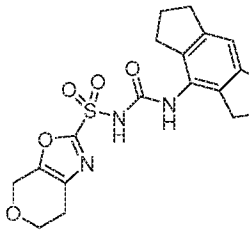
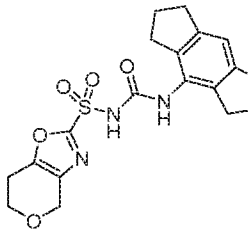
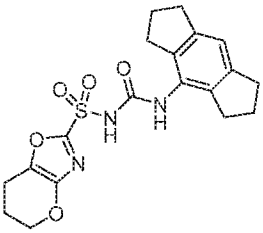
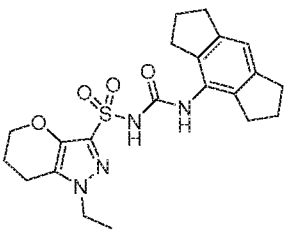
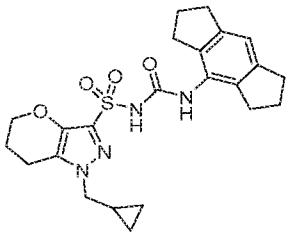
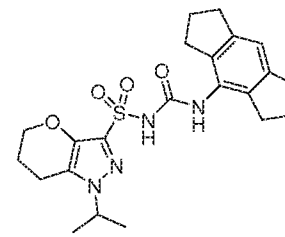
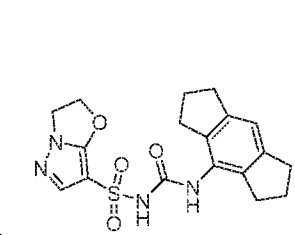
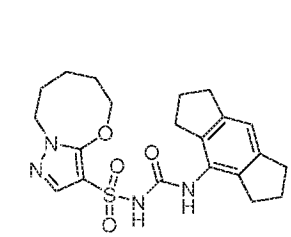
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

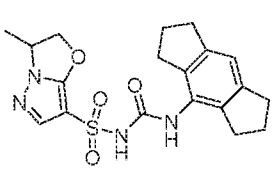
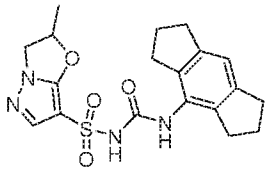
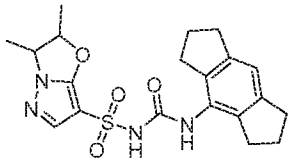
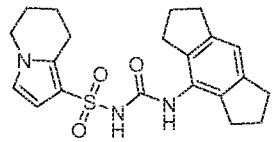
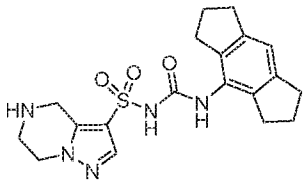
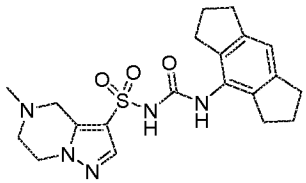
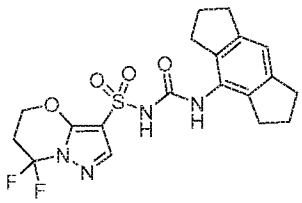
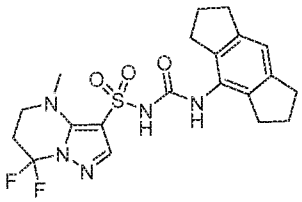
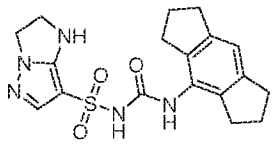
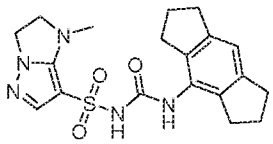
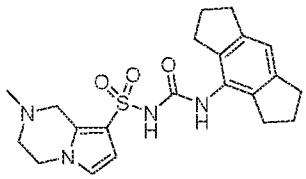
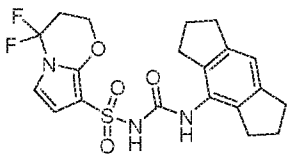
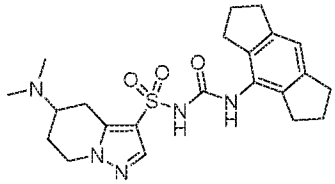
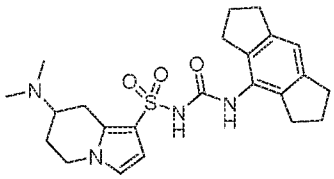
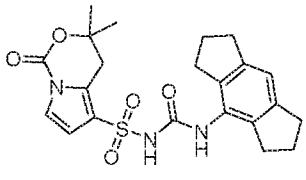
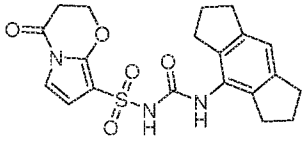
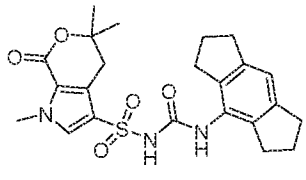
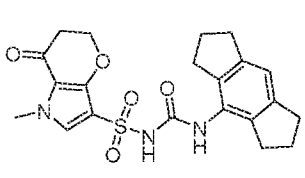
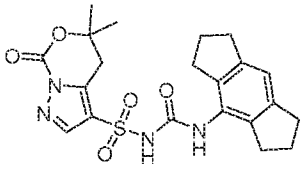
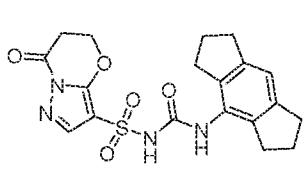
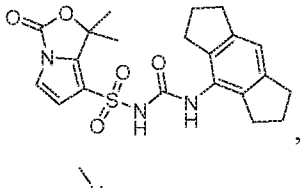
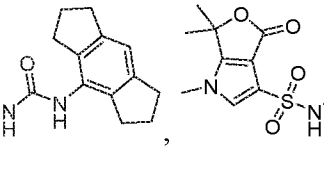
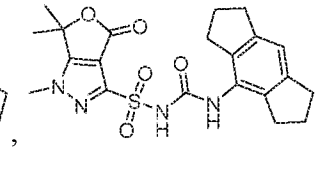
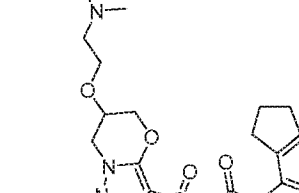

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

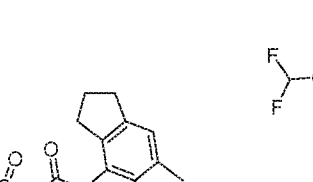
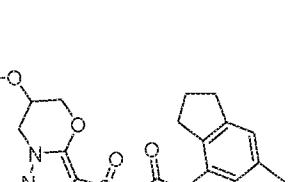
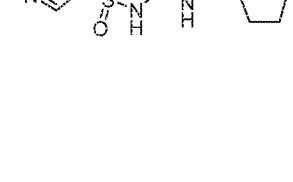
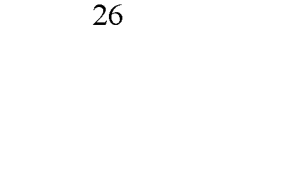
,

,

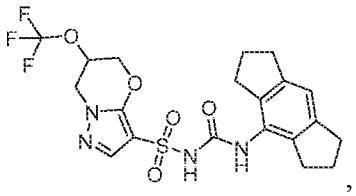
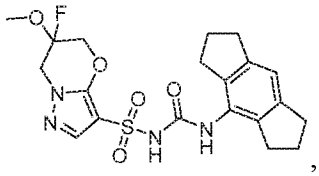
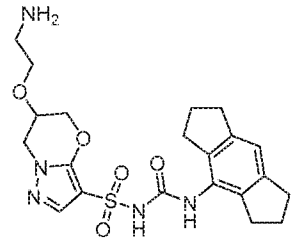
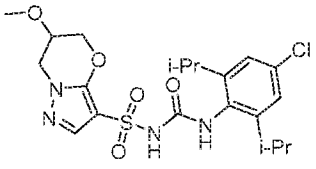
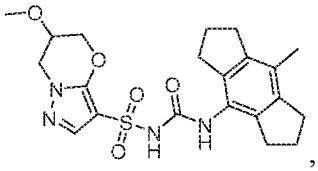
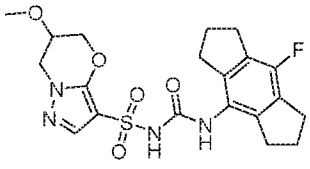
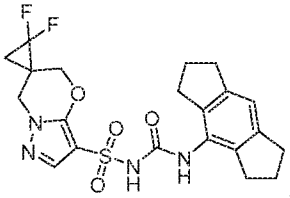
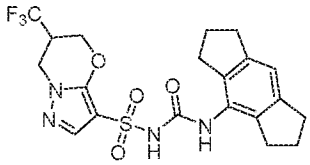
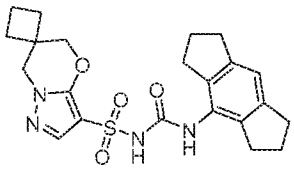
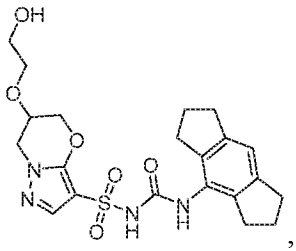
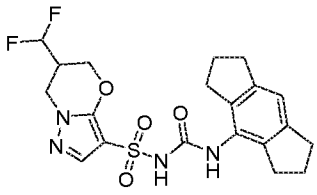
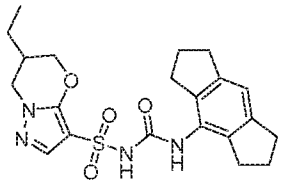
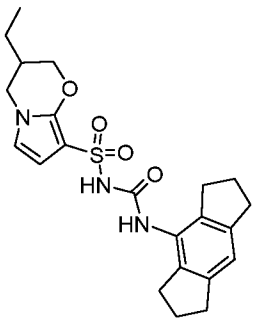
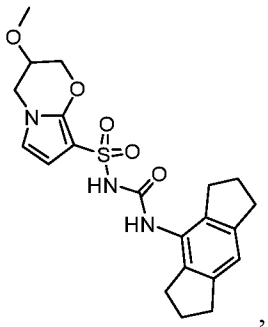
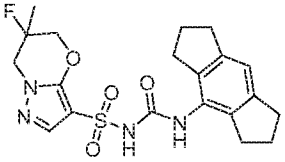
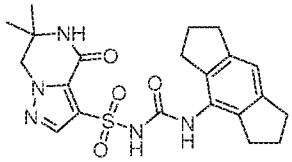
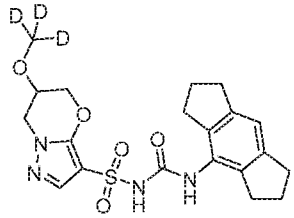
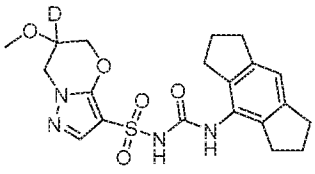
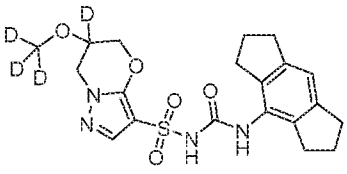
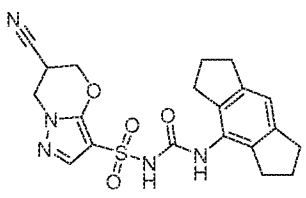
,

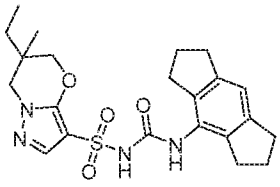
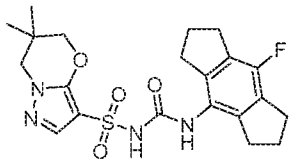
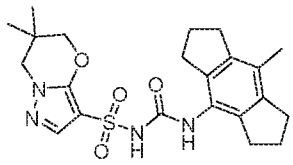
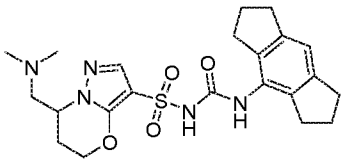
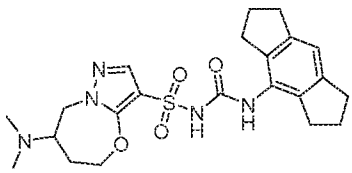
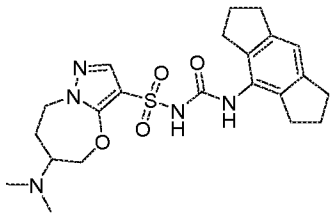
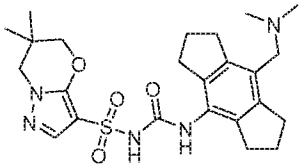
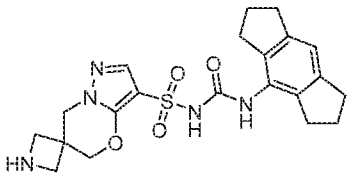
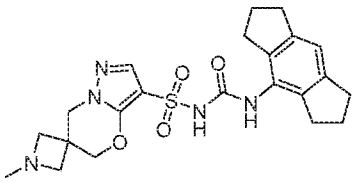
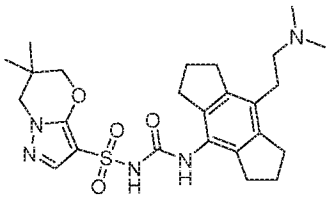
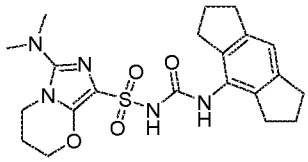
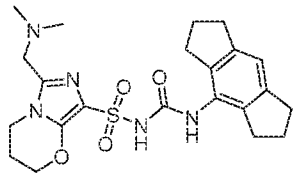
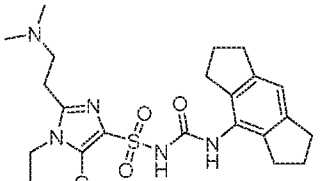
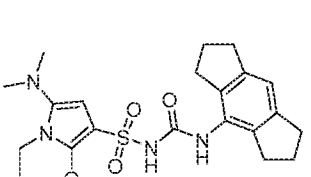
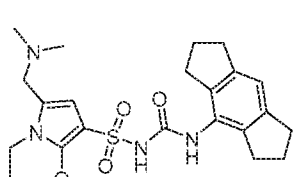
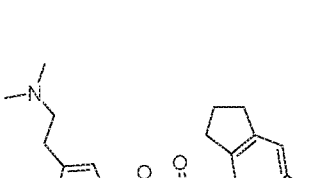
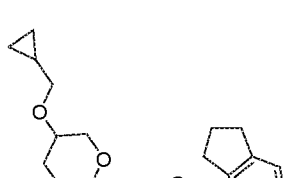
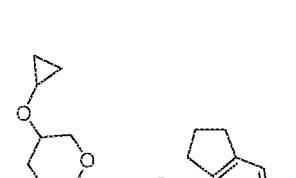
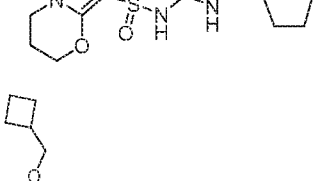
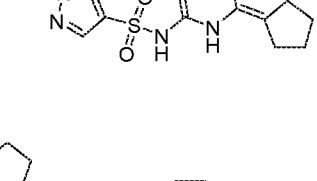
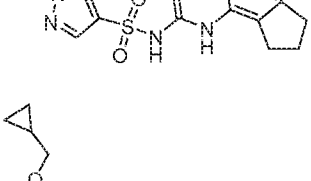
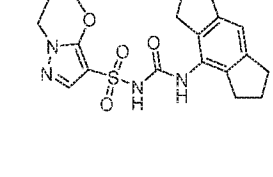
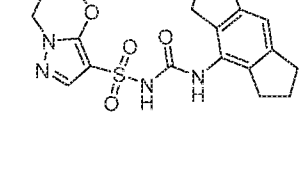
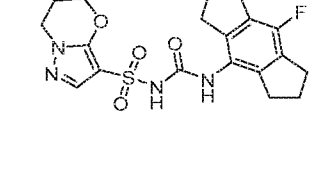
,

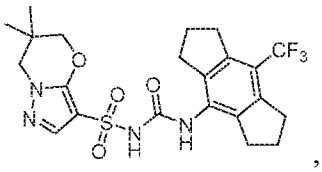
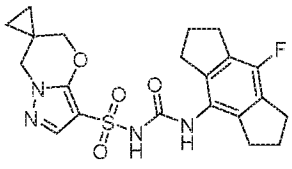
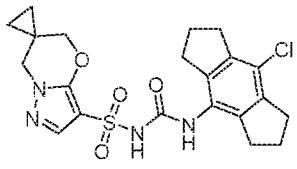
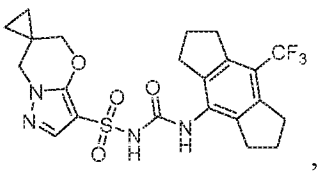
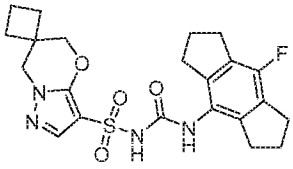
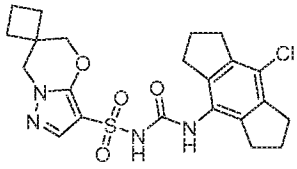
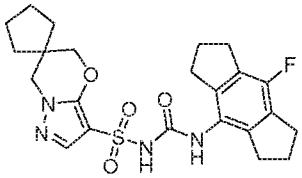
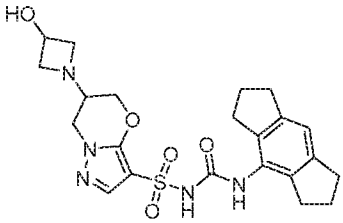
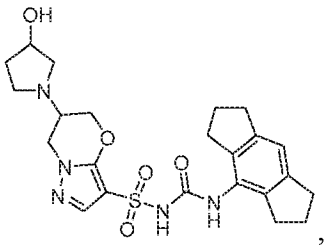
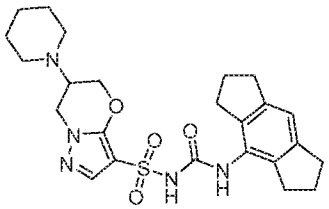
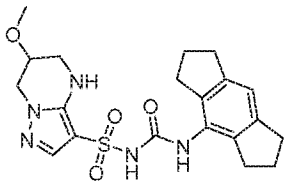
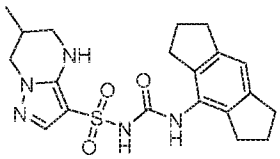
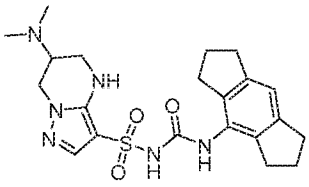
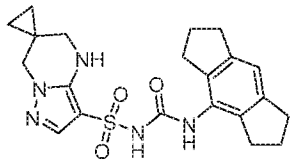
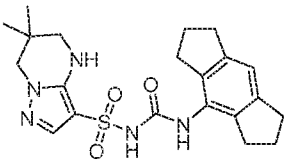
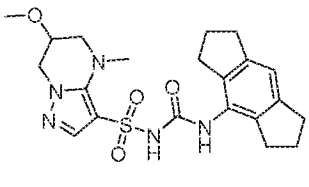
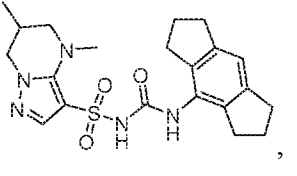
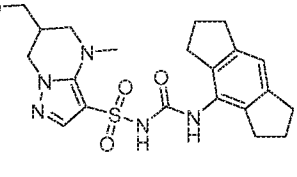
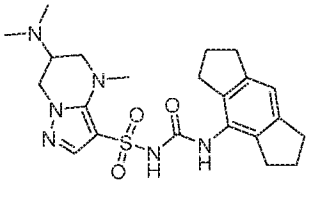
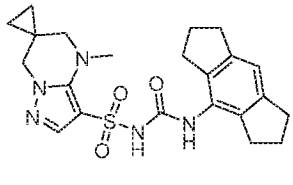
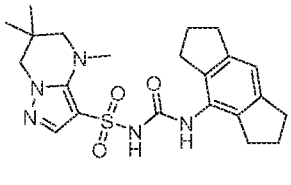

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

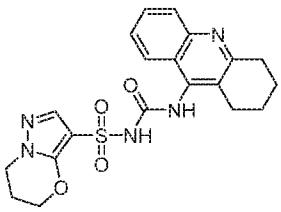
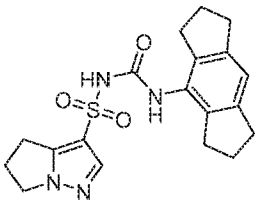
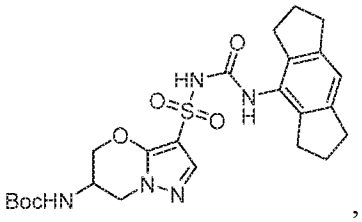
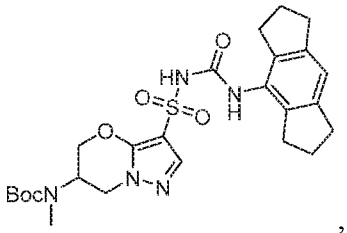
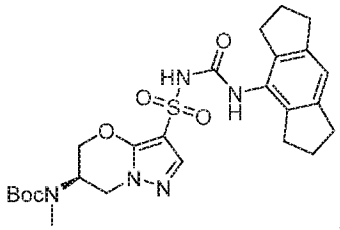
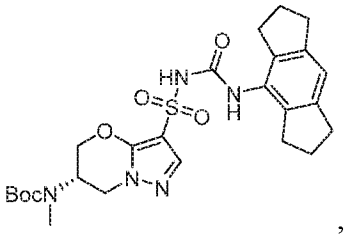
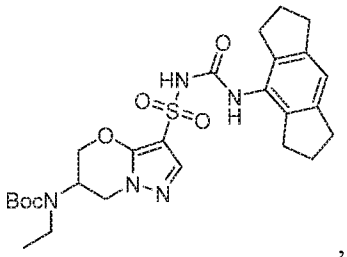
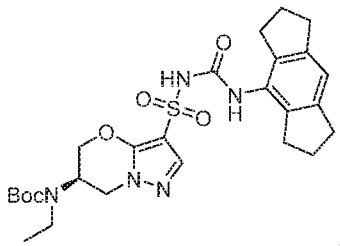
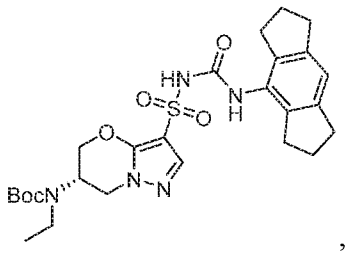
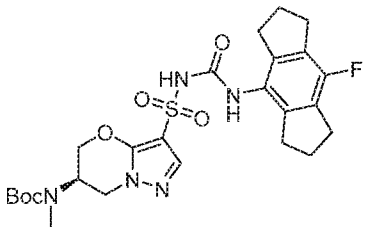
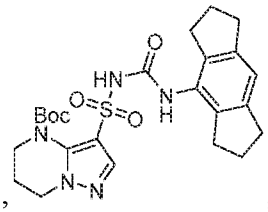
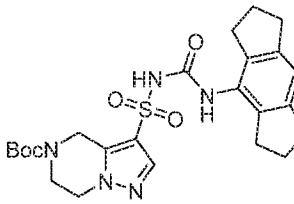
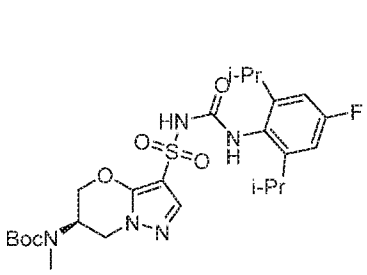
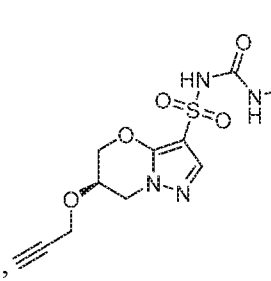
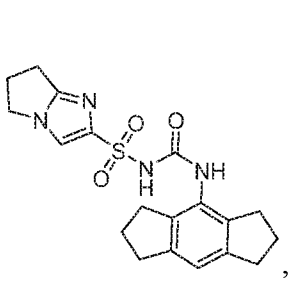

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

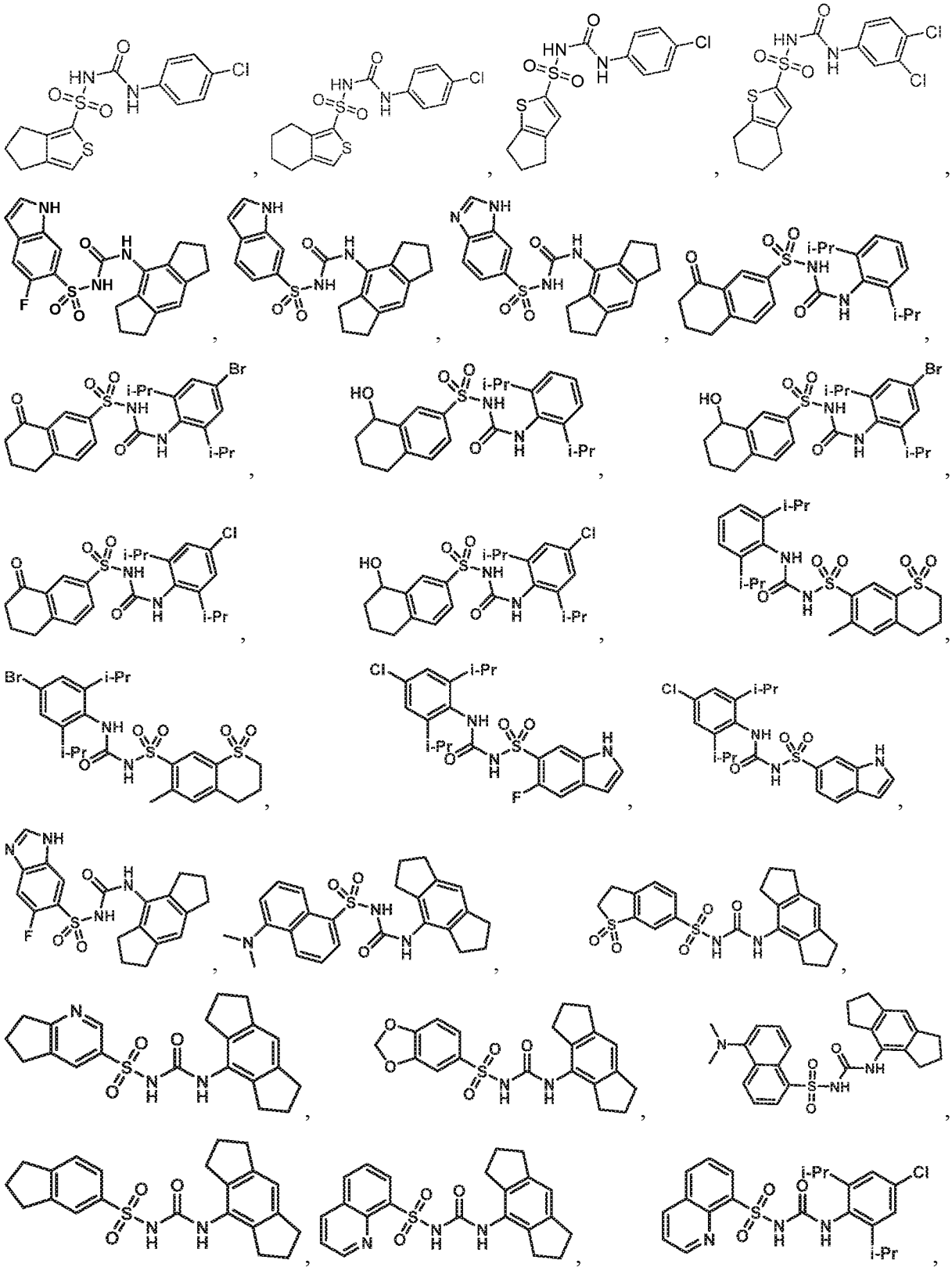
,

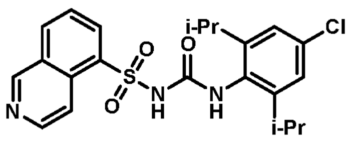
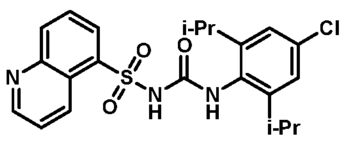
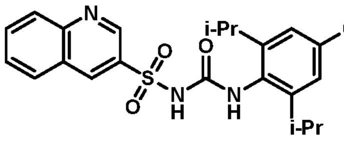
,

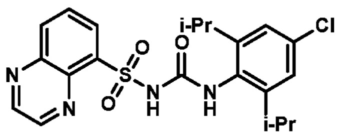
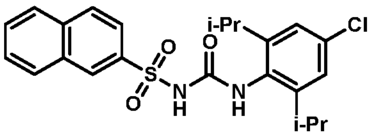
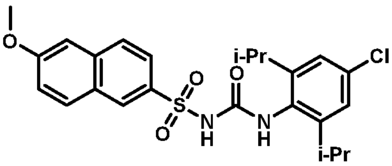
,

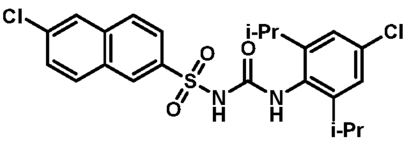
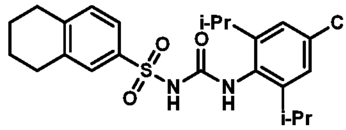
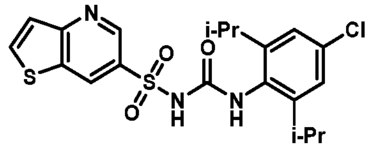
,

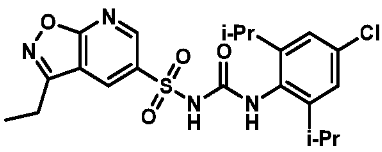
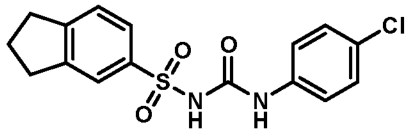
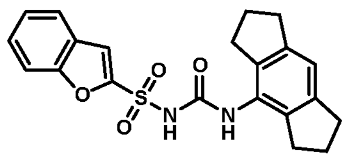
,

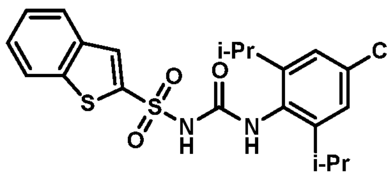
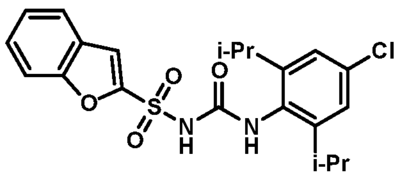
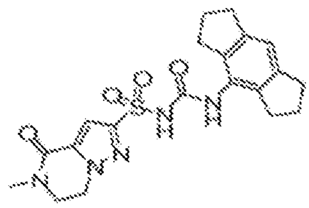


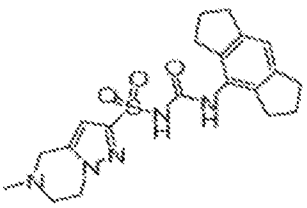
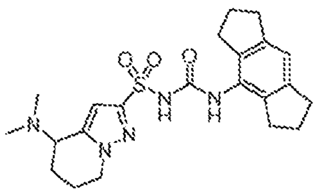
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

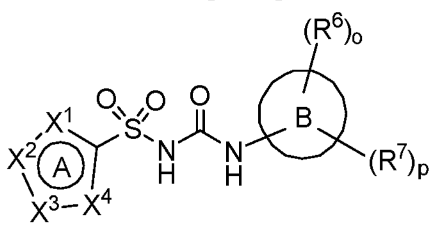
 ,  ,  ,

 ,  ,  ,

 , and  ;

or a pharmaceutically acceptable salt thereof.

In one aspect, provided herein is a compound of Formula AA



Formula AA

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;

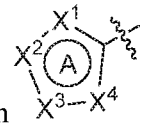
X^3 is O, S, N, CR^3, or NR^3;

X^4 is O, S, N, CR^4, NR^4, or $–X^5$-X^6-;

X^5 is N or CR^5;

X^6 is N or CR^6;

when X^4 is -X^5-X^6-, then: X^1 is N or CR^1, X^2 is N or CR^2, and X^3 is N or CR^3;

when X^4 is other than -X^5-X^6-, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is -X^5-X^6-, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

from two to four of R^1, R^2, R^3, and R^4 are present or from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and

wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least of the two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20};

R^{20} is selected from the group consisting of: hydroxy, halo, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{21}, C_2-C_6 alkenyl optionally substituted with one or more R^{21}, C_2-C_6 alkynyl optionally substituted with one or more R^{21}, C_1-C_6 alkoxy optionally substituted with one or more R^{21}, OC_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{21}, $S(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, $OS(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, C_6-C_{10} aryl optionally substituted with one or more R^{21}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{21}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{21}, -$OC(O)NHC_6$-$_{10}$ aryl optionally substituted with one or more R^{21}, and $CONR^8R^9$;

or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

R^{21} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

or at least one pair of R^{21} on adjacent atoms, taken together with the atoms connecting them, independently forms a C_4-C_{12} cycloalkyl ring or a 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

wherein any of R^1, R^2, R^3, R^4, R^5, and R^6 that are not taken together with the atoms connecting them to form a ring, when present, are each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NH\text{-}(C{=}NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl

optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};
R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;
R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

B is a 5-10-membered heteroaryl or C_6-C_{10} aryl ring;

o = 1 or 2;
p = 0, 1, 2, or 3;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one

or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25},

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered

heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;

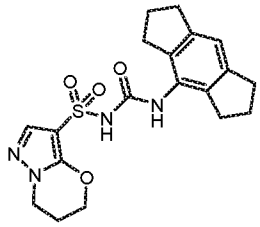
each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;

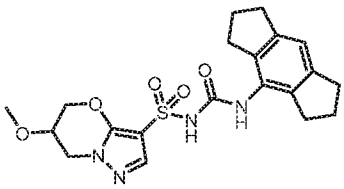
R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

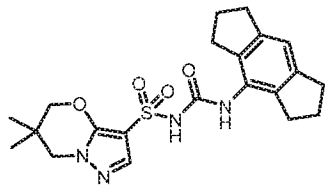
provided that when B is 5-10-membered heteroaryl with from 2-3 ring nitrogen atoms, at least one R^6 is bonded to B at a position *ortho* to the $–HNC(=O)NHS(O)_2$- moiety of Formula AA;

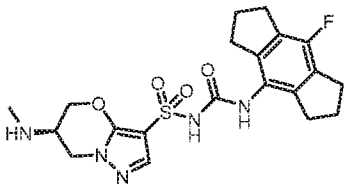
when B is 2-pyridyl, pyrimidin-6-yl, or pyrimidin-4-yl, B is not substituted with a cyano group at a position *ortho* to the $–HNC(=O)NHS(O)_2$- moiety of Formula AA;

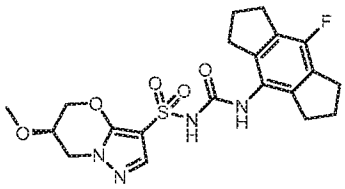
and

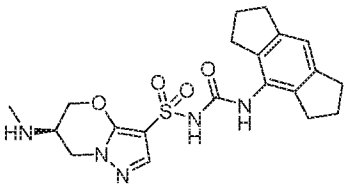


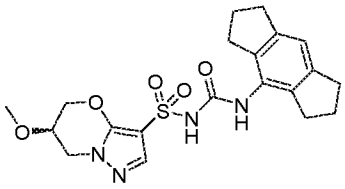


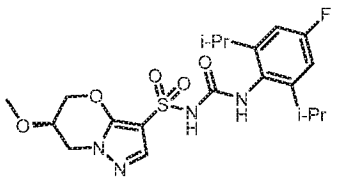


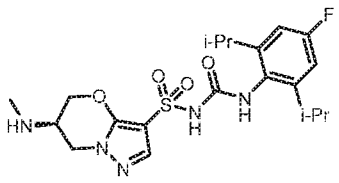


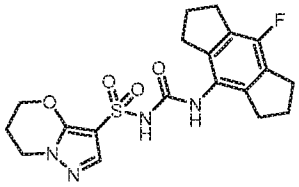


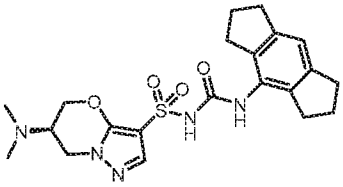


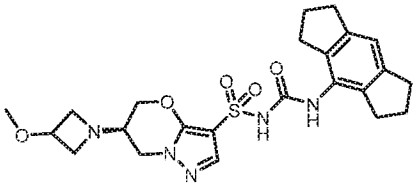


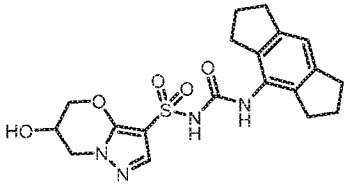


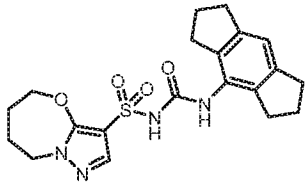


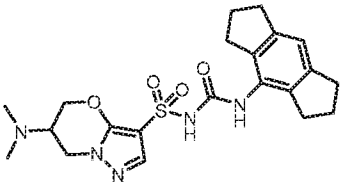


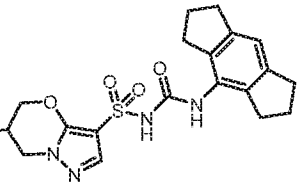


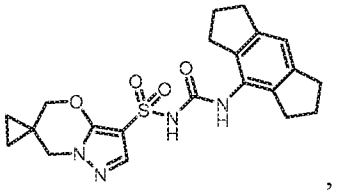


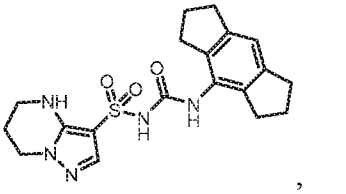


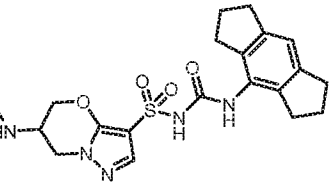


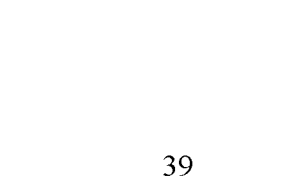












with the proviso that the compound of Formula AA is not a compound selected from the group consisting of:

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

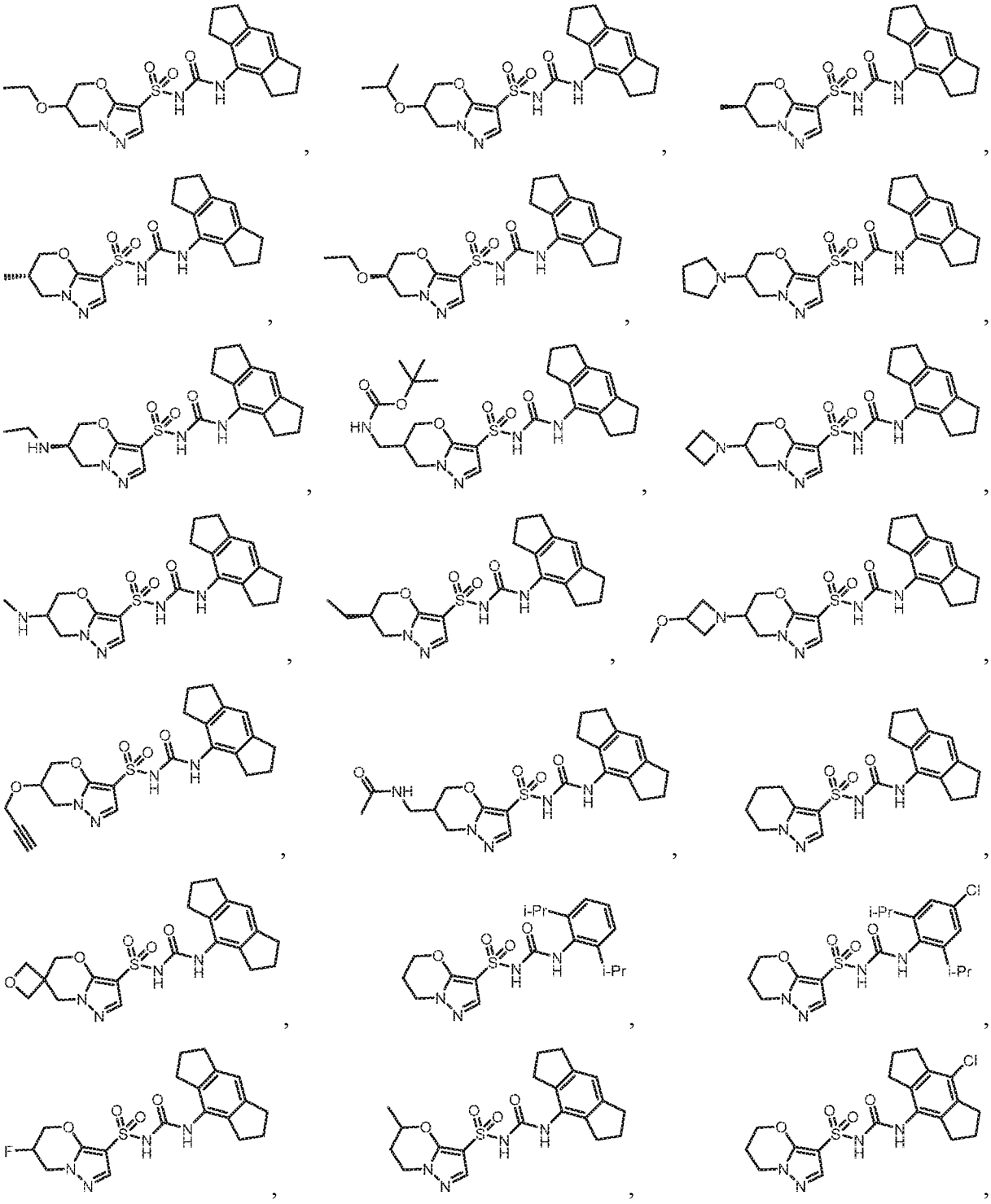
,

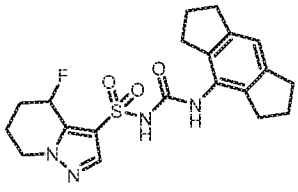
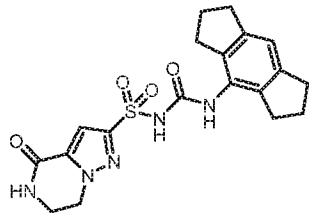
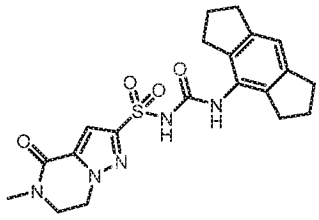
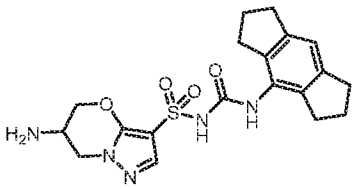
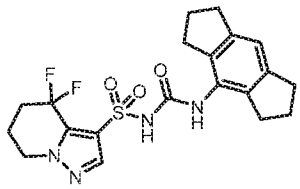
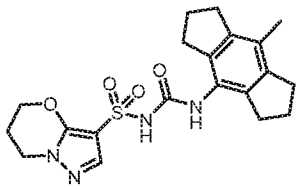
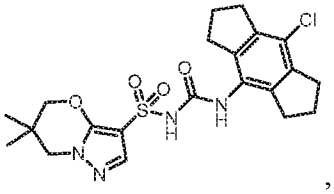
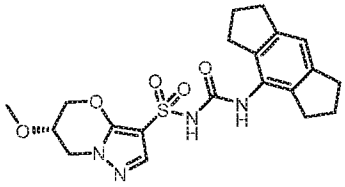
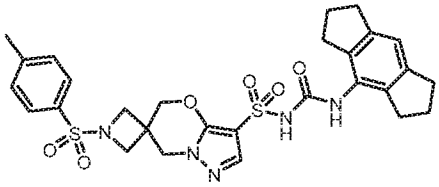
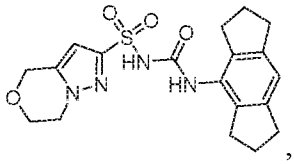
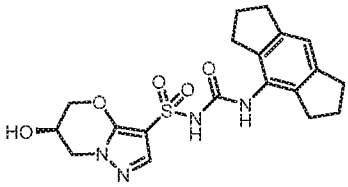
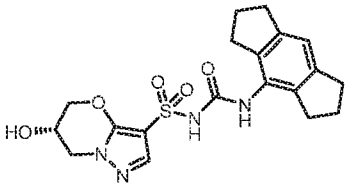
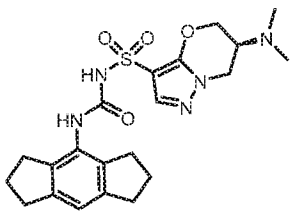
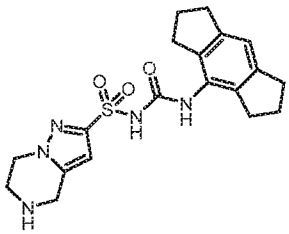
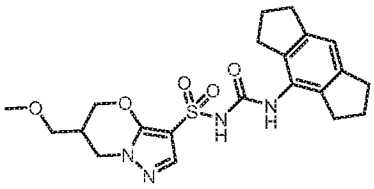
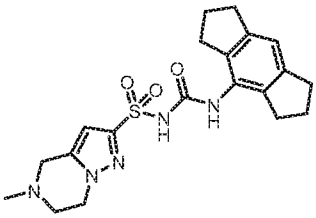
,

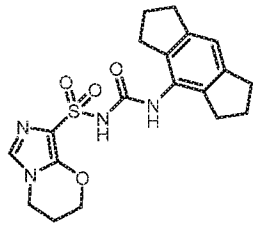
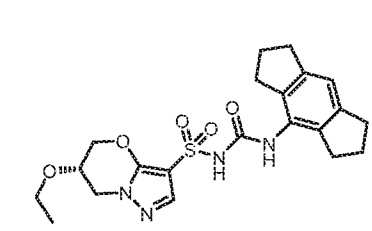
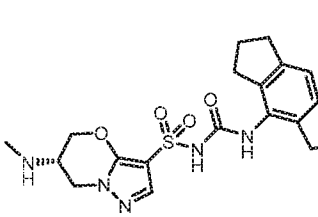
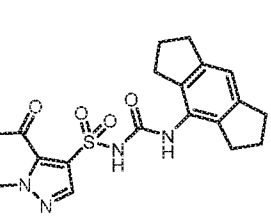
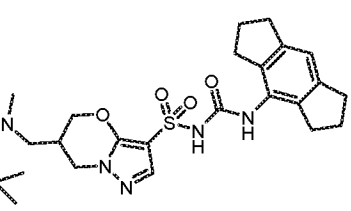
,

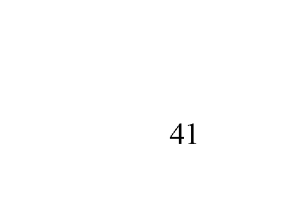
,

,

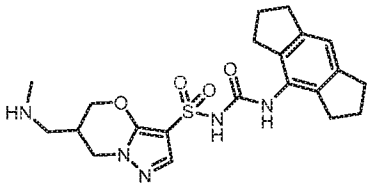
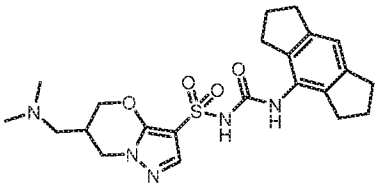
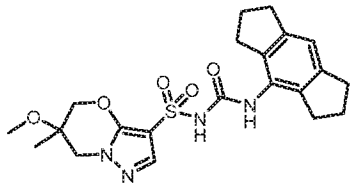
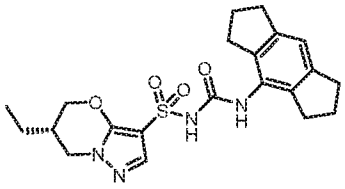
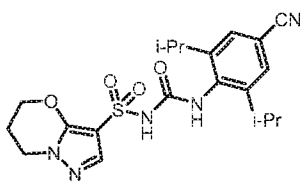
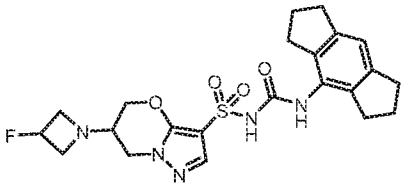
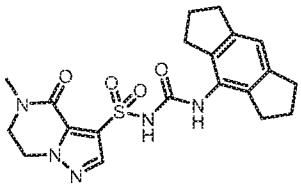
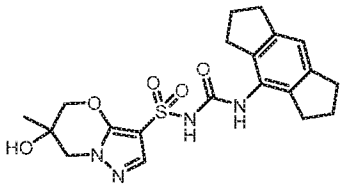
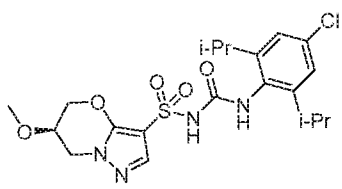
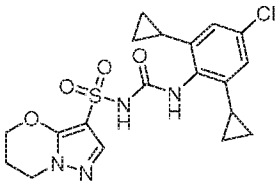
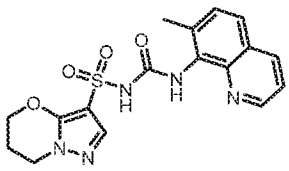
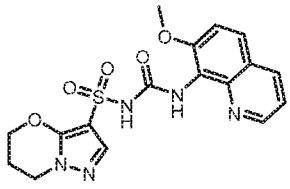
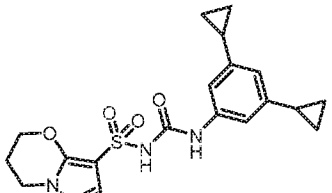
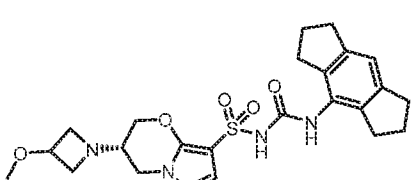
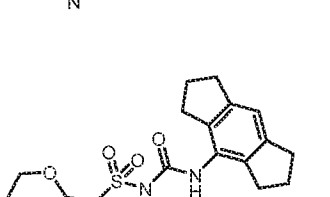
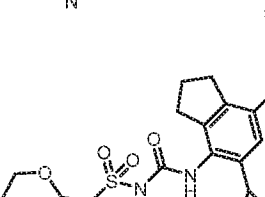
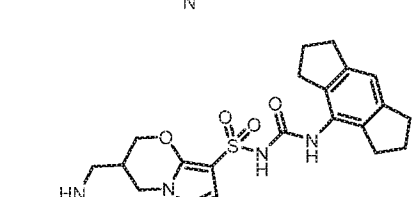
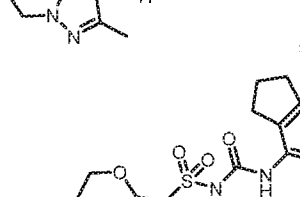
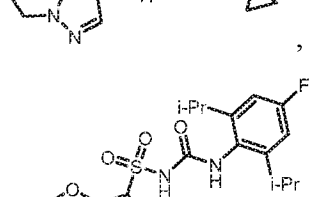
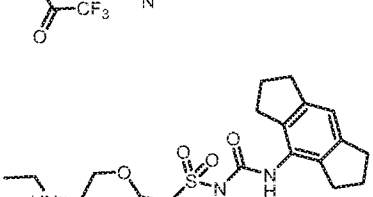
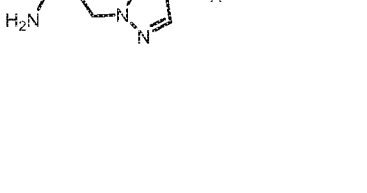
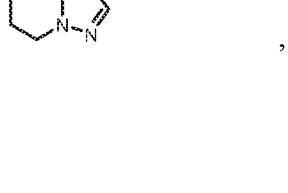



,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

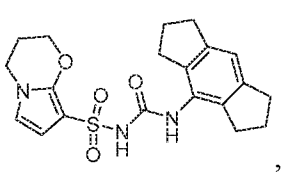
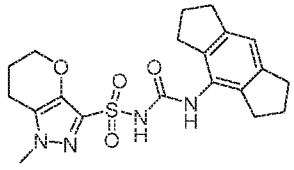
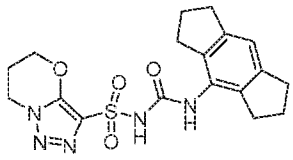
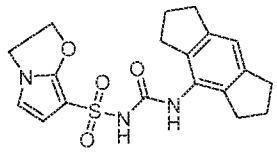
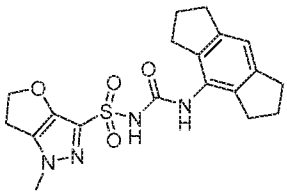
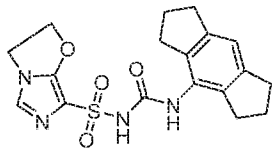
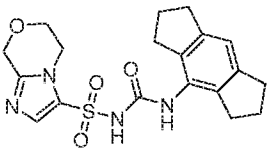
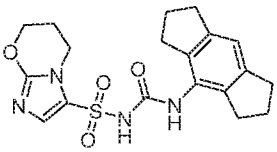
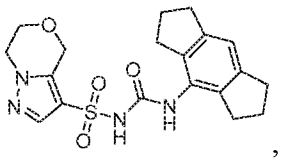
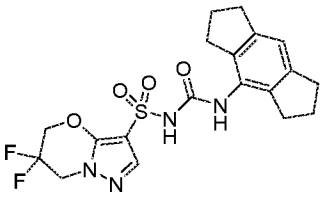
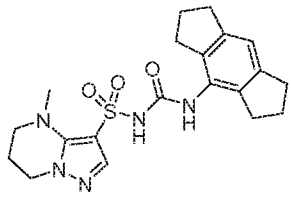
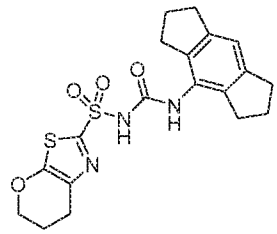
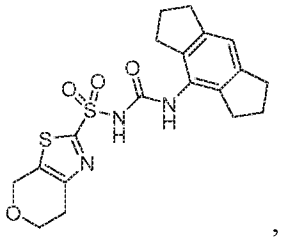
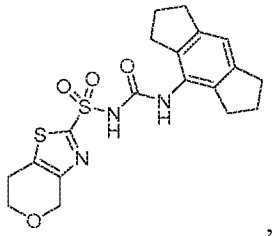
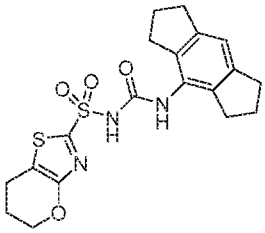
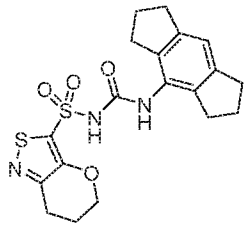
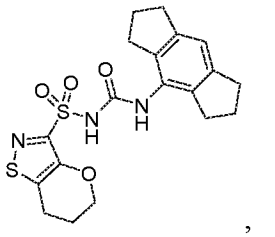
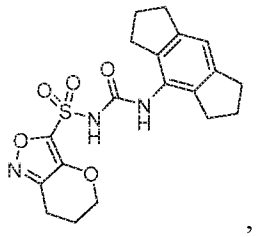
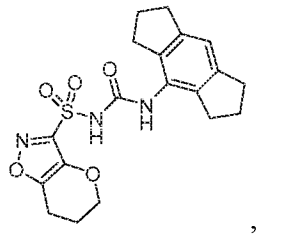
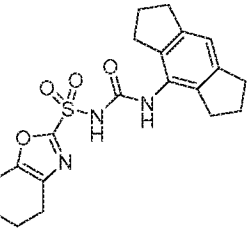
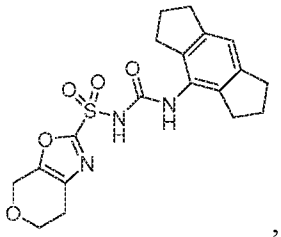
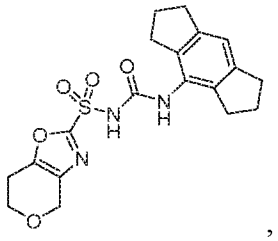
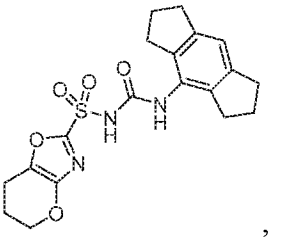
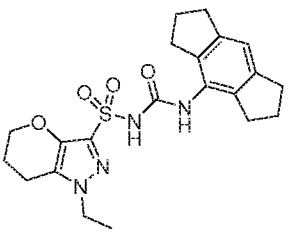
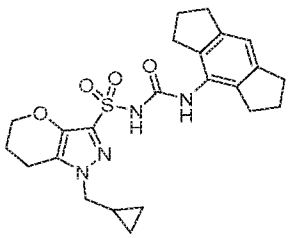
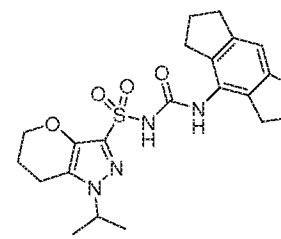
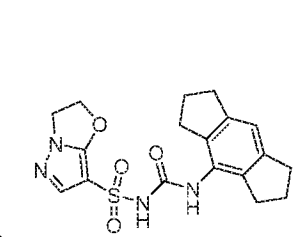
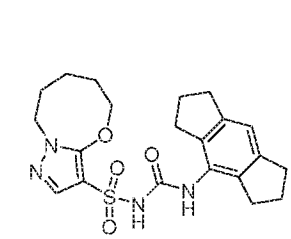
,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

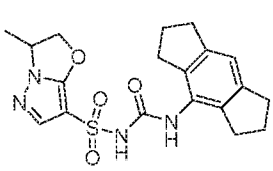
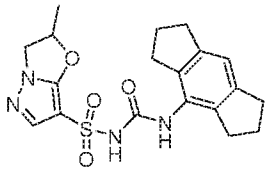
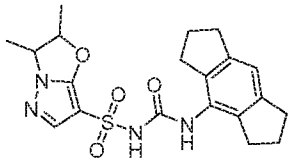
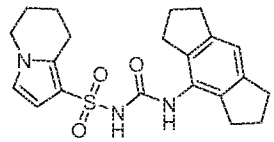
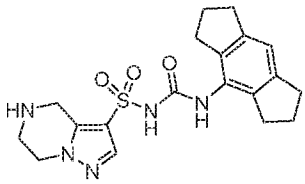
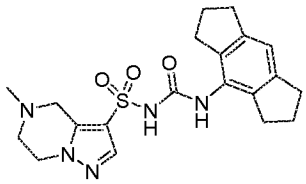
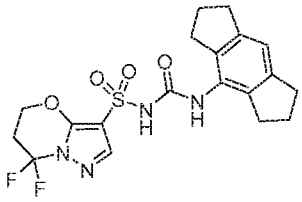
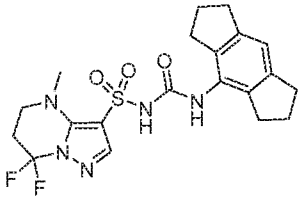
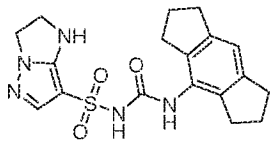
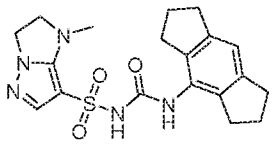
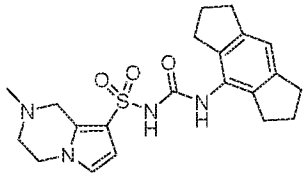
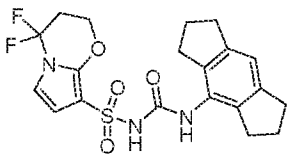
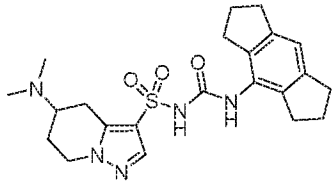
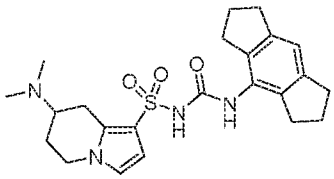
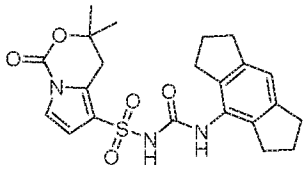
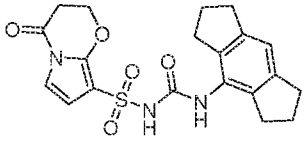
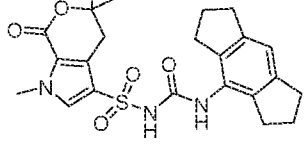
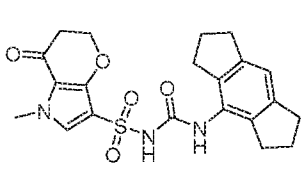
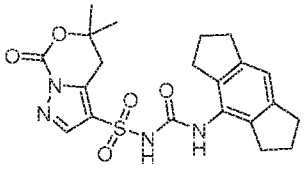
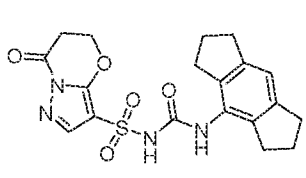
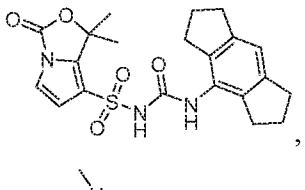
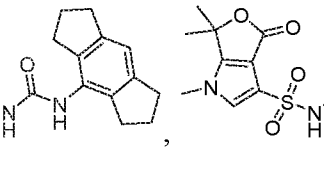
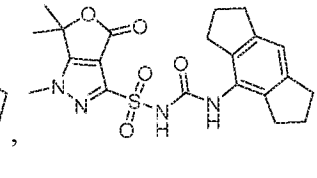
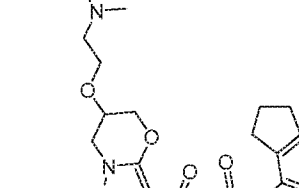

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

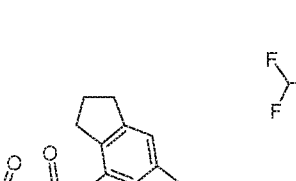
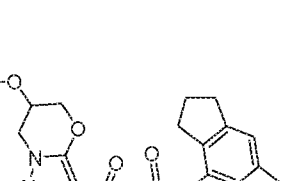
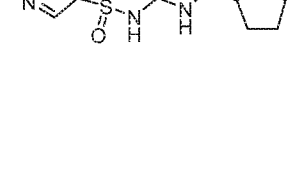
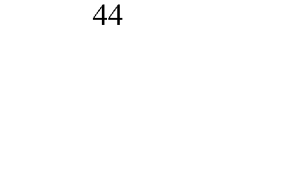
,

,

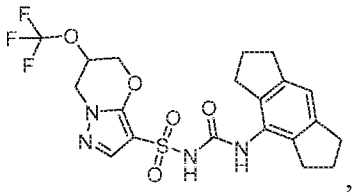
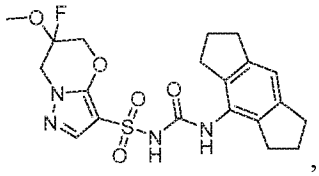
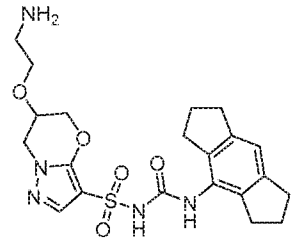
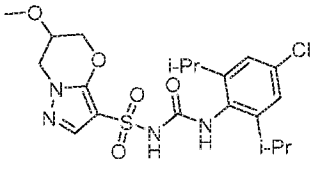
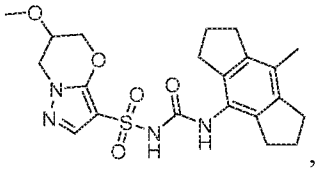
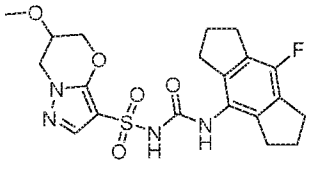
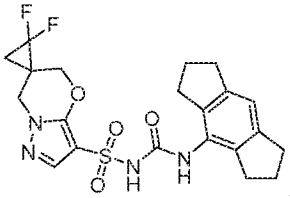
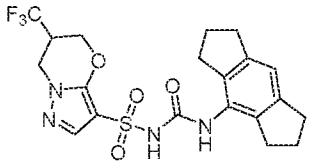
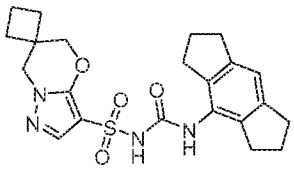
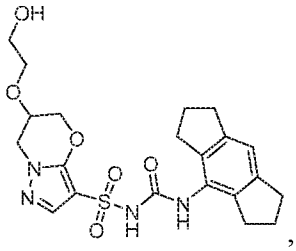
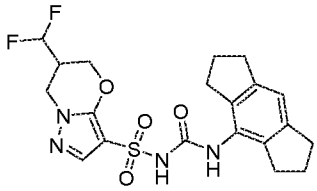
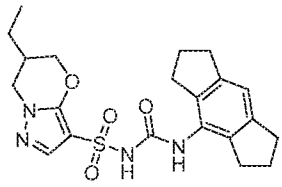
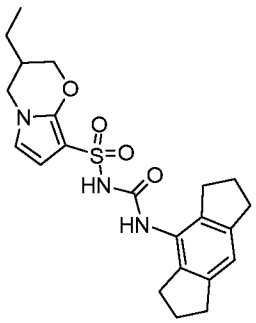
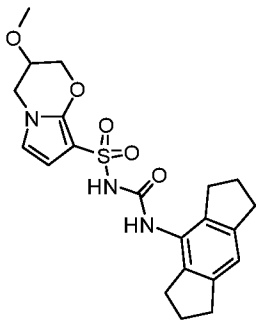
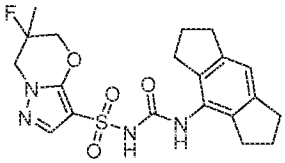
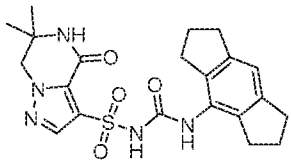
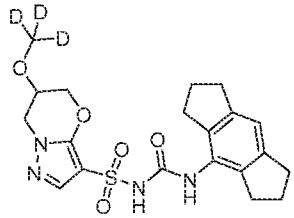
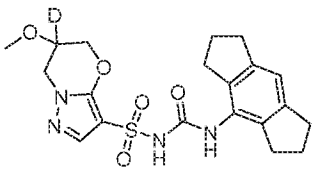
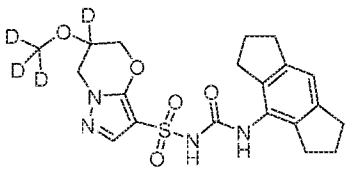
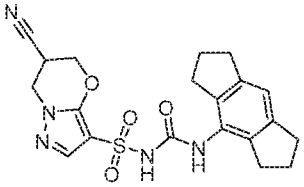
,

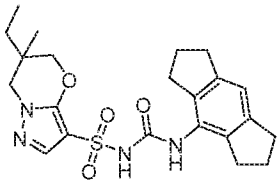
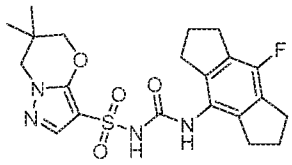
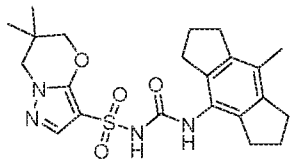
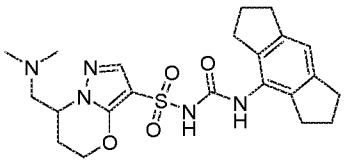
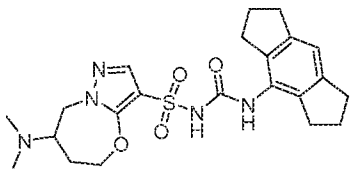
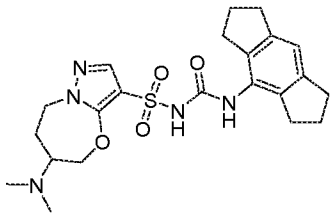
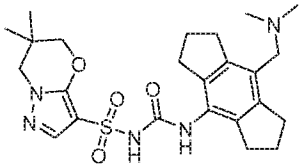
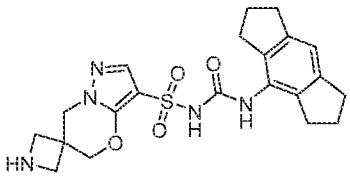
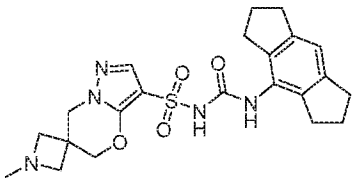
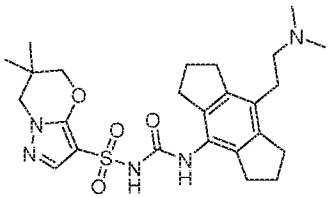
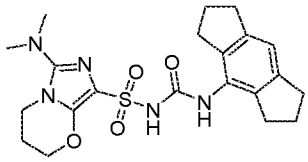
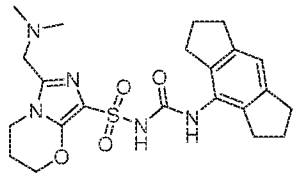
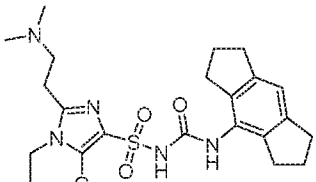
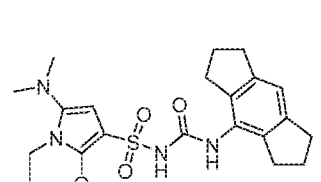
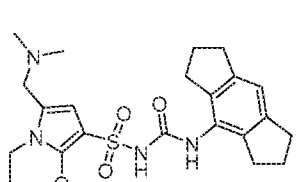
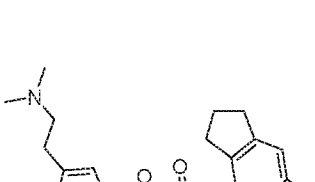
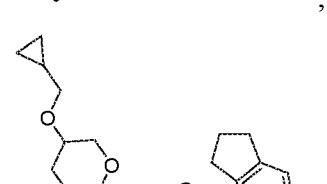
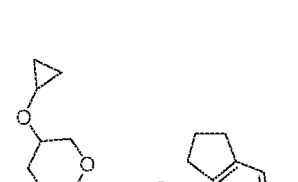
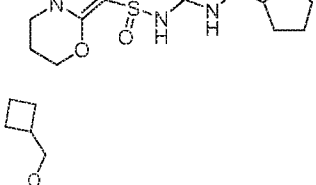
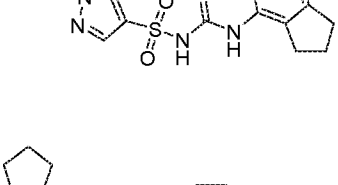
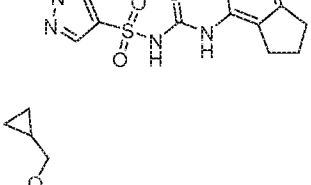
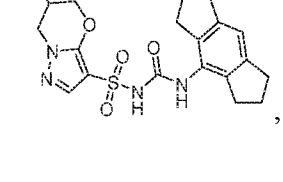
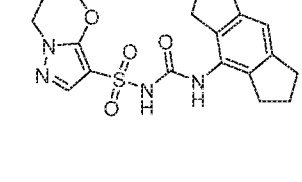
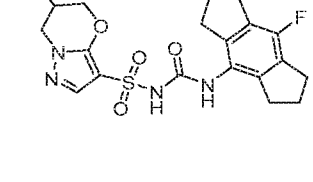
,

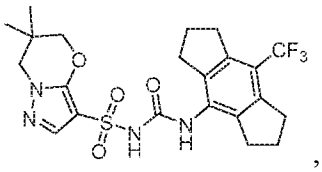
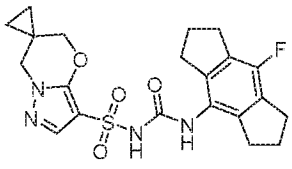
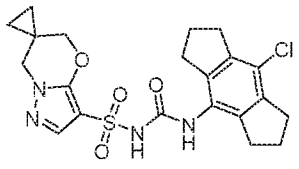
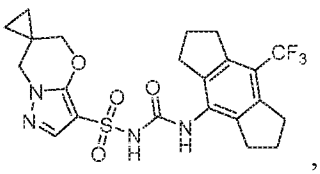
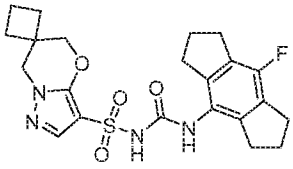
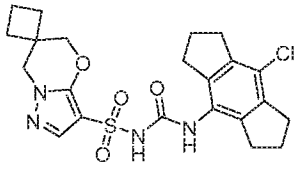
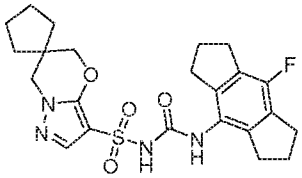
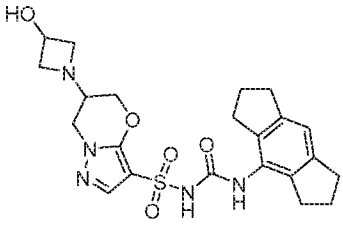
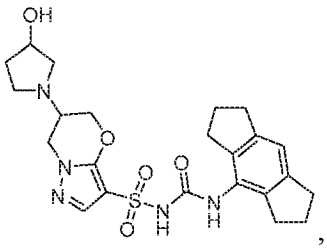
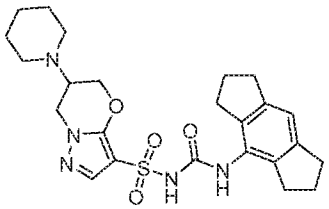
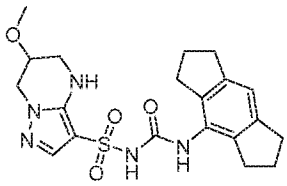
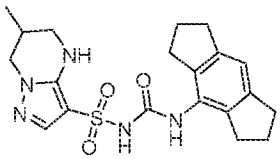
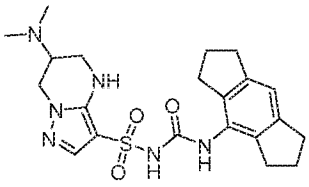
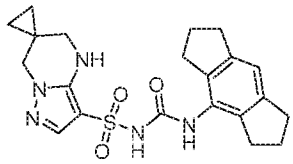
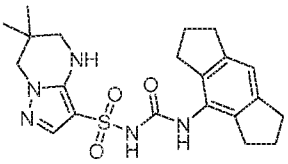
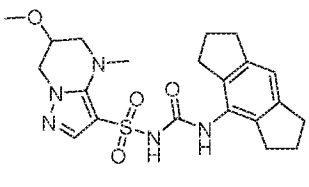
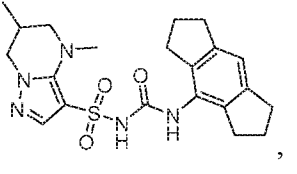
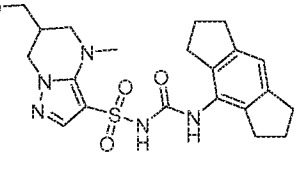
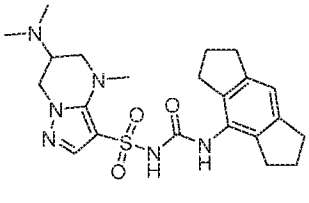
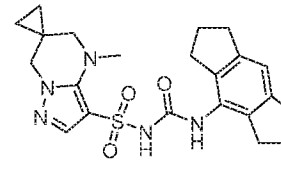
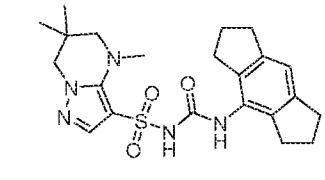

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

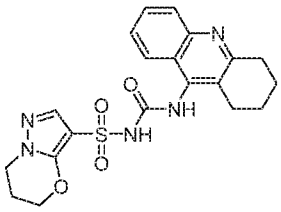
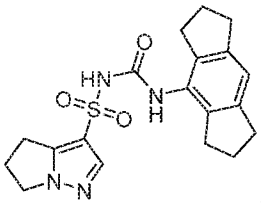
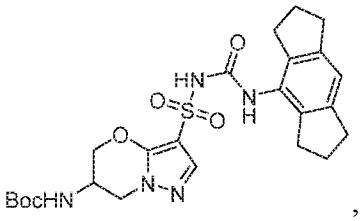
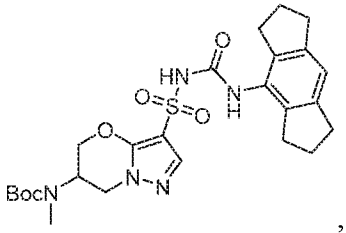
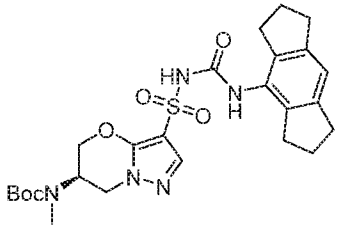
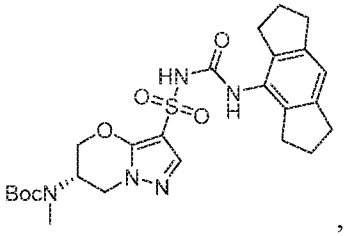
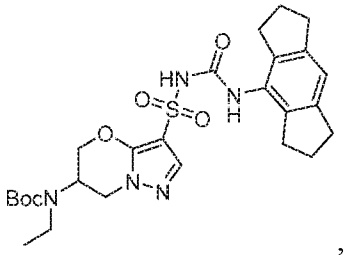
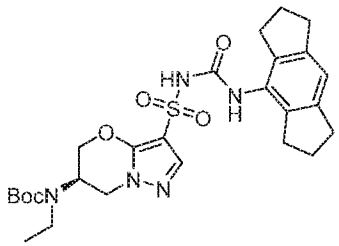
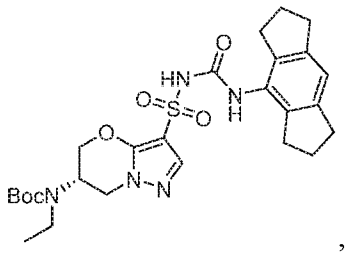
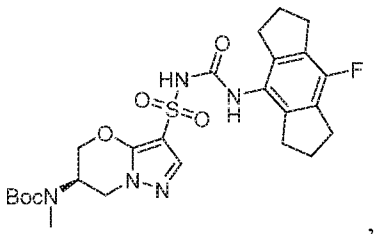
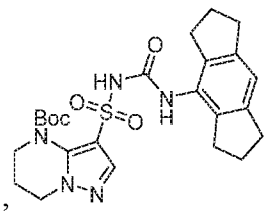
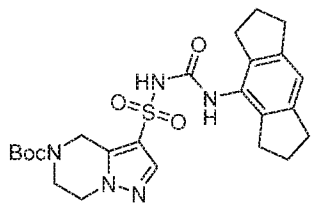
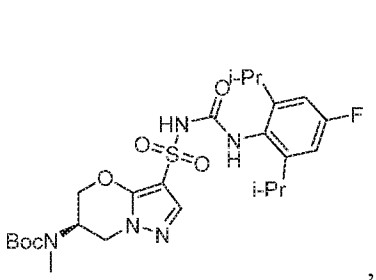
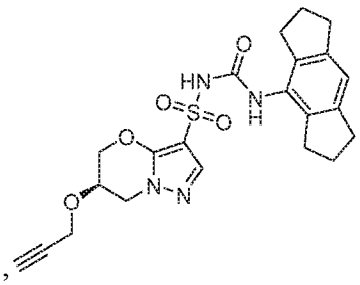
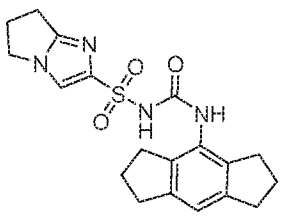
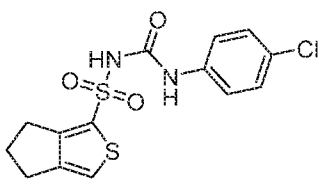
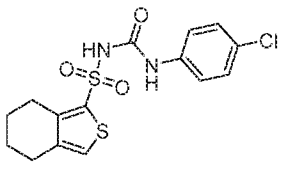
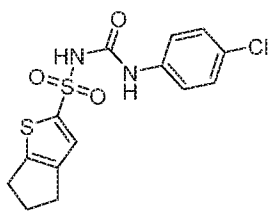
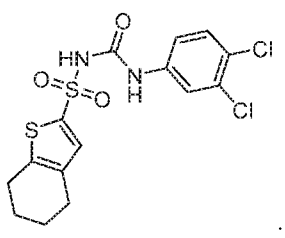

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

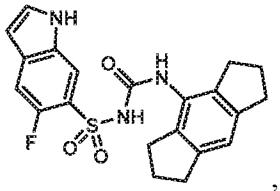
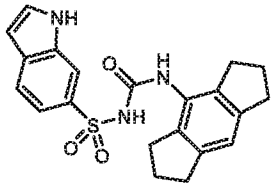
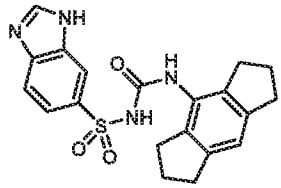
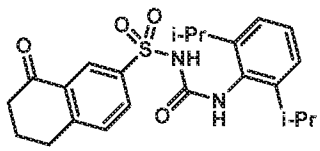
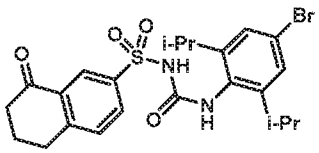
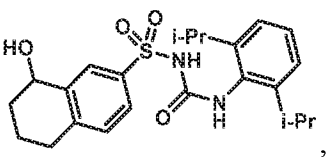
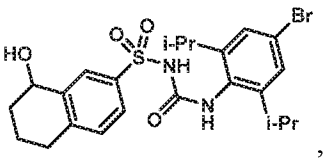
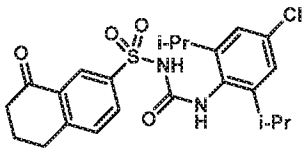
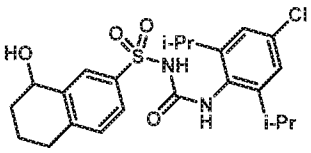
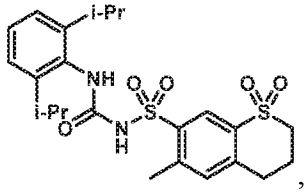
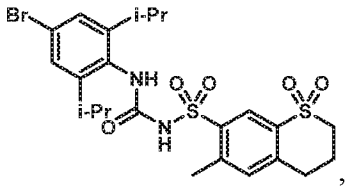
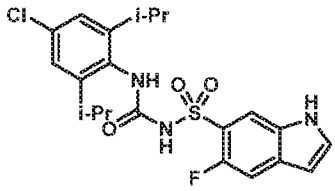
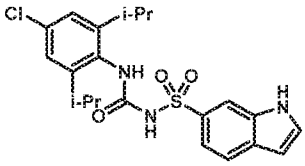
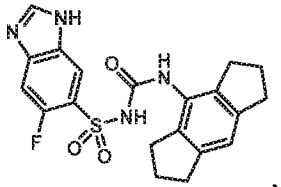
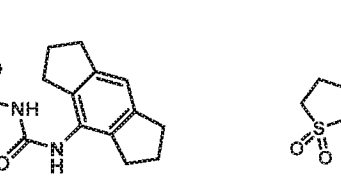
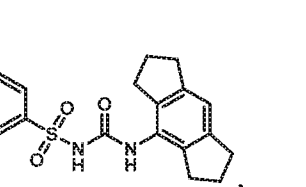

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

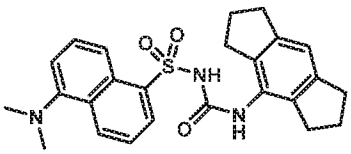
,

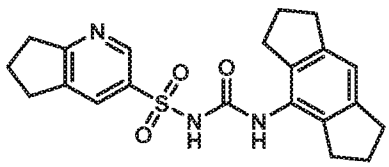
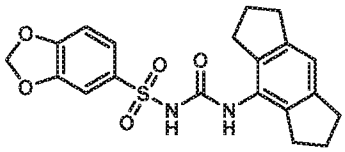
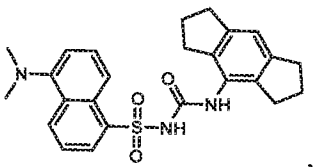
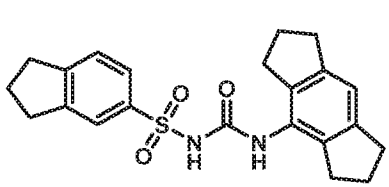
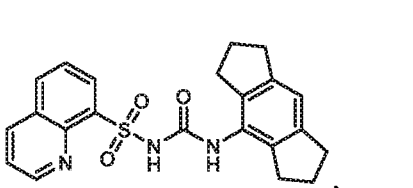
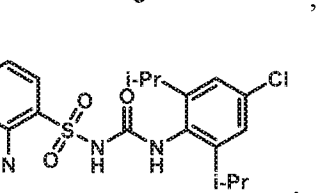
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

.


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

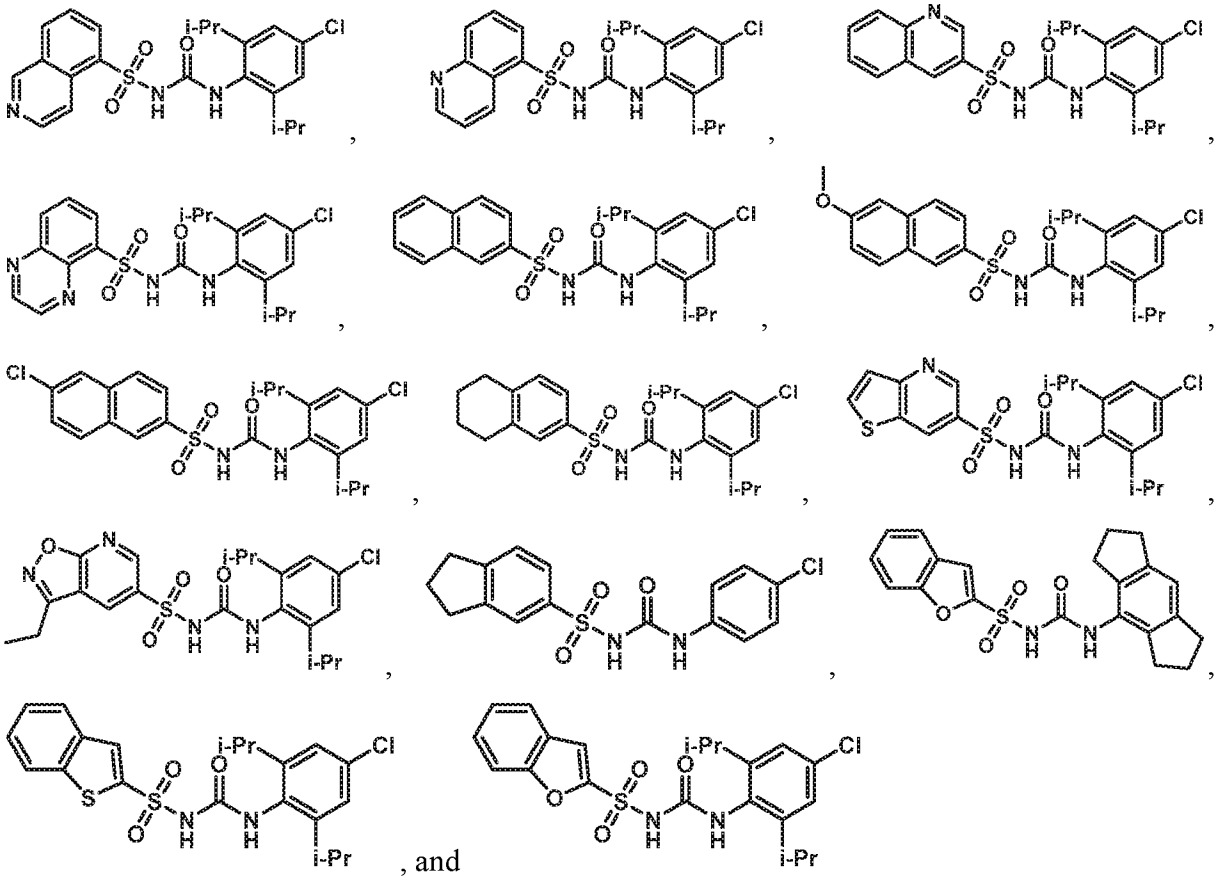
,

,

,

,

,

,

,

,

,

,

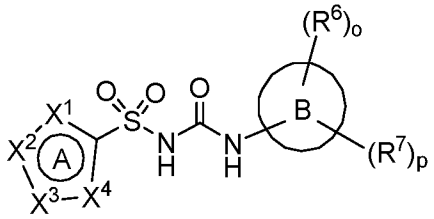
,

,



or a pharmaceutically acceptable salt thereof.

In one aspect, provided herein is a compound of Formula AA



Formula AA

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;

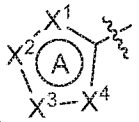
X^3 is O, S, N, CR^3, or NR^3;

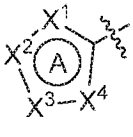
X^4 is O, S, N, CR^4, NR^4, or $–X^5$-X^6-;

X^5 is N or CR^5;

X^6 is N or CR^6;

when X^4 is -X^5-X^6, then: X^1 is N or CR^1, X^2 is N or CR^2, and X^3 is N or CR^3;

when X^4 is other than -X^5-X^6-, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is -X^5-X^6-, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

from two to four of R^1, R^2, R^3, and R^4 are present or from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and

wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least of the two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20};

R^{20} is selected from the group consisting of: hydroxy, halo, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{21}, C_2-C_6 alkenyl optionally substituted with one or more R^{21}, C_2-C_6 alkynyl optionally substituted with one or more R^{21}, C_1-C_6 alkoxy optionally substituted with one or more R^{21}, OC_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{21}, $S(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, $OS(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, C_6-C_{10} aryl optionally substituted with one or more R^{21}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{21}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{21}, and $CONR^8R^9$;

or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

R^{21} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

wherein any of R^1, R^2, R^3, R^4, R^5, and R^6 that are not taken together with the atoms connecting them to form a ring, when present, are each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered

heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, NH-$(C=NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;
R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

B is a 5-10-membered heteroaryl or C_6-C_{10} aryl ring;

o = 1 or 2;
p = 0, 1, 2, or 3;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25},

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered

heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;

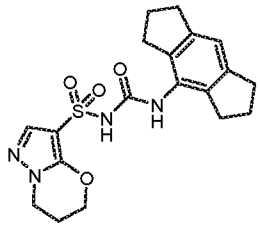
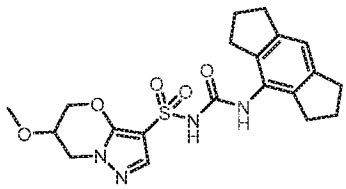
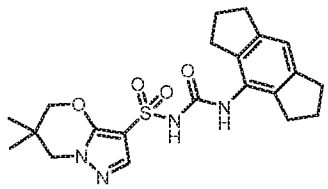
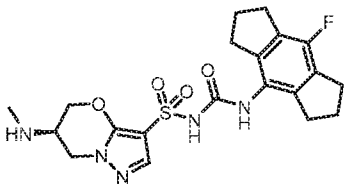
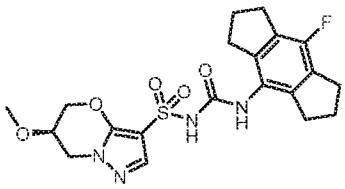
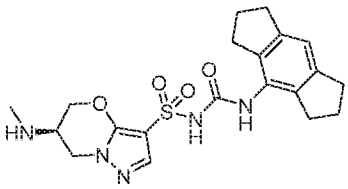
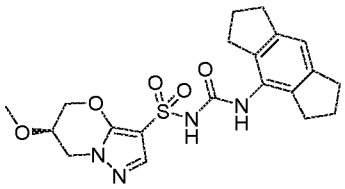
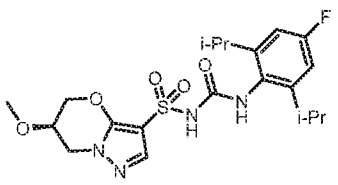
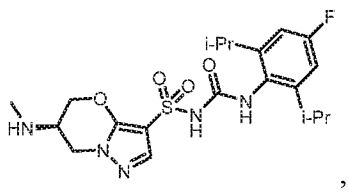
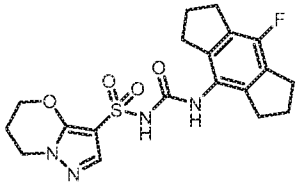
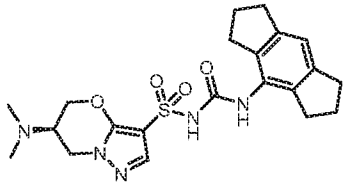
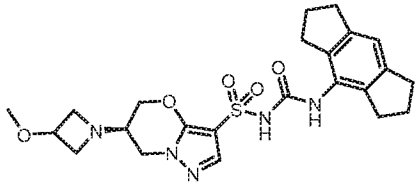
R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

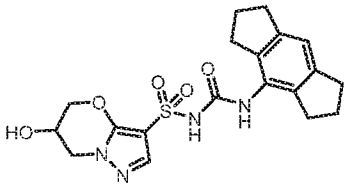
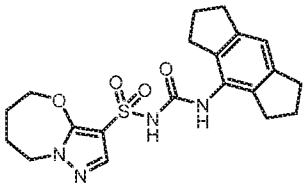
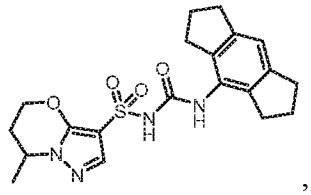
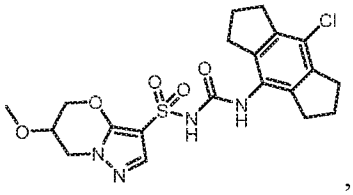
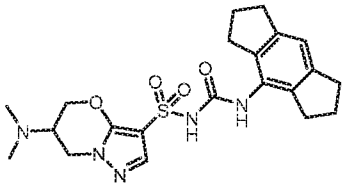
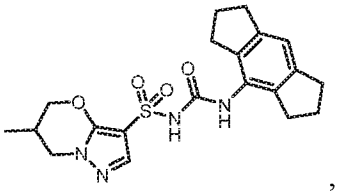
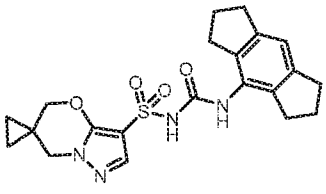
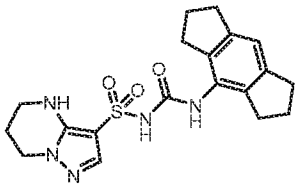
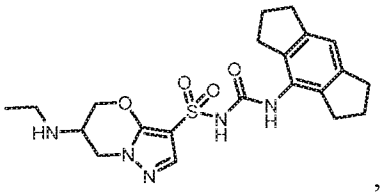
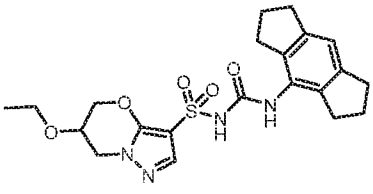
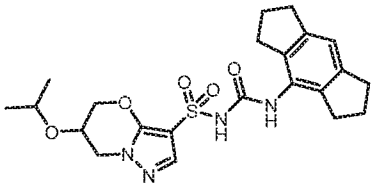
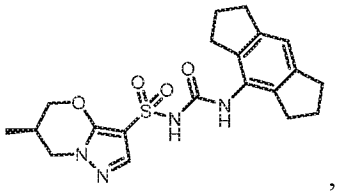
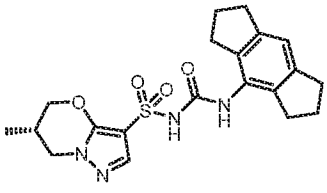
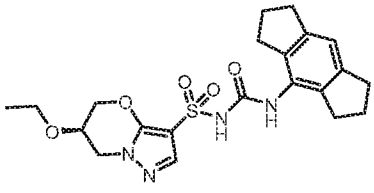
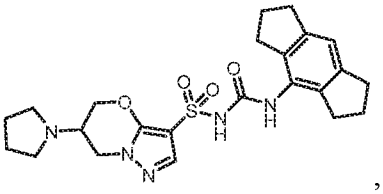
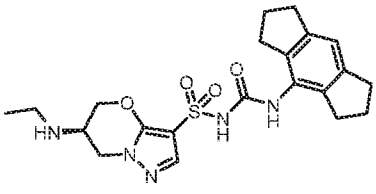
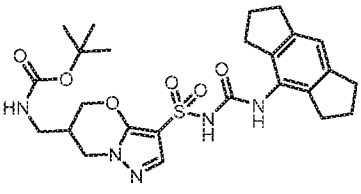
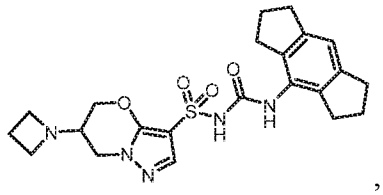
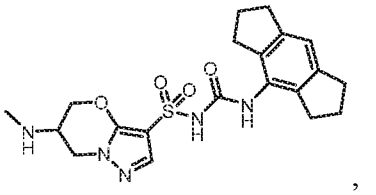
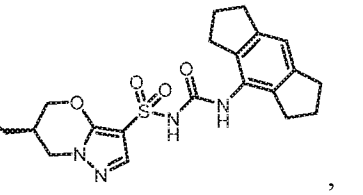
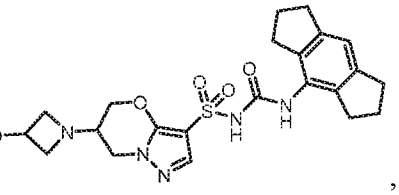
provided that when B is 5-10-membered heteroaryl with from 2-3 ring nitrogen atoms, at least one R^6 is bonded to B at a position *ortho* to the –HNC(=O)NHS(O)$_2$- moiety of Formula AA;

when B is 2-pyridyl, pyrimidin-6-yl, or pyrimidin-4-yl, B is not substituted with a cyano group at a position *ortho* to the –HNC(=O)NHS(O)$_2$- moiety of Formula AA;

and

with the proviso that the compound of Formula AA is not a compound selected from the group consisting of:

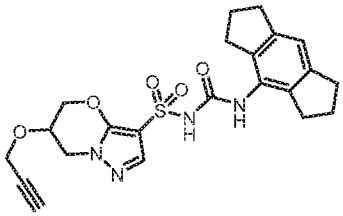
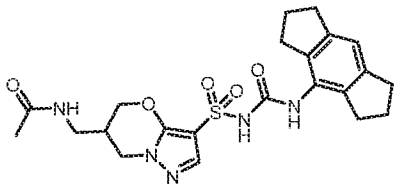
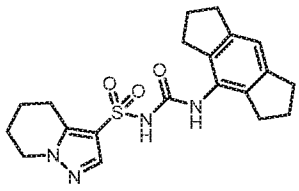
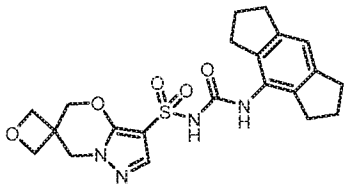
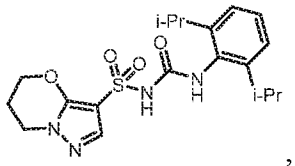
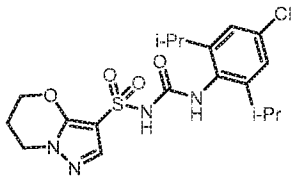
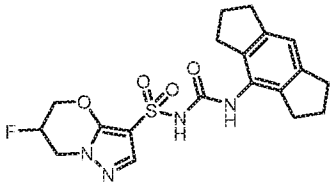
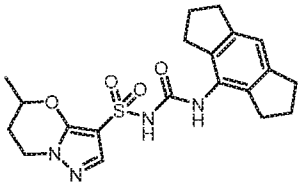
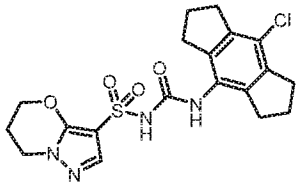
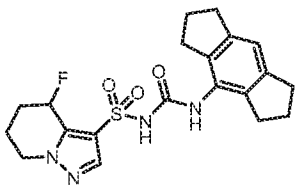
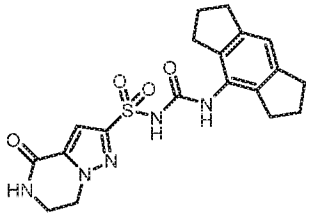
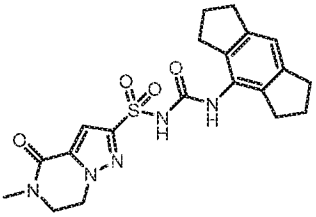
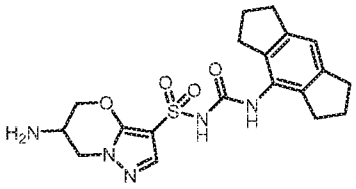
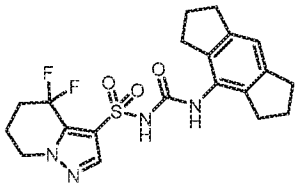
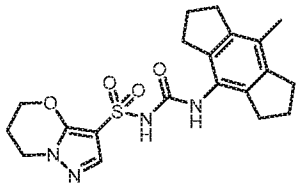

,

,

,

,

,

,

,

,

,

,

,

,

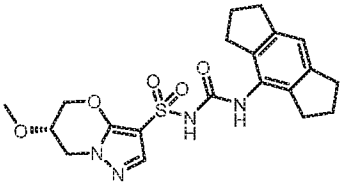
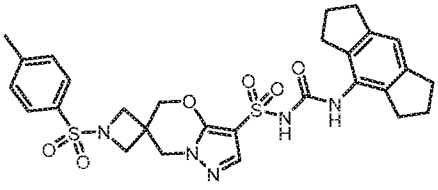
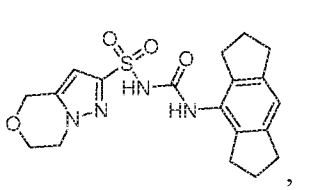
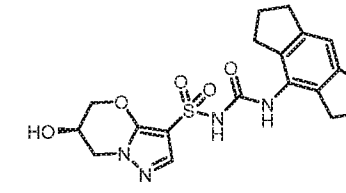
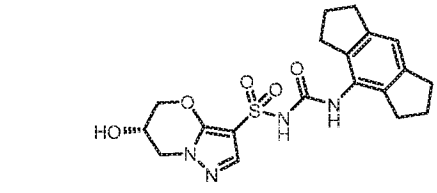

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

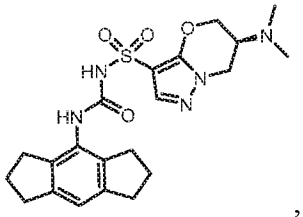
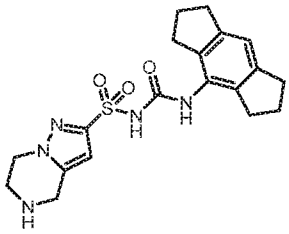
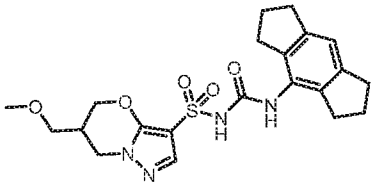
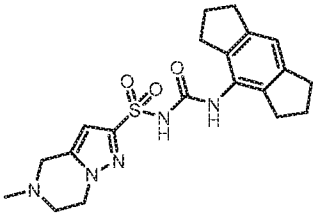
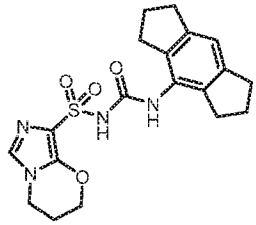
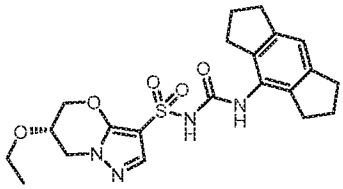
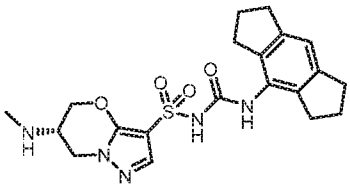
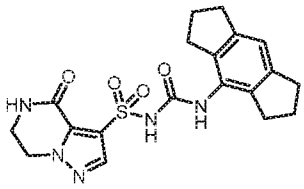
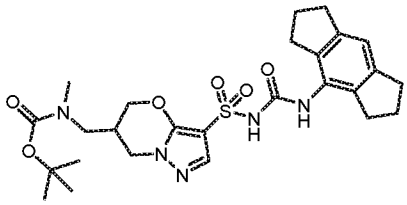
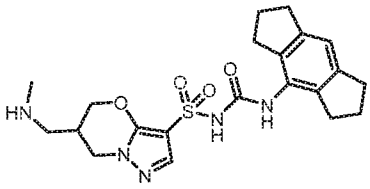
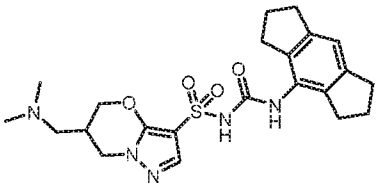
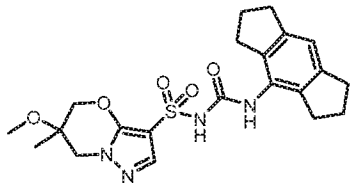
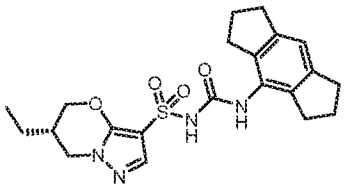
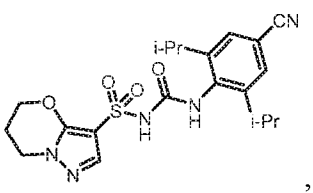
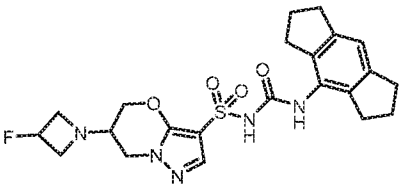
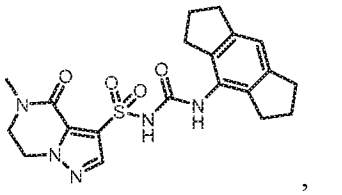
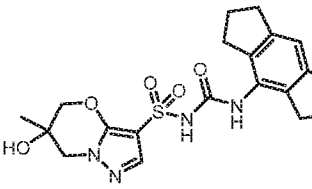
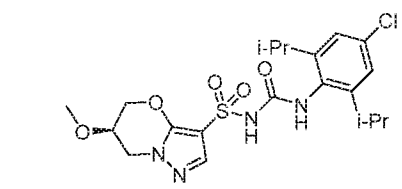
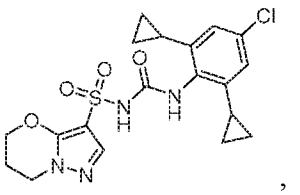
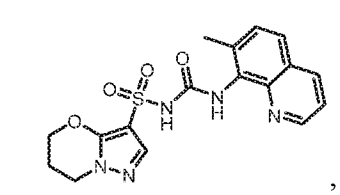
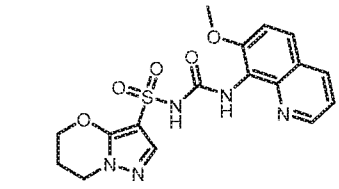

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

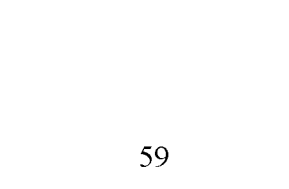
,

,

,

,

,

,

,

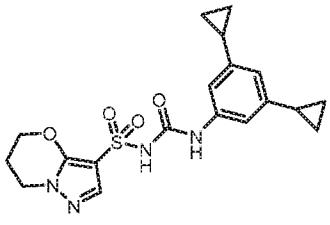
,

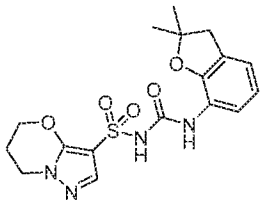
,

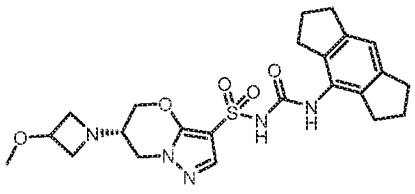

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

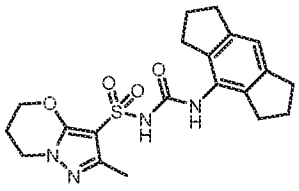
,

,

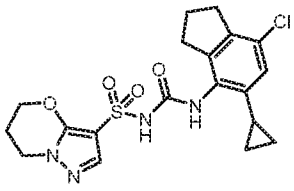
,

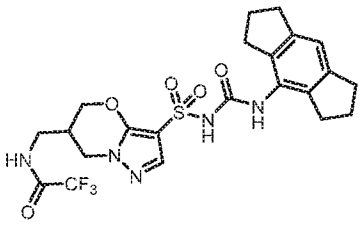


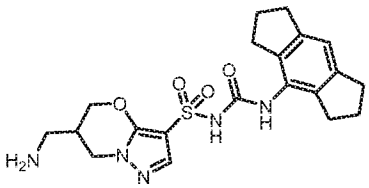


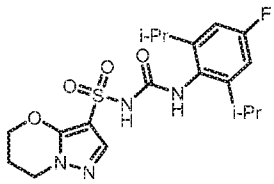


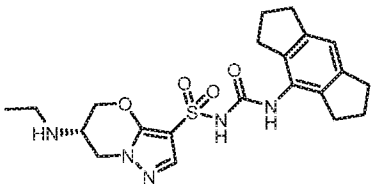


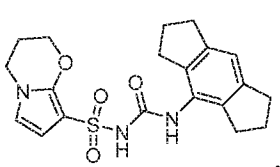


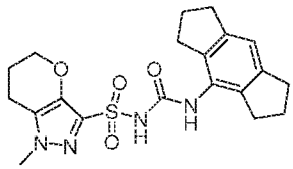


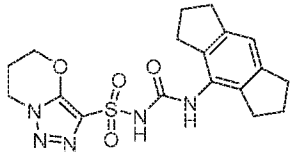


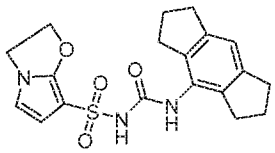


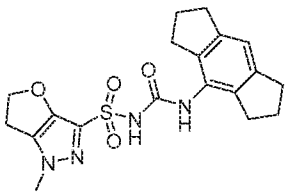


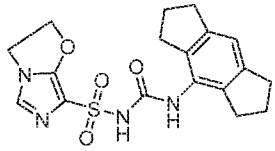


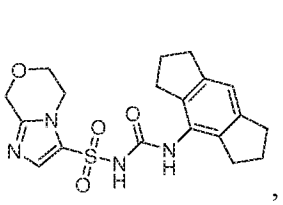


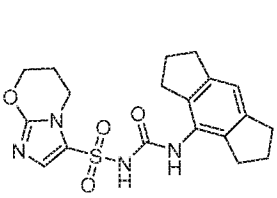


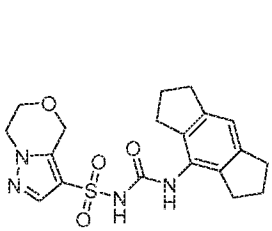


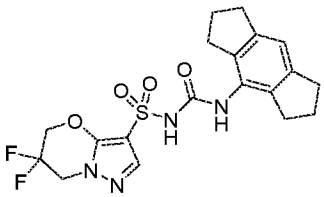


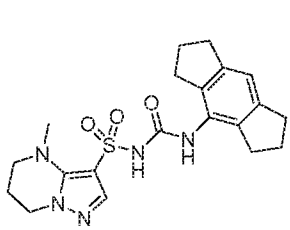


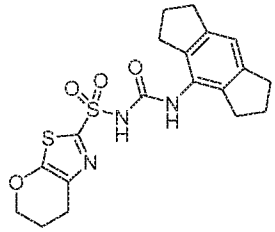


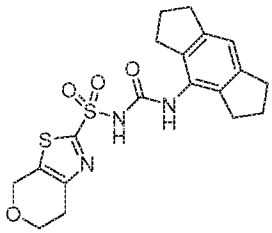


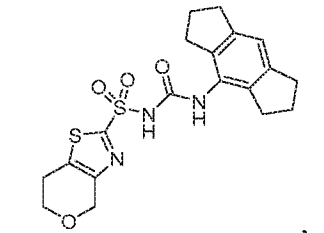


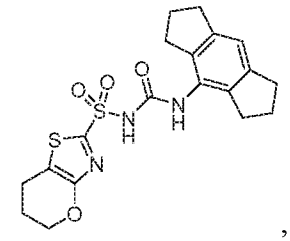


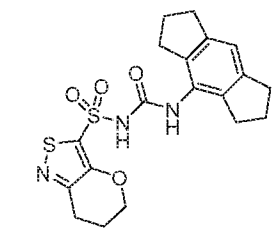












,

,

,

,

Cl
,

HN
CF3
O
,

H2N
,

i-Pr
F
i-Pr
,

,

,

,

,

,

,

,

,

,

,

F
F
,

,

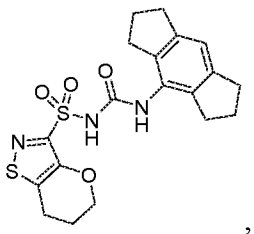
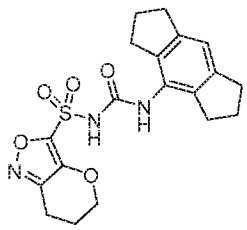
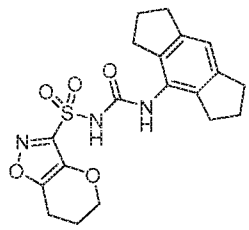
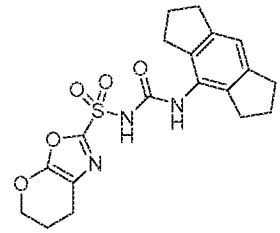
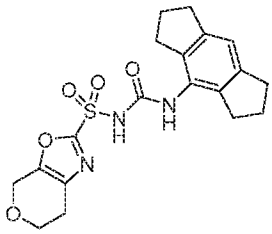
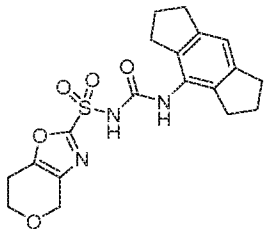
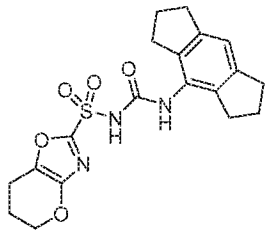
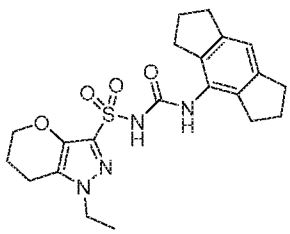
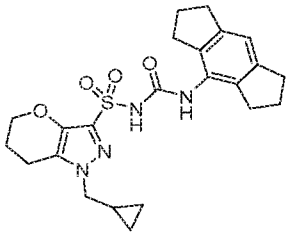
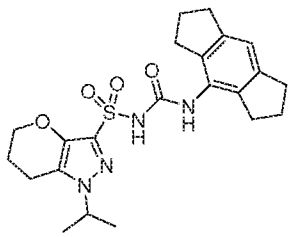
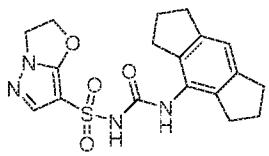
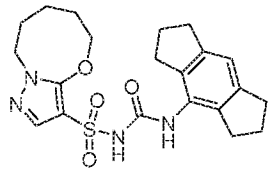
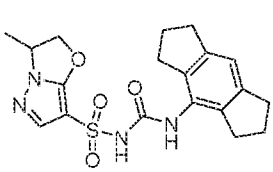
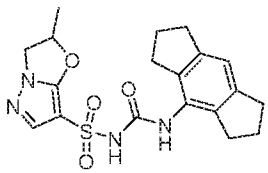
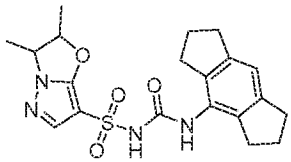
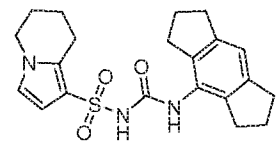
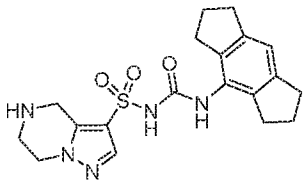
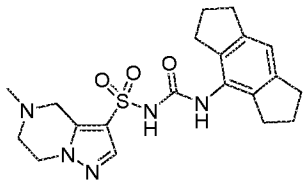
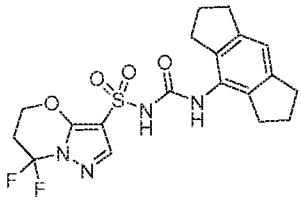
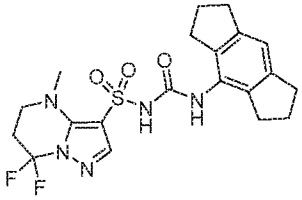
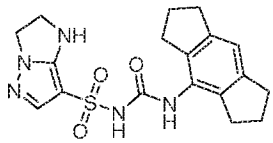
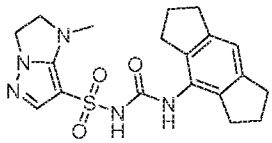
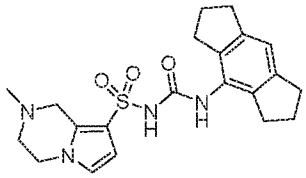
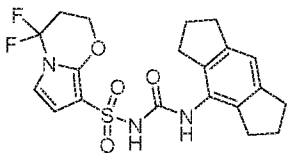
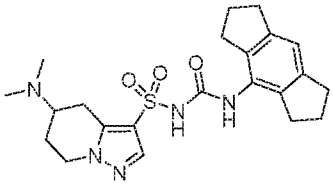
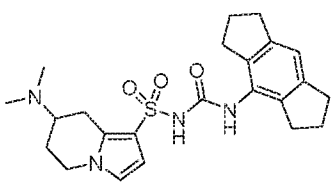
,

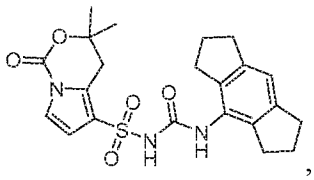
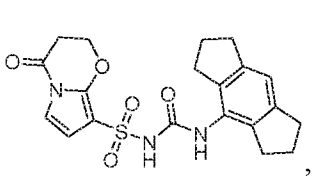
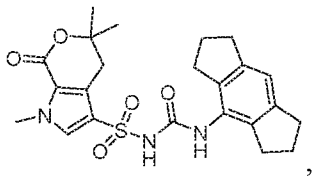
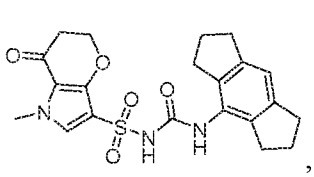
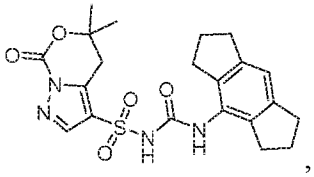
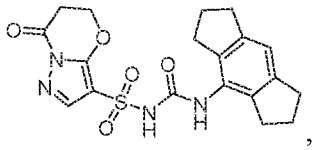
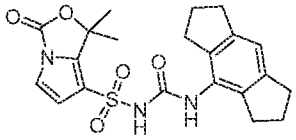
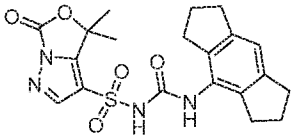
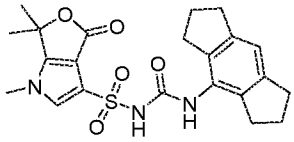
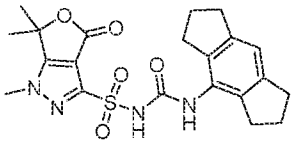
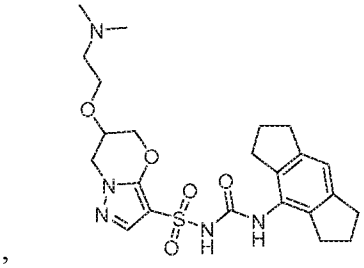
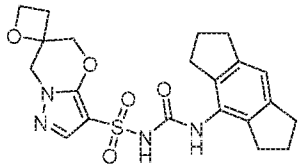
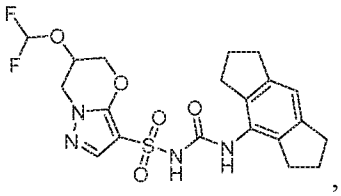
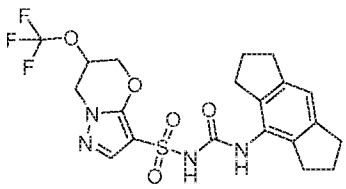
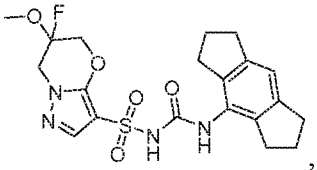
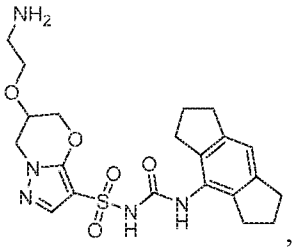
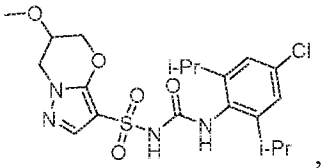
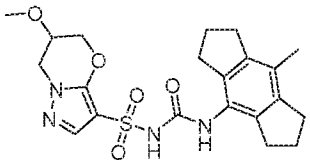
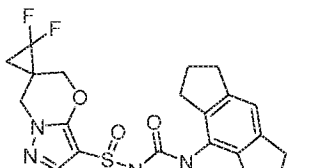
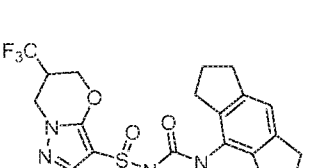
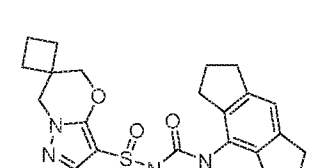
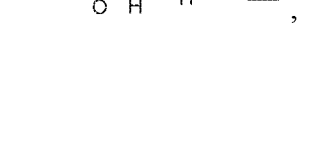
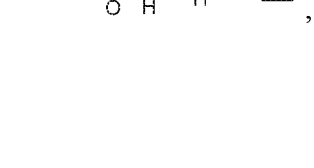
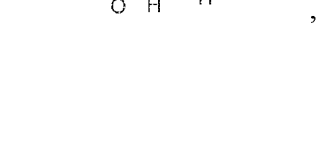
,

,

,

,

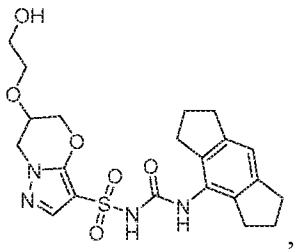
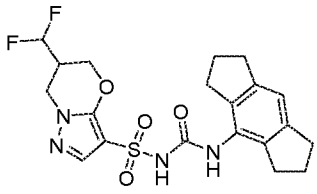
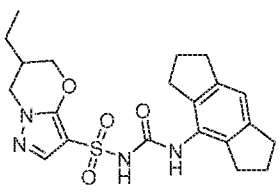
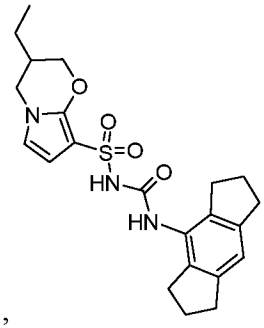
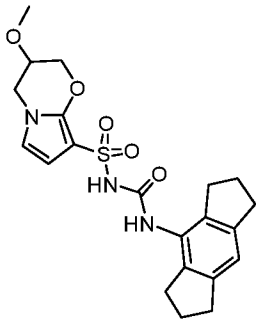
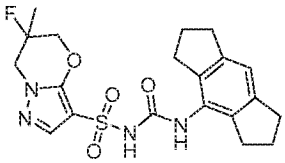
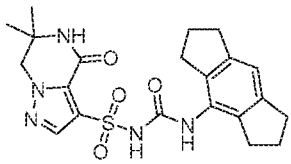
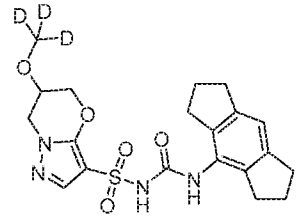
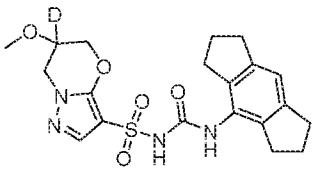
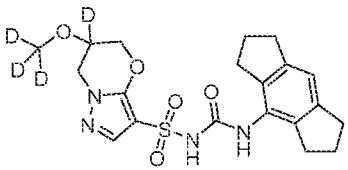
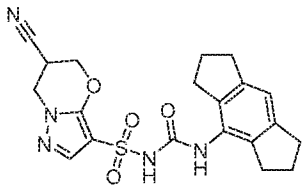
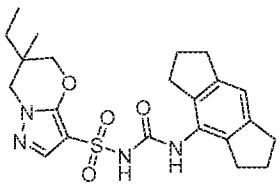
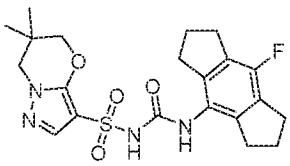
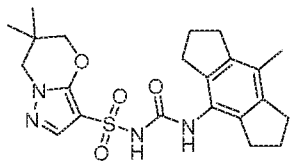
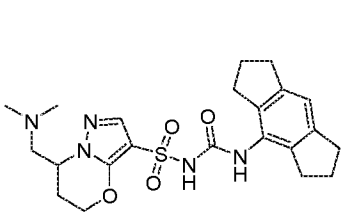
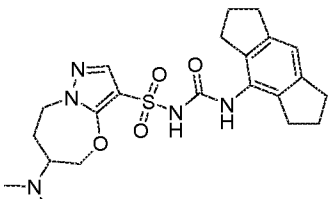

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

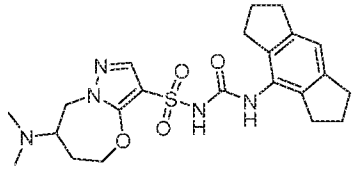

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

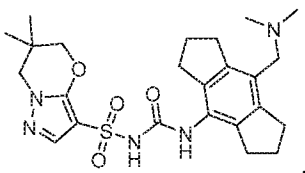
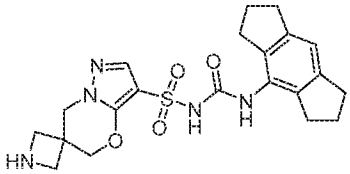
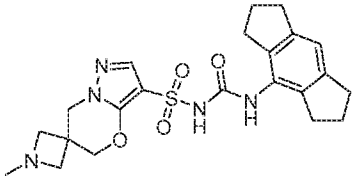
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

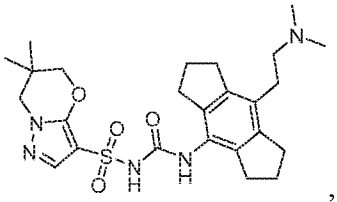
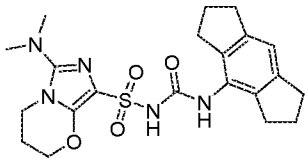
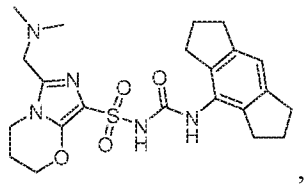
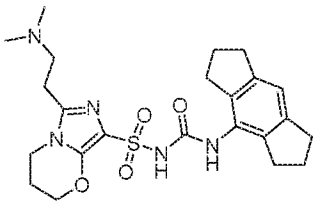
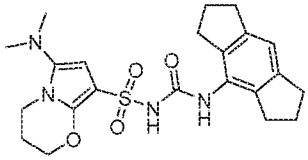
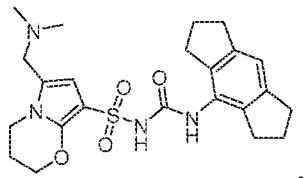
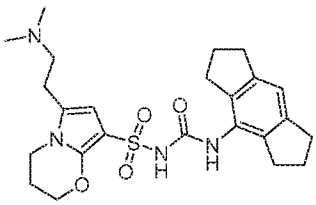
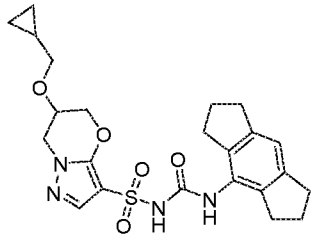
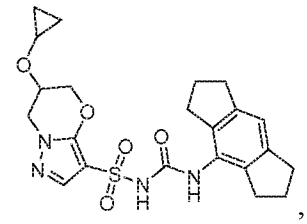
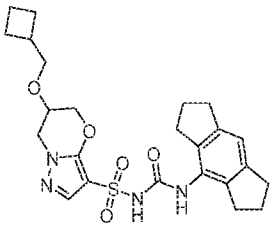
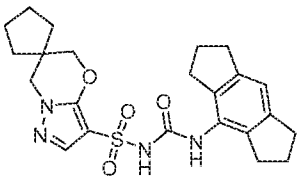
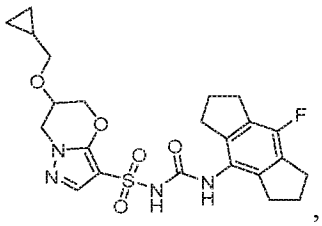
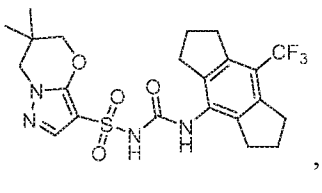
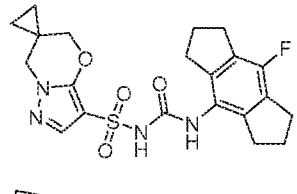
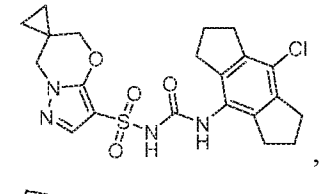
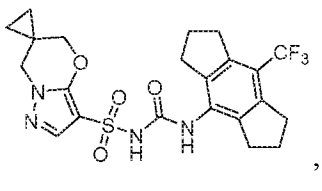
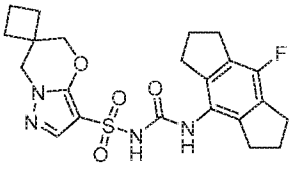
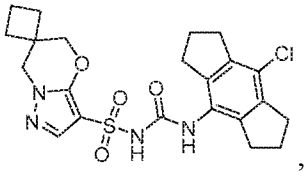
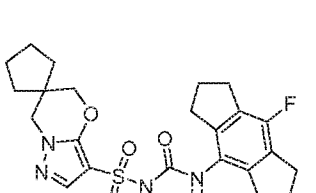
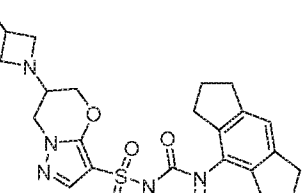
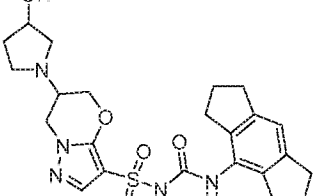
,

,

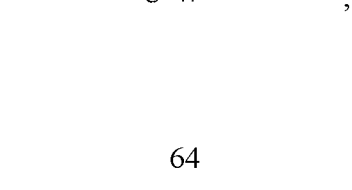
,

,

,

,

,

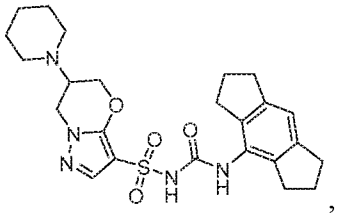
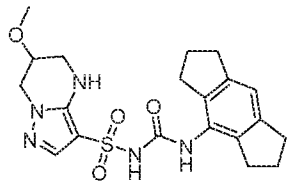
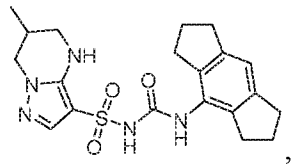
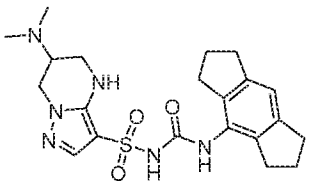
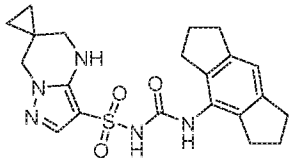
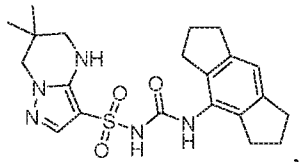
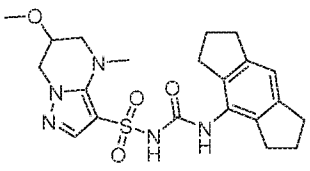
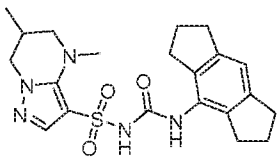
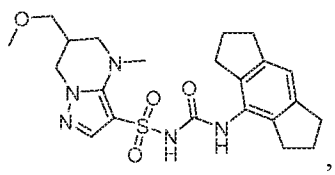
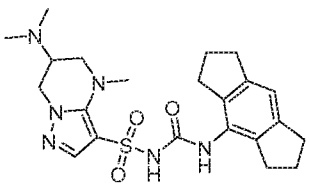
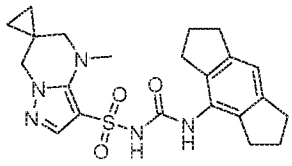
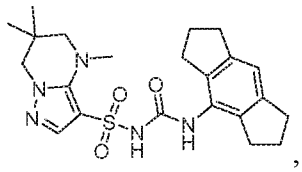
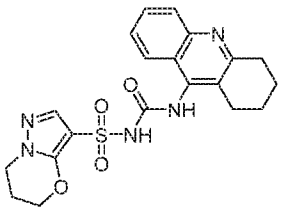
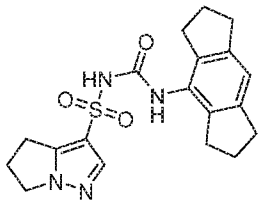
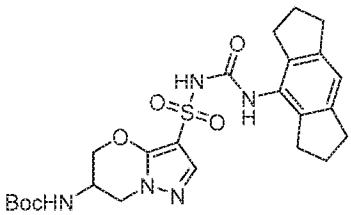
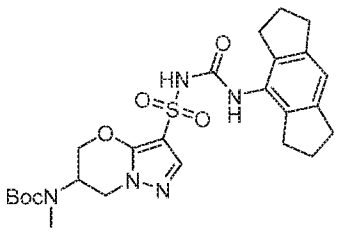
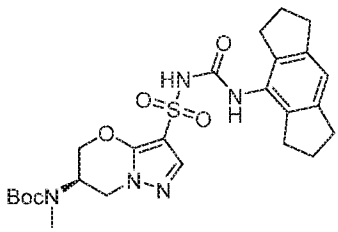
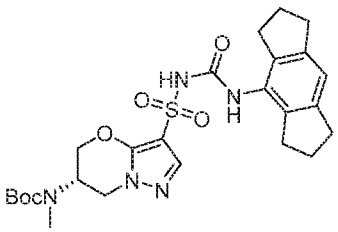
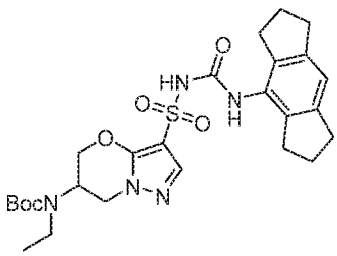
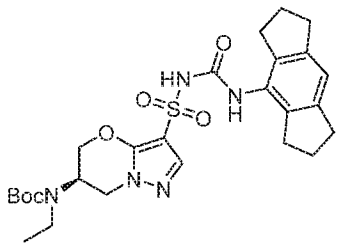
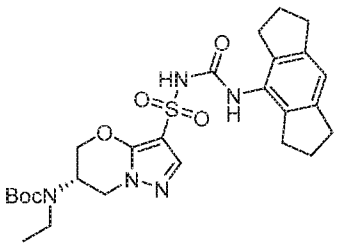
,

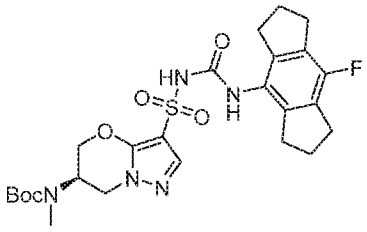
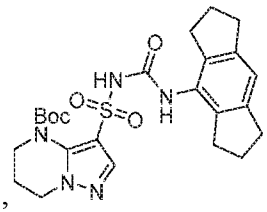
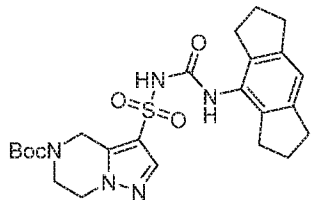
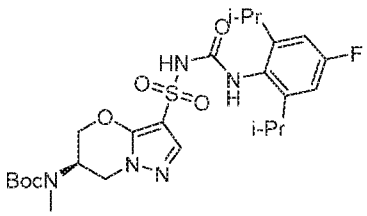
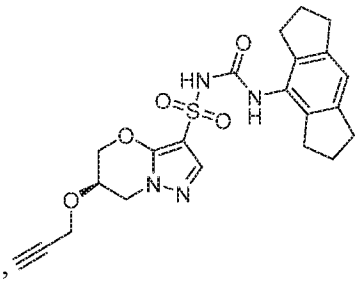
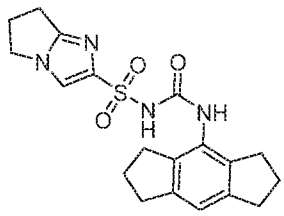
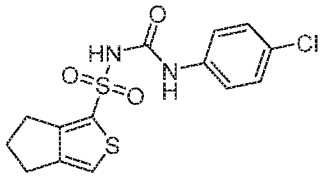
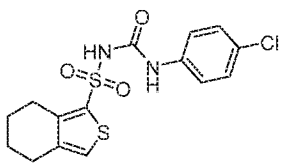
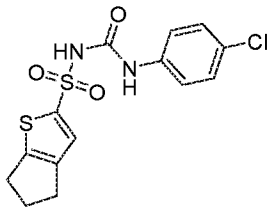
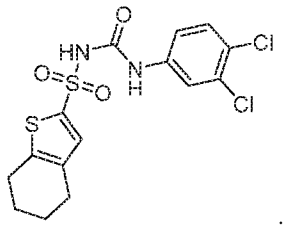
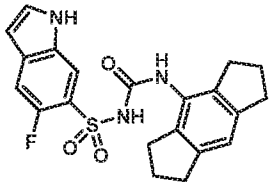
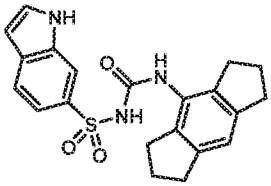
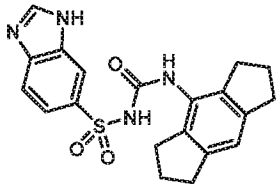
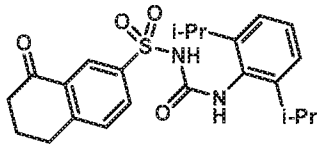
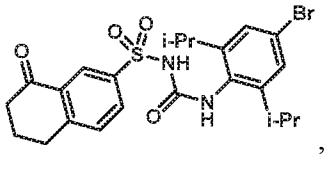
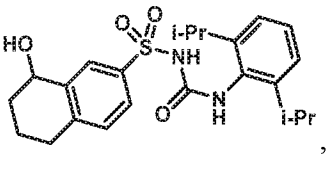
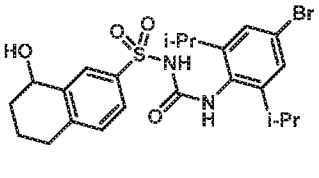
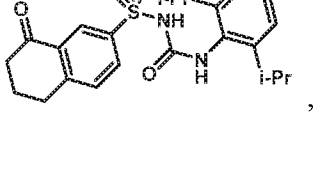
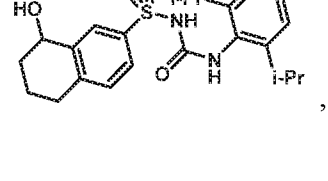
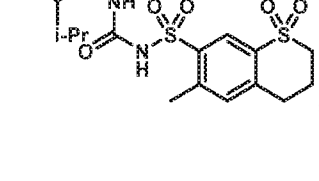
,

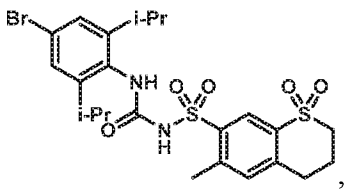

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

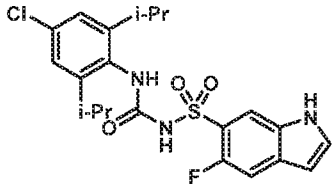
,

,

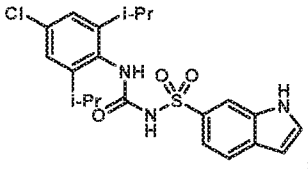
,

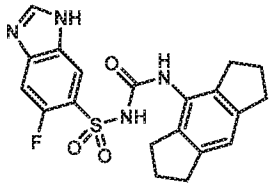

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

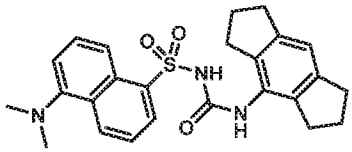





















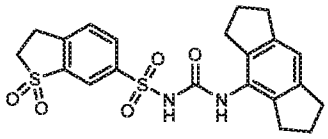


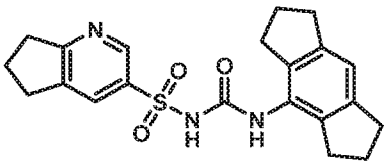


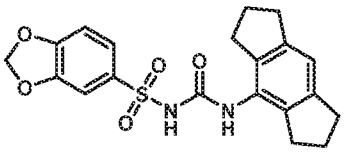


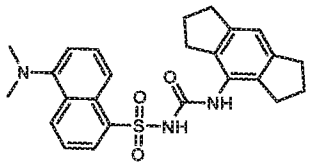


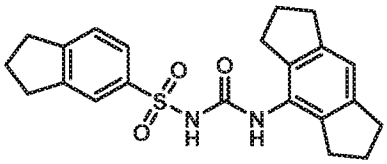


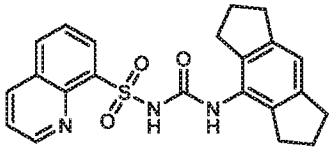


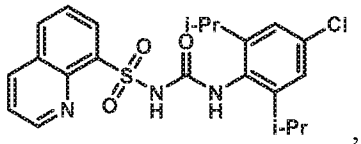


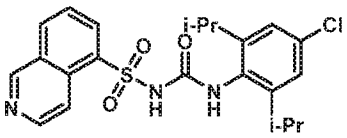


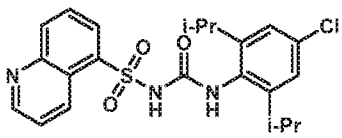


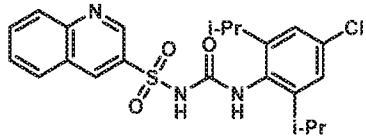


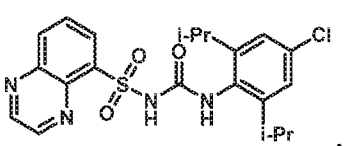


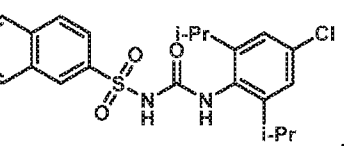


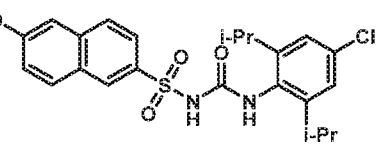


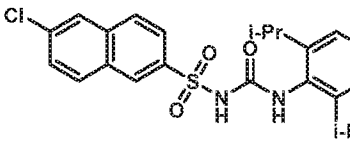


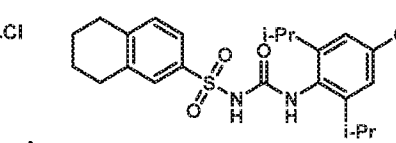


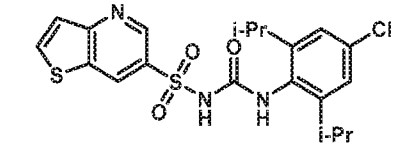


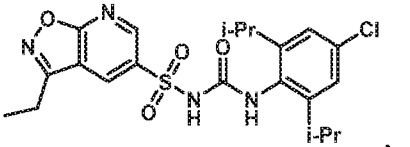


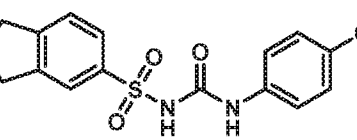


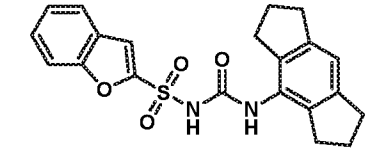


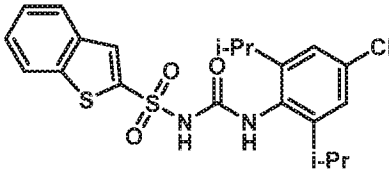


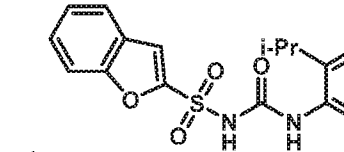












Br
i-Pr
NH
i-Pr
O
N
H
S
O O
O O
S
,

Cl
i-Pr
NH
i-Pr
O
N
H
S
O O
H
N
F
,

Cl
i-Pr
NH
i-Pr
O
N
H
S
O O
H
N
,

N
NH
F
S
O O
NH
O
H
N
,

N
S
O O
NH
O
N
H
,

S
O O
S
O O
N
H
O
N
H
,

N
S
O O
N
H
O
N
H
,

O
O
S
O O
N
H
O
N
H
,

N
S
O O
NH
O
NH
,

S
O O
N
H
O
N
H
,

N
S
O O
N
H
O
N
H
,

N
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

N
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

N
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

N
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

N
N
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

O
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

Cl
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

N
S
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

O
N
N
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
,

S
O O
N
H
O
N
H
Cl
,

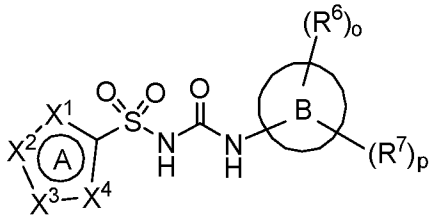
O
S
O O
N
H
O
N
H
,

S
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr
, and

O
S
O O
N
H
O
N
H
i-Pr
Cl
i-Pr

or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a compound of Formula AA



Formula AA

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;

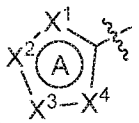
X^3 is O, S, N, CR^3, or NR^3;

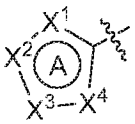
X^4 is O, S, N, CR^4, NR^4, or $–X^5$-X^6-;

X^5 is N or CR^5;

X^6 is N or CR^6;

when X^4 is -X^5-X^6, then: X^1 is N or CR^1, X^2 is N or CR^2, and X^3 is N or CR^3;

when X^4 is other than -X^5-X^6-, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is -X^5-X^6-, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

from two to four of R^1, R^2, R^3, and R^4 are present or from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and

wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least of two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20};

R^{20} is selected from the group consisting of: hydroxy, halo, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{21}, C_2-C_6 alkenyl optionally substituted with one or more R^{21}, C_2-C_6 alkynyl optionally substituted with one or more R^{21}, C_1-C_6 alkoxy optionally substituted with one or more R^{21}, OC_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{21}, $S(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, $OS(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, C_6-C_{10} aryl optionally substituted with one or more R^{21}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{21}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{21}, and $CONR^8R^9$; or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or

heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

or at least one pair of R^{20} on the adjacent atoms, taken together with the atoms connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

R^{21} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

wherein any of R^1, R^2, R^3, R^4, R^5, and R^6 that are not taken together with the atoms connecting them to form a ring, when present, are each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-

C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, NH-(C=NR^{13})$NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, =NR^{10}, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;

R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

B is a 5-10-membered heteroaryl or C_6-C_{10} aryl ring;

o = 1 or 2;

p = 0, 1, 2, or 3;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25},

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl

optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

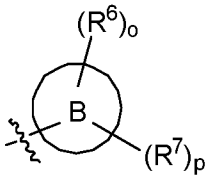
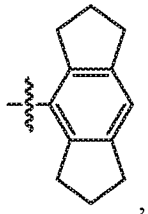
R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

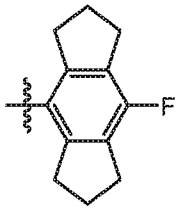
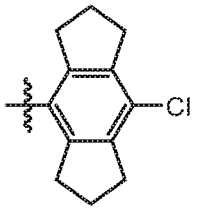
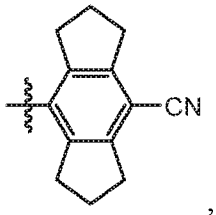
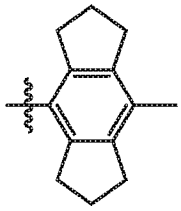
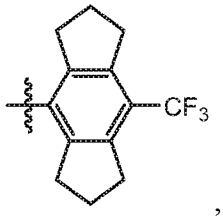
or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

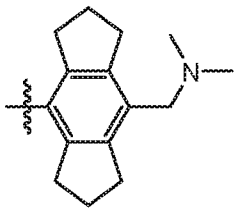
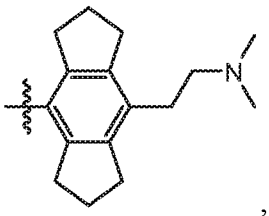
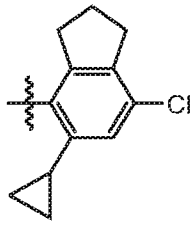
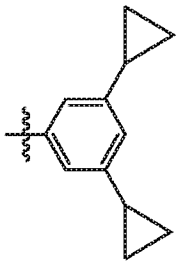
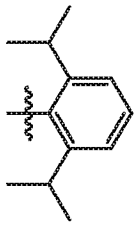
R^{10} is C_1-C_6 alkyl;
each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;
R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and
each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

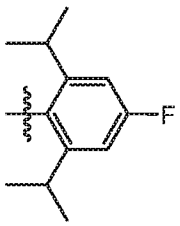
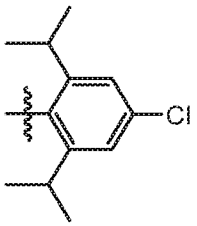
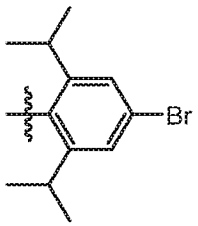
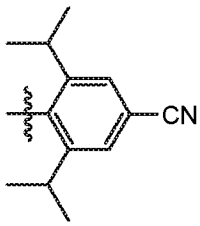
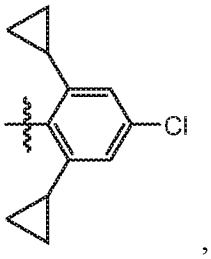
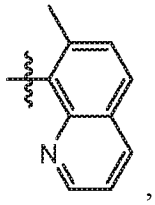
provided that when B is 5-10-membered heteroaryl with from 2-3 ring nitrogen atoms, at least one R^6 is attached to B at a position *ortho* to the $-HNC(=O)NHS(O)_2-$ moiety of Formula AA;

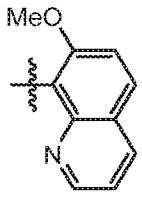
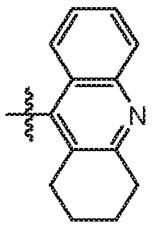
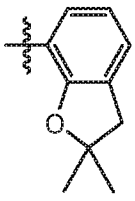
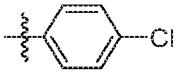
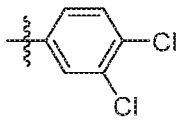
when B is 2-pyridyl, pyrimidin-6-yl, or pyrimidin-4-yl, B is not substituted with a cyano group at a position *ortho* to the $-HNC(=O)NHS(O)_2-$ moiety of Formula AA; and

with the proviso that  is not selected from the group consisting of:  ,

 ,  ,  ,  ,  ,

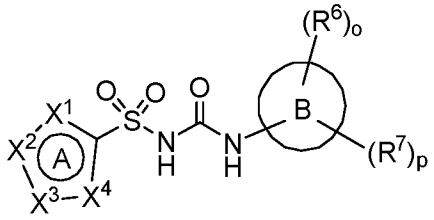
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

MeO  ,  ,  ,  , and  .

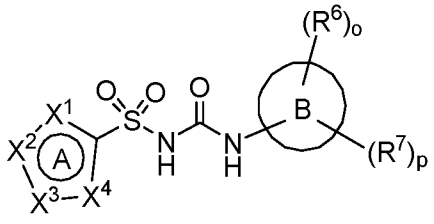
or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a compound of Formula AA

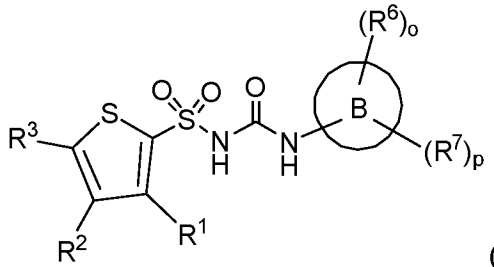


Formula AA

wherein the compound of Formula AA is selected from



(Formula AA-1)



(Formula AA-2)

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;

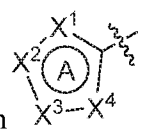
X^3 is O, S, N, CR^3, or NR^3;

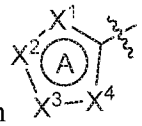
X^4 is O, S, N, CR^4, NR^4, or $–X^5$-X^6-;

X^5 is N or CR^5;

X^6 is N or CR^6;

when X^4 is -X^5-X^6, then: X^1 is N or CR^1, X^2 is N or CR^2, and X^3 is N or CR^3;

when X^4 is other than -X^5-X^6-, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is $-X^5-X^6-$, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

wherein when X^1 is S, X^4 is other than CR^4;
wherein when X^4 is S, X^1 is other than CR^1;

wherein when the compound of Formula AA is a compound of Formula AA-1,
from two to four of R^1, R^2, R^3, and R^4 are present or from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and
wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least of two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms;

wherein when the compound of Formula AA is a compound of Formula AA-1, any two adjacent R^1, R^2, R^3, and R^4 or any two adjacent R^1, R^2, R^3, R^5, and R^6 are taken together with the atoms connecting them to form a ring; and wherein when the compound of Formula AA is a compound of Formula AA-2, any two adjacent R^1, R^2, and R^3 are taken together with the atoms connecting them to form a ring; wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4 when the compound of Formula AA is a compound of Formula AA-1, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4 when the compound of Formula AA is a compound of Formula AA-1, and wherein the heteroaryl ring is optionally substituted with one or more R^{20};

R^{20} is selected from the group consisting of: hydroxy, halo, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{21}, C_2-C_6 alkenyl optionally substituted with one or more R^{21}, C_2-C_6 alkynyl optionally substituted with one or more R^{21}, C_1-C_6 alkoxy optionally substituted with one or more R^{21}, OC_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{21}, $S(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, $OS(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, C_6-C_{10} aryl optionally substituted with one or more R^{21}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{21}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{21}, and $CONR^8R^9$; or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, -$OC(O)NHC_{6\text{-}10}$ aryl optionally substituted with one or more R^{21}, and $CONR^8R^9$;

or at least one pair of R^{20} on the adjacent atoms, taken together with the atoms connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-

C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

R^{21} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

or at least one pair of R^{21} on adjacent atoms, taken together with the atoms connecting them, independently forms a C_4-C_{12} cycloalkyl ring or a 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

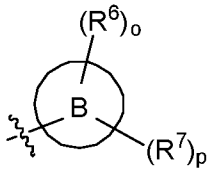
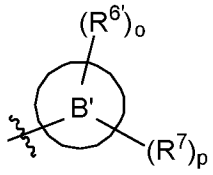
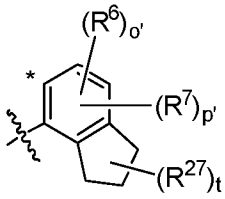
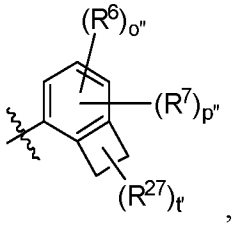
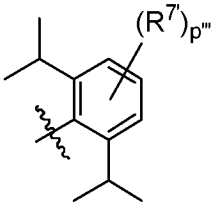
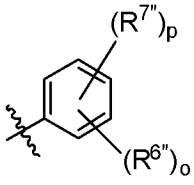
wherein the remaining R^1, R^2, R^3, and R^4, when present, are each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22},

$NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, NH-(C=NR^{13})$NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, =NR^{10}, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;

R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

wherein when the compound is a compound of Formula AA-1,  is selected from the group consisting of:  ,  ,  ,  , and 

wherein * denotes that the ring position the * is closest to is unsubstituted;

B is a 5-10-membered heteroaryl or C_6-C_{10} aryl ring;

B' is a 5-6-membered heteroaryl, wherein when the 5-6 membered heteroaryl contains two or three nitrogen ring members, the 5-6-membered heteroaryl additionally contains one or more non-nitrogen heteroatom or heteroatomic group ring members; 4-pyrimidinyl; 5-pyrimidinyl; 6-pyrimidinyl; pyridazinyl; pyrazinyl; 1,2,3-triazinyl; 1,2,4-triazinyl; tetrazinyl; imidazolyl; pyrazolyl; 1,2,3-triazolyl; tetrazolyl; or C_7-C_{10} aryl;

o = 1 or 2;

p = 0, 1, 2, or 3;

o' = 0 or 1;

p' = 0 or 1;

o'' = 0 or 1;

p'' = 0, 1, or 2;

p''' = 1, 2, or 3;

t is 0, 1, 2, 3, 4, 5, or 6;

t' is 0, 1, 2, 3, or 4;

R^6 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

$R^{6'}$ at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

R^7 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

$R^{7'}$, at each occurrence, is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, I, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with

one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25},

each occurrence of $R^{6''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

each occurrence of $R^{7''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally

substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

or at least one pair of $R^{6'}$ and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 (e.g, C_4-C_5 or C_7-C_8) cycloalkyl ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

or at least one pair of $R^{6''}$ and $R^{7''}$ on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4 or C_6-C_8 carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more R^{27};

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26},

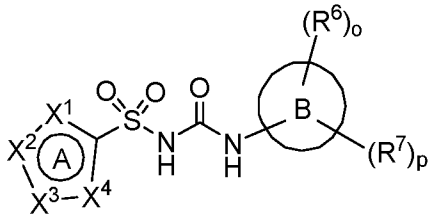
NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

R^{27}, at each occurrence, is independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

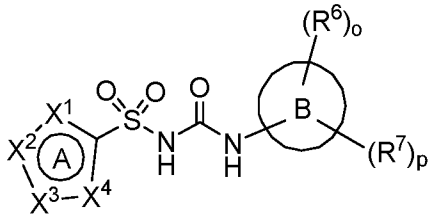
R^{10} is C_1-C_6 alkyl;
each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;
R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and
each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;
or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a compound of Formula AA

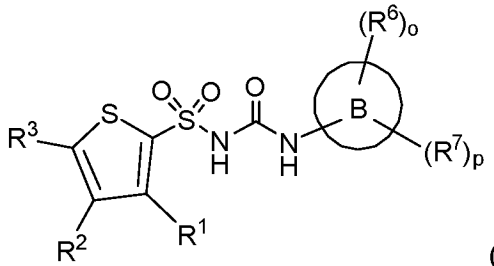


Formula AA

wherein the compound of Formula AA is selected from



(Formula AA-1)



(Formula AA-2)

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;

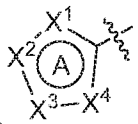
X^3 is O, S, N, CR^3, or NR^3;

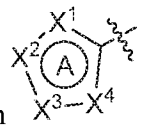
X^4 is O, S, N, CR^4, NR^4, or $–X^5$-X^6-;

X^5 is N or CR^5;

X^6 is N or CR^6;

when X^4 is -X^5-X^6-, then: X^1 is N or CR^1, X^2 is N or CR^2, and X^3 is N or CR^3;

when X^4 is other than -X^5-X^6-, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is -X^5-X^6-, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

wherein when X^1 is S, X^4 is other than CR^4;

wherein when X^4 is S, X^1 is other than CR^1;

wherein when the compound of Formula AA is a compound of Formula AA-1,
from two to four of R^1, R^2, R^3, and R^4 are present or from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and
wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least of two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms;

wherein when the compound of Formula AA is a compound of Formula AA-1, any two adjacent R^1, R^2, R^3, and R^4 or any two adjacent R^1, R^2, R^3, R^5, and R^6 are taken together with the atoms connecting them to form a ring; and wherein when the compound of Formula AA is a compound of Formula AA-2, any two adjacent R^1, R^2, and R^3 are taken together with the atoms connecting them to form a ring; wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4 when the compound of Formula AA is a compound of Formula AA-1, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4 when the compound of Formula AA is a compound of Formula AA-1, and wherein the heteroaryl ring is optionally substituted with one or more R^{20};

R^{20} is selected from the group consisting of: hydroxy, halo, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{21}, C_2-C_6 alkenyl optionally substituted with one or more R^{21}, C_2-C_6 alkynyl optionally substituted with one or more R^{21}, C_1-C_6 alkoxy optionally substituted with one or more R^{21}, OC_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{21}, $S(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, $OS(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, C_6-C_{10} aryl optionally substituted with one or more R^{21}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{21}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{21}, and $CONR^8R^9$; or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

or at least one pair of R^{20} on the adjacent atoms, taken together with the atoms connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

R^{21} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

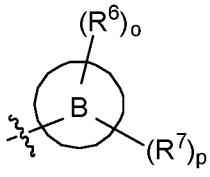
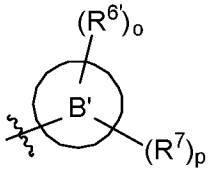
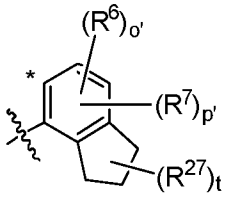
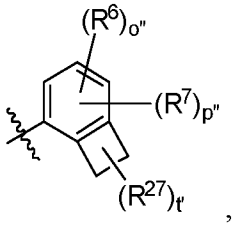
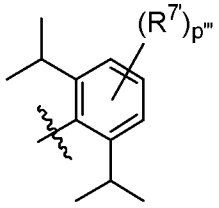
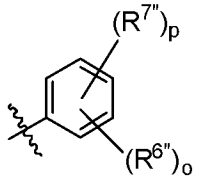
wherein the remaining R^1, R^2, R^3, and R^4, when present, are each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, NH-$(C{=}NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered

heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;

R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

wherein when the compound is a compound of Formula AA-1,  is selected from the group consisting of:  ,  ,  ,  , and 

wherein * denotes that the ring position the * is closest to is unsubstituted;

B is a 5-10-membered heteroaryl or C_6-C_{10} aryl ring;

B' is a 5-6-membered heteroaryl, wherein when the 5-6 membered heteroaryl contains two or three nitrogen ring members, the 5-6-membered heteroaryl additionally contains one or more non-nitrogen heteroatom or heteroatomic group ring members; 4-pyrimidinyl; 5-pyrimidinyl; 6-

pyrimidinyl; pyridazinyl; pyrazinyl; 1,2,3-triazinyl; 1,2,4-triazinyl; tetrazinyl; imidazolyl; pyrazolyl; 1,2,3-triazolyl; tetrazolyl; or C_7-C_{10} aryl;

o = 1 or 2;
p = 0, 1, 2, or 3;
o' = 0 or 1;
p' = 0 or 1;
o'' = 0 or 1;
p'' = 0, 1, or 2;
p''' = 1, 2, or 3;
t is 0, 1, 2, 3, 4, 5, or 6;
t' is 0, 1, 2, 3, or 4;
R^6 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

$R^{6'}$ at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25},

halo, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

R^7 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

$R^{7'}$, at each occurrence, is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, I, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25},

each occurrence of $R^{6''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

each occurrence of $R^{7''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

or at least one pair of $R^{6'}$ and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 (e.g, C_4-C_5 or C_7-C_8) cycloalkyl ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

or at least one pair of $R^{6''}$ and $R^{7''}$ on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4 or C_6-C_8 carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more R^{27};

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

R^{27}, at each occurrence, is independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

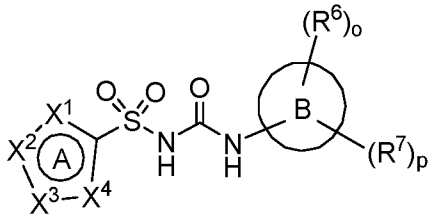
R^{10} is C_1-C_6 alkyl;
each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered

heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and

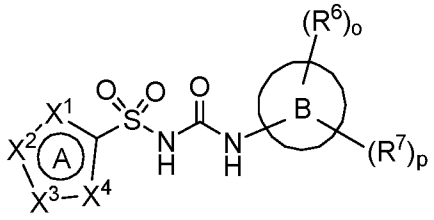
each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a compound of Formula AA

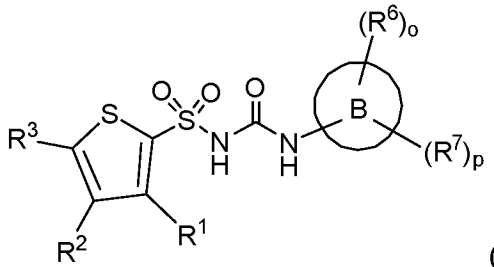


Formula AA

wherein the compound of Formula AA is selected from



(Formula AA-1)



(Formula AA-2)

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;

X^3 is O, S, N, CR^3, or NR^3;

X^4 is O, S, N, CR^4, NR^4, or $-X^5$-X^6-;

X^5 is N or CR^5;

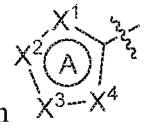
X^6 is N or CR^6;

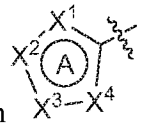
wherein when X^4 is $-X^5-X^6$, then:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

when X^4 is other than $-X^5-X^6-$, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is $-X^5-X^6-$, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

wherein when X^1 is S, X^4 is other than CR^4;

wherein when X^4 is S, X^1 is other than CR^1;

wherein when the compound of Formula AA is a compound of Formula AA-1, from two to four of R^1, R^2, R^3, and R^4 are present or from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least of two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms;

wherein when the compound of Formula AA is a compound of Formula AA-1, any two adjacent R^1, R^2, R^3, and R^4 or any two adjacent R^1, R^2, R^3, R^5, and R^6 are taken together with the atoms connecting them to form a ring; and wherein when the compound of Formula AA is a compound of Formula AA-2, any two adjacent R^1, R^2, and R^3 are taken together with the atoms connecting them to form a ring; wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4 when the compound of Formula AA is a compound of Formula AA-1, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4 when the compound of Formula AA is a compound of Formula AA-1, and wherein the heteroaryl ring is optionally substituted with one or more R^{20};

R^{20} is selected from the group consisting of: hydroxy, halo, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{21}, C_2-C_6 alkenyl optionally substituted with one or more R^{21}, C_2-C_6 alkynyl optionally substituted with one or more R^{21}, C_1-C_6 alkoxy optionally substituted with one or more R^{21}, OC_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{21}, $S(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, $OS(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, C_6-C_{10} aryl optionally substituted with one or more R^{21}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{21}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{21}, and $CONR^8R^9$;

or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

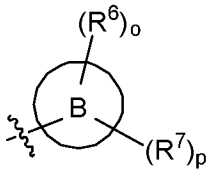
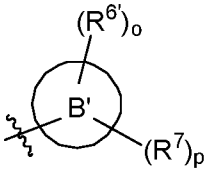
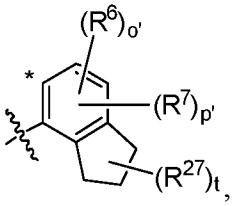
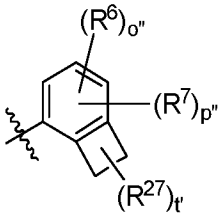
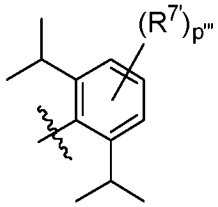
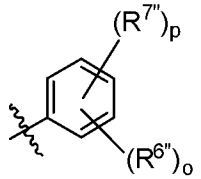
R^{21} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

wherein the remaining R^1, R^2, R^3, and R^4, when present, are each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, NH-$(C=NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23},

C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;
R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

wherein when the compound is a compound of Formula AA-1,  is selected from the group consisting of:  ,  ,  ,  ,  ,

wherein * denotes that the ring position the * is closest to is unsubstituted;

B is a 5-10-membered heteroaryl or C_6-C_{10} aryl;

B' is a 5-6-membered heteroaryl, wherein when the 5-6 membered heteroaryl contains two or three nitrogen ring members, the 5-6-membered heteroaryl additionally contains one or more non-nitrogen heteroatom or heteroatomic group ring members; 5-pyrimidinyl; 6-pyrimidinyl; pyridazinyl; pyrazinyl; 1,2,3-triazinyl; 1,2,4-triazinyl; tetrazinyl; imidazolyl; pyrazolyl; 1,2,3-triazolyl; tetrazolyl; or C_7-C_{10} aryl;

o = 1 or 2;
p = 0, 1, 2, or 3;
o' = 0 or 1;
p' = 0 or 1;
o'' = 0 or 1;
p'' = 0, 1, or 2;
p''' = 1, 2, or 3;
t is 0, 1, 2, 3, 4, 5, or 6;
t' is 0, 1, 2, 3, or 4;

R^6 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

$R^{6'}$ at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

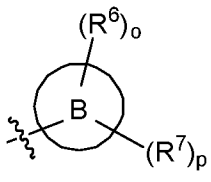
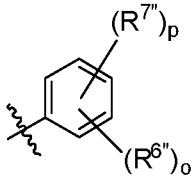
R^7 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-

membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

$R^{7'}$, at each occurrence, is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, I, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25},

each occurrence of $R^{6''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl

optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

wherein when  is  , at least one $R^{6''}$ is *ortho* to the bond connecting the B ring to the NH(CO) group of Formula AA;

each occurrence of $R^{7''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

or at least one pair of $R^{6'}$ and R^{7} on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 cycloalkyl ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

or at least one pair of $R^{6''}$ and $R^{7''}$ on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4 or C_6-C_8 carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more R^{27};

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

R^{27}, at each occurrence, is independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C{=}NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;

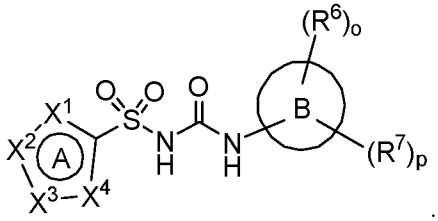
R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and

each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

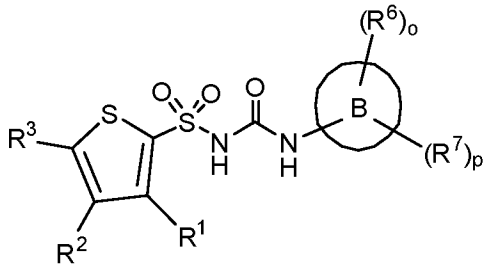
or a pharmaceutically acceptable salt thereof.

The Formula AA

In some embodiments, the compound of Formula AA is a compound of Formula AA-1:

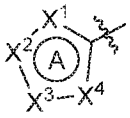
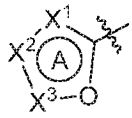
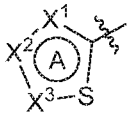
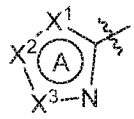
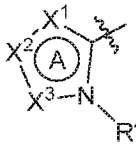
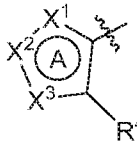


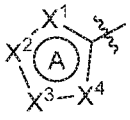
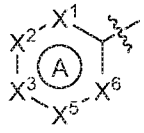
In some embodiments, the compound of Formula AA is a compound of Formula AA-2:

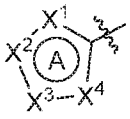
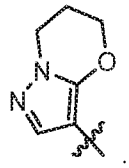


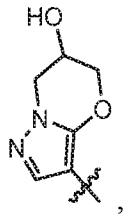
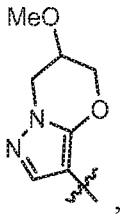
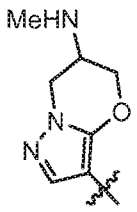
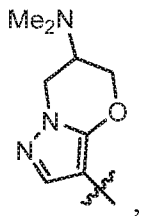
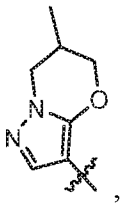
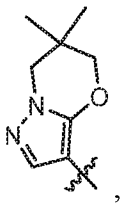
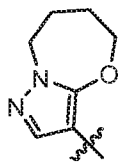
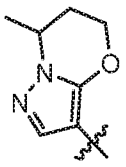
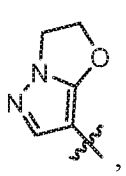
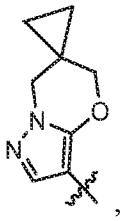
In some embodiments the variables shown in the formulae herein are as follows:

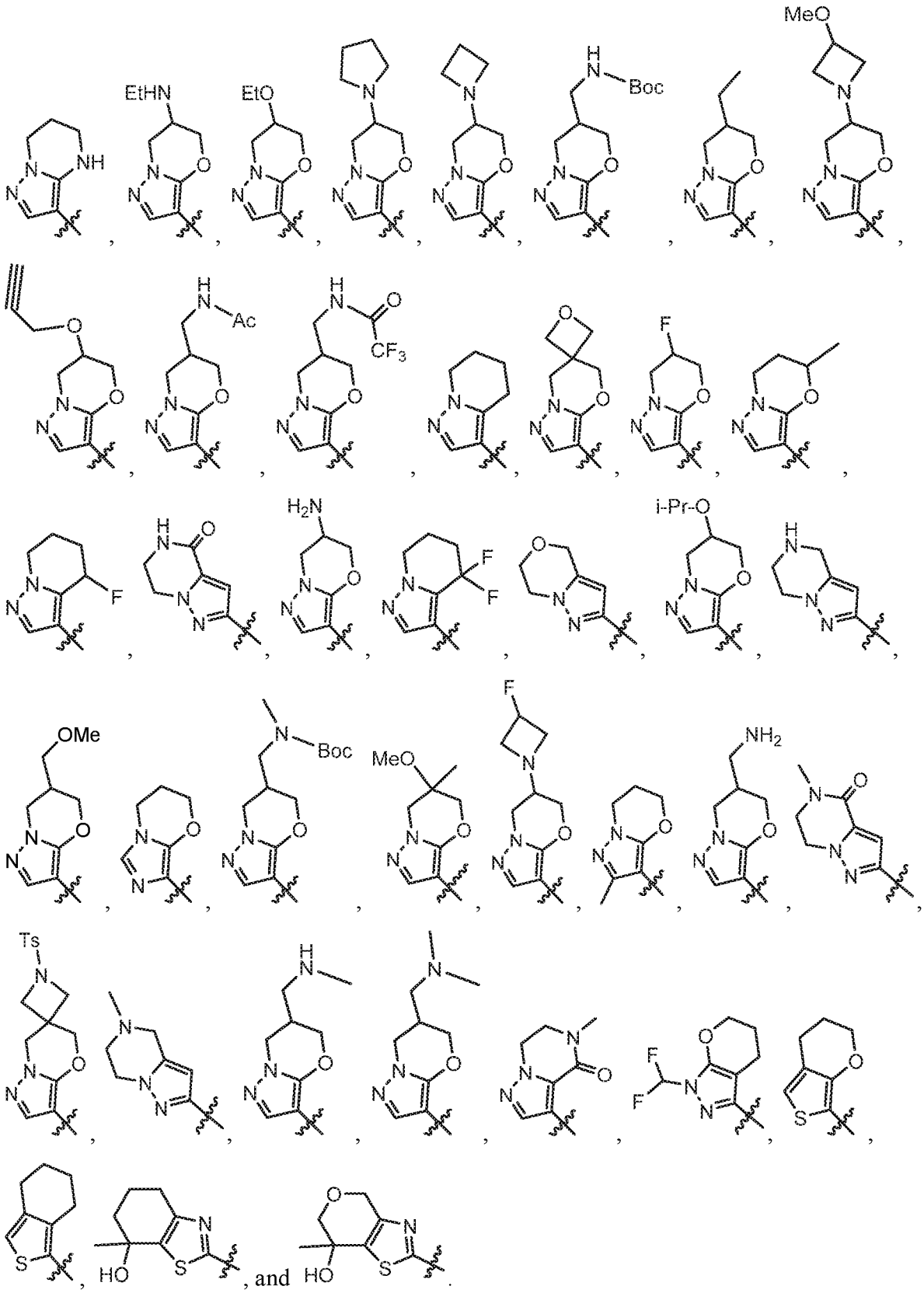
The Moiety 

In some embodiments,  is selected from the group consisting of:  ,  ,  ,  , and  .

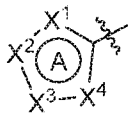
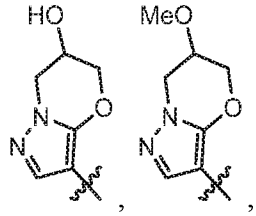
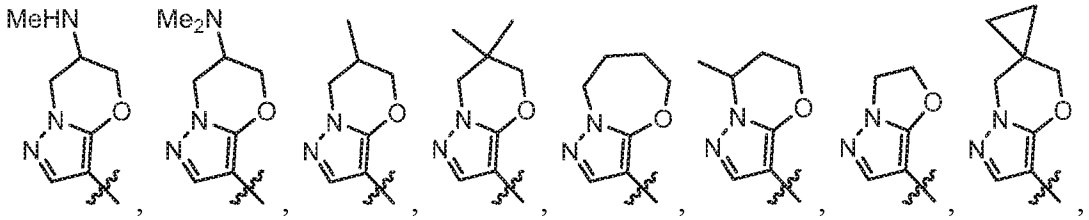
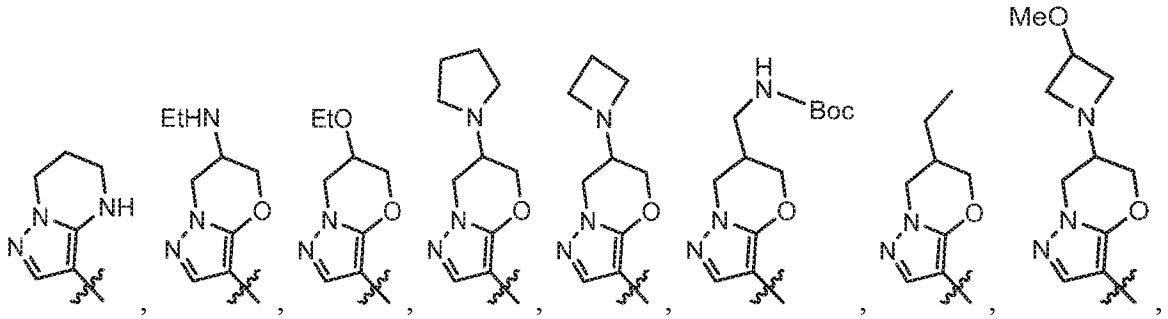
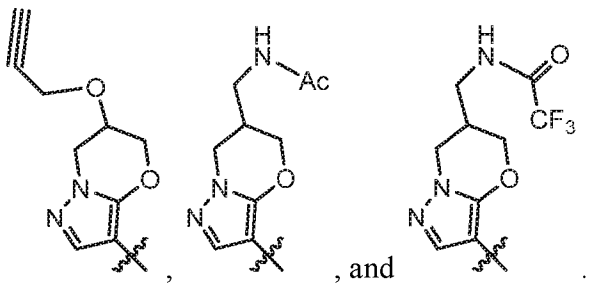
In some embodiments,  is  .

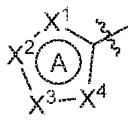
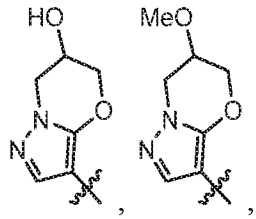
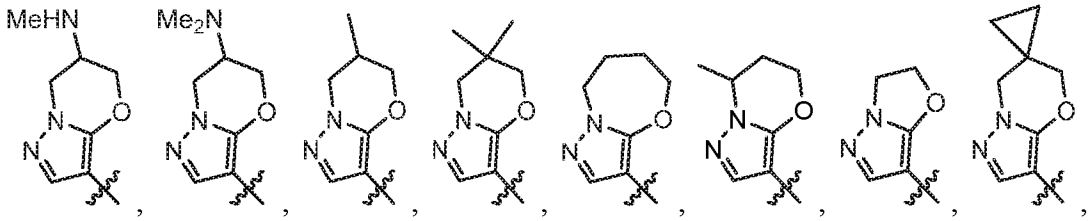
In some embodiments,  is  .

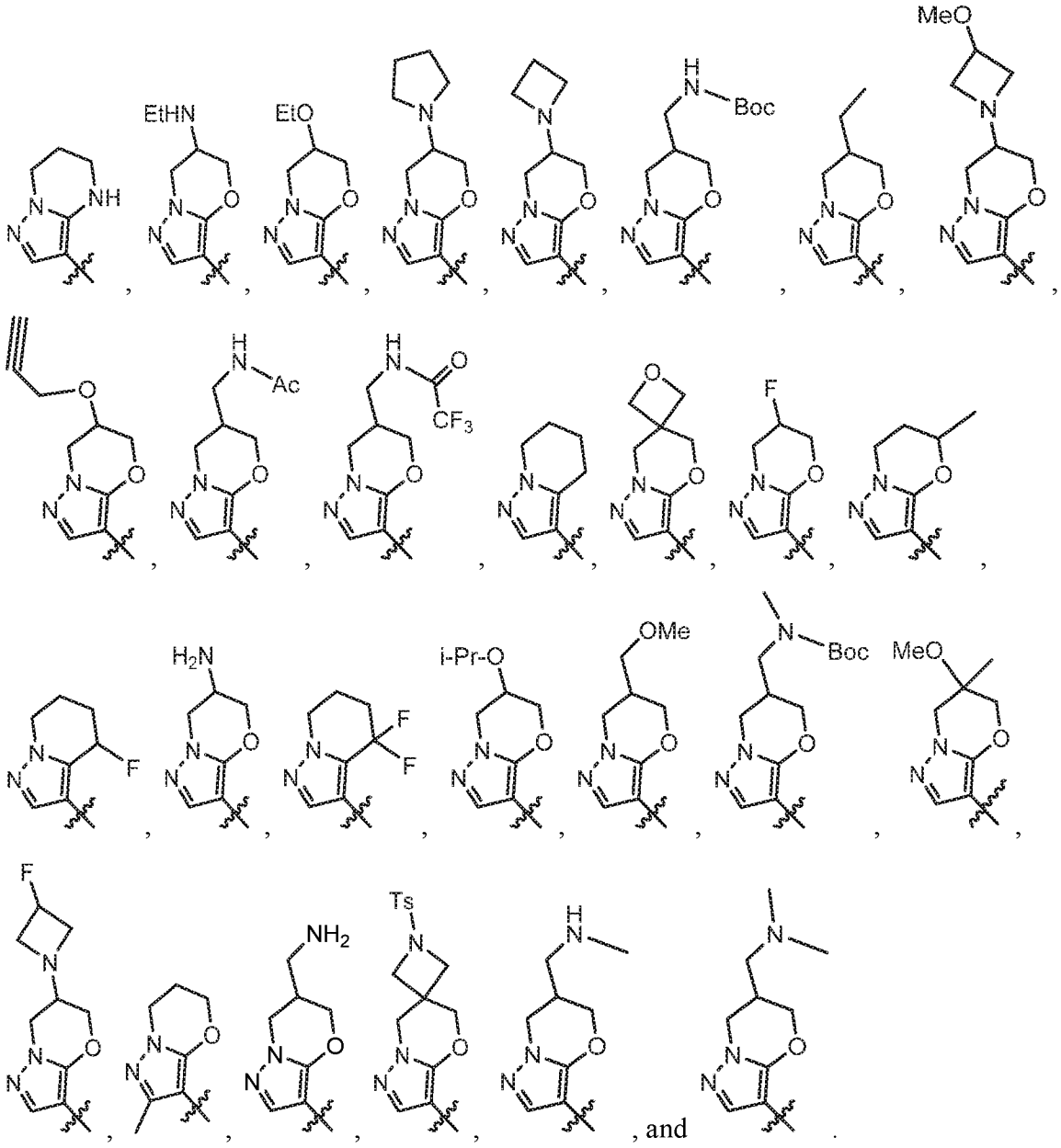
In some embodiments,  is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  , .

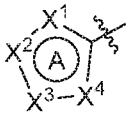
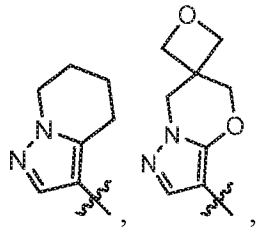
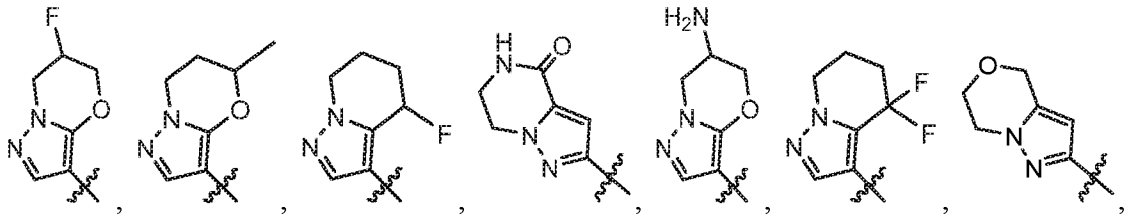
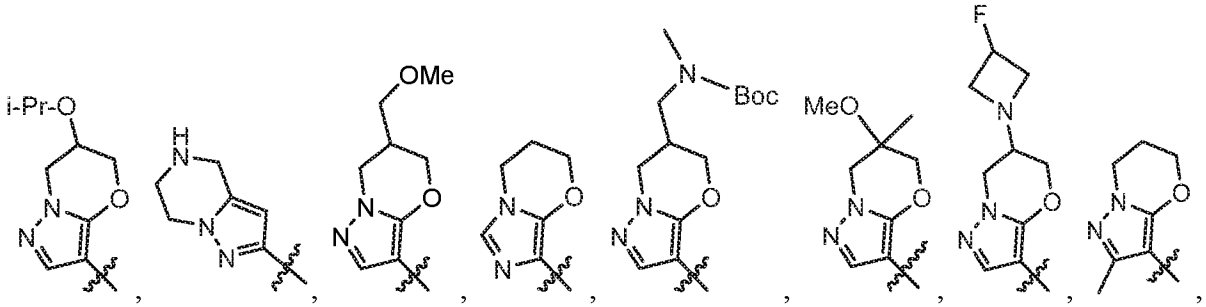
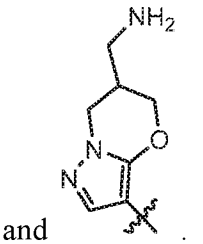


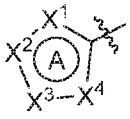
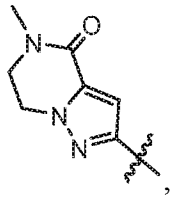
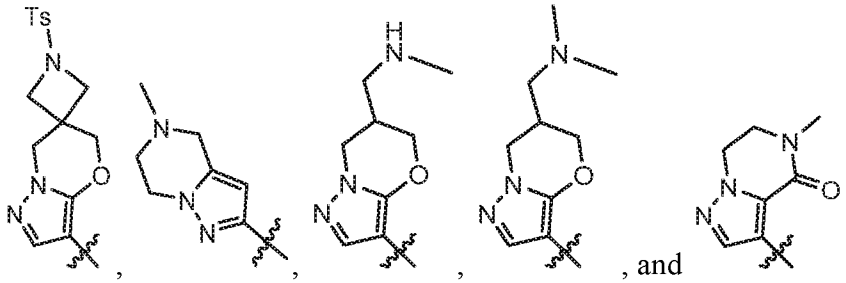
, and .

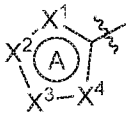
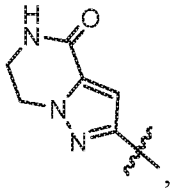
In some embodiments,  is selected from the group consisting of:  ,  ,  ,  , and .

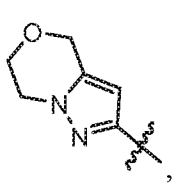
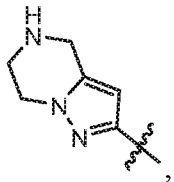
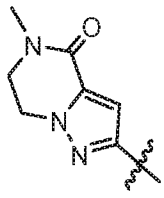
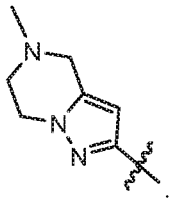
In some embodiments,  is selected from the group consisting of:  ,  .

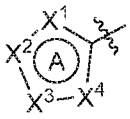
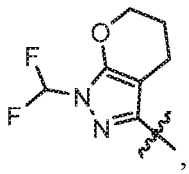


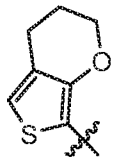
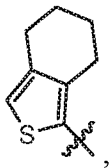
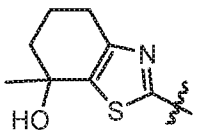
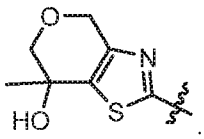
In some embodiments,  is selected from the group consisting of:  ,  ,  ,  , and .

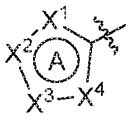
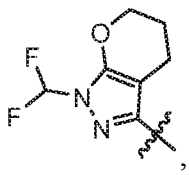
In some embodiments,  is selected from the group consisting of:  ,  , and .

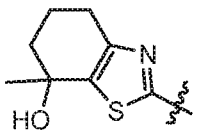
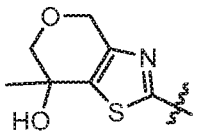
In some embodiments,  is selected from the group consisting of:  ,

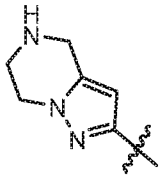
 ,  ,  , and  .

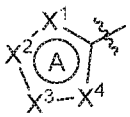
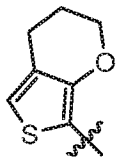
In some embodiments,  is selected from the group consisting of:  ,

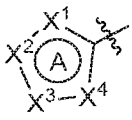
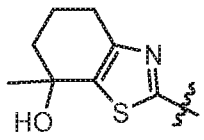
 ,  ,  , and  .

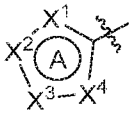
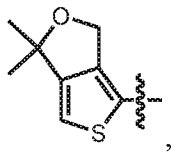
In some embodiments,  is selected from the group consisting of:  ,

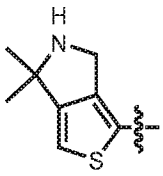
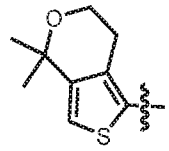
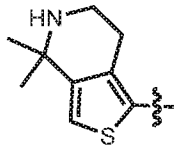
 , and  .

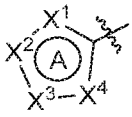
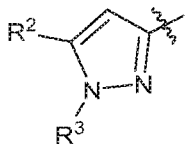
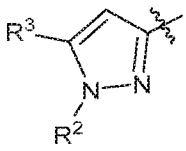
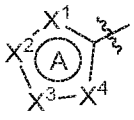
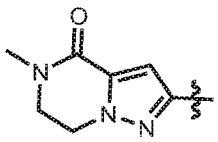
In some embodiments,  is  .

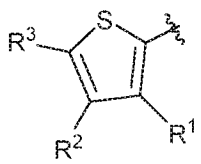
In some embodiments,  is  .

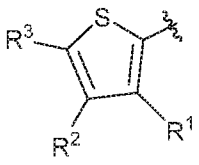
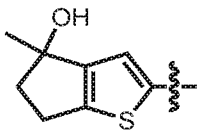
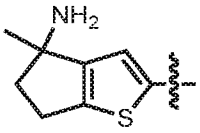
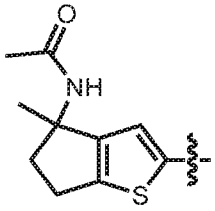
In some embodiments,  is  .

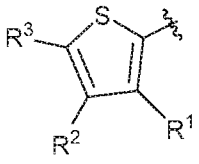
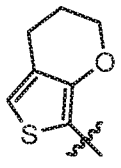
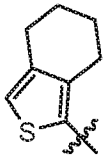
In some embodiments,  is selected from the group consisting of:  ,

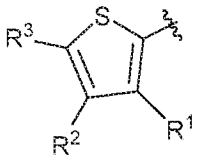
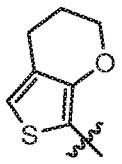
 ,  , and  .

In some embodiments,  is other than  and  . For example,  is other than  .

The Moiety 

In some embodiments,  is selected from the group consisting of:  ,  , and  .

In some embodiments,  is selected from the group consisting of:,  and  .

In some embodiments,  is  .

The variables X^1, X^2, X^3, X^4, X^5, and X^6

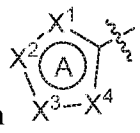
In some embodiments, when X^4 is other than $-X^5-X^6-$, each of X^1, X^2, X^3, X^4, X^5, and X^6 is other than N.

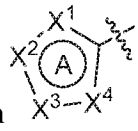
In some embodiments, when (i) X^4 is other than $-X^5-X^6-$, and (ii) each of X^1, X^2, X^3, X^4, X^5, and X^6 is other than N, then at least two of the two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms,

and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, when X^4 is other than $-X^5-X^6-$, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4.

In some embodiments, when X^4 is $-X^5-X^6-$, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6.

In some embodiments, X^1 and X^4 are each other than O.

In some embodiments, X^1 and X^4 are each other than N.

In some embodiments, when one of X^1 and X^4 is N; the other of X^1 and X^4 is other than O.

In some embodiments, when one of X^1 and X^4 is O; the other of X^1 and X^4 is other than N.

In certain embodiments, when: X^4 is other than $-X^5-X^6-$; one of X^1 and X^4 is selected from the group consisting of O, S, and NH; the other of X^1 and X^4 is N, CR^1, or CR^4; X^2 is CR^2; X^3 is CR^3; and R^2 and R^3 are taken together with the atoms connecting them to form a ring; then B is other than phenyl or 4-pyridyl.

In some embodiments, X^4 is $-X^5-X^6-$.

In some embodiments, X^5 is N.

In some embodiments, X^5 is CR^5.

In some embodiments, X^6 is NR^5.

In some embodiments, X^6 is CR^5.

In some embodiments, X^1 is O.

In some embodiments, X^1 is S.

In some embodiments, X^1 is N.

In some embodiments, X^1 is NR^1.

In some embodiments, X^1 is CR^1.

In some embodiments, X^2 is O.

In some embodiments, X^2 is S.

In some embodiments, X^2 is N.

In some embodiments, X^2 is NR^2.

In some embodiments, X^2 is CR^2.

In some embodiments, X^3 is O.

In some embodiments, X^3 is S.

In some embodiments, X^3 is N.

In some embodiments, X^3 is NR^3.

In some embodiments, X^3 is CR^3.

In some embodiments, X^4 is O.

In some embodiments, X^4 is S.

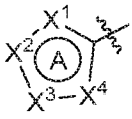
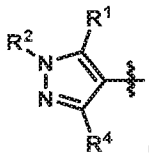
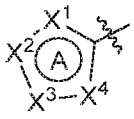
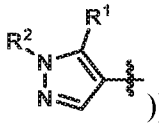
In some embodiments, X^4 is N.

In some embodiments, X^4 is NR^4.

In some embodiments, X^4 is CR^4.

In certain embodiments, X^1 is CR^1; and X^2 is NR^2.

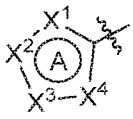
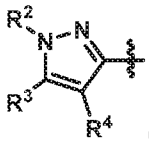
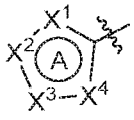
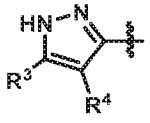
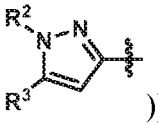
In some embodiments, X^3 is N; and X^4 is CR^4.

In certain embodiments, X^1 is CR^1; X^2 is NR^2; X^3 is N; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is )).

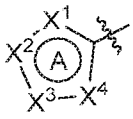
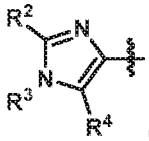
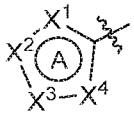
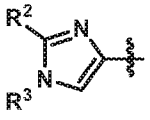
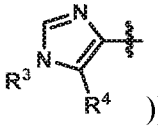
In some embodiments, X^1 is N.

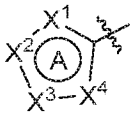
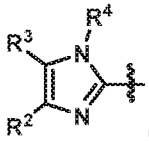
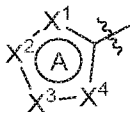
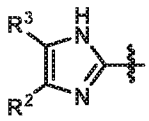
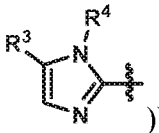
In certain embodiments, X^2 is NR^2; and X^3 is CR^3.

In certain embodiments, X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is N; X^2 is NR^2; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is  or )).

In certain embodiments, X^3 is NR^3; and X^4 is CR^4.

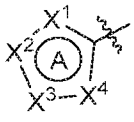
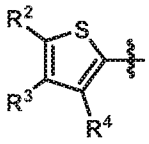
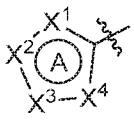
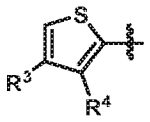
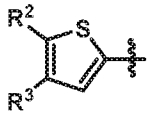
In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is NR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is  or )).

In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is CR^3; and X^4 is NR^4 (i.e., the  moiety is  (e.g.,  is  or )).

In some embodiments, X^1 is S; and X^2 is CR^2.

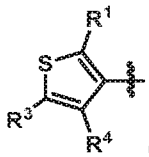
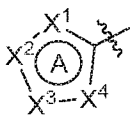
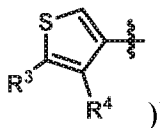
In certain embodiments, X^2 is CR^2; and X^3 is CR^3.

In certain embodiments, X^3 is CR^3; and X^4 is CR^4.

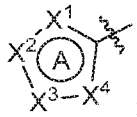
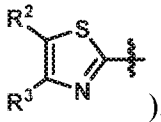
In certain embodiments, X^1 is S; X^2 is CR^2; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is  or )).

In some embodiments, X^1 is CR^1; and X^2 is S.

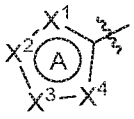
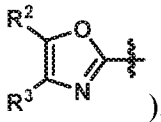
In some embodiments X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is CR^1; X^2 is S; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is )).

In certain embodiments, X^2 is CR^2; and X^3 is CR^3.

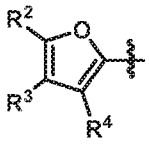
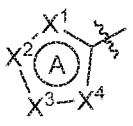
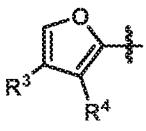
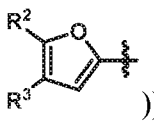
In certain embodiments, X^1 is S; X^2 is CR^2; X^3 is CR^3; and X^4 is N (i.e., the  moiety is ).

In certain embodiments, X^2 is CR^2; and X^3 is CR^3.

In certain embodiments, X^1 is O; X^2 is CR^2; X^3 is CR^3; and X^4 is N (i.e., the  moiety is ).

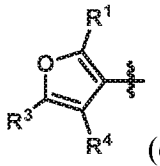
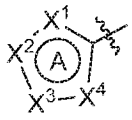
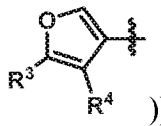
In certain embodiments, X^2 is CR^2; and X^3 is CR^3.

In certain embodiments, X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is O; X^2 is CR^2; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is  or )).

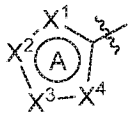
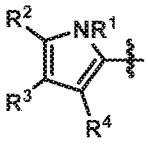
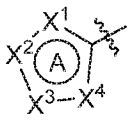
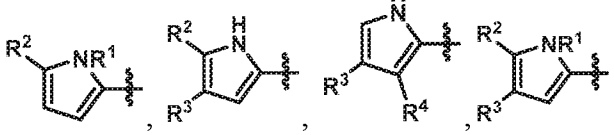
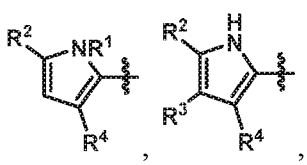
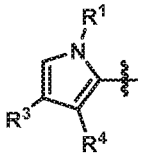
In some embodiments, X^1 is CR^1; and X^2 is O.

In some embodiments X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is CR^1; X^2 is O; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is )).

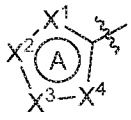
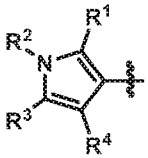
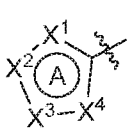
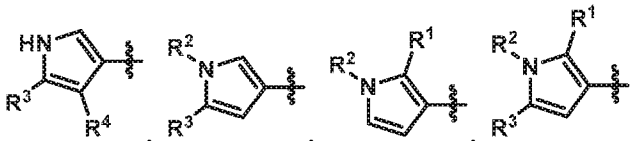
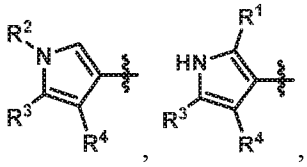
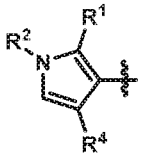
In certain embodiments, X^2 is CR^2; and X^3 is CR^3.

In certain embodiments, X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is NR^1; X^2 is CR^2; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is   , , or )).

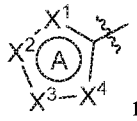
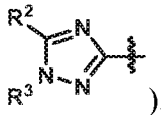
In some embodiments, X^1 is CR^1; and X^2 is NR^2.

In some embodiments X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is CR^1; X^2 is NR^2; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is   , , or )).

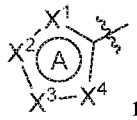
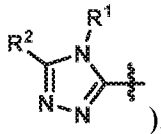
In some embodiments, X^1 is N; and X^2 is CR^2.

In some embodiments X^3 is NR^3; and X^4 is N.

In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is NR^3; and X^4 is N (i.e., the  moiety is ).

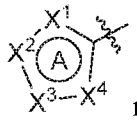
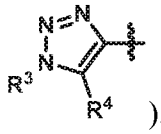
In some embodiments, X^1 is NR^1; and X^2 is CR^2.

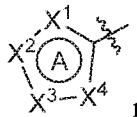
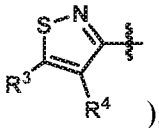
In some embodiments X^3 is N; and X^4 is N.

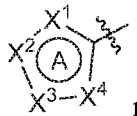
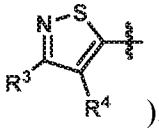
In certain embodiments, X^1 is NR^1; X^2 is CR^2; X^3 is N; and X^4 is N (i.e., the  moiety is ).

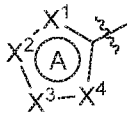
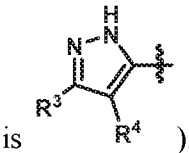
In some embodiments, X^1 is N; and X^2 is N.

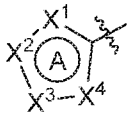
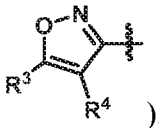
In some embodiments X^3 is NR^3; and X^4 is CR^4.

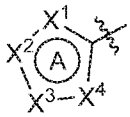
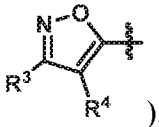
In certain embodiments, X^1 is N; X^2 is N; X^3 is NR^3; and X^4 is CR^4 (i.e., the  moiety is ).

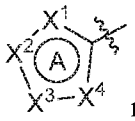
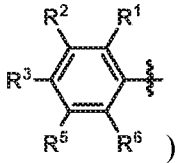
In certain embodiments, X^1 is N; X^2 is S; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

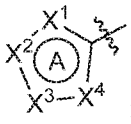
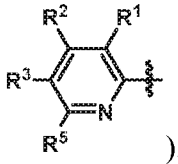
In certain embodiments, X^1 is S; X^2 is N; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

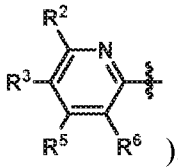
In certain embodiments, X^1 is NH; X^2 is N; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

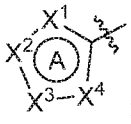
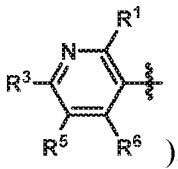
In certain embodiments, X^1 is N; X^2 is O; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

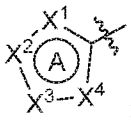
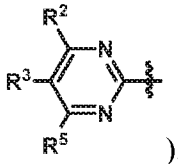
In certain embodiments, X^1 is O; X^2 is N; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

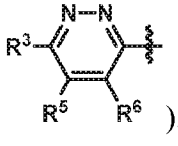
In certain embodiments, X^1 is CR^1; X^2 is CR^2; X^3 is CR^3; and X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

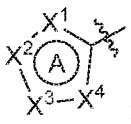
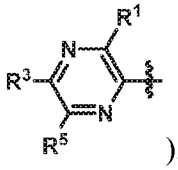
In certain embodiments, X^1 is CR^1; X^2 is CR^2; X^3 is CR^3; X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

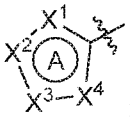
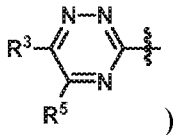
In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is CR^3 ; X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

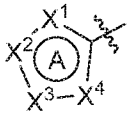
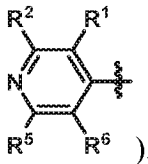
In certain embodiments, X^1 is CR^1; X^2 is N; X^3 is CR^3; X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

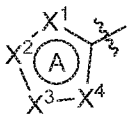
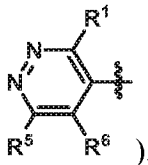
In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is CR^3; X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

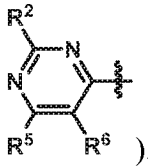
In certain embodiments, X^1 is N; X^2 is N; X^3 is CR^3; X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

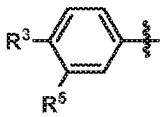
In certain embodiments, X^1 is CR^1; X^2 is N; X^3 is CR^3; X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

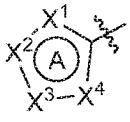
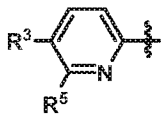
In certain embodiments, X^1 is N; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

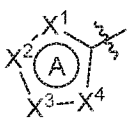
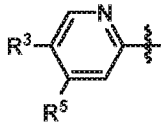
In certain embodiments, X^1 is CR^1; X^2 is CR^2; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

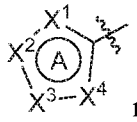
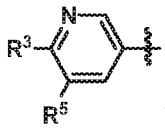
In certain embodiments, X^1 is CR^1; X^2 is N; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

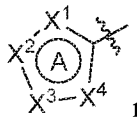
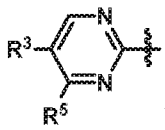
In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

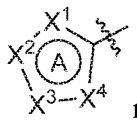
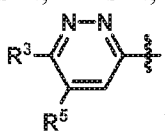
In certain embodiments, X^1 is CH; X^2 is CH; X^3 is CR^3; and X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CH (i.e., the  moiety is ).

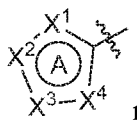
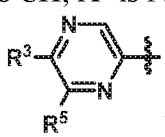
In certain embodiments, X^1 is CH; X^2 is CH; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

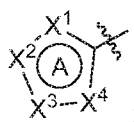
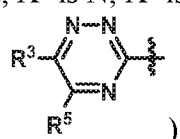
In certain embodiments, X^1 is N; X^2 is CH; X^3 is CR^3 ; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CH (i.e., the  moiety is ).

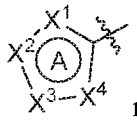
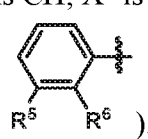
In certain embodiments, X^1 is CH; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CH (i.e., the  moiety is ).

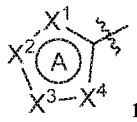
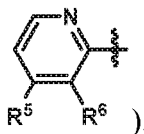
In certain embodiments, X^1 is N; X^2 is CH; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

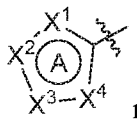
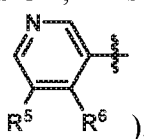
In certain embodiments, X^1 is N; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CH (i.e., the  moiety is ).

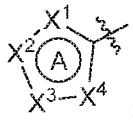
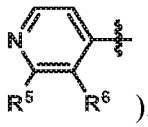
In certain embodiments, X^1 is CH; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

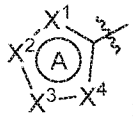
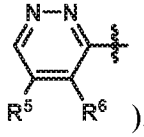
In certain embodiments, X^1 is N; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

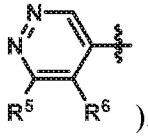
In certain embodiments, X^1 is CH; X^2 is CH; X^3 is CH; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

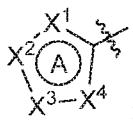
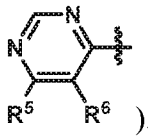
In certain embodiments, X^1 is N; X^2 is CH; X^3 is CH; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

In certain embodiments, X^1 is CH; X^2 is N; X^3 is CH; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

In certain embodiments, X^1 is CH; X^2 is CH; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

In certain embodiments, X^1 is N; X^2 is N; X^3 is CH; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

In certain embodiments, X^1 is CH; X^2 is N; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

In certain embodiments, X^1 is N; X^2 is CH; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

The variables X^1, X^2, X^3, and X^4 when Formula AA is Formula AA-1

In some embodiments, when X^4 is other than $–X^5$-X^6-, each of X^1, X^2, X^3, X^4, X^5, and X^6 is other than N.

In some embodiments, when (i) X^4 is other than $–X^5$-X^6-, and (ii) each of X^1, X^2, X^3, X^4, X^5, and X^6 is other than N, then at least two of the two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, X^1 and X^4 are each other than O.

In some embodiments, X^1 and X^4 are each other than N.

In some embodiments, when one of X^1 and X^4 is N; the other of X^1 and X^4 is other than O.

In some embodiments, when one of X^1 and X^4 is O; the other of X^1 and X^4 is other than N.

In some embodiments, X^4 is other than $–X^5\text{-}X^6\text{-}$.

In some embodiments, X^1 is O.

In some embodiments, X^1 is S.

In some embodiments, X^1 is N.

In some embodiments, X^1 is NR^1.

In some embodiments, X^1 is CR^1.

In some embodiments, X^2 is O.

In some embodiments, X^2 is S.

In some embodiments, X^2 is N.

In some embodiments, X^2 is NR^2.

In some embodiments, X^2 is CR^2.

In some embodiments, X^3 is O.

In some embodiments, X^3 is S.

In some embodiments, X^3 is N.

In some embodiments, X^3 is NR^3.

In some embodiments, X^3 is CR^3.

In some embodiments, X^4 is O.

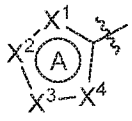
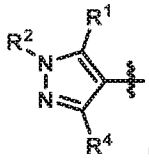
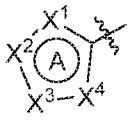
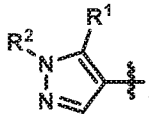
In some embodiments, X^4 is S.

In some embodiments, X^4 is N.

In some embodiments, X^4 is NR^4.

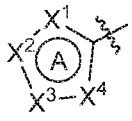
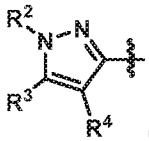
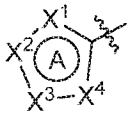
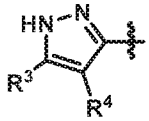
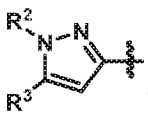
In some embodiments, X^4 is CR^4.

In certain embodiments, X^1 is CR^1; and X^2 is NR^2.

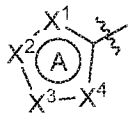
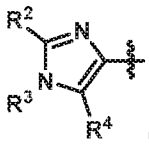
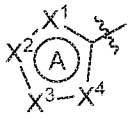
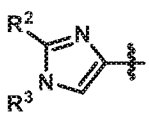
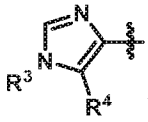
In certain embodiments, X^1 is CR^1; X^2 is NR^2; X^3 is N; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is )).

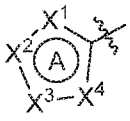
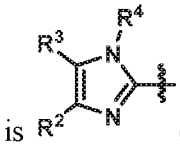
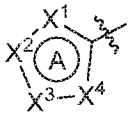
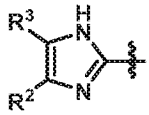
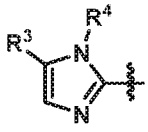
In certain embodiments, X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is N; X^2 is NR^2; X^3 is CR^3; and X^4 is CR^4.

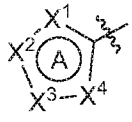
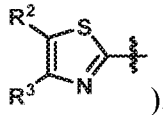
In certain embodiments, X^1 is N; X^2 is NR^2; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is  or )).

In certain embodiments, X^3 is NR^3; and X^4 is CR^4.

In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is NR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is  or )).

In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is CR^3; and X^4 is NR^4 (i.e., the  moiety is  (e.g.,  is  or )).

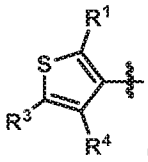
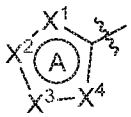
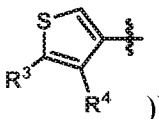
In certain embodiments, X^2 is CR^2; and X^3 is CR^3.

In certain embodiments, X^1 is S; X^2 is CR^2; X^3 is CR^3; and X^4 is N (i.e., the  moiety is ).

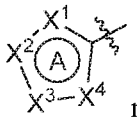
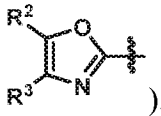
In some embodiments, X^1 is CR^1; and X^2 is S.

In some embodiments X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is CR^1; X^2 is S; X^3 is CR^3; and X^4 is CR^4.

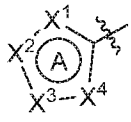
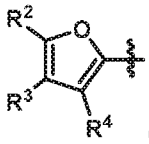
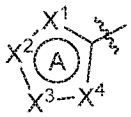
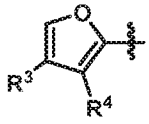
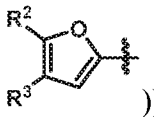
In certain embodiments, X^1 is CR^1; X^2 is S; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is )).

In certain embodiments, X^2 is CR^2; and X^3 is CR^3.

In certain embodiments, X^1 is O; X^2 is CR^2; X^3 is CR^3; and X^4 is N (i.e., the  moiety is ).

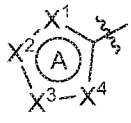
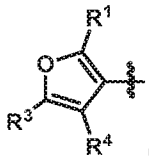
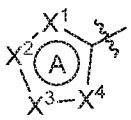
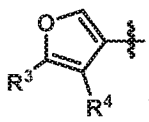
In certain embodiments, X^2 is CR^2; and X^3 is CR^3.

In certain embodiments, X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is O; X^2 is CR^2; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is  or )).

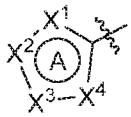
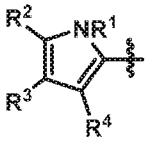
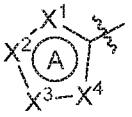
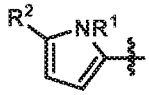
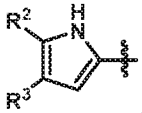
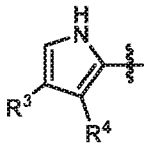
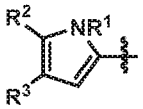
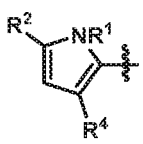
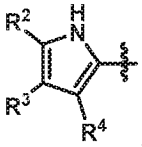
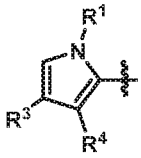
In some embodiments, X^1 is CR^1; and X^2 is O.

In some embodiments X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is CR^1; X^2 is O; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is )).

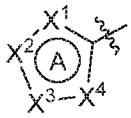
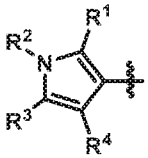
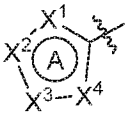
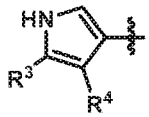
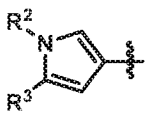
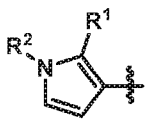
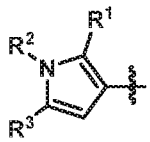
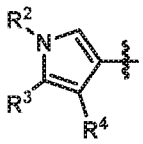
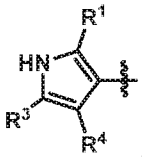
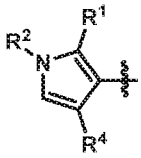
In certain embodiments, X^2 is CR^2; and X^3 is CR^3.

In certain embodiments, X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is NR^1; X^2 is CR^2; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is  ,  ,  ,  ,  ,  , or )).

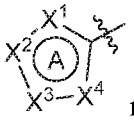
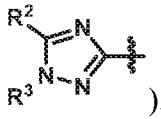
In some embodiments, X^1 is CR^1; and X^2 is NR^2.

In some embodiments X^3 is CR^3; and X^4 is CR^4.

In certain embodiments, X^1 is CR^1; X^2 is NR^2; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is  (e.g.,  is  ,  ,  ,  ,  ,  , or )).

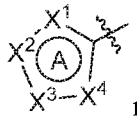
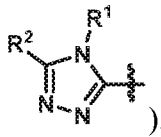
In some embodiments, X^1 is N; and X^2 is CR^2.

In some embodiments X^3 is NR^3; and X^4 is N.

In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is NR^3; and X^4 is N (i.e., the  moiety is ).

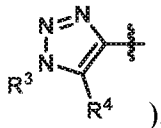
In some embodiments, X^1 is NR^1; and X^2 is CR^2.

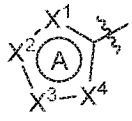
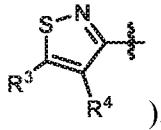
In some embodiments X^3 is N; and X^4 is N.

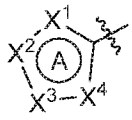
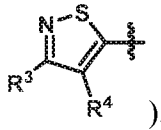
In certain embodiments, X^1 is NR^1; X^2 is CR^2; X^3 is N; and X^4 is N (i.e., the  moiety is ).

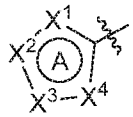
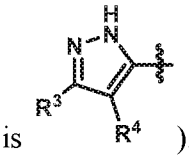
In some embodiments, X^1 is N; and X^2 is N.

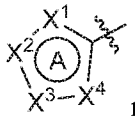
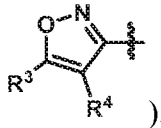
In some embodiments X^3 is NR^3; and X^4 is CR^4.

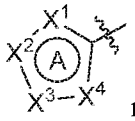
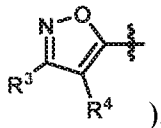
In certain embodiments, X^1 is N; X^2 is N; X^3 is NR^3; and X^4 is CR^4 (i.e., the  moiety is ).

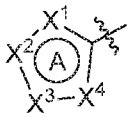
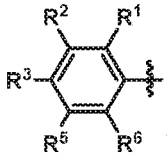
In certain embodiments, X^1 is N; X^2 is S; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

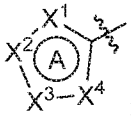
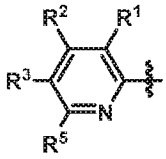
In certain embodiments, X^1 is S; X^2 is N; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

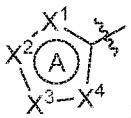
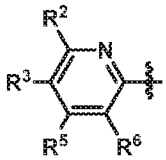
In certain embodiments, X^1 is NH; X^2 is N; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

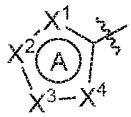
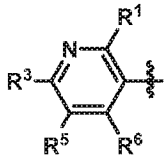
In certain embodiments, X^1 is N; X^2 is O; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

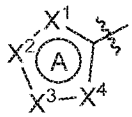
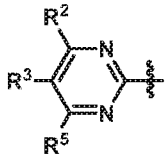
In certain embodiments, X^1 is O; X^2 is N; X^3 is CR^3; and X^4 is CR^4 (i.e., the  moiety is ).

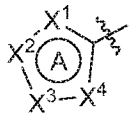
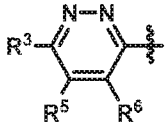
In certain embodiments, X^1 is CR^1; X^2 is CR^2; X^3 is CR^3; and X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

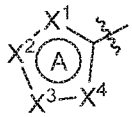
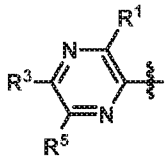
In certain embodiments, X^1 is CR^1; X^2 is CR^2; X^3 is CR^3; X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

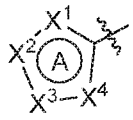
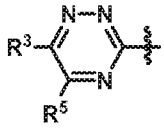
In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is CR^3 ; X^4 is $–X^5\text{-}X^6\text{-}$; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

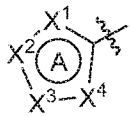
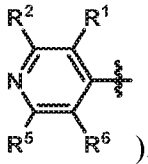
In certain embodiments, X^1 is CR^1; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

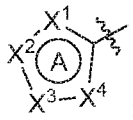
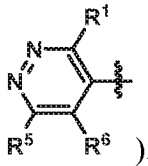
In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

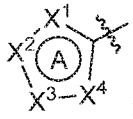
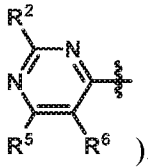
In certain embodiments, X^1 is N; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

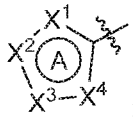
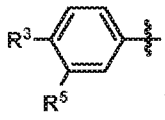
In certain embodiments, X^1 is CR^1; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

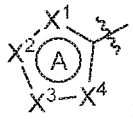
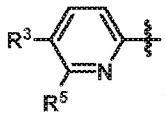
In certain embodiments, X^1 is N; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

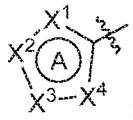
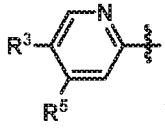
In certain embodiments, X^1 is CR^1; X^2 is CR^2; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

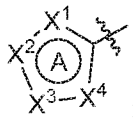
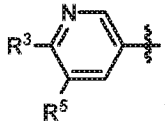
In certain embodiments, X^1 is CR^1; X^2 is N; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

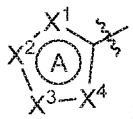
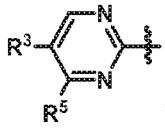
In certain embodiments, X^1 is N; X^2 is CR^2; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

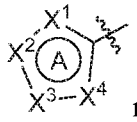
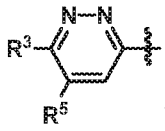
In certain embodiments, X^1 is CH; X^2 is CH; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CH (i.e., the  moiety is ).

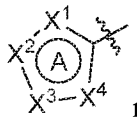
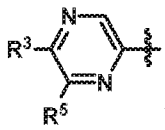
In certain embodiments, X^1 is CH; X^2 is CH; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

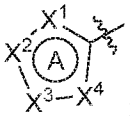
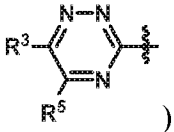
In certain embodiments, X^1 is N; X^2 is CH; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CH (i.e., the  moiety is ).

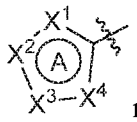
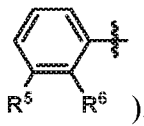
In certain embodiments, X^1 is CH; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CH (i.e., the  moiety is ).

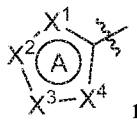
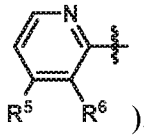
In certain embodiments, X^1 is N; X^2 is CH; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

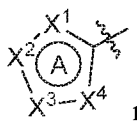
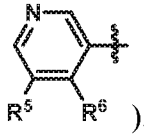
In certain embodiments, X^1 is N; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CH (i.e., the  moiety is ).

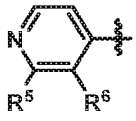
In certain embodiments, X^1 is CH; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

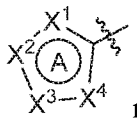
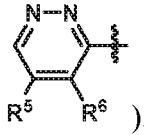
In certain embodiments, X^1 is N; X^2 is N; X^3 is CR^3; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is N (i.e., the  moiety is ).

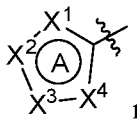
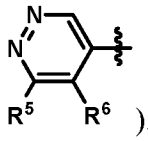
In certain embodiments, X^1 is CH; X^2 is CH; X^3 is CH; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

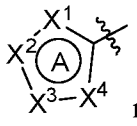
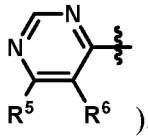
In certain embodiments, X^1 is N; X^2 is CH; X^3 is CH; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

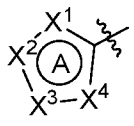
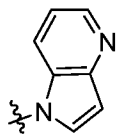
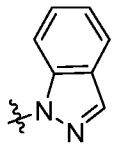
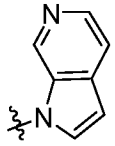
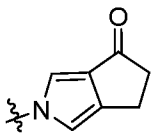
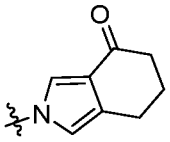
In certain embodiments, X^1 is CH; X^2 is N; X^3 is CH; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

In certain embodiments, X^1 is CH; X^2 is CH; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

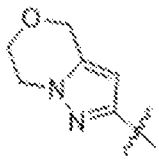
In certain embodiments, X^1 is N; X^2 is N; X^3 is CH; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

In certain embodiments, X^1 is CH; X^2 is N; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

In certain embodiments, X^1 is N; X^2 is CH; X^3 is N; X^4 is $–X^5$-X^6-; X^5 is CR^5; and X^6 is CR^6 (i.e., the  moiety is ).

In some embodiments,  is selected from  ,  ,  ,  , and  .

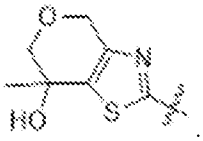
The Groups R^1, R^2, R^3, R^4, R^5, and R^6

For purposes of clarification, when a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring or 5-10 membered heteroaryl ring contains 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, the 1-3 cumulative heteroatom or heteroatomic group are a set that does not include the values selected for X^1, X^2, X^3, and X^4. For example, in  , there is 1 heteroatom (i.e., oxygen) cumulative with the values selected for X^1, X^2, X^3, and X^4.

For purposes of clarification, definitions along the lines of "wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least two of the two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} are

intended to encompass structures, in which one of the adjacent ring atoms is N (i.e., a bridgehead N) e.g.,  or  .

For purposes of clarification, definitions along the lines of "wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least two of the two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, are intended to encompass structures, in which **i)** one or neither of the adjacent ring atoms is N; and **ii)** at least one other ring atom in addition to said adjacent ring atoms is a heteroatom, e.g.,

 ,  , and  .

It is understood that in embodiments of any applicable formulae herein that when any two adjacent substituents selected from R^1, R^2, R^3, R^4, R^5, and R^6 are taken together with the atoms connecting them to form a cycloalkyl ring, the atoms connecting the two substituents that are taken together are selected from C and N.

For example, when R^1 and R^2 on adjacent atoms are taken together with the atoms connecting them to form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}, then X^1 is selected from CR^1 and XR^1, and X^2 is selected from CR^2 and NR^2.

For example, when R^2 and R^3 on adjacent atoms are taken together with the atoms connecting them to form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}, then X^2 is selected from CR^2 and XR^2, and X^3 is selected from CR^3 and NR^3.

For example, when R^3 and R^4 on adjacent atoms are taken together with the atoms connecting them to form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted

with one or more R^{20}, then X^3 is selected from CR^3 and XR^3, and X^4 is selected from CR^4 and NR^4.

For example, when R^4 and R^5 on adjacent atoms are taken together with the atoms connecting them to form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}, then X^4 is selected from CR^4 and XR^4, and X^5 is selected from CR^5 and NR^5.

For example, when R^5 and R^6 on adjacent atoms are taken together with the atoms connecting them to form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}, then X^5 is selected from CR^5 and XR^5, and X^6 is selected from CR^6 and NR^6.

In some embodiments of Formula AA and Formula AA-1 herein, X^4 is $–X^5$-X^6-; from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and wherein at least of two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments of Formula AA and Formula AA-1 herein, X^4 is $–X^5$-X^6-; from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and wherein at least two of the two to five R^1, R^2, R^3,

R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}, and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments of Formula AA, Formula AA-1, and Formula AA-2 herein, X^4 is other than $-X^5$-X^6-; from two to four of R^1, R^2, R^3, and R^4 are present; and wherein at least two of the two to four R^1, R^2, R^3, and R^4 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, wherein the heteroaryl ring is optionally substituted with one or more R^{20};

In some embodiments of Formula AA, Formula AA-1, and Formula AA-2 herein, X^4 is other than $-X^5$-X^6-; from two to four of R^1, R^2, R^3, and R^4 are present; and wherein at least two of the two to four R^1, R^2, R^3, and R^4 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}, and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S (e.g., O and NH), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, when one of X^1 and X^2 is NR^1 or NR^2, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing no heteroatoms and/or heteroatomic groups cumulative with the N of X^1 or X^2, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, when one of X^1 and X^2 is NR^1 or NR^2, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing no heteroatoms and/or heteroatomic groups cumulative with the N of X^1 or X^2, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments when R^1 and R^2 are taken together to form a ring (e.g., monocyclic ring or bicyclic ring), R^4 is H or CH_3.

In some embodiments, R^2 and R^3 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S (e.g., O and NH), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, when one of X^2 and X^3 is NR^2 or NR^3, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing no heteroatoms and/or heteroatomic groups cumulative with the N of X^2 or X^3, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, when one of X^2 and X^3 is NR^2 or NR^3, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing no heteroatoms and/or heteroatomic groups cumulative with the N of X^2 or X^3, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3 wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments when R^2 and R^3 are taken together to form a ring (e.g., monocyclic ring or bicyclic ring), R^4 is H or CH_3.

In some embodiments, R^3 and R^4 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S (e.g., O and NH), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-6 membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, when one of X^3 and X^4 is NR^3 or NR^4, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing no heteroatoms and/or heteroatomic groups cumulative with the N of X^3 or X^4, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, when one of X^3 and X^4 is NR^3 or NR^4, R^3 and R^4, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing no heteroatoms and/or heteroatomic groups cumulative with the N of X^3 or X^4, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or

heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments, monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments, when R^3 and R^4 are taken together to form a ring, R^2 is H or CH_3 (e.g., H).

In some embodiments, R^3 and R^5 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S (e.g., O and NH), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-6 membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments, monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments, when R^3 and R^5 are taken together to form a ring, each of R^1, R^2, and R^6 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halo.

In some embodiments, R^5 and R^6 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S (e.g., O and NH), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-6 membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments, monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments, when R^5 and R^6 are taken together to form a ring, each of R^1, R^2, and R^3 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halo.

The Groups R^1, R^2, R^3, R^4, R^5, and R^6 when Formula AA is Formula AA-1

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments when R^1 and R^2 are taken together to form a ring (e.g., monocyclic ring or bicyclic ring), R^4 is H or CH_3.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, and NR^{13} and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with from 1-2 R^{20}.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 heteroatom or heteroatomic group selected from O and NH, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3.

In certain embodiments of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments when R^2 and R^3 are taken together to form a ring (e.g., monocyclic ring or bicyclic ring), R^4 is H or CH_3.

In some embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments when R^3 and R^4 are taken together to form a ring (e.g., monocyclic ring or bicyclic ring), R^4 is H or CH_3.

In some embodiments, R^3 and R^5 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S (e.g., O and NH), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-6 membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^3 and R^5, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments, monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments, when R^3 and R^5 are taken together to form a ring, each of R^1, R^2, and R^6 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halo.

In some embodiments, R^5 and R^6 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S (e.g., O and NH), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-6 membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, R^5 and R^6, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments, monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments, when R^5 and R^6 are taken together to form a ring, each of R^1, R^2, and R^3 is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halo.

The Groups R^1, R^2, R^3, and R^4 when Formula AA is Formula AA-2

In some embodiments, R^1 and R^2 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In certain embodiments, the ring is a monocyclic 5-6 membered cycloalkyl ring optionally substituted with one or more R^{20}, or a monocyclic 5-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, or NH, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, the ring is a monocyclic 5-6-membered heterocycloalkyl ring containing one heteroatom or heteroatomic group independently selected from O, or NH, wherein the heterocycloalkyl ring is optionally substituted with one or more (e.g., two) R^{20}.

In some embodiments, R^2 and R^3 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

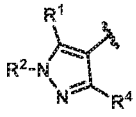
(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In certain embodiments, the ring is a monocyclic 5-6 membered cycloalkyl ring optionally substituted with one or more R^{20}, or a monocyclic 5-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, or NH, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

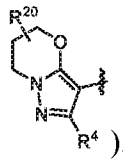
In certain embodiments, the ring is a monocyclic 5-6-membered heterocycloalkyl ring containing one heteroatom or heteroatomic group independently selected from O or NH, wherein the heterocycloalkyl ring is optionally substituted with one or more (e.g., two) R^{20}.

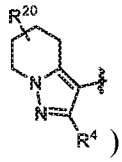
Non-Limiting Combinations of X^1-X^4 and R^1-R^4

[1]

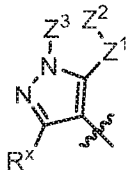
In some embodiments, X^1 is CR^1; X^2 is NR^2; X^3 is N; and/or X^4 is CR^4 (e.g., ring A is ); and

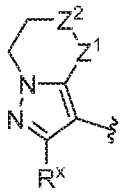
R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the value selected for X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3 (e.g., O)), wherein the heteroatom or heteroatomic group is cumulative with the value selected for X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}. As a non-limiting example of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom (e.g., ring A is ).

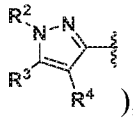
In certain other embodiments, R^1 and R^2, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing no heteroatoms or heteroatomic groups cumulative with the value selected for X^2, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}. As a non-limiting example of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom (e.g., ring A is ).

In certain embodiments of **[1]**, R^4 is H or CH_3.

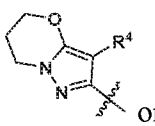
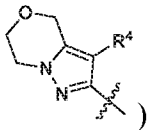
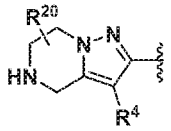
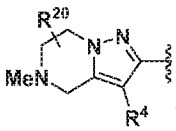
In certain embodiments, A is  , wherein R^x is selected from the group consisting of H and C_1-C_6 alkyl (e.g., methyl); Z^1 is selected from the group consisting of O, NH, and -CH_2- optionally substituted with 1-2 R^{20}; Z^2 is selected from the group consisting of NH and -CH_2- optionally substituted with 1-2 R^{20}; Z^3 is selected from the group consisting of -CH_2- optionally substituted with 1-2 R^{20}, -CH_2CH_2- optionally substituted with 1-2 R^{20}, and -$CH_2CH_2CH_2$- optionally substituted with 1-2 R^{20}; R^{20} is selected from the group consisting of hydroxy, halo (e.g., fluoro), oxo, C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}, C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}, NR^8R^9, 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}, or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom optionally substituted with $OS(O)_2Ph$; R^{21} is selected from the group consisting of halo (e.g., fluoro), NR^8R^9, C_2-C_6 alkynyl (e.g., ethynyl), and C_1-C_6 alkoxy (e.g., methoxy); R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl (e.g., methyl or ethyl), COR^{13}, and CO_2R^{13}; R^{13} is selected from the group consisting of: C_1-C_6 alkyl (e.g., methyl or *t*-butyl) and C_1-C_6 haloalkyl (e.g., trifluoromethyl).

In certain embodiments of the foregoing, A is  (e.g., Z^1 is O; and Z^2 is CH_2 optionally substituted with 1 R^{20}).

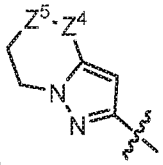
[2]

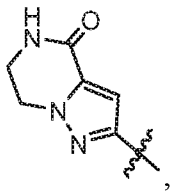
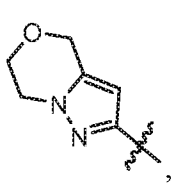
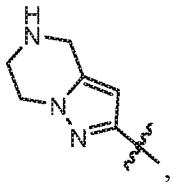
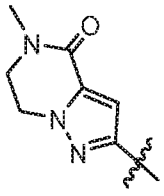
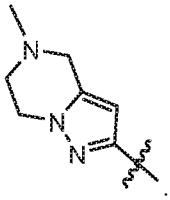
In some embodiments, X^1 is N; X^2 is NR^2; X^3 is CR^3; and/or X^4 is CR^4 (e.g., ring A ); and

R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the value selected for X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

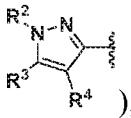
In certain embodiments, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the value selected for X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}. As a non-limiting example of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom (e.g., ring A is  or ); or the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 NH or NMe (e.g., the ring including X^1-X^4 is  or ).

In certain embodiments of **[2]**, R^4 is H or CH_3.

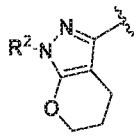
In some embodiments, A is  , wherein Z^4 is selected from the group consisting of $–CH_2$-, –C(O)-, and NH; Z^5 is selected from the group consisting of O, NH, N-CH_3, and $–CH_2$-.

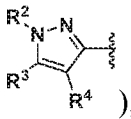
In some embodiments, A is selected from the group consisting of:  ,  ,  ,  , and  .

[3]

In some embodiments, X^1 is N; X^2 is NR^2; X^3 is CR^3; and/or X^4 is CR^4 (e.g., ring A is ); and

R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

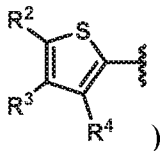
In certain embodiments, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}. As a non-limiting example of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom (e.g., ring A is ); or the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 NH or NMe.

In some embodiments, X^1 is N; X^2 is NR^2; X^3 is CR^3; and/or X^4 is CR^4 (e.g., ring A is ); and

R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In certain embodiments of **[3]**, R^2 is H, C_1-C_6 alkyl, or C_1-C_6 haloalkyl (e.g., R^2 can be CF_2H).

[4]

In some embodiments, X^1 is S; X^2 is CR^2; X^3 is CR^3; and/or X^4 is CR^4 (e.g., ring A is ); and

R^3 and R^4 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In certain embodiments of foregoing, R^3 and R^4 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

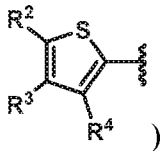
(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments, R^3 and R^4 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

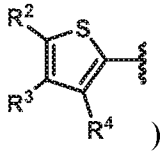
(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to 6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In some embodiments, X^1 is S; X^2 is CR^2; X^3 is CR^3; and/or X^4 is CR^4 (e.g., ring A is ); and

R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, X^1 is S; X^2 is CR^2; X^3 is CR^3; and/or X^4 is CR^4 (e.g., ring A is ); and

R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups

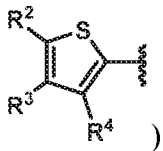
independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, N, NH, and NR^{13} (e.g., O, N, NH, or NCH_3), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}. As a non-limiting example of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

In certain embodiments of **[4]**, R^2 is H or CH_3.

In certain embodiments of **[4]**, R^{20} is C_1-C_6 alkyl (e.g., methyl).

[5]

In some embodiments, X^1 is S; X^2 is CR^2; X^3 is CR^3; and/or X^4 is CR^4 (e.g., ring A is ); and

R^2 and R^3 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, the ring is selected from:

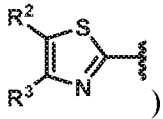
(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments, the ring is a monocyclic 5-6 membered cycloalkyl ring optionally substituted with one or more R^{20}.

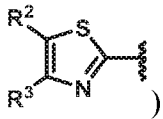
In certain embodiments of **[5]**, each R^{20} is independently selected from hydroxy, C_1-C_6 alkyl (e.g., methyl), and NR^8R^9.

[6]

In some embodiments, X^1 is S; X^2 is CR^2; X^3 is CR^3; and/or X^4 is N (e.g., ring A is ); and

R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

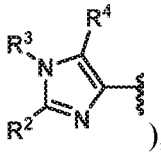
In certain embodiments of the foregoing, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

In some embodiments, X^1 is S; X^2 is CR^2; X^3 is CR^3; and/or X^4 is N (e.g., ring A is ); and

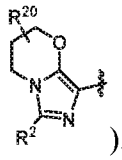
R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, R^2 and R^3, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}. As a non-limiting example of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring can contain 1 heteroatom or heteroatomic group selected from O and NH.

[7]

In some embodiments, X^1 is N; X^2 is CR^2; X^3 is NR^3; and/or X^4 is CR^4 (e.g., ring A is ); and

R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

In certain embodiments of the foregoing, R^3 and R^4, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}. As a non-limiting example of the foregoing, the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom (e.g., ring A is ).

In certain embodiments of **[1]**, R^2 is H or CH_3.

The variable R^{20}

In some embodiments, R^{20} is selected from the group consisting of: hydroxy, halo (e.g., fluoro), oxo, C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}, C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}, NR^8R^9, 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}, or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom, wherein the ring is optionally substituted with $OS(O)_2Ph$.

In some embodiments, R^{20} is hydroxy,

In some embodiments, R^{20} is halo (e.g., fluoro).

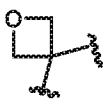
In some embodiments, R^{20} is oxo,

In some embodiments, R^{20} is C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}.

In some embodiments, R^{20} is C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}.

In some embodiments, R^{20} is NR^8R^9 (e.g., NHMe, NHEt, NH_2, NHBoc, NMeBoc).

In some embodiments, R^{20} is 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}.

In some embodiments, R^{20} is or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom, wherein the ring is optionally substituted with $OS(O)_2Ph$ (e.g., the ring can be  or ).

The variable R^{20} when Formula AA is Formula AA-1

In some embodiments, R^{20} is selected from the group consisting of: hydroxy, halo (e.g., fluoro), oxo, C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}, C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}, NR^8R^9, 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}, or at least one pair of R^{20} on the same atom, taken together with the atom connecting them,

independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom optionally substituted with $OS(O)_2Ph$.

In some embodiments, R^{20} is hydroxy,

In some embodiments, R^{20} is halo (e.g., fluoro).

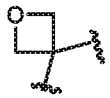
In some embodiments, R^{20} is oxo,

In some embodiments, R^{20} is C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}.

In some embodiments, R^{20} is C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}.

In some embodiments, R^{20} is NR^8R^9 (e.g., NHMe, NHEt, NH_2, NHBoc, NMeBoc).

In some embodiments, R^{20} is 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}.

In some embodiments, R^{20} is or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom, wherein the ring is optionally substituted with $OS(O)_2Ph$ (e.g., the ring can be  or ).

The variable R^{20} when Formula AA is Formula AA-2

In some embodiments (e.g., when R^1 and R^2 are taken together to form a ring), R^{20} is C_1-C_6 alkyl (e.g., methyl).

In some embodiments (e.g., when R^2 and R^3 are taken together to form a ring), R^{20} is selected from hydroxy, C_1-C_6 alkyl (e.g., methyl), and NR^8R^9.

In some embodiments, R^{20} is hydroxyl.

In some embodiments, R^{20} is C_1-C_6 alkyl (e.g., methyl).

In some embodiments, R^{20} is NR^8R^9.

In some embodiments, R^{20} is halo.

The variable R^{21}

In some embodiments of Formula AA, AA-1 or AA-2, R^{21} is selected from the group consisting of halo (e.g., fluoro), NR^8R^9, C_2-C_6 alkynyl (e.g., ethynyl), and C_1-C_6 alkoxy (e.g., methoxy).

In some embodiments of Formula AA, AA-1 or AA-2, R^{21} is halo (e.g., fluoro).

In some embodiments of Formula AA, AA-1 or AA-2, R^{21} is NR^8R^9. In certain embodiments of the foregoing, each of R^8 and R^9 is independently hydrogen or C_1-C_6 alkyl (e.g., R^{21} is NHMe, NH_2, or NMe_2). In certain embodiments, one of R^8 and R^9 is selected from COR^{13} and CO_2R^{13} (e.g., R^{21} is NHBoc; or R^{21} is NHAc or $NHC(=O)CF_3$).

In some embodiments of Formula AA, AA-1 or AA-2, R^{21} is C_2-C_6 alkynyl (e.g., ethynyl).

In some embodiments of Formula AA, AA-1 or AA-2, R^{21} is C_1-C_6 alkoxy (e.g., methoxy).

In certain embodiments, R^{21} is selected from the group consisting of F, NH_2, NHMe, NMe_2, NHBoc, NMeBoc, NHAc, ethynyl, and OMe.

The variable R^{22}

In some embodiments, R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23}.

In some embodiments, R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one R^{23}, C_1-C_6 alkoxy optionally substituted with one R^{23}, NR^8R^9, $COOC_1$-C_6 alkyl optionally substituted with one R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one R^{23}, C_6-C_{10} aryl optionally substituted with one R^{24}, 5- to 10-membered heteroaryl optionally substituted

with one R^{24}, $NHCOC_1$-C_6 alkyl optionally substituted with one R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23}.

In some embodiments, R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl.

In some embodiments, R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, and $NHCOC_1$-C_6 alkyl.

In some embodiments, R^{22} at each occurrence is selected from the group consisting of hydroxyl, halo (e.g., fluoro), CN, NR^8R^9, C_2-C_6 alkynyl (e.g., ethynyl), and C_1-C_6 alkoxy (e.g., methoxy).

The variable R^{23}

In some embodiments, R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_4 alkyl, OC_1-C_4 alkyl, and oxo.

In some embodiments, R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_4 alkyl, and OC_1-C_4 alkyl.

The variable R^{24}

In some embodiments, R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_4 alkyl, OC_1-C_4 alkyl, and oxo.

In some embodiments, R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9 (e.g., $NHC(O)R^{13}$, NH_2, $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl)$_2$, $NHC(O)OR^{13}$), C_1-C_4 alkyl, and OC_1-C_4 alkyl.

The variable R^{25}

In some embodiments, R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26}.

In some embodiments, R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy, NR^8R^9, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl.

In some embodiments, R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9 (e.g., $NHC(O)R^{13}$, NH_2, $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl)$_2$, $NHC(O)OR^{13}$), $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6

alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl.

The variable R^{26}

In some embodiments, R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl.

In some embodiments, R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, phenyl, NR^8R^9, C_1-C_4 alkyl, and OC_1-C_4 alkyl.

In some embodiments, R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_4 alkyl, and OC_1-C_4 alkyl.

In some embodiments, R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, $NHC(O)R^{13}$, NH_2, $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl$)_2$, $NHC(O)OR^{13}$, C_1-C_4 alkyl, and OC_1-C_4 alkyl.

The variable R^{27}

In some embodiments, R^{27}, at each occurrence, is independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In certain embodiments, R^{27}, at each occurrence, is independently hydroxyl, oxo, halo (e.g., F), or C_1-C_6 alkyl. As a non-limiting example of the foregoing, R^{27} at each occurrence can be independently C_1-C_6 alkyl.

The variables o, o', o'', p, p', p'', and p'''

In some embodiments, o=1 or 2.

In some embodiments, o=1.

In some embodiments, o=2.

In some embodiments, p=0, 1, 2, or 3.

In some embodiments, p=0.

In some embodiments, p=1.

In some embodiments, p=2.

In some embodiments, o=1 and p=0.

In some embodiments, o=2 and p=0.

In some embodiments, o=1 and p=1.

In some embodiments, o=1 and p=2.

In some embodiments, o=2 and p=1.

In some embodiments, o=2 and p=2.

In some embodiments, o=2 and p=3.

In some embodiments, o'=0 or 1.

In some embodiments, o'=0.

In some embodiments, o'=1.

In some embodiments, p'=0 or 1.

In some embodiments, p'=0.

In some embodiments, p'=1.

In some embodiments, o'=1 and p'=0.

In some embodiments, o'=1 and p'=1.

In some embodiments, o'=0 and p'=1.

In some embodiments, o'=0 and p'=0.

In some embodiments, o''=0 or 1.

In some embodiments, o''=0.

In some embodiments, o''=1.

In some embodiments, p''=0, 1, or 2.

In some embodiments, p''=0.

In some embodiments, p''=1.

In some embodiments, o''=1 and p''=0.

In some embodiments, o''=1 and p''=1.

In some embodiments, o''=1 and p''=2.

In some embodiments, o''=0 and p''=1.

In some embodiments, o''=0 and p''=0.

In some embodiments, o''=0 and p''=2.

In some embodiments p'''= 1, 2, or 3.

In some embodiments p'''=1.

In some embodiments p'''=2.

In some embodiments p'''=3.

In some embodiments, p'''=1 or 2.

The variables t and t'

In some embodiments, t is 0, 1, 2, 3, 4, 5, or 6.

In some embodiments, t is 0, 1, 2, or 3.

In some embodiments, t is 0, 1, or 2.

In some embodiments, t is 0.

In some embodiments, t is 1.

In some embodiments, t is 2.

In some embodiments, t' is 0, 1, 2, 3, or 4.

In some embodiments, t' is 0, 1, 2, or 3.

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

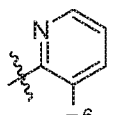
In some embodiments, t' is 0.

In some embodiments, t' is 1.

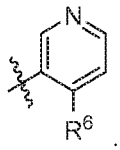
In some embodiments, t' is 2.

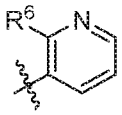
The ring B and substitutions on the ring B

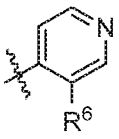
In some embodiments, B is one of the rings disclosed hereinbelow, substituted as disclosed hereinbelow, wherein in each case the bond that is shown as being broken by the wavy line connects B to the NHC(O) group of Formula AA.

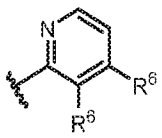
In some embodiments, the optionally substituted ring B is 

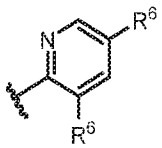
.

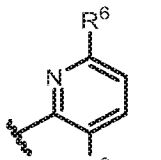


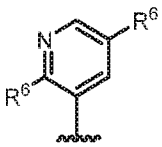


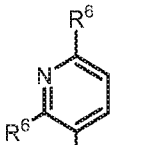


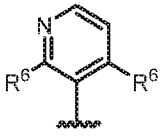












In some embodiments, the optionally substituted ring B is .

In some embodiments, the optionally substituted ring B is .

In some embodiments, the optionally substituted ring B is .

In some embodiments, the optionally substituted ring B is .

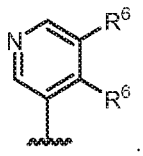
In some embodiments, the optionally substituted ring B is .

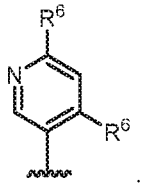
In some embodiments, the optionally substituted ring B is .

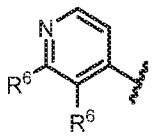
In some embodiments, the optionally substituted ring B is .

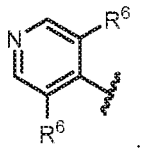
In some embodiments, the optionally substituted ring B is .

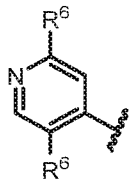
In some embodiments, the optionally substituted ring B is .

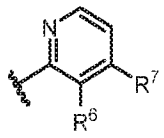
In some embodiments, the optionally substituted ring B is  .

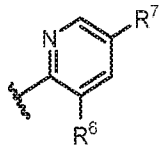
In some embodiments, the optionally substituted ring B is  .

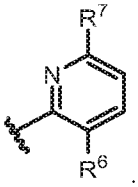
In some embodiments, the optionally substituted ring B is  .

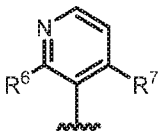
In some embodiments, the optionally substituted ring B is  .

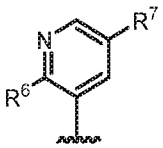
In some embodiments, the optionally substituted ring B is  .

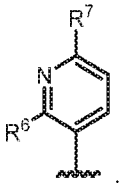
In some embodiments, the optionally substituted ring B is  .

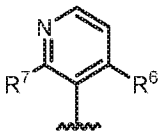
In some embodiments, the optionally substituted ring B is  .

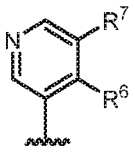
In some embodiments, the optionally substituted ring B is  .

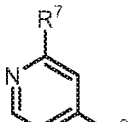


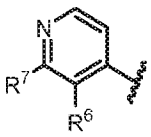


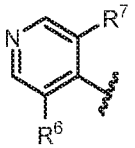


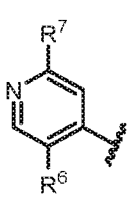












In some embodiments, the optionally substituted ring B is .

In some embodiments, the optionally substituted ring B is .

In some embodiments, the optionally substituted ring B is .

In some embodiments, the optionally substituted ring B is .

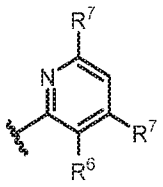
In some embodiments, the optionally substituted ring B is .

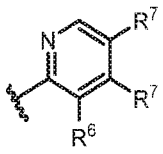
In some embodiments, the optionally substituted ring B is .

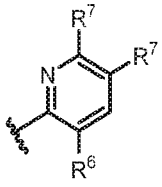
In some embodiments, the optionally substituted ring B is .

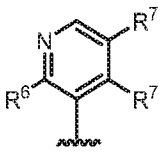
In some embodiments, the optionally substituted ring B is .

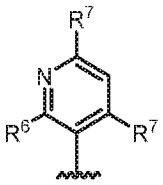
In some embodiments, the optionally substituted ring B is .

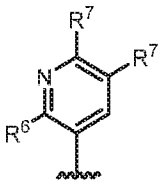
In some embodiments, the optionally substituted ring B is  .

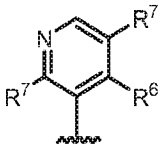
In some embodiments, the optionally substituted ring B is  .

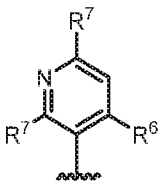
In some embodiments, the optionally substituted ring B is  .

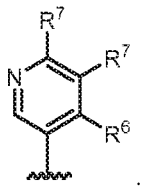
In some embodiments, the optionally substituted ring B is  .

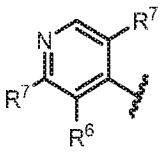
In some embodiments, the optionally substituted ring B is  .

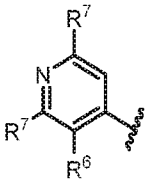
In some embodiments, the optionally substituted ring B is  .

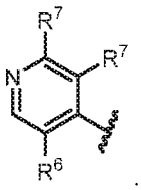
In some embodiments, the optionally substituted ring B is  .

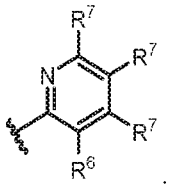
In some embodiments, the optionally substituted ring B is  .

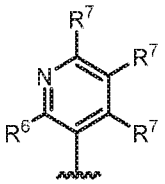
In some embodiments, the optionally substituted ring B is  .

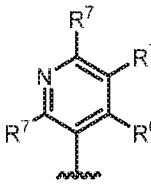
In some embodiments, the optionally substituted ring B is  .

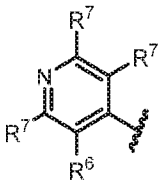
In some embodiments, the optionally substituted ring B is  .

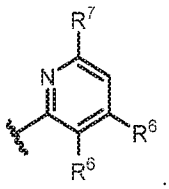
In some embodiments, the optionally substituted ring B is  .

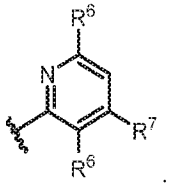
In some embodiments, the optionally substituted ring B is  .

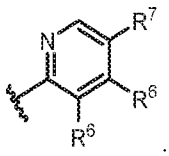
In some embodiments, the optionally substituted ring B is  .

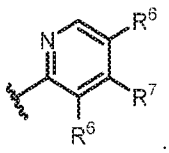
In some embodiments, the optionally substituted ring B is  .

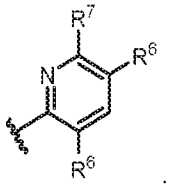
In some embodiments, the optionally substituted ring B is  .

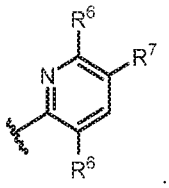
In some embodiments, the optionally substituted ring B is  .

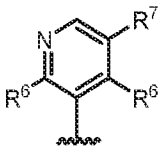
In some embodiments, the optionally substituted ring B is  .

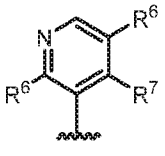
In some embodiments, the optionally substituted ring B is  .

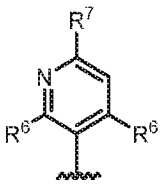
In some embodiments, the optionally substituted ring B is  .

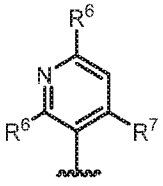
In some embodiments, the optionally substituted ring B is  .

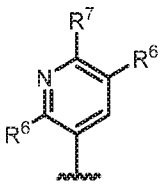
In some embodiments, the optionally substituted ring B is  .

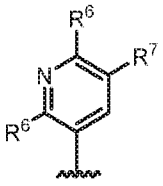
In some embodiments, the optionally substituted ring B is  .

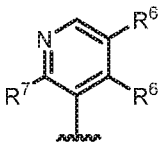
In some embodiments, the optionally substituted ring B is  .

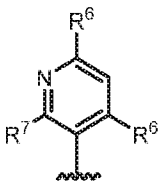
In some embodiments, the optionally substituted ring B is  .

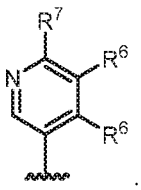
In some embodiments, the optionally substituted ring B is  .

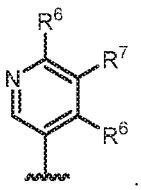
In some embodiments, the optionally substituted ring B is  .

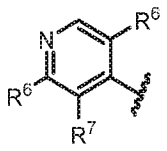
In some embodiments, the optionally substituted ring B is  .

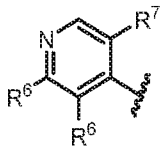
In some embodiments, the optionally substituted ring B is  .

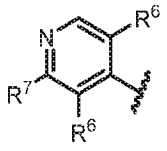
In some embodiments, the optionally substituted ring B is  .

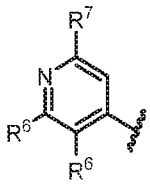
In some embodiments, the optionally substituted ring B is  .

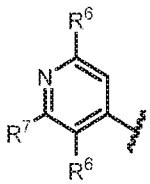
In some embodiments, the optionally substituted ring B is  .

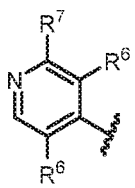
In some embodiments, the optionally substituted ring B is  .

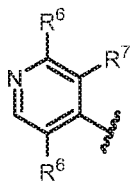
In some embodiments, the optionally substituted ring B is  .

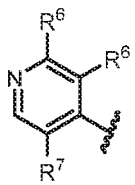
In some embodiments, the optionally substituted ring B is  .

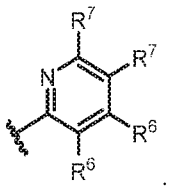
In some embodiments, the optionally substituted ring B is  .

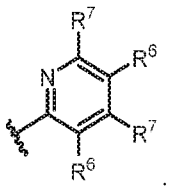
In some embodiments, the optionally substituted ring B is  .

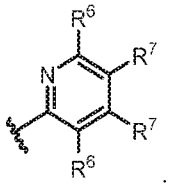
In some embodiments, the optionally substituted ring B is  .

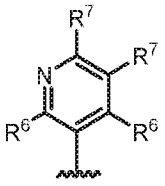
In some embodiments, the optionally substituted ring B is  .

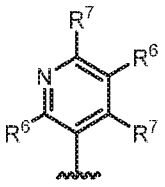
In some embodiments, the optionally substituted ring B is  .

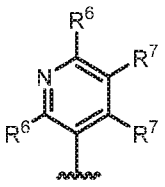
In some embodiments, the optionally substituted ring B is  .

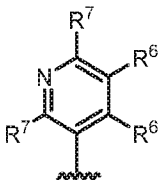
In some embodiments, the optionally substituted ring B is  .

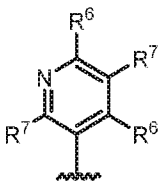
In some embodiments, the optionally substituted ring B is  .

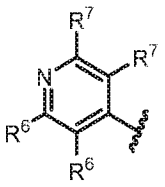
In some embodiments, the optionally substituted ring B is  .

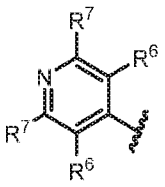
In some embodiments, the optionally substituted ring B is  .

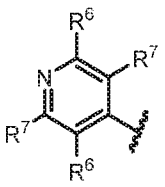
In some embodiments, the optionally substituted ring B is  .

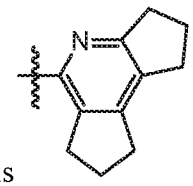
In some embodiments, the optionally substituted ring B is  .

In some embodiments, the optionally substituted ring B is  .

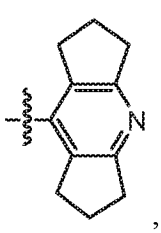
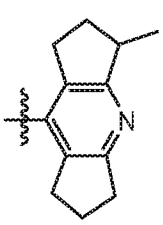
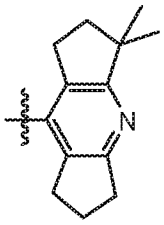
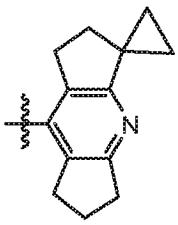
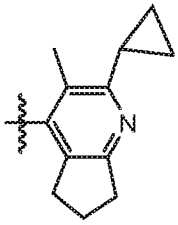
In some embodiments, the optionally substituted ring B is  .

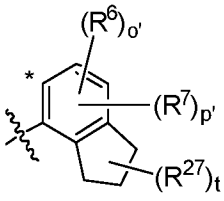
In some embodiments, the optionally substituted ring B is  .

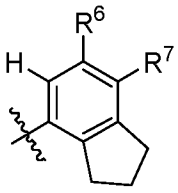
In some embodiments, the optionally substituted ring B is  .

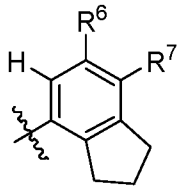
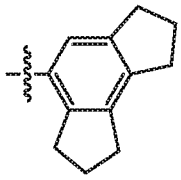
In some embodiments, the optionally substituted ring B is  .

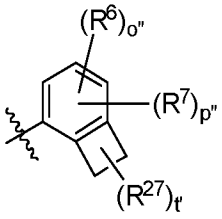
In some embodiments, the optionally substituted ring B is selected from the group consisting of:

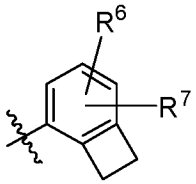
 ,  ,  ,  , and  .

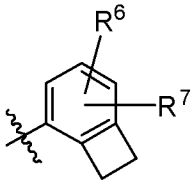
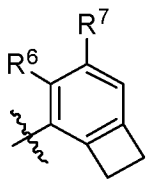
In some embodiments, the optionally substituted ring B is  .

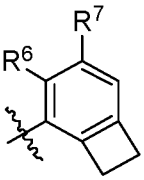
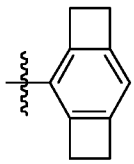
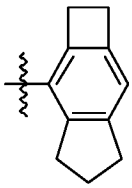
In certain embodiments of the foregoing, the optionally substituted ring B is  .

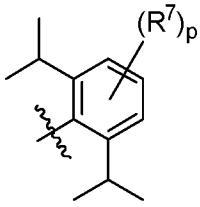
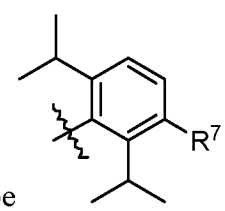
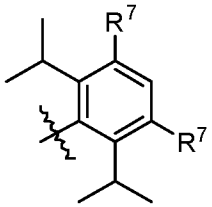
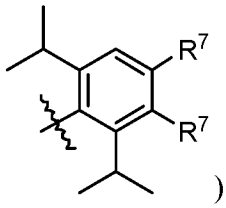
As a non-limiting example of the foregoing,  is  .

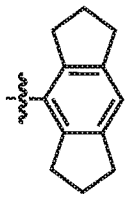
In some embodiments, the optionally substituted ring B is  .

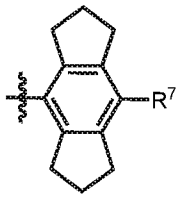
In certain embodiments of the foregoing, the optionally substituted ring B is  .

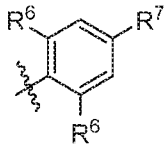
In certain embodiments of the foregoing,  is  .

As non-limiting examples of the foregoing,  is selected from  and  .

In some embodiments, the optionally substituted ring B is  (e.g., the optionally substituted ring B can be  ,  , or ).

In some embodiments (when X^1 is S), the optionally substituted ring B is  .

In some embodiments (when X^1 is S), the optionally substituted ring B is  .

In some embodiments, the substituted ring B is  .

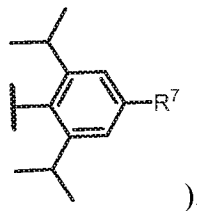
In certain of the foregoing embodiments, each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl, $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl, and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-

C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein each of the C_2-C_6 alkynyl and C_1-C_6 alkyl is optionally substituted with from 1-2 substituents each independently selected from oxo, C_1-C_6 alkoxy, C_3-C_{10} cycloalkyl, 3- to 7-membered heterocycloalkyl, and C_3-C_{10} cycloalkoxy.

In certain of the foregoing embodiments, one R^6 is C_1-C_6 alkyl (e.g., isopropyl).

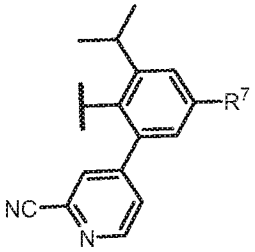
In certain of these embodiments, the other R^6 is C_1-C_6 alkyl. For example, each R^6 is isopropyl (i.e., the substituted ring B is 

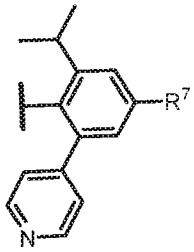
).

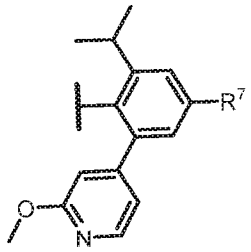
In certain other embodiments, one R^6 is C_1-C_6 alkyl; and the other R^6 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more substituents each independently selected from: hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl.

In certain of these embodiments, one R^6 is C_1-C_6 alkyl; and the other R^6 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl optionally substituted with a substituent selected from halo, CN, C_1-C_6 alkyl, and C_1-C_6 alkoxy. For example, R^6 is 5-6 (e.g., 6) membered heteroaryl (e.g., pyridinyl (e.g., pyridin-4-yl), pyrimidinyl, pyridazinyl, oxazolyl, or thiazolyl) optionally substituted with a substituent selected from halo, CN, C_1-C_6 alkyl, and C_1-C_6 alkoxy.

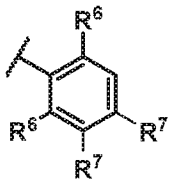
As a non-limiting example of the foregoing embodiments, substituted ring B is selected from:

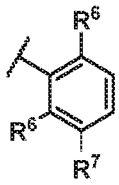


,


,


(e.g., R^7 is halo (e.g., fluoro)).

In some embodiments, B is 

or 

.

In certain of the foregoing embodiments, each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl, $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl, and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein each of the C_2-C_6 alkynyl and C_1-C_6 alkyl is optionally substituted with from 1-2 substituents each independently

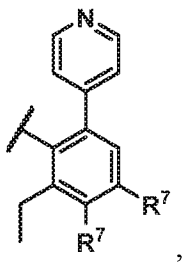
selected from oxo, C_1-C_6 alkoxy, C_3-C_{10} cycloalkyl, 3- to 7-membered heterocycloalkyl, and C_3-C_{10} cycloalkoxy.

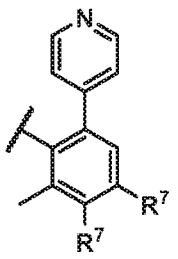
In certain of these embodiments, one R^6 is C_1-C_6 alkyl; and the other R^6 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more substituents each independently selected from: hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl.

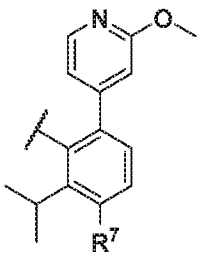
In certain of these embodiments, one R^6 is C_1-C_6 alkyl; and the other R^6 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl optionally substituted with a substituent selected from halo, CN, C_1-C_6 alkyl, and C_1-C_6 alkoxy. For example, R^6 is 5-6 (e.g., 6) membered heteroaryl (e.g., pyridinyl (e.g., pyridin-4-yl), pyrimidinyl, pyridazinyl, oxazolyl, or thiazolyl) optionally substituted with a substituent selected from hydroxyl, halo, CN, C_1-C_6 alkyl, and C_1-C_6 alkoxy.

In certain of the foregoing embodiments, each R^7 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, or cyano,

As a non-limiting example of the foregoing embodiments, substituted ring B is:

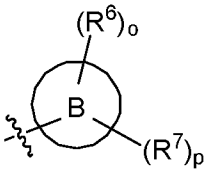


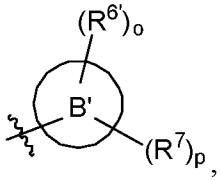
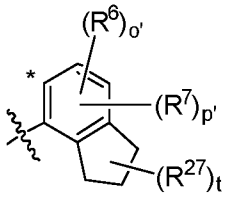
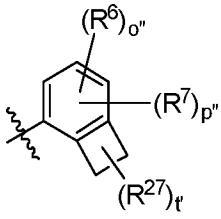
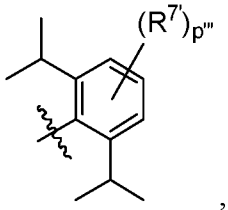
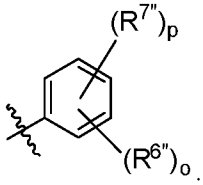
,


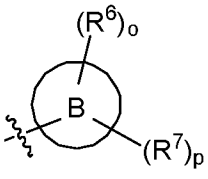
or


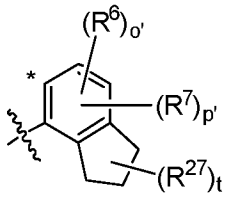
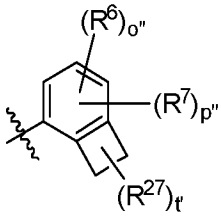
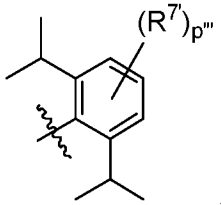
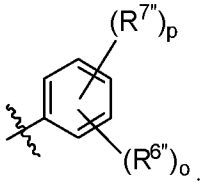
(e.g., each R^7 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, or cyano).

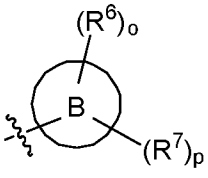
The Optionally Substituted Ring B when Formula AA is Formula AA-1

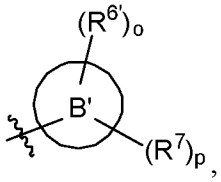
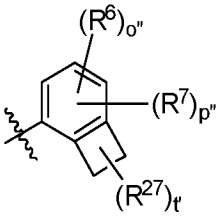
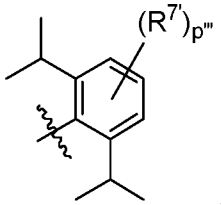
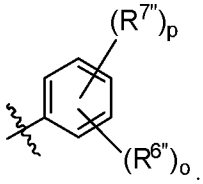
In some embodiments,  is selected from the group consisting of:

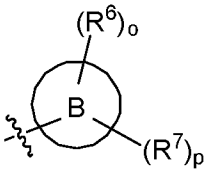
 ,  ,  ,  , and  .

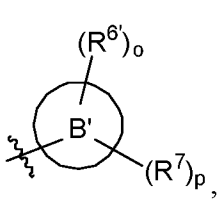
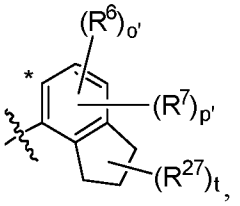
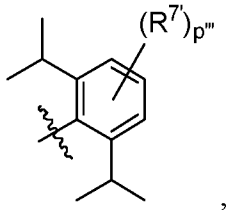
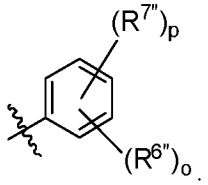
In some embodiments,  is selected from the group consisting of:

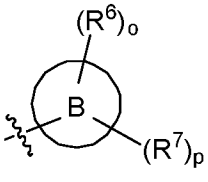
 ,  ,  , and  .

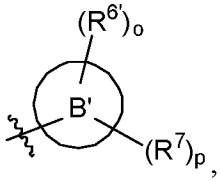
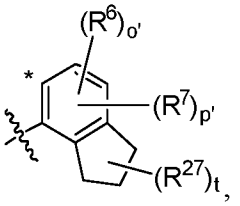
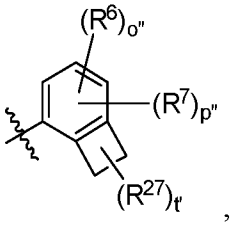
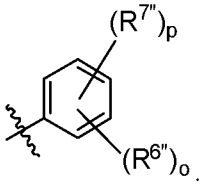
In some embodiments,  is selected from the group consisting of:

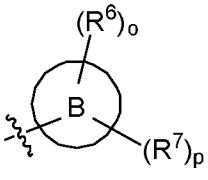
 ,  ,  , and  .

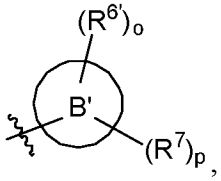
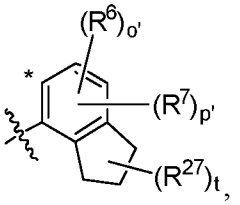
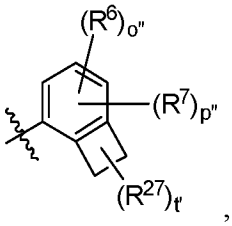
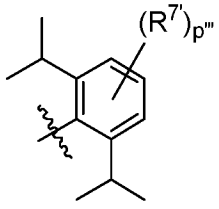
In some embodiments,  is selected from the group consisting of:

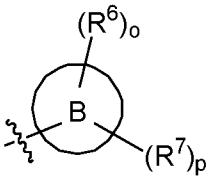
 ,  ,  , and  .

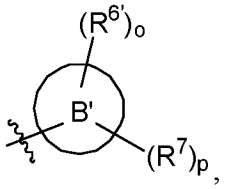
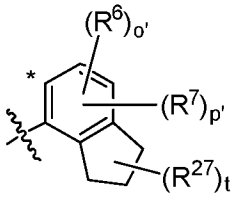
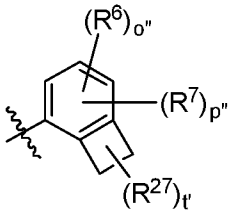
In some embodiments,  is selected from the group consisting of:

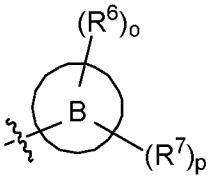
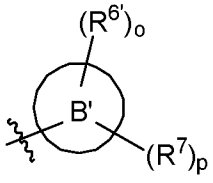
 ,  ,  , and  .

In some embodiments,  is selected from the group consisting of:

 ,  ,  , and  .

In some embodiments,  is selected from the group consisting of:

 ,  , and  .

In some embodiments,  is  .

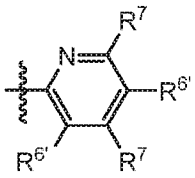
In some embodiments, B' is a 5-6-membered heteroaryl, wherein when the 5-6 membered heteroaryl contains two or three nitrogen ring members, the 5-6-membered heteroaryl additionally contains one or more non-nitrogen heteroatom or heteroatomic group ring members; 4-pyrimidinyl; 5-pyrimidinyl; 6-pyrimidinyl; pyridazinyl; pyrazinyl; 1,2,3-triazinyl; 1,2,4-triazinyl; tetrazinyl; imidazolyl; pyrazolyl; 1,2,3-triazolyl; tetrazolyl; or C_7-C_{10} aryl

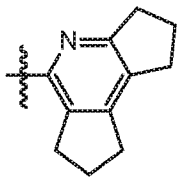
In some embodiments, B' is a 5-6-membered heteroaryl, wherein when the 5-6 membered heteroaryl contains two or three nitrogen ring members, the 5-6-membered heteroaryl additionally contains one or more non-nitrogen heteroatom or heteroatomic group ring members; 5-pyrimidinyl; 6-pyrimidinyl; pyridazinyl; pyrazinyl; 1,2,3-triazinyl; 1,2,4-triazinyl; tetrazinyl; imidazolyl; pyrazolyl; 1,2,3-triazolyl; tetrazolyl; or C_7-C_{10} aryl.

In some embodiments, B' is a 5-6-membered heteroaryl, wherein when the 5-6 membered heteroaryl contains two or three nitrogen ring members, the 5-6-membered heteroaryl additionally contains one or more non-nitrogen heteroatom or heteroatomic group ring members; 4-pyrimidinyl; 5-pyrimidinyl; 6-pyrimidinyl; pyridazinyl; pyrazinyl; 1,2,3-triazinyl; 1,2,4-triazinyl; tetrazinyl; imidazolyl; pyrazolyl; 1,2,3-triazolyl; tetrazolyl; or C_7-C_{10} aryl; and wherein at least one $R^{6'}$ is *ortho* to the bond connecting the B' ring to the NH(CO) group of Formula AA.

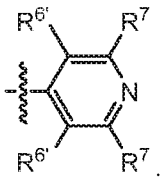
In some embodiments, B' is a 5-6-membered heteroaryl, wherein when the 5-6 membered heteroaryl contains two or three nitrogen ring members, the 5-6-membered heteroaryl additionally contains one or more non-nitrogen heteroatom or heteroatomic group ring members. In certain embodiments of foregoing, B' is pyridyl (e.g., 2-pyridyl or 4-pyridyl).

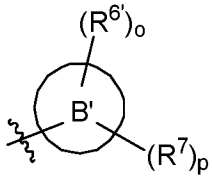
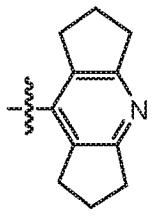
In some embodiments, B' is 2-pyridyl.

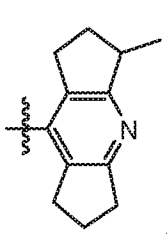
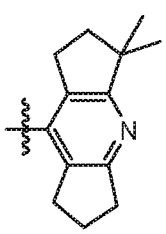
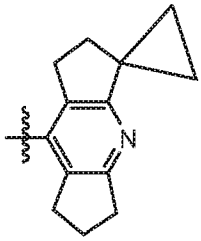
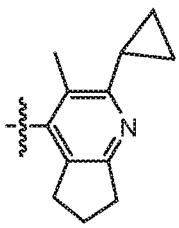
In certain embodiments, the optionally substituted ring B' is  .

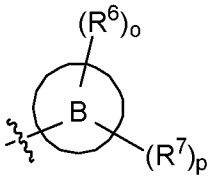
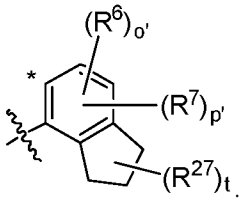
As a non-limiting example of the foregoing, the optionally substituted ring B' is  .

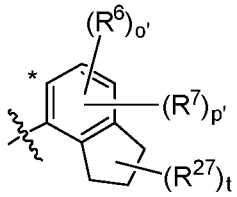
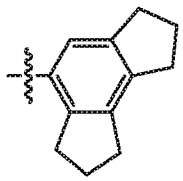
In some embodiments, B' is 4-pyridyl.

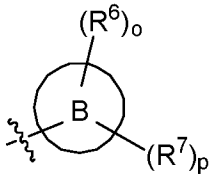
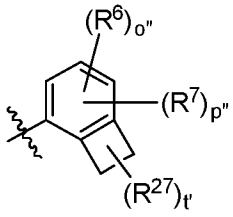
In certain embodiments, the optionally substituted ring B' is  .

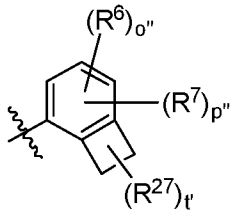
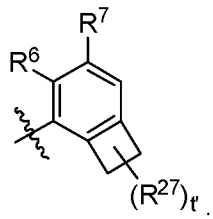
In certain embodiments,  is selected from the group consisting of:  ,

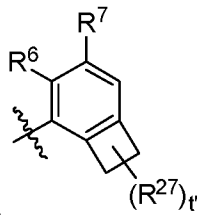
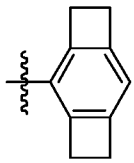
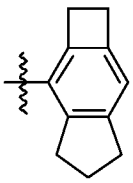
 ,  ,  , and  .

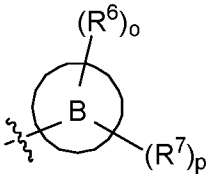
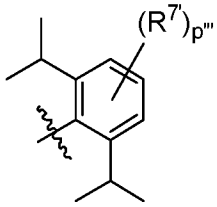
In some embodiment,  is  .

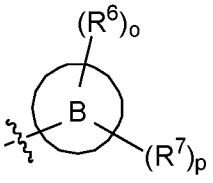
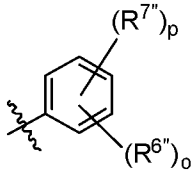
In certain embodiments,  is  .

In some embodiments,  is  .

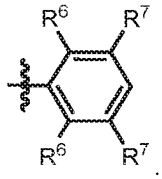
In certain embodiments,  is  .

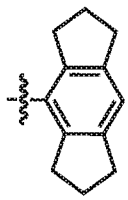
As non-limiting examples of the foregoing,  is selected from  and  .

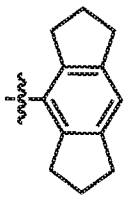
In some embodiments,  is  .

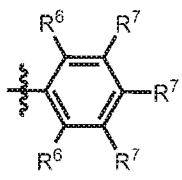
In some embodiments,  is  .

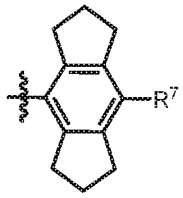
The Optionally Substituted Ring B when Formula AA is Formula AA-2

In some embodiments, the optionally substituted ring B is  .

In some embodiments, the optionally substituted ring B is  .

In some embodiments, the optionally substituted ring B is other than  .

In some embodiments, the optionally substituted ring B is  .

In some embodiments, the optionally substituted ring B is 

.

The groups R^6, $R^{6'}$, R^7, and $R^{7'}$

The Groups R^6 and R^7

In some embodiments, at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

In some embodiments, R^6 and R^7, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

In some embodiments, R^6 and R^7, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic rings or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups

independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings optionally independently substituted with one or more R^{27}.

In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic ring or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings optionally independently substituted with one or more R^{27}.

The Groups R^6 and R^7 when Formula AA is Formula AA-1 or Formula AA-2

In some embodiments, R^6 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with

one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25}.

In some embodiments, R^7 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25}.

In some embodiments, at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

In some embodiments, R^6 and R^7, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

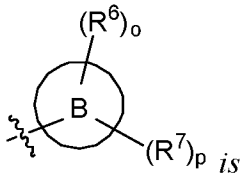
In some embodiments, R^6 and R^7, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

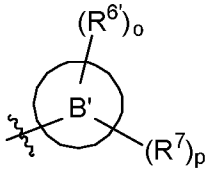
In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic rings or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings optionally independently substituted with one or more R^{27}.

In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic ring or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings optionally independently substituted with one or more R^{27}.

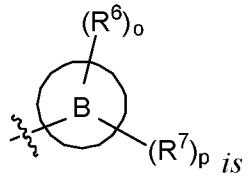
The groups $R^{6'}$ and R^7 when Formula AA is Formula AA-1 and  *is*

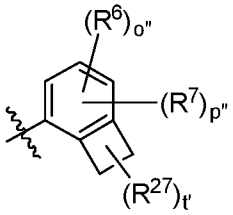


In some embodiments, at least one pair of $R^{6'}$ and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 (e.g, C_4-C_5 or C_7-C_8) cycloalkyl ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

In some embodiments, two pairs of $R^{6'}$ and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form a C_4-C_8 cycloalkyl ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

In some embodiments, at least one $R^{6'}$ is *ortho* to the bond connecting the B' ring to the NH(CO) group of Formula AA.

The groups R^6 and R^7 when Formula AA is Formula AA-1 and  *is*



In some embodiments, R^6 and R^7, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

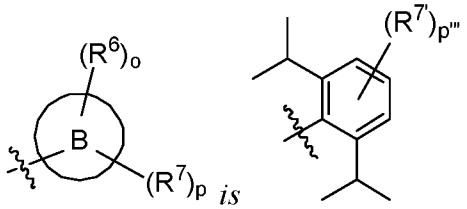
The groups R^6 and R^7 when Formula AA is Formula AA-2

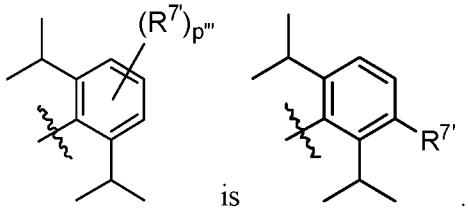
In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic rings or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

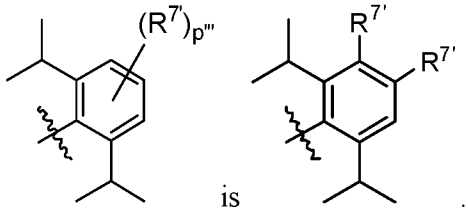
In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings optionally independently substituted with one or more R^{27}.

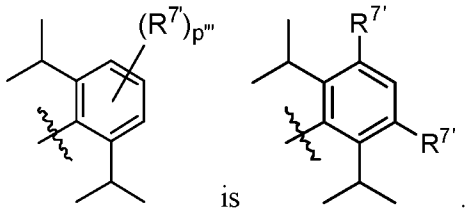
In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic ring or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

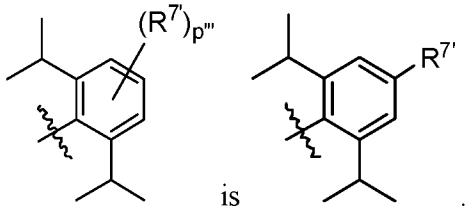
In some embodiments, two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings optionally independently substituted with one or more R^{27}.

The group $R^{7'}$ when Formula AA is Formula AA-1 and  *is* .

In some embodiments,  is .

In some embodiments,  is .

In some embodiments,  is .

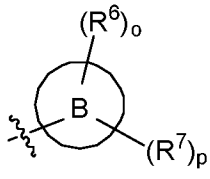
In some embodiments,  is .

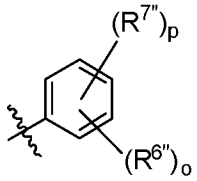
In certain embodiments of the foregoing, $R^{7'}$, at each occurrence, is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, I, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25},

CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25}.

In certain embodiments of the foregoing, $R^{7'}$, at each occurrence, is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, I, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}.

In certain embodiments of the foregoing, $R^{7'}$, at each occurrence, is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, I, C_1-C_6 haloalkoxy, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, C_3-C_{10} cycloalkyl, and 3- to 10-membered heterocycloalkyl.

The groups $R^{6''}$ and $R^{7''}$ when Formula AA is Formula AA-1 and  *is*



In some embodiments, each occurrence of $R^{6''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25}.

In some embodiments, each occurrence of $R^{7''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl)

optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25}.

In some embodiments, each occurrence of $R^{6''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}.

In some embodiments, each occurrence of $R^{7''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}.

In some embodiments, each occurrence of $R^{6''}$ is independently selected from C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_2-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}.

In some embodiments, each occurrence of $R^{7''}$ is independently selected from C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_2-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}.

In some embodiments, at least one $R^{6''}$ is *ortho* to the bond connecting the B ring to the NH(CO) group of Formula AA.

The group R^{10}

In some embodiments, R^{10} is C_1-C_6 alkyl.

In some embodiments, R^{10} is methyl.
In some embodiments, R^{10} is ethyl.

The groups R^8 and R^9

In some embodiments, each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, $(C{=}NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to.

In some embodiments, each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, $(C{=}NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to.

In some embodiments, each of R^8 and R^9 at each occurrence is hydrogen,
In some embodiments, each R^8 at each occurrence is hydrogen and each R^9 at each occurrence is C_1-C_6 alkyl.
In some embodiments, each R^8 at each occurrence is hydrogen and each R^9 at each occurrence is methyl.
In some embodiments, each R^8 at each occurrence is hydrogen and each R^9 at each occurrence is ethyl.
In some embodiments, each of R^8 and R^9 at each occurrence is methyl.
In some embodiments, each of R^8 and R^9 at each occurrence is ethyl.
In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 3-membered ring.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 4-membered ring.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 5-membered ring.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 6-membered ring optionally containing one or more oxygen atoms in addition to the nitrogen they are attached to.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 6-membered ring optionally containing one or more nitrogen atoms in addition to the nitrogen they are attached to.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 7-membered ring.

In some embodiments, one of R^8 and R^9 is $C(O)R^{13}$.

In some embodiments, one of R^8 and R^9 is $C(O)_2R^{13}$.

In certain embodiments of foregoing (when one of R^8 and R^9 is $C(O)R^{13}$ or $C(O)_2R^{13}$), the other one of R^8 and R^9 is selected from H and C_{1-6} alkyl.

The group R^{13}

In some embodiments, R^{13} is C_1-C_6 alkyl.

In some embodiments, R^{13} is methyl.

In some embodiments, R^{13} is ethyl.

In some embodiments, R^{13} is C_6-C_{10} aryl.

In some embodiments, R^{13} is phenyl.

In some embodiments, R^{13} is 5- to 10-membered heteroaryl.

The groups R^{11} and R^{12}

In some embodiments, each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl.

In some embodiments, each of R^{11} and R^{12} at each occurrence is hydrogen,

In some embodiments, each R^{11} at each occurrence is hydrogen; and each R^{12} at each occurrence is C_1-C_6 alkyl.

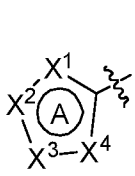
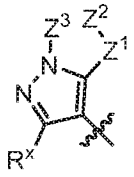
In some embodiments, each R^{11} at each occurrence is hydrogen; and each R^{12} at each occurrence is methyl.

In some embodiments, each R^{11} at each occurrence is hydrogen; and each R^{12} at each occurrence is ethyl.

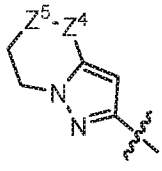
In some embodiments, each of R^{11} and R^{12} at each occurrence is methyl.

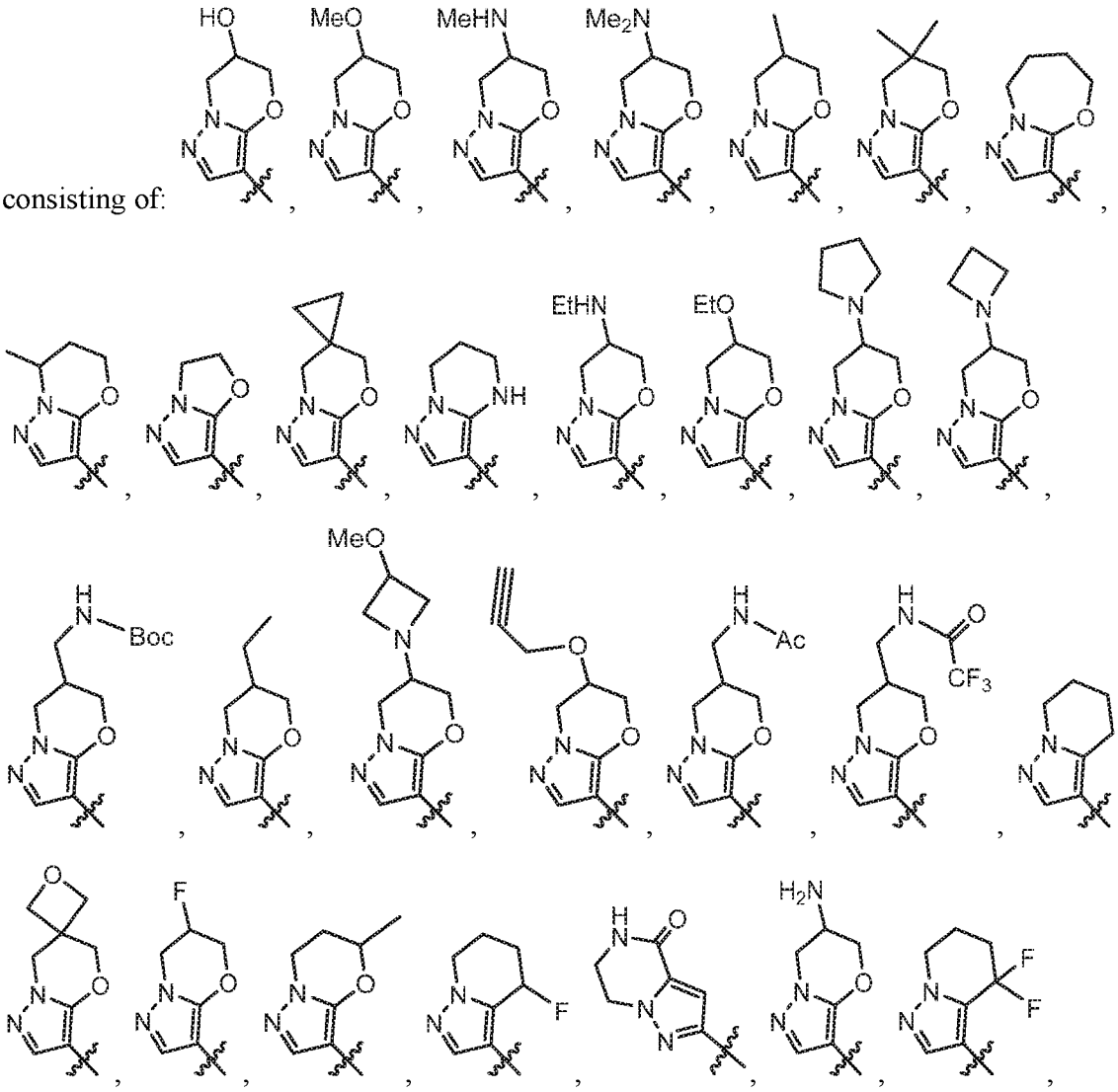
In some embodiments, each of R^{11} and R^{12} at each occurrence is ethyl.

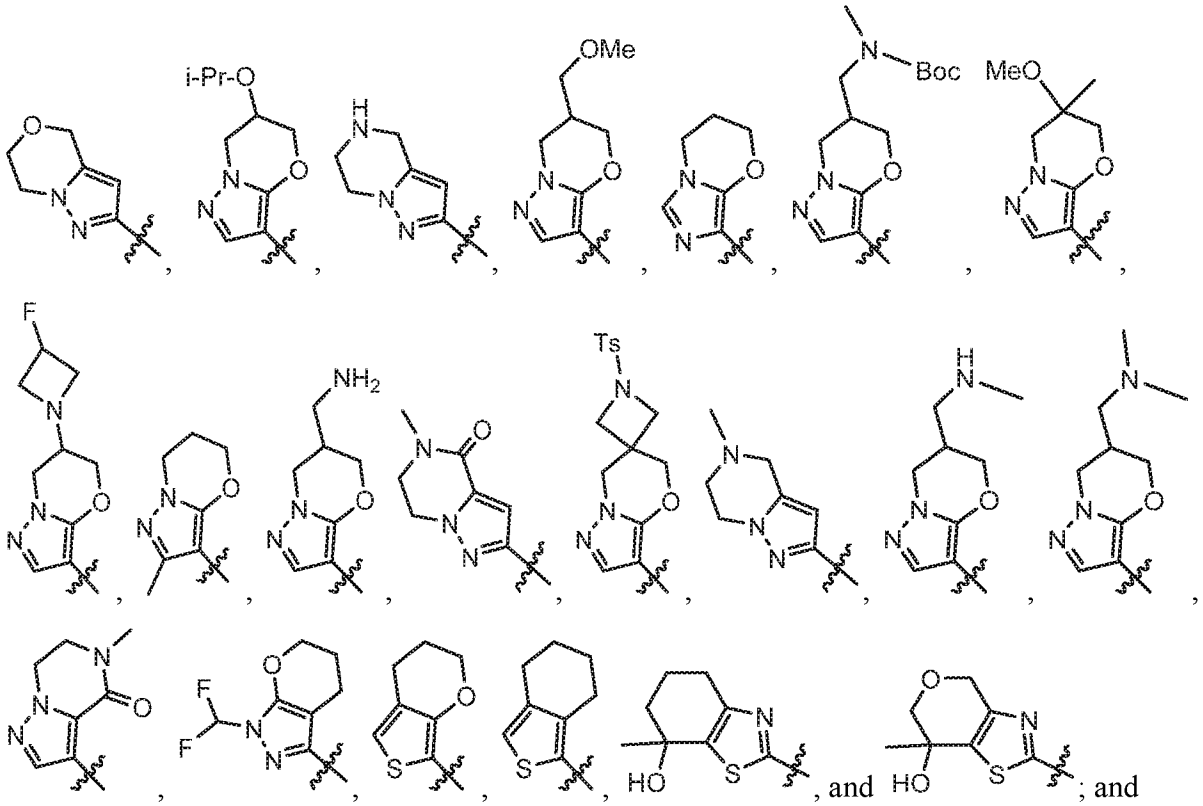
Non-Limiting Combinations

In some embodiments,  is  , wherein R^x is selected from the group consisting of H and C_1-C_6 alkyl (e.g., methyl); Z^1 is selected from the group consisting of O, NH, and -CH_2- optionally substituted with 1-2 R^{20}; Z^2 is selected from the group consisting of NH and -CH_2- optionally substituted with 1-2 R^{20}; Z^3 is selected from the group consisting of -CH_2- optionally substituted with 1-2 R^{20}, -CH_2CH_2- optionally substituted with 1-2 R^{20}, and -$CH_2CH_2CH_2$- optionally substituted with 1-2 R^{20}; R^{20} is selected from the group consisting of hydroxy, halo (e.g., fluoro), oxo, C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}, C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}, NR^8R^9, 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}, or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom optionally substituted with $OS(O)_2Ph$; R^{21} is selected from the group consisting of halo (e.g., fluoro), NR^8R^9, C_2-C_6 alkynyl (e.g., ethynyl), and C_1-C_6 alkoxy (e.g., methoxy); R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl (e.g., methyl or ethyl), COR^{13}, and

CO_2R^{13}; R^{13} is selected from the group consisting of: C_1-C_6 alkyl (e.g., methyl or *t*-butyl) and C_1-C_6 haloalkyl (e.g., trifluoromethyl).

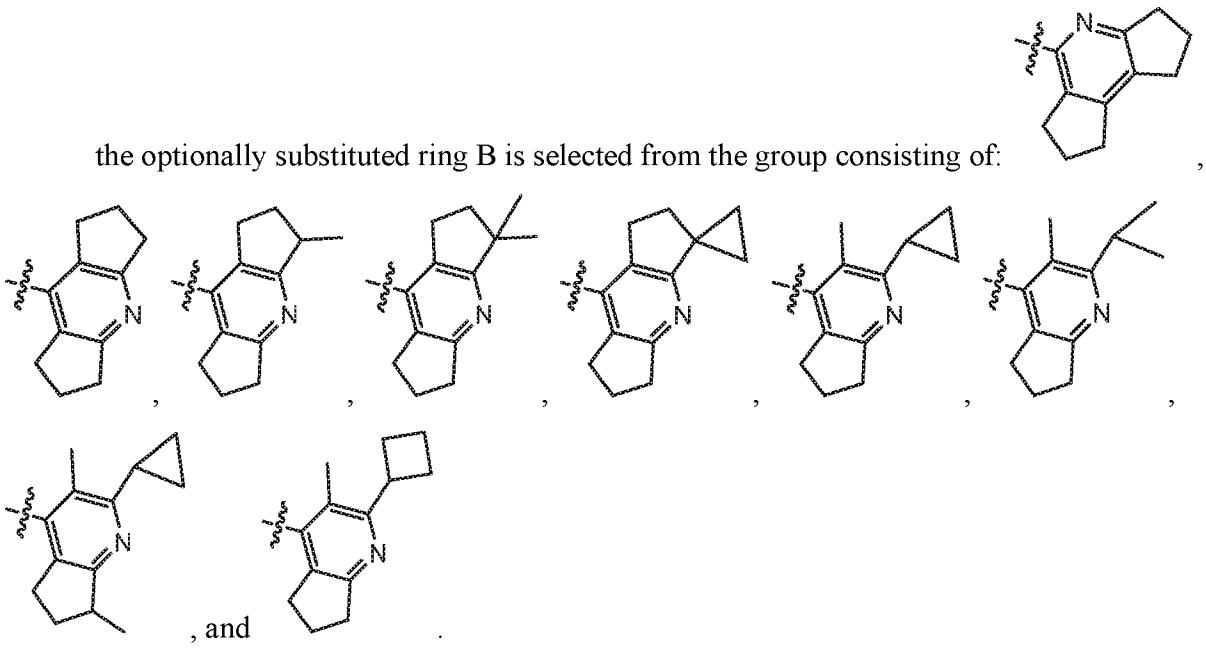
In some embodiments, ring A is  , wherein Z^4 is selected from the group consisting of –CH_2-, –C(O)-, and NH; Z^5 is selected from the group consisting of O, NH, N-CH_3, and –CH_2-.

In some embodiments, the optionally substituted ring A is selected from the group consisting of: 



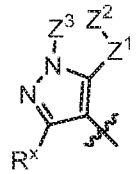
; and

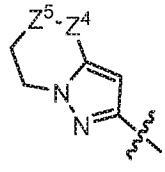
the optionally substituted ring B is selected from the group consisting of:

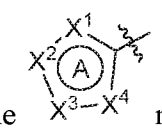
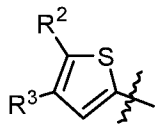


, and

Non-limiting combinations when Formula AA is Formula AA-1

In some embodiments, A is  , wherein R^x is selected from the group consisting of H and C_1-C_6 alkyl (e.g., methyl); Z^1 is selected from the group consisting of O, NH, and -CH_2- optionally substituted with 1-2 R^{20}; Z^2 is selected from the group consisting of NH and -CH_2- optionally substituted with 1-2 R^{20}; Z^3 is selected from the group consisting of -CH_2- optionally substituted with 1-2 R^{20}, -CH_2CH_2- optionally substituted with 1-2 R^{20}, and -$CH_2CH_2CH_2$- optionally substituted with 1-2 R^{20}; R^{20} is selected from the group consisting of hydroxy, halo (e.g., fluoro), oxo, C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}, C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}, NR^8R^9, 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}, or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom optionally substituted with $OS(O)_2Ph$; R^{21} is selected from the group consisting of halo (e.g., fluoro), NR^8R^9, C_2-C_6 alkynyl (e.g., ethynyl), and C_1-C_6 alkoxy (e.g., methoxy); R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl (e.g., methyl or ethyl), COR^{13}, and CO_2R^{13}; R^{13} is selected from the group consisting of: C_1-C_6 alkyl (e.g., methyl or *t*-butyl) and C_1-C_6 haloalkyl (e.g., trifluoromethyl).

In some embodiments, A is  , wherein Z^4 is selected from the group consisting of –CH_2-, –C(O)-, and NH; Z^5 is selected from the group consisting of O, NH, N-CH_3, and –CH_2-.

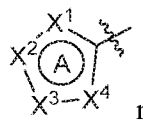
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

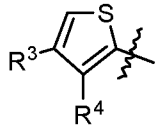
(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments the 

moiety is 

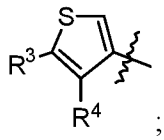
; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

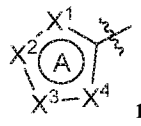
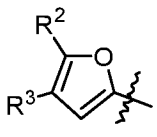
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

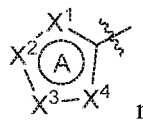
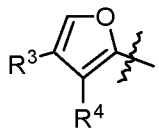
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

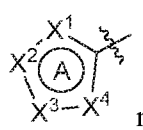
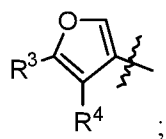
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

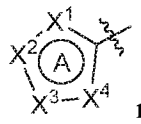
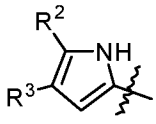
(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S,

wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

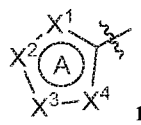
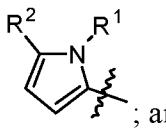
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

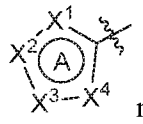
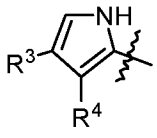
In some embodiments the  moiety is  ; and R^1 and R^2 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

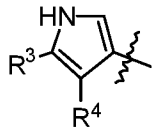
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

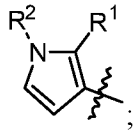
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments the  moiety is  ; and R^1 and R^2 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

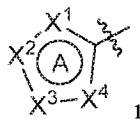
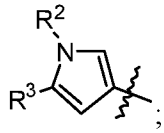
(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the

heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

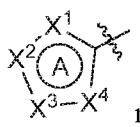
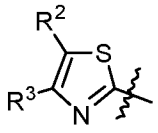
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

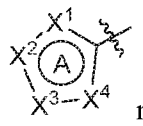
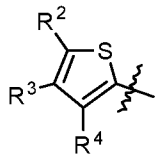
(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S,

wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

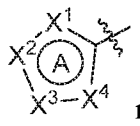
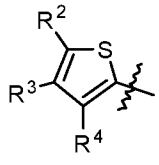
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

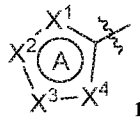
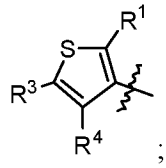
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

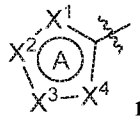
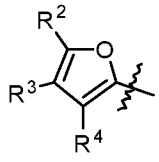
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

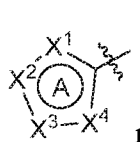
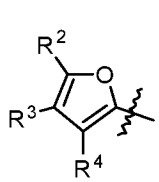
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

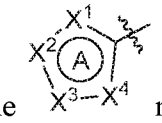
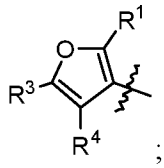
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

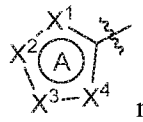
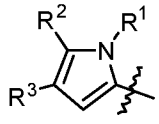
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

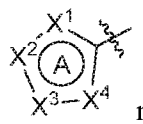
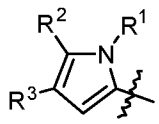
In some embodiments the  moiety is  ; and R^1 and R^2 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

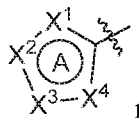
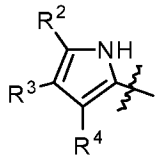
(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the

heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

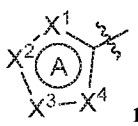
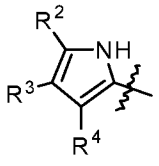
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

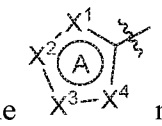
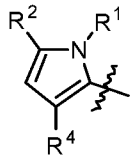
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

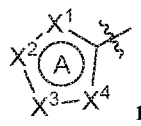
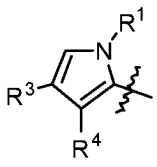
In some embodiments the  moiety is  ; and R^1 and R^2 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

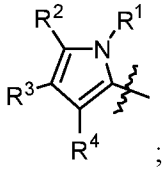
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments the  moiety is  ; and R^1 and R^2 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

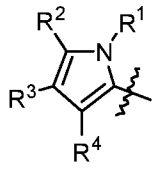
(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the

heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

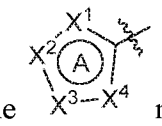
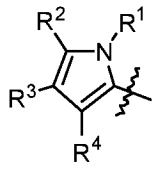
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

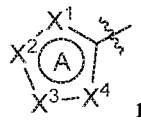
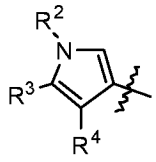
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

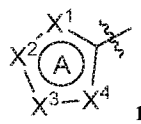
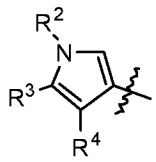
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

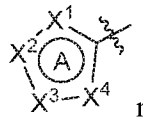
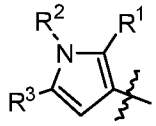
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

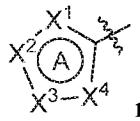
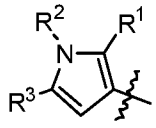
In some embodiments the  moiety is  ; and R^1 and R^2 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

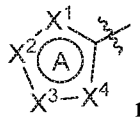
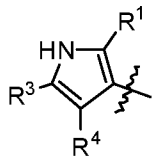
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

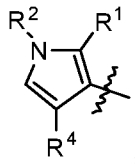
(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the

heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

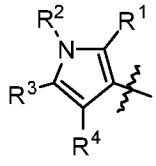
In some embodiments the  moiety is  ; and R^1 and R^2 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

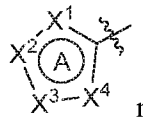
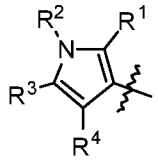
In some embodiments the  moiety is  ; and R^1 and R^2 and taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

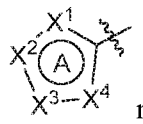
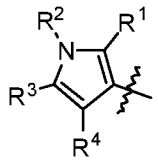
In some embodiments the  moiety is  ; and R^2 and R^3 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

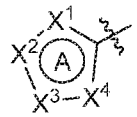
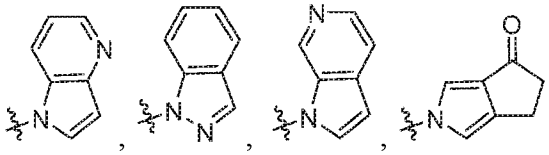
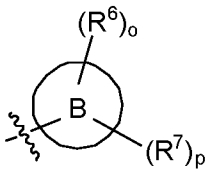
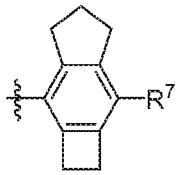
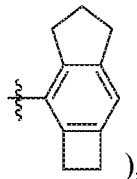
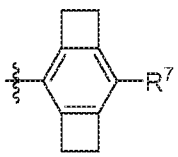
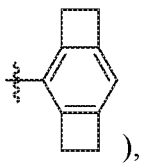
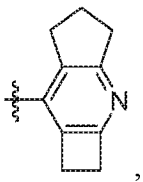
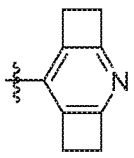
In some embodiments the  moiety is  ; and R^3 and R^4 taken together with the atoms connecting them independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

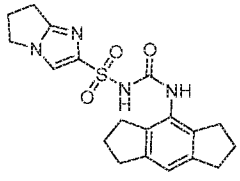
(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

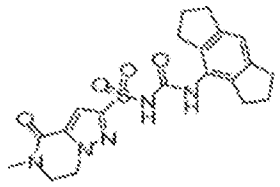
(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

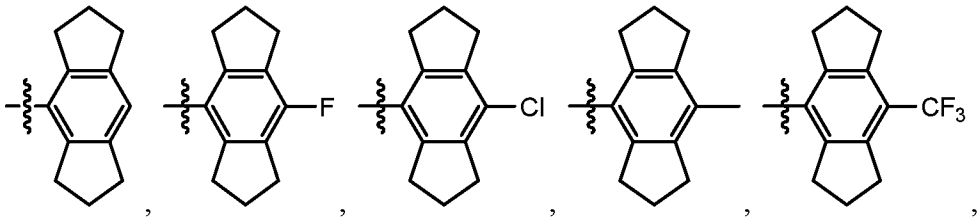
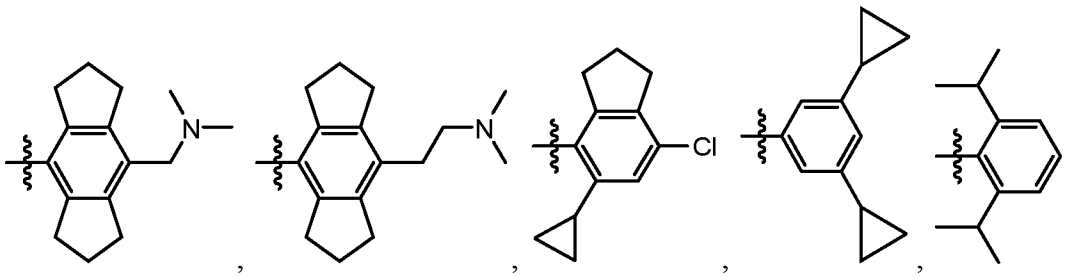
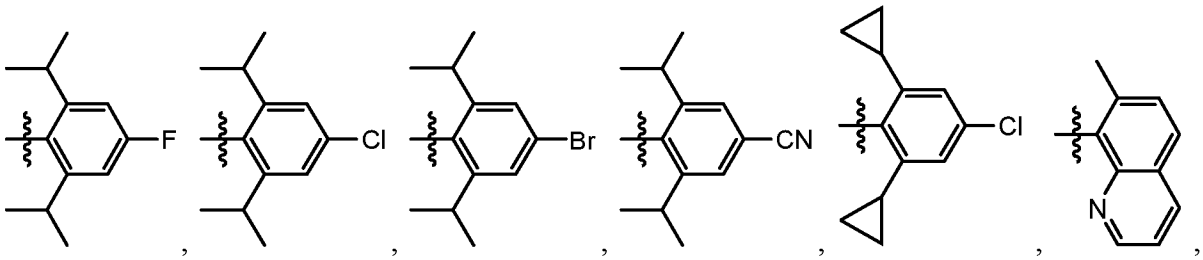
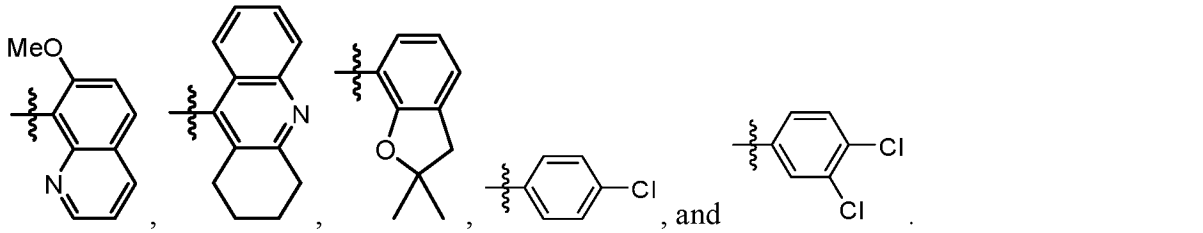
In some embodiments of the compound of Formula AB,  is selected from  ; and  is selected from  (e.g., ),  (e.g., ),  , and  .

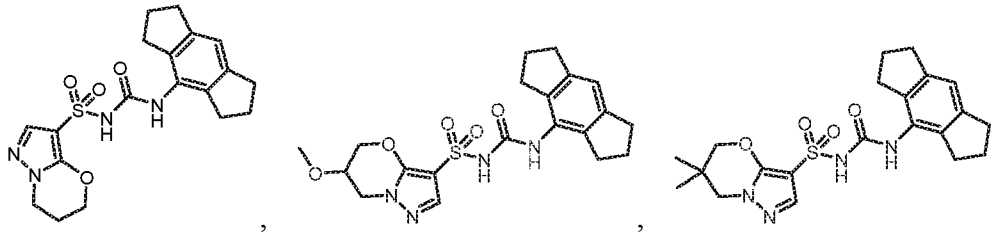
Additional Features of the Embodiments Herein

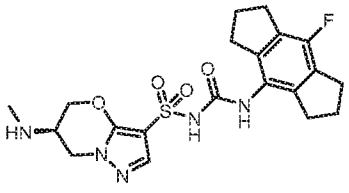
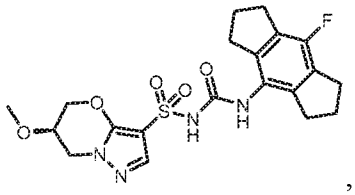
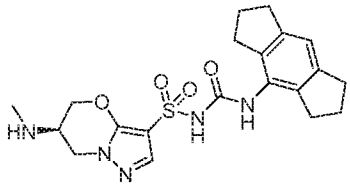
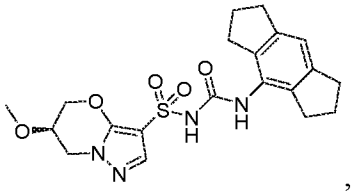
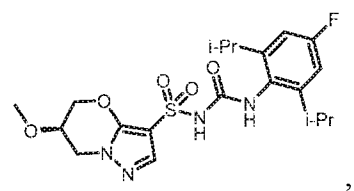
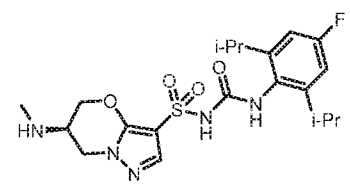
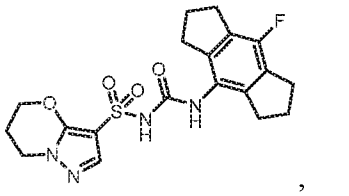
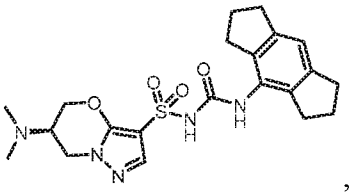
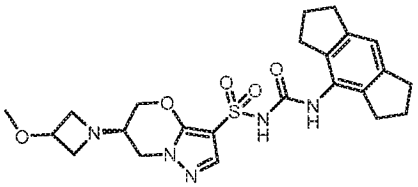
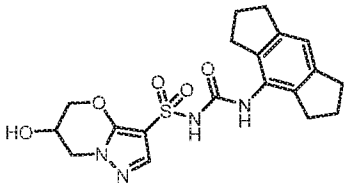
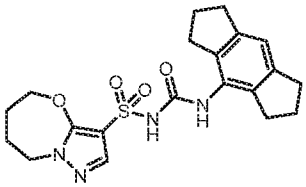
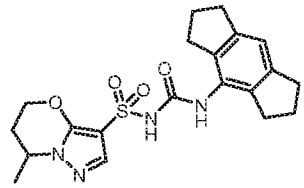
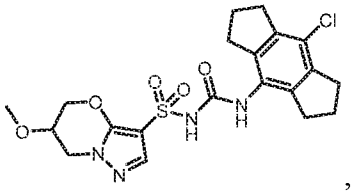
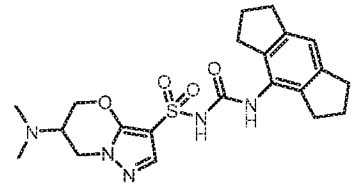
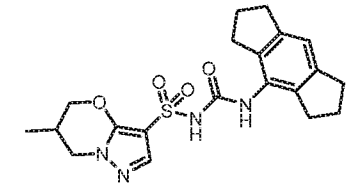
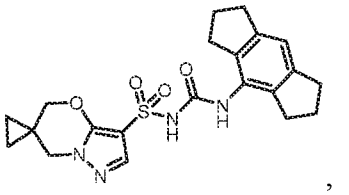
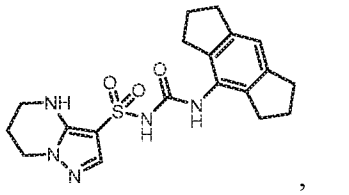
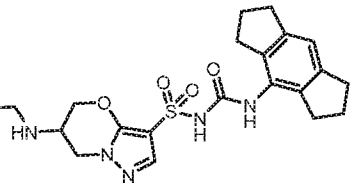
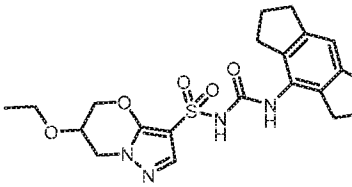
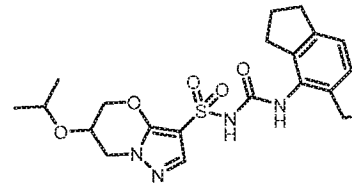
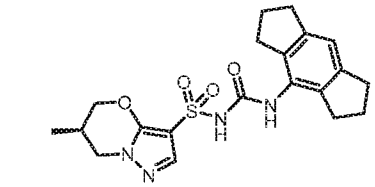
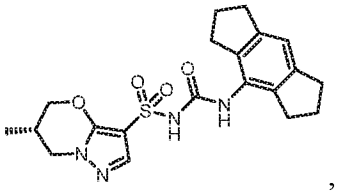
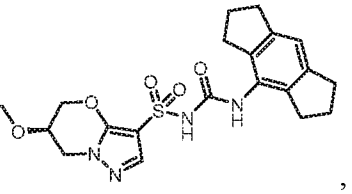
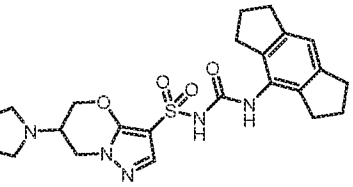
In some embodiments, the compound of Formula AA is not  .

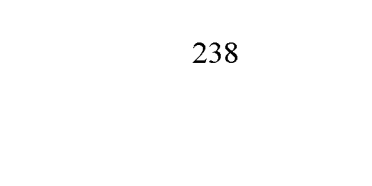
In some embodiments, the compound of Formula AA is not  .

In some embodiments, the optionally substituted ring B in the compound of Formula AA is not selected from the group consisting of:

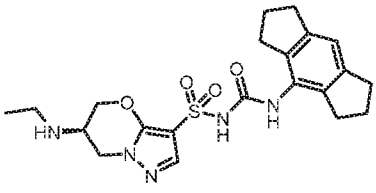
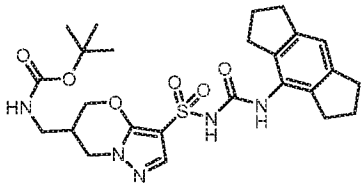
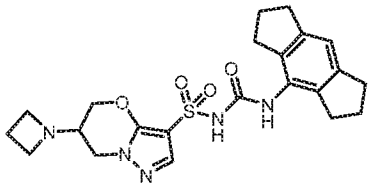
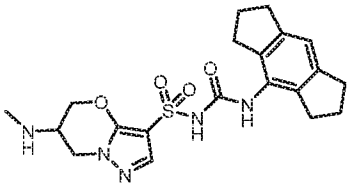
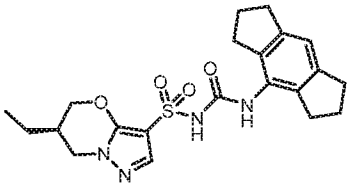
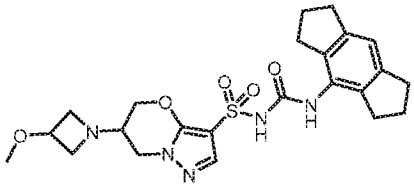
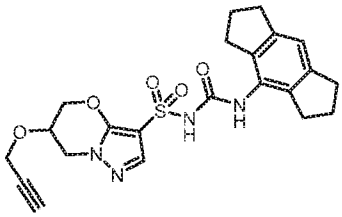
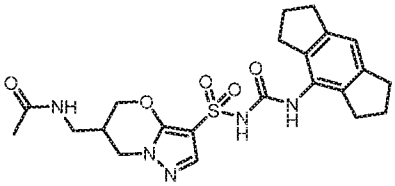
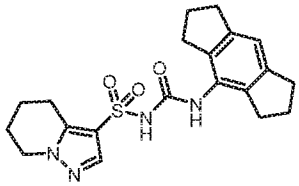
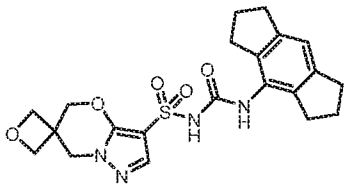
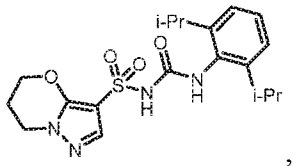
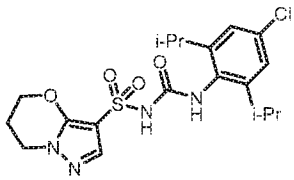
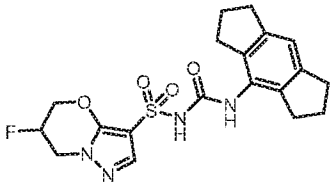
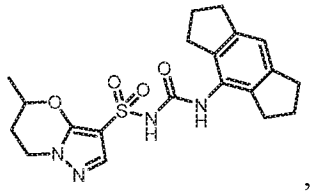
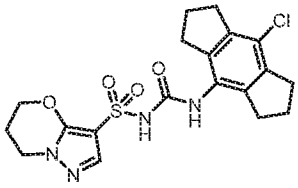
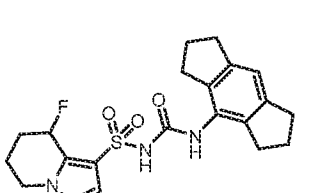
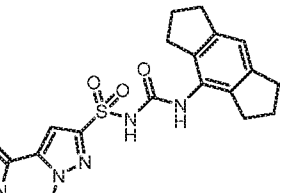
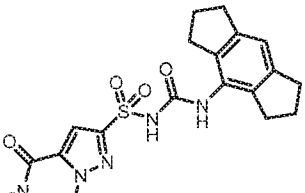
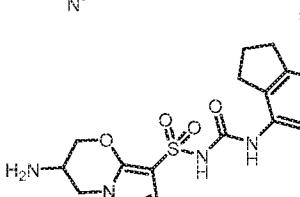
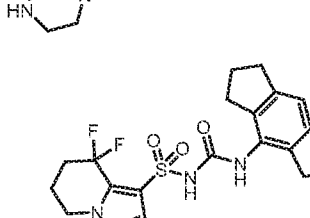
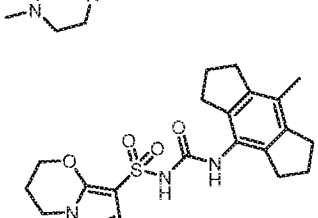
 ,
 ,
 ,
 , and
.

In some embodiments, the compound of Formula AA is not a compound selected from the group consisting of:  .


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

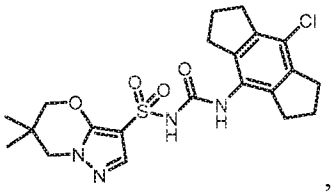
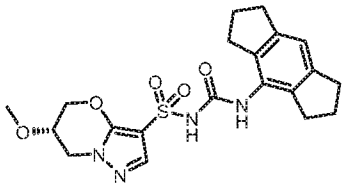
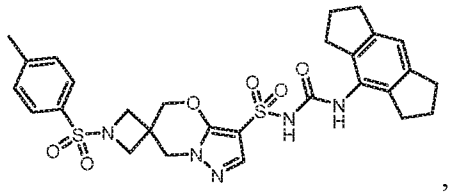
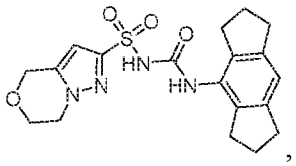
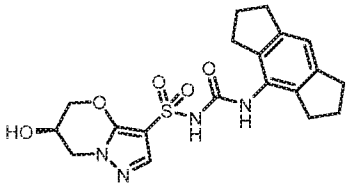
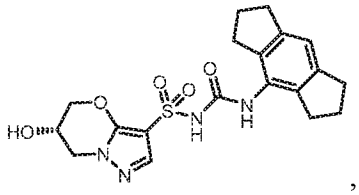
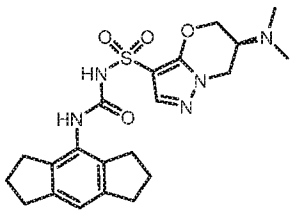
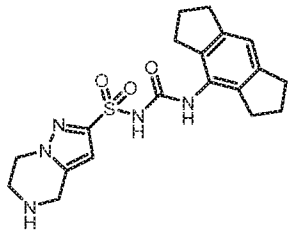
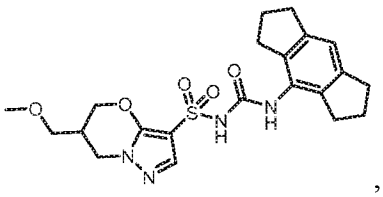
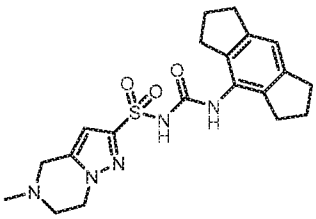
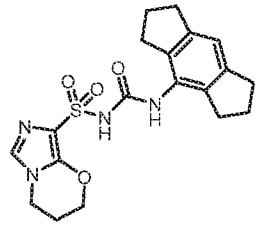
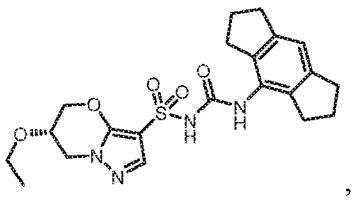
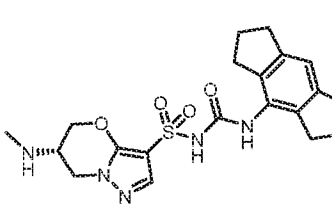
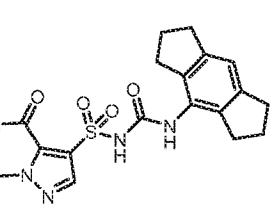
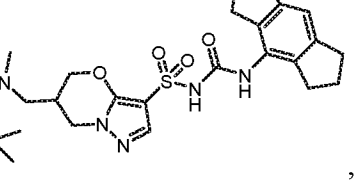
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

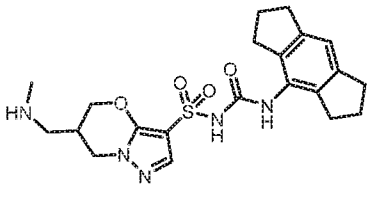
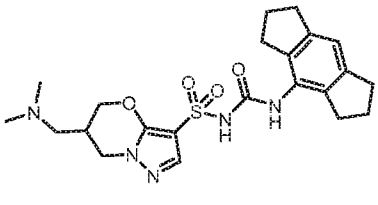
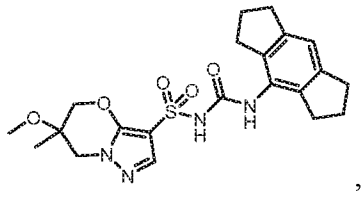
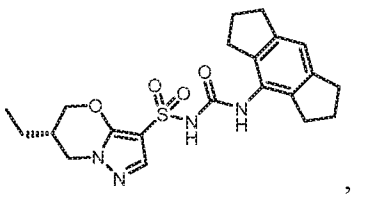
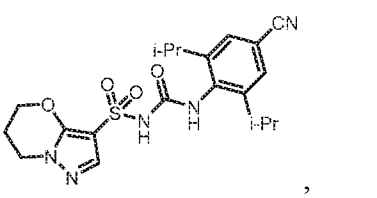
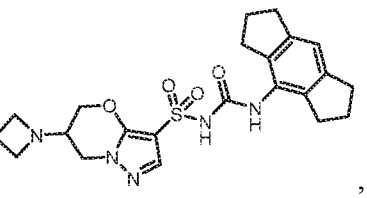
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

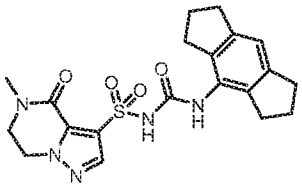
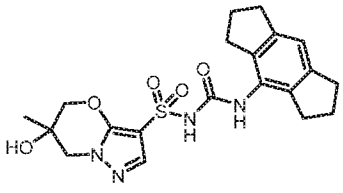
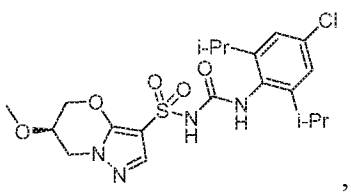
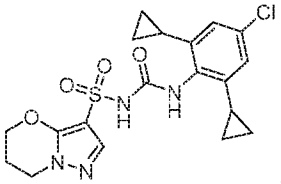
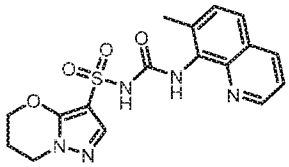
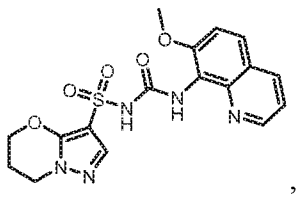
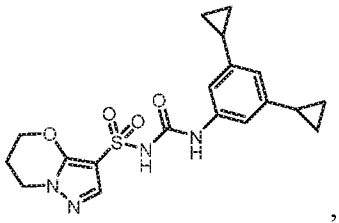
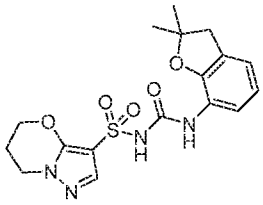
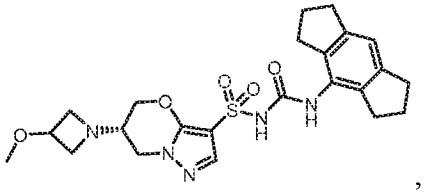
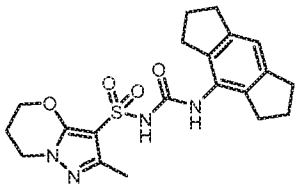
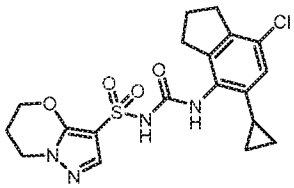
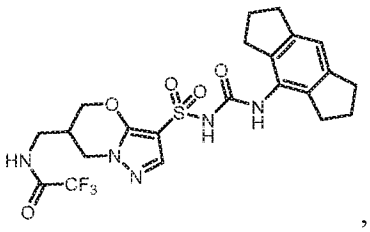
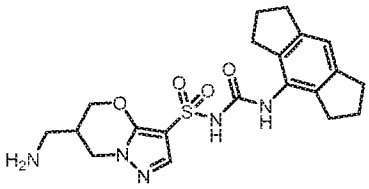
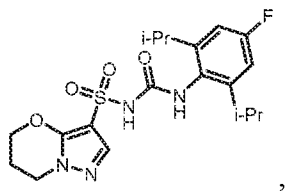
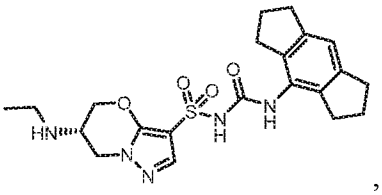
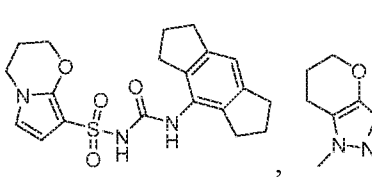
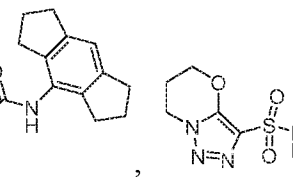
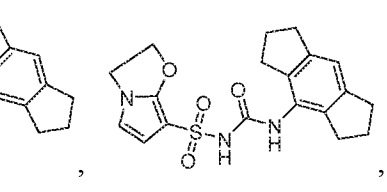
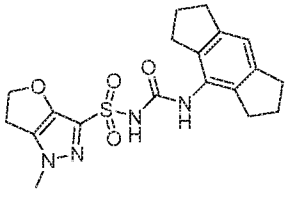
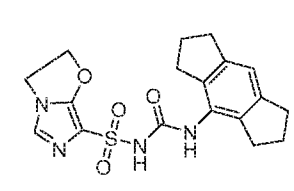
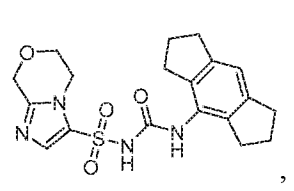
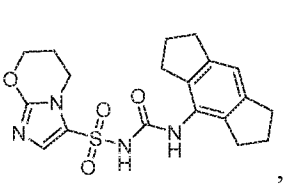
,

,

,

,

,

,

,

,

,

,

,

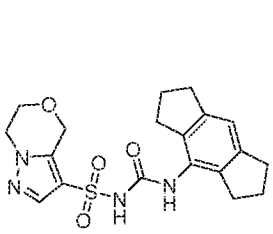
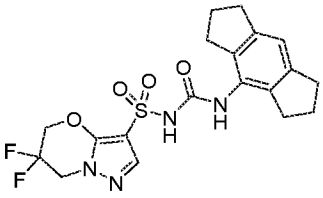
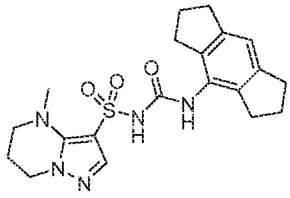
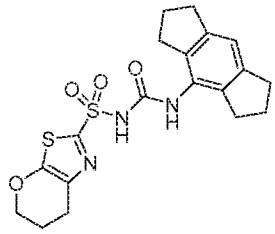
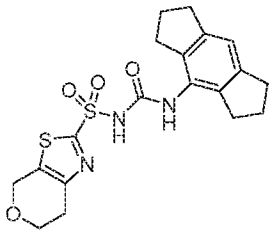
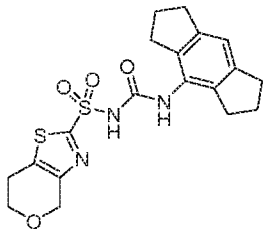
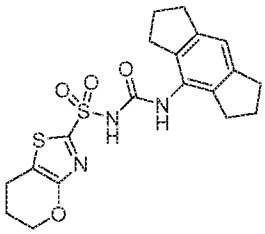
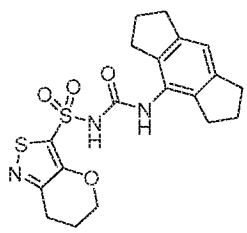
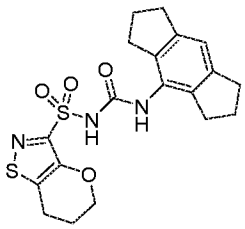
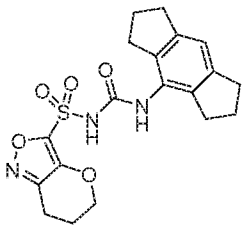
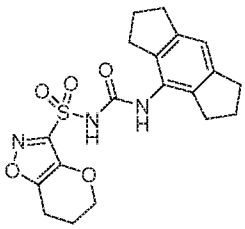
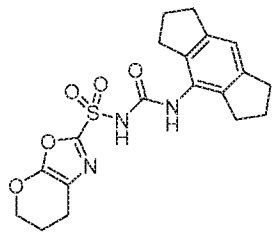
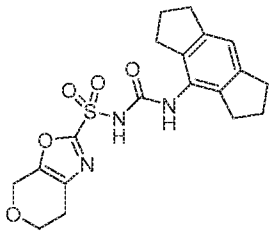
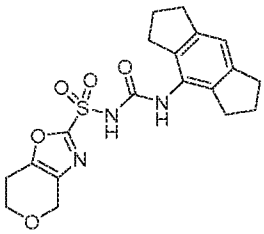
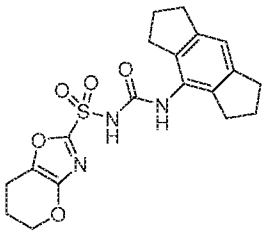
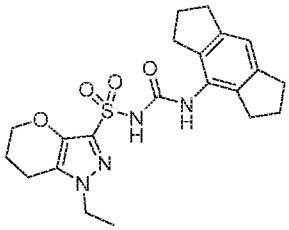
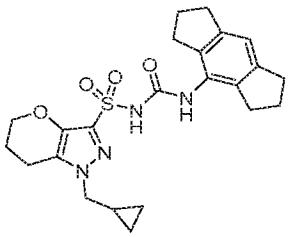
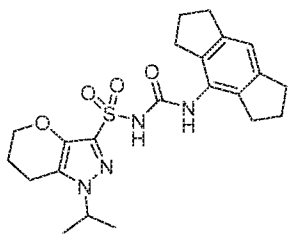
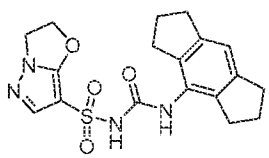
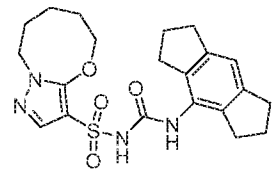
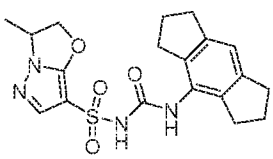
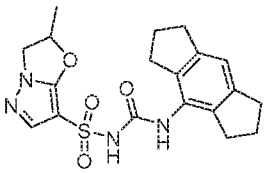
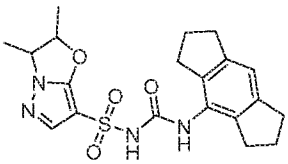
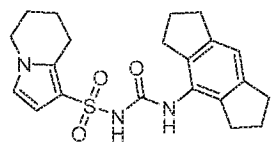
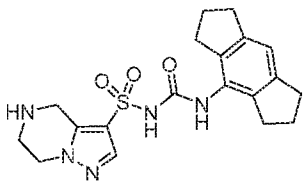
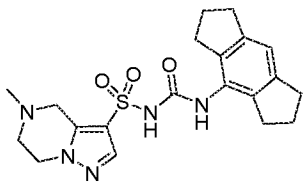
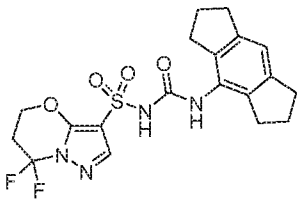

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

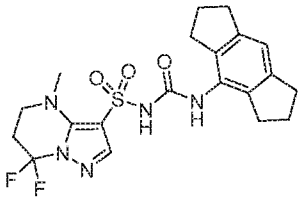
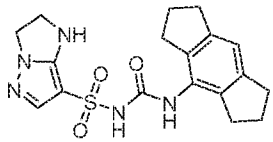
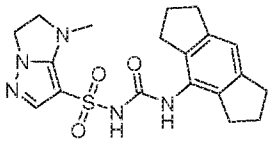
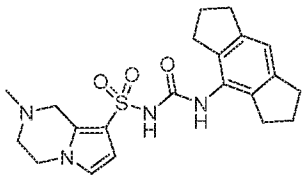
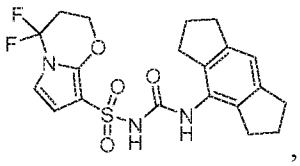
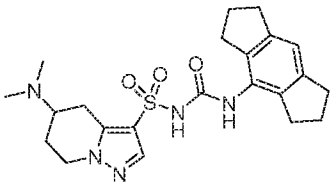
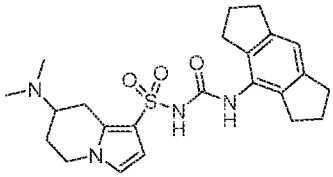
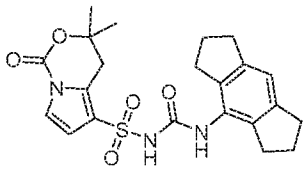
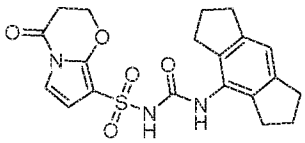
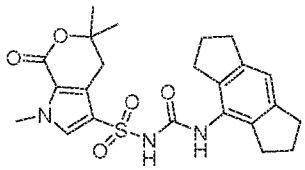
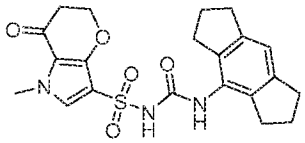
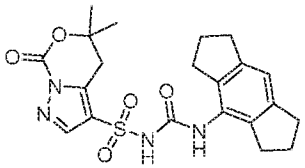
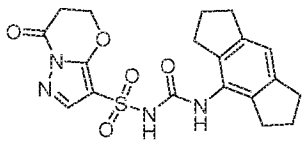
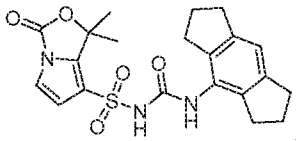
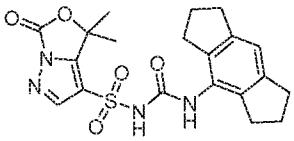
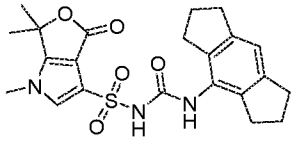
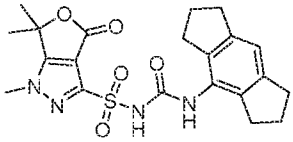
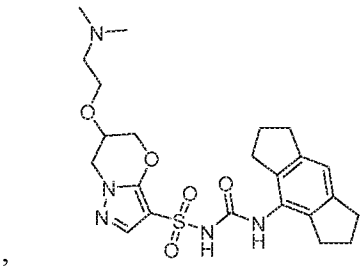
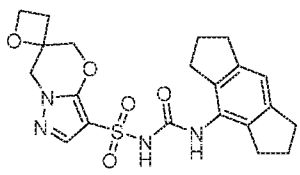
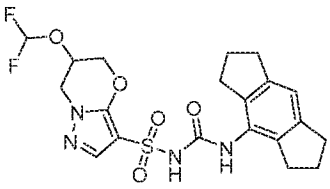
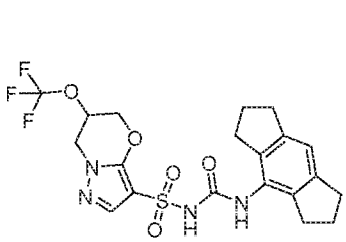
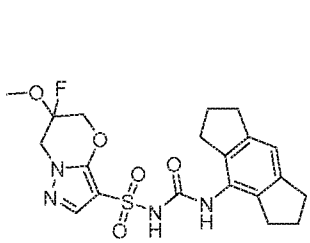
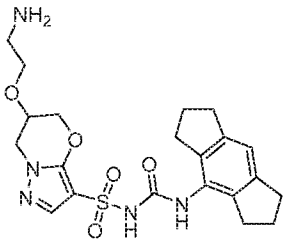
,

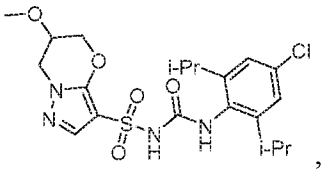
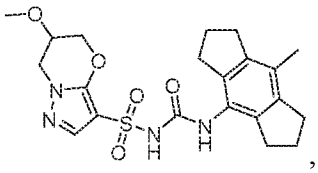
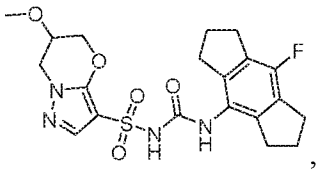
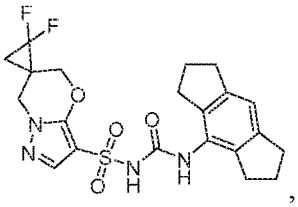
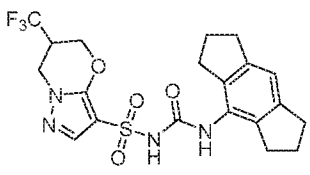
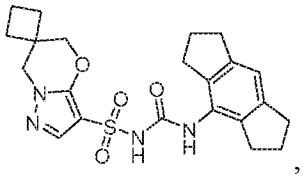
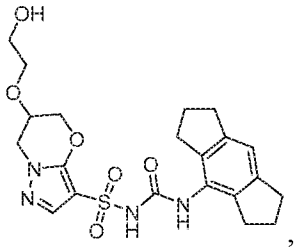
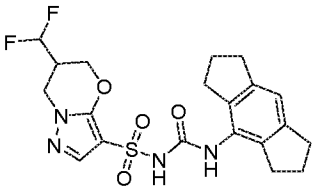
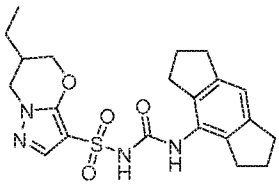
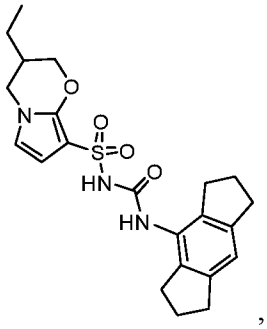
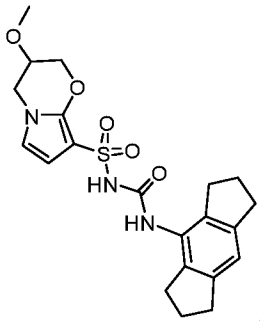
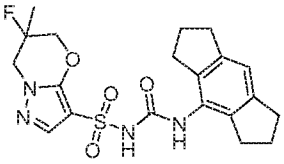
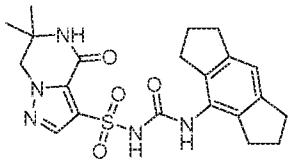
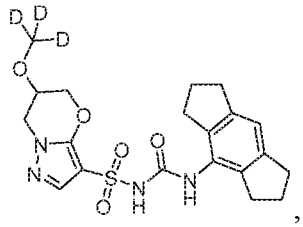
,

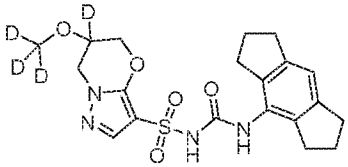
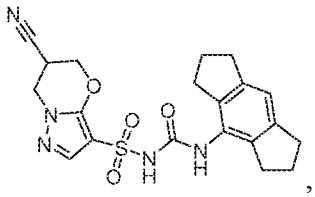
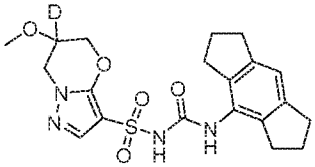
,

,

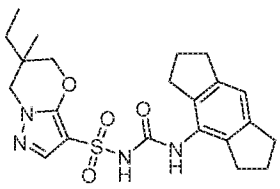
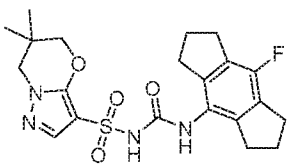
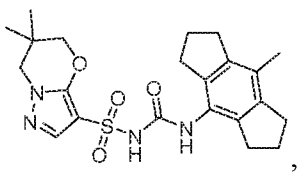

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

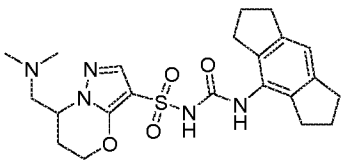
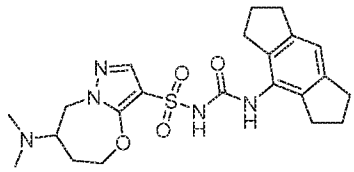
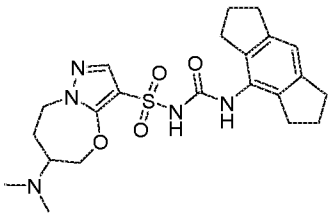
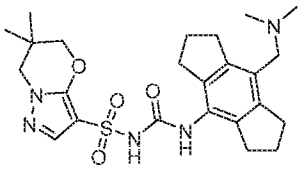
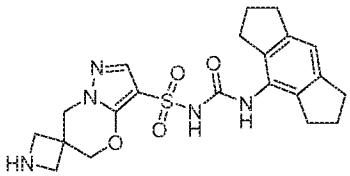
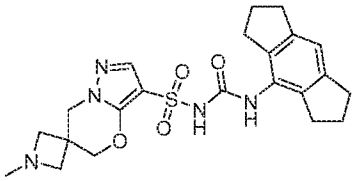
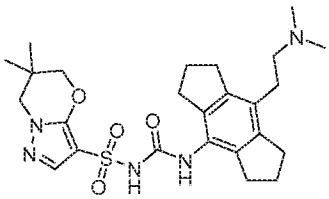
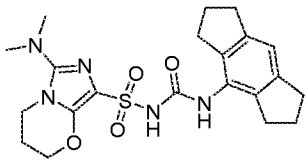
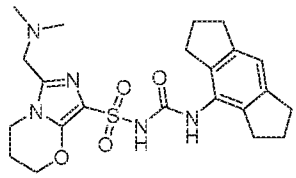
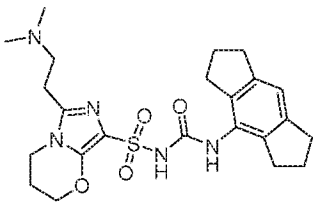
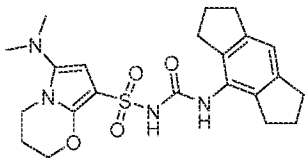
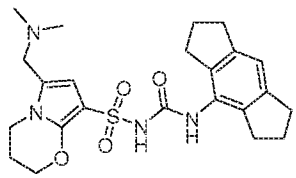
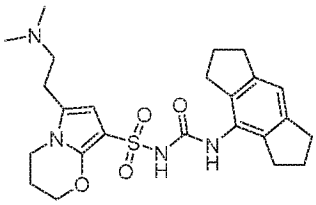

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

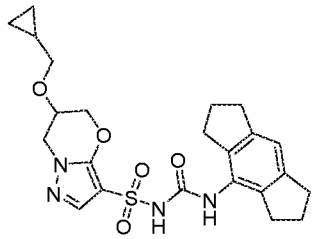
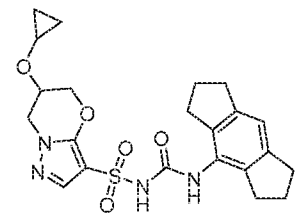
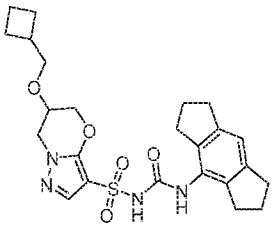
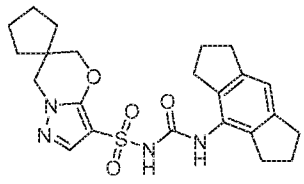
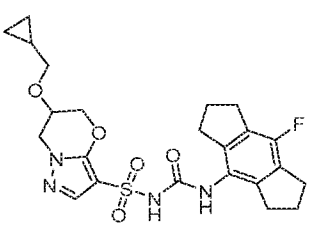
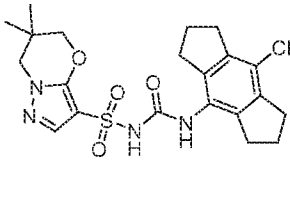
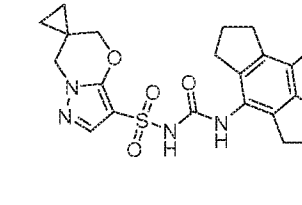
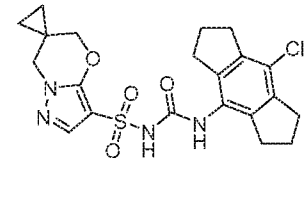

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

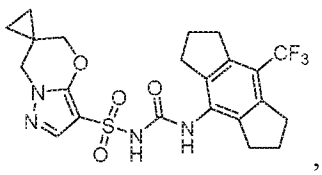
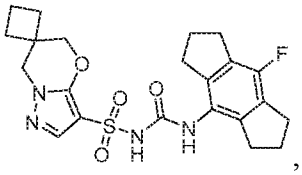
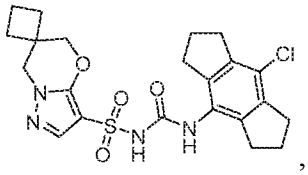
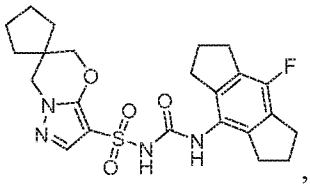
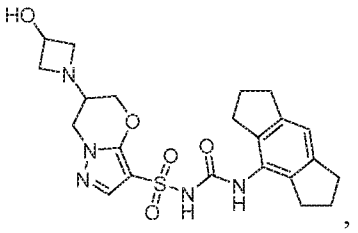
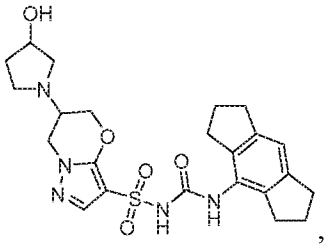
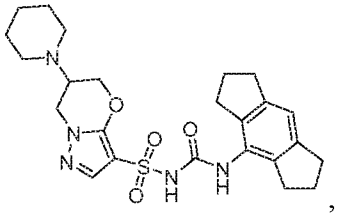
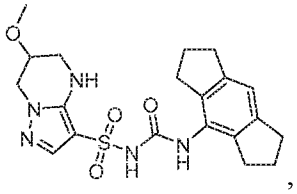
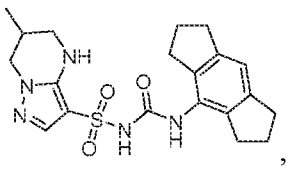
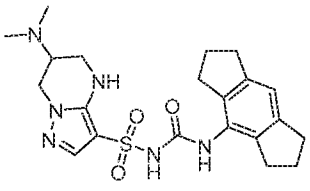
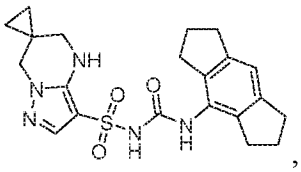
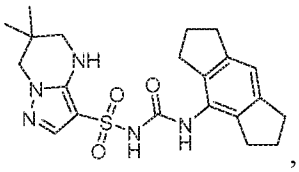
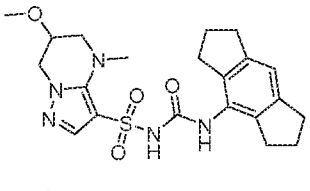
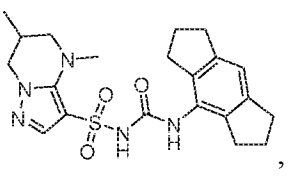
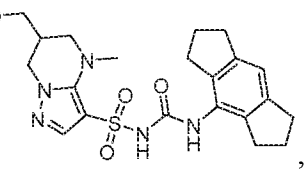
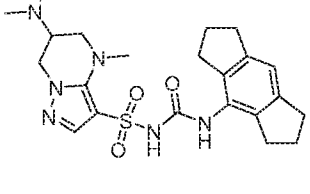
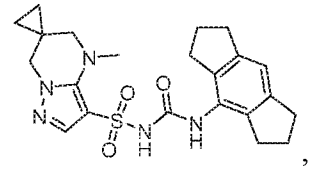
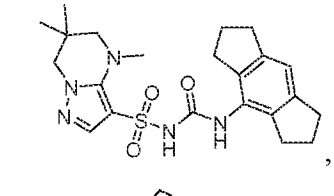
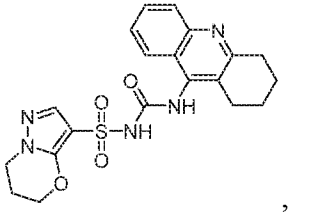
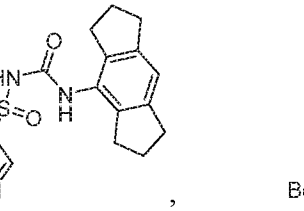
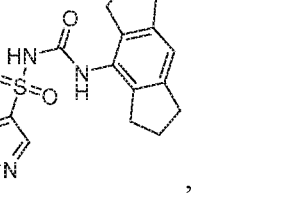
,

,

,

,

,

,

,

,

,

,

,

,

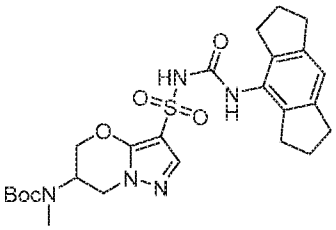
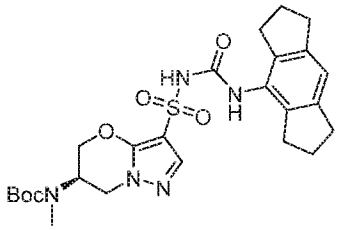
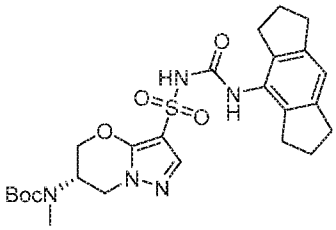
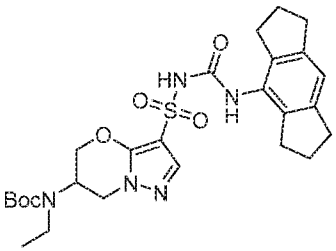
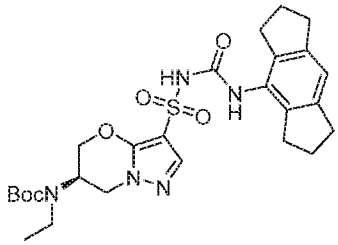
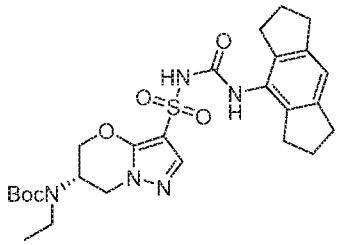
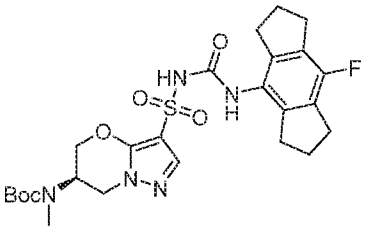
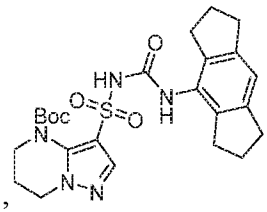
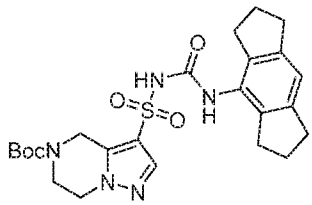
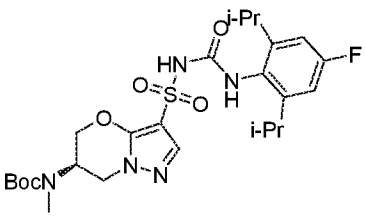
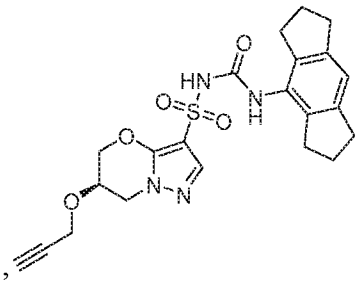
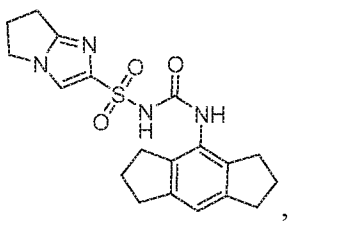
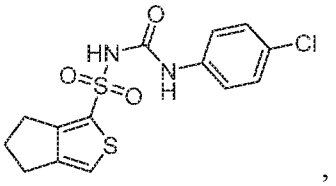
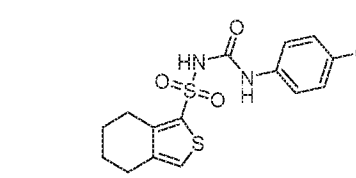
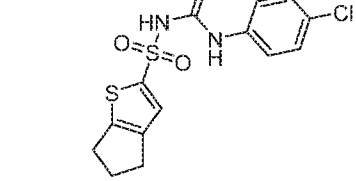
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

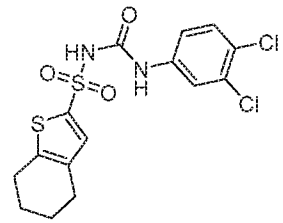
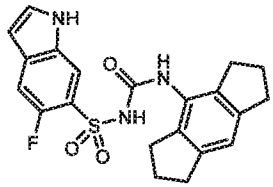
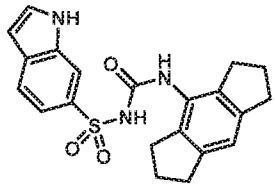
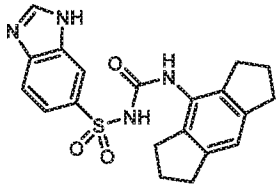
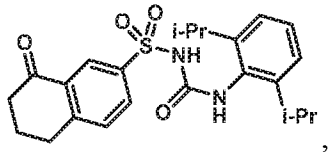
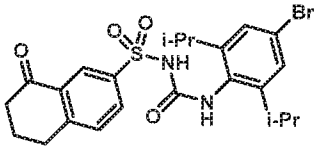
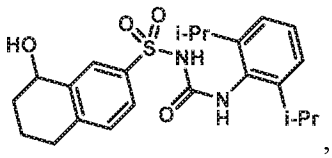
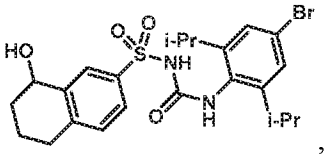
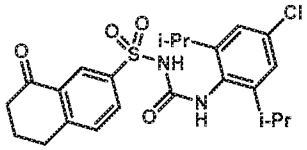
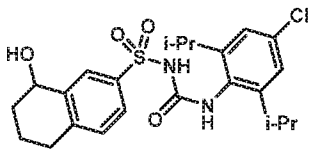
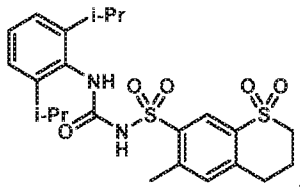
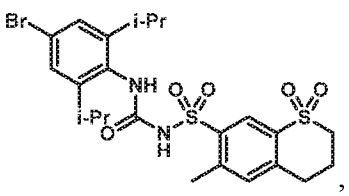
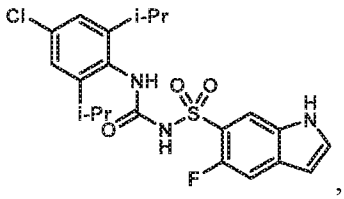
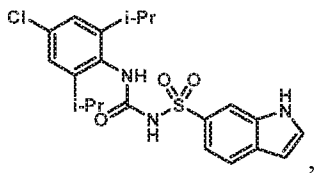
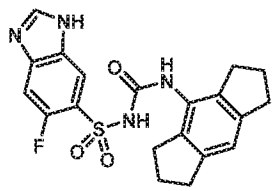
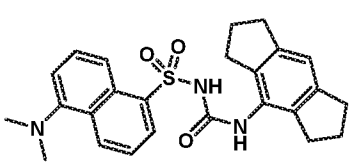
,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

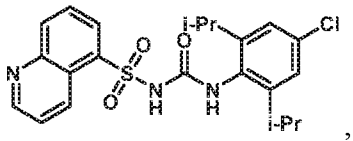
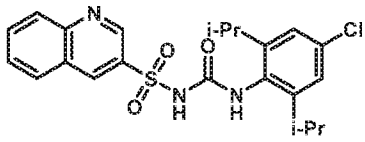
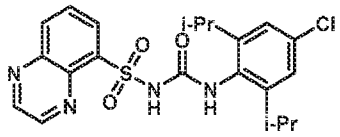
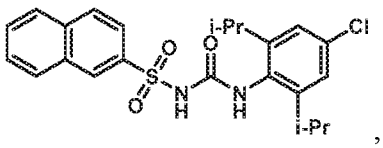
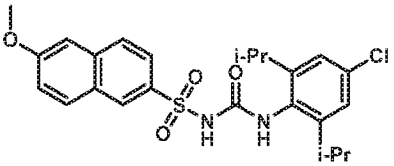
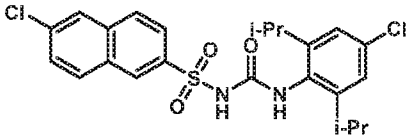
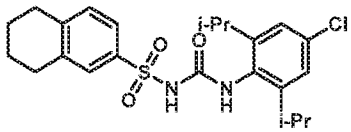
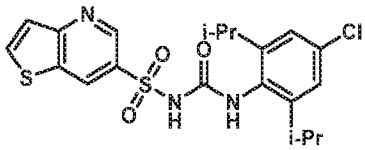
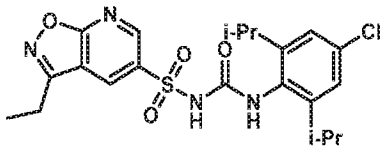
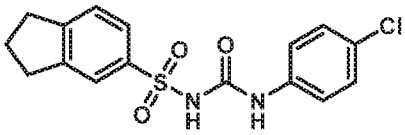
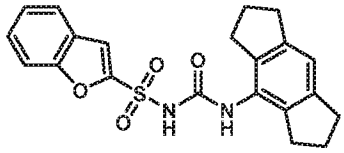
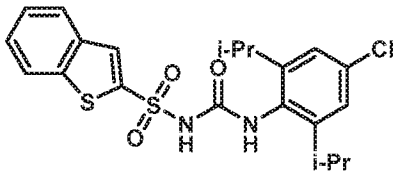
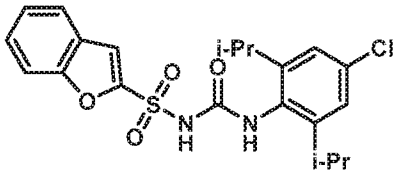
,

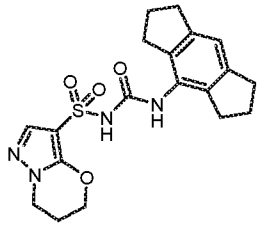
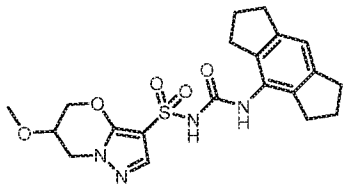
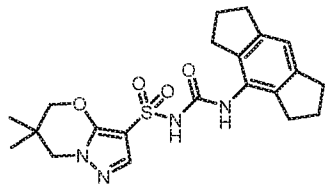
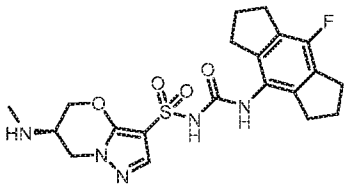
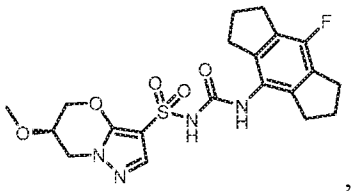
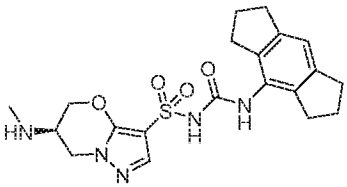
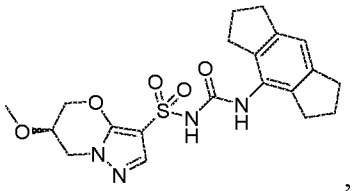
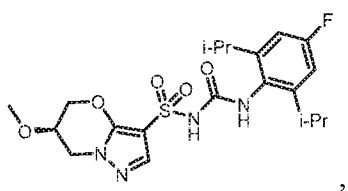
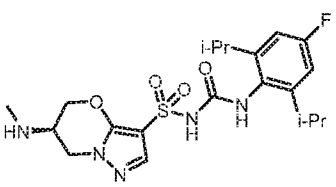
,

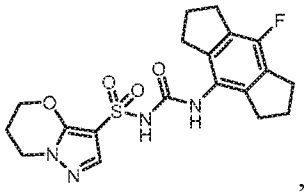
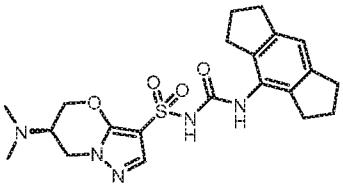
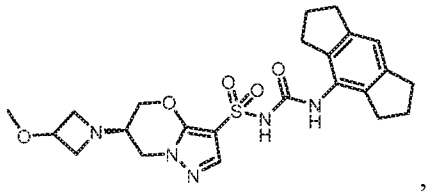
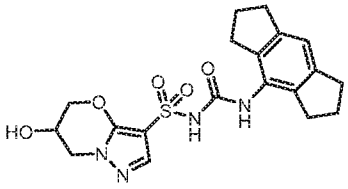
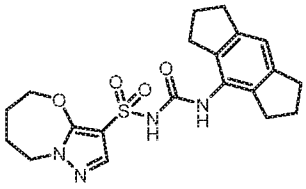
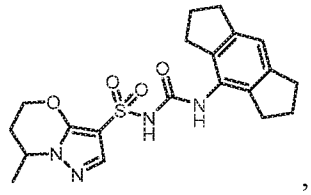
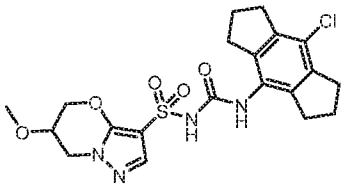
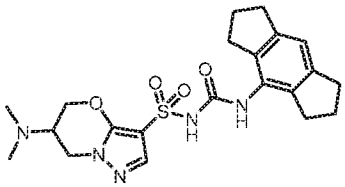
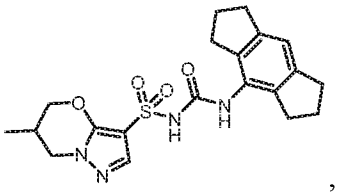
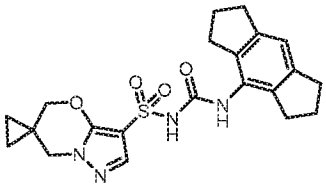
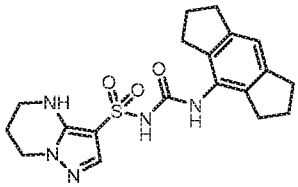
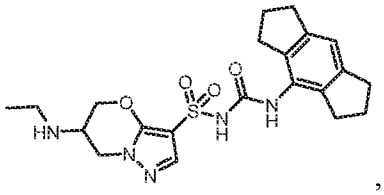
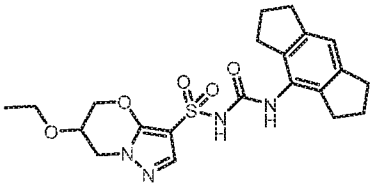
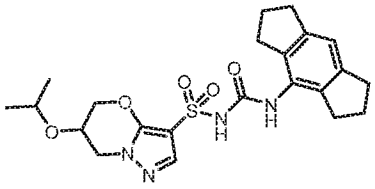
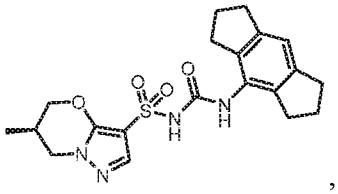
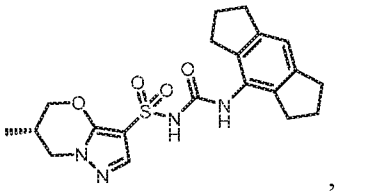
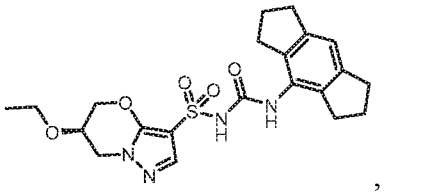
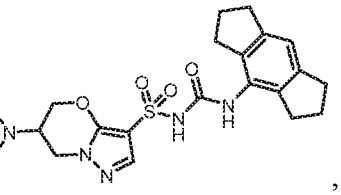
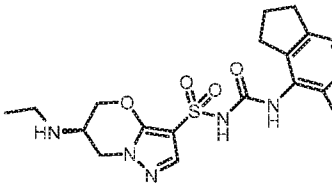
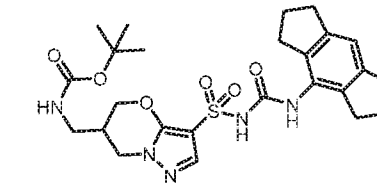
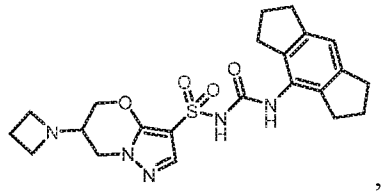
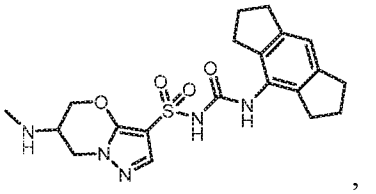
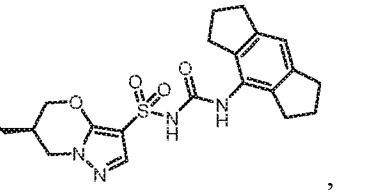
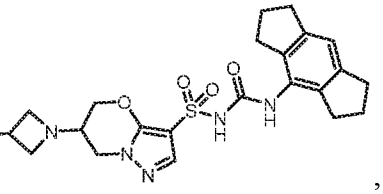
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

and .

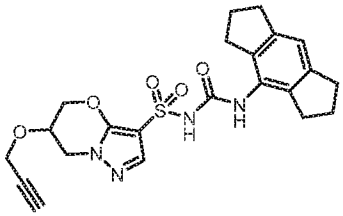
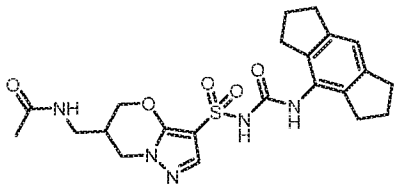
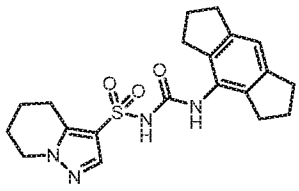
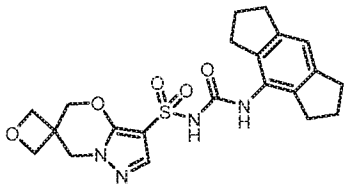
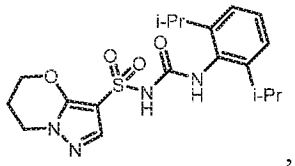
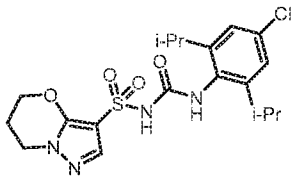
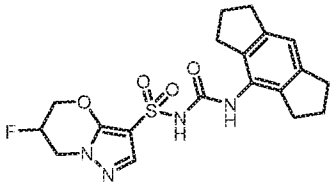
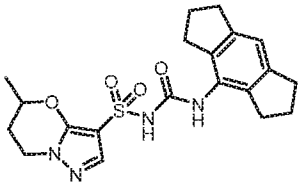
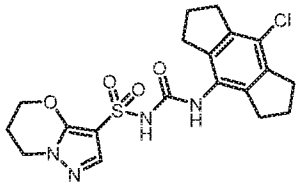
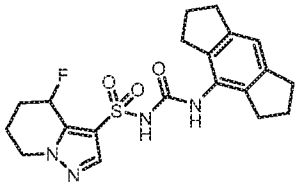
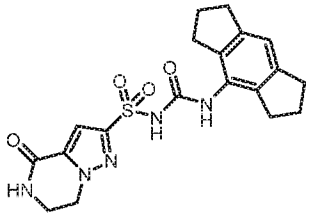
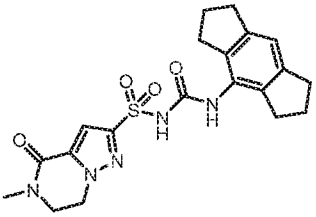
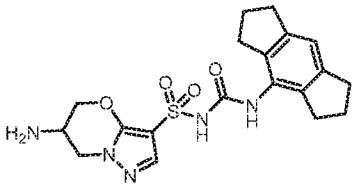
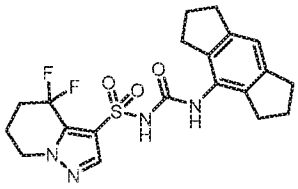
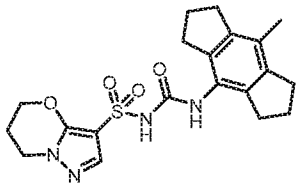
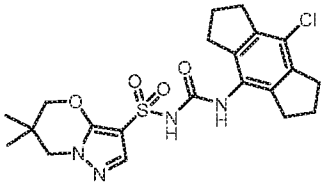
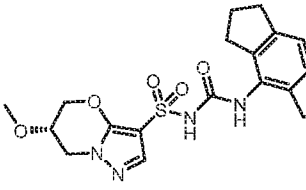
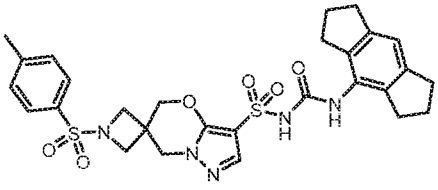
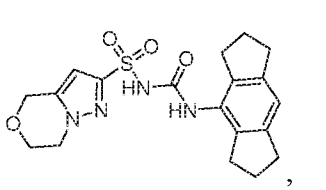
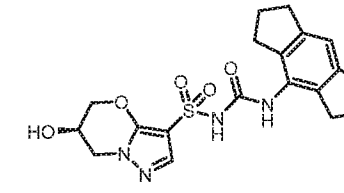
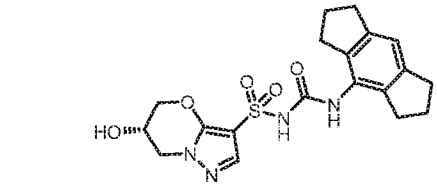
In some embodiments, the compound of Formula AA is not a compound selected from the group consisting of:

,

,

,

,

,

,

,

,

,

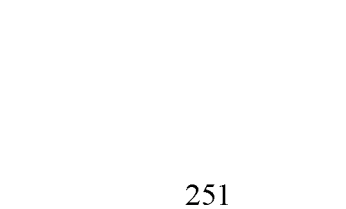

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

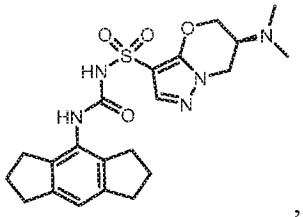
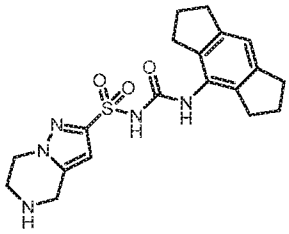
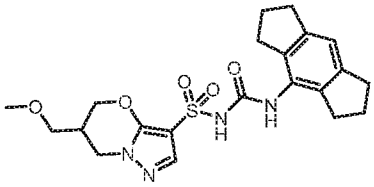
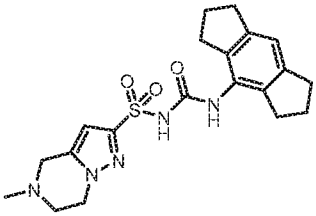
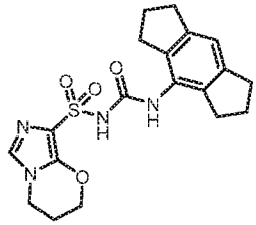
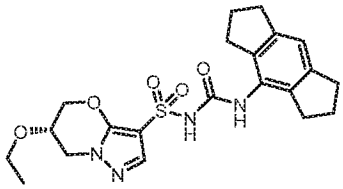
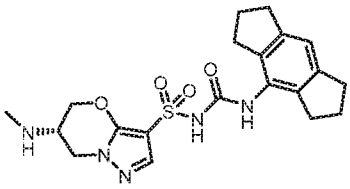
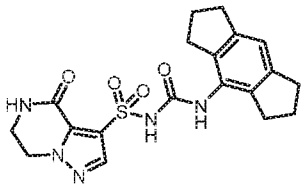
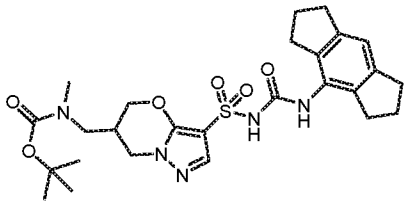
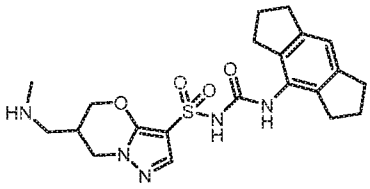
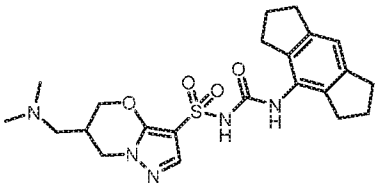
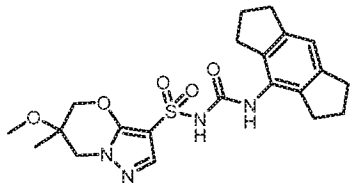
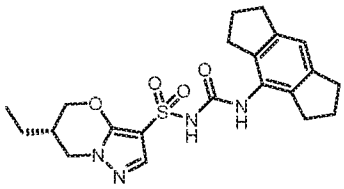
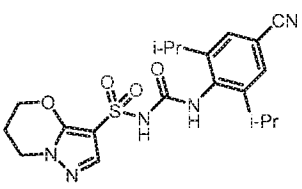
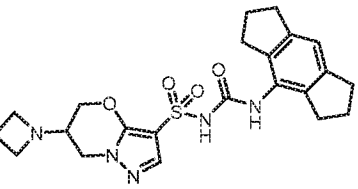
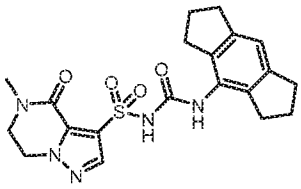
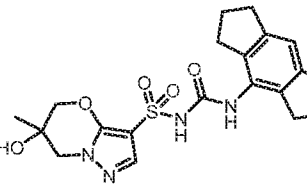
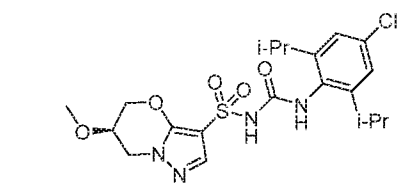
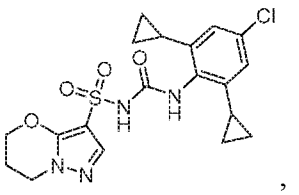
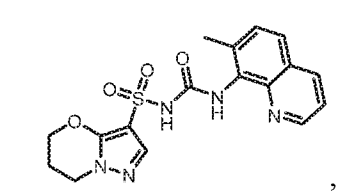
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

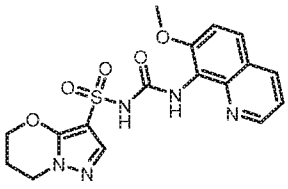
,

,

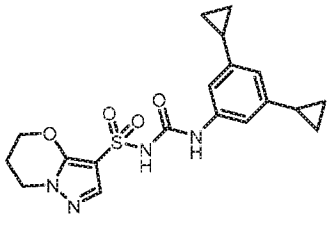
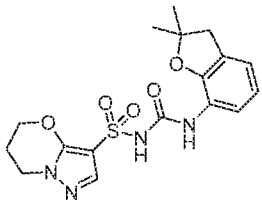
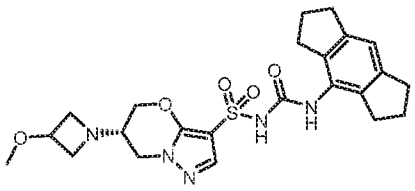
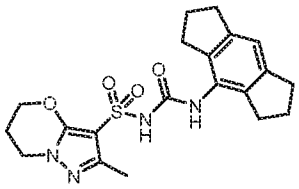
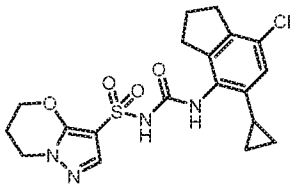
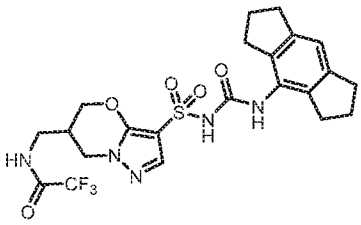
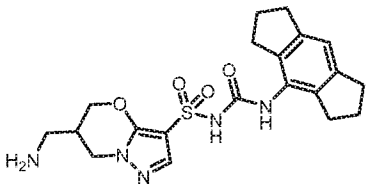
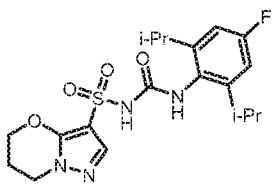
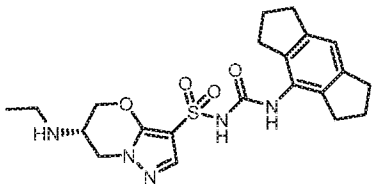
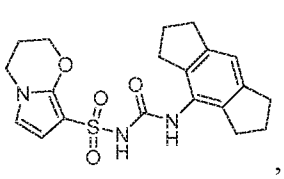
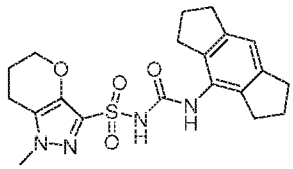
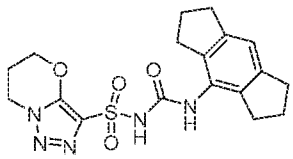
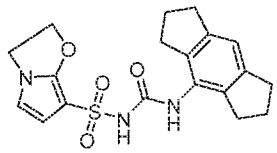
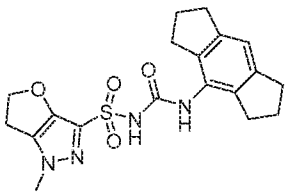
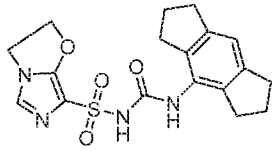
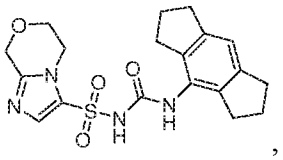
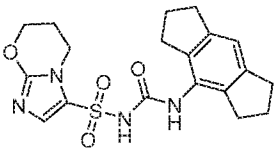
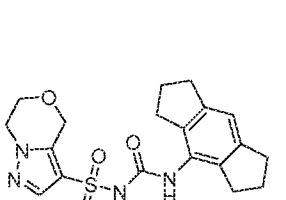
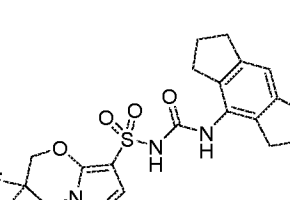
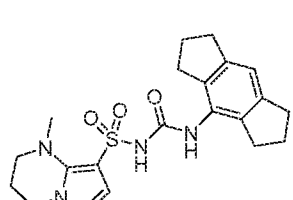
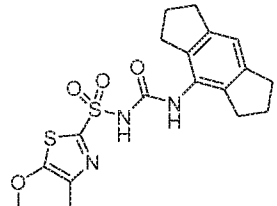
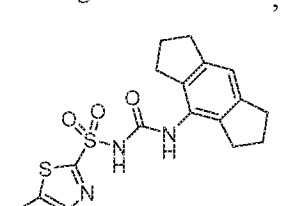
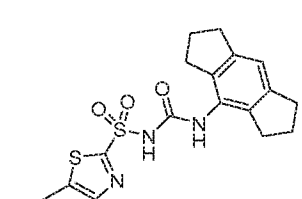
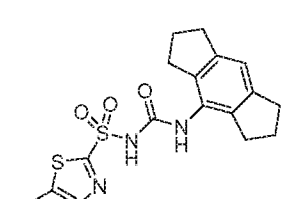
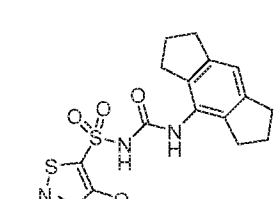
,

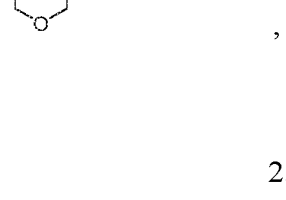
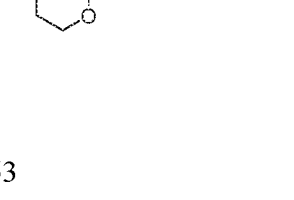
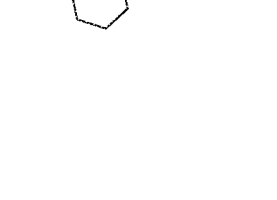

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

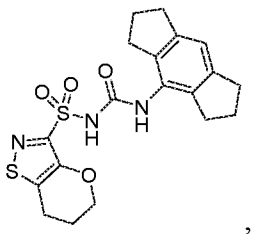
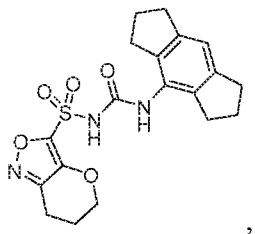
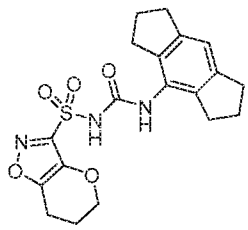
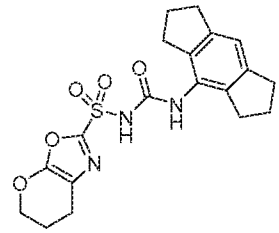
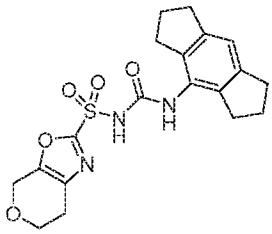
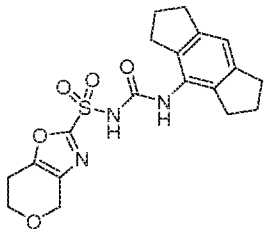
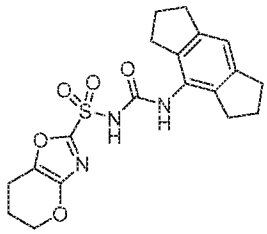
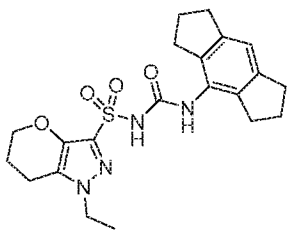
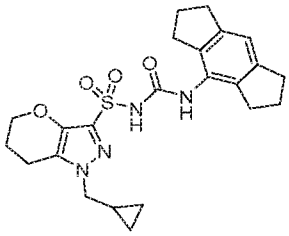
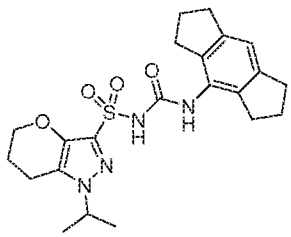
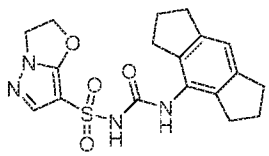
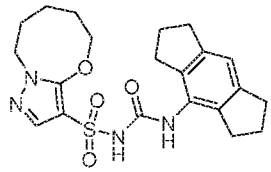
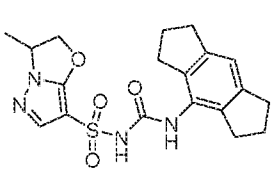
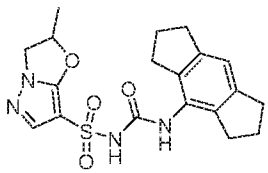
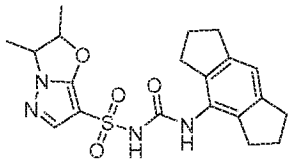
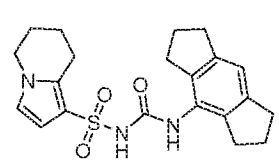
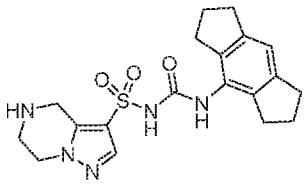
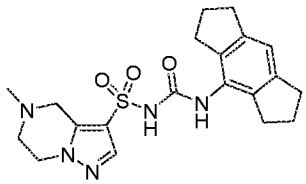
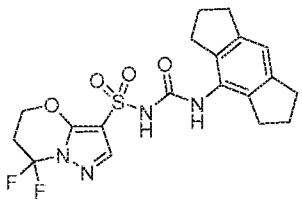
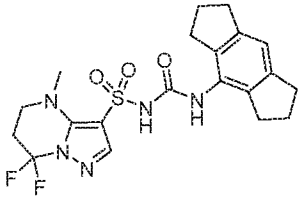
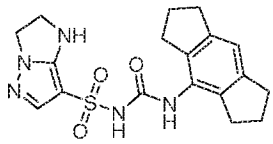
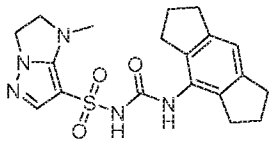
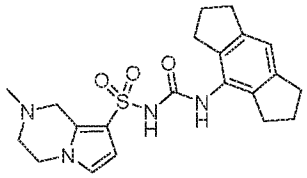
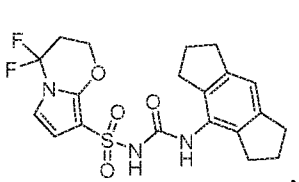
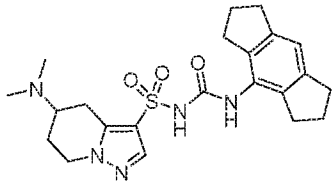
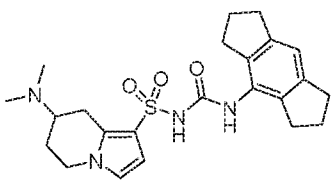
,

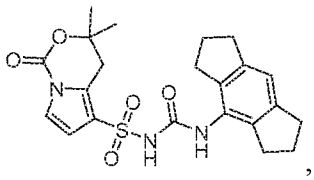
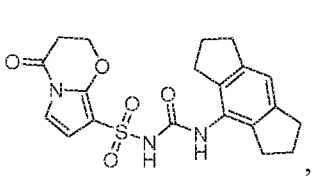
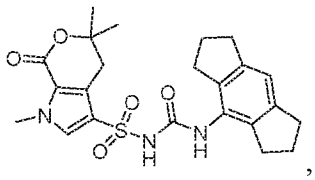
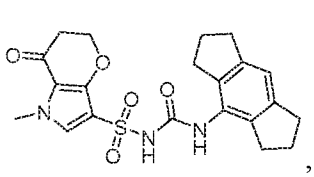
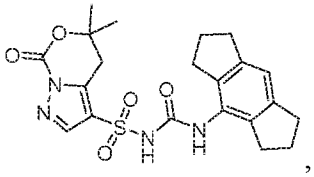
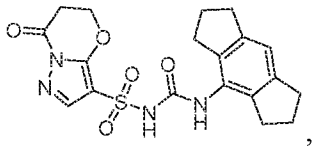
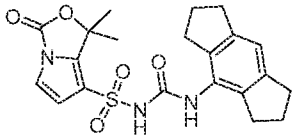
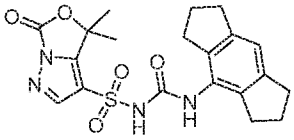
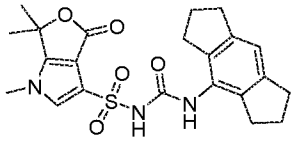
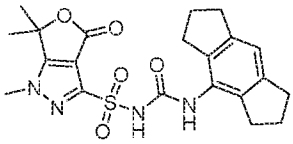
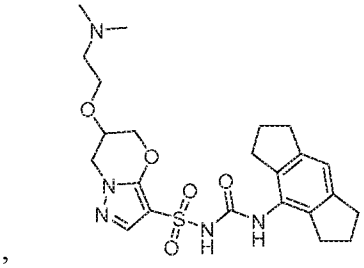
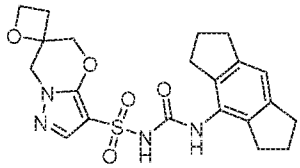
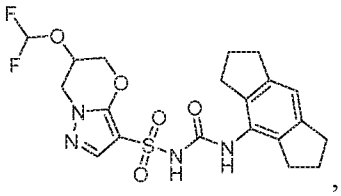
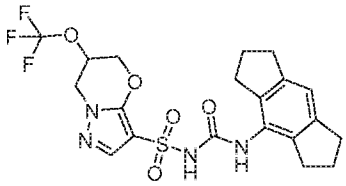
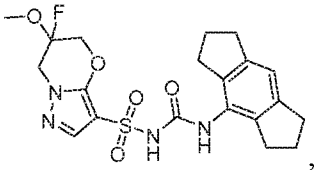
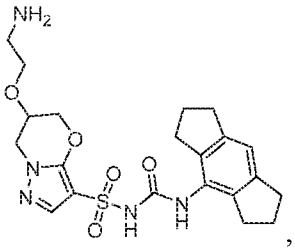
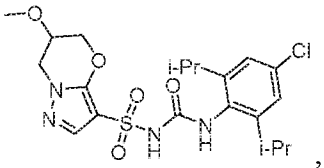
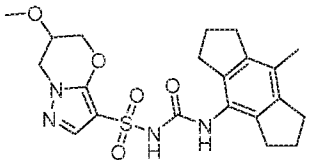
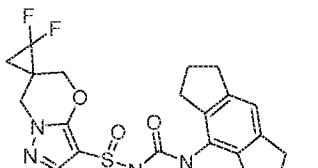
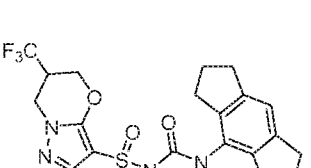
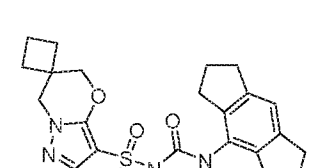
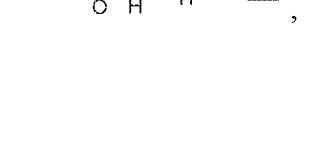
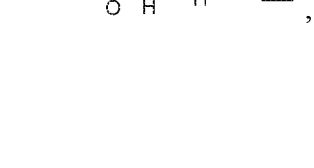
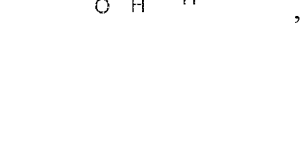
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

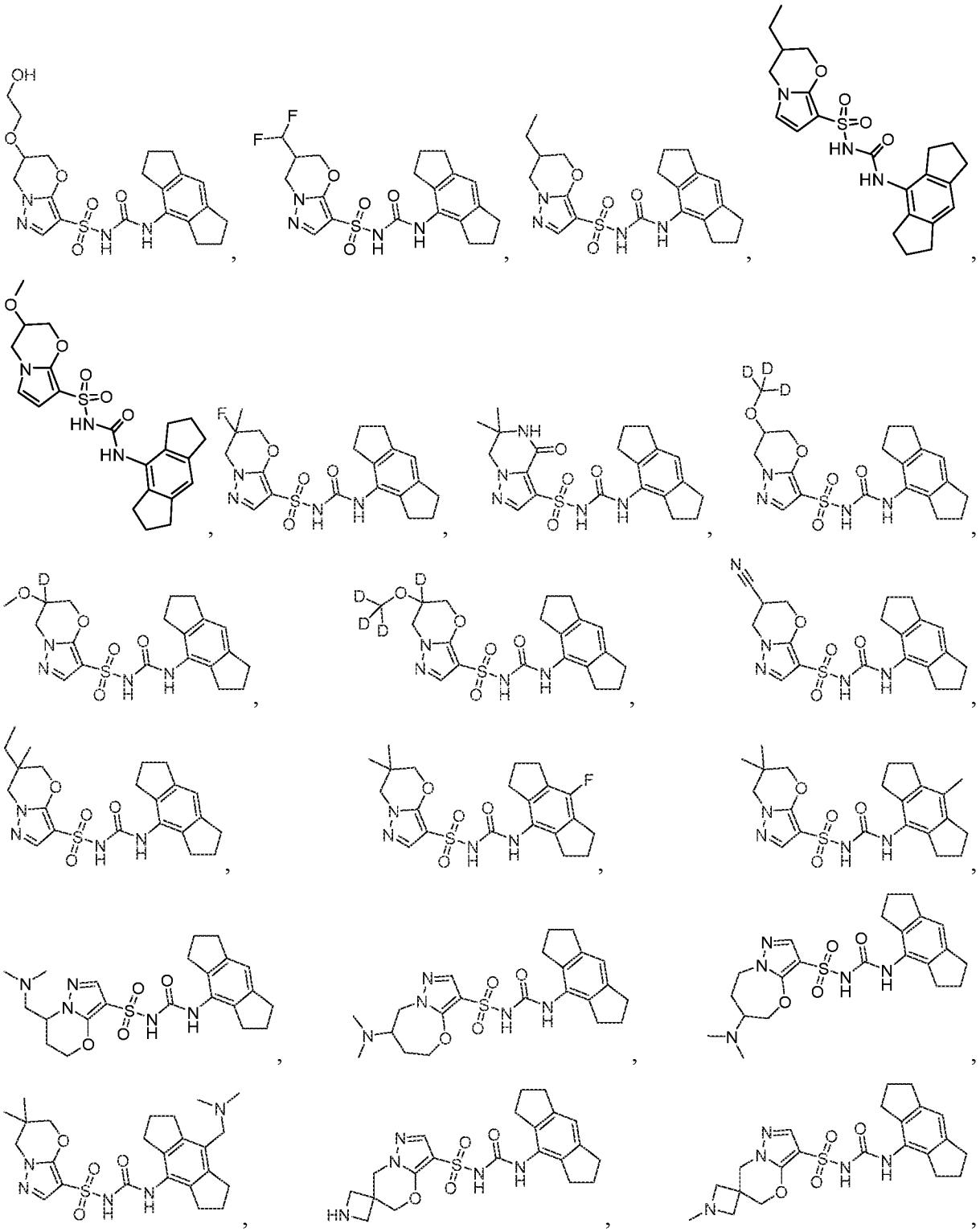

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

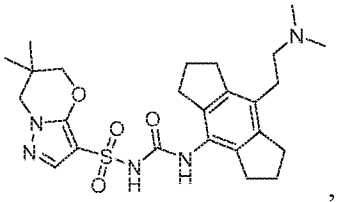
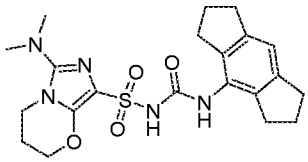
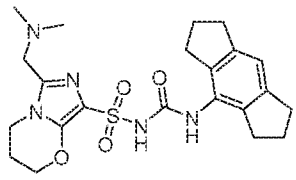
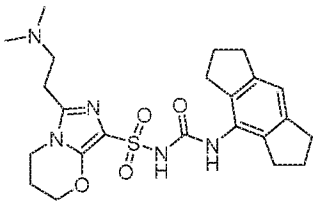
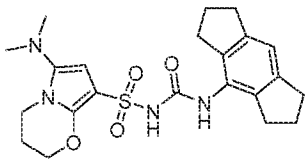
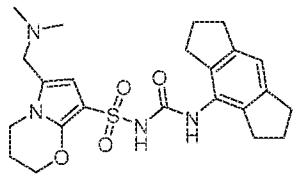
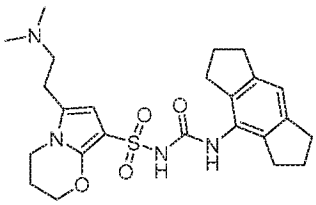
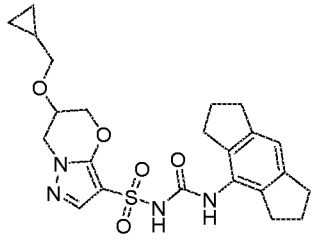
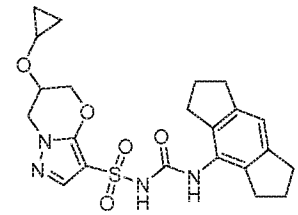
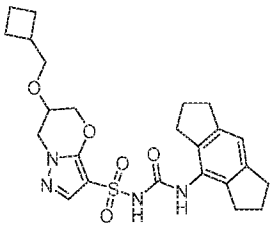
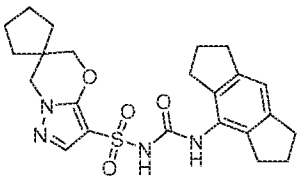
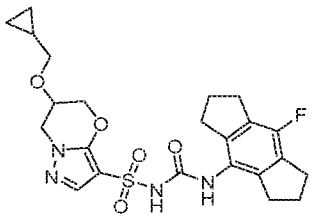
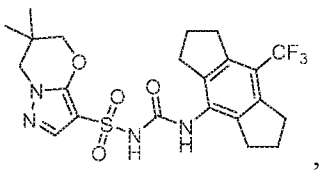
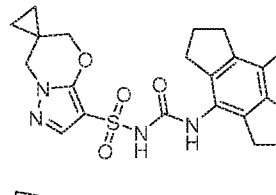
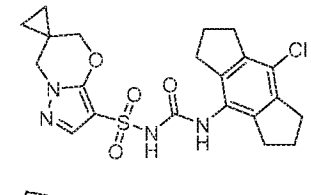
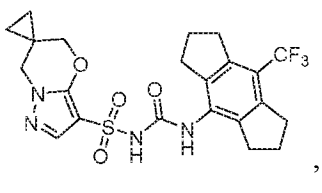
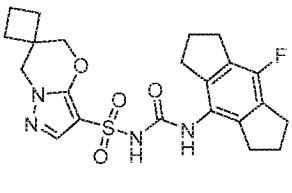
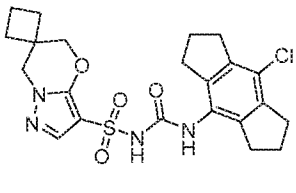
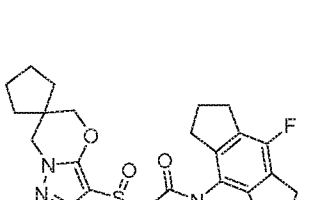
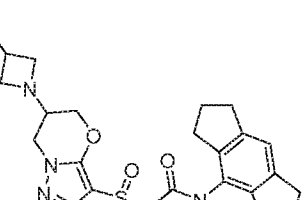
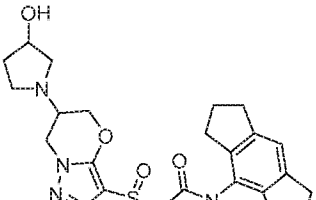
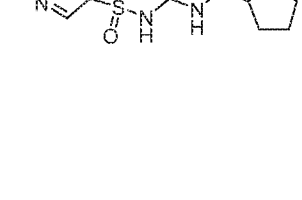
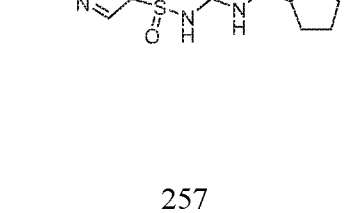
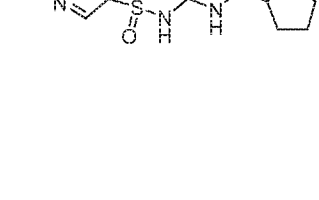

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

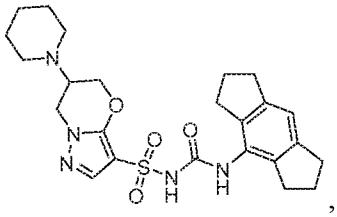
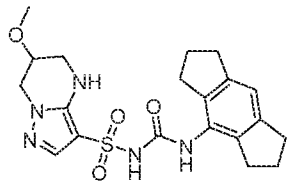
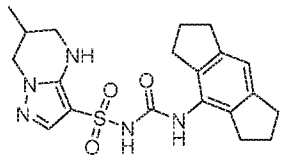
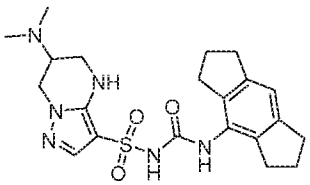
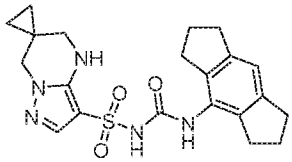
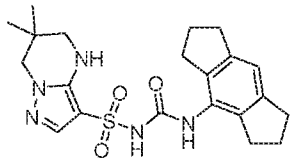
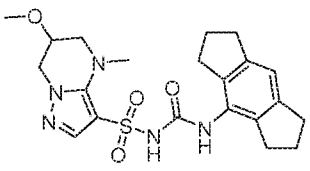
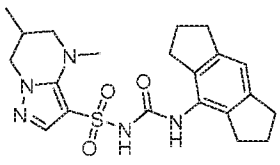
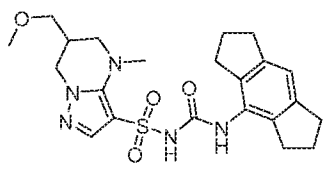
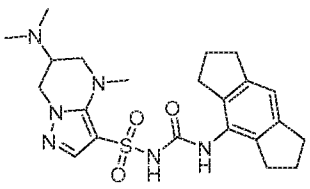
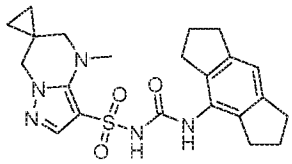
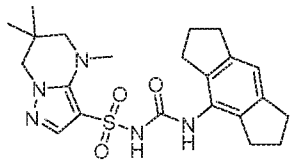
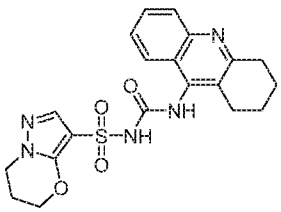
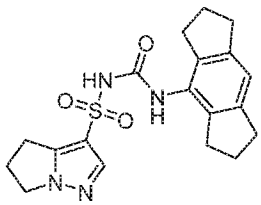
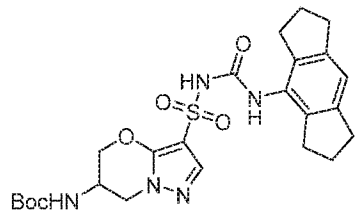
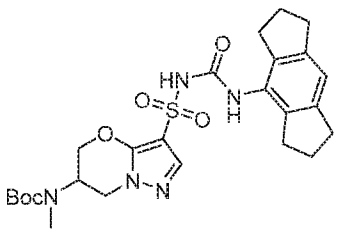
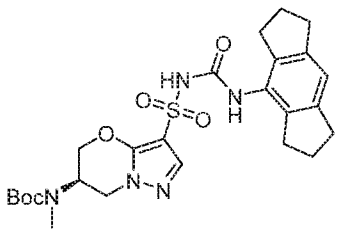
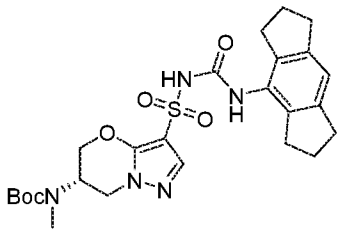
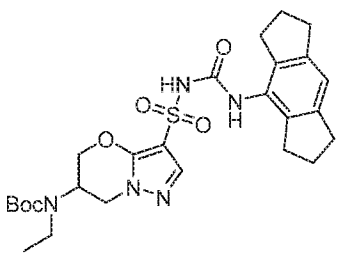
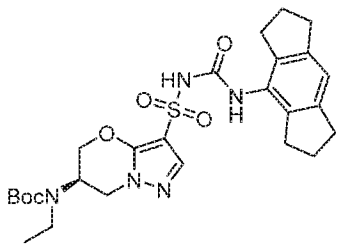
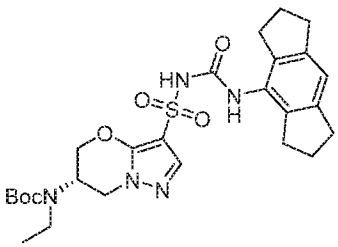
,

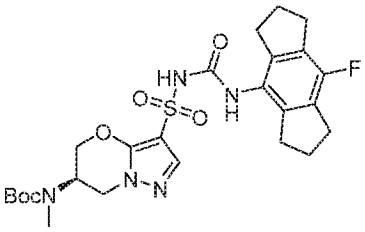
,

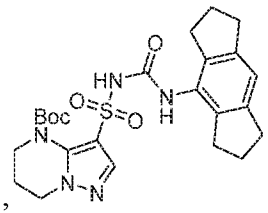
,

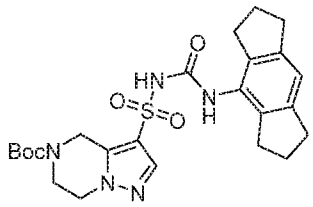


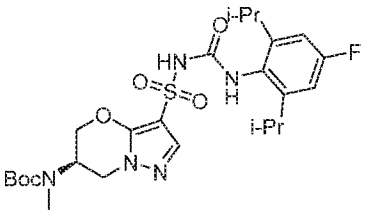

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

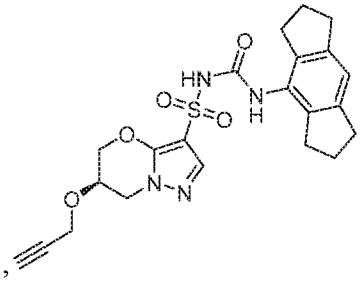

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

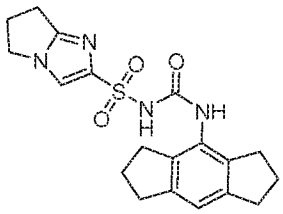

O
HN
O=S=O
N
H
F
O
BocN
N-N
,

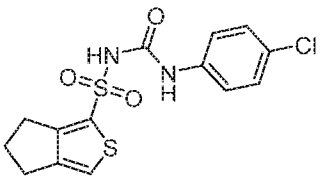

O
HN
O=S=O
N
H
Boc
N
N-N
,

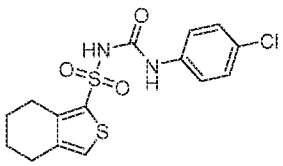

O
HN
O=S=O
N
H
BocN
N-N
,

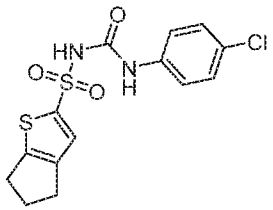

O
i-Pr
HN
N
H
F
O=S=O
i-Pr
O
BocN
N-N
,

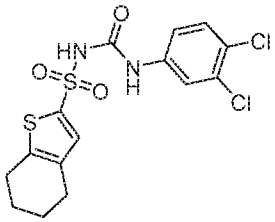

O
HN
O=S=O
N
H
O
O
N-N
,

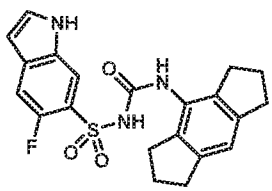

N
N
O
O
S
O
N
H
NH
,

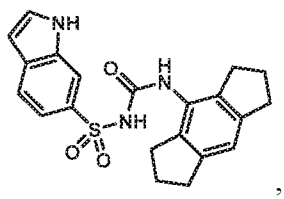

O
HN
O=S=O
N
H
Cl
S
,

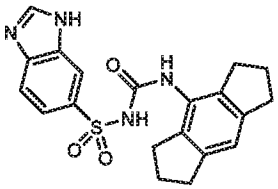

O
HN
O=S=O
N
H
Cl
S
,

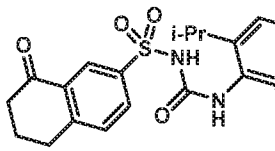

O
HN
O=S=O
N
H
Cl
S
,

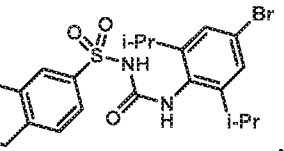

O
HN
O=S=O
N
H
Cl
Cl
S
,

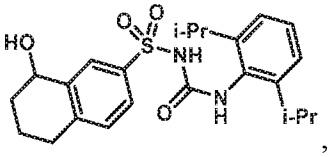

NH
O
H
N
F
S
NH
O O
,

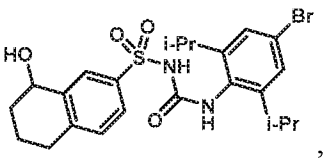

NH
O
H
N
S
NH
O O
,

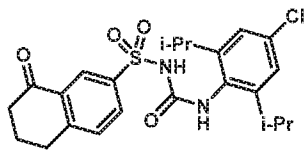

N
NH
O
H
N
S
NH
O O
,

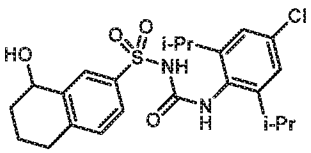

O
O O
S
i-Pr
NH
O
N
H
i-Pr
,

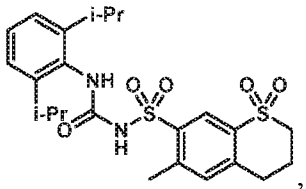

Br
O
O O
S
i-Pr
NH
O
N
H
i-Pr
,

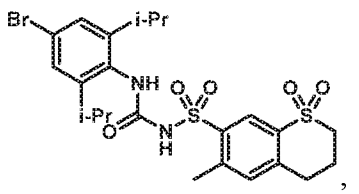

HO
O O
S
i-Pr
NH
O
N
H
i-Pr
,

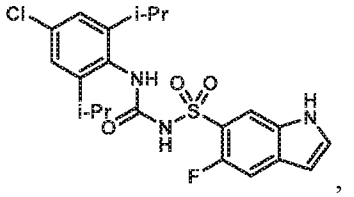
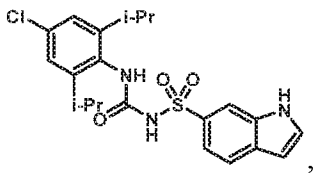
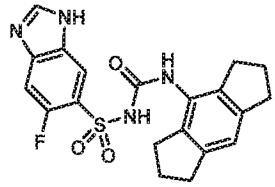
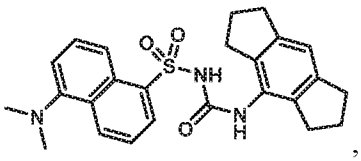
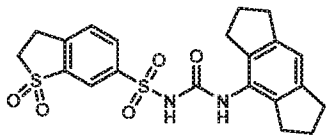
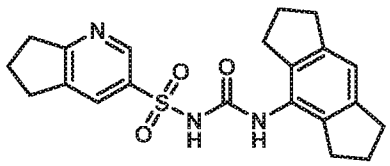
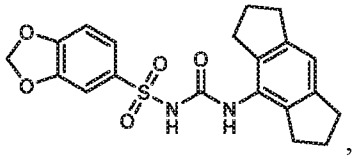
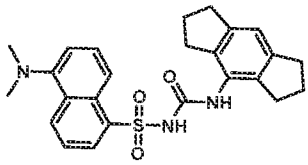
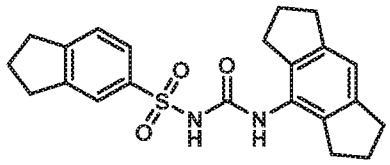
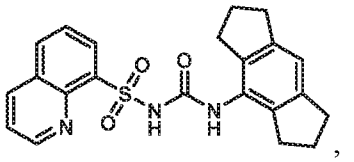
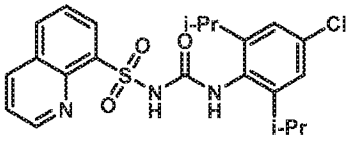
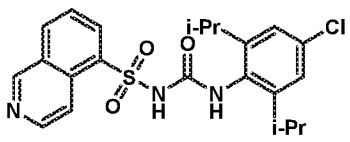
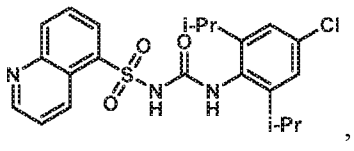
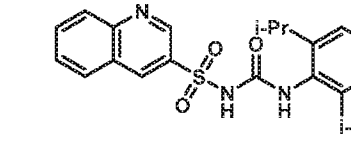
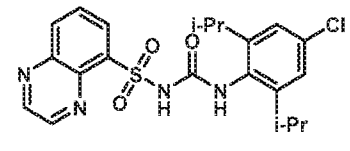
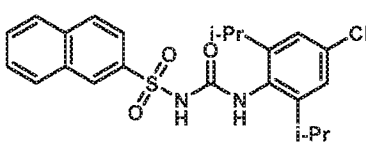
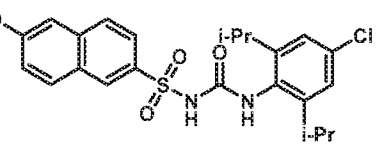
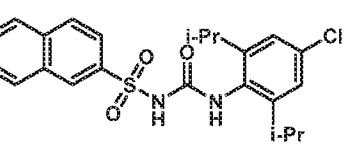
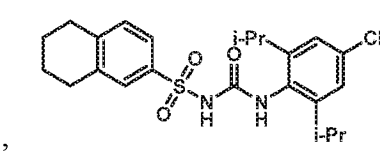
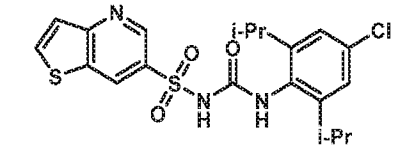
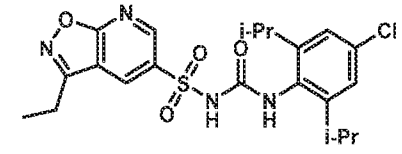

Br
HO
O O
S
i-Pr
NH
O
N
H
i-Pr
,


Cl
O
O O
S
i-Pr
NH
O
N
H
i-Pr
,


Cl
HO
O O
S
i-Pr
NH
O
N
H
i-Pr
,


i-Pr
NH
i-Pr
O O
S
O
N
H
O O
S
,


Br
i-Pr
NH
i-Pr
O O
S
O
N
H
O O
S
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

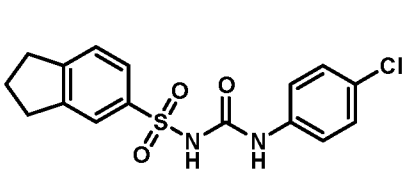
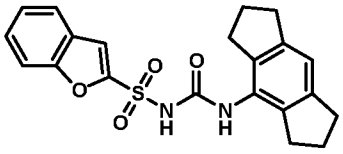
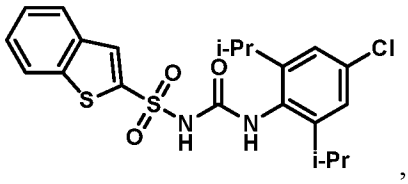
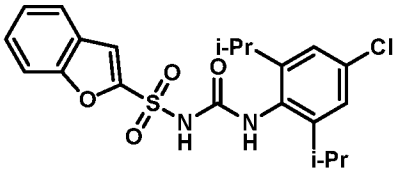
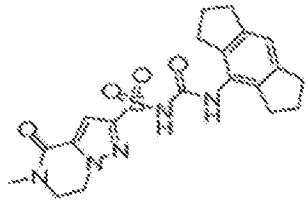
,

,

,

,

,


,

,

,

, and

.

In some embodiments, when B is 5-10-membered heteroaryl including from 2-3 ring nitrogen atoms, at least one R^6 is attached to B at a position *ortho* to the –HNC(=O)NHS(O)$_2$- moiety of Formula AA.

In some embodiments, when B is 2-pyridyl, pyrimidin-6-yl, or pyrimidin-4-yl, B is not substituted with a cyano group at a position *ortho* to the –HNC(=O)NHS(O)$_2$- moiety of Formula AA.

In some embodiments, the compound of Formula AA is not selected from the compounds disclosed in WO 2018/136890.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in any of Examples 1-150 of patent publication WO2001/019390, which are incorporated by reference herein.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in patent publication WO2001/019390, which is incorporated by reference herein.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in any of Examples 1-130 of patent publication WO 98/32733, which are incorporated by reference herein.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in patent publication WO 98/32733, which is incorporated by reference herein.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in any of the Examples at [00123] of patent publication WO2016/131098, which are incorporated by reference herein.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in patent publication WO2016/131098, which is incorporated by reference herein.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in DK 2006/00313, which is incorporated by reference herein.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in US 4,927,453, which is incorporated by reference herein.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in EP 03/18620, which is incorporated by reference herein.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in EP 02/05348, which is incorporated by reference herein.

In some embodiments, the compound of any of the formulae herein is not a compound disclosed in *J. Med. Chem.* **1992**, *35*, 3012-3016, which is incorporated by reference herein.

In some embodiments, the compound of any of the formulae herein is not a compound disclosed in WO 2018/015445 and EP 32/72739, which is incorporated by reference herein.

In some embodiments, the compound of any of the formulae herein is not a compound disclosed in US 5,356,862, which is incorporated by reference herein.

In some embodiments, the compound of any of the formulae herein is not a compound disclosed in WO 91/110668, which is incorporated by reference herein.

In some embodiments, the compound of any of the formulae herein is not a compound disclosed in US 4,671,817, which is incorporated by reference herein.

In some embodiments, the compound of any of the formulae herein is not a compound disclosed in EP 02/38070, which is incorporated by reference herein.

In some embodiments, the compound of any of the formulae herein is not a compound disclosed in EP 15/2286, which is incorporated herein by reference.

In some embodiments the compound of any of the formulae herein is not a compound disclosed in WO2019034686, WO2019034688, WO2019034690, WO2019034692, WO2019034693, WO2019034696, and/or WO2019034697.

In some embodiments, the compound of any of the formulae herein is not a compound disclosed in WO 2018/136890, WO2001/019390, WO 98/32733, WO2016/131098, DK 2006/00313, US 4,927,453, EP 03/18620, EP 02/05348, WO 2018/015445, EP 32/72739, US 5,356,862, WO 91/110668, US 4,671,817, EP 02/38070, EP 15/2286, *J. Med. Chem.* **1992**, *35*,

3012-3016, WO2019034686, WO2019034688, WO2019034690, WO2019034692, WO2019034693, WO2019034696, and/or WO2019034697.

In some embodiments, the compound is not a compound disclosed in WO 2019/008029, which is incorporated by reference in its entirety.

Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

In one embodiment, provided herein is a combination of a compound of any preceding embodiemnt, for use in the treatment or the prevention of a condition mediated by TNF-α, in a patient in need thereof, wherein the compound is administered to said patient at a therapeutically effective amount. Preferably, the subject is resistant to treatment with an anti-TNFα agent. Preferably, the condition is a gut disease or disorder.

In one embodiment, provided herein is a pharmaceutical composition of comprising a compound of any preceding embodiment, and an anti-TNFα agent disclosed herein. Preferably wherein the anti-TNFα agent is Infliximab, Etanercept, Certolizumab pegol, Golimumab or Adalimumab, more preferably wherein the anti-TNFα agent is Adalimumab.

In one embodiment, provided herein is a pharmaceutical combination of a compound of any preceding embodiment, and an anti-TNFα agent Preferably wherein the anti-TNFα agent is Infliximab, Etanercept, Certolizumab pegol, Golimumab or Adalimumab, more preferably wherein the anti-TNFα agent is Adalimumab.

In one embodiment, the present invention relates to an NLRP3 antagonist for use in the treatment or the prevention of a condition mediated by TNF-α, in particular a gut disease or disorder, in a patient in need thereof, wherein the NLRP3 antagonist is administered to said patient at a therapeutically effective amount.

In one embodiment, the present invention relates to an NLRP3 antagonist for use in the treatment or the prevention of a condition, in particular a gut disease or disorder, in a patient in need thereof wherein the NLRP3 antagonist is administered to said patient at a therapeutically effective amount.

In one embodiment, the present invention relates to an NLRP3 antagonist for use in the treatment, stabilization or lessening the severity or progression of gut disease or disorder, in a

patient in need thereof wherein the NLRP3 antagonist is administered to said patient at a therapeutically effective amount.

In one embodiment, the present invention relates to an NLRP3 antagonist for use in the slowing, arresting, or reducing the development of a gut disease or disorder, in a patient in need thereof wherein the NLRP3 antagonist is administered to said patient at a therapeutically effective amount.

In one embodiment, the present invention relates to an NLRP3 antagonist for use according to above listed embodiments wherein the NLRP3 antagonist is a gut-targeted NLRP3 antagonist.

In one embodiment, the present invention relates ton NLRP3 antagonist for use according to any of the above embodiments, wherein the gut disease is IBD.

In one embodiment, the present invention relates to an NLRP3 antagonist for use according to any of the above embodiments, wherein the gut disease is US or CD.

In one embodiment, the present invention relates to a method for the treatment or the prevention of a condition mediated by TNF-α, in particular a gut disease or disorder, in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a gut-targeted NLRP3 antagonist.

In one embodiment, the present invention relates to a method for the treatment or the prevention of a condition, in particular a gut disease or disorder, in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a gut-targeted NLRP3 antagonist.

In one embodiment, the present invention relates to a method for the treatment, stabilization or lessening the severity or progression of gut disease or disorder, in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a gut-targeted NLRP3 antagonist.

In one embodiment, the present invention relates to a method for slowing, arresting, or reducing the development of a gut disease or disorder, in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a gut-targeted NLRP3 antagonist.

In one embodiment, the present invention relates to a method according to any of the above embodiments, wherein the gut disease is IBD.

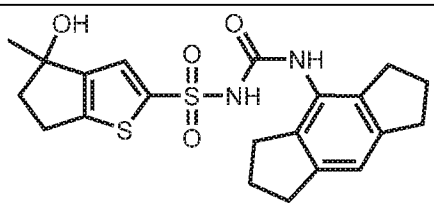
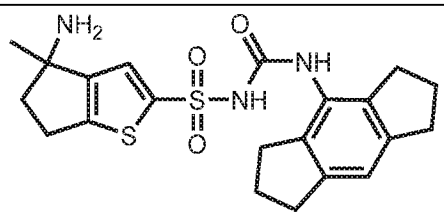
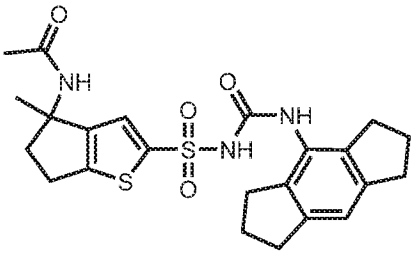
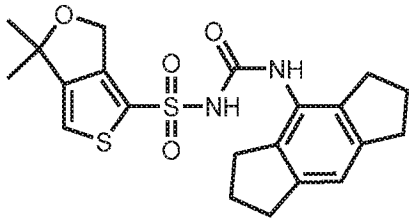
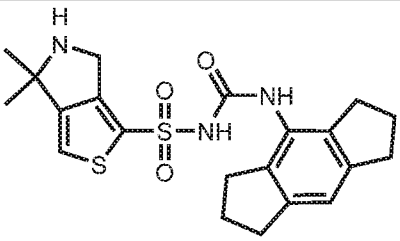
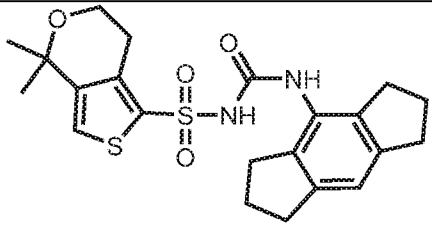
In one embodiment, the present invention relates to a method according to any of the above embodiments x to xx, wherein the gut disease is UC or CD.

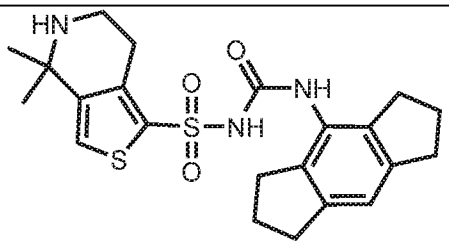
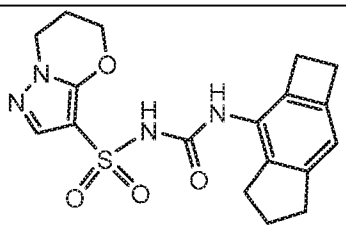
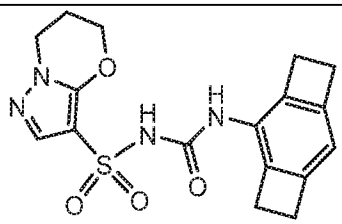
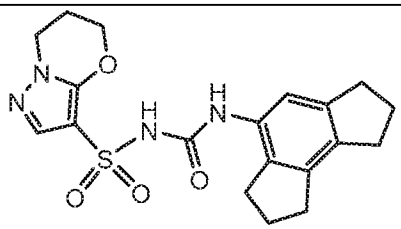
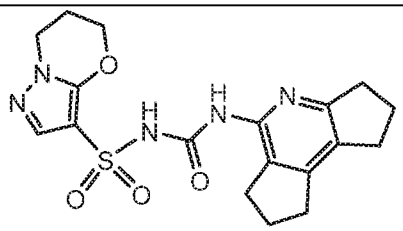
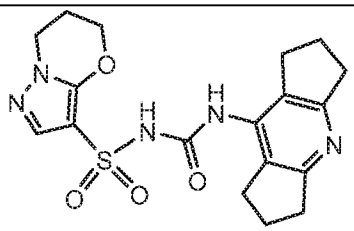
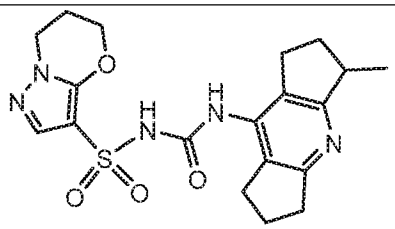
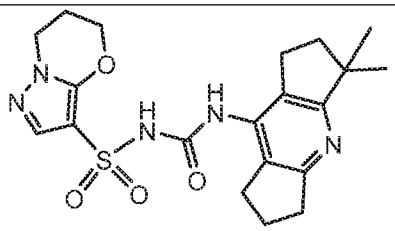
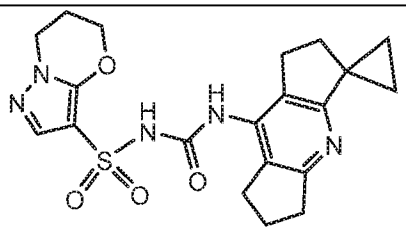
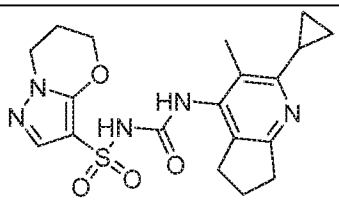
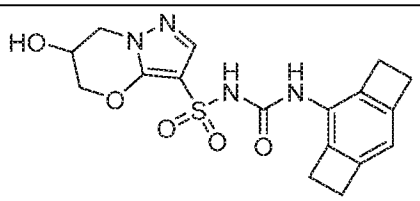
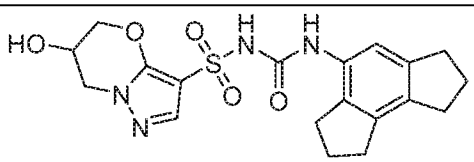
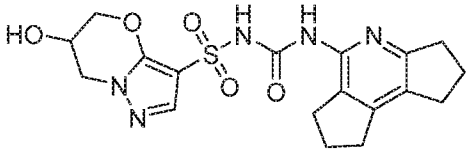
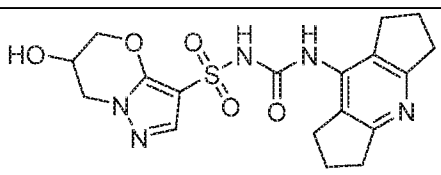
In one embodiment, the present invention relates to a method for the treatment or the prevention of a condition mediated by TNF-α, in particular a gut disease or disorder, in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a gut-targeted NLRP3 antagonist.

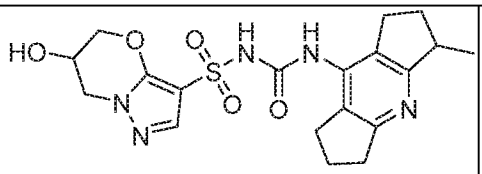
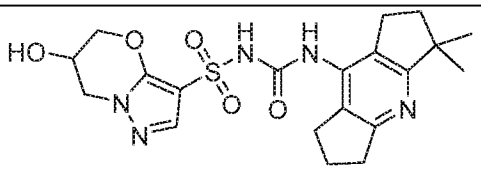
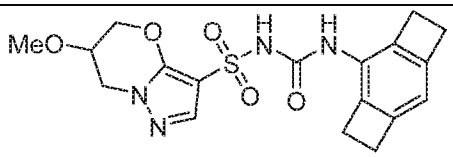
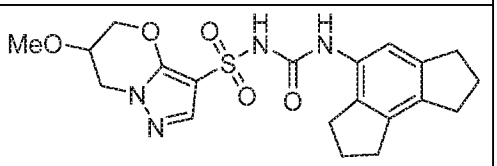
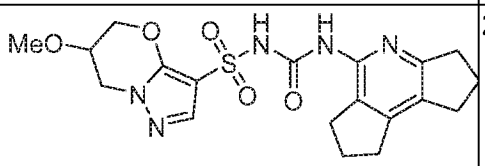
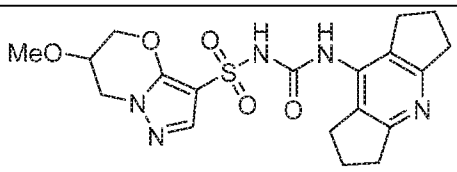
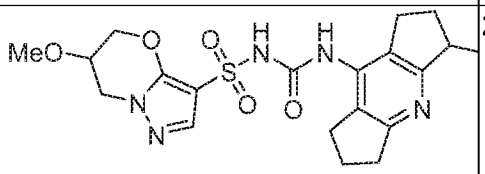
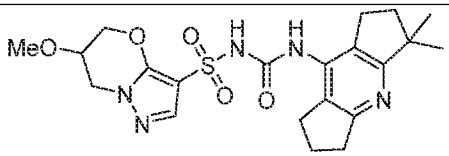
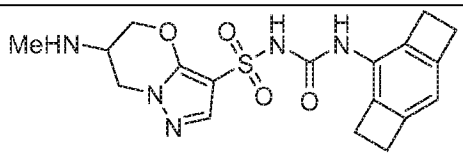
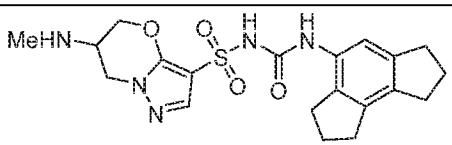
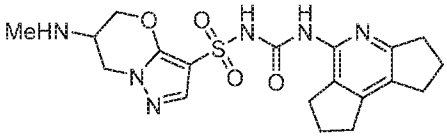
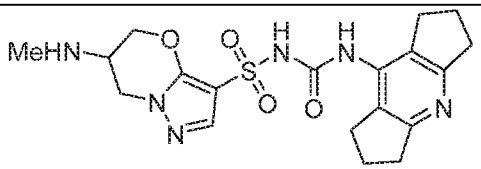
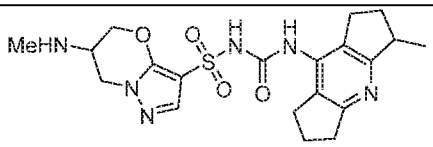
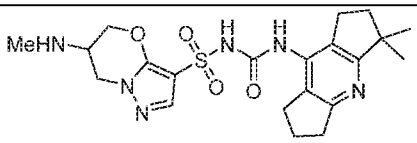
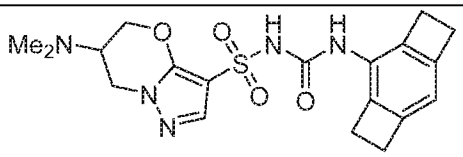
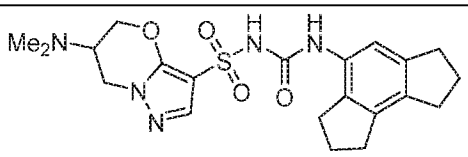
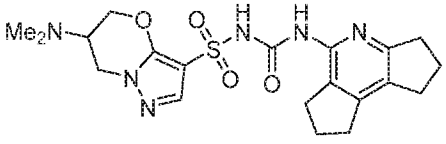
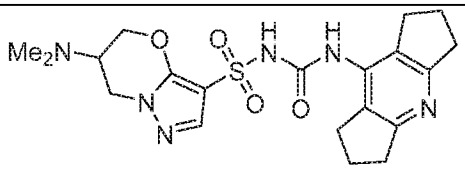
It is understood that the combination of variables in the formulae herein is such that the compounds are stable.

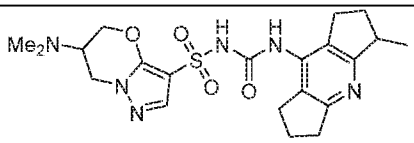
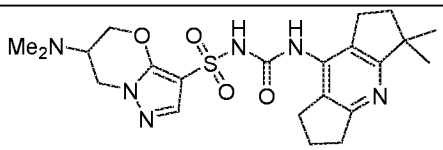
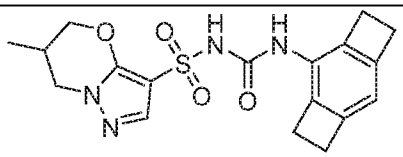
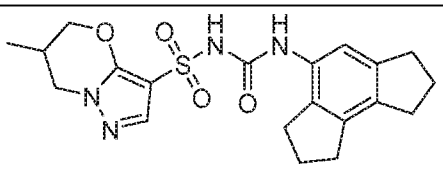
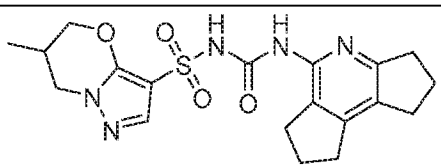
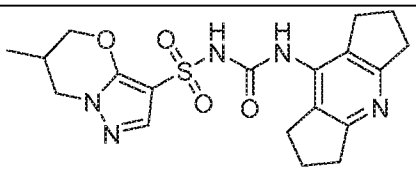
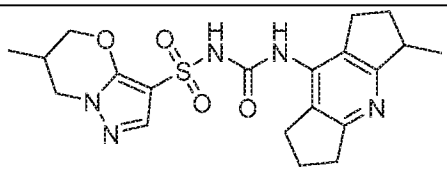
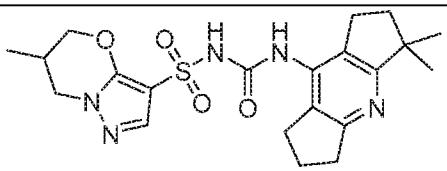
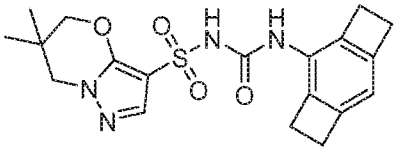
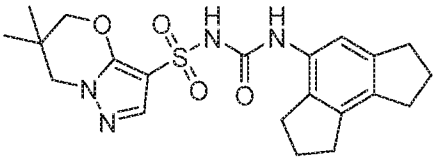
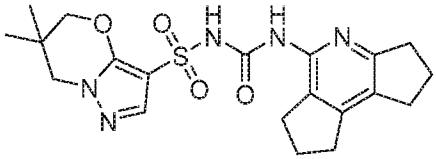
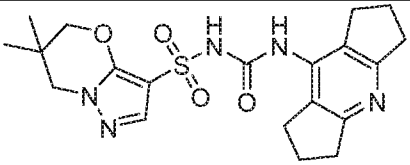
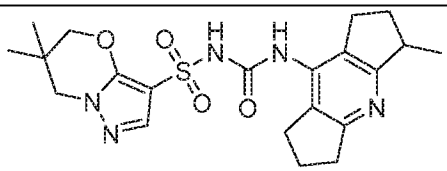
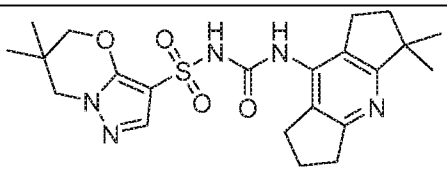
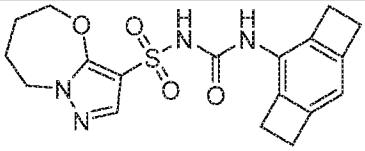
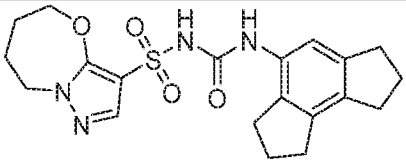
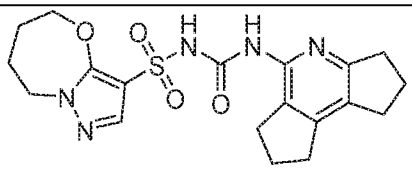
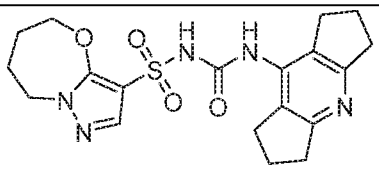
In some embodiments, provided herein is a compound that is selected from the group consisting of the compounds in Table 1A:

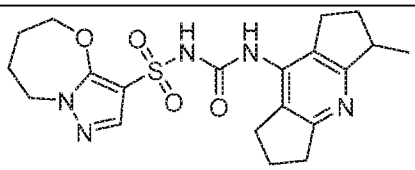
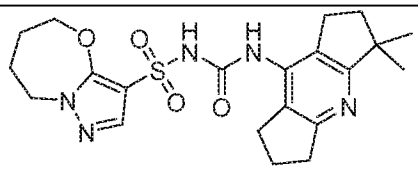
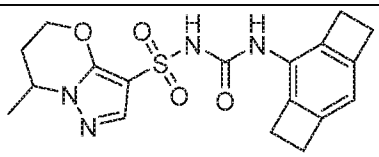
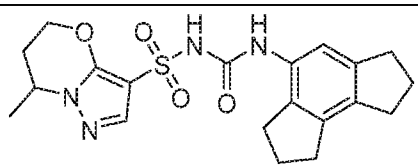
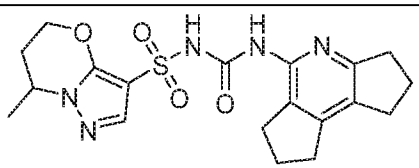
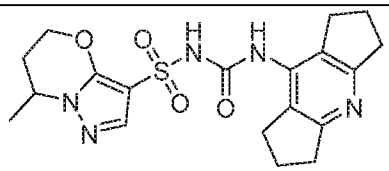
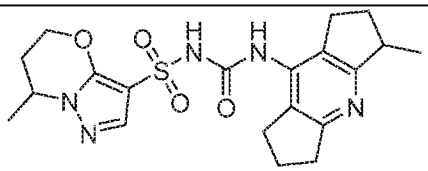
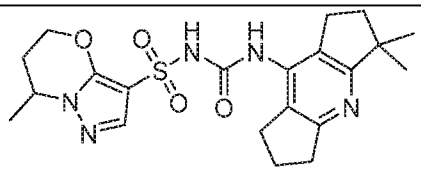
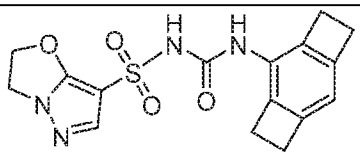
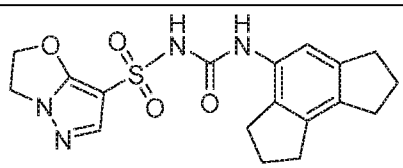
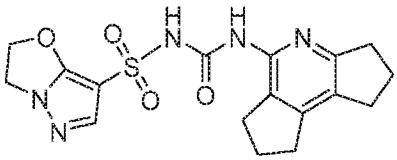
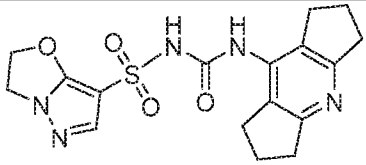
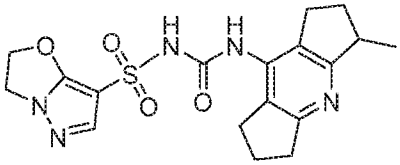
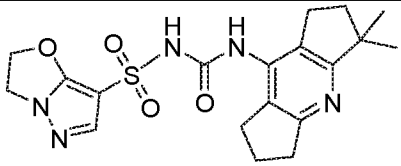
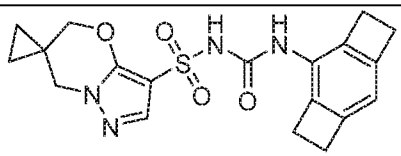
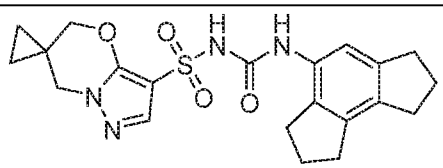
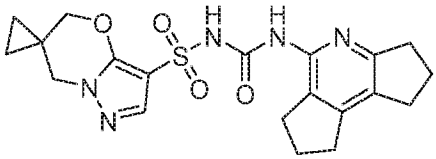
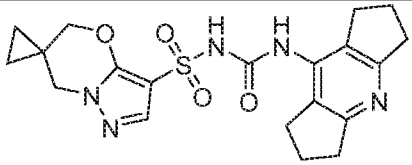
Table 1A.

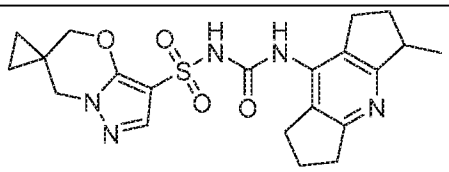
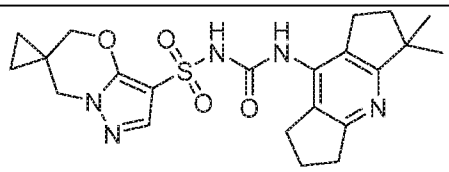
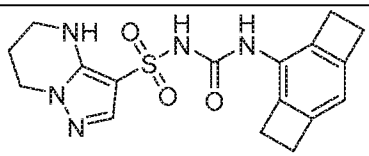
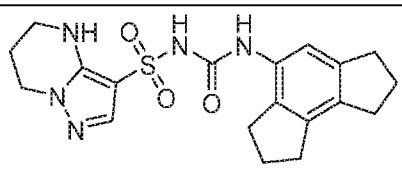
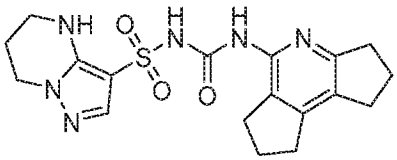
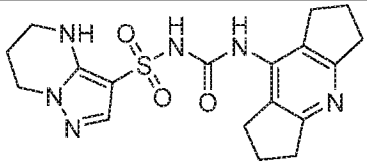
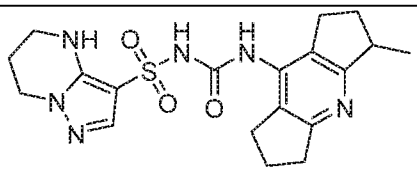
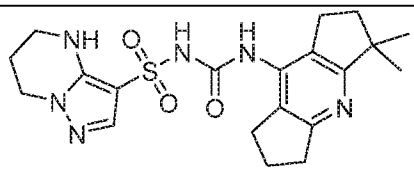
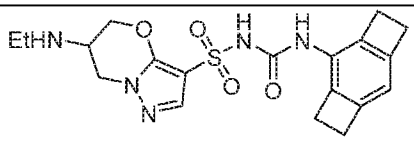
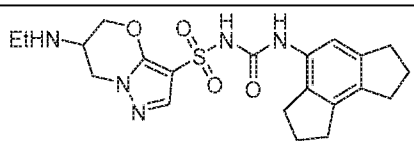
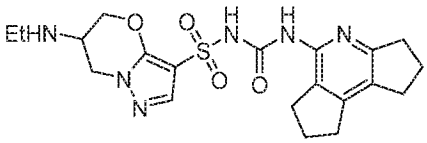
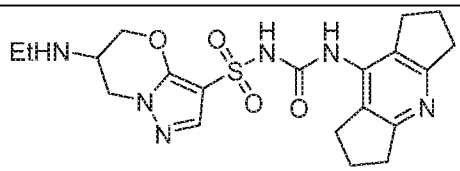
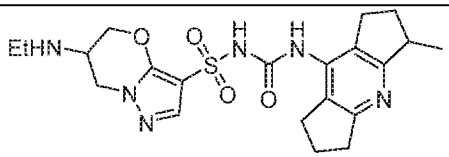
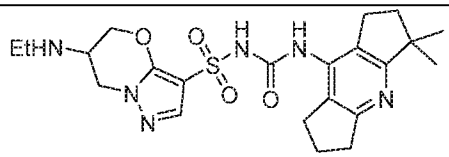
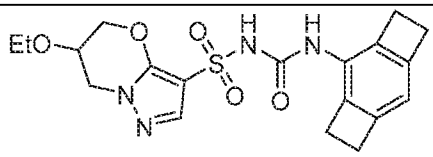
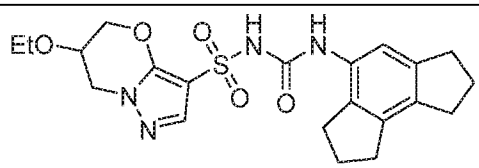
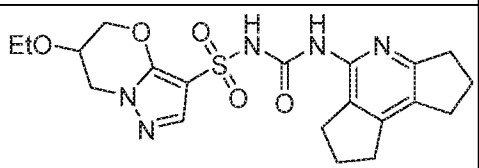
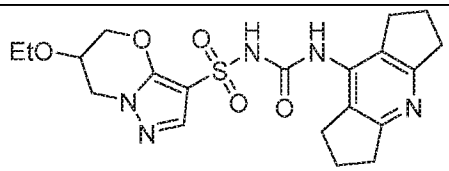
Comp. No.	Structure	Comp. No.	Structure
1		2	
3		4	
5		6	

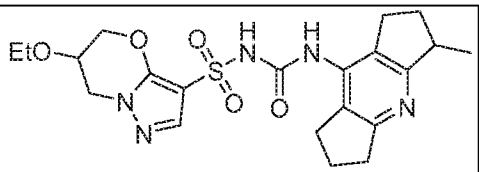
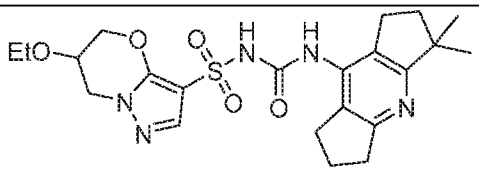
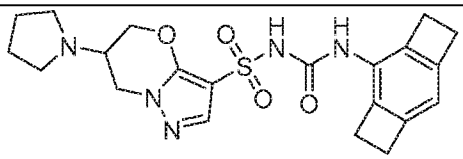
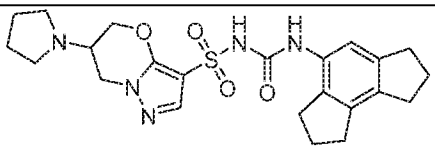
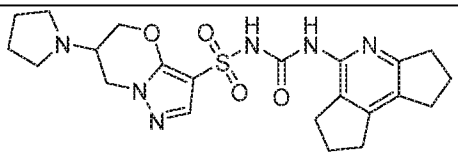
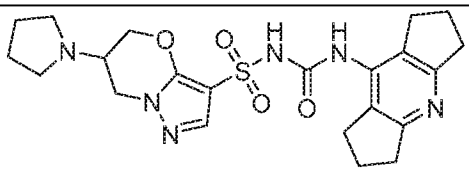
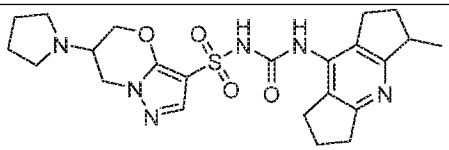
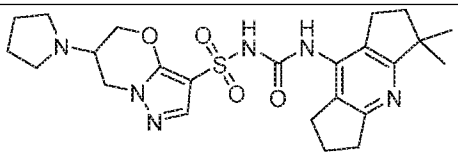
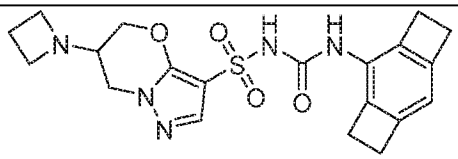
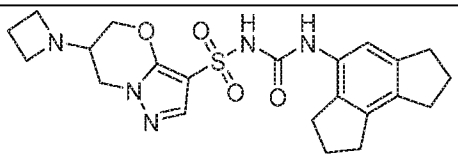
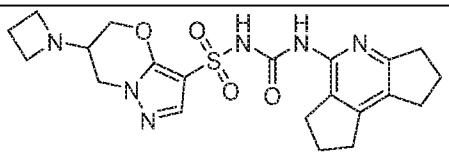
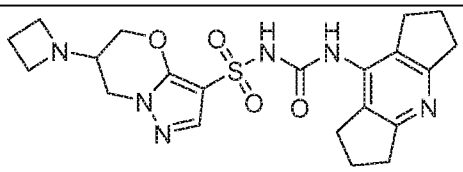
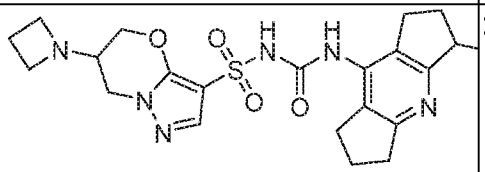
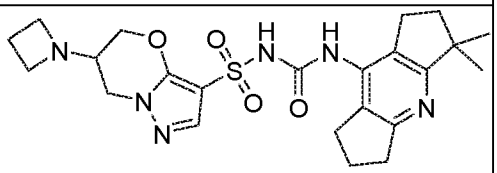
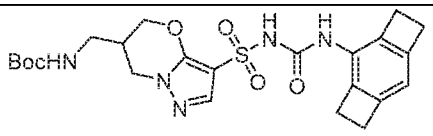
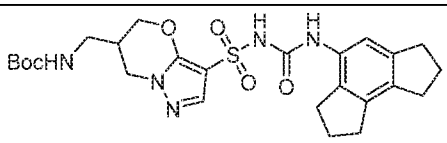
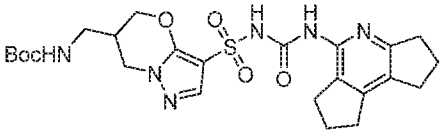
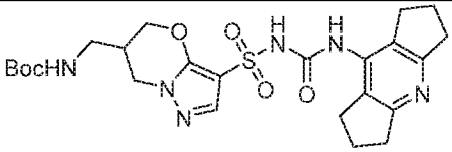
7		8	
9		10	
11		12	
13		14	
15		16	
17		18	
19		20	

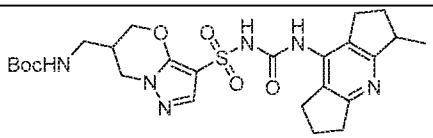
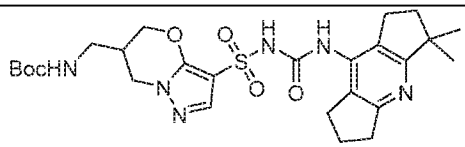
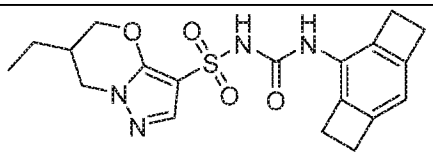
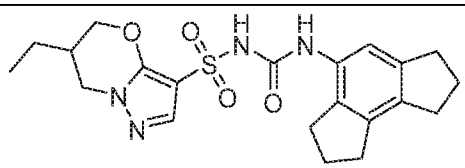
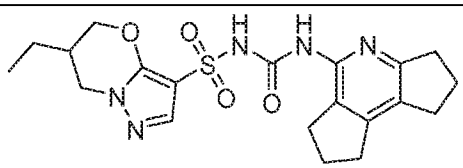
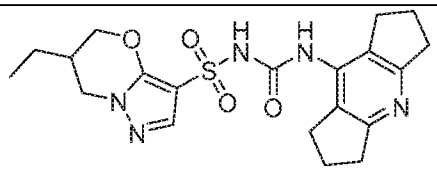
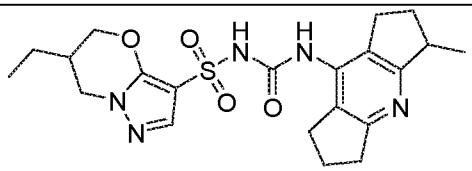
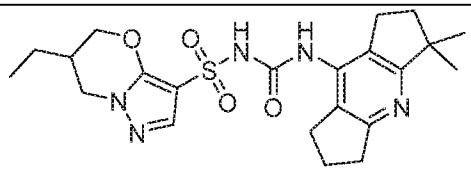
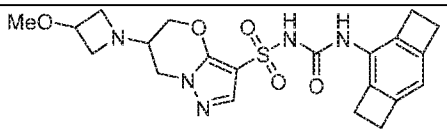
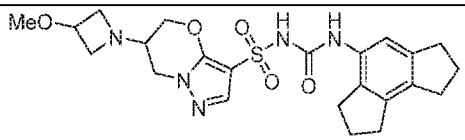
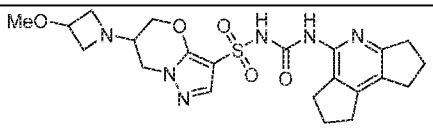
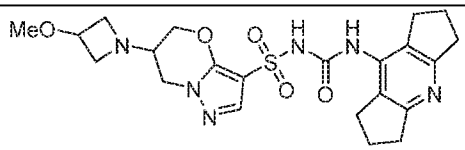
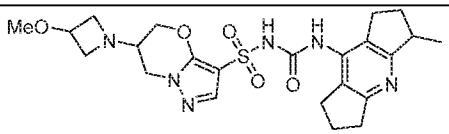
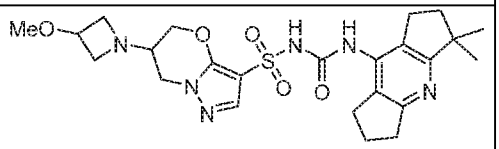
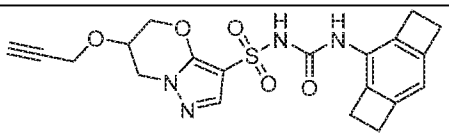
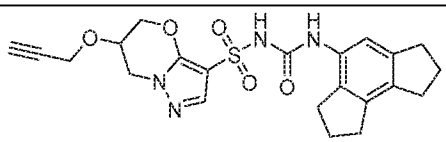
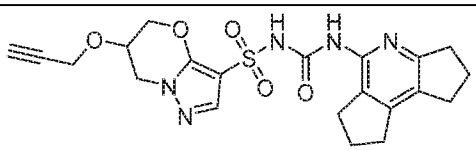
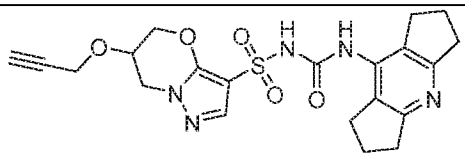
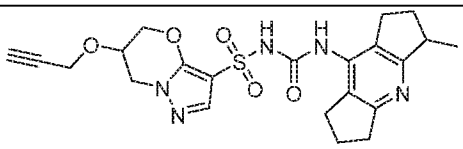
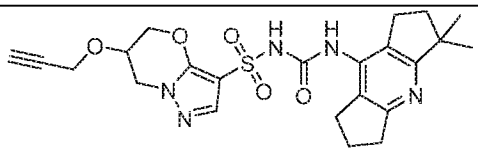
21		22	
23		24	
25		26	
27		28	
29		30	
31		32	
33		34	
35		36	
37		38	

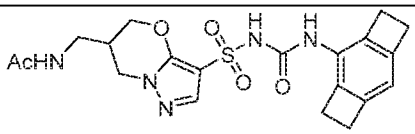
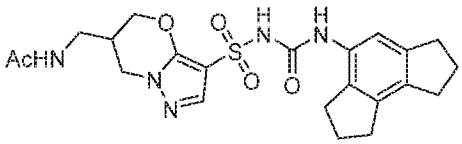
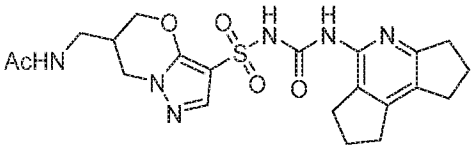
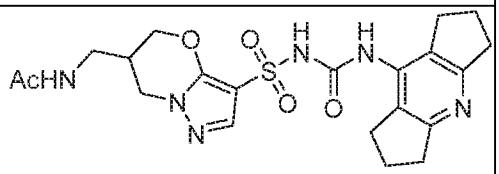
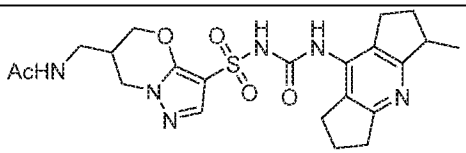
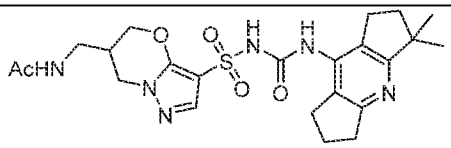
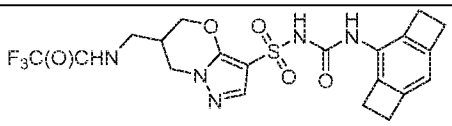
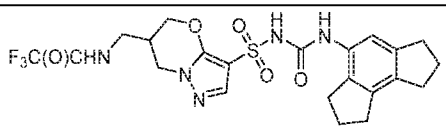
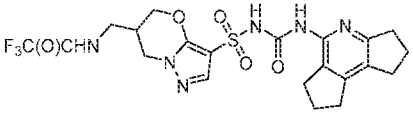
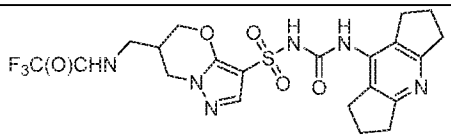
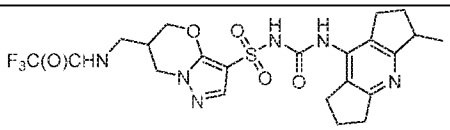
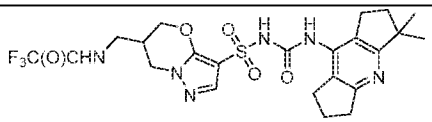
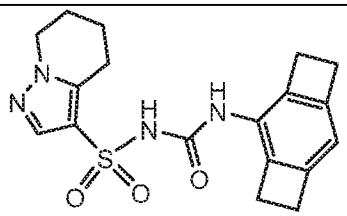
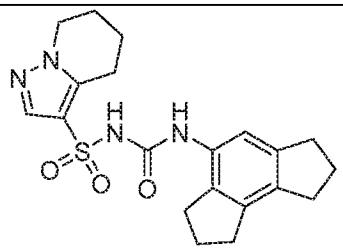
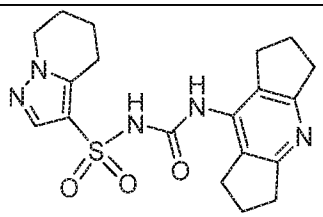
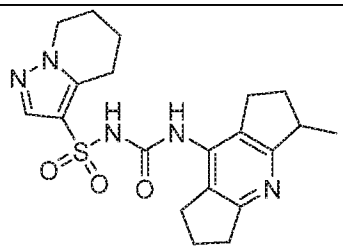
39		40	
41		42	
43		44	
45		46	
47		48	
49		50	
51		52	
53		54	
55		56	

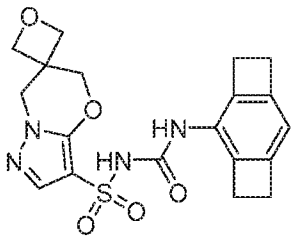
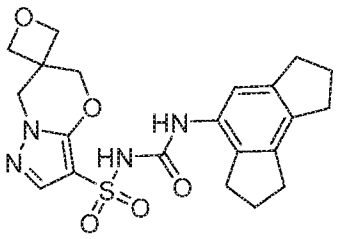
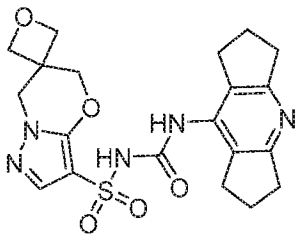
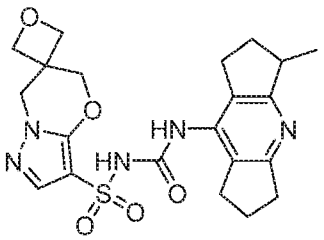
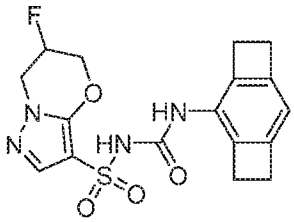
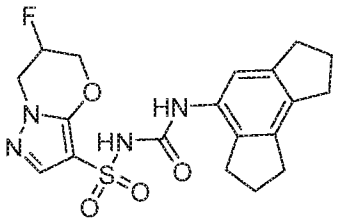
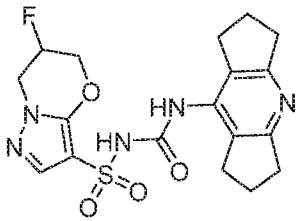
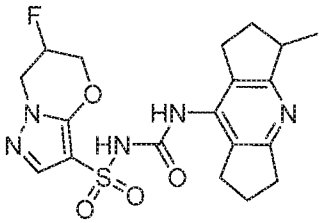
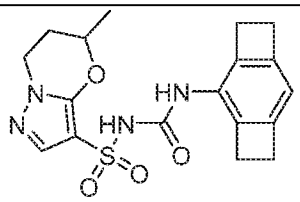
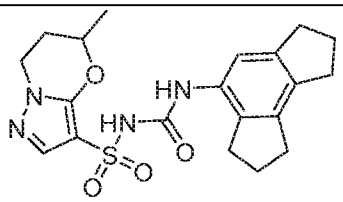
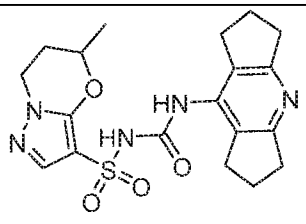
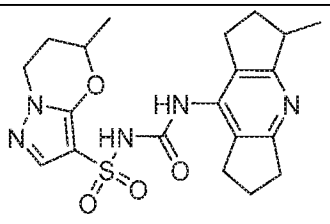
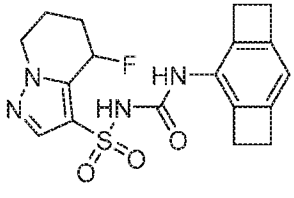
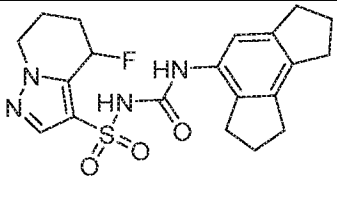
57		58	
59		60	
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	
73		74	

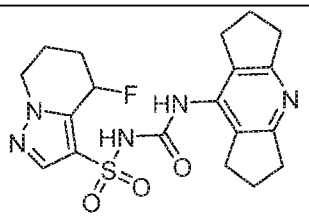
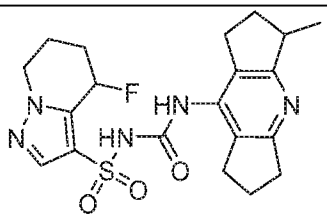
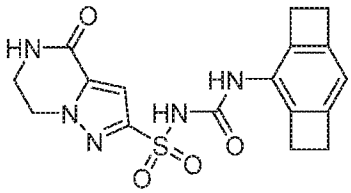
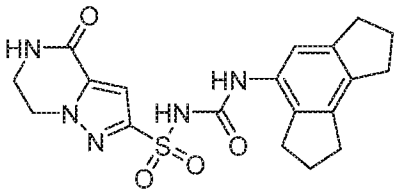
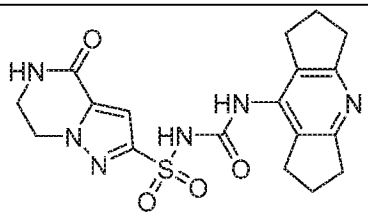
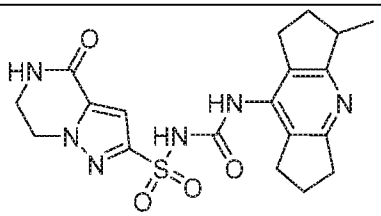
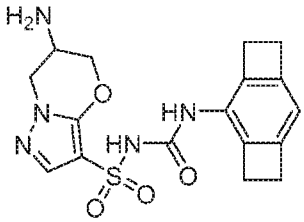
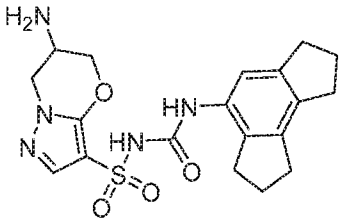
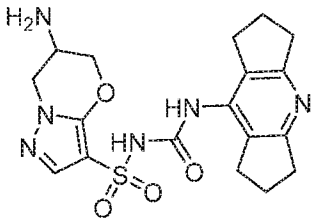
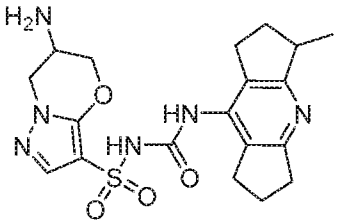
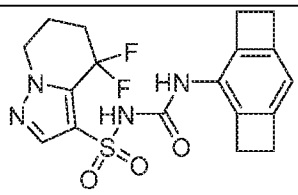
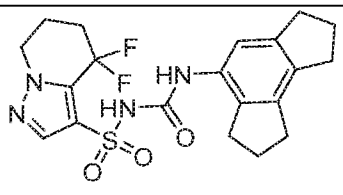
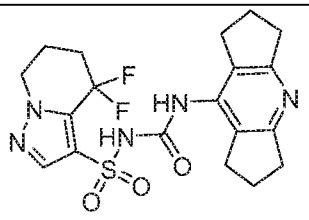
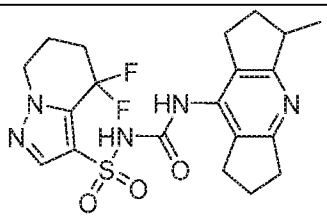
75		76	
77		78	
79		80	
81		82	
83		84	
85		86	
87		88	
89		90	
91		92	

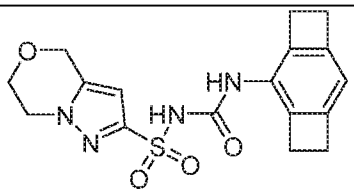
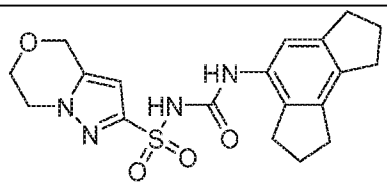
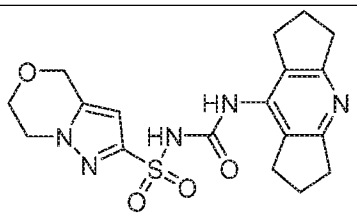
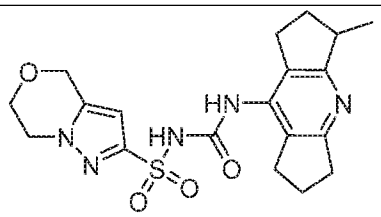
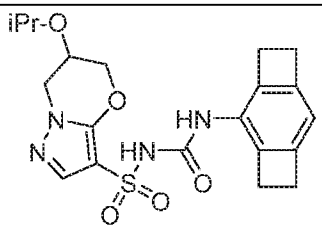
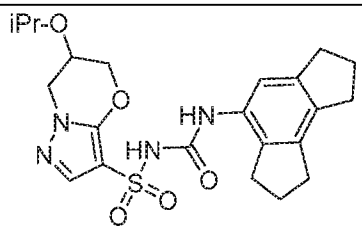
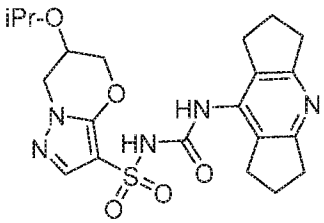
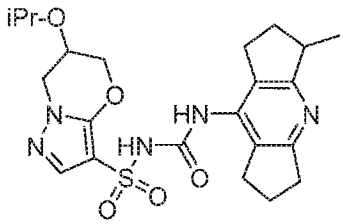
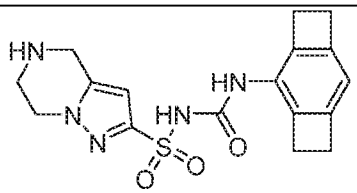
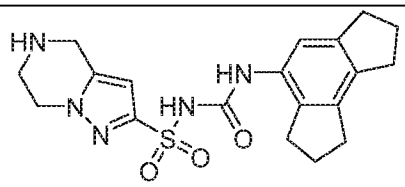
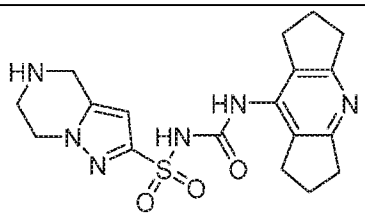
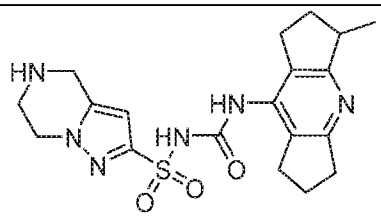
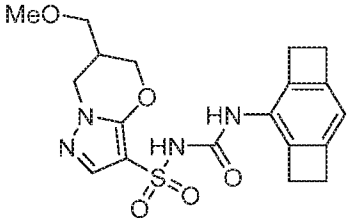
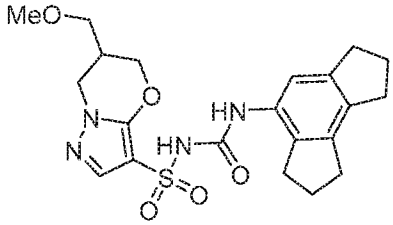
93		94	
95		96	
97		98	
99		100	
101		102	
103		104	
105		106	
107		108	
109		110	

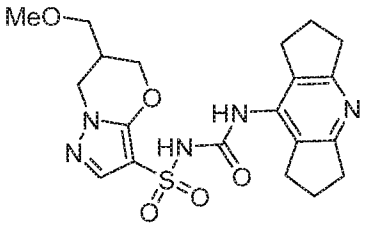
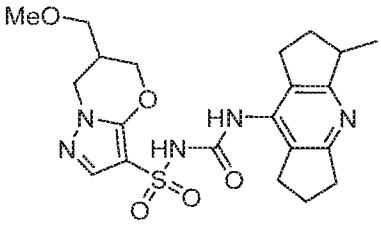
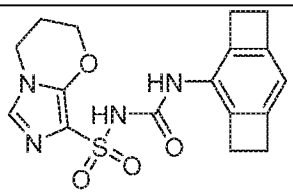
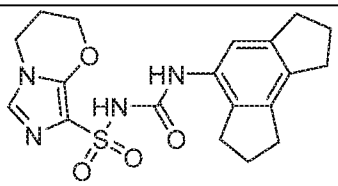
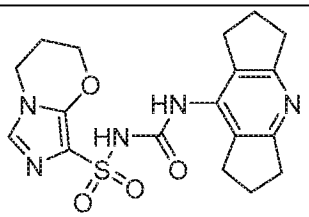
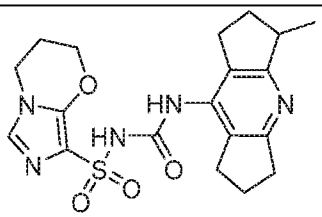
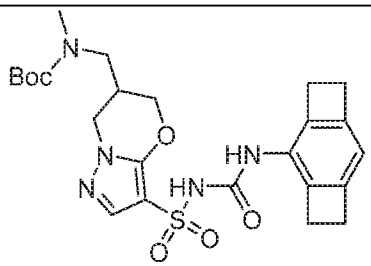
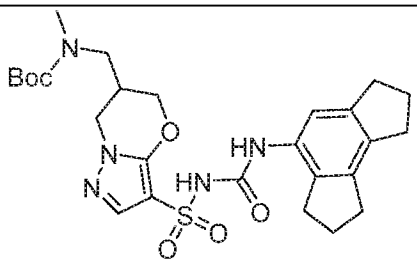
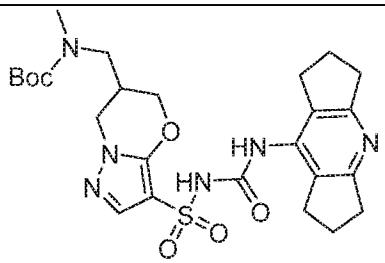
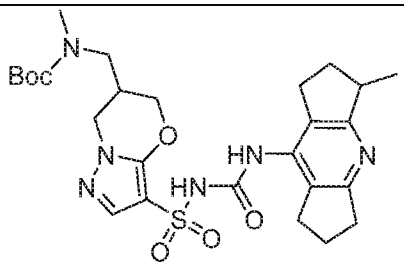
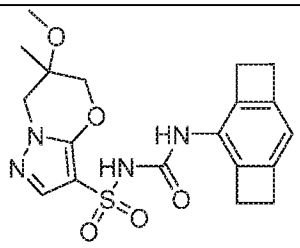
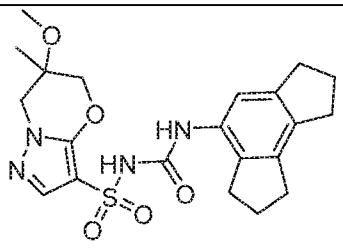
111		112	
113		114	
115		116	
117		118	
119		120	
121		122	
123		124	
125		126	
127		128	
129		130	

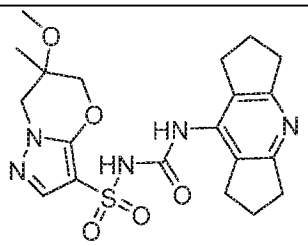
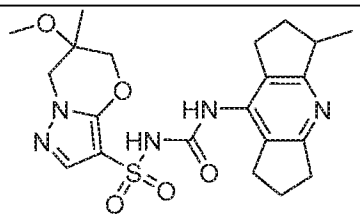
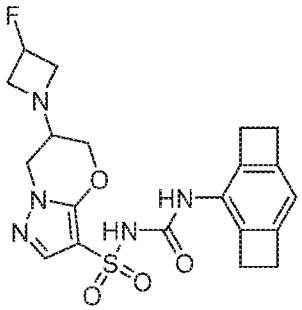
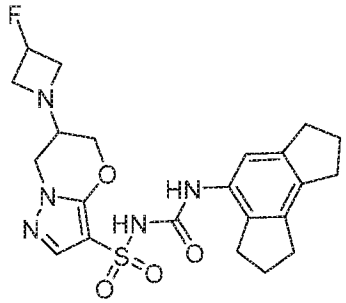
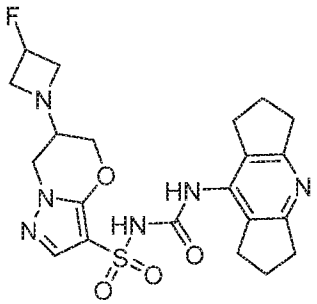
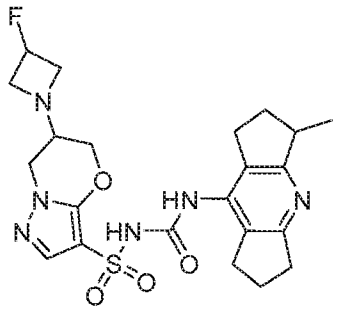
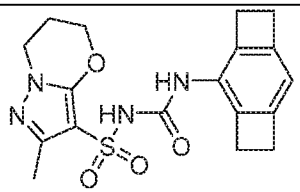
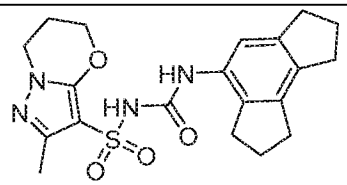
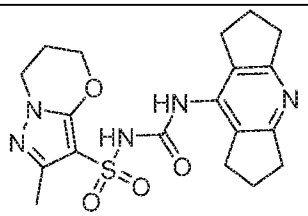
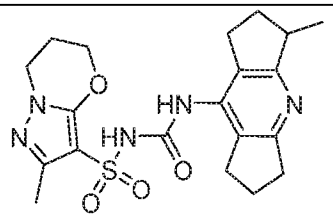
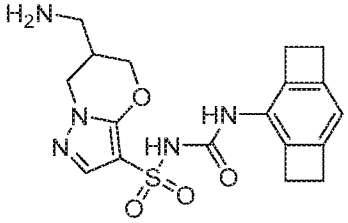
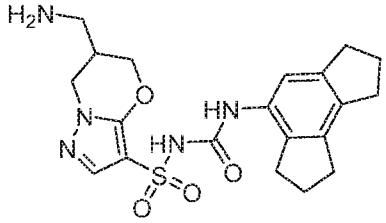
131		132	
133		134	
135		136	
137		138	
139		140	
141		142	
143		144	
145		146	

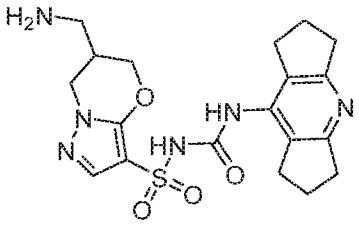
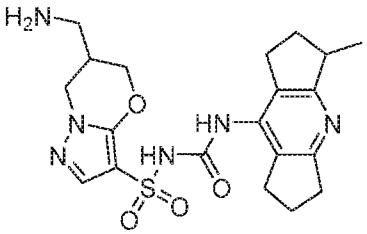
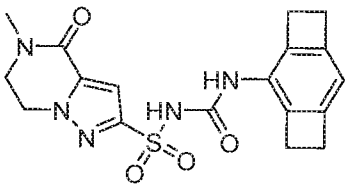
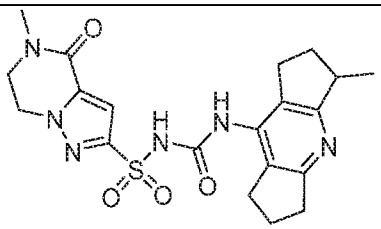
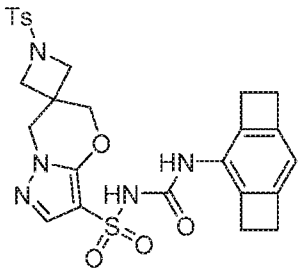
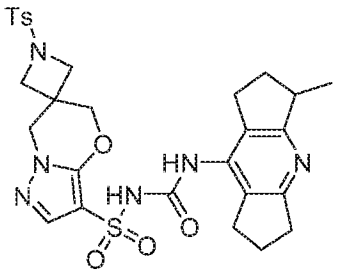
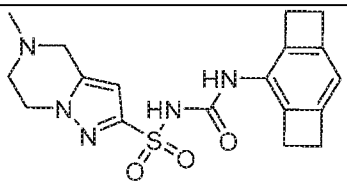
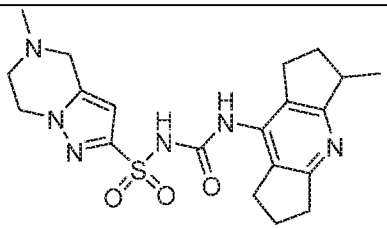
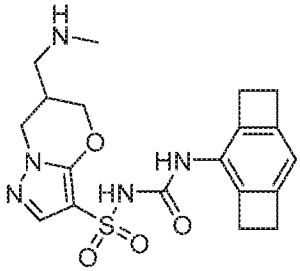
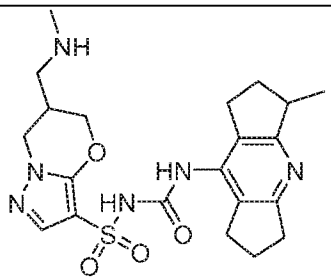
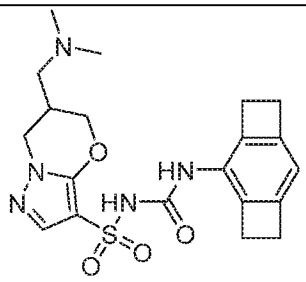
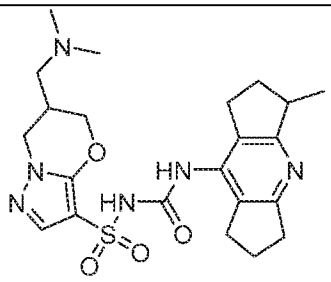
147		148	
149		150	
151		152	
153		154	
155		156	
157		158	
159		160	

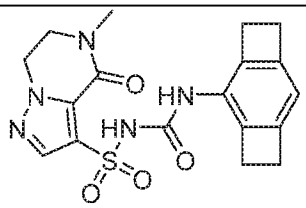
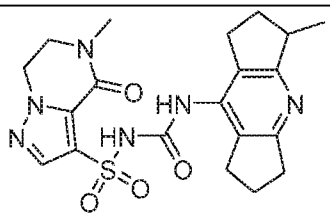
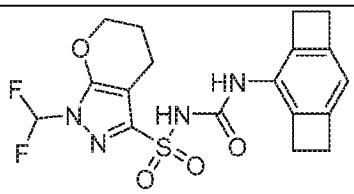
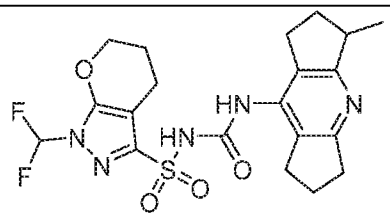
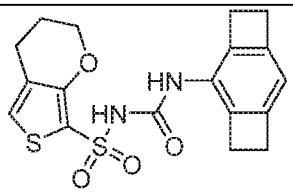
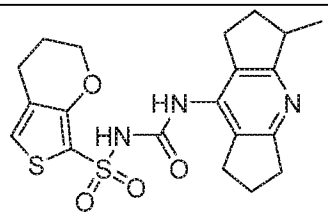
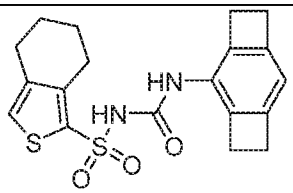
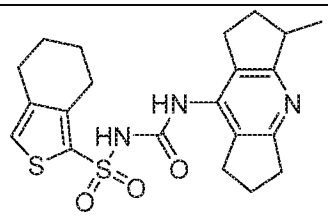
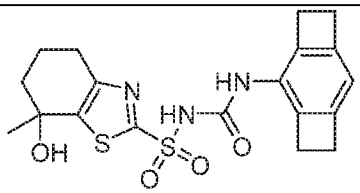
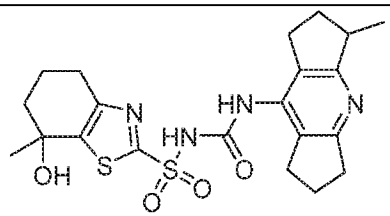
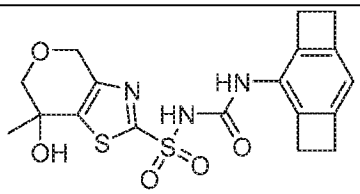
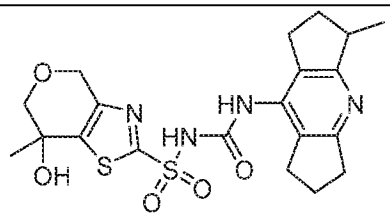
161		162	
163		164	
165		166	
167		168	
169		170	
171		172	
173		174	

175		176	
177		178	
179		180	
181		182	
183		184	
185		186	
187		188	

189		190	
191		192	
193		194	
195		196	
197		198	
199		200	

201		202	
203		204	
205		206	
207		208	
209		210	
211		212	

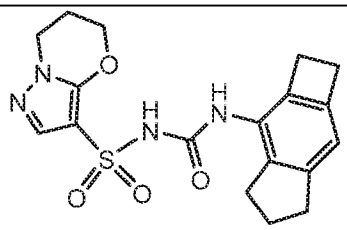
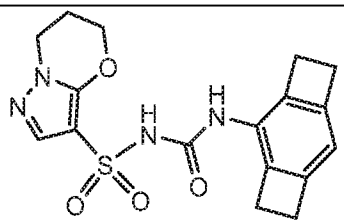
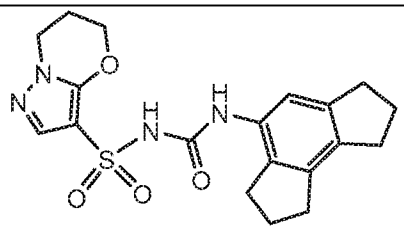
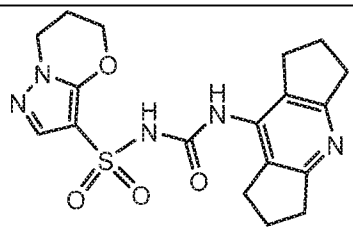
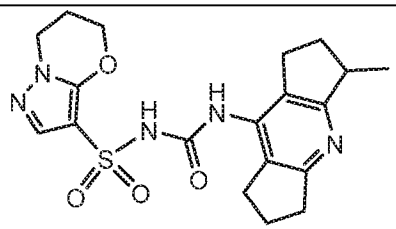
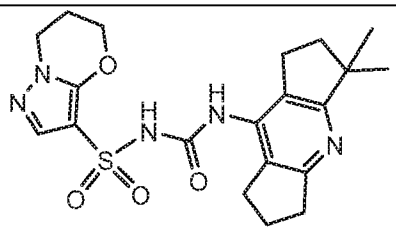
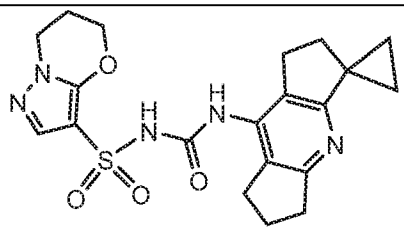
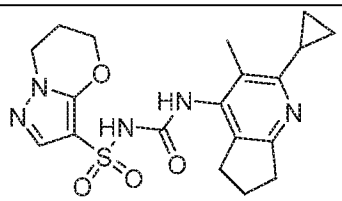
213		**214**	
215		**216**	
217		**218**	
219		**220**	
221		**222**	
223		**224**	

225		226	
227		228	
229		230	
231		232	
233		234	
235		236	

and pharmaceutically acceptable salts thereof.

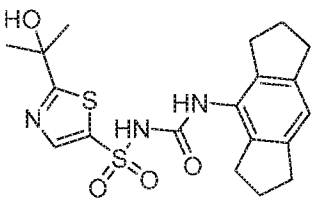
In some embodiments, provided herein is a compound that is selected from the group consisting of the compounds in Table 1B:

Table 1B.

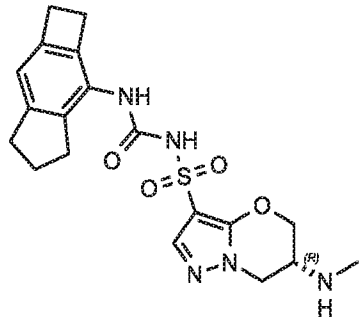
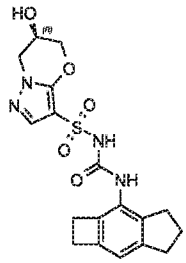
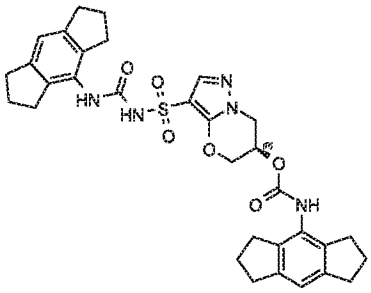
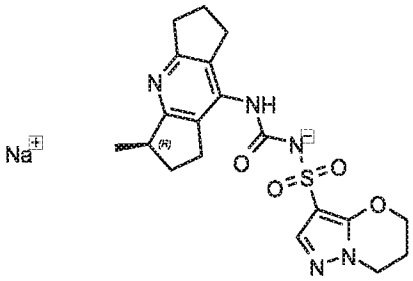
Comp. No.	Structure	Comp. No.	
8		9	
10		12	
13		14	
15		16	

and pharmaceutically acceptable salts thereof.

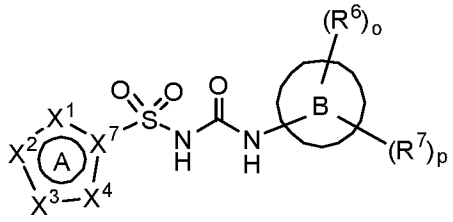
In another aspect, provided herein is a compound having the structure:

 (compound **300**).

In some embodiments, provided herein is a compound that is selected from the group consisting of the compounds in Table 1C:

Comp. No.	Structure	Comp. No.	
401		402	
403		404	

In another aspect, provided herein is a compound of Formula AB,



Formula AB

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;
X^3 is O, S, N, CR^3, or NR^3;
X^4 is O, S, N, CR^4, or NR^4;
X^7 is N or C;

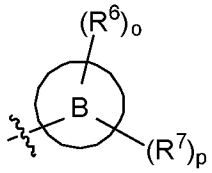
each of R^1, R^2, R^3, and R^4, when present, is each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, NH-$(C{=}NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

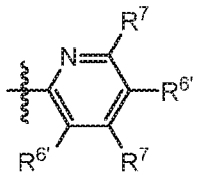
R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or

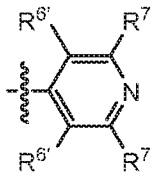
more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;

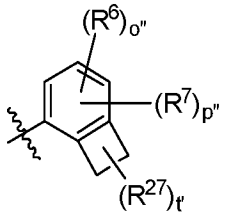
R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;



is selected from the group consisting of:


,


, and,



;

o'' = 0 or 1;

p'' = 0, 1, or 2;

t' is 0, 1, 2, 3, or 4;

R^6 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally

substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

R^7 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

or one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

$R^{6'}$ at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

or at least one pair of $R^{6'}$ and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 cycloalkyl ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted

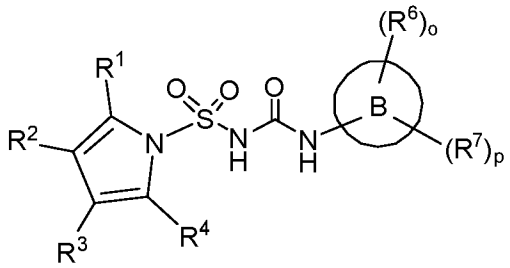
with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

R^{27}, at each occurrence, is independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;
each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;
R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and
each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;
or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a compound of Formula AB,



Formula AB

wherein

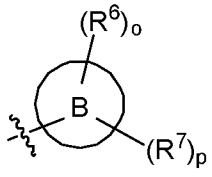
each of R^1, R^2, R^3, and R^4, when present, is each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, NH-$(C{=}NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl

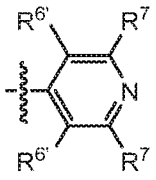
optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

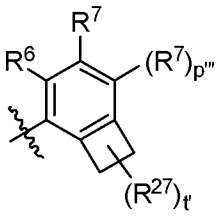
R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;

R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;



is selected from the group consisting of:


, and,


;

p''' = 0 or 1;

t' is 0, 1, 2, 3, or 4;

R^6 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

R^7 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

or one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

both pairs of $R^{6'}$ and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 cycloalkyl ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

R^{27}, at each occurrence, is independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

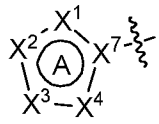
R^{10} is C_1-C_6 alkyl;

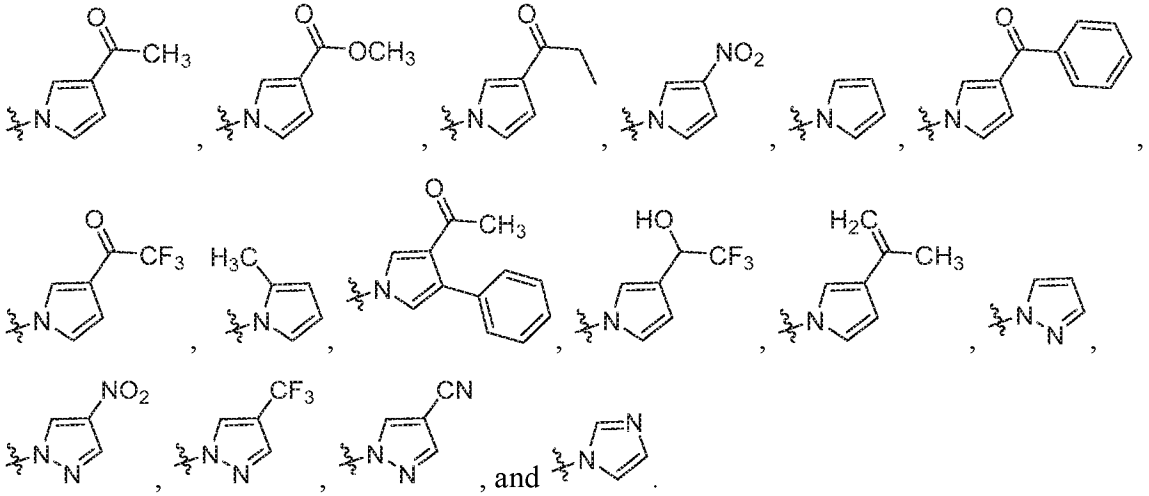
each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;

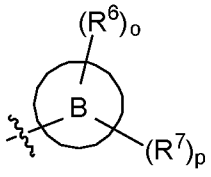
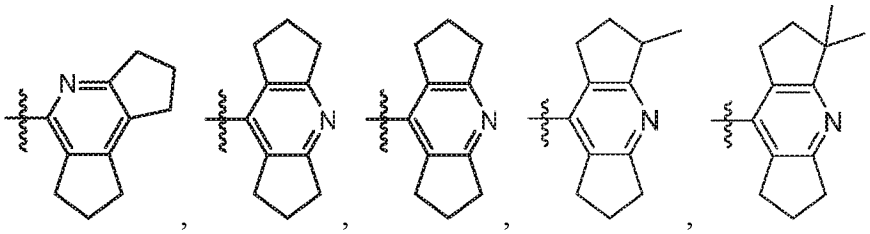
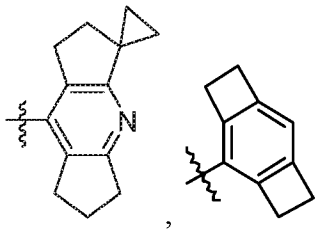
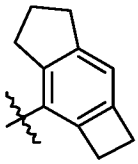
R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and

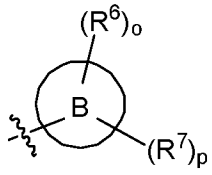
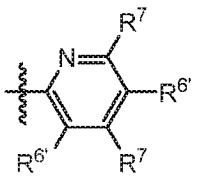
each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

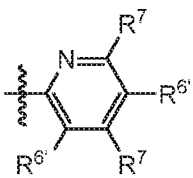
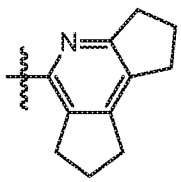
or a pharmaceutically acceptable salt thereof.

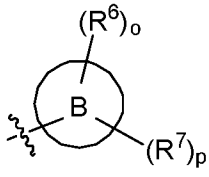
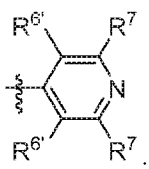
In some embodiments of the compound of Formula AB,  is selected from

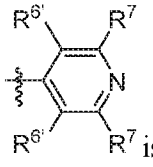
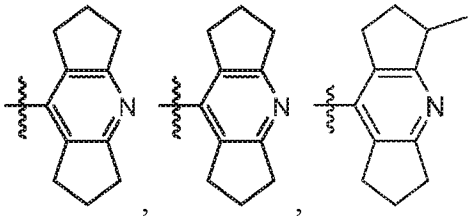
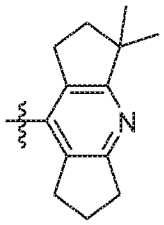
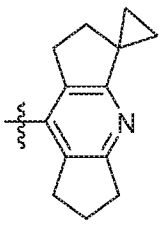


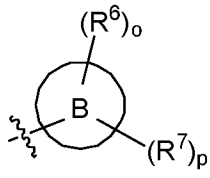
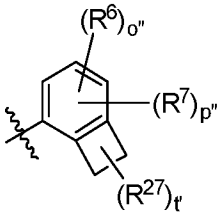
In some embodiments of the compound of Formula AB,  is selected from the group consisting of:  ,  , , and  .

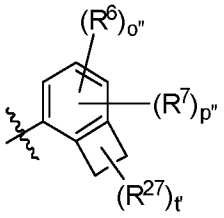
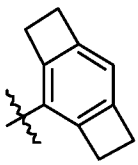
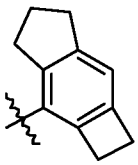
In some embodiments of the compound of Formula AB,  is  .

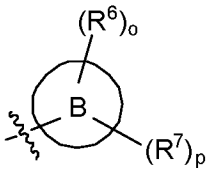
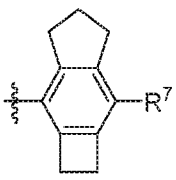
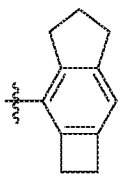
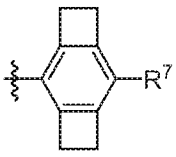
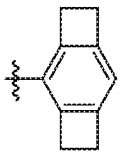
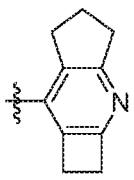
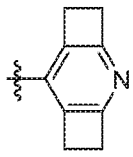
In certain embodiments,  is  .

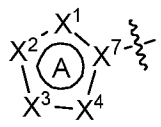
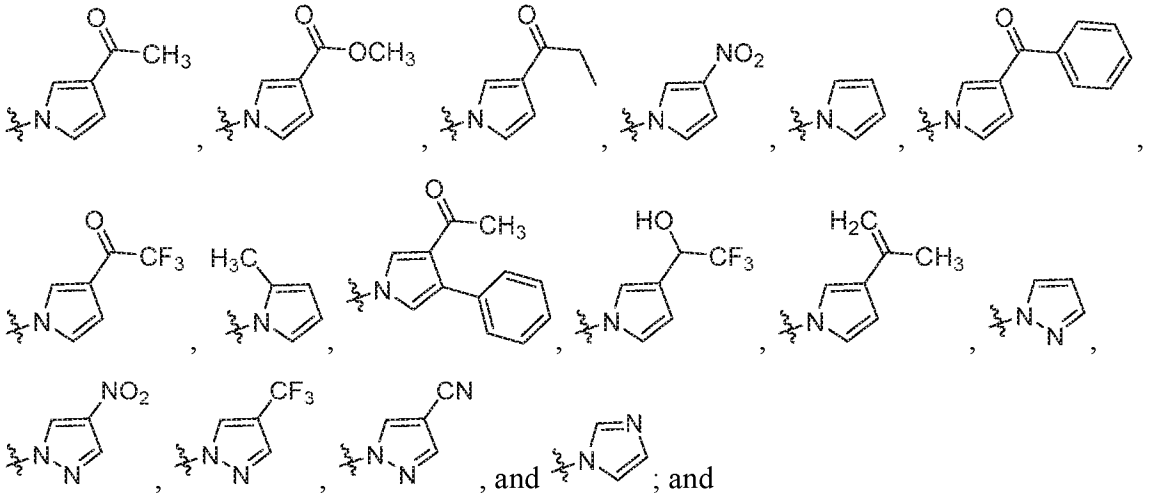
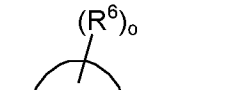
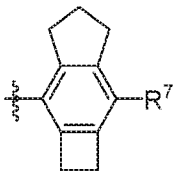
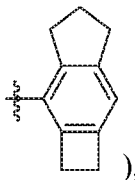
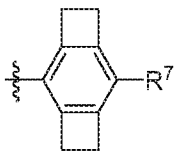
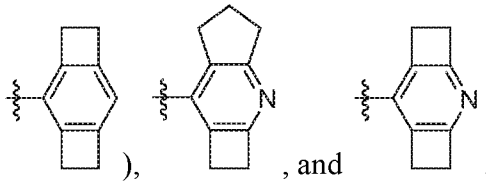
In some embodiments of the compound of Formula AB,  is  .

In certain embodiments,  is selected from  ,  , and  .

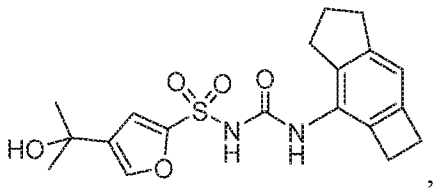
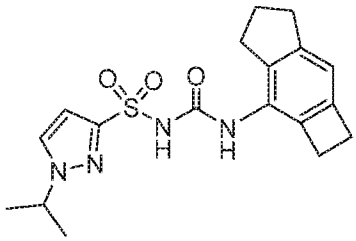
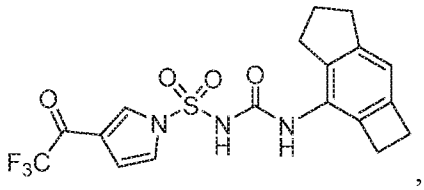
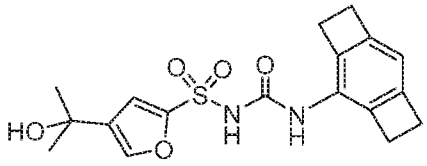
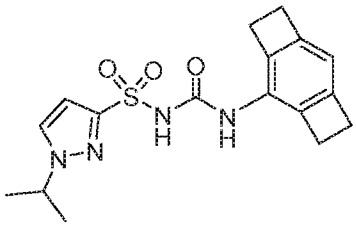
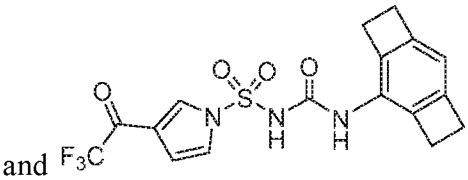
In some embodiments of the compound of Formula AB,  is  .

In certain embodiments,  is selected from  and  .

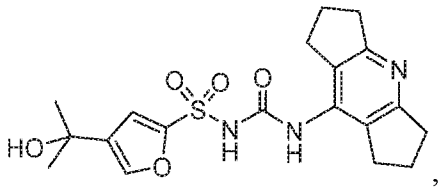
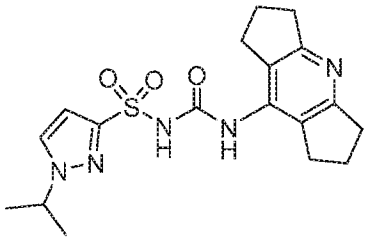
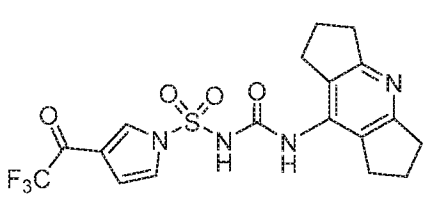
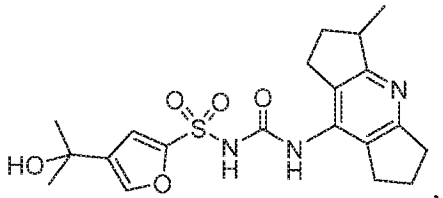
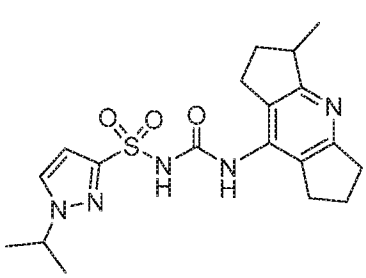
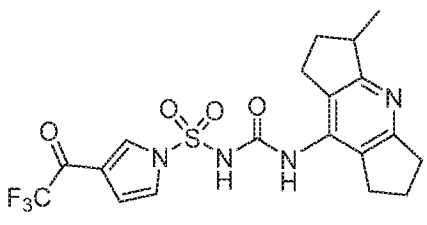
In some embodiments of the compound of Formula AB,  is selected from  (e.g., ),  (e.g., ),  , and  .

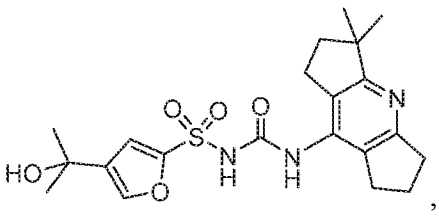
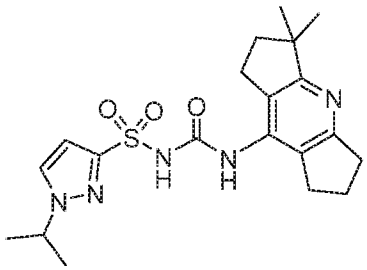
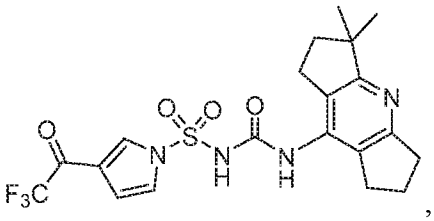
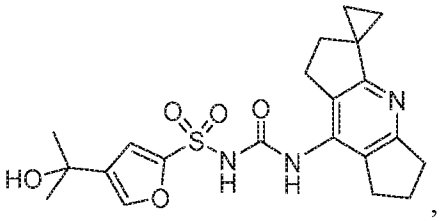
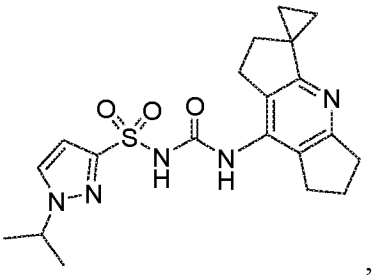
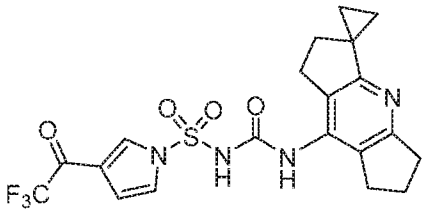
In some embodiments of the compound of Formula AB,  is selected from   is selected from  (e.g., ),  (e.g., ), , and .

In some embodiments of the compound of Formula AB, the compound is selected from the group consisting of:

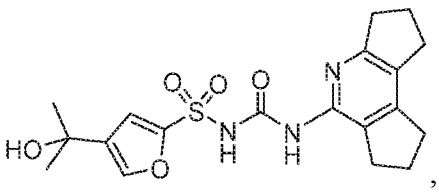
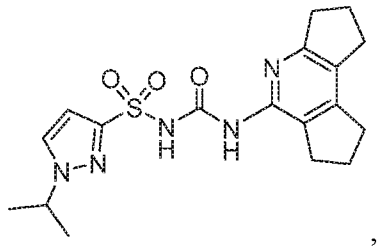
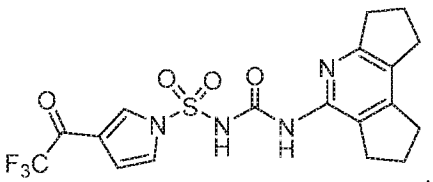

,

,

,

,

,
and 
.

In some embodiments of the compound of Formula AB, the compound is selected from the group consisting of:

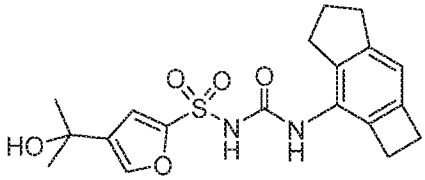

,

,

,

,

,

,

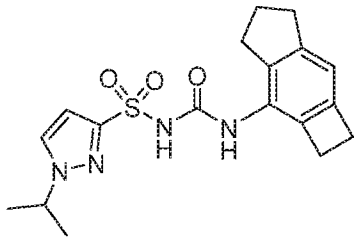

,

,

,

,

,
and

.

In some embodiments of the compound of Formula AB, the compound is selected from the group consisting of:

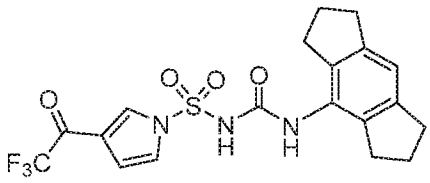

,

, and

.

In some embodiments of the compound of Formula AB, the compound is selected from the group consisting of:



(Compound **301**) and 

(Compound **302**).

In some embodiments, a compound provided herein is 

.

Pharmaceutical Compositions and Administration

General

In some embodiments, a chemical entity (e.g., a compound that modulates (e.g., antagonizes) NLRP3, or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination thereof) is administered as a pharmaceutical composition that includes the chemical entity and one or more pharmaceutically acceptable excipients, and optionally one or more additional therapeutic agents as described herein.

In some embodiments, the chemical entities can be administered in combination with one or more conventional pharmaceutical excipients. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α-, β, and γ-cyclodextrin, or chemically modified

derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a chemical entity as described herein in the range of 0.005% to 100% with the balance made up from non-toxic excipient may be prepared. The contemplated compositions may contain 0.001%-100% of a chemical entity provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 22nd Edition (Pharmaceutical Press, London, UK. 2012).

In some embodiments, an NLRP3 antagonist and/or an anti-TNFα agent disclosed herein is administered as a pharmaceutical composition that includes the NLRP3 antagonist and/or anti-TNFα agent and one or more pharmaceutically acceptable excipients, and optionally one or more additional therapeutic agents as described herein. Preferably the pharmaceutical composition that includes an NLRP3 antagonist and an anti-TNFα agent.

Preferably the above pharmaceutical composition embodiments comprise an NLRP3 antagonist disclosed herein. More preferably the above pharmaceutical composition embodiments comprise an NLRP3 antagonist and an anti-TNFα agent disclosed herein.

Routes of Administration and Composition Components

In some embodiments, the chemical entities described herein or a pharmaceutical composition thereof can be administered to subject in need thereof by any accepted route of administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusial, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral and vaginal. In certain embodiments, a preferred route of administration is parenteral (e.g., intratumoral).

Compositions can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified. The preparation of such formulations will be known to those of skill in the art in light of the present disclosure.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Intratumoral injections are discussed, e.g., in Lammers, et al., *"Effect of Intratumoral Injection on the Biodistribution and the Therapeutic Potential of HPMA Copolymer-Based Drug Delivery Systems" Neoplasia*. **2006,** *10*, 788–795.

In certain embodiments, the chemical entities described herein or a pharmaceutical composition thereof are suitable for local, topical administration to the digestive or GI tract, e.g., rectal administration. Rectal compositions include, without limitation, enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, and enemas (e.g., retention enemas).

Pharmacologically acceptable excipients usable in the rectal composition as a gel, cream, enema, or rectal suppository, include, without limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), glycerine, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol Vaseline, anhydrous lanolin, shark liver oil, sodium saccharinate, menthol, sweet almond oil, sorbitol, sodium benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbomers, carbopol, methyloxybenzoate, macrogol cetostearyl ether, cocoyl caprylocaprate, isopropyl alcohol, propylene glycol, liquid paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium metabisulfite, grapefruit seed extract, methyl sulfonyl methane (MSM) , lactic acid, glycine, vitamins, such as vitamin A and E and potassium acetate.

In certain embodiments, suppositories can be prepared by mixing the chemical entities described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum and release the active compound. In other embodiments, compositions for rectal administration are in the form of an enema.

In other embodiments, the compounds described herein or a pharmaceutical composition thereof are suitable for local delivery to the digestive or GI tract by way of oral administration (e.g., solid or liquid dosage forms.).

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the chemical entity is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders

such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a chemical entity provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, marume, solution or suspension (*e.g.*, in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more chemical entities provided herein or additional active agents are physically separated are also contemplated; *e.g.*, capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also contemplated.

Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid.

In certain embodiments the excipients are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well-known sterilization techniques. For various oral dosage form excipients such as tablets and capsules sterility is not required. The USP/NF standard is usually sufficient.

In certain embodiments, solid oral dosage forms can further include one or more components that chemically and/or structurally predispose the composition for delivery of the chemical entity to the stomach or the lower GI; e.g., the ascending colon and/or transverse colon and/or distal colon and/or small bowel. Exemplary formulation techniques are described in, e.g., Filipski, K.J., et al., *Current Topics in Medicinal Chemistry,* **2013,** *13,* 776-802, which is incorporated herein by reference in its entirety.

Examples include upper-GI targeting techniques, e.g., Accordion Pill (Intec Pharma), floating capsules, and materials capable of adhering to mucosal walls.

Other examples include lower-GI targeting techniques. For targeting various regions in the intestinal tract, several enteric/pH-responsive coatings and excipients are available. These materials are typically polymers that are designed to dissolve or erode at specific pH ranges, selected based upon the GI region of desired drug release. These materials also function to protect acid labile drugs from gastric fluid or limit exposure in cases where the active ingredient may be irritating to the upper GI (e.g., hydroxypropyl methylcellulose phthalate series, Coateric (polyvinyl acetate phthalate), cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate, Eudragit series (methacrylic acid–methyl methacrylate copolymers), and Marcoat). Other techniques include dosage forms that respond to local flora in the GI tract, Pressure-controlled colon delivery capsule, and Pulsincap.

Ocular compositions can include, without limitation, one or more of any of the following: viscogens (e.g., Carboxymethylcellulose, Glycerin, Polyvinylpyrrolidone, Polyethylene glycol); Stabilizers (e.g., Pluronic (triblock copolymers), Cyclodextrins); Preservatives (e.g., Benzalkonium chloride, ETDA, SofZia (boric acid, propylene glycol, sorbitol, and zinc chloride; Alcon Laboratories, Inc.), Purite (stabilized oxychloro complex; Allergan, Inc.)).

Topical compositions can include ointments and creams. Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic,

cationic or amphoteric surfactant. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing.

In any of the foregoing embodiments, pharmaceutical compositions described herein can include one or more one or more of the following: lipids, interbilayer crosslinked multilamellar vesicles, biodegradeable poly(D,L-lactic-co-glycolic acid) [PLGA]-based or poly anhydride-based nanoparticles or microparticles, and nanoporous particle-supported lipid bilayers.

Enema Formulations

In some embodiments, enema formulations containing the chemical entities described herein are provided in "ready-to-use" form.

In some embodiments, enema formulations containing the chemical entities described herein are provided in one or more kits or packs. In certain embodiments, the kit or pack includes two or more separately contained/packaged components, e.g. two components, which when mixed together, provide the desired formulation (e.g., as a suspension). In certain of these embodiments, the two component system includes a first component and a second component, in which: (**i**) the first component (e.g., contained in a sachet) includes the chemical entity (as described anywhere herein) and optionally one or more pharmaceutically acceptable excipients (e.g., together formulated as a solid preparation, e.g., together formulated as a wet granulated solid preparation); and (**ii**) the second component (e.g., contained in a vial or bottle) includes one or more liquids and optionally one or more other pharmaceutically acceptable excipients together forming a liquid carrier. Prior to use (e.g., immediately prior to use), the contents of (**i**) and (**ii**) are combined to form the desired enema formulation, e.g., as a suspension. In other embodiments, each of component (**i**) and (**ii**) is provided in its own separate kit or pack.

In some embodiments, each of the one or more liquids is water, or a physiologically acceptable solvent, or a mixture of water and one or more physiologically acceptable solvents. Typical such solvents include, without limitation, glycerol, ethylene glycol, propylene glycol, polyethylene glycol and polypropylene glycol. In certain embodiments, each of the one or more liquids is water. In other embodiments, each of the one or more liquids is an oil, e.g. natural and/or synthetic oils that are commonly used in pharmaceutical preparations.

Further pharmaceutical excipients and carriers that may be used in the pharmaceutical products herein described are listed in various handbooks (e.g. D. E. Bugay and W. P. Findlay

(Eds) Pharmaceutical excipients (Marcel Dekker, New York, 1999), E-M Hoepfner, A. Reng and P. C. Schmidt (Eds) Fiedler Encyclopedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas (Edition Cantor, Munich, 2002) and H. P. Fielder (Ed) Lexikon der Hilfsstoffe für Pharmazie, Kosmetik and angrenzende Gebiete (Edition Cantor Aulendorf, 1989)).

In some embodiments, each of the one or more pharmaceutically acceptable excipients can be independently selelcted from thickeners, viscosity enhancing agents, bulking agents, mucoadhesive agents, penetration enhanceers, buffers, preservatives, diluents, binders, lubricants, glidants, disintegrants, fillers, solubilizing agents, pH modifying agents, preservatives, stabilizing agents, anti-oxidants, wetting or emulsifying agents, suspending agents, pigments, colorants, isotonic agents, chelating agents, emulsifiers, and diagnostic agents.

In certain embodiments, each of the one or more pharmaceutically acceptable excipients can be independently selelcted from thickeners, viscosity enhancing agents, mucoadhesive agents, buffers, preservatives, diluents, binders, lubricants, glidants, disintegrants, and fillers.

In certain embodiments, each of the one or more pharmaceutically acceptable excipients can be independently selelcted from thickeners, viscosity enhancing agents, bulking agents, mucoadhesive agents, buffers, preservatives, and fillers.

In certain embodiments, each of the one or more pharmaceutically acceptable excipients can be independently selelcted from diluents, binders, lubricants, glidants, and disintegrants.

Examples of thickeners, viscosity enhancing agents, and mucoadhesive agents include without limitation: gums, e.g. xanthan gum, guar gum, locust bean gum, tragacanth gums, karaya gum, ghatti gum, cholla gum, psyllium seed gum and gum arabic; poly(carboxylic acid-containing) based polymers, such as poly (acrylic, maleic, itaconic, citraconic, hydroxyethyl methacrylic or methacrylic) acid which have strong hydrogen-bonding groups, or derivatives thereof such as salts and esters; cellulose derivatives, such as methyl cellulose, ethyl cellulose, methylethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl ethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose or cellulose esters or ethers or derivatives or salts thereof; clays such as manomorillonite clays, e.g. Veegun, attapulgite clay; polysaccharides such as dextran, pectin, amylopectin, agar, mannan or polygalactonic acid or starches such as hydroxypropyl starch or carboxymethyl starch; polypeptides such as casein, gluten, gelatin, fibrin glue; chitosan, e.g. lactate or glutamate or carboxymethyl chitin; glycosaminoglycans such as hyaluronic acid; metals or water soluble salts of alginic acid such as

sodium alginate or magnesium alginate; schleroglucan; adhesives containing bismuth oxide or aluminium oxide; atherocollagen; polyvinyl polymers such as carboxyvinyl polymers; polyvinylpyrrolidone (povidone); polyvinyl alcohol; polyvinyl acetates, polyvinylmethyl ethers, polyvinyl chlorides, polyvinylidenes, and/or the like; polycarboxylated vinyl polymers such as polyacrylic acid as mentioned above; polysiloxanes; polyethers; polyethylene oxides and glycols; polyalkoxys and polyacrylamides and derivatives and salts thereof. Preferred examples can include cellulose derivatives, such as methyl cellulose, ethyl cellulose, methylethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl ethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose or cellulose esters or ethers or derivatives or salts thereof (e.g., methyl cellulose); and polyvinyl polymers such as polyvinylpyrrolidone (povidone).

Examples of preservatives include without limitation: benzalkonium chloride, benzoxonium chloride, benzethonium chloride, cetrimide, sepazonium chloride, cetylpyridinium chloride, domiphen bromide (Bradosol®), thiomersal, phenylmercuric nitrate, phenylmercuric acetate, phenylmercuric borate, methylparaben, propylparaben, chlorobutanol, benzyl alcohol, phenyl ethyl alcohol, chlorohexidine, polyhexamethylene biguanide, sodium perborate, imidazolidinyl urea, sorbic acid, Purite®), Polyquart®), and sodium perborate tetrahydrate and the like.

In certain embodiments, the preservative is a paraben, or a pharmaceutically acceptable salt thereof. In some embodiments, the paraben is an alkyl substituted 4-hydroxybenzoate, or a pharmaceutically acceptable salt or ester thereof. In certain embodiments, the alkyl is a C1-C4 alkyl. In certain embodiments, the preservative is methyl 4-hydroxybenzoate (methylparaben), or a pharmaceutically acceptable salt or ester thereof, propyl 4-hydroxybenzoate (propylparaben), or a pharmaceutically acceptable salt or ester thereof, or a combination thereof.

Examples of buffers include without limitation: phosphate buffer system (sodium dihydrogen phospahate dehydrate, disodium phosphate dodecahydrate, bibasic sodium phosphate, anhydrous monobasic sodium phosphate), bicarbonate buffer system, and bisulfate buffer system.

Examples of disintegrants include, without limitation: carmellose calcium, low substituted hydroxypropyl cellulose (L-HPC), carmellose, croscarmellose sodium, partially pregelatinized starch, dry starch, carboxymethyl starch sodium, crospovidone, polysorbate 80 (polyoxyethylenesorbitan oleate), starch, sodium starch glycolate, hydroxypropyl cellulose

pregelatinized starch, clays, cellulose, alginine, gums or cross linked polymers, such as cross-linked PVP (Polyplasdone XL from GAF Chemical Corp). In certain embodiments, the disintegrant is crospovidone.

Examples of glidants and lubricants (aggregation inhibitors) include without limitation: talc, magnesium stearate, calcium stearate, colloidal silica, stearic acid, aqueous silicon dioxide, synthetic magnesium silicate, fine granulated silicon oxide, starch, sodium laurylsulfate, boric acid, magnesium oxide, waxes, hydrogenated oil, polyethylene glycol, sodium benzoate, stearic acid glycerol behenate, polyethylene glycol, and mineral oil. In certain embodiments, the glidant/lubricant is magnesium stearate, talc, and/or colloidal silica; e.g., magnesium stearate and/or talc.

Examples of diluents, also referred to as "fillers" or "bulking agents" include without limitation: dicalcium phosphate dihydrate, calcium sulfate, lactose (e.g., lactose monohydrate), sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed starches, pregelatinized starch, silicone dioxide, titanium oxide, magnesium aluminum silicate and powdered sugar. In certain embodiments, the diluent is lactose (e.g., lactose monohydrate).

Examples of binders include without limitation: starch, pregelatinized starch, gelatin, sugars (including sucrose, glucose, dxtrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia tragacanth, sodium alginate cellulose, including hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, and veegum, and synthetic polymers such as acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone (povidone). In certain embodiments, the binder is polyvinylpyrrolidone (povidone).

In some embodiments, enema formulations containing the chemical entities described herein include water and one or more (e.g., all) of the following excipients:

- One or more (e.g., one, two, or three) thickeners, viscosity enhancing agents, binders, and/or mucoadhesive agents (e.g., cellulose or cellulose esters or ethers or derivatives or salts thereof (e.g., methyl cellulose); and polyvinyl polymers such as polyvinylpyrrolidone (povidone);

- One or more (e.g., one or two; e.g., two) preservatives, such as a paraben, e.g., methyl 4-hydroxybenzoate (methylparaben), or a pharmaceutically acceptable salt or ester thereof, propyl 4-hydroxybenzoate (propylparaben), or a pharmaceutically acceptable salt or ester thereof, or a combination thereof;
- One or more (e.g., one or two; e.g., two) buffers, such as phosphate buffer system (e.g., sodium dihydrogen phospahate dehydrate, disodium phosphate dodecahydrate);
- One or more (e.g., one or two, e.g., two) glidants and/or lubricants, such as magnesium stearate and/or talc;
- One or more (e.g., one or two; e.g., one) disintegrants, such as crospovidone; and
- One or more (e.g., one or two; e.g., one) diluents, such as lactose (e.g., lactose monohydrate).

In certain of these embodiments, the chemical entity is a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof.

In certain embodiments, enema formulations containing the chemical entities described herein include water, methyl cellulose, povidone, methylparaben, propylparaben, sodium dihydrogen phospahate dehydrate, disodium phosphate dodecahydrate, crospovidone, lactose monohydrate, magnesium stearate, and talc. In certain of these embodiments, the chemical entity is a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof.

In certain embodiments, enema formulations containing the chemical entities described herein are provided in one or more kits or packs. In certain embodiments, the kit or pack includes two separately contained/packaged components, which when mixed together, provide the desired formulation (e.g., as a suspension). In certain of these embodiments, the two component system includes a first component and a second component, in which: (**i**) the first component (e.g., contained in a sachet) includes the chemical entity (as described anywhere herein) and one or more pharmaceutically acceptable excipients (e.g., together formulated as a solid preparation, e.g., together formulated as a wet granulated solid preparation); and (**ii**) the second component (e.g., contained in a vial or bottle) includes one or more liquids and one or more one or more other

pharmaceutically acceptable excipients together forming a liquid carrier. In other embodiments, each of component (**i**) and (**ii**) is provided in its own separate kit or pack.

In certain of these embodiments, component (**i**) includes the chemical entitiy (e.g., a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound of Formula AA) and one or more (e.g., all) of the following excipients:

(**a**) One or more (e.g., one) binders (e.g., a polyvinyl polymer, such as polyvinylpyrrolidone (povidone);

(**b**) One or more (e.g., one or two, e.g., two) glidants and/or lubricants, such as magnesium stearate and/or talc;

(**c**) One or more (e.g., one or two; e.g., one) disintegrants, such as crospovidone; and

(**d**) One or more (e.g., one or two; e.g., one) diluents, such as lactose (e.g., lactose monohydrate).

In certain embodiments, component (**i**) includes from about 40 weight percent to about 80 weight percent (e.g., from about 50 weight percent to about 70 weight percent, from about 55 weight percent to about 70 weight percent; from about 60 weight percent to about 65 weight percent; e.g., about 62.1 weight percent) of the chemical entity (e.g., a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof).

In certain embodiments, component (**i**) includes from about 0.5 weight percent to about 5 weight percent (e.g., from about 1.5 weight percent to about 4.5 weight percent, from about 2 weight percent to about 3.5 weight percent; e.g., about 2.76 weight percent) of the binder (e.g., povidone).

In certain embodiments, component (**i**) includes from about 0.5 weight percent to about 5 weight percent (e.g., from about 0.5 weight percent to about 3 weight percent, from about 1 weight percent to about 3 weight percent; about 2 weight percent e.g., about 1.9 weight percent) of the disintegrant (e.g., crospovidone).

In certain embodiments, component (**i**) includes from about 10 weight percent to about 50 weight percent (e.g., from about 20 weight percent to about 40 weight percent, from about 25 weight percent to about 35 weight percent; e.g., about 31.03 weight percent) of the diluent (e.g., lactose, e.g., lactose monohydrate).

In certain embodiments, component (**i**) includes from about 0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent) of the glidants and/or lubricants.

In certain embodiments (e.g., when component (**i**) includes one or more lubricants, such as magnesium stearate), component (**i**) includes from about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 1 weight percent; from about 0.1 weight percent to about 1 weight percent; from about 0.1 weight percent to about 0.5 weight percent; e.g., about 0.27 weight percent) of the lubricant (e.g., magnesium stearate).

In certain embodiments (when component (**i**) includes one or more lubricants, such as talc), component (**i**) includesfrom about 0.5 weight percent to about 5 weight percent (e.g., from about 0.5 weight percent to about 3 weight percent, from about 1 weight percent to about 3 weight percent; from about 1.5 weight percent to about 2.5 weight percent; from about 1.8 weight percent to about 2.2 weight percent; about 1.93 weight percent) of the lubricant (e.g., talc).

In certain of these embodiments, each of (**a**), (**b**), (**c**), and (**d**) above is present.

In certain embodiments, component (**i**) includes the ingredients and amounts as shown in Table A.

Table A

Ingredient	Weight Percent
A compound of Formula AA	40 weight percent to about 80 weight percent (e.g., from about 50 weight percent to about 70 weight percent, from about 55 weight percent to about 70 weight percent; from about 60 weight percent to about 65 weight percent; e.g., about 62.1 weight percent)
Crospovidone (Kollidon CL)	0.5 weight percent to about 5 weight percent (e.g., from about 0.5 weight percent to about 3 weight percent, from about 1 weight percent to about 3 weight percent; about 1.93 weight percent
lactose monohydrate (Pharmatose 200M)	about 10 weight percent to about 50 weight percent (e.g., from about 20 weight percent to about 40 weight percent, from about 25 weight percent to about 35 weight percent; e.g., about 31.03 weight percent
Povidone (Kollidon K30)	about 0.5 weight percent to about 5 weight percent (e.g., from about 1.5 weight percent to about 4.5 weight percent, from about 2 weight percent to about 3.5 weight percent; e.g., about 2.76 weight percent

talc	0.5 weight percent to about 5 weight percent (e.g., from about 0.5 weight percent to about 3 weight percent, from about 1 weight percent to about 3 weight percent; from about 1.5 weight percent to about 2.5 weight percent; from about 1.8 weight percent to about 2.2 weight percent;e.g., about 1.93 weight percent
Magnesium stearate	about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 1 weight percent; from about 0.1 weight percent to about 1 weight percent; from about 0.1 weight percent to about 0.5 weight percent; e.g., about 0.27 weight percent

In certain embodiments, component (**i**) includes the ingredients and amounts as shown in Table B.

Table B

Ingredient	Weight Percent
A compound of Formula AA	About 62.1 weight percent)
Crospovidone (Kollidon CL)	About 1.93 weight percent
lactose monohydrate (Pharmatose 200M)	About 31.03 weight percent
Povidone (Kollidon K30)	About 2.76 weight percent
talc	About 1.93 weight percent
Magnesium stearate	About 0.27 weight percent

In certain embodiments, component (**i**) is formulated as a wet granulated solid preparation. In certain of these embodiments an internal phase of ingredients (the chemical entity, disintegrant, and diluent) are combined and mixed in a high-shear granulator. A binder (e.g., povidone) is dissolved in water to form a granulating solution. This solution is added to the Inner Phase mixture resulting in the development of granules. While not wishing to be bound by theory, granule development is believed to be facilitated by the interaction of the polymeric binder with the materials of the internal phase. Once the granulation is formed and dried, an external phase (e.g., one or more lubricants - not an intrinsic component of the dried granulation), is added to the dry granulation. It is believed that lubrication of the granulation is important to the flowability of the granulation, in particular for packaging.

In certain of the foregoing embodiments, component (**ii**) includes water and one or more (e.g., all) of the following excipients:

(**a'**) One or more (e.g., one, two; e.g., two) thickeners, viscosity enhancing agents, binders, and/or mucoadhesive agents (e.g., cellulose or cellulose esters or ethers or derivatives or salts thereof (e.g., methyl cellulose); and polyvinyl polymers such as polyvinylpyrrolidone (povidone);

(**b'**) One or more (e.g., one or two; e.g., two) preservatives, such as a paraben, e.g., methyl 4-hydroxybenzoate (methylparaben), or a pharmaceutically acceptable salt or ester thereof, propyl 4-hydroxybenzoate (propylparaben), or a pharmaceutically acceptable salt or ester thereof, or a combination thereof; and

(**c'**) One or more (e.g., one or two; e.g., two) buffers, such as phosphate buffer system (e.g., sodium dihydrogen phospahate dihydrate, disodium phosphate dodecahydrate);

In certain of the foregoing embodiments, component (**ii**) includes water and one or more (e.g., all) of the following excipients:

(**a''**) a first thickener, viscosity enhancing agent, binder, and/or mucoadhesive agent (e.g., a cellulose or cellulose ester or ether or derivative or salt thereof (e.g., methyl cellulose));

(**a'''**) a second thickener, viscosity enhancing agent, binder, and/or mucoadhesive agent (e.g., a polyvinyl polymer, such as polyvinylpyrrolidone (povidone));

(**b''**) a first preservative, such as a paraben, e.g., propyl 4-hydroxybenzoate (propylparaben), or a pharmaceutically acceptable salt or ester thereof;

(**b''**) a second preservative, such as a paraben, e.g., methyl 4-hydroxybenzoate (methylparaben), or a pharmaceutically acceptable salt or ester thereof,

(**c''**) a first buffer, such as phosphate buffer system (e.g., disodium phosphate dodecahydrate);

(**c'''**) a second buffer, such as phosphate buffer system (e.g., sodium dihydrogen phospahate dehydrate),

In certain embodiments, component (**ii**) includes from about 0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent, from about 0.1 weight percent to about 3 weight percent; e.g., about 1.4 weight percent) of (**a''**).

In certain embodiments, component (**ii**) includes from about 0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent, from about 0.1 weight percent to about 2 weight percent; e.g., about 1.0 weight percent) of (**a'''**).

In certain embodiments, component (**ii**) includes from about 0.005 weight percent to about 0.1 weight percent (e.g., from about 0.005 weight percent to about 0.05 weight percent; e.g., about 0.02 weight percent) of (**b''**).

In certain embodiments, component (**ii**) includes from about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 0.5 weight percent; e.g., about 0.20 weight percent) of (**b'''**).

In certain embodiments, component (**ii**) includes from about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 0.5 weight percent; e.g., about 0.15 weight percent) of (**c''**).

In certain embodiments, component (**ii**) includes from about 0.005 weight percent to about 0.5 weight percent (e.g., from about 0.005 weight percent to about 0.3 weight percent; e.g., about 0.15 weight percent) of (**c'''**).

In certain of these embodiments, each of (**a''**) - (**c'''**) is present.

In certain embodiments, component (**ii**) includes water (up to 100%) and the ingredients and amounts as shown in Table C.

Table C

Ingredient	Weight Percent
methyl cellulose (Methocel A15C premium)	0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent, from about 0.1 weight percent to about 3 weight percent; e.g., about 1.4 weight percent
Povidone (Kollidon K30)	0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent, from about 0.1 weight percent to about 2 weight percent; e.g., about 1.0 weight percent
propyl 4-hydroxybenzoate	about 0.005 weight percent to about 0.1 weight percent (e.g., from about 0.005 weight percent to about 0.05 weight percent; e.g., about 0.02 weight percent)

methyl 4-hydroxybenzoate	about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 0.5 weight percent; e.g., about 0.20 weight percent)
disodium phosphate dodecahydrate	about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 0.5 weight percent; e.g., about 0.15 weight percent)
sodium dihydrogen phospahate dihydrate	about 0.005 weight percent to about 0.5 weight percent (e.g., from about 0.005 weight percent to about 0.3 weight percent; e.g., about 0.15 weight percent)

In certain embodiments, component (**ii**) includes water (up to 100%) and the ingredients and amounts as shown in Table D.

Table D

Ingredient	Weight Percent
methyl cellulose (Methocel A15C premium)	about 1.4 weight percent
Povidone (Kollidon K30)	about 1.0 weight percent
propyl 4-hydroxybenzoate	about 0.02 weight percent
methyl 4-hydroxybenzoate	about 0.20 weight percent
disodium phosphate dodecahydrate	about 0.15 weight percent
sodium dihydrogen phospahate dihydrate	about 0.15 weight percent

Ready-to-use" enemas are generally be provided in a "single-use" sealed disposable container of plastic or glass. Those formed of a polymeric material preferably have sufficient flexibility for ease of use by an unassisted patient. Typical plastic containers can be made of polyethylene. These containers may comprise a tip for direct introduction into the rectum. Such containers may also comprise a tube between the container and the tip. The tip is preferably provided with a protective shield which is removed before use. Optionally the tip has a lubricant to improve patient compliance.

In some embodiments, the enema formulation (e.g., suspension) is poured into a bottle for delivery after it has been prepared in a separate container. In certain embodiments, the bottle is a

plastic bottle (e.g., flexible to allow for delivery by squeezing the bottle), which can be a polyethylene bottle (e.g., white in color). In some embodiments, the bottle is a single chamber bottle, which contains the suspension or solution. In other embodiments, the bottle is a multichamber bottle, where each chamber contains a separate mixture or solution. In still other embodiments, the bottle can further include a tip or rectal cannula for direct introduction into the rectum. In some embodiments, the enema formulation can be delivered in the device shown in FIGS. 3A-3C, which includes a plastic bottle, a breakable capsule, and a rectal cannula and single flow pack.

Dosages

The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation can be determined by one skilled in the medical arts. The total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

In some embodiments, the compounds described herein are administered at a dosage of from about 0.001 mg/Kg to about 500 mg/Kg (e.g., from about 0.001 mg/Kg to about 200 mg/Kg; from about 0.01 mg/Kg to about 200 mg/Kg; from about 0.01 mg/Kg to about 150 mg/Kg; from about 0.01 mg/Kg to about 100 mg/Kg; from about 0.01 mg/Kg to about 50 mg/Kg; from about 0.01 mg/Kg to about 10 mg/Kg; from about 0.01 mg/Kg to about 5 mg/Kg; from about 0.01 mg/Kg to about 1 mg/Kg; from about 0.01 mg/Kg to about 0.5 mg/Kg; from about 0.01 mg/Kg to about 0.1 mg/Kg; from about 0. 1 mg/Kg to about 200 mg/Kg; from about 0. 1 mg/Kg to about 150 mg/Kg; from about 0. 1 mg/Kg to about 100 mg/Kg; from about 0.1 mg/Kg to about 50 mg/Kg; from about 0. 1 mg/Kg to about 10 mg/Kg; from about 0. 1 mg/Kg to about 5 mg/Kg; from about 0. 1 mg/Kg to about 1 mg/Kg; from about 0. 1 mg/Kg to about 0.5 mg/Kg).

In some embodiments, enema formulations include from about 0.5 mg to about 2500 mg (e.g., from about 0.5 mg to about 2000 mg, from about 0.5 mg to about 1000 mg, from about 0.5 mg to about 750 mg, from about 0.5 mg to about 600 mg, from about 0.5 mg to about 500 mg, from about 0.5 mg to about 400 mg, from about 0.5 mg to about 300 mg, from about 0.5 mg to about 200 mg; e.g., from about 5 mg to about 2500 mg, from about 5 mg to about 2000 mg, from about 5 mg to about 1000 mg; from about 5 mg to about 750 mg; from about 5 mg to about 600

mg; from about 5 mg to about 500 mg; from about 5 mg to about 400 mg; from about 5 mg to about 300 mg; from about 5 mg to about 200 mg; e.g., from about 50 mg to about 2000 mg, from about 50 mg to about 1000 mg, from about 50 mg to about 750 mg, from about 50 mg to about 600 mg, from about 50 mg to about 500 mg, from about 50 mg to about 400 mg, from about 50 mg to about 300 mg, from about 50 mg to about 200 mg; e.g., from about 100 mg to about 2500 mg, from about 100 mg to about 2000 mg, from about 100 mg to about 1000 mg, from about 100 mg to about 750 mg, from about 100 mg to about 700 mg, from about 100 mg to about 600 mg, from about 100 mg to about 500 mg, from about 100 mg to about 400 mg, from about 100 mg to about 300 mg, from about 100 mg to about 200 mg; e.g., from about 150 mg to about 2500 mg, from about 150 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 150 mg to about 750 mg, from about 150 mg to about 700 mg, from about 150 mg to about 600 mg, from about 150 mg to about 500 mg, from about 150 mg to about 400 mg, from about 150 mg to about 300 mg, from about 150 mg to about 200 mg; e.g., from about 150 mg to about 500 mg; e.g., from about 300 mg to about 2500 mg, from about 300 mg to about 2000 mg, from about 300 mg to about 1000 mg, from about 300 mg to about 750 mg, from about 300 mg to about 700 mg, from about 300 mg to about 600 mg; e.g., from about 400 mg to about 2500 mg, from about 400 mg to about 2000 mg, from about 400 mg to about 1000 mg, from about 400 mg to about 750 mg, from about 400 mg to about 700 mg, from about 400 mg to about 600 from about 400 mg to about 500 mg; e.g., 150 mg or 450 mg) of the chemical entity in from about 1 mL to about 3000 mL (e.g., from about 1 mL to about 2000 mL, from about 1 mL to about 1000 mL, from about 1 mL to about 500 mL, from about 1 mL to about 250 mL, from about 1 mL to about 100 mL, from about 10 mL to about 1000 mL, from about 10 mL to about 500 mL, from about 10 mL to about 250 mL, from about 10 mL to about 100 mL, from about 30 mL to about 90 mL, from about 40 mL to about 80 mL; from about 50 mL to about 70 mL; e.g., about 1 mL, about 5 mL, about 10 mL, about 15 mL, about 20 mL, about 25 mL, about 30 mL, about 35 mL, about 40 mL, about 45 mL,about 50 mL, about 55 mL, about 60 mL, about 65 mL, about 70 mL, about 75 mL, about 100 mL, about 250 mL, or about 500 mL, or about 1000 mL, or about 2000mL, or about 3000 mL; e.g., 60 mL) of liquid carrier.

In certain embodiments, enema formulations include from about 50 mg to about 250 mg (e.g., from about 100 mg to about 200; e.g., about 150 mg) of the chemical entity in from about 10 mL to about 100 mL (e.g., from about 20 mL to about 100 mL, from about 30 mL to about 90 mL,

from about 40 mL to about 80 mL; from about 50 mL to about 70 mL) of liquid carrier. In certain embodiments, enema formulations include about 150 mg of the chemical entity in about 60 mL of the liquid carrier. In certain of these embodiments, the chemical entity is a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof. For example, enema formulations can include about 150 mg of a compound of Formula AA in about 60 mL of the liquid carrier.

In certain embodiments, enema formulations include from about 350 mg to about 550 mg (e.g., from about 400 mg to about 500; e.g., about 450 mg) of the chemical entity in from about 10 mL to about 100 mL (e.g., from about 20 mL to about 100 mL, from about 30 mL to about 90 mL, from about 40 mL to about 80 mL; from about 50 mL to about 70 mL) of liquid carrier. In certain embodiments, enema formulations include about 450 mg of the chemical entity in about 60 mL of the liquid carrier. In certain of these embodiments, the chemical entity is a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof. For example, enema formulations can include about 450 mg of a compound of Formula AA in about 60 mL of the liquid carrier.

In some embodiments, enema formulations include from about from about 0.01 mg/mL to about 50 mg/mL (e.g., from about 0.01 mg/mL to about 25 mg/mL; from about 0.01 mg/mL to about 10 mg/mL; from about 0.01 mg/mL to about 5 mg/mL; from about 0.1 mg/mL to about 50 mg/mL; from about 0.01 mg/mL to about 25 mg/mL; from about 0.1 mg/mL to about 10 mg/mL; from about 0.1 mg/mL to about 5 mg/mL; from about 1 mg/mL to about 10 mg/mL; from about 1 mg/mL to about 5 mg/mL; from about 5 mg/mL to about 10 mg/mL; e.g., about 2.5 mg/mL or about 7.5 mg/mL) of the chemical entity in liquid carrier. In certain of these embodiments, the chemical entity is a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof. For example, enema formulations can include about 2.5 mg/mL or about 7.5 mg/mL of a compound of Formula AA in liquid carrier.

Regimens

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weeks, once every two weeks, once a month).

In some embodiments, the period of administration of a compound described herein is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 1 1 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 1 1 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 1 1 months, 12 months, or more. In an embodiment, a therapeutic compound is administered to an individual for a period of time followed by a separate period of time. In another embodiment, a therapeutic compound is administered for a first period and a second period following the first period, with administration stopped during the second period, followed by a third period where administration of the therapeutic compound is started and then a fourth period following the third period where administration is stopped. In an aspect of this embodiment, the period of administration of a therapeutic compound followed by a period where administration is stopped is repeated for a determined or undetermined period of time. In a further embodiment, a period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

Methods of Treatment

In some embodiments, methods for treating a subject having condition, disease or disorder in which a decrease or increase in NLRP3 activity (e.g., an increase, e.g., NLRP3 signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder are provided, comprising administering to a subject an effective amount of a chemical

entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

Indications

In some embodiments, the condition, disease or disorder is selected from: inappropriate host responses to infectious diseases where active infection exists at any body site, such as septic shock, disseminated intravascular coagulation, and/or adult respiratory distress syndrome; acute or chronic inflammation due to antigen, antibody and/or complement deposition; inflammatory conditions including arthritis, cholangitis, colitis, encephalitis, endocarditis, glomerulonephritis, hepatitis, myocarditis, pancreatitis, pericarditis, reperfusion injury and vasculitis, immune-based diseases such as acute and delayed hypersensitivity, graft rejection, and graft-versus-host disease; auto-immune diseases including Type 1 diabetes mellitus and multiple sclerosis. For example, the condition, disease or disorder may be an inflammatory disorder such as rheumatoid arthritis, osteoarthritis, septic shock, COPD and periodontal disease.

In some embodiments, the condition, disease or disorder is an autoimmune diseases. Non-limiting examples include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel diseases (IBDs) comprising Crohn disease (CD) and ulcerative colitis (UC), which are chronic inflammatory conditions with polygenic susceptibility. In certain embodiments, the condition is an inflammatory bowel disease. In certain embodiments, the condition is Crohn's disease, autoimmune colitis, iatrogenic autoimmune colitis, ulcerative colitis, colitis induced by one or more chemotherapeutic agents, colitis induced by treatment with adoptive cell therapy, colitis associated by one or more alloimmune diseases (such as graft-vs-host disease, e.g., acute graft vs. host disease and chronic graft vs. host disease), radiation enteritis, collagenous colitis, lymphocytic colitis, microscopic colitis, and radiation enteritis. In certain of these embodiments, the condition is alloimmune disease (such as graft-vs-host disease, e.g., acute graft vs. host disease and chronic graft vs. host disease), celiac disease, irritable bowel syndrome, rheumatoid arthritis, lupus, scleroderma, psoriasis, cutaneous T-cell lymphoma, uveitis, and mucositis (e.g., oral mucositis, esophageal mucositis or intestinal mucositis).

In some embodiments, the condition, disease or disorder is selected from major adverse cardiovascular events such as carbiovascular death, non-fatal myocardial infarction and non-fatal stroke in patients with a prior hear attack and inflammatory atherosclerosis (see for example, NCT01327846).

In some embodiments, the condition, disease or disorder is selected from metabolic disorders such as type 2 diabetes, atherosclerosis, obesity and gout, as well as diseases of the central nervous system, such as Alzheimer's disease and multiple sclerosis and Amyotrophic Lateral Sclerosis and Parkinson disease, lung disease, such as asthma and COPD and pulmonary idiopathic fibrosis, liver disease, such as NASH syndrome, viral hepatitis and cirrhosis, pancreatic disease, such as acute and chronic pancreatitis, kidney disease, such as acute and chronic kidney injury, intestinal disease such as Crohn's disease and Ulcerative Colitis, skin disease such as psoriasis, musculoskeletal disease such as scleroderma, vessel disorders, such as giant cell arteritis, disorders of the bones, such as Osteoarthritis , osteoporosis and osteopetrosis disorders eye disease, such as glaucoma and macular degeneration, diseased caused by viral infection such as HIV and AIDS, autoimmune disease such as Rheumatoid Arthritis, Systemic Lupus Erythematosus, Autoimmune Thyroiditis, Addison's disease, pernicious anemia, cancer and aging.

In some embodiments, the condition, disease or disorder is a cardiovascular indication. In some embodiments, the condition, disease or disorder is myocardial infraction. In some embodiments, the condition, disease or disorder is stroke.

In some embodiments, the condition, disease or disorder is obesity.

In some embodiments, the condition, disease or disorder is Type 2 Diabetes.

In some embodiments, the condition, disease or disorder is NASH.

In some embodiments, the condition, disease or disorder is Alzheimer's disease.

In some embodiments, the condition, disease or disorder is gout.

In some embodiments, the condition, disease or disorder is SLE.

In some embodiments, the condition, disease or disorder is rheumatoid arthritis.

In some embodiments, the condition, disease or disorder is IBD.

In some embodiments, the condition, disease or disorder is multiple sclerosis.

In some embodiments, the condition, disease or disorder is COPD.

In some embodiments, the condition, disease or disorder is asthma.

In some embodiments, the condition, disease or disorder is scleroderma.

In some embodiments, the condition, disease or disorder is pulmonary fibrosis.

In some embodiments, the condition, disease or disorder is age related macular degeneration (AMD).

In some embodiments, the condition, disease or disorder is cystic fibrosis.

In some embodiments, the condition, disease or disorder is Muckle Wells syndrome.

In some embodiments, the condition, disease or disorder is familial cold autoinflammatory syndrome (FCAS).

In some embodiments, the condition, disease or disorder is chronic neurologic cutaneous and articular syndrome.

In some embodiments, the condition, disease or disorder is selected from: myelodysplastic syndromes (MDS); non-small cell lung cancer, such as non-small cell lung cancer in patients carrying mutation or overexpression of NLRP3; acute lymphoblastic leukemia (ALL), such as ALL in patients resistant to glucocorticoids treatment; Langerhan's cell histiocytosis (LCH); multiple myeloma; promyelocytic leukemia; acute myeloid leukemia (AML) chronic myeloid leukemia (CML); gastric cancer; and lung cancer metastasis.

In some embodiments, the condition, disease or disorder is selected from: myelodysplastic syndromes (MDS); non-small cell lung cancer, such as non-small cell lung cancer in patients carrying mutation or overexpression of NLRP3; acute lymphoblastic leukemia (ALL), such as ALL in patients resistant to glucocorticoids treatment; Langerhan's cell histiocytosis (LCH); multiple myeloma; promyelocytic leukemia; gastric cancer; and lung cancer metastasis.

In some embodiments, the indication is MDS.

In some embodiments, the indication is non-small lung cancer in patients carrying mutation or overexpression of NLRP3.

In some embodiments, the indication is ALL in patients resistant to glucocorticoids treatment.

In some embodiments, the indication is LCH.

In some embodiments, the indication is multiple myeloma.

In some embodiments, the indication is promyelocytic leukemia.

In some embodiments, the indication is gastric cancer.

In some embodiments, the indication is lung cancer metastasis.

Combination therapy

This disclosure contemplates both monotherapy regimens as well as combination therapy regimens.

In some embodiments, the methods described herein can further include administering one or more additional therapies (e.g., one or more additional therapeutic agents and/or one or more therapeutic regimens) in combination with administration of the compounds described herein.

In certain embodiments, the second therapeutic agent or regimen is administered to the subject prior to contacting with or administering the chemical entity (e.g., about one hour prior, or about 6 hours prior, or about 12 hours prior, or about 24 hours prior, or about 48 hours prior, or about 1 week prior, or about 1 month prior).

In other embodiments, the second therapeutic agent or regimen is administered to the subject at about the same time as contacting with or administering the chemical entity. By way of example, the second therapeutic agent or regimen and the chemical entity are provided to the subject simultaneously in the same dosage form. As another example, the second therapeutic agent or regimen and the chemical entity are provided to the subject concurrently in separate dosage forms.

In still other embodiments, the second therapeutic agent or regimen is administered to the subject after contacting with or administering the chemical entity (e.g., about one hour after, or about 6 hours after, or about 12 hours after, or about 24 hours after, or about 48 hours after, or about 1 week after, or about 1 month after).

Patient Selection

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related to NLRP3 polymorphism.

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related to NLRP3 where polymorphism is a gain of function

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related to NLRP3 polymorphism found in CAPS syndromes.

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related NLRP3 polymorphism where the polymorphism is VAR_014104 (R262W)

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related NLRP3 polymorphism where the polymorphism is a natural variant reported in http://www.uniprot.org/uniprot/Q96P20.

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related to point mutation of NLRP3 signaling.

Anti-TNFα Agents

The term "anti-TNFα agent" refers to an agent which directly or indirectly blocks, down-regulates, impairs, inhibits, impairs, or reduces TNFα activity and/or expression. In some embodiments, an anti-TNFα agent is an antibody or an antigen-binding fragment thereof, a fusion protein, a soluble TNFα receptor (a soluble tumor necrosis factor receptor superfamily member 1A (TNFR1) or a soluble tumor necrosis factor receptor superfamily 1B (TNFR2)), an inhibitory nucleic acid, or a small molecule TNFα antagonist. In some embodiments, the inhibitory nucleic acid is a ribozyme, small hairpin RNA, a small interfering RNA, an antisense nucleic acid, or an aptamer.

Exemplary anti-TNFα agents that directly block, down-regulate, impair, inhibit, or reduce TNFα activity and/or expression can, e.g., inhibit or decrease the expression level of TNFα or a receptor of TNFα (TNFR1 or TNFR2) in a cell (e.g., a cell obtained from a subject, a mammalian cell), or inhibit or reduce binding of TNFα to its receptor (TNFR1 and/or TNFR2) and/or. Non-limiting examples of anti-TNFα agents that directly block, down-regulate, impair, inhibit, or reduce TNFα activity and/or expression include an antibody or fragment thereof, a fusion protein, a soluble TNFα receptor (e.g., a soluble TNFR1 or soluble TNFR2), inhibitory nucleic acids (e.g., any of the examples of inhibitory nucleic acids described herein), and a small molecule TNFα antagonist.

Exemplary anti-TNFα agents that can indirectly block, down-regulate, impair, inhibitreduce TNFα activity and/or expression can, e.g., inhibit or decrease the level of downstream signaling of a TNFα receptor (e.g., TNFR1 or TNFR2) in a mammalian cell (e.g.,

decrease the level and/or activity of one or more of the following signaling proteins: AP-1, mitogen-activated protein kinase kinase kinase 5 (ASK1), inhibitor of nuclear factor kappa B (IKK), mitogen-activated protein kinase 8 (JNK), mitogen-activated protein kinase (MAPK), MEKK 1/4, MEKK 4/7, MEKK 3/6, nuclear factor kappa B (NF-κB), mitogen-activated protein kinase kinase kinase 14 (NIK), receptor interacting serine/threonine kinase 1 (RIP), TNFRSF1A associated via death domain (TRADD), and TNF receptor associated factor 2 (TRAF2), in a cell), and/or decrease the level of TNFα-induced gene expression in a mammalian cell (e.g., decrease the transcription of genes regulated by, e.g., one or more transcription factors selected from the group of activating transcription factor 2 (ATF2), c-Jun, and NF-κB). A description of downstream signaling of a TNFα receptor is provided in Wajant et al., *Cell Death Differentiation* 10:45-65, 2003 (incorporated herein by reference). For example, such indirect anti-TNFα agents can be an inhibitory nucleic acid that targets (decreases the expression) a signaling component downstream of a TNFα-induced gene (e.g., any TNFα-induced gene known in the art), a TNFα receptor (e.g., any one or more of the signaling components downstream of a TNFα receptor described herein or known in the art), or a transcription factor selected from the group of NF-κB, c-Jun, and ATF2.

In other examples, such indirect anti-TNFα agents can be a small molecule inhibitor of a protein encoded by a TNFα-induced gene (e.g., any protein encoded by a TNFα-induced gene known in the art), a small molecule inhibitor of a signaling component downstream of a TNFα receptor (e.g., any of the signaling components downstream of a TNFα receptor described herein or known in the art), and a small molecule inhibitor of a transcription factor selected from the group of ATF2, c-Jun, and NF-κB.

In other embodiments, anti-TNFα agents that can indirectly block, down-regulate, impair, or reduce one or more components in a cell (e.g., acell obtained from a subject, a mammalian cell) that are involved in the signaling pathway that results in TNFα mRNA transcription, TNFα mRNA stabilization, and TNFα mRNA translation (e.g., one or more components selected from the group of CD14, c-Jun, ERK1/2, IKK, IκB, interleukin 1 receptor associated kinase 1 (IRAK), JNK, lipopolysaccharide binding protein (LBP), MEK1/2, MEK3/6, MEK4/7, MK2, MyD88, NF-κB, NIK, PKR, p38, AKT serine/threonine kinase 1 (rac), raf kinase (raf), ras, TRAF6, TTP). For example, such indirect anti-TNFα agents can be an inhibitory nucleic acid that targets (decreases the expression) of a component in a mammalian cell that is involved in the signaling

pathway that results in TNFα mRNA transcription, TNFα mRNA stabilization, and TNFα mRNA translation (e.g., a component selected from the group of CD14, c-Jun, ERK1/2, IKK, IκB, IRAK, JNK, LBP, MEK1/2, MEK3/6, MEK4/7, MK2, MyD88, NF-κB, NIK, IRAK, lipopolysaccharide binding protein (LBP), PKR, p38, rac, raf, ras, TRAF6, TTP). In other examples, an indirect anti-TNFα agents is a small molecule inhibitor of a component in a mammalian cell that is involved in the signaling pathway that results in TNFα mRNA transcription, TNFα mRNA stabilization, and TNFα mRNA translation (e.g., a component selected from the group of CD14, c-Jun, ERK1/2, IKK, IκB, IRAK, JNK, lipopolysaccharide binding protein (LBP), MEK1/2, MEK3/6, MEK4/7, MK2, MyD88, NF-κB, NIK, IRAK, lipopolysaccharide binding protein (LBP), PKR, p38, rac, raf, ras, TRAF6, TTP).

Antibodies

In some embodiments, the anti-TNFα agent is an antibody or an antigen-binding fragment thereof (e.g., a Fab or a scFv). In some embodiments, an antibody or antigen-binding fragment of an antibody described herein can bind specifically to TNFα. In some embodiments, an antibody or antigen-binding fragment described herein binds specifically to any one of TNFα, TNFR1, or TNFR2. In some embodiments, an antibody or antigen-binding fragment of an antibody described herein can bind specifically to a TNFα receptor (TNFR1 or TNFR2).

In some embodiments, the antibody can be a humanized antibody, a chimeric antibody, a multivalent antibody, or a fragment thereof. In some embodiments, an antibody can be a scFv-Fc, a VHH domain, a VNAR domain, a (scFv)2, a minibody, or a BiTE.

In some embodiments, an antibody can be a crossmab, a diabody, a scDiabody, a scDiabody-CH3, a Diabody-CH3, a DutaMab, a DT-IgG, a diabody-Fc, a scDiabody-HAS, a charge pair antibody, a Fab-arm exchange antibody, a SEEDbody, a Triomab, a LUZ-Y, a Fcab, a kλ-body, an orthogonal Fab, a DVD-IgG, an IgG(H)-scFv, a scFv-(H)IgG, an IgG(L)-scFv, a scFv-(L)-IgG, an IgG (L,H)-Fc, an IgG(H)-V, a V(H)-IgG, an IgG(L)-V, a V(L)-IgG, an KIH IgG-scFab, a 2scFv-IgG, an IgG-2scFv, a scFv4-Ig, a Zybody, a DVI-IgG, a nanobody, a nanobody-HSA, a DVD-Ig, a dual-affinity re-targeting antibody (DART), a triomab, a kih IgG with a common LC, an ortho-Fab IgG, a 2-in-1-IgG, IgG-ScFv, scFv2-Fc, a bi-nanobody, tanden antibody, a DART-Fc, a scFv-HAS-scFv, a DAF (two-in-one or four-in-one), a DNL-Fab3, knobs-in-holes common LC, knobs-in-holes assembly, a TandAb, a Triple Body, a miniantibody,

a minibody, a TriBi minibody, a scFv-CH3 KIH, a Fab-scFv, a scFv-CH-CL-scFv, a F(ab')2-scFV2, a scFv-KIH, a Fab-scFv-Fc, a tetravalent HCAb, a scDiabody-Fc, a tandem scFv-Fc, an intrabody, a dock and lock bispecific antibody, an ImmTAC, a HSAbody, a tandem scFv, an IgG-IgG, a Cov-X-Body, and a scFv1-PEG-scFv2.

Non-limiting examples of an antigen-binding fragment of an antibody include an Fv fragment, a Fab fragment, a F(ab')2 fragment, and a Fab' fragment. Additional examples of an antigen-binding fragment of an antibody is an antigen-binding fragment of an antigen-binding fragment of an IgA (e.g., an antigen-binding fragment of IgA1 or IgA2) (e.g., an antigen-binding fragment of a human or humanized IgA, e.g., a human or humanized IgA1 or IgA2); an antigen-binding fragment of an IgD (e.g., an antigen-binding fragment of a human or humanized IgD); an antigen-binding fragment of an IgE (e.g., an antigen-binding fragment of a human or humanized IgE); an IgG (e.g., an antigen-binding fragment of IgG1, IgG2, IgG3, or IgG4) (e.g., an antigen-binding fragment of a human or humanized IgG, e.g., human or humanized IgG1, IgG2, IgG3, or IgG4); or an antigen-binding fragment of an IgM (e.g., an antigen-binding fragment of a human or humanized IgM).

Non-limiting examples of anti-TNFα agents that are antibodies that specifically bind to TNFα are described in Ben-Horin et al., *Autoimmunity Rev.* 13(1):24-30, 2014; Bongartz et al., *JAMA* 295(19):2275-2285, 2006; Butler et al., *Eur. Cytokine Network* 6(4):225-230, 1994; Cohen et al., *Canadian J. Gastroenterol. Hepatol.* 15(6):376-384, 2001; Elliott et al., *Lancet* 1994; 344: 1125-1127, 1994; Feldmann et al., *Ann. Rev. Immunol.* 19(1):163-196, 2001; Rankin et al., *Br. J. Rheumatol.* 2:334-342, 1995; Knight et al., *Molecular Immunol.* 30(16):1443-1453, 1993; Lorenz et al., *J. Immunol.* 156(4):1646-1653, 1996; Hinshaw et al., *Circulatory Shock* 30(3):279-292, 1990; Ordas et al., *Clin. Pharmacol. Therapeutics* 91(4):635-646, 2012; Feldman, *Nature Reviews Immunol.* 2(5):364-371, 2002; Taylor et al., *Nature Reviews Rheumatol.* 5(10):578-582, 2009; Garces et al., *Annals Rheumatic Dis.* 72(12):1947-1955, 2013; Palladino et al., *Nature Rev. Drug Discovery* 2(9):736-746, 2003; Sandborn et al., *Inflammatory Bowel Diseases* 5(2):119-133, 1999; Atzeni et al., *Autoimmunity Reviews* 12(7):703-708, 2013; Maini et al., *Immunol. Rev.* 144(1):195-223, 1995; Wanner et al., *Shock* 11(6):391-395, 1999; and U.S. Patent Nos. 6,090,382; 6,258,562; and 6,509,015).

In certain embodiments, the anti-TNFα agent can include or is golimumab (golimumabTM), adalimumab (Humira™), infliximab (Remicade™), CDP571, CDP 870, or

certolizumab pegol (Cimzia™). In certain embodiments, the anti-TNFα agent can be a TNFα inhibitor biosimilar. Examples of approved and late-phase TNFα inhibitor biosimilars include, but are not limited to, infliximab biosimilars such as Flixabi™ (SB2) from Samsung Bioepis, Inflectra® (CT-P13) from Celltrion/Pfizer, GS071 from Aprogen, Remsima™, PF-06438179 from Pfizer/Sandoz, NI-071 from Nichi-Iko Pharmaceutical Co., and ABP 710 from Amgen; adalimumab biosimilars such as Amgevita® (ABP 501) from Amgen and Exemptia™ from Zydus Cadila, BMO-2 or MYL-1401-A from Biocon/Mylan, CHS-1420 from Coherus, FKB327 from Kyowa Kirin, and BI 695501 from Boehringer Ingelheim;Solymbic®, SB5 from Samsung Bioepis, GP-2017 from Sandoz, ONS-3010 from Oncobiologics, M923 from Momenta, PF-06410293 from Pfizer, and etanercept biosimilars such as Erelzi™ from Sandoz/Novartis, Brenzys™ (SB4) from Samsung Bioepis, GP2015 from Sandoz, TuNEX® from Mycenax, LBEC0101 from LG Life, and CHS-0214 from Coherus.

In some embodiments of any of the methods described herein, the anti-TNFα agent is selected from the group consisting of: adalimumab, certolizumab, etanercept, golimumab, infliximabm, CDP571, and CDP 870.

In some embodiments, any of the antibodies or antigen-binding fragments described herein has a dissociation constant (K_D) of less than 1 x 10^{-5} M (e.g., less than 0.5 x 10^{-5} M, less than 1 x 10^{-6} M, less than 0.5 x 10^{-6} M, less than 1 x 10^{-7} M, less than 0.5 x 10^{-7} M, less than 1 x 10^{-8} M, less than 0.5 x 10^{-8} M, less than 1 x 10^{-9} M, less than 0.5 x 10^{-9} M, less than 1 x 10^{-10} M, less than 0.5 x 10^{-10} M, less than 1 x 10^{-11} M, less than 0.5 x 10^{-11} M, or less than 1 x 10^{-12} M), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

In some embodiments, any of the antibodies or antigen-binding fragments described herein has a K_D of about 1 x 10^{-12} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, about 0.5 x 10^{-8} M, about 1 x 10^{-9} M, about 0.5 x 10^{-9} M, about 1 x 10^{-10} M, about 0.5 x 10^{-10} M, about 1 x 10^{-11} M, or about 0.5 x 10^{-11} M (inclusive); about 0.5 x 10^{-11} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, about 0.5 x 10^{-8} M, about 1 x 10^{-9} M, about 0.5 x 10^{-9} M, about 1 x 10^{-10} M, about 0.5 x 10^{-10} M, or about 1 x 10^{-11} M (inclusive); about 1 x 10^{-11} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, about 0.5 x 10^{-8} M, about 1 x 10^{-9} M, about 0.5 x 10^{-9} M, about 1 x 10^{-10} M, or about 0.5 x 10^{-10} M (inclusive); about

0.5×10^{-10} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, about 0.5×10^{-8} M, about 1×10^{-9} M, about 0.5×10^{-9} M, or about 1×10^{-10} M (inclusive); about 1×10^{-10} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, about 0.5×10^{-8} M, about 1×10^{-9} M, or about 0.5×10^{-9} M (inclusive); about 0.5×10^{-9} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, about 0.5×10^{-8} M, or about 1×10^{-9} M (inclusive); about 1×10^{-9} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, or about 0.5×10^{-8} M (inclusive); about 0.5×10^{-8} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, or about 1×10^{-8} M (inclusive); about 1×10^{-8} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, or about 0.5×10^{-7} M (inclusive); about 0.5×10^{-7} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, or about 1×10^{-7} M (inclusive); about 1×10^{-7} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, or about 0.5×10^{-6} M (inclusive); about 0.5×10^{-6} M to about 1×10^{-5} M, about 0.5×10^{-5} M, or about 1×10^{-6} M (inclusive); about 1×10^{-6} M to about 1×10^{-5} M or about 0.5×10^{-5} M (inclusive); or about 0.5×10^{-5} M to about 1×10^{-5} M (inclusive), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

In some embodiments, any of the antibodies or antigen-binding fragments described herein has a K_{off} of about 1×10^{-6} s^{-1} to about 1×10^{-3} s^{-1}, about 0.5×10^{-3} s^{-1}, about 1×10^{-4} s^{-1}, about 0.5×10^{-4} s^{-1}, about 1×10^{-5} s^{-1}, or about 0.5×10^{-5} s^{-1} (inclusive); about 0.5×10^{-5} s^{-1} to about 1×10^{-3} s^{-1}, about 0.5×10^{-3} s^{-1}, about 1×10^{-4} s^{-1}, about 0.5×10^{-4} s^{-1}, or about 1×10^{-5} s^{-1} (inclusive); about 1×10^{-5} s^{-1} to about 1×10^{-3} s^{-1}, about 0.5×10^{-3} s^{-1}, about 1×10^{-4} s^{-1}, or about 0.5×10^{-4} s^{-1} (inclusive); about 0.5×10^{-4} s^{-1} to about 1×10^{-3} s^{-1}, about 0.5×10^{-3} s^{-1}, or about 1×10^{-4} s^{-1} (inclusive); about 1×10^{-4} s^{-1} to about 1×10^{-3} s^{-1}, or about 0.5×10^{-3} s^{-1} (inclusive); or about 0.5×10^{-5} s^{-1} to about 1×10^{-3} s^{-1} (inclusive), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

In some embodiments, any of the antibodies or antigen-binding fragments described herein has a K_{on} of about 1×10^{2} $M^{-1}s^{-1}$ to about 1×10^{6} $M^{-1}s^{-1}$, about 0.5×10^{6} $M^{-1}s^{-1}$, about 1×10^{5} $M^{-1}s^{-1}$, about 0.5×10^{5} $M^{-1}s^{-1}$, about 1×10^{4} $M^{-1}s^{-1}$, about 0.5×10^{4} $M^{-1}s^{-1}$, about 1×10^{3} $M^{-1}s^{-1}$, or about 0.5×10^{3} $M^{-1}s^{-1}$ (inclusive); about 0.5×10^{3} $M^{-1}s^{-1}$ to about 1×10^{6} $M^{-1}s^{-1}$, about

0.5 x 10^6 $M^{-1}s^{-1}$, about 1 x 10^5 $M^{-1}s^{-1}$, about 0.5 x 10^5 $M^{-1}s^{-1}$, about 1 x 10^4 $M^{-1}s^{-1}$, about 0.5 x 10^4 $M^{-1}s^{-1}$, or about 1 x 10^3 $M^{-1}s^{-1}$ (inclusive); about 1 x 10^3 $M^{-1}s^{-1}$ to about 1 x 10^6 $M^{-1}s^{-1}$, about 0.5 x 10^6 $M^{-1}s^{-1}$, about 1 x 10^5 $M^{-1}s^{-1}$, about 0.5 x 10^5 $M^{-1}s^{-1}$, about 1 x 10^4 $M^{-1}s^{-1}$, or about 0.5 x 10^4 $M^{-1}s^{-1}$ (inclusive); about 0.5 x 10^4 $M^{-1}s^{-1}$ to about 1 x 10^6 $M^{-1}s^{-1}$, about 0.5 x 10^6 $M^{-1}s^{-1}$, about 1 x 10^5 $M^{-1}s^{-1}$, about 0.5 x 10^5 $M^{-1}s^{-1}$, or about 1 x 10^4 $M^{-1}s^{-1}$ (inclusive); about 1 x 10^4 $M^{-1}s^{-1}$ to about 1 x 10^6 $M^{-1}s^{-1}$, about 0.5 x 10^6 $M^{-1}s^{-1}$, about 1 x 10^5 $M^{-1}s^{-1}$, or about 0.5 x 10^5 $M^{-1}s^{-1}$ (inclusive); about 0.5 x 10^5 $M^{-1}s^{-1}$ to about 1 x 10^6 $M^{-1}s^{-1}$, about 0.5 x 10^6 $M^{-1}s^{-1}$, or about 1 x 10^5 $M^{-1}s^{-1}$ (inclusive); about 1 x 10^5 $M^{-1}s^{-1}$ to about 1 x 10^6 $M^{-1}s^{-1}$, or about 0.5 x 10^6 $M^{-1}s^{-1}$ (inclusive); or about 0.5 x 10^6 $M^{-1}s^{-1}$ to about 1 x 10^6 $M^{-1}s^{-1}$ (inclusive), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

Fusion Proteins

In some embodiments, the anti-TNFα agent is a fusion protein (e.g., an extracellular domain of a TNFR fused to a partner peptide, e.g., an Fc region of an immunoglobulin, e.g., human IgG) (see, e.g., Deeg et al., *Leukemia* 16(2):162, 2002; Peppel et al., *J. Exp. Med.* 174(6):1483-1489, 1991) or a soluble TNFR (e.g., TNFR1 or TNFR2) that binds specifically to TNFα. In some embodiments, the anti-TNFα agent includes or is a soluble TNFα receptor (e.g., Bjornberg et al., *Lymphokine Cytokine Res.* 13(3):203-211, 1994; Kozak et al., *Am. J. Physiol. Reg. Integrative Comparative Physiol.* 269(1):R23-R29, 1995; Tsao et al., *Eur Respir J.* 14(3):490-495, 1999; Watt et al., *J Leukoc Biol.* 66(6):1005-1013, 1999; Mohler et al., *J. Immunol.* 151(3):1548-1561, 1993; Nophar et al., *EMBO J.* 9(10):3269, 1990; Piguet et al., *Eur. Respiratory J.* 7(3):515-518, 1994; and Gray et al., *Proc. Natl. Acad. Sci. U.S.A.* 87(19):7380-7384, 1990). In some embodiments, the anti-TNFα agent includes or is etanercept (Enbrel™) (see, e.g., WO 91/03553 and WO 09/406,476, incorporated by reference herein). In some embodiments, the anti-TNFα agent inhibitor includes or is r-TBP-I (e.g., Gradstein et al., *J. Acquir. Immune Defic. Syndr.* 26(2): 111-117, 2001).

Inhibitory Nucleic Acids

Inhibitory nucleic acids that can decrease the expression of AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA expression in a mammalian cell include antisense nucleic acid molecules, i.e., nucleic acid molecules whose nucleotide sequence is fully or partially complementary to all or part of a AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA (e.g., fully or partially complementary to all or a part of any one of the sequences presented in Table E).

Table E.

Human gene	**mRNA GenBank accession number(s)**
Tumor necrosis factor (TNF, a.k.a. TNF-alpha)	NM_000594
TNF receptor superfamily member 1A (TNFRSF1A) (a.k.a. TNFR1)	NM_001065 NM_001346091 NM_001346092
TNF receptor superfamily member 1B (TNFRSF1B) (a.k.a. TNFR2)	NM_001066 XM_011542060 XM_011542063 XM_017002214 XM_017002215 XM_017002211
TNFRSF1A associated via death domain (TRADD)	NM_003789 NM_001323552 XM_005256213 XM_017023815
TNF receptor associated factor 2 (TRAF2)	NM_021138 XM_011518976 XM_011518977 XM_011518974
JunD proto-oncogene, AP-1 transcription factor subunit (JUND)	NM_001286968 NM_005354
Mitogen-activated protein kinase kinase kinase 5 (MAP3K5) (a.k.a. ASK1)	NM_005923 XM_017010875 XM_017010872 XM_017010873

	XM_017010877 XM_017010874 XM_017010871 XM_017010870 XM_017010876 XM_011535839
CD14	NM_000591 NM_001040021 NM_001174104 NM_001174105
Mitogen-activated protein kinase 3 (MAPK3) (a.k.a. ERK1)	NM_001040056 NM_001109891 NM_002746
Mitogen-activated protein kinase 1 (MAPK1) (a.k.a. ERK2)	NM_002745 NM_138957
Inhibitor of nuclear factor kappa B kinase subunit beta (IKBKB)	NM_001190720 NM_001242778 NM_001556 XM_005273491 XM_005273496 XM_005273493 XM_005273498 XM_011544518 XM_005273492 XM_005273490 XM_005273494 12XM_017013396 XM_011544521 XM_011544522 XM_005273495 XM_011544517 XM_011544520 XM_011544519
NFKB inhibitor alpha (NFKBIA)	NM_020529
Interleukin 1 receptor associated kinase 1 (IRAK1)	NM_001025242 NM_001025243 NM_001569 XM_005274668
Mitogen-activated protein kinase 8 (MAPK8) (a.k.a. JNK)	NM_001278547 NM_001278548 NM_001323302 NM_001323320 NM_001323321 NM_001323322 NM_001323323 NM_001323324

	NM_001323325 NM_001323326 NM_001323327 NM_001323328 NM_001323329 NM_001323330 NM_001323331 NM_139046 NM_139049 XM_024448079 XM_024448080
Lipopolysaccharide binding protein (LBP)	NM_004139
Mitogen-activated protein kinase kinase 1 (MAP2K1) (a.k.a. MEK1)	NM_002755 XM_017022411 XM_011521783 XM_017022412 XM_017022413
Mitogen-activated protein kinase kinase 2 (MAP2K2) (a.k.a. MEK2)	NM_030662 XM_006722799 XM_017026990 XM_017026989 XM_017026991
Mitogen-activated protein kinase kinase 3 (MAP2K3) (a.k.a. MEK3)	NM_001316332 NM_002756 NM_145109 XM_017024859 XM_005256723 XM_017024857 XM_011523959 XM_017024858 XM_011523958
Mitogen-activated protein kinase kinase 6 (MAP2K6) (a.k.a. MEK6)	NM_001330450 NM_002758 XM_005257516 XM_011525027 XM_011525026 XM_006721975
Mitogen-activated protein kinase kinase kinase 1 (MAP3K1) (a.k.a. MEKK1)	NM_005921 XM_017009485 XM_017009484
Mitogen-activated protein kinase kinase kinase 3 (MAP3K3) (a.k.a. MEKK3)	NM_001330431 NM_001363768 NM_002401 NM_203351 XM_005257378

Mitogen-activated protein kinase kinase kinase 4 (MAP3K4) (a.k.a. MEKK4)	NM_001291958 NM_001301072 NM_001363582 NM_005922 NM_006724 XM_017010869
Mitogen-activated protein kinase kinase kinase 6 (MAP3K6) (a.k.a. MEKK6)	NM_001297609 NM_004672 XM_017002771 XM_017002772
Mitogen-activated protein kinase kinase kinase 7 (MAP3K7) (a.k.a. MEKK7)	NM_003188 NM_145331 NM_145332 NM_145333 XM_006715553 XM_017011226
MAPK activated protein kinase 2 (MAPKAPK2) (a.k.a. MK2)	NM_004759 NM_032960 XM_005273353 XM_017002810
MYD88, innate immune signal transduction adaptor (MYD88)	NM_001172566 NM_001172567 NM_001172568 NM_001172569 NM_001365876 NM_001365877 NM_002468
Nuclear factor kappa B subunit 1 (NFKB1)	NM_001165412 NM_001319226 NM_003998 XM_024454069 XM_024454067 XM_011532006 XM_024454068
Mitogen-activated protein kinase kinase kinase 14 (MAP3K14) (a.k.a. NIK)	NM_003954 XM_011525441
Mitogen-activated protein kinase 14 (MAPK14) (a.k.a. p38)	NM_001315 NM_139012 NM_139013 NM_139014 XM_011514310 XM_017010300 XM_017010299 XM_017010301 XM_017010304 XM_017010303

	XM_017010302 XM_006714998
Eukaryotic translation initiation factor 2 alpha kinase 2 (EIF2AK2) (a.k.a. PKR)	NM_001135651 NM_001135652 NM_002759 XM_011532987 XM_017004503
AKT serine/threonine kinase 1 (AKT1) (a.k.a. RAC)	NM_001014431 NM_001014432 NM_005163
Zinc fingers and homeoboxes 2 (ZHX2) (a.k.a. RAF)	NM_001362797 NM_014943 XM_011516932 XM_005250836
KRAS proto-oncogene, GTPase (KRAS)	NM_001369786 NM_001369787 NM_004985 NM_033360
NRAS proto-oncogene, GTPase (NRAS)	NM_002524
Receptor interacting serine/threonine kinase 1 (RIPK1) (a.k.a. RIP)	NM_001317061 NM_001354930 NM_001354931 NM_001354932 NM_001354933 NM_001354934 NM_003804 XM_017011405 XM_006715237 XM_017011403 XM_017011404
TNF receptor associated factor 6 (TRAF6)	NM_004620 NM_145803 XM_017018220
ZFP36 ring finger protein (ZFP36) (a.k.a. TTP)	NM_003407

An antisense nucleic acid molecule can be fully or partially complementary to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP protein. Non-coding regions (5' and 3' untranslated regions)

are the 5' and 3' sequences that flank the coding region in a gene and are not translated into amino acids.

Based upon the sequences disclosed herein (e.g., in Table E), one of skill in the art can easily choose and synthesize any of a number of appropriate antisense nucleic acids to target a nucleic acid encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP protein described herein. Antisense nucleic acids targeting a nucleic acid encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP protein can be designed using the software available at the Integrated DNA Technologies website.

An antisense nucleic acid can be, for example, about 5, 10, 15, 18, 20, 22, 24, 25, 26, 28, 30, 32, 35, 36, 38, 40, 42, 44, 45, 46, 48, or 50 nucleotides or more in length. An antisense oligonucleotide can be constructed using enzymatic ligation reactions and chemical synthesis using procedures known in the art. For example, an antisense nucleic acid can be chemically synthesized using variously modified nucleotides or naturally occurring nucleotides designed to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides or to increase the biological stability of the molecules.

Examples of modified nucleotides which can be used to generate an antisense nucleic acid include 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w,

and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest).

The antisense nucleic acid molecules described herein can be prepared in vitro and administered to a subject, e.g., a human subject. Alternatively, they can be generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP protein to thereby inhibit expression, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarities to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. The antisense nucleic acid molecules can be delivered to a mammalian cell using a vector (e.g., an adenovirus vector, a lentivirus, or a retrovirus).

An antisense nucleic acid can be an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual, β-units, the strands run parallel to each other (Gaultier et al., *Nucleic Acids Res.* 15:6625-6641, 1987). The antisense nucleic acid can also comprise a chimeric RNA-DNA analog (Inoue et al., *FEBS Lett.* 215:327-330, 1987) or a 2'-O-methylribonucleotide (Inoue et al., *Nucleic Acids Res.* 15:6131-6148, 1987).

Another example of an inhibitory nucleic acid is a ribozyme that has specificity for a nucleic acid encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA, e.g., specificity for any one of the sequences presented in Table E). Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes (described in Haselhoff and Gerlach, *Nature* 334:585-591, 1988)) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. An AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP,

MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, e.g., Bartel et al., *Science* 261:1411-1418, 1993.

Alternatively, a ribozyme having specificity for an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA can be designed based upon the nucleotide sequence of any of the AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA sequences disclosed herein. For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA (see, e.g., U.S. Patent. Nos. 4,987,071 and 5,116,742).

An inhibitory nucleic acid can also be a nucleic acid molecule that forms triple helical structures. For example, expression of an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP polypeptide can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP polypeptide (e.g., the promoter and/or enhancer, e.g., a sequence that is at least 1 kb, 2 kb, 3 kb, 4 kb, or 5 kb upstream of the transcription initiation start state) to form triple helical structures that prevent transcription of the gene in target cells. See generally Maher, *Bioassays* 14(12):807-15, 1992; Helene, *Anticancer Drug Des.* 6(6):569-84, 1991; and Helene, *Ann. N.Y. Acad. Sci.* 660:27-36, 1992.

In various embodiments, inhibitory nucleic acids can be modified at the sugar moiety, the base moiety, or phosphate backbone to improve, e.g., the solubility, stability, or hybridization, of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see, e.g., Hyrup et al., *Bioorganic Medicinal Chem.* 4(1):5-23, 1996). Peptide nucleic acids (PNAs) are nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs allows for specific hybridization to RNA and DNA under conditions of low ionic strength. PNA oligomers can be synthesized using standard solid phase peptide synthesis protocols (see, e.g., Perry-O'Keefe et al., *Proc. Natl. Acad. Sci. U.S.A.* 93:14670-675, 1996). PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication.

Small Molecules

In some embodiments, the anti-TNFα agent is a small molecule. In some embodiments, the small molecule is a tumor necrosis factor-converting enzyme (TACE) inhibitor (e.g., Moss et al., *Nature Clinical Practice Rheumatology* 4: 300-309, 2008). In some embodiments, the anti-TNFα agent is C87 (Ma et al., *J. Biol. Chem.* 289(18):12457-66, 2014). In some embodiments, the small molecule is LMP-420 (e.g., Haraguchi et al., *AIDS Res. Ther.* 3:8, 2006). In some embodiments, the TACE inhibitor is TMI-005 and BMS-561392. Additional examples of small molecule inhibitors are described in, e.g., He et al., *Science* 310(5750):1022-1025, 2005.

In some examples, the anti-TNFα agent is a small molecule that inhibits the activity of one of AP-1, ASK1, IKK, JNK, MAPK, MEKK 1/4, MEKK4/7, MEKK 3/6, NIK, TRADD, RIP, NF-κB, and TRADD in a cell (e.g., in a cell obtained from a subject, a mammalian cell).

In some examples, the anti-TNFα agent is a small molecule that inhibits the activity of one of CD14, MyD88 (see, e.g., Olson et al., *Scientific Reports* 5:14246, 2015), ras (e.g., Baker et al., *Nature* 497:577-578, 2013), raf (e.g., vemurafenib (PLX4032, RG7204), sorafenib tosylate, PLX-4720, dabrafenib (GSK2118436), GDC-0879, RAF265 (CHIR-265), AZ 628, NVP-BHG712, SB590885, ZM 336372, sorafenib, GW5074, TAK-632, CEP-32496, encorafenib (LGX818), CCT196969, LY3009120, RO5126766 (CH5126766), PLX7904, and MLN2480).

In some examples, the anti-TNFα agent TNFα inhibitor is a small molecule that inhibits the activity of one of MK2 (PF 3644022 and PHA 767491), JNK (e.g., AEG 3482, BI 78D3, CEP 1347, c-JUN peptide, IQ 1S, JIP-1 (153-163), SP600125, SU 3327, and TCS JNK6o), c-jun (e.g., AEG 3482, BI 78D3, CEP 1347, c-JUN peptide, IQ 1S, JIP-1 (153-163), SP600125, SU 3327, and TCS JNK6o), MEK3/6 (e.g., Akinleye et al., *J. Hematol. Oncol.* 6:27, 2013), p38 (e.g., AL 8697, AMG 548, BIRB 796, CMPD-1, DBM 1285 dihydrochloride, EO 1428, JX 401, ML 3403, Org 48762-0, PH 797804, RWJ 67657, SB 202190, SB 203580, SB 239063, SB 706504, SCIO 469, SKF 86002, SX 011, TA 01, TA 02, TAK 715, VX 702, and VX 745), PKR (e.g., 2-aminopurine or CAS 608512-97-6), TTP (e.g., CAS 329907-28-0), MEK1/2 (e.g., Facciorusso et al., *Expert Review Gastroentrol. Hepatol.* 9:993-1003, 2015), ERK1/2 (e.g., Mandal et al., *Oncogene* 35:2547-2561, 2016), NIK (e.g., Mortier et al., *Bioorg. Med. Chem. Lett.* 20:4515-4520, 2010), IKK (e.g., Reilly et al., *Nature Med.* 19:313-321, 2013), IκB (e.g., Suzuki et al., *Expert. Opin. Invest. Drugs* 20:395-405, 2011), NF-κB (e.g., Gupta et al., *Biochim. Biophys. Acta* 1799(10-12):775-787, 2010), rac (e.g., U.S. Patent No. 9,278,956), MEK4/7, IRAK (Chaudhary et al., *J. Med. Chem.* 58(1):96-110, 2015), LBP (see, e.g., U.S. Patent No. 5,705,398), and TRAF6 (e.g., 3-[(2,5-Dimethylphenyl)amino]-1-phenyl-2-propen-1-one).

In some embodiments of any of the methods described herein, the inhibitory nucleic acid can be about 10 nucleotides to about 50 nucleotides (e.g., about 10 nucleotides to about 45 nucleotides, about 10 nucleotides to about 40 nucleotides, about 10 nucleotides to about 35 nucleotides, about 10 nucleotides to about 30 nucleotides, about 10 nucleotides to about 28 nucleotides, about 10 nucleotides to about 26 nucleotides, about 10 nucleotides to about 25 nucleotides, about 10 nucleotides to about 24 nucleotides, about 10 nucleotides to about 22 nucleotides, about 10 nucleotides to about 20 nucleotides, about 10 nucleotides to about 18 nucleotides, about 10 nucleotides to about 16 nucleotides, about 10 nucleotides to about 14 nucleotides, about 10 nucleotides to about 12 nucleotides, about 12 nucleotides to about 50 nucleotides, about 12 nucleotides to about 45 nucleotides, about 12 nucleotides to about 40 nucleotides, about 12 nucleotides to about 35 nucleotides, about 12 nucleotides to about 30 nucleotides, about 12 nucleotides to about 28 nucleotides, about 12 nucleotides to about 26 nucleotides, about 12 nucleotides to about 25 nucleotides, about 12 nucleotides to about 24 nucleotides, about 12 nucleotides to about 22 nucleotides, about 12 nucleotides to about 20 nucleotides, about 12 nucleotides to about 18 nucleotides, about 12 nucleotides to about 16

nucleotides, about 12 nucleotides to about 14 nucleotides, about 15 nucleotides to about 50 nucleotides, about 15nucleotides to about 45 nucleotides, about 15nucleotides to about 40 nucleotides, about 15nucleotides to about 35 nucleotides, about 15 nucleotides to about 30 nucleotides, about 15nucleotides to about 28 nucleotides, about 15nucleotides to about 26 nucleotides, about 15nucleotides to about 25 nucleotides, about 15nucleotides to about 24 nucleotides, about 15nucleotides to about 22 nucleotides, about 15nucleotides to about 20 nucleotides, about 15nucleotides to about 18 nucleotides, about 15nucleotides to about 16 nucleotides, about 16 nucleotides to about 50 nucleotides, about 16 nucleotides to about 45 nucleotides, about 16 nucleotides to about 40 nucleotides, about 16 nucleotides to about 35 nucleotides, about 16 nucleotides to about 30 nucleotides, about 16 nucleotides to about 28 nucleotides, about 16 nucleotides to about 26 nucleotides, about 16 nucleotides to about 25 nucleotides, about 16 nucleotides to about 24 nucleotides, about 16 nucleotides to about 22 nucleotides, about 16 nucleotides to about 20 nucleotides, about 16 nucleotides to about 18 nucleotides, about 18 nucleotides to about 20 nucleotides, about 20 nucleotides to about 50 nucleotides, about 20 nucleotides to about 45 nucleotides, about 20 nucleotides to about 40 nucleotides, about 20 nucleotides to about 35 nucleotides, about 20 nucleotides to about 30 nucleotides, about 20 nucleotides to about 28 nucleotides, about 20 nucleotides to about 26 nucleotides, about 20 nucleotides to about 25 nucleotides, about 20 nucleotides to about 24 nucleotides, about 20 nucleotides to about 22 nucleotides, about 24 nucleotides to about 50 nucleotides, about 24 nucleotides to about 45 nucleotides, about 24 nucleotides to about 40 nucleotides, about 24 nucleotides to about 35 nucleotides, about 24 nucleotides to about 30 nucleotides, about 24 nucleotides to about 28 nucleotides, about 24 nucleotides to about 26 nucleotides, about 24 nucleotides to about 25 nucleotides, about 26 nucleotides to about 50 nucleotides, about 26 nucleotides to about 45 nucleotides, about 26 nucleotides to about 40 nucleotides, about 26 nucleotides to about 35 nucleotides, about 26 nucleotides to about 30 nucleotides, about 26 nucleotides to about 28 nucleotides, about 28 nucleotides to about 50 nucleotides, about 28 nucleotides to about 45 nucleotides, about 28 nucleotides to about 40 nucleotides, about 28 nucleotides to about 35 nucleotides, about 28 nucleotides to about 30 nucleotides, about 30 nucleotides to about 50 nucleotides, about 30 nucleotides to about 45 nucleotides, about 30 nucleotides to about 40 nucleotides, about 30 nucleotides to about 38 nucleotides, about 30 nucleotides to about 36 nucleotides, about 30 nucleotides to about 34

nucleotides, about 30 nucleotides to about 32 nucleotides, about 32 nucleotides to about 50 nucleotides, about 32 nucleotides to about 45 nucleotides, about 32 nucleotides to about 40 nucleotides, about 32 nucleotides to about 35 nucleotides, about 35 nucleotides to about 50 nucleotides, about 35 nucleotides to about 45 nucleotides, about 35 nucleotides to about 40 nucleotides, about 40 nucleotides to about 50 nucleotides, about 40 nucleotides to about 45 nucleotides, about 42 nucleotides to about 50 nucleotides, about 42 nucleotides to about 45 nucleotides, or about 45 nucleotides to about 50 nucleotides) in length. One skilled in the art will appreciate that inhibitory nucleic acids may comprises at least one modified nucleic acid at either the 5' or 3' end of DNA or RNA.

In some embodiments, the inhibitory nucleic acid can be formulated in a liposome, a micelle (e.g., a mixed micelle), a nanoemulsion, or a microemulsion, a solid nanoparticle, or a nanoparticle (e.g., a nanoparticle including one or more synthetic polymers). Additional exemplary structural features of inhibitory nucleic acids and formulations of inhibitory nucleic acids are described in US 2016/0090598.

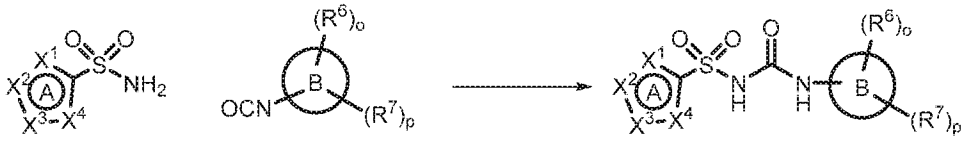
In some embodiments, the inhibitory nucleic acid (e.g., any of the inhibitory nucleic acid described herein) can include a sterile saline solution (e.g., phosphate-buffered saline (PBS)). In some embodiments, the inhibitory nucleic acid (e.g., any of the inhibitory nucleic acid described herein) can include a tissue-specific delivery molecule (e.g., a tissue-specific antibody).

Compound Preparation and Biological Assays

As can be appreciated by the skilled artisan, methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and RGM. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

In some embodiments, a compound of Formulae AA, AA-1, or AA-2 is prepared as shown in **Scheme A-1** through the coupling between sulfonamide (A-**1**) and isocyanate (A-**2**).

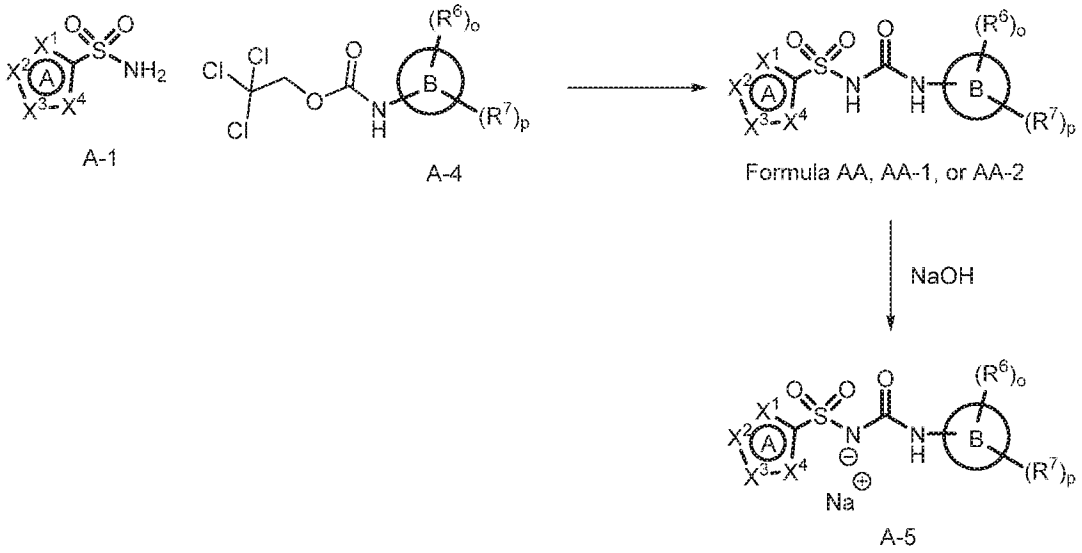
Scheme A-1



For example, the coupling between A-1 and A-2 can be conducted in the presence of sodium hydride (NaH) (e.g., in THF).

Alternatively, A-1 can be coupled with A-4 (e.g., in the presence of NaH and THF) as shown in Scheme A-2 below to provide a compound of Formulae AA, AA-1, or AA-2 which may be converted into a salt (e.g., a sodium salt such as A-5) upon treatment with base (e.g., NaOH).

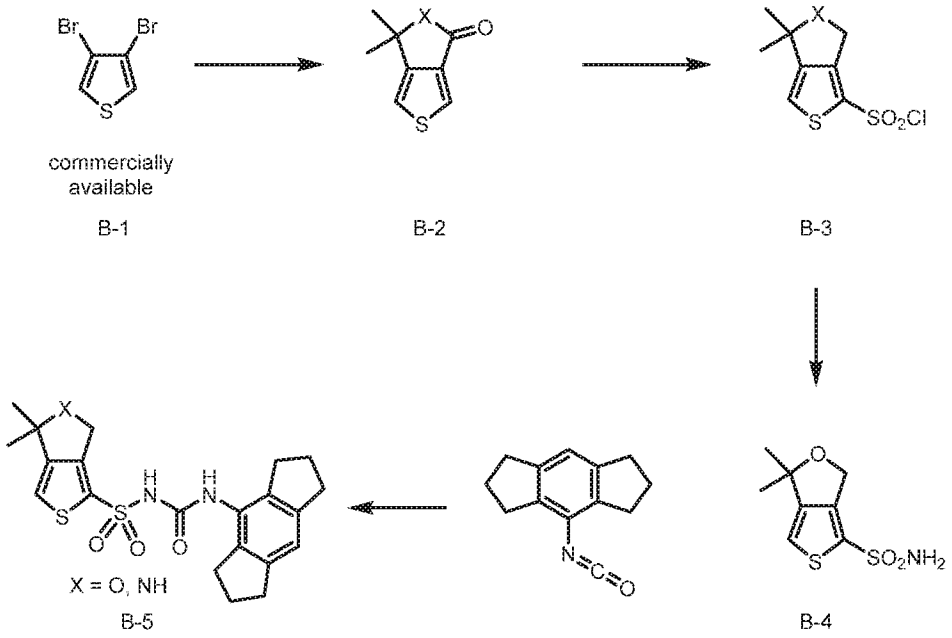
Scheme A-2



Scheme B (below) depicts one example for the synthesis of a compound of Formula AA or AA-2. Commercially available compound B-1 can be subjected to annulation conditions (e.g., those described in *Heterocycles* **1987**, *26*, 2657) to afford compound B-2. Compound B-2 can be sulfonated, whereupon treatment of the intermediate with a chlorination reagent can lead to compound B-3. Compound B-3 can be converted into its corresponding sulfonamide B-4 on treatment with ammonia. Compound B-4 can be coupled with 4-isocyanato-1,2,3,5,6,7-

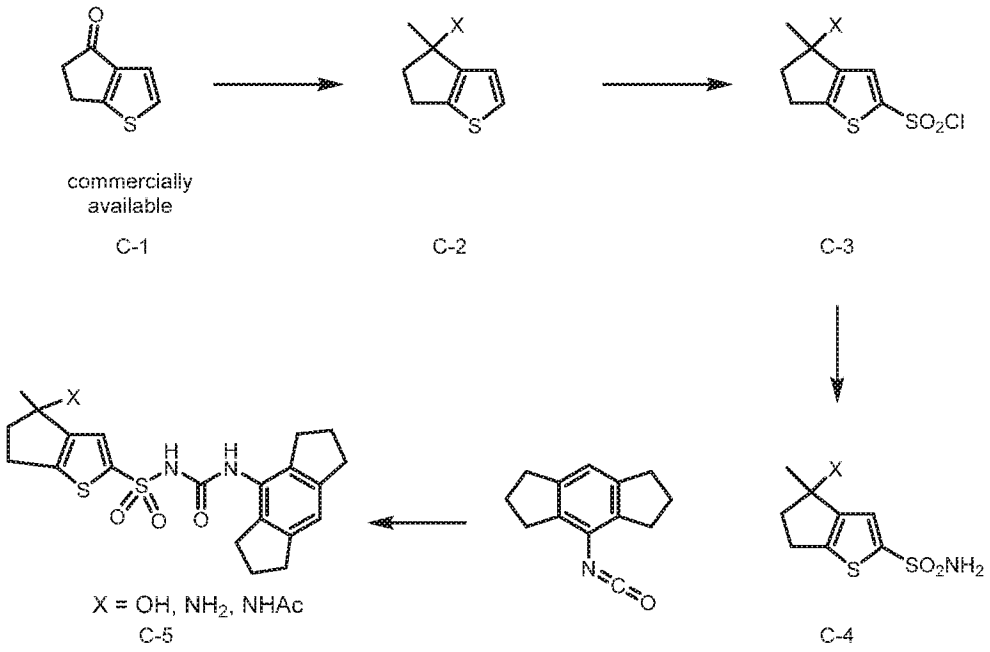
hexahydro-s-indacene to afford compound B-5 which is a compound of Formula AA or AA-2.

Scheme B



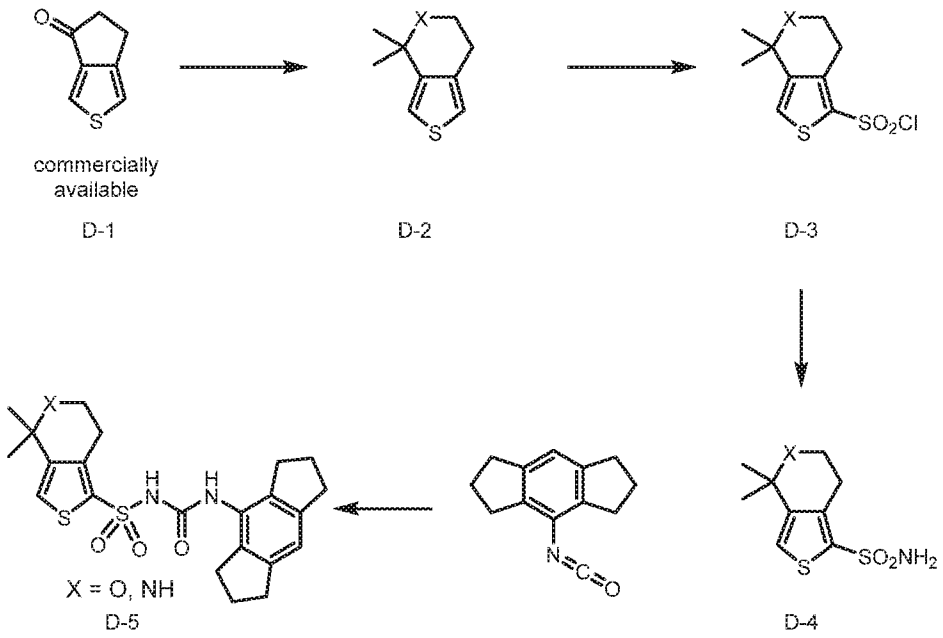
Scheme C (below) depicts another example for the synthesis of a compound of Formula AA or AA-2. Commercially available compound C-1 can be derivatized at the carbonyl group to form compound C-2 (e.g., by means of Grignard addition, or imine formation followed by Grignard addition). Compound C-2 can be sulfonated, whereupon treatment of the intermediate with a chlorination reagent can lead to compound C-3. The hydroxyl group in compound C-2 is optionally protected with a hydroxyl protecting group prior to conversion to C-3. Compound C-3 can be converted into its corresponding sulfonamide C-4 on treatment with ammonia. Compound C-4 can be coupled with 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene to afford compound C-5 which is a compound of Formulae AA or AA-2, following the removal of protecting group if present. Compound C-5 is optionally subjected to chiral resolution to yield its two enantiomers which are each a compound of Formulae AA or AA-2.

Scheme C



Scheme D depicts yet another example for the synthesis of a compound of Formula AA or AA-2. Commercially available compound D-1 can undergo ring expansion (e.g., via oxidative cleavage of the corresponding enol acetate) to provide a compound of Formula D-2. Sulfonation of D-2, followed by the treatment of the resulting intermediate with a chlorinating agent can provide compound D-3. Treatment of D-3 with ammonia can yield sulfonamide D-4 which can then be coupled with 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene to afford compound D-5 which is a compound of Formulae AA or AA-2.

Scheme D



Preparation of Exemplary Compounds

The following abbreviations have the indicated meanings:

ACN = acetonitrile

BTC = trichloromethyl chloroformate

Boc = *t*-butyloxy carbonyl

DCM = dichloromethane

DMF = N,N-dimethylformamide

DMSO = dimethyl sulfoxide

DIEA = N,N-diisopropylethylamine

HPLC = high performance liquid chromatography

LC-MS = liquid chromatography – mass spectrometry

Me = methyl

MeOH = methanol

MSA = methanesulfonic acid

NIS = N-iodosuccinimide

NMR = nuclear magnetic resonance

Py = pyridine$Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0)

PE = petroleum ether

RT = room temperature

Sat. = saturated

TEA = triethylamine

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

TsOH = 4-methylbenzenesulfonic acid

UV = ultraviolet

Xphos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

General

The progress of reactions was often monitored by TLC or LC-MS. The identity of the products was often confirmed by LC-MS. The LC-MS was recorded using one of the following methods.

Method A: Shim-pack XR-ODS, C18, 3x50 mm, 2.5 um column, 1.0 uL injection, 1.5 mL/min flow rate, 90-900 amu scan range, 190-400 nm UV range, 5-100% (1.1 min), 100% (0.6 min) gradient with ACN (0.05% TFA) and water (0.05% TFA), 2 minute total run time.

Method B: Kinetex EVO, C18, 3x50 mm, 2.2 um column, 1.0 uL injection, 1.5 mL/min flow rate, 90-900 amu scan range, 190-400 nm UV range, 10-95% (1.1 min), 95% (0.6 min) gradient with ACN and water (0.5% NH_4HCO_3), 2 minute total run time.

Method C: Shim-pack XR-ODS, C18, 3x50 mm, 2.5 um column, 1.0 uL injection, 1.5 mL/min flow rate, 90-900 amu scan range, 190-400 nm UV range, 5-100% (2.1 min), 100% (0.6 min) gradient with ACN (0.05% TFA) and water (0.05% TFA), 3 minute total run time.

Method D: Kinetex EVO, C18, 3x50 mm, 2.2 um column, 1.0 uL injection, 1.5 mL/min flow rate, 90-900 amu scan range, 190-400 nm UV range, 10-95% (2.1 min), 95% (0.6 min) gradient with ACN and water (0.5% NH_4HCO_3), 3 minute total run time.

Method F: Phenomenex, CH0-7644, Onyx Monolithic C18, 50 x 4.6 mm, 10.0 uL injection, 1.5 mL/min flow rate, 100-1500 amu scan range, 220 and 254 nm UV detection, 5% with ACN (0.1% TFA) to 100% water (0.1% TFA) over 9.5 min, with a stay at 100% (ACN, 0.1% TFA) for 1 min, then equilibration to 5% (ACN, 0.1% TFA) over 1.5 min.

The final targets were purified by Prep-HPLC. The Prep-HPLC was carried out using the following method.

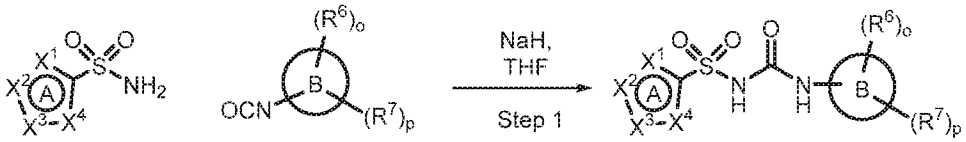
Method E: Prep-HPLC: Column, XBridge Shield RP18 OBD (19x250 mm, 10 um); mobile phase, Water (10mmol/L NH_4HCO_3) and ACN, UV detection 254/210 nm.

Method G: Prep-HPLC: Higgins Analytical Proto 200, C18 Column, 250 x 20 mm, 10 um; mobile phase, Water (0.1% TFA) and ACN (0.1% TFA), UV detection 254/210 nm.

NMR was recorded on BRUKER NMR 300.03 MHz, DUL-C-H, ULTRASHIELD™300, AVANCE II 300 B-ACS™120 or BRUKER NMR 400.13 MHz, BBFO, ULTRASHIELD™400, AVANCE III 400, B-ACS™120.

Scheme of final targets: Schemes below illustrate several conditions used for coupling of sulfonamide and isocyanate to afford aminocarbonyl sulfonamide.

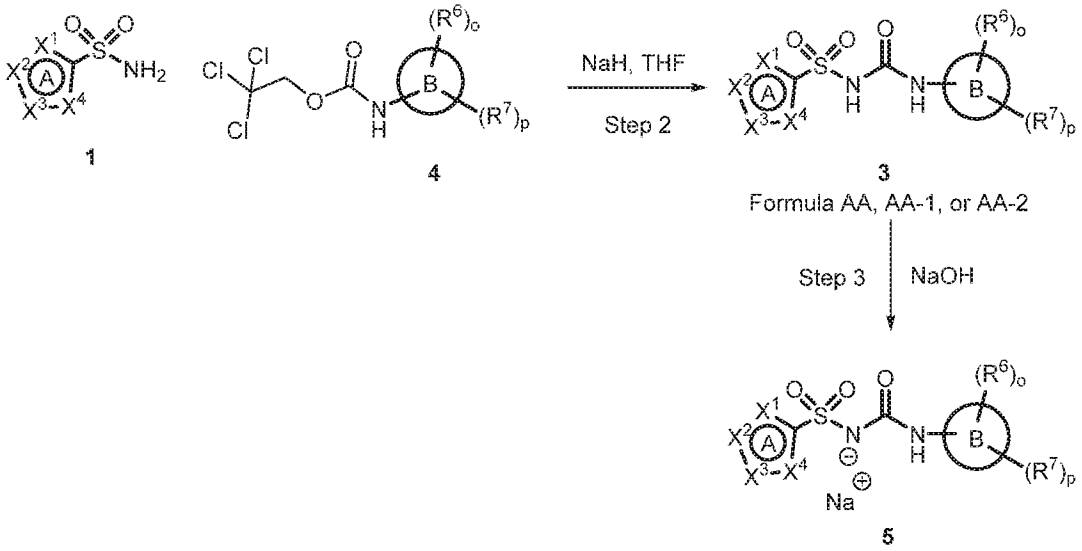
Scheme 1



1 2 3

Formula AA, AA-1, or AA-2

Scheme 2

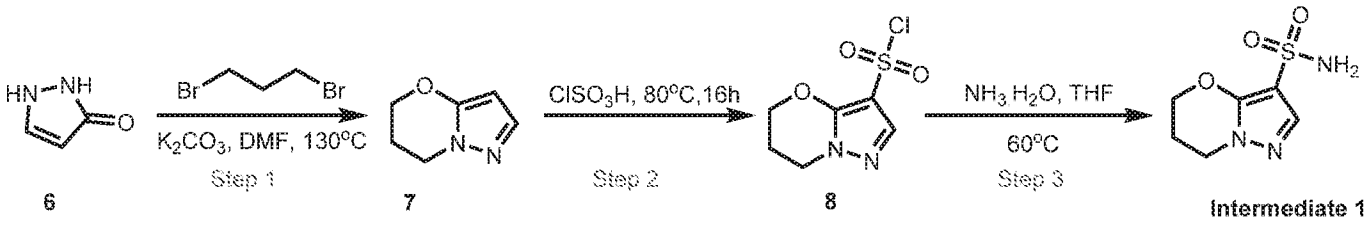


1 4 3 5

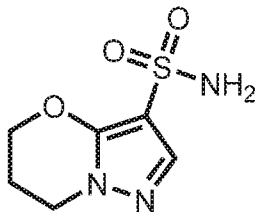
Formula AA, AA-1, or AA-2

Schemes for the preparation of Intermediates:

Scheme 3:



Intermediate 1



6,7-Dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide

Step 1: 6,7-Dihydro-5H-pyrazolo[5,1-b][1,3]oxazine

1,2-Dihydro-pyrazol-3-one (5.3 g, 63.1 mmol) and K_2CO_3 (30.5 g, 221 mmol) were heated to 130°C in DMF (100 mL). 1,3-Dibromopropane (14 g, 69.3 mmol) was added and the mixture was heated for 8 h and then concentrated. The resulting solution was diluted with 50 mL of water and extracted with EtOAc (20 mL x 8). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column (PE/EA=3/1) to give the title compound (3.0 g, 40% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 2.0 Hz, 1H), 5.48 (d, J = 2.0 Hz, 1H), 4.28 (t, J = 5.2 Hz, 2H), 4.18 (t, J = 6.2 Hz, 2H), 2.30-2.23 (m, 2H)

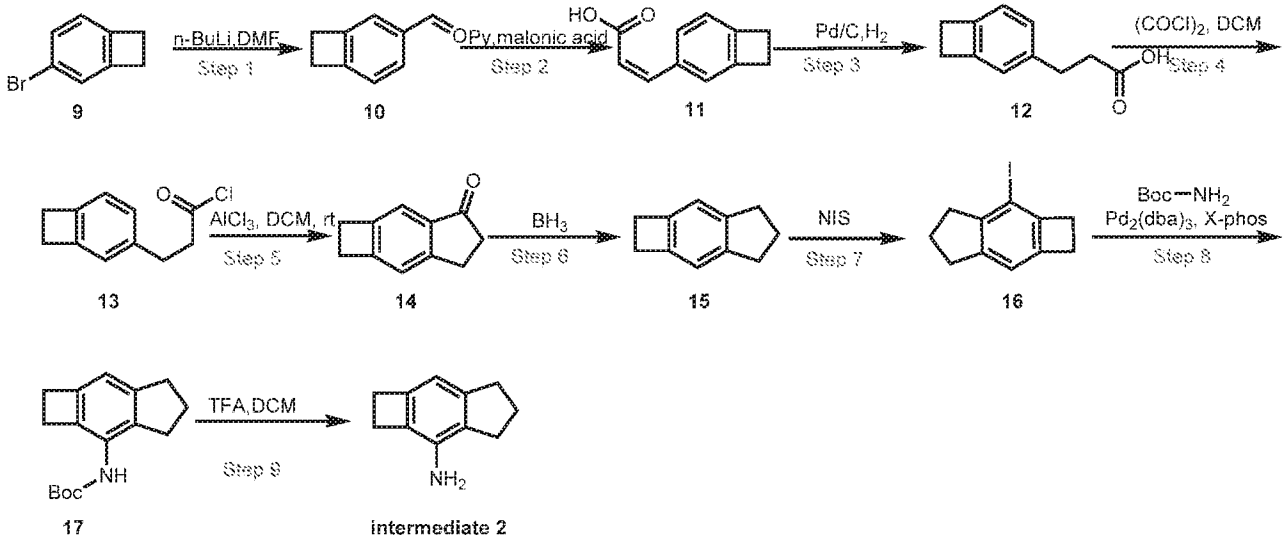
Step 2: 6,7-Dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonyl chloride

6,7-Dihydro-5H-pyrazolo[5,1-b][1,3]oxazine (3.0 g, 24.2 mmol) was added dropwise to $ClSO_3H$ (200 mL) at 0°C. After being stirred at 80°C for 16 h, the reaction mixture was added dropwise to a mixture of ice-water/EtOAc (1.5 L/500 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (300 mL x 2). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated. The residue was washed with PE (50 mL) to give the title compound (3.2 g, y = 60%) as a yellow solid. MS-ESI: 223/225 (M+1).

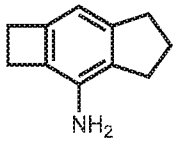
Step 3: 6,7-Dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide

To a solution of 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonyl chloride (3.2 g, 14.5 mmol) in THF (100 mL) was added $NH_3 \cdot H_2O$ (25%-28% wt.) (50 mL). After being stirred at 60°C for 16 h, the reaction mixture was concentrated to dryness. The residue was washed with aq. HCl (0.2 M, 30 mL), H_2O (40 mL), and dried to give 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide (2.3 g, y=78%) as a yellow solid. MS-ESI: 204 (M+1). ^{1}H NMR (300 MHZ, DMSO-d_6): δ 7.47 (s, 1H), 7.08 (s, 2H), 4.40 (t, J = 5.1 Hz, 2H), 4.10 (t, J = 6.0 Hz, 2H), 2.25-2.15 (m, 2H).

Scheme 4:



Intermediate 2



2,4,5,6-Tetrahydro-1H-cyclobuta[f]inden-3-amine

Step 1: Bicyclo[4.2.0]octa-1(6),2,4-triene-3-carbaldehyde

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-bromobicyclo[4.2.0]octa-1(6),2,4-triene (70 g, 382 mmol) in THF (300 mL). This was followed by the addition of n-BuLi (184 mL, 459 mmol) dropwise with stirring at about -70°C. After addition, the reaction mixture was stirred at this temperature for 30 min. To this solution was added DMF (36.3 g, 497 mmol) dropwise with stirring at -70°C. The resulting solution was stirred for 30 min at -70°C in a liquid nitrogen bath. The reaction was slowly warmed to RT and then quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x200 ml of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, after which the organic layers was concentrated. This resulted in 50 g (98.9%) of the title compound as light yellow oil. MS-ESI: 133 (M+1).

Step 2: (Z)-3-(bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)acrylic acid

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed bicyclo[4.2.0]octa-1(6),2,4-triene-3-carbaldehyde (17 g, 129 mmol) in pyridine (200 mL), propanedioic acid (19.9 g, 192 mmol) and piperidine (1.1 g, 12.9 mmol). The resulting

solution was stirred for overnight at 90°C in an oil bath. The resulting mixture was concentrated. This resulted in 35 g (crude) of the title compound as a solid. MS-ESI: 173 (M-1).

Step 3: 3-(Bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)propanoic acid

Into a 1000-mL round-bottom flask, was placed a solution of 2-(Z or E)-3-[bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl]prop-2-enoic acid (35 g, crude) in MeOH (500 mL). To the solution was added Pd/C (10% wt., 2 g). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 12 h at RT under an atmosphere of hydrogen. The Pd/C catalysts were filtered out, and the filtrate was concentrated under vacuum. The residue was dissolved in DCM (2000 mL) and then washed with HCl (1 N, 1000 mL), the organic phase was dried over anhydrous Na_2SO_4 then concentrated. This resulted in 21 g (92.6% over 2 steps) of the title compound as a solid. MS-ESI: 175 (M-1).

Step 4: 3-(Bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)propanoyl chloride

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-[bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl]propanoic acid (10 g, 56.8 mmol) in DCM (100 mL). This was followed by the addition of oxalyl chloride (7.2 g, 56.8 mmol) dropwise with stirring at 0°C. The resulting solution was stirred for 2 h at 0°C in a water/ice bath. The resulting mixture was concentrated. This resulted in 10 g (crude) of the title compound as light yellow oil which was used in next step without purification.

Step 5: 1,2,5,6-Tetrahydro-4H-cyclobuta[f]inden-4-one

Into a 100-mL round-bottom flask, was placed 3-[bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl]propanoyl chloride (10 g, crude) in DCM (100 mL). This was followed by the addition of $AlCl_3$ (6.8 g, 51.4 mmol) in portions at 0°C over 10 min. The resulting solution was stirred for 1 h at 0°C in a water/ice bath. The reaction was then quenched by the addition of 200 mL of water. The resulting solution was extracted with 2x100 mL of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:20 to 1:15). This resulted in 3.5 g (40.0% over 2 steps) of the title compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.17 (s, 1H), 3.31-3.22 (m, 4H), 3.18–3.00 (m, 2H), 2.73–2.63 (m, 2H).

Step 6: 2,4,5,6-Tetrahydro-1H-cyclobuta[f]indene

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen,

was placed 1,2,5,6-tetrahydrocyclobuta[f]inden-4-one (20 g, 126 mmol) in THF (200 mL). This was followed by the addition of BH_3-Me_2S (25.3 mL, 253 mmol, 10 M) dropwise at 0°C in an ice bath. The resulting solution was stirred for 14 h at 70°C in an oil bath. The reaction was then quenched by the addition of 20 mL of MeOH. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:100 to 1:50). This resulted in 15 g (82.3%) of the title compound as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 2H), 3.10 (s, 4H), 2.88 (t, J = 7.4 Hz, 4H), 2.04-2.02 (m, 2H).

Step 7: 3-Iodo-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene

Into a 500-mL round-bottom flask, was placed acetic acid (100 mL), 2,4,5,6-tetrahydro-1H-cyclobuta [f]indene (15 g, 104 mmol) and NIS (35.1 g, 156 mmol). The resulting solution was stirred for 3 h at 50°C in an oil bath. The resulting solution was diluted with 200 mL of water. The mixture was extracted with 3x100 mL of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:100 to 1:80). This resulted in 5.0 g (17.8%) of the title compound as yellow oil.

Step 8: Tert-butyl (2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamate

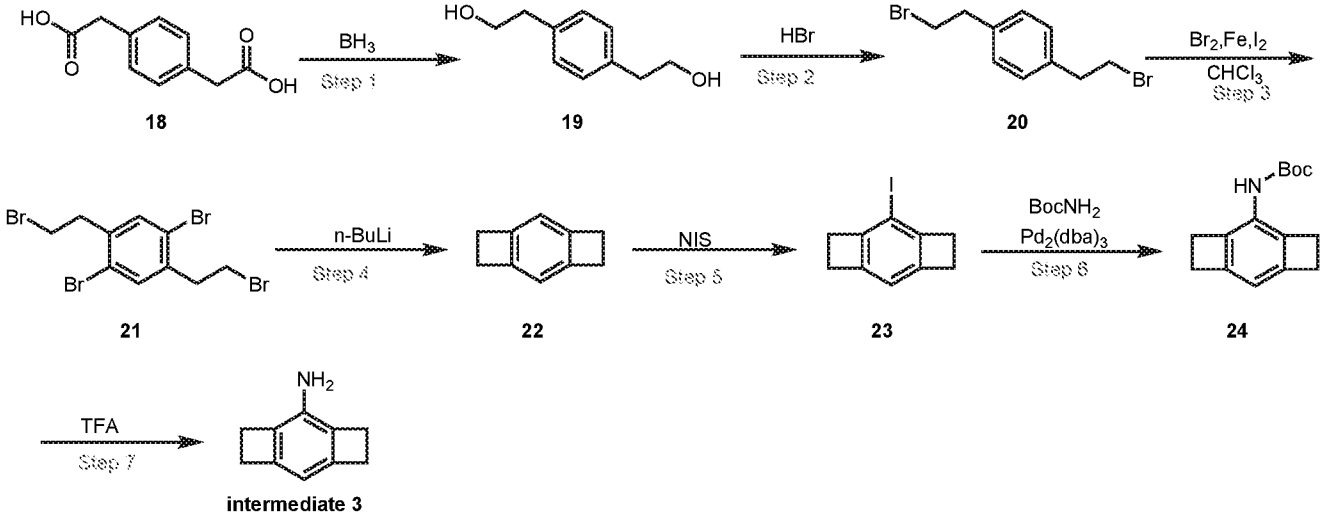
Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-iodo-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene (5.0 g, 18.5 mmol) in toluene (100 mL), tert-butyl carbamate (6.5 g, 55.5 mmol), X-phos (900 mg, 1.85 mmol), $Pd_2(dba)_3$ (800 mg, 0.93 mmol), t-BuOK (6.2 g, 55.5 mmol). The resulting solution was stirred for 14 h at 100°C in an oil bath. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:50 to 1:20). This resulted in 3.0 g (83.3%) of the title compound as a white solid. MS-ESI: 260 (M+1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.13 (br, 1H), 3.26 (d, J = 4.5 Hz, 2H), 3.01 (d, J = 4.5 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H), 2.75 (t, J = 7.4 Hz, 2H), 2.08-2.04 (m, 2H), 1.52 (s, 9H).

Step 9: 2,4,5,6-Tetrahydro-1H-cyclobuta[f]inden-3-amine

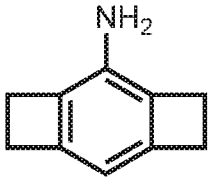
Into a 100-mL round-bottom flask, was placed tert-butyl2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3- ylcarbamate (3.0 g, 11.6 mmol) in DCM (20 mL). To the solution was added 2,2,2-trifluoroacetic acid (5.0 mL). The resulting solution was stirred for 2 h at RT. The resulting solution was diluted with 50 mL of water. The pH value of the solution was adjusted to 10 with sat. aqueous Na_2CO_3. The resulting solution was extracted with 3x20 mL of DCM. The organic layers were

combined, dried over anhydrous Na_2SO_4, and then concentrated. This resulted in 1.5 g (81.4%) of the title compound as a yellow solid. MS-ESI: 160 (M+1).

Scheme 5:



Intermediate 3



Tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-amine

Step 1: 2,2'-(1,4-Phenylene)bis(ethan-1-ol)

Into a 1.0-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-[4-(carboxymethyl)phenyl]acetic acid (40 g, 200 mmol) in THF (500 mL). This was followed by the addition of BH_3-Me_2S (60 mL, 600 mmol, 10 M) dropwise with stirring at 0°C. The resulting solution was stirred for 24 h at RT. The reaction was then quenched by the addition of 200 mL of water. The resulting solution was extracted with 2x150 mL of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated. The resulting residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:10 to 1:3). This resulted in 28 g (81.8%) of the title compound as brown oil. MS-ESI: 167 (M+1).

Step 2: 1,4-Bis(2-bromoethyl)benzene

Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-[4-(2-hydroxyethyl)phenyl]ethan-1-ol (28 g, 168 mmol) in aq. HBr (300 mL, 40%wt.).

The resulting solution was stirred for 5 h at 100°C in an oil bath. The resulting solution was diluted with 500 mL of water and was then extracted with 3x200 mL of DCM. The organic layers were combined and concentrated. This resulted in 40 g (81.4%) of the title compound as a white solid. MS-ESI: 291/293/295 (M+1).

Step 3: 1,4-Dibromo-2,5-bis(2-bromoethyl)benzene

Into a 500-mL round-bottom flask, was placed 1,4-bis(2-bromoethyl)benzene (30 g, 103 mmol) in trichloromethane (200 mL). To the above solution was added I_2 (0.78 g, 3.08 mmol), iron powder (0.75 g, 13.4 mmol), and Br_2 (41 g, 257 mmol). The resulting solution was stirred for 24 h at RT. The reaction was then quenched by the addition of aqueous Na_2SO_3. The resulting solution was extracted with 3x200 mL DCM. The organic layers were combined, dried over anhydrous Na_2SO_4, and then concentrated. This resulted in 40 g (86.6%) of the title compound as a white solid. MS-ESI: 449/451/453 (M+1).

Step 4: Tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene

Into a 1000-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1,4-dibromo-2,5-bis(2-bromoethyl)benzene (40 g, 88.9 mmol) in THF (400 mL). This was followed by the addition of n-BuLi (74.7 mL, 187 mmol, 2.5 M) dropwise with stirring at -78°C in a liquid nitrogen bath. The resulting solution was stirred for 30 min at -78°C. The reaction was then quenched by the addition of aqueous NH_4Cl (300 ml) and extracted with 2x200 mL of DCM and the organic layers was combined and dried over anhydrous Na_2SO_4 then concentrated. This resulted in 8.0 g (69.1%) of the title compound as a light yellow solid.

Step 5: 2-Iodotricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene (8 g, 61.45 mmol) in acetic acid (50 mL) and NIS (20.7 g, 92.2 mmol). The resulting solution was stirred for 3 h at 50°C in an oil bath. The resulting solution was diluted with 100 mL of water. The reaction was then quenched by the addition of aqueous Na_2SO_3. The resulting solution was extracted with 3x50 mL of DCM. The organic layers were combined, dried over anhydrous Na_2SO_4, and then concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:100). This resulted in 2.5 g (18.2%) of the title compound as a white solid.

Step 6: *Tert*-butyl tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-ylcarbamate

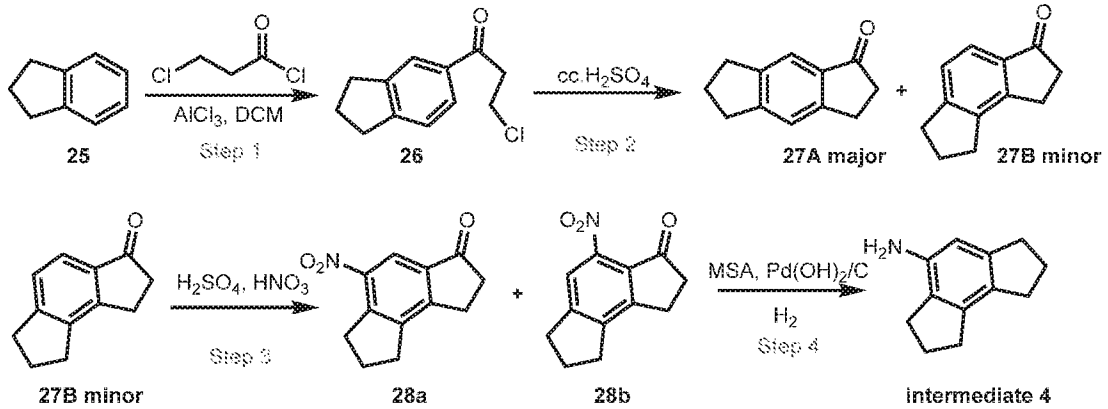
Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen,

was placed 2-iodotricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene (2.5 g, 9.76 mmol) in toluene (50 mL). To the stirred solution was added tert-butyl carbamate (3.43 g, 29.3 mmol), $Pd_2(dba)_3$ (447 mg, 0.49 mmol), Xphos (466 mg, 0.98 mmol), and t-BuOK (3.29 g, 29.3 mmol). The resulting solution was stirred for 14 h at 100°C in an oil bath. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:50 to 1:30). This resulted in 1.5 g (62.6%) of the title compound as a light yellow solid. MS-ESI: 246 (M+1).

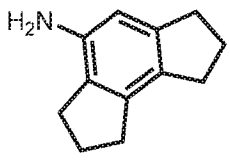
Step 7: Tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-amine

Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl N-[tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-yl]carbamate (1.5 g, 6.1 mmol) in DCM (20 mL) and 2,2,2-trifluoroacetic acid (4.0 mL). The resulting solution was stirred for 2 h at RT. The resulting mixture was concentrated. This resulted in 800 mg (90.1%) of the title compound as a brown solid. MS-ESI: 146 (M+1).

Scheme 6:



Intermediate 4



1,2,3,6,7,8-Hexahydro-*as*-indacen-4-amine

Step 1: 3-Chloro-1-(2,3-dihydro-1H-inden-5-yl)propan-1-one

Into a 3000-mL round-bottom flask was placed a solution of $AlCl_3$ (111 g, 834 mmol) in DCM (1200 mL). This was followed by the addition of a solution of 2,3-dihydro-1H-indene (90 g, 762 mmol) and 3-chloropropanoyl chloride (96.3 g, 759 mmol) in DCM (300 mL) dropwise with

stirring at -10°C in 30 min. The resulting solution was stirred for 16 h at RT. Then the reaction mixture was added dropwise to cold HCl aq. (3 N, 1200 mL) over 45 min at -10°C. The resulting solution was extracted with 3x600 mL of DCM and the organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under vacuum. This resulted in 160.5 g (crude) of the title compound as a yellow solid. The crude product was used in the next step.

Step 2: 3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one and 1,6,7,8-tetrahydro-*as*-indacen-3(2H)-one

Into a 1000-mL round-bottom flask was placed a solution of 3-chloro-1-(2,3-dihydro-1H-inden-5-yl)propan-1-one (160.5 g, 759 mmol) in conc. H_2SO_4 (900 mL). The resulting solution was stirred for 16 h at 55°C, after which the reaction was quenched by adding the reaction mixture carefully to 4500 mL of water/ice. The solids were collected by filtration and dried over infrared lamp for 24 h. The crude mixture was purified by chromatography and eluted with ethyl acetate/petroleum ether (1:100). This resulted in 112.2 g (85%) of 3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one (**27A major**) and 10 g (7.6%) of 1,6,7,8-tetrahydro-*as*-indacen-3(2H)–one (**27B minor**) as a yellow solid.

27A major: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (s, 1H), 7.39 (s, 1H), 3.13 – 2.79 (m, 6H), 2.70 – 2.55 (m, 2H), 2.20 – 1.90 (m, 2H).

27B minor: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 3.19 – 2.98 (m, 4H), 2.93 – 2.80 (m, 2H), 2.68 – 2.54 (m, 2H), 2.15 – 1.95 (m, 2H).

Step 3: 5-nitro-1,6,7,8-tetrahydro-*as*-indacen-3(2H)-one and 4-nitro-1,6,7,8-tetrahydro-*as*-indacen -3(2H)-one

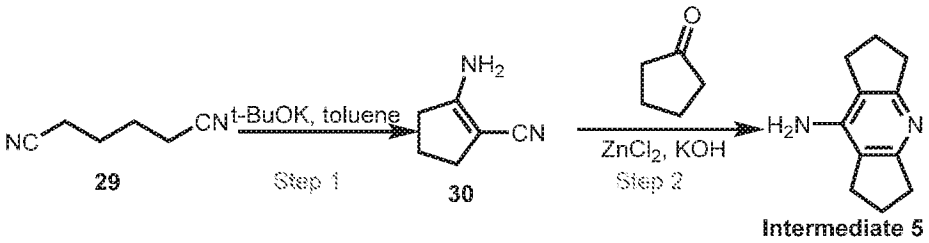
Into a 1000-mL round-bottom flask was placed a solution of 1,6,7,8-tetrahydro-as-indacen-3(2H)-one (9.8 g, 46.5 mmol) in H_2SO_4 (50 mL). Then HNO_3 (5.85 g, 92.9 mmol) was added dropwise over 10 min at 0°C. The resulting solution was stirred for 1 h at 0°C. The reaction mixture was slowly added to a mixture of water/ice (100 mL) and DCM (50 mL) with ice bath cooling. The organic layer was collected, dried over Na_2SO_4 and concentrated under vacuum. This resulted in 11 g (89%) of the title mixture compound as a yellow solid.

Step 4: 1,2,3,6,7,8-Hexahydro-as-indacen-4-amine

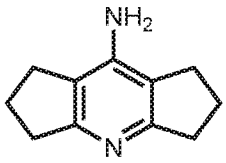
Into a 100-mL round-bottom flask was placed a solution of the mixture of 5-nitro-1,6,7,8-tetrahydro-as-indacen-3(2H)-one and 4-nitro-1,6,7,8-tetrahydro-as-indacen-3(2H)-one (2.17 g, 10 mmol) in MeOH (30 mL). To the solution was added MSA (1.15 g, 12 mmol). Then $Pd(OH)_2$/C (20% wt., 550 mg) was added. The flask was evacuated and filled three times with hydrogen. The

resulting mixture was stirred for 16 h at RT under hydrogen (50 psi). The solids were filtered out and washed with MeOH. The MeOH filtrate was diluted with water (50 mL) and the pH was adjusted to 10.6 with 2 N NaOH. The resulting mixture was filtered and the crude solids were recrystallized from MeOH/water (9:1) with heating. This resulted in 1.38 g (80%) of the title compound as an off-white solid. MS-ESI: 174 (M+1).

Scheme 7A:



Intermediate 5



1,2,3,5,6,7-Hexahydrodicyclopenta[b,e]pyridin-8-amine

Step 1: 2-Aminocyclopent-1-ene-1-carbonitrile

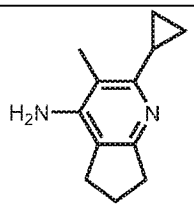
Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a mixture of adiponitrile (10.8 g, 100 mmol) in toluene (250 mL). The reaction mixture was heated to 65°C, when t-BuOK (112 g, 100 mmol) was added into the solution at 65°C in portions. The resulting solution was stirring for at 80°C for 8 h. The reaction was cooled to RT, and then quenched by the addition of 200 mL of water/ice. The solids were collected by filtration. The filter cake was washed with water (100mL) and hexane (200 mL), then dried under an infra-red lamp. This resulted in 9.18 g (85%) of the title compound as an off-white solid. MS-ESI: 109 (M+1).

Step 2: 1,2,3,5,6,7-Hexahydrodicyclopenta[b,e]pyridin-8-amine

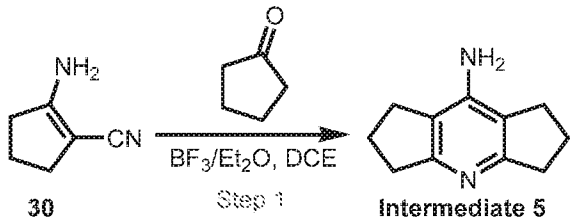
Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-aminocyclopent-1-ene-1-carbonitrile (5.0 g, 46.2 mmol) in xylene (125 mL). To the above solution was added cyclopentanone (7.8 g, 93 mmol) and $ZnCl_2$ (6.9 g, 51 mmol). The

resulting solution was stirred for overnight at 140°C in an oil bath. The resulting solution was diluted with 150 mL of MeOH. Then the solution of KOH (25 mL, 5.0 M) was dropped into the solution. The solids were filtered out. The resulting mixture was concentrated. The residue was dissolved in 250 mL of EtOAc. The solids were collected by filtration. This resulted in 4.2 g (52%) of the title compound as a brown solid. MS-ESI: 175 (M+1).

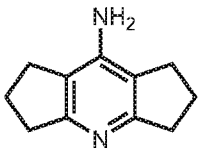
Table S1. The Intermediates in the following Table were prepared using the similar procedures for converting compound **29** to Intermediate **5** shown in Scheme 7A from appropriated starting materials

Intermediate #	Structure	IUPAC Name	Exact Mass$[M+H]^+$
Intermediate 6		2-Cyclopropyl-3-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-4-amine	189

Scheme 7B:



Intermediate 5



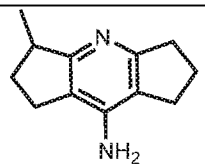
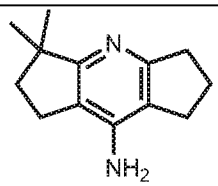
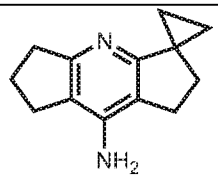
1,2,3,5,6,7-Hexahydrodicyclopenta[b,e]pyridin-8-amine

Step 1: 1,2,3,5,6,7-Hexahydrodicyclopenta[b,e]pyridin-8-amine

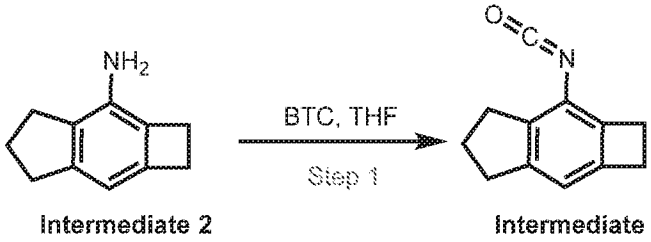
Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a mixture of 2-aminocyclopent-1-enecarbonitrile (5.4 g, 50 mmol) in DCE

(125 mL). To this solution was added cyclopentanone (8.4 g, 100 mmol). Then $BF_3.Et_2O$ (46.5%wt., 14.5 g) was added to this solution at 0°C in an ice bath. The reaction was heat to 75°C for 6 h, after which the reaction was cooled to RT, quenched by the addition of 100 mL of water/ice, and extracted with DCM (2x50 mL). The aqueous phase was collected, and its pH value was adjusted to 14 with NaOH (6 M) until a solid precipitated. The solids were collected by filtration. The filter cake was washed with water (150 mL) then dried by infra-red drying, this resulted of the title compound (7.0 g, yield 80%, light yellow solid). MS-ESI: 175 (M+1).

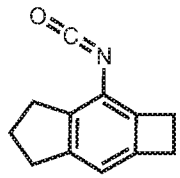
Table S2. The Intermediates in the following Table were prepared using the similar procedures for converting compound **30** to Intermediate **5** shown in **Scheme 7B** from appropriated starting materials.

Intermediate #	Structure	IUPAC Name	Exact Mass[M+H]$^+$
Intermediate 7		3-Methyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-amine	189
Intermediate 8		3,3-Dimethyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-amine	203
Intermediate 9		1',5',6',7'-Tetrahydro-2'H-spiro[cyclopropane-1,3'-dicyclopenta[b,e]pyridin]-8'-amine	201

Scheme 8:



Intermediate 10

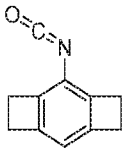
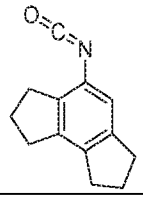


3-Isocyanato-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene

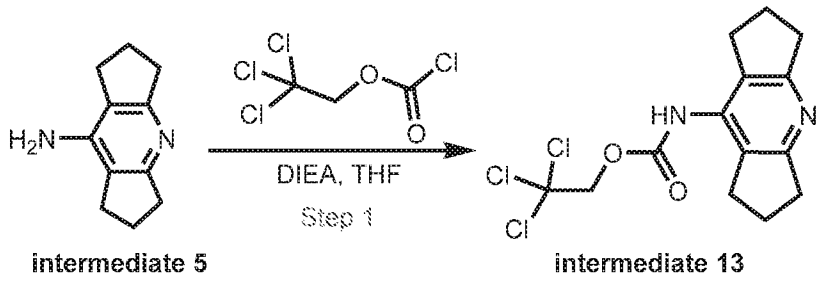
Step 1: 3-Isocyanato-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene

Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-amine (30.0 mg, 0.19 mmol) in THF (5.0 mL), TEA, and bistrichloromethyl carbonate (22.4 mg, 0.08 mmol). The resulting solution was stirred for 1 h at 70°C. The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification.

Table S3. The Intermediates in the following Table were prepared using similar procedure as shown in **Scheme 8** above for converting **Intermediate 2** to **Intermediate 10**.

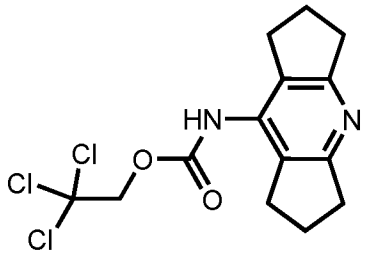
Intermediate #	Structure	IUPAC Name
Intermediate 11		2-Isocyanatotricyclo[6.2.0.03,6]deca-1,3(6),7-triene
Intermediate 12		4-Isocyanato-1,2,3,6,7,8-hexahydro-as-indacene

Scheme 9:



intermediate 5 intermediate 13

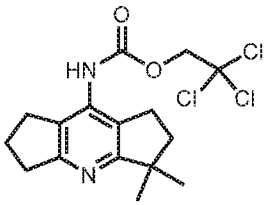
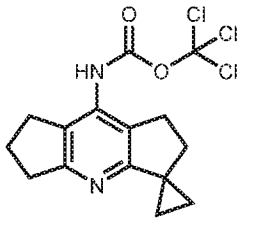
Intermediate 13

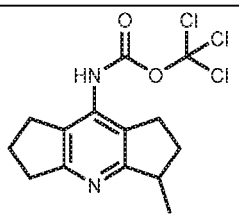
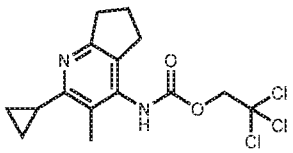


2,2,2-Trichloroethyl (1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamate

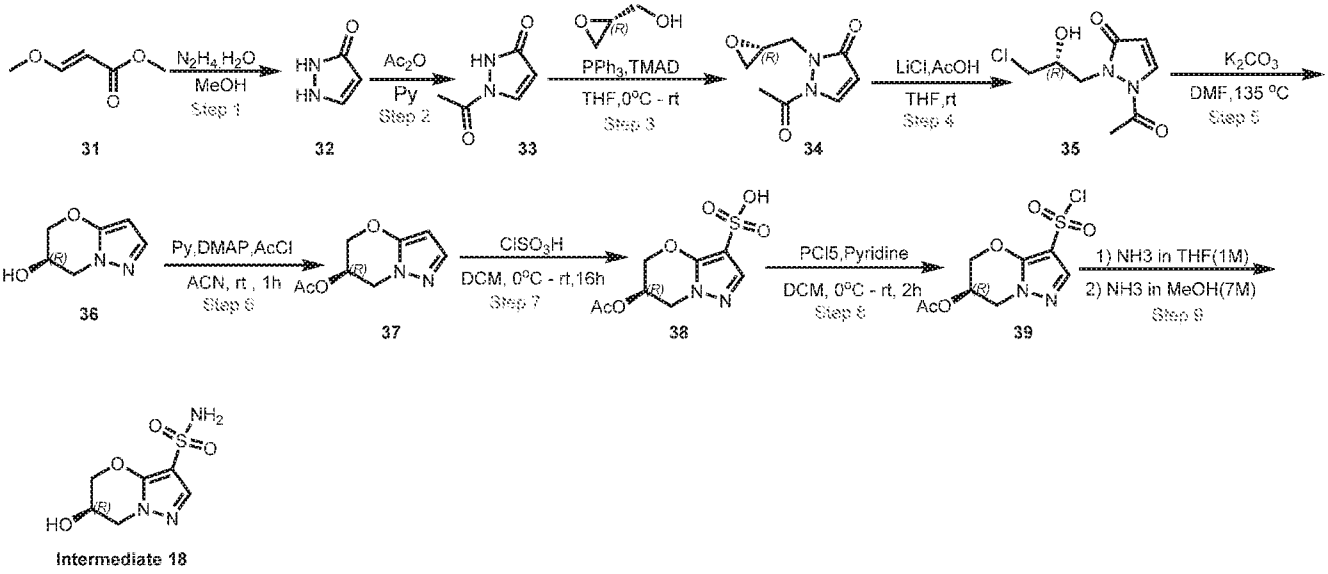
Into a 1-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-amine (6.7 g, 38 mmol) in THF (500 mL). To the above solution was added DIEA (9.92 g, 76.9 mmol) dropwise at RT. Then 2,2,2-trichloroethyl chloroformate (16 g, 76.9 mmol) was dropped into the reaction solution at 0°C. The resulting solution was stirred for 16 h at RT. The resulting mixture was concentrated. The residue was eluted from silica gel with EtOAc/hexane (1:4). This resulted in 7.3 g (54.4%) of the title compound as a yellow solid. MS-ESI: 349/351 (M+1).

Table S4. The Intermediates in the following Table were prepared using the similar procedures for converting intermediate **5** to Intermediate **13** shown in **Scheme 9** from appropriated starting materials.

Intermediate #	Structure	IUPAC Name	Exact Mass[M+H]$^+$
Intermediate 14		2,2,2-Trichloroethyl (3,3-dimethyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamate	377/379
Intermediate 15		Trichloromethyl (1',5',6',7'-tetrahydro-2'H-spiro[cyclopropane-1,3'-dicyclopenta[b,e]pyridin]-8'-yl)carbamate	361/363

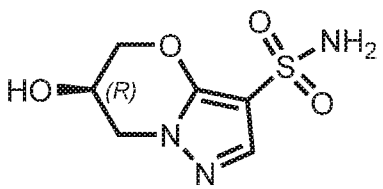
Intermediate 16		Trichloromethyl (3-methyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamate	349/351
Intermediate 17		2,2,2-Trichloroethyl (2-cyclopropyl-3-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-4-yl)carbamate	363/365

Scheme 10:



Intermediate 18

Intermediate 18



(R)-6-hydroxy-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide

Step 1: 1,2-Dihydro-3H-pyrazol-3-one

To a 5 L 4-neck flask containing a solution of methyl (E)-3-methoxyacrylate (2000 g, 17.2 mol)

in MeOH (2.0 L) was added hydrazine hydrate (921 g, 18.4 mol) dropwise at RT under nitrogen. The resulting mixture was stirred for 90 min at 60 °C under nitrogen. The resulting mixture was concentrated under reduced pressure. This resulted in the title compound (1467 g, 68%wt, yield 69%) as an off-white solid. MS-ESI: 85 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (br, 2H), 7.18 (q, J = 2.5 Hz, 1H), 5.26 (q, J = 2.5 Hz, 1H).

Step 2: 2-Acetyl-1,2-dihydropyrazol-5-one

To a 10 L 4-neck flask containing a solution of 1,2-dihydropyrazol-5-one (1467 g, 68%wt, 11.9 mol) in pyridine (6.0 L) was added Ac_2O (1214 g, 11.9 mol) at RT under nitrogen. The resulting mixture was stirred for 1.5 h at 95 °C under nitrogen. The resulting mixture was concentrated under reduced pressure. The residue was slurry with MeOH (1x3000 mL). The resulting mixture was filtered, the filter cake was washed with MeOH (1x500 mL). The filter cake was dried under reduced pressure. This resulted in the title compound (1630 g, 78%wt, 85%) as an off-white solid. MS-ESI: 127 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 3.0 Hz, 1H), 6.00 (d, J = 3.0 Hz, 1H), 2.48 (s, 3H), 2.44 (s, 1H).

Step 3: (R)-2-acetyl-1-(oxiran-2-ylmethyl)-1,2-dihydropyrazol-5-one

To a 10 L 4-neck flask containing a solution of 2-acetyl-1,2-dihydropyrazol-5-one (400 g, 78%wt， 3.17 mol) and R-glycidol (246 g, 3.33 mol) in THF (4.0 L), to the stirred solution was added PPh_3 (915 g, 3.49 mol). To the above mixture was added TMAD (705 g, 3488 mmol) in portions at 0 °C. The resulting mixture was stirred for additional 1 h at RT. The resulting mixture was quenched with 1x4.0 L of water. The aqueous layer was extracted with EtOAc (3x1.0 L). The organic layers were combined and washes with brine (1 L), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was slurry in PE/EtOAc (10:1, 16 L) for 4 h. The resulting mixture was filtered. The filter cake was washed with PE/EtOAc (10:1, 1x1000 mL). The filtrate was concentrated under reduced pressure. This resulted in the title compound (470 g, 84%wt, 87%) as an off-white solid. MS-ESI: 183 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 3.0 Hz, 1H), 6.27 (d, J = 3.0 Hz, 1H), 4.56 (dd, J = 11.8, 2.7 Hz, 1H), 4.02 (dd, J = 11.8, 6.8 Hz, 1H), 3.40-3.34 (m, 1H), 2.86 (dd, J = 5.1, 4.3 Hz, 1H), 2.74 (dd, J = 5.1, 2.6 Hz, 1H), 2.54 (s, 3H).

Step 4: (R)-2-acetyl-1-(3-chloro-2-hydroxypropyl)-1,2-dihydropyrazol-5-one

To a 10 L 3-neck flask was placed a solution of (R)-2-acetyl-1-(oxiran-2-ylmethyl)-1,2-dihydropyrazol -5-one (500 g, 84%wt, 2.74 mol) in THF (2.5 L), to the stirred solution was added AcOH (494 g, 8233 mmol) dropwise and LiCl (186 g, 4391 mmol) in portions at 0 °C under nitrogen. The resulting mixture was stirred for 16 h at RT under nitrogen. The reaction was quenched with water at RT. The aqueous layer was extracted with EtOAc (3x3.0 L). The organic layers were combined and washed with 2x3.0 L of sat. $NaHCO_3$ and 5.0 L of brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. This resulted in the title compound (552 g, 82%wt, yield 90%) as an off-white solid. MS-ESI: 219 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 3.0 Hz, 1H), 6.02 (d, J = 3.0 Hz, 1H), 4.44 (d, J = 5.0 Hz, 2H), 4.29-4.23 (m, 1H), 3.81- 3.67 (m, 2H), 2.61 (s, 3H).

Step 5: (R)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-ol

To a 10 L 3-neck flask was placed a solution of (R)-2-acetyl-1-(3-chloro-2-hydroxypropyl)-1,2-dihydropyrazol-5-one (500 g, 82%wt, 2.29 mol) in DMF (5.0 L), to the stirred solution was added K_2CO_3 (948 g, 6.86 mol) under nitrogen. The resulting mixture was stirred for 16 h at 135 °C under nitrogen and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (20:1) to afford (152 g, yield 58%) of the title compound as an off-white solid. MS-ESI: 141 (M+1). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.11 (d, J = 2.1 Hz, 1H), 5.31 (d, J = 2.1 Hz, 1H), 4.19 – 4.12 (m, 1H), 4.12 – 3.98 (m, 3H), 3.90 – 3.81 (m, 1H).

Step 6: (R)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl acetate

To a stirred solution of (R)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-ol (55.0 g, 392 mmol) in MeCN (825 mL) in a 2-L 3-necked round-bottom flask under nitrogen was added pyridine (93.1 g, 1.18 mol) and DMAP (4.79 g, 39.2 mmol). This was followed by the addition of acetyl chloride (43.1 g, 549 mmol) dropwise with stirring at 0 °C. The resulting solution was stirred for 2 h at RT. LCMS showed reaction was completed. The resulting mixture was concentrated directly. The residue was eluted from silica gel with EtOAc/PE (1:4). This resulted in 58 g (81%) of the title compound as a light yellow solid. MS-ESI: 183 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 2.0 Hz, 1H), 5.57 (d, J = 2.0 Hz, 1H), 5.45-5.36 (m, 1H), 4.49-4.41 (m, 1H), 4.40-4.27 (m, 2H), 4.24 (dd, J = 12.1, 1.5 Hz, 1H), 2.14 (s, 3H).

Step 7: (R)-6-acetoxy-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonic acid

To a stirred solution of (R)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl acetate (58.0 g, 318 mmol) in DCM (120 mL) in a 2-L 3-necked round-bottom flask under nitrogen was added chlorosulfonic acid (81.3 g, 700 mmol) dropwise at 0 °C. The resulting solution was stirred for 12 h at RT. LCMS showed the conversion was completed. The reaction mixture was used directly in the next step. MS-ESI: 263 (M+1).

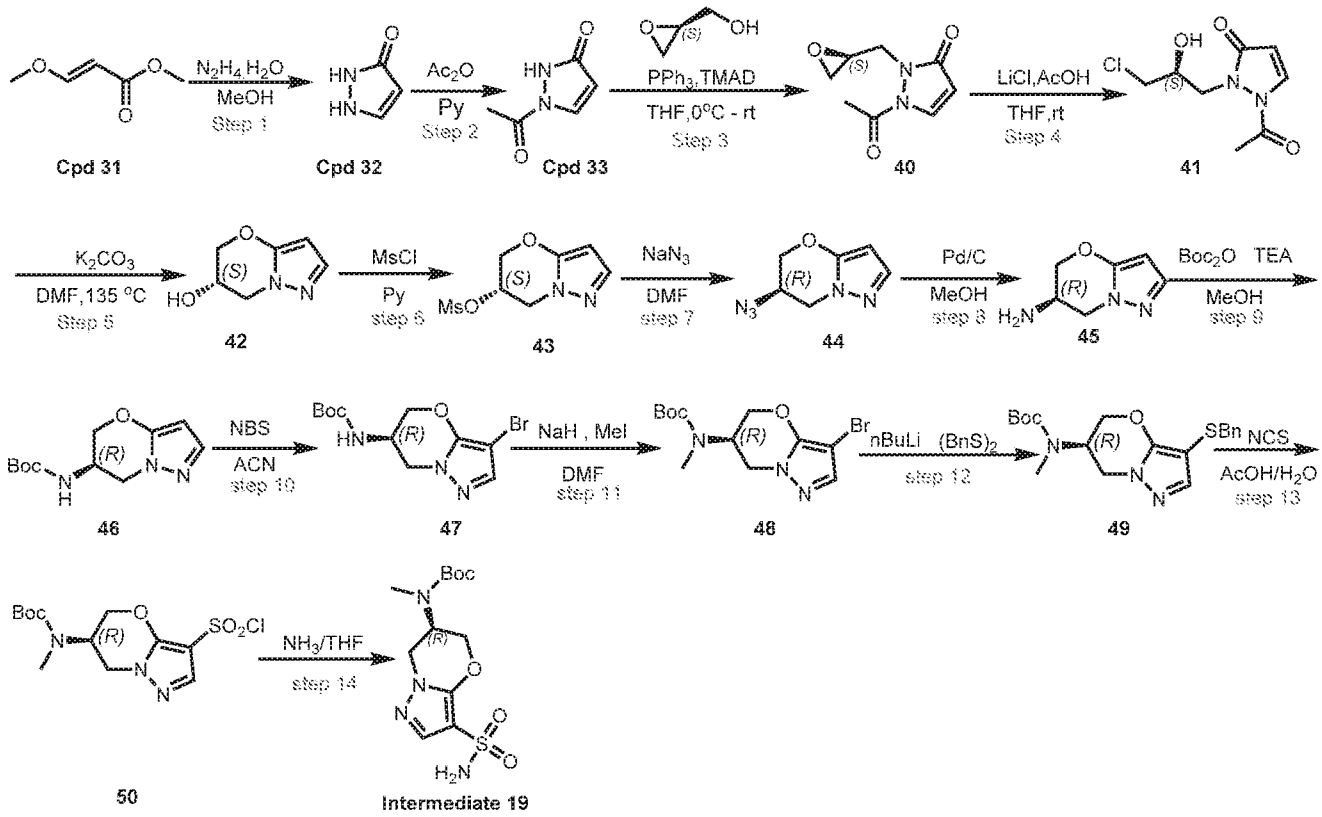
Step 8: (R)-3-(chlorosulfonyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl acetate

To a stirred solution of (R)-6-acetoxy-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonic acid in DCM (crude from step 7) in a 2-L 3-necked round-bottom flask under nitrogen was added pyridine (55.1 g, 696 mmol) dropwise at 0 °C. To this was added PCl_5 (144 g, 696 mmol) in portions at 0 °C. The resulting solution was stirred for 2 h at RT. The reaction was then quenched by the addition of 1 L of water/ice. The resulting solution was extracted with 3x300 mL of EtOAc. The resulting mixture was washed with 2 x500 ml of $NaHCO_3$ and 1 x500 mL of H_2O. The resulting mixture was washed with 1x500 mL of NaCl (aq.). The mixture was dried over anhydrous Na_2SO_4 and concentrated under vacuum. This resulted in 76 g (crude) of the title compound as a light yellow solid. MS-ESI: 281/283 (M+1).

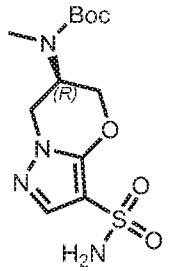
Step 9: (R)-6-hydroxy-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide

To a stirred solution of NH_3 in THF (1 M, 730 ml) in a 3-L round-bottom flask was added (R)-3-(chlorosulfonyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3] oxazin-6-yl acetate (73.0 g) in several batches. The flask was then filled with NH_3 (balloon). The resulting solution was stirred overnight at 40 °C in an oil bath. After reaction completed, the solids were filtered out. The filtrate was concentrated. The residue was diluted with NH_3 (7 M in MeOH, 730 mL). The resulting solution was stirred for 2h at RT. LC showed the reaction was complete. The MeOH solution was concentrated under reduced pressure to a final volume of about 100 mL. Et_2O (360 ml) was charged to the resulting solution and kept stirring for 30 min. The mixture was filtered, and the cake washed with Et_2O (100 mL). The white solid was dried under vacuum. This resulted in 37 g (53% for 3 steps) of the title compound as a white solid. MS-ESI: 220 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (s, 1H), 7.06 (s, 2H), 5.64 (d, J = 2.3 Hz, 1H), 4.30 (s, 3H), 4.30 – 4.18 (m, 1H), 4.00 – 3.90 (m, 1H).

Scheme 11:



Intermediate 19



Tert-butyl (R)-methyl(3-sulfamoyl-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl)carbamate

Steps 1-5 used similar procedures for converting compound **31** to compound **36** shown in Scheme 10 to afford compound **42** from compound **31**. MS-ESI: 141 (M+1).

Step 6: (*S*)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl methanesulfonate

To a stirred solution of (*S*)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-ol (40 g, 285 mmol) in pyridine (280 mL) in a 500 mL 3-neck flask under nitrogen was added MsCl (39 g, 343 mmol) dropwise at RT. The resulting mixture was stirred for 30 min at RT. The resulting mixture was concentrated under reduced pressure. The crude was diluted with 500 mL of water. The resulting

mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with water (3x200 mL) and brine 100 mL, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in the title compound (57 g, 92%) as an off-white solid. MS-ESI: 219 (M+1).

Step 7: (*R*)-6-azido-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine

To a stirred solution of (*S*)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl methanesulfonate (46 g, 211 mmol) in DMF (313 mL) in a 1 L 3-neck flask under nitrogen was added NaN_3 (21 g, 316 mmol) at RT. The resulting mixture was stirred for 6 h at 80 °C. LCMS showed reaction was complete. This was used directly in the next step. MS-ESI: 166 (M+1).

Step 8: (*R*)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-amine

To a 1 L 1-neck flask placed solution of (*R*)-6-azido-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine (46 g, 279 mmol) in MeOH (313 mL), to the stirred solution was added Pd/C (10%wt., 10 g) under nitrogen in a 1 L round-bottom flask. The mixture was hydrogenated at RT for 5 h under hydrogen atmosphere using a hydrogen balloon. LCMS showed reaction was complete. The mixture was filtered through a pad of Celite and concentrated. This was used directly in the next step. MS-ESI: 140 (M+1).

Step 9: *Tert*-butyl (*R*)-(6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl)carbamate

To a 1 L 3-neck flask placed solution of (*R*)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-amine(46 g, 331 mmol) in DMF (313 mL) from last step was added MeOH (313 mL), then to the stirred solution was added TEA (50 g, 496 mmol), followed by the addition of di-tert-butyl dicarbonate (79 g, 364 mmol) at RT under nitrogen. The resulting mixture was stirred for 16 h at RT and then quenched with 500 mL of water. The resulting mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with H_2O (2x600 mL) and brine (1x600 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in the title compound (45.9 g, 91%, for 3 steps) as an off-white solid. MS-ESI: 240 (M+1).

Step 10: *Tert*-butyl (*R*)-(3-bromo-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl)carbamate

To a stirred solution of *tert*-butyl (R)-(6,7-dihydro-5H-pyrazolo[5,1-b][1,3] oxazin-6-

yl)carbamate (140 g, 585 mmol) in MeCN (2.1 L) in a 3 L 3-neck flask under nitrogen was added NBS (115 g, 644 mmol) at 0 °C. The resulting mixture was stirred for 2 h at RT. The resulting mixture was diluted with 2000 mL of water and extracted with EtOAc (3 x 800 mL). The combined organic layers were washed with brine (1x800 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in the title compound (167 g, 90%) as an off-white solid. MS-ESI: 318/320 (M+1).

Step 11: *Tert*-butyl (*R*)-(3-bromo-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl)(methyl)carbamate

To a stirred solution of *tert*-butyl(*R*)-(3-bromo-6,7-dihydro-5H-pyrazolo-[5,1-b][1,3]oxazin-6-yl)carbamate (170 g, 534 mmol) in DMF (1.19 L) in a 3 L 3-neck flask under nitrogen was added sodium hydride (60% oil dispersion, 26 g, 650 mmol) in portions at 0 °C. The mixture was stirred for 1 h at 0 °C. Then MeI (379 g, 2.67 mol) was added and the mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was quenched by water and extracted with EtOAc (3*800 mL), the organic layers were washed with H_2O (3x500 mL) and brine (1x800 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (8:1) to afford the title compound (153 g, 86%) as an off-white solid. MS-ESI: 332/334 (M+1).

Step 12: *Tert*-butyl(*R*)-(3-(benzylthio)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl)(methyl) carbamate

To a stirred solution of *tert*-butyl(*R*)-(3-bromo-6,7-dihydro-5H-pyrazolo-[5,1-b][1,3]oxazin-6-yl)(methyl) carbamate (130 g, 391 mmol) in THF (1.3 L) in a 3 L 3-neck flask under nitrogen was added n-BuLi (188 mL, 470 mmol, 2.5 mol/L) dropwise at -78 °C. The resulting mixture was stirred for 1 h at -78 °C. To the above mixture was added bis(phenylmethyl) disulfide (145 g, 587 mmol) in THF (300 mL) dropwise at -78 °C. The resulting mixture was stirred for additional 2 h at RT. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (500 mL) at RT. The resulting mixture was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (1x800 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (6:1) to afford the title compound (106 g, 72%) as an off-white solid. MS-ESI: 376 (M+1).

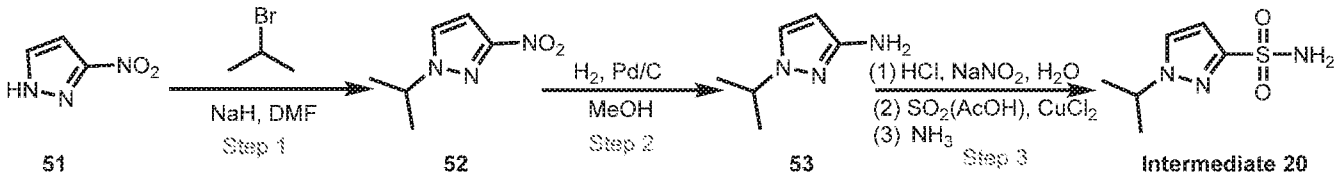
Step 13: Tert-butyl (R)-(3-(chlorosulfonyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl)(methyl) carbamate

To a stirred solution of tert-butyl (R)-(3-(benzylthio)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl) (methyl)carbamate (110 g, 293 mmol) in AcOH (3.67 L)/H_2O (1.83 L) in a 10 L 3-neck flask under nitrogen was added NCS (155 g, 1.17 mol) in portions at 0 °C. The resulting mixture was stirred for 1 h at RT. The reaction was quenched with water/ice at RT. The resulting mixture was extracted with MTBE (3 x 1 L). The combined organic layers were washed with water (2 x 1.0 L), $NaHCO_3$ (L) and brine (1x1 L), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in the title compound (80 g, crude) as a yellow solid. MS-ESI: 374/376 (M+Na).

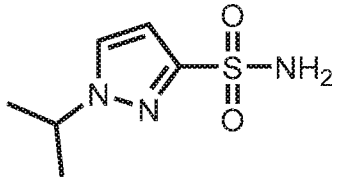
Step 14: Tert-butyl (R)-methyl(3-sulfamoyl-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl)carbamate

To a stirred solution of tert-butyl (R)-(3-(chlorosulfonyl)-6,7-dihydro-5H-pyrazolo [5,1-b][1,3]oxazin-6-yl) (methyl)carbamate (80 g, 227 mmol) in NH_3 in THF (1 M, 800 mL, 800 mmol) in a 2 L 3-neck flask under nitrogen. The flask was then filled with NH_3 (balloon). The resulting mixture was stirred for overnight at 60 °C. The reaction mixture was quenched by water and extracted with MTBE (3x800 mL), the organic layers were washed with H_2O (3x500 mL) and brine (1x800 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The precipitated solid was slurry with MTBE (1x100 mL). This resulted in the title compound (36 g, 40.0% for 2 steps) as an off-white solid. MS-ESI: 333 (M+1).

Scheme 12:



Intermediate 20



1-Isopropyl-1H-pyrazole-3-sulfonamide

Step 1: 1-Isopropyl-3-nitro-1*H*-pyrazole

To a stirred solution of 3-nitro-1H-pyrazole (10 g, 88.4 mmol) in DMF (100 mL) in a 250-mL round-bottom flask under nitrogen was added NaH (60% wt. dispersion in mineral oil, 3.9 g, 97.5 mmol) in portions at 0 °C. The resulting solution was stirred for 0.5 h at 0 °C. This was followed by the addition of 2-bromopropane (14.1 g, 1.15 mol) dropwise with stirring at 0 °C in 10 min. The resulting solution was stirred for 16 h at RT and then was quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x100 mL of EtOAc. The organic layers were combined and dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was eluted from silica gel with a gradient of EtOAc/PE (1:5 to 1:3). This resulted in 11.8 g (86%) of the title compound as yellow oil. MS-ESI: 156 (M+1).

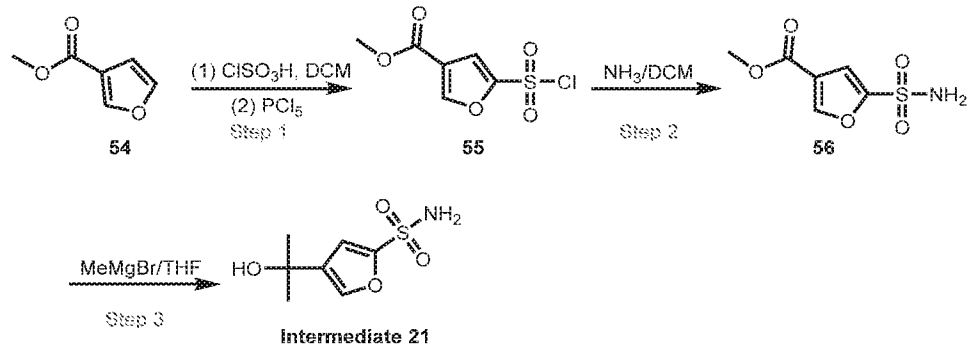
Step 2: 3-Amino-1-(propan-2-yl)-1*H*-pyrazole

To a stirred solution of 1-isopropyl-3-nitro-1*H*-pyrazole (10.8 g, 69.6 mmol) in MeOH (100 mL) in a 250-mL round-bottom flask under nitrogen was added Pd/C (10% wt., 1.5 g) in portions at 0 °C. The flask was evacuated and flushed three times with hydrogen. The mixture was stirred for 24 h at RT under an atmosphere of hydrogen with a balloon. The solids were filtered out. The resulting filtrate was concentrated under vacuum. This resulted in 7.27 g (83%) of the title compound as yellow oil. MS-ESI: 126.1 (M+1).

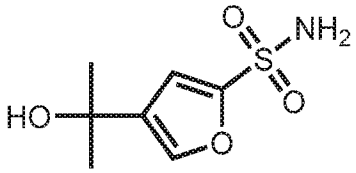
Step 3: 1-Isopropyl-1H-pyrazole-3-sulfonamide

To a stirred solution of 1-isopropyl-1H-pyrazol-3-amine (2.5 g, 20.0 mmol) in HCl (6 M, 30 mL) in a 250-mL 3-necked round-bottom flask under nitrogen was added a solution of $NaNO_2$ (1.66 g, 24.0 mmol) in H_2O (5 mL) dropwise with stirring at 0 °C, the solution was stirred for 30 min, this solution was assigned as solution A. Then $CuCl_2$ (1.34 g, 10.0 mmol) was added to a 250-mL single necked round-bottom flask with AcOH (40 mL) as the solvent. Then SO_2 (g) was bubbled to the reaction mixture with stirring at RT for 20 min, this solution was assigned as solution B. To the solution B was added solution A dropwise with stirring at 0 °C. The resulting solution was stirred for 2 h at RT. The reaction mixture was diluted with 100 mL of water, extracted with 3x100 mL of DCM and the organic layers were combined and dried over anhydrous Na_2SO_4. To the crude DCM solution (~300 mL) was bubbled NH_3 (g) with stirring at 0 °C for 10 min. The resulting solution was stirred for 2 h at RT. The solution was concentrated under vacuum. The crude product was eluted from silica gel with EtOAc/PE (1:1). This resulted in 2.61 g (69 %) of the title compound as yellow oil. MS-ESI: 188 (M-1).

Scheme 13:



Intermediate 21



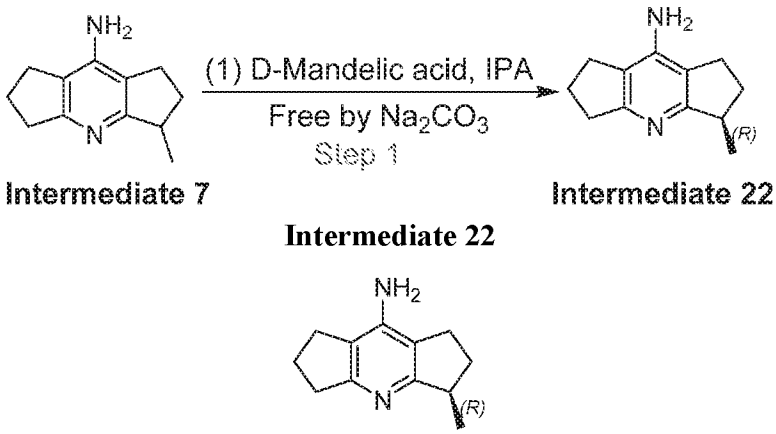
4-(2-Hydroxypropan-2-yl)furan-2-sulfonamide

Steps 1-2 used similar procedures for converting compound **7** to Intermediate **1** shown in Scheme 3 to afford compound **54** from compound **56**. MS-ESI: 204 (M-1)

Step 3: 4-(2-Hydroxypropan-2-yl)furan-2-sulfonamide

To a stirred solution of methyl 5-sulfamoylfuran-3-carboxylate (4.55 g, 22.2 mmol) in THF (300 mL) in a 500-mL 3-necked round-bottom flask under nitrogen was added MeMgBr/THF (3 M, 74 mL, 222 mmol) dropwise at 0 °C. The resulting solution was stirred for 16 h at RT. The reaction was then quenched with 50 mL of NH_4Cl (aq). The resulting solution was extracted with 3x100 ml of EtOAc and the organic layers were combined and dried over Na_2SO_4 and concentrated under vacuum. The residue was eluted from silica gel with DCM/MeOH (60:1). This resulted in 2.46 g (54.1%) of the title compound as a light yellow solid. MS-ESI: 204 (M-1).

Scheme 14:



(R)-3-methyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-amine

Step 1: (R)-3-Methyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-amine

A stirred solution of 3-methyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-amine (47 g, 250 mmol) in isopropyl alcohol (423 mL) was heated to 80 °C in a 1 L 3-neck flask with condenser and a stirring bar. The solution was kept stirring for 0.5 h. The solution was cooled to about 50 °C. The solution was filtered at that temperature though a Buchner funnel, to remove insoluble impurities. The solid was washed with isopropyl alcohol (3x10 mL). The filtrate was transfer to a round bottle and concentrated to 350 g. The solution was transferred to a 2 L 3-necked round-bottom flask equipped with a mechanical stir and reflux condenser in an oil bath. The round bottle was washed with 27 g isopropyl alcohol to remove all the material to the 2L 3-necks flask. The resulting solution was heated to 80 °C and a solution of (R)-(-)-Mandelic acid (38 g, 250 mmol) in isopropyl alcohol (188 mL) was added dropwise at that temperature. The resulting mixture was stirred at 80 °C for 5 minute. The system was cooled in 5 °C step and a small amount of the seed crystals of the product was added. If the seed dissolved, repeat the above operation. When the system was cooled to 65 °C, the seed was undissolved and crystals started to grow, the system turned to cloudy slowly, the solution was stirred for 30 minute at this temperature. From then on, the solution was stirred and maintained for 30 minute while the temperature was cooled in 5 °C steps until the system temperature was 40 °C. Turn off the heating switch of oil bath and the mixture was slowly cooled to 28 °C. After 16 h, the ee value of solid was monitored (96%ee). The solid was collected by filtered. The resulting solid was slurry in isopropyl alcohol (180 mL) for 1h and filtrated again. The filtrate was decanted, and the precipitate was washed with chromatographic

isopropyl alcohol (30 mL) to give the title compound as a white solid (35 g, 40.5% yield, 98%ee, which contain 13.8% IPA). The solid was dissolved in water (420 mL) and concentrated to afford 29.2 g white solid (KF=5.1%). The mother liquid was combined and concentrated to afford 56.7 g S-isomer (75%ee, contain 17.8% IPA) as a foam. Then 26.9 g (R) salt was freed by aq. Na_2CO_3 (4 M, 500 mL) and exacted with 3x300 mL EA, then the organic phase was washed with 500 mL of brine and dried over anhydrous Na_2SO_4 and concentrated under vacuum. This resulted in 14.3g (38% yield, 98%ee, LCAP=96%) of the title compound as a white solid. MS-ESI: 189 (M+1). Chiral analysis method: Column, CHIRALPAK IC 4.6*150 mm, 3 μm. Mobile phase: Hex (0.1% DEA):IPA=85:15. Column Temperature: 30°C. Flow Rate: 1.0 mL/min. Monitor: UV 254 nm. Intermediate **161** is the first peak with a retention time of 5.8 min. The S enantiomer is the second peak with a retention time of 7.0 min.

Table 9. The Intermediates in the following table was prepared using similar procedure as shown in Scheme **6** above for converting compound **27B** to Intermediate **4** starting from 27A.

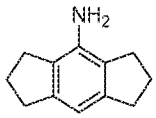
Intermediate #	Structure	IUPAC Name	Exact Mass$[M+H]^+$
Intermediate 23		1,2,3,5,6,7-Hexahydro-*s*-indacen-4-amine	174

Table 10. The Intermediates in the following table were prepared using the similar procedures for converting Intermediate **2** to Intermediate **10** shown in Scheme 8 from appropriated starting materials.

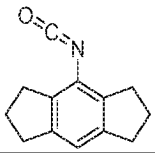
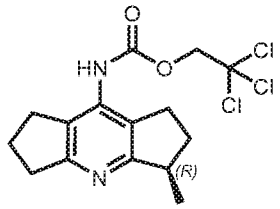
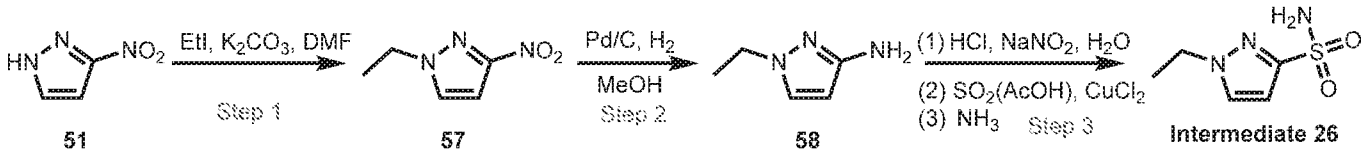
Intermediate #	Structure	IUPAC Name
Intermediate 24		4-Isocyanato-1,2,3,5,6,7-hexahydro-s-indacene

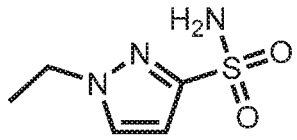
Table 11. The Intermediates in the following Table were prepared using the similar procedures for converting Intermediate **5** to Intermediate **13** shown in Scheme 9 from appropriated starting materials.

Intermediate #	Structure	IUPAC Name	Exact Mass[M+H]$^+$
Intermediate 25		2,2,2-trichloroethyl (R)-(3-methyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamate	363/365/367

Scheme 15:



Intermediate 26



1-Ethyl-1H-pyrazole-3-sulfonamide

Step 1: 1-Ethyl-3-nitro-1H-pyrazole

To a stirred solution of 3-nitro-1H-pyrazole (20 g, 177 mmol) in DMF (100 mL) in a 250-mL round-bottom flask were added K_2CO_3 (49 g, 354 mmol) in portions at RT, followed by the addition of iodoethane (55 g, 354 mmol) dropwise at RT. The reaction mixture was stirred for 16 h at 80 °C in an oil bath. The reaction mixture was diluted with 200 mL of H_2O. The mixture was extracted with 3x200 mL of EtOAc and the organic layers were combined and dried over anhydrous Na_2SO_4. The mixture was concentrated under vacuum. The residue was eluted from silica gel with EtOAc/PE (1:4). This resulted in 22.6 g (91%) of the title compound as yellow oil. MS-ESI: 142 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 2.5 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 4.27 (q, J = 7.3 Hz, 2H), 1.42 (t, J = 7.3 Hz, 3H).

Step 2: 1-Ethyl-1H-pyrazol-3-amine

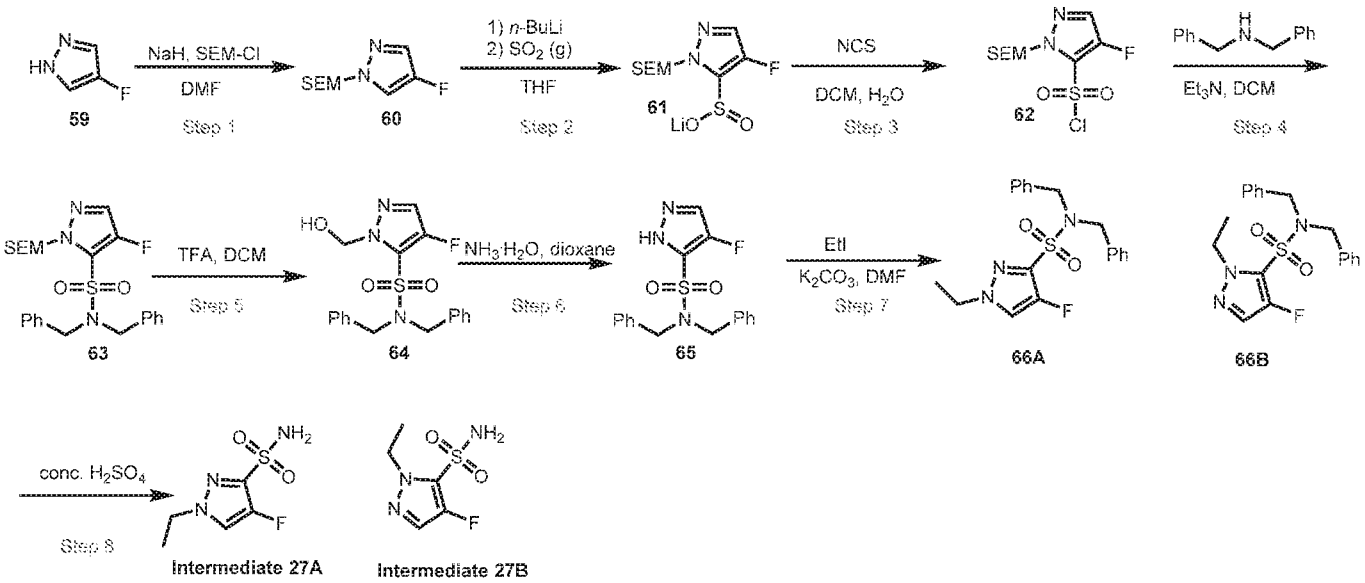
To a stirred solution of 1-ethyl-3-nitro-1H-pyrazole (22 g, 156 mmol) in MeOH (100 mL) in a 250-mL round-bottom flask under nitrogen was added Pd/C (10% wt., 2.2 g) in portions at 0

°C. The flask was evacuated and refilled three times with hydrogen. The reaction mixture was stirred overnight at RT under atmosphere of hydrogen with a balloon. The solids were filtered out. The filtrate was concentrated under vacuum. This resulted in 13.8 g (80%) of the title compound as yellow oil. MS-ESI: 112 (M+1).

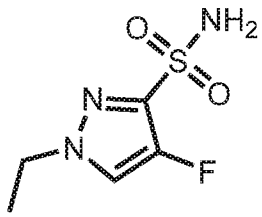
Step 3: 1-Ethyl-1H-pyrazole-3-sulfonamide

To a stirred solution of 1-ethyl-1H-pyrazol-3-amine (3.4 g, 31 mmol,) in HCl (6 M, 20 mL) in a 100-mL round-bottom flask was added $NaNO_2$ (2.53 g, 37 mmol) in H_2O (5.0 mL) dropwise slowly at 0 °C over 25 min. The reaction solution was stirred for 40 min at 0 °C, this solution was assigned as solution A. Then $CuCl_2$ (8.23 g, 61 mmol) was added to a 250-mL single necked round-bottom flask with AcOH (100 mL) as the solvent, SO_2 (g) was bubbled to the mixture with stirring at 0 °C for 20 min, this mixture was assigned as solution B. To the mixture B was added solution A dropwise with stirring at 0 °C. The reaction mixture was stirred for additional 2 h at 0 °C. The reaction mixture was diluted with 100 mL of H_2O. The mixture was extracted with 3x150 mL of DCM. The organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was dissolved in 30 mL of DCM and NH_3 (g) was bubbled for 15 min at 0 °C. The reaction was stirred for 2 h at RT. The reaction mixture was concentrated under vacuum. The residue was eluted from silica gel with PE/EtOAc (3:1). This resulted in 1.75 g (33%) of the title compound as a yellow solid. MS-ESI: 174 (M-1).

Scheme 16:

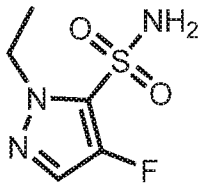


Intermediate 27A



1-Ethyl-4-fluoro-1H-pyrazole-3-sulfonamide

Intermediate 27B



1-Ethyl-4-fluoro-1H-pyrazole-5-sulfonamide

Step 1: 4-Fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole

To a stirred solution of 4-fluoro-1H-pyrazole (5.0 g, 58 mmol) in DMF (53 mL) in a 250-mL 3-necked round-bottom flask under nitrogen was added NaH (60% wt. dispersion in mineral oil, 5.36 g, 134 mmol) in portions at 0 °C in an ice/water bath over 10 min. The resulting solution was stirred for 30 min at 10 °C. To this was added SEM-Cl (22 g, 134 mmol) dropwise with

stirring at 0 °C over 10 min. The resulting solution was stirred overnight at RT. The reaction was then quenched with 60 mL of water. The resulting solution was extracted with 60 mL of EtOAc. The organic layer was washed with 5x60 mL of sat. NaCl solution. The resulting filtrate was concentrated. The residue was eluted from silica gel column EtOAc/PE (1:100). This resulted in 13.7 g (crude) of the title compound as a light yellow liquid. MS-ESI: 217 (M+1).

Step 2: Lithium 4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-5-sulfinate

To a stirred solution of 4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (13.7 g, 63 mmol) in THF (150 mL) in a 500-mL 3-necked round-bottom flask under nitrogen was added n-BuLi in hexane (2.5 M, 28 mL, 70 mmol) dropwise at -78 °C over 15 min. The resulting solution was stirred for 1 h at -78 °C. Then to the mixture was introduced SO_2 (g) bubble for 20 min -78 °C. The resulting solution was stirred for 1 h at RT. The resulting mixture was concentrated. This resulted in 20.4 g (crude) of the title compound as a white solid. MS-ESI: 279 (M-1).

Step 3: 4-Fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-5-sulfonyl chloride

To a stirred solution of lithium 4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-5-sulfinate (20.4 g, crude from last step) in DCM (396 mL) and H_2O (198 mL) was added NCS (10 g, 78 mmol) in portions at 0 °C. The resulting solution was stirred for 1 h at 10 °C. The crude product was used directly without work-up.

Step 4: N,N-dibenzyl-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-5-sulfonamide

To the stirred solution of 4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-5-sulfonyl chloride in DCM (396 mL) and H_2O (198 mL) from last step was added Et_3N (8.85 g, 87 mmol) and dibenzylamine (17 g, 84 mmol) dropwise at 0 °C. The resulting solution was stirred for 1 h at 8 °C. The reaction was then quenched by the addition of 300 mL of water. The resulting solution was extracted with 3x300 mL of DCM. The organic layers were combined and washed with brine (300 mL) and dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was eluted from silica gel with EtOAc/PE (1:19). This resulted in 22.5 g (81% over 4 steps) of the title compound as light yellow oil. MS-ESI: 476 (M+1).

Step 5: N,N-dibenzyl-4-fluoro-1-(hydroxymethyl)-1H-pyrazole-5-sulfonamide

To a stirred solution of N,N-dibenzyl-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-5- sulfonamide (22.5 g, 47 mmol) in DCM (25 mL) in a 250-mL round-bottom flask was added TFA (25 mL). The resulting solution was stirred 16 h at RT. The resulting mixture was concentrated under vacuum. The residue was eluted from silica gel with EtOAc/PE (1:4). This resulted in 15 g (85%) of the title compound as yellow oil. MS-ESI: 376 (M+1).

Step 6: N,N-dibenzyl-4-fluoro-1H-pyrazole-5-sulfonamide

To a stirred solution of N,N-dibenzyl-4-fluoro-1-(hydroxymethyl)-1H-pyrazole-5-sulfonamide (15 g, 40 mmol) in dioxane (50 mL) in a 500-mL round-bottom flask was added $NH_3 \cdot H_2O$ (30%wt., 50 mL) dropwise at 0 °C. The resulting solution was stirred for 3 h at RT. The resulting mixture was concentrated. The residue was eluted from silica gel with EtOAc/PE (1:1). This resulted in 12 g (87%) of the title compound as a white solid. MS-ESI: 346 (M+1).

Step 7: N,N-dibenzyl-1-ethyl-4-fluoro-1H-pyrazole-3-sulfonamide and N,N-dibenzyl-1-ethyl-4-fluoro -1H-pyrazole-5-sulfonamide

To a stirred solution of N,N-dibenzyl-4-fluoro-1H-pyrazole-5-sulfonamide (1.1 g, 3.2 mmol) in DMF (20 mL) in a 100-mL 3-necked round-bottom flask under nitrogen was added K_2CO_3 (0.88 g, 6.4 mmol) in portions at RT and ethyl iodide (0.99 g, 6.4 mmol) dropwise at RT. The resulting solution was stirred for 3 h at 110 °C. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 2x20 mL of EtOAc. The organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was eluted from silica gel with EtOAc/PE (3:17). This resulted in 218 mg (18%) of **66B** followed by 764 mg (64%) of **66A** both as a light yellow solid. MS-ESI: 374 (M+1).

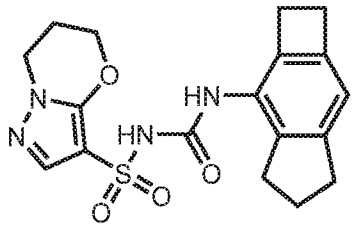
Step 8: 1-Ethyl-4-fluoro-1H-pyrazole-3-sulfonamide and 1-ethyl-4-fluoro-1H-pyrazole-5-sulfonamide

To a stirred solution of N,N-dibenzyl-1-ethyl-4-fluoro-1H-pyrazole-3-sulfonamide (764 mg, 2.0 mmol) in DCM (1.5 mL) in a 25-mL round-bottom flask was added H_2SO_4 (98% wt., 3.00 mL) dropwise at 0 °C. The resulting solution was stirred for 1 h at RT. The reaction was then quenched by the addition of 5.0 mL of water/ice. The mixture was extracted with EtOAc (3x50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced vacuum. The residue was eluted from silica gel with DCM/MeOH (93:7). This resulted in 317

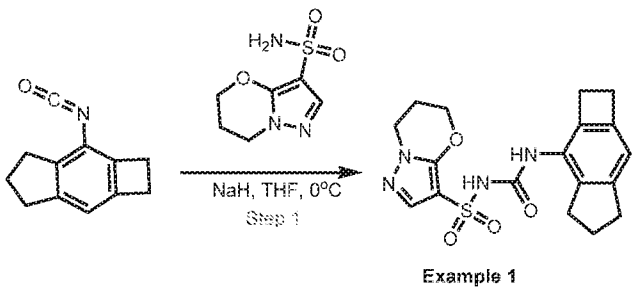
mg (80%) of **Intermediate 27A** as a white solid. MS-ESI: 194 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (d, J = 4.7 Hz, 1H), 7.77 (s, 2H), 4.14 (q, J = 7.3 Hz, 2H), 1.39 (t, J = 7.3 Hz, 3H). Ar-H 8.08 (d, J = 4.7 Hz, 1H) has correlations with CH_2 from Et at 4.14 (q, J = 7.3 Hz, 2H) and CH_3 from Et at 1.39 (t, J = 7.3 Hz, 3H) in NOESY.

Similar procedure used for converting compound **66A** to **Intermediate 27A** shown in Scheme 16 was used to afford **Intermediate 27B** from compound **66B**. MS-ESI: 194 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 2H), 7.67 (d, J = 4.5 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H). NH_2 at 8.20 (s, 2H) has correlations with CH_2 from Et at 4.33 (q, J = 7.2 Hz, 2H) and CH_3 from Et at 1.35 (t, J = 7.2 Hz, 3H) in NOESY.

Example 1 (Compound 8)



N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide (Scheme 1)



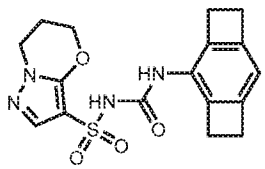
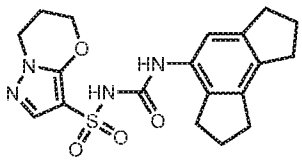
Example 1

Step 1: N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide

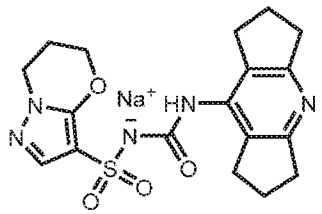
Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide (102 mg, 0.5 mmol) in THF (10 mL). Then NaH (60% wt. oil dispersion, 24 mg, 1.0 mmol) was added in portions at 0°C. The resulting mixture was stirred for 5 min at room temperature, after which 3-isocyanato-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene (90 mg, 0.5 mmol) was added. The resulting

solution was stirred for 1 h at room temperature. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was eluted from a silica gel column with dichloromethane/methanol (1:20). The product was further purified by Prep-HPLC with the following conditions: Column, XBridge Shield RP18 OBD Column, 19*250 mm, 10 um; mobile phase, Water (10 mM NH_4HCO_3) and ACN (19% Phase B up to 27% in 7 min); Detector, 210 nm UV. This resulted in 73.6 mg of the title compound as a white solid. (ES, *m/z*): $[M+1]^+$ = 389. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.79 (s, 1H), 7.52 (s, 1H), 6.63 (s, 1H), 4.38 (t, *J* = 5.2 Hz, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.06 (t, *J* = 4.4 Hz, 2H), 2.87 (t, *J* = 4.3 Hz, 2H), 2.81 (t, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 2.30-2.10 (m, 2H), 2.09-1.85 (m, 2H).

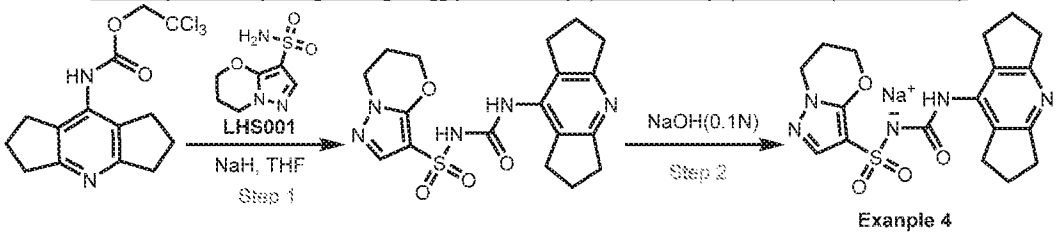
Table S5. Examples in the following table were prepared using similar conditions as described in Example 1 and Scheme **1** from appropriate starting materials.

Example #	Compound #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
2	**9**		N-(tricyclo[6.2.0.03,6]deca-1,3(6),7-trien-2-ylcarbamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide	375
3	**10**		N-((1,2,3,6,7,8-hexahydro-as-indacen-4-yl)carbamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide	403

Example 4 (Compound 12, sodium salt)



Sodium ((6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-yl)sulfonyl)((1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)amide (Scheme 2)



Step 1: N-((1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide

Into a 25-mL round-bottom flask purged and maintained with an inert of atmosphere of nitrogen, was placed 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide (100 mg, 0.49 mmol) in THF (8.0 mL). NaH (60% wt. oil dispersion, 88.6 mg, 1.48 mmol) was added at 0°C. The solution was stirred for 15 min. Then 2,2,2-trichloroethyl (1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamate (172 mg, 0.49 mmol) was added into the above solution at 0°C. The resulting solution was stirred for 4 h at room temperature. The reaction was then quenched by the addition of 5 mL of water. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (5:1). The crude product (160 mg) was further purified by Prep-HPLC with the following conditions (Column: XBridge Prep C_{18} OBD Column 19×150 mm 5 um; Mobile Phase A: Water (10 mM NH_4HCO_3+0.1%$NH_3 \cdot H_2O$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 5% B to 11% B in 7 min; 254/210 nm; Rt: 5.77 min). This resulted in the title compound (22 mg, 10.5%) as a white solid. MS-ESI: 430 (M+1).

Step 2: Sodium ((6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-yl)sulfonyl)((1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)amide

N-((1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide (22 mg, 0.06 mmol) obtained in the last step was dissolved in NaOH (0.1N) (0.44 mL, 0.04 mmol), after which the solution was washed with DCM

(1.0 mL). The aqueous phase was collected and filtered, then lyophilized to obtain 13.9 mg (59.9%) of title compound as white solid (mono sodium salt). MS-ESI: 418 (M+1), 416 (M-1). ^{1}H-NMR (400 MHz, D_2O) δ 7.55 (s, 1H), 4.36–4.29 (m, 2H), 4.03 (t, J = 6.1 Hz, 2H), 3.00-2.50 (m, 8H), 2.17-2.10 (m, 2H), 2.10-1.90 (m, 4H).

Table S6. Examples in the following table were prepared using similar conditions as described in Example 4 and Scheme **2** from appropriate starting materials.

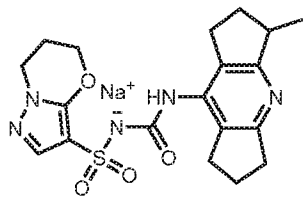
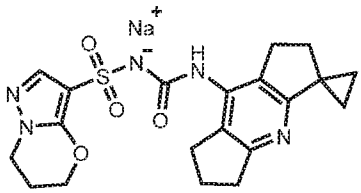
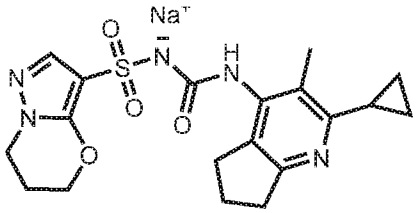
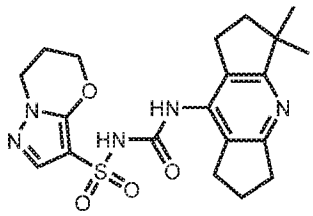
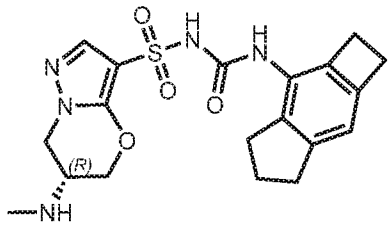
Example #	Compound #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
5	**13** (sodium salt)		Sodium ((6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-yl)sulfonyl)((3-methyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)amide	418
6	**15** (sodium salt)		Sodium ((6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-yl)sulfonyl)((1',5',6',7'-tetrahydro-2'H-spiro[cyclopropane-1,3'-dicyclopenta[b,e]pyridin]-8'-yl)carbamoyl)amide	430
7	**16** (sodium salt)		Sodium ((2-cyclopropyl-3-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-4-yl)carbamoyl)((6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-yl)sulfonyl)amide	418

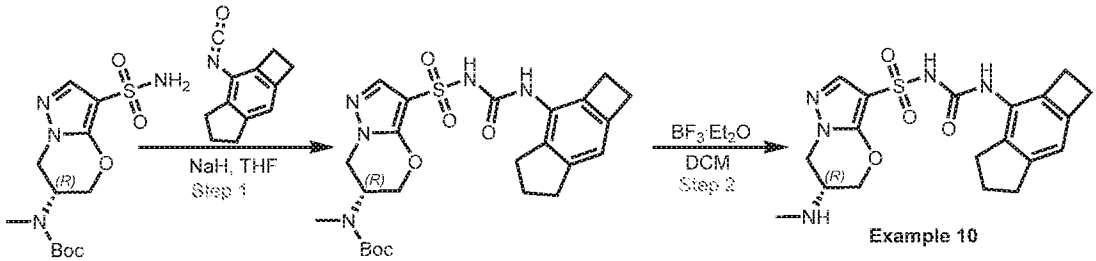
Table S7. Examples in the following table were prepared using similar conditions as described in Example 4 and Scheme **2** from appropriate starting materials.

Example #	Final Target #	Structure	IUPAC Name	Exact Mass [M+H]+
8	**14**		N-((3,3-dimethyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide	432

Example 10 (Compound 401)



(R)-6-(methylamino)-N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide (Scheme I)

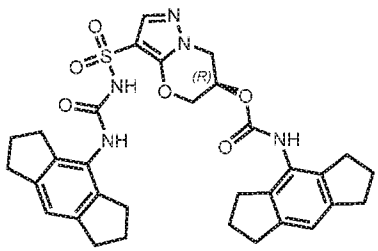
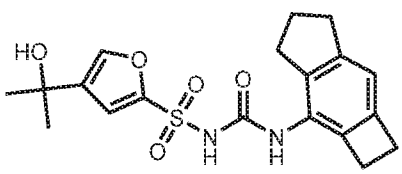


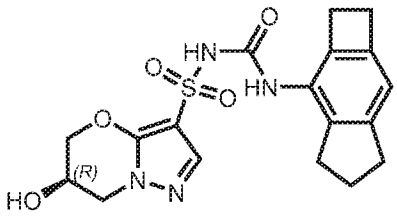
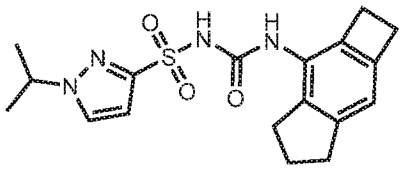
Step 1: Tert-butyl (R)-methyl(3-(N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl) sulfamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl)carbamate

To a stirred solution of tert-butyl (R)-methyl(3-sulfamoyl-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl) carbamate (66.4 mg, 0.20 mmol) in THF (10 mL) in a 100-mL round-bottom flask under nitrogen was added NaH (60% wt. dispersion in mineral oil, 24 mg, 0.60 mmol) at 0

°C. The resulting solution was stirred for 10 min at RT. To the solution was added 3-isocyanato-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene (37 mg, 0.20 mmol) in THF (1.0 mL) dropwise at RT. The resulting solution was stirred for 1 h at RT. The reaction was then quenched by the addition of 5 mL of MeOH. The resulting mixture was concentrated. The residue was eluted from silica gel with DCM/MeOH (10:1). This resulted in 98 mg (95%) of the title compound as a light brown solid. MS-ESI: 518 (M+1).

Step 2: (R)-6-(methylamino)-N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)-6,7- dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide

Example #	Compound Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
11	**403**		(R)-3-(N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)sulfamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl (1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamate	618
12	**301**		4-(2-Hydroxypropan-2-yl)-N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)furan-2-sulfonamide	391

13	**402**		(R)-6-hydroxy-N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide	405
14	**302**		1-Isopropyl-N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)-1H-pyrazole-3-sulfonamide	375

To a stirred solution of tert-butyl (R)-methyl(3-(N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)- carbamoyl)sulfamoyl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-6-yl)carbamate (90 mg, 0.17 mmol) in DCM (10 mL) in a 100-mL round-bottom flask was added $BF_3 \cdot Et_2O$ (47% wt., 25 mg, 0.17 mmol) at RT. The resulting solution was stirred for 1 h at RT. The resulting mixture was concentrated. The residue was eluted from silica gel with DCM/MeOH (10:1). The crude product was purified by Prep-HPLC with the following conditions: XSelect CSH Prep C18 OBD Column, 5 um, 19*150 mm ; Mobile Phase A: water (10 mM NH_4HCO_3+0.1% $NH_3 \cdot H_2O$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient:17% B to 27% B over 7 min; UV 210/254 nm; Rt1: 4.50 min. This resulted in 12.6 mg (17%) of the title compound as an off-white solid. MS-ESI: 418 (M+1). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.91 (br, s, 1H), 7.60 (s, 1H), 6.67 (s, 1H), 4.39-4.28 (m, 2H), 4.23-4.19 (m, 1H), 3.96-3.92 (m, 1H), 3.21-3.13 (m, 1H), 3.09-3.01 (m, 2H), 2.91-2.85 (m, 2H), 2.84-2.78 (m, 2H), 2.71-2.62 (m, 2H), 2.31 (s, 3H), 2.03-1.89 (m, 2H).

Table 12. Examples in the following table were prepared using similar conditions as described in Example 1 and Scheme **1** from appropriate starting materials.

Table 13. Examples in the following table were prepared using similar conditions as described in Example 4 and Scheme **2** from appropriate starting materials.

Example #	Compound Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$

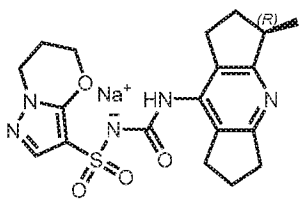
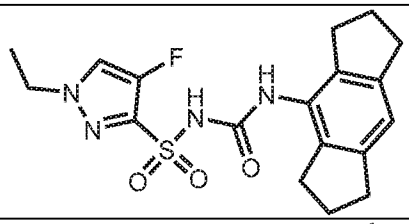
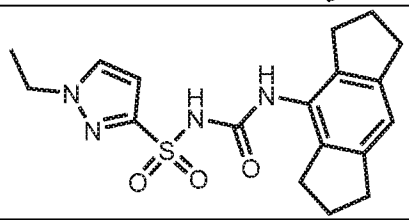
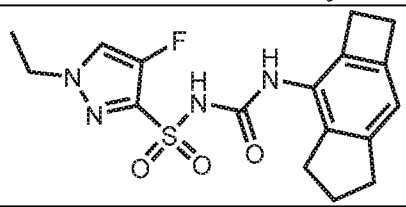
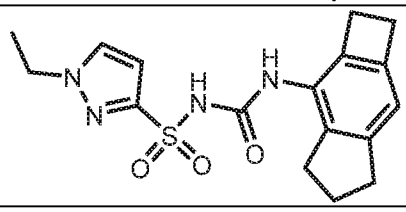
15	**404**		Sodium (R)-((6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-yl)sulfonyl)((3-methyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)amide	440

Table 14. Examples in the following table were prepared using similar conditions as described in Example 1 and Scheme **1** from appropriate starting materials.

Example #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
16		1-Ethyl-4-fluoro-N-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide	393
17		1-Ethyl-N-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide	375
18		1-Ethyl-4-fluoro-N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)-1H-pyrazole-3-sulfonamide	379
19		1-Ethyl-N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)-1H-pyrazole-3-sulfonamide	361

In one embodiment, provided herein is a pharmaceutical composition comprising a specific compound of the invention defined herein (e.g. any one of examples 1 to 19, or tables 1A to 1C, 2, 3 or 4), and an anti-TNFα agent disclosed herein. Preferably wherein the anti-

TNFα agent is Infliximab, Etanercept, Certolizumab pegol, Golimumab or Adalimumab, more preferably wherein the anti-TNFα agent is Adalimumab.

In one embodiment, provided herein is a pharmaceutical combination comprising a specific compound of the invention defined herein (e.g. any one of examples 1 to 19, or tables 1A to 1C, 2, 3 or 4), and an anti-TNFα agent Preferably wherein the anti-TNFα agent is Infliximab, Etanercept, Certolizumab pegol, Golimumab or Adalimumab, more preferably wherein the anti-TNFα agent is Adalimumab.

The following protocol is suitable for testing the activity of the compounds disclosed herein.

Procedure 1: IL-1β production in PMA-differentiated THP-1 cells stimulated with Gramicidin.

THP-1 cells were purchased from the American Type Culture Collection and sub-cultured according to instructions from the supplier. Prior to experiments, cells were cultured in complete RPMI 1640 (containing 10% heat inactivated FBS, penicillin (100 units/ml) and streptomycin (100 µg/ml)), and maintained in log phase prior to experimental setup. Prior to the experiment THP-1 were treated with PMA (Phorbol 12-myristate 13-acetate) (20 ng/ml) for 16-18 hours. Compounds were dissolved in dimethyl sulfoxide (DMSO) to generate a 30mM stock. On the day of the experiment the media was removed and adherent cells were detached with trypsin for 5 minutes. Cells were then harvested, washed with complete RPMI 1640, spun down, resuspended in RPMI 1640 (containing 2% heat inactivated FBS, penicillin (100 units/ml) and streptomycin (100 µg/ml) . The cells were plated in a 384-well plate at a density of 50,000 cells/well (final assay volume 50 µl). Compounds were first dissolved in assay medium to obtain a 5x top concentration of 500µM. 10 step dilutions (1:3) were then undertaken in assay medium containing 1.67% DMSO. 5x compound solutions were added to the culture medium to achieve desired final concentration (e.g. 100, 33, 11, 3.7, 1.2, 0.41, 0.14, 0.046, 0.015, 0.0051, 0.0017 µM). Final DMSO concentration was at 0.37%. Cells were incubated with compounds for 1 hour and then stimulated with gramicidin (5µM) (Enzo) for 2 hours. Plates were then centrifuged at 340g for 5 min. Cell free supernatant (40µL) was collected using a 96-channel PlateMaster (Gilson) and the production of IL-1β was evaluated by HTRF (cisbio). A vehicle only control and a dose titration of CRID3 (100 - 0.0017 µM) were run concurrently with each experiment.

Data was normalized to vehicle-treated samples (equivalent to 0% inhibition) and CRID3 at 100 μM (equivalent to 100% inhibition). Compounds exhibited a concentration-dependent inhibition of IL-1β production in PMA-differentiated THP-1 cells.

Procedure 2

1. **Experimental procedure**

1.1 Cell Culture

1) Culture THP-1 cells in the complete RPMI-1640 medium with 10%FBS at 37°C, 5% CO_2.

2) Passage the cells every 3 days by inoculating $3x10^5$ cells per ml.

1.2 Compound Preparation

Prepare the 3-fold serial dilution of the compounds with DMSO in a 384-well LDV Microplate using TECAN EVO system to generate the compound source plate with 10 concentrations. Top concentration is 30 mM.

1.3 Cell preparation

1) Centrifuge THP-1 cells at 350g for 5 min.

2) Re-suspend cells with complete RMPI-1640 medium, and count cells.

3) Seed cells in T225 flask, about $2.5x10^7$ per flask, treat cells with 20ng/ml PMA (final DMSO concentration< 1%).

4) Incubate overnight.

1.4 THP-1 Stimulation

1) Wash adherent THP-1 cells with PBS, and detach cells with 4ml trypsin for T225 flask.

2) Centrifuge cells at 350g for 5 min, re-suspend cells with RPMI-1640 containing 2% FBS and count cells with trypan blue.

3) Transfer 50 nl/well the serial dilution of test compound to 384-well plate by Echo; For the high control and first point of CRID3 (MCC950), transfer 165 nl, then backfill to make the DMSO concentration is consistent in all wells, the plate layout is as below.

4) Seed 50k cells in 40ul RPMI-1640 with 2% FBS per well in 384-well plate.

5) Incubate for 1h at 37°C, 5% CO_2.

6) Prepare 5x gramicidin, add 10 µl per well, the final concentration is 5 µM, incubate for 2hrs at 37°C, 5% CO_2.

7) Centrifuge at 350 g for 1 min.
8) Pipet 16µl supernatant by apricot, and transfer into white 384 proxiplate. FIG. 3 depicts the layout of the plates: HC: 100 µM CRID3 (MCC950) + 5 µM gramicidin LC：5 µM Gramicidin.

1.5 IL-1β detection

1) Homogenize the 5x diluent #5 with a vortex and add 1 volume of stock solution in 4 volumes of distilled water.

2) Thaw 20x stock solution of anti-IL1β-Cryptate-antibody and anti-IL1β XL-antibody. Dilute these two antibodies to 1x with detection buffer #3.

3) Pre-mix the two ready-to-use antibody solutions just prior to use.

4) Dispense 4ul of pre-mixed Anti-IL1β antibodies working solution into all wells.

5) Seal the plate and incubate overnight at 4 °C.

6) Read the cell plate using EnVison and plot Readout vs. the test compound concentration to calculate the IC_{50}.

2. Data Analysis:

1. IC_{50} of compounds can be calculated using the following formulas

Formula for IC_{50}

$$\% \text{ inhibition} = 100 - 100 \times [HC_{ave} - \text{Readout} / (HC_{ave} - LC_{ave})]$$

2. Fit the normalized data in a dose-response manner using XLfit, and calculate the compound concentration.

Tables 2 and 3 show the biological activity of compounds in hTHP-1 assay containing 2% fetal bovine serum and Table 4 shows the biological activity of compounds in hTHP-1 assay containing 10% fetal bovine serum: <0.008 µM = "++++++"; ≥0.008 and <0.04 µM = "+++++"; ≥0.04 and <0.2 µM = "++++"; ≥0.2 and <1 µM = "+++"; ≥1 and <5 µM = "++"; ≥5 and <30 µM = "+".

Table 2. Average IC_{50} of compounds in hTHP-1 assay

Compound Number	hTHP-1 IC_{50}
8	+++
9	++++
10	++
12	+++
13	+++
14	++
15	++
16	++
401	++++++
402	++++
403	+
404	+++

Table 3. Average IC_{50} of compounds in hTHP-1 assay

Compound	hTHP-1 IC_{50}
301	++++
302	++
303	++

Table 4. Average IC_{50} of compounds in hTHP-1 assay

Example #	**hTHP-1 IC_{50} in 10% FBS**
16	+++
17	++
18	+++
19	+++

Study Example 1.

The CARD8 gene is located within the inflammatory bowel disease (IBD) 6 linkage region on chromosome 19. CARD8 interacts with NLRP3, and Apoptosis-associated Speck-like protein to form a caspase-1 activating complex termed the NLRP3 inflammasome. The NLRP3 inflammasome mediates the production and secretion of interleukin-1β, by processing pro-IL-1β

into mature secreted IL-1β. In addition to its role in the inflammasome, CARD8 is also a potent inhibitor of nuclear factor NF-κB. NF-κB activation is essential for the production of pro-IL-1β. Since over-production of IL-1β and dyregulation of NF-κB are hallmarks of Crohn's disease, CARD8 is herein considered to be a risk gene for inflammatory bowel disease. A significant association of CARD8 with Crohn's disease was detected in two British studies with a risk effect for the minor allele of the non-synonymous single-nucleotide polymorphism (SNP) of a C allele at rs2043211. This SNP introduces a premature stop codon, resulting in the expression of a severely truncated protein. This variant CARD8 protein is unable to suppress NF-κB activity, leading to constitutive production of pro-IL-1β , which is a substrate for the NLRP3 inflammasome. It is believed that a gain-of-function mutation in an NLRP3 gene (e.g., any of the gain-of-function mutations described herein, e.g., any of the gain-of-function mutations in an NLRP3 gene described herein) combined with a loss-of-function mutation in a CARD8 gene (e.g., a C allele at rs2043211) results in the development of diseases related to increased NLRP3 inflammasome expression and/or activity. Patients having, e.g., a gain-of-function mutation in an NLRP3 gene and/or a loss-of-function mutation in a CARD8 gene are predicted to show improved therapeutic response to treatment with an NLRP3 antagonist.

A study is designed to determine: whether NLRP3 antagonists inhibit inflammasome function and inflammatory activity in cells and biopsy specimens from patients with Crohn's disease or ulcerative colitis; and whether the specific genetic variants identify patients with Crohn's disease or ulcerative colitis who are most likely to respond to treatment with an NLRP3 antagonist.

The secondary objectives of this study are to: determine if an NLRP3 antagonist reduces inflammasome activity in Crohn's disease and ulcerative biopsy samples (comparing Crohn's disease and ulcerative colitis results with control patient results); determine if an NLRP3 antagonist reduced inflammatory cytokine RNA and protein expression in Crohn's disease and ulcerative colitis samples; determine if baseline (no ex vivo treatment) RNA levels of NLRP3, ASC, and IL-1β are greater in biopsy samples from patients with anti-TNFα agent resistance status; and stratify the results according to presence of specific genetic mutations in genes encoding ATG16L1, NLRP3, and CARD8 (e.g., any of the mutations in the ATG16L1 gene, NLRP3 gene, and CARD8 gene described herein).

Methods

- Evaluation of baseline expression of NLRP3 RNA and quantify inhibition of inflammasome activity by an NLRP3 antagonist in biopsies of disease tissue from patients with Crohn's disease and ulcerative colitis.
- Determine if NLRP3 antagonist treatment reduces the inflammatory response in biopsies of disease from patients with Crohn's disease based on decreased expression of inflammatory gene RNA measured with Nanostring.
- Sequence patient DNA to detect specific genetic mutations in the ATG16L1 gene, NLRP3 gene, and CARD8 gene (e.g., any of the exemplary mutations in these genes described herein) and then stratify the results of functional assays according to the presence of these genetic mutations.

Experimental Design

- Human subjects and tissue:

  Endoscopic or surgical biopsies from areas of disease in patients with Crohn's disease and ulcerative colitis who are either anti-TNFα treatment naïve or resistant to anti-TNFα treatment; additionally biopsies from control patients (surveillance colonoscopy or inflammation-free areas from patients with colorectal cancer) are studied.

- Ex vivo Treatment Model:

  Organ or LPMC culture as determined appropriate

- Endpoints to be measured:

  Before ex vivo treatment-- NLRP3 RNA level

  After ex vivo treatment- inflammasome activity (either processed IL-1β, processed caspase-1, or secreted IL-1β); RNA for inflammatory cytokines (Nanostring); viable T cell number and/or T cell apoptosis.

- Data Analysis Plan:
  - Determine if NLRP3 antagonist treatment decreases processed IL-1β, processed caspase-1 or secreted IL-1β , and inflammatory cytokine RNA levels.

- Stratify response data according to treatment status at biopsy and the presence of genetic mutations in the NLRP3 gene, CARD8 gene, and ATG16L1 gene (e.g., any of the exemplary genetic mutations of these genes described herein).

Study Example 2. Treatment of anti-TNFα resistant patients with NLRP3 antagonists

PLoS One 2009 Nov 24;4(11):e7984, describes that mucosal biopsies were obtained at endoscopy in actively inflamed mucosa from patients with Ulcerative Colitis, refractory to corticosteroids and/or immunosuppression, before and 4-6 weeks after their first infliximab (an anti-TNFα agent) infusion and in normal mucosa from control patients. The patients in this study were classified for response to infliximab based on endoscopic and histologic findings at 4-6 weeks after first infliximab treatment as responder or non-responder. Transcriptomic RNA expression levels of these biopsies were accessed by the inventors of the invention disclosed herein from GSE 16879, the publically available Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE16879). Expression levels of RNA encoding NLRP3 and IL-1β were determined using GEO2R (a tool available on the same website), based on probe sets 207075_at and 205067_at, respectively. It was surprisingly found that in Crohn's disease patients that are non-responsive to the infliximab (an anti-TNFα agent) have higher expression of NLRP3 and IL-1β RNA than responsive patients (figures 1 and 2). Similar surprising results of higher expression of NLRP3 and IL-1β RNA in UC patients that are non-responsive to infliximab (an anti-TNFα agent) compared to infliximab (an anti-TNFα agent) responsive patients (figures 3 and 4) were found.

Said higher levels of NLRP3 and IL-1β RNA expression levels in anti-TNFα agent non-responders, is hypothesised herein to lead to NLRP3 activation which in turns leads ot release of IL-1β that induces IL-23 production, leading to said resistance to anti-TNFα agents. Therefore, treatment of Crohn's and UC anti-TNFα non-responders with an NLRP3 antagonist would prevent this cascade, and thus prevent development of non-responsiveness to anti-TNFα agents. Indeed, resistance to anti-TNFα agents is common in other inflammatory or autoimmune diseases. Therefore, use of an NLRP3 antagonist for the treatment of inflammatory or autoimmune diseases will block the mechanism leading to non-responsiveness to anti-TNFα

agents. Consequently, use of NLRP3 antagonists will increase the sensitivity of patients with inflammatory or autoimmune diseases to anti-TNFα agents, resulting in a reduced dose of anti-TNFα agents for the treatment of these diseases. Therefore, a combination of an NLRP3 antagonist and an anti-TNFα agent can be used in the treatment of diseases wherein TNFα is overexpressed, such as inflammatory or autoimmune diseases, to avoid such non-responsive development of patients to anti-TNFα agents. Preferably, this combination threatment can be used in the treatment of IBD, for example Crohn's disease and UC.

Further, use of NLRP3 antagonists offers an alternative to anti-TNFα agents for the treatment of diseases wherein TNFα is overexpressed. Therefore, NLRP3 antagonists offers an alternative to anti-TNFα agents inflammatory or autoimmune diseases, such as IBD (e.g. Crohn's diesease and UC).

Systemtic anti-TNFα agents are also known to increase the risk of infection. Gut restricted NLRP3 antagonists, however, offers a gut targeted treatment (i.e. non-systemic treatment), preventing such infections. Therefore, treatment of TNFα gut diseases, such as IBD (i.e. Crohn's diesase and UC), with gut restricted NLRP3 antagonists has the additional advantage of reducing the risk of infection compared to anti-TNFα agents.

Proposed Experiment:

Determine the expression of NLRP3 and caspase-1 in LPMCs and epithelial cells in patients with non-active disease, in patients with active disease, in patients with active disease resistant to corticosteroids, patients with active disease resistant to TNF-blocking agents. The expression of NLRP3 and caspase-1 in LPMCs and epithelial cells will be analyzed by RNAScope technology. The expression of active NLRP3 signature genes will be analyzed by Nanostring technology. A pilot analysis to determine feasibility will be performed with 5 samples from control, 5 samples from active CD lesions, and 5 samples from active UC lesions.

Study Example 3.

It is presented that NLRP3 antagonists reverse resistance to anti-TNF induced T cell depletion/apoptosis in biopsy samples from IBD patients whose disease is clinically considered resistant or unresponsive to anti-TNF therapy.

A study is designed to determine: whether NLRP3 antagonists inhibit inflammasome function and inflammatory activity in cells and biopsy specimens from patients with Crohn's disease or ulcerative colitis; and whether an NLRP3 antagonist will synergize with anti-TNFα therapy in patients with Crohn's disease or ulcerative colitis.

The secondary objectives of this study are to: determine if an NLRP3 antagonist reduces inflammasome activity in Crohn's disease and ulcerative biopsy samples (comparing Crohn's disease and ulcerative colitis results with control patient results); determine if an NLRP3 antagonist reduced inflammatory cytokine RNA and protein expression in Crohn's disease and ulcerative colitis samples; determine if an NLRP3 antagonist in the absence of co-treatment with anti-TNFα antibody induces T cell depletion in Crohn's disease and ulcerative colitis biopsy samples; and determine if baseline (no ex vivo treatment) RNA levels of NLRP3, ASC, and IL-1β are greater in biopsy samples from patients with anti-TNFα agent resistance status.

Methods

- Evaluation of baseline expression of NLRP3 RNA and quantify inhibition of inflammasome activity by an NLRP3 antagonist in biopsies of disease tissue from patients with Crohn's disease and ulcerative colitis.
- Determine if there is synergy between an NLRP3 antagonist and anti-TNF antibody with respect to effects on T cell depletion/apoptosis in biopsies of disease from patients with Crohn's disease and ulcerative colitis.
- Determine if NLRP3 antagonist treatment reduces the inflammatory response in biopsies of disease from patients with Crohn's disease based on decreased expression of inflammatory gene RNA measured with Nanostring.

Experimental Design

- Human subjects and tissue:

Endoscopic or surgical biopsies from areas of disease in patients with Crohn's disease and ulcerative colitis who are either anti-TNFα treatment naïve or resistant to anti-TNFα treatment; additionally biopsies from control patients (surveillance colonoscopy or inflammation-free areas from patients with colorectal cancer) are studied.

- Ex vivo Treatment Model:

  Organ or LPMC culture as determined appropriate

- Ex vivo Treatments:

  NLRP3 antagonist (2 concentrations), negative control (vehicle), positive control (caspase-1 inhibitor) each in the presence or absence of anti-TNF antibody at a concentration appropriate to distinguish differences in the T cell apoptotic between biopsies from anti-TNF resistant and anti-TNF-sensitive Crohn's disease patients. Each treatment condition is evaluated in a minimum in duplicate samples.

- Endpoints to be measured:

  Before ex vivo treatment-- NLRP3 RNA level

  After ex vivo treatment- inflammasome activity (either processed IL-1β, processed caspase-1, or secreted IL-1β); RNA for inflammatory cytokines (Nanostring); viable T cell number and/or T cell apoptosis.

- Data Analysis Plan:
  - Determine if NLRP3 antagonist co-treatment increases T cell apoptosis/deletion in response to anti-TNF.
  - Determine if the level of NLRP3 RNA expression is greater in TNF-resistant Crohn's disease and ulcerative colitis samples compared to anti-TNF treatment-naïve samples.
  - Determine if NLRP3 antagonist treatment decreases processed IL-1β, processed caspase-1 or secreted IL-1β, and inflammatory cytokine RNA levels.

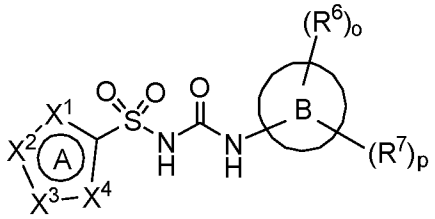
Biological Assay - Nigericin-stimulated IL-1β secretion assay in THP-1 cells

Monocytic THP-1 cells (ATCC: TIB-202) were maintained according to providers' instructions in RPMI media (RPMI/Hepes +10% fetal bovine serum + Sodium Pyruvate + 0.05 mM Beta-mercaptoethanol (1000x stock) + Pen-Strep). Cells were differentiated in bulk with 0.5 μM phorbol 12-myristate 13-acetate (PMA; Sigma # P8139) for 3 hours, media was exchanged, and cells were plated at 50,000 cells per well in a 384-well flat-bottom cell culture plates (Greiner, #781986), and allowed to differentiate overnight. Compound in a 1:3.16 serial dilution series in DMSO was added 1:100 to the cells and incubated for 1 hour. The NLRP3 inflammasome was activated with the addition of 15 μM (final concentration) Nigericin (Enzo Life Sciences, #BML-CA421-0005), and cells were incubated for 3 hours. 10 μL supernatant was removed, and IL-1β levels were monitored using an HTRF assay (CisBio, #62IL1PEC) according to manufacturers' instructions. Viability and pyroptosis was monitored with the addition of PrestoBlue cell viability reagent (Life Technologies, #A13261) directly to the cell culture plate.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula AA



Formula AA

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;

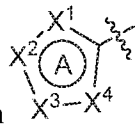
X^3 is O, S, N, CR^3, or NR^3;

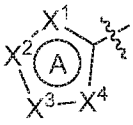
X^4 is O, S, N, CR^4, NR^4, or $–X^5$-X^6-;

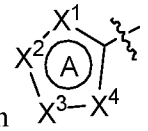
X^5 is N or CR^5;

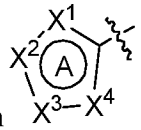
X^6 is N or CR^6;

when X^4 is -X^5-X^6, then: X^1 is N or CR^1, X^2 is N or CR^2, and X^3 is N or CR^3;

when X^4 is other than -X^5-X^6-, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is -X^5-X^6-, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

when X^4 is other than -X^5-X^6-, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is -X^5-X^6-, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

from two to four of R^1, R^2, R^3, and R^4 are present or from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and

wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least two of the two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20};

R^{20} is selected from the group consisting of: hydroxy, halo, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{21}, C_2-C_6 alkenyl optionally substituted with one or more R^{21}, C_2-C_6 alkynyl optionally substituted with one or more R^{21}, C_1-C_6 alkoxy optionally substituted with one or more R^{21}, OC_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{21}, $S(O_2)C_6$-C_{10} aryl optionally substituted with

one or more R^{21}, $OS(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, C_6-C_{10} aryl optionally substituted with one or more R^{21}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{21}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{21}, and $CONR^8R^9$; or

at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

R^{21} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

wherein any of R^1, R^2, R^3, R^4, R^5, and R^6 that are not taken together with the atoms connecting them to form a ring, when present, are each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with

one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, NH-(C=NR^{13})$NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, =NR^{10}, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;

R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

B is a 5-10-membered heteroaryl or C_6-C_{10} aryl ring;
o = 1 or 2;

p = 0, 1, 2, or 3;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally

substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;

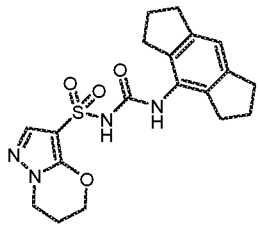
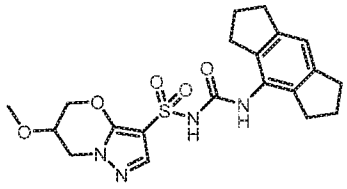
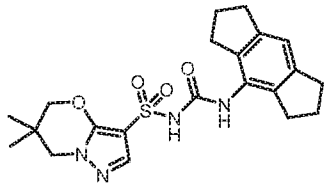
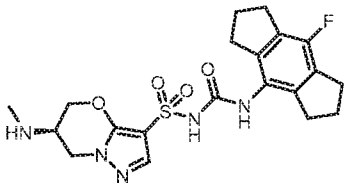
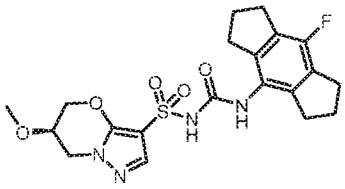
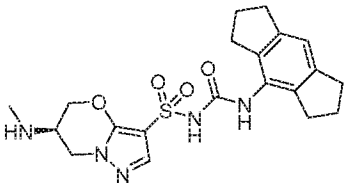
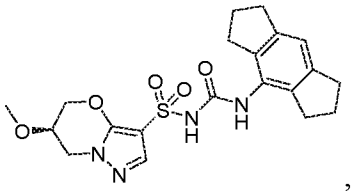
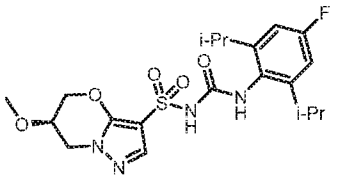
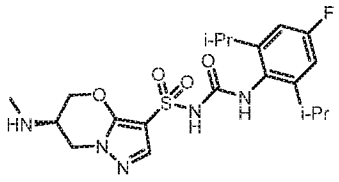
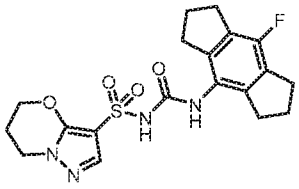
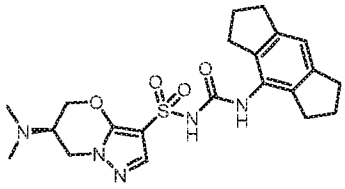
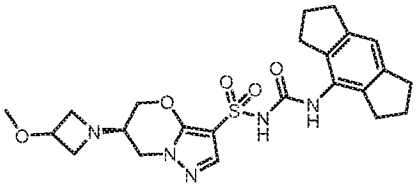
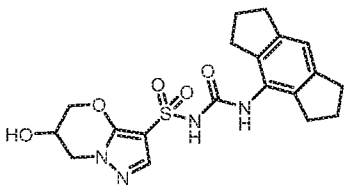
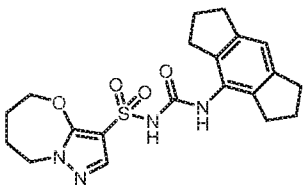
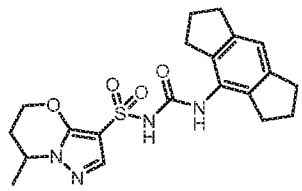
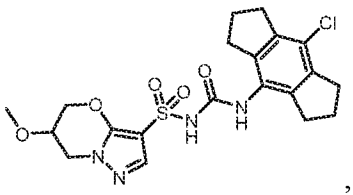
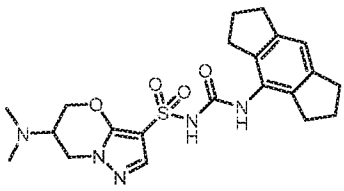
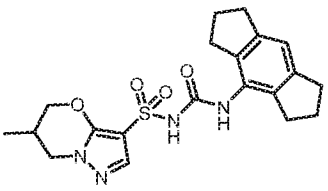
R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and

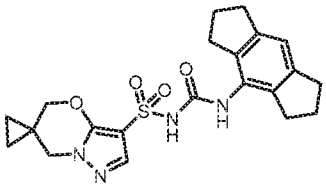
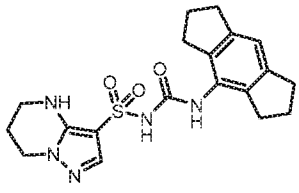
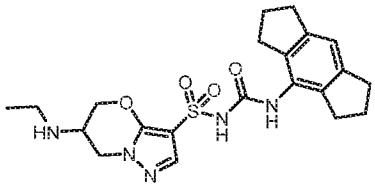
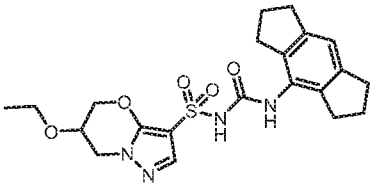
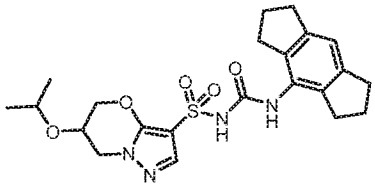
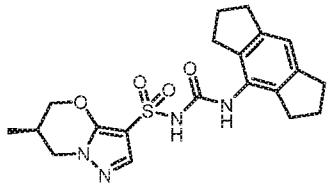
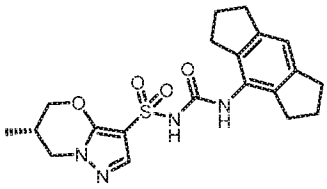
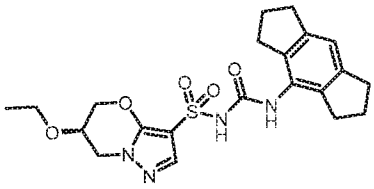
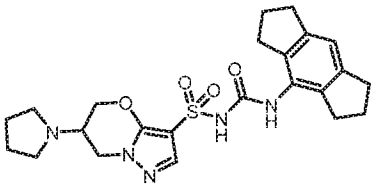
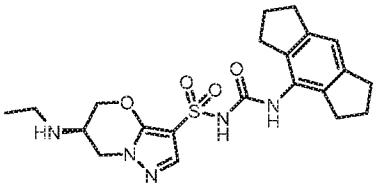
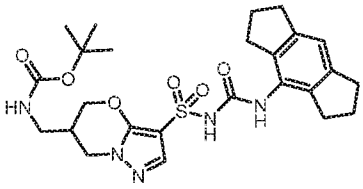
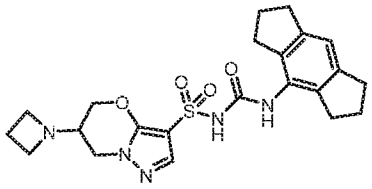
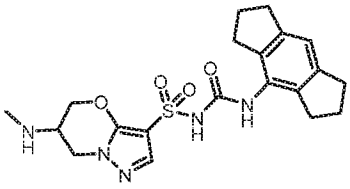
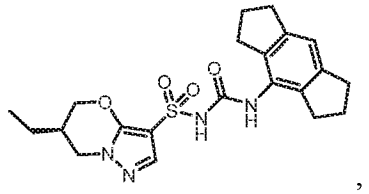
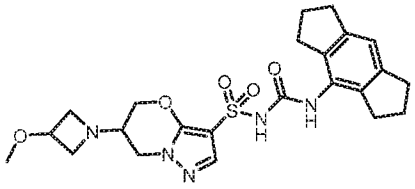
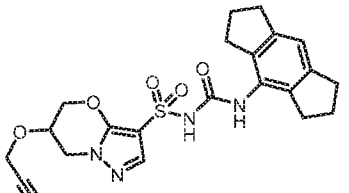
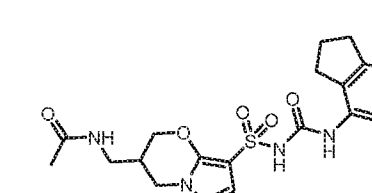
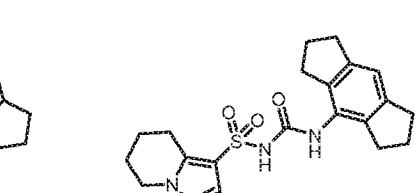
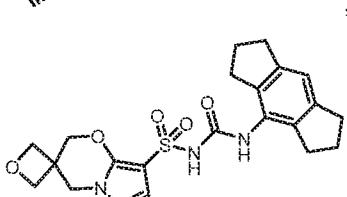
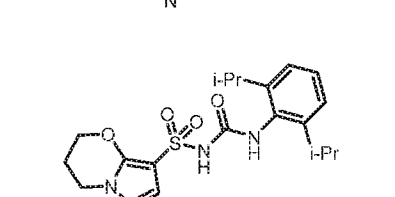
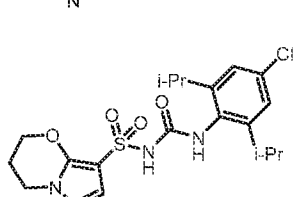
each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

provided that when B is 5-10-membered heteroaryl including from 2-3 ring nitrogen atoms, at least one R^6 is attached to B at a position *ortho* to the $-HNC(=O)NHS(O)_2$- moiety of Formula AA;

when B is 2-pyridyl, pyrimidin-6-yl, or pyrimidin-4-yl, B is not substituted with a cyano group at a position *ortho* to the –HNC(=O)NHS(O)$_2$- moiety of Formula AA;

and

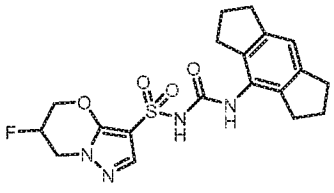
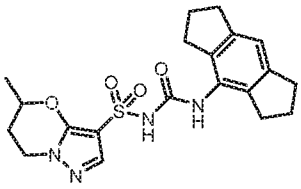
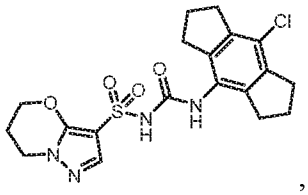
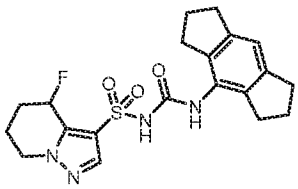
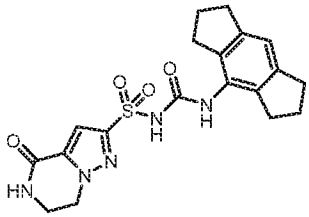
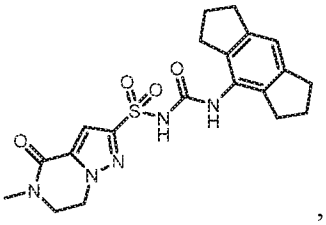
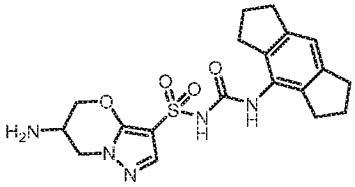
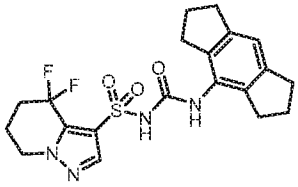
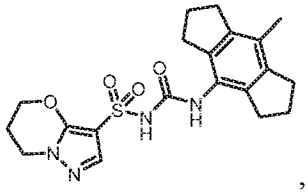
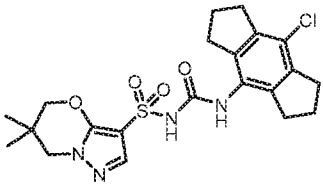
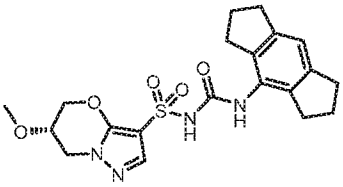
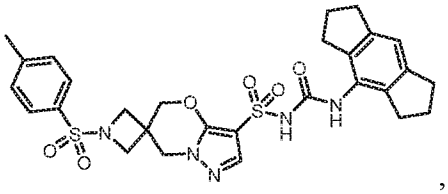
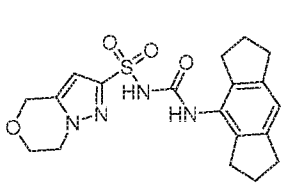
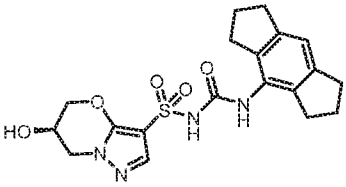
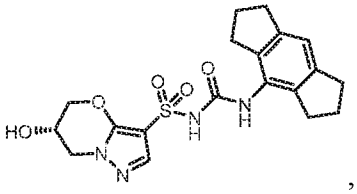
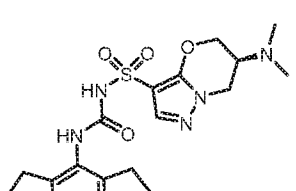
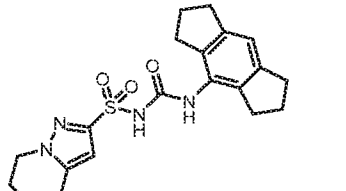
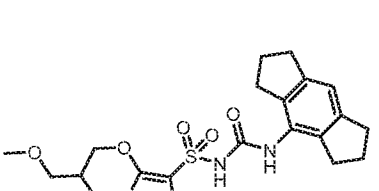
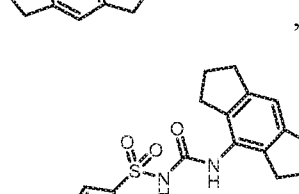
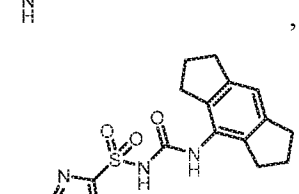
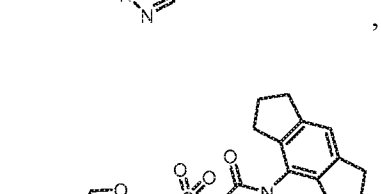
with the proviso that the compound of Formula AA is not a compound selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

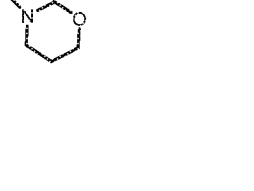
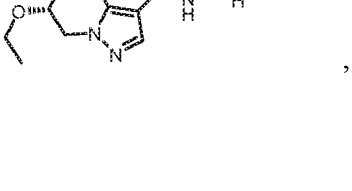

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

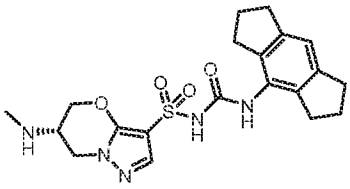
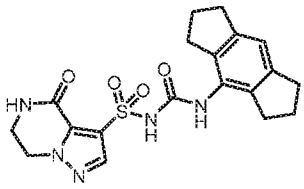
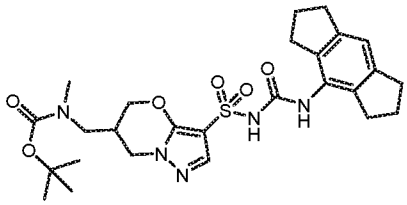
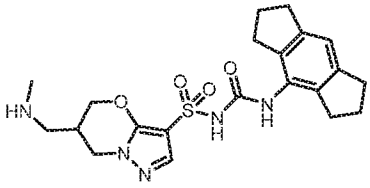
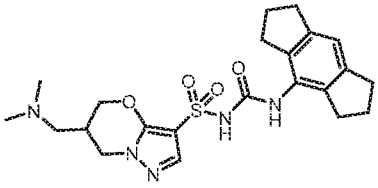
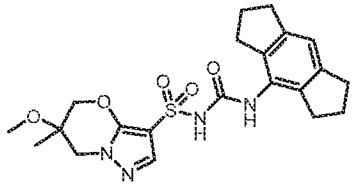
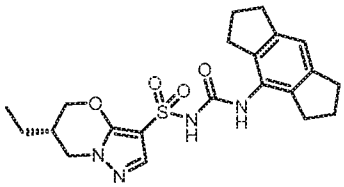
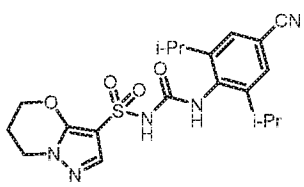
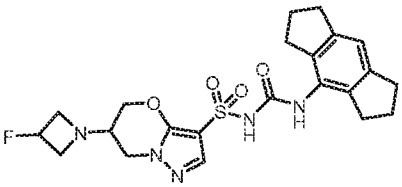
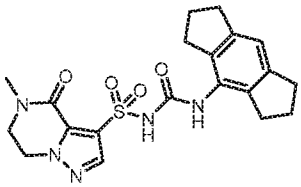
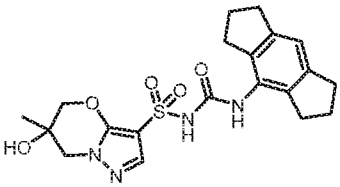
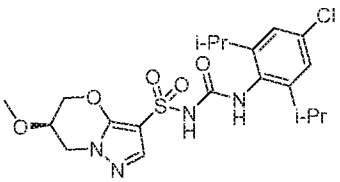
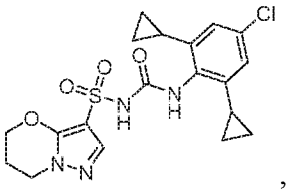
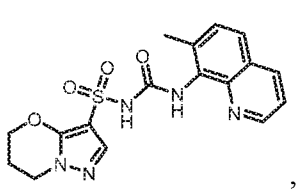
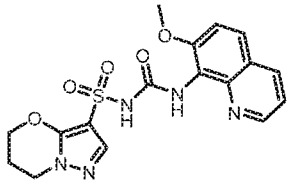
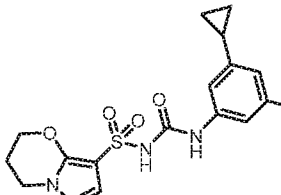
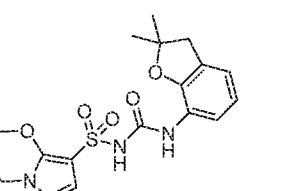
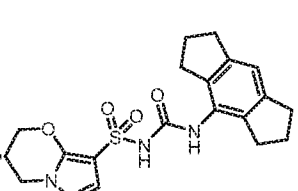
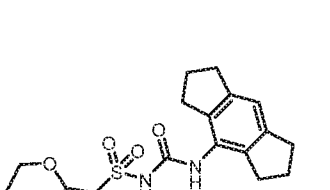
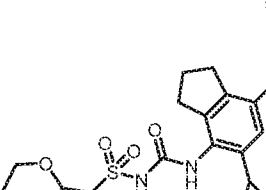
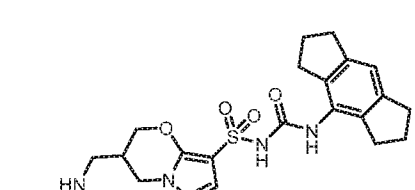
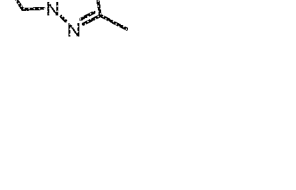
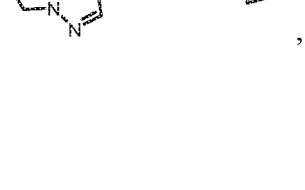
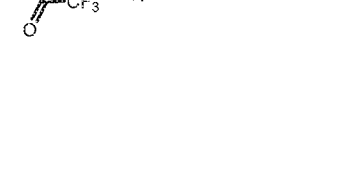
,

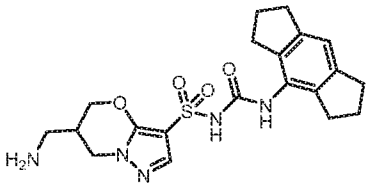
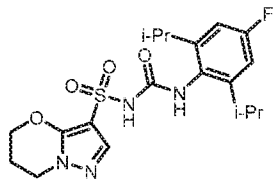
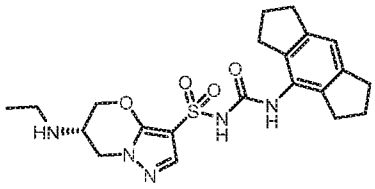
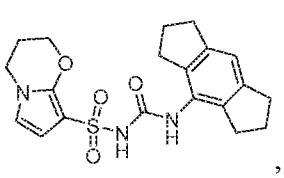
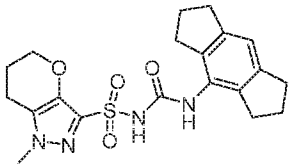
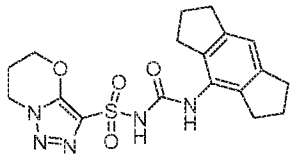
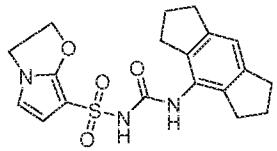
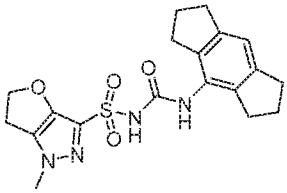
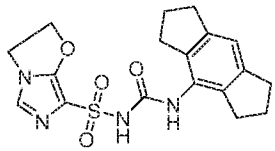
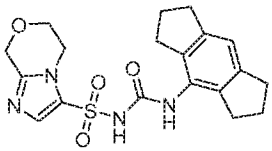
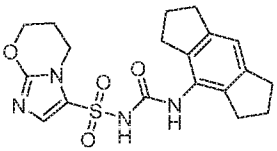
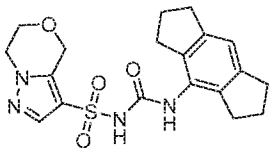
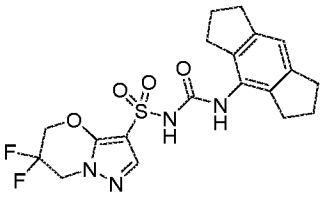
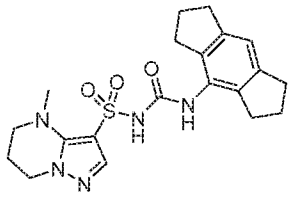
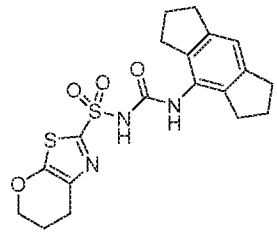
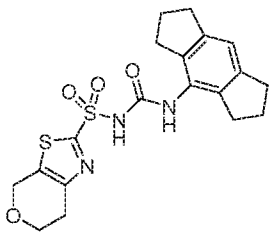
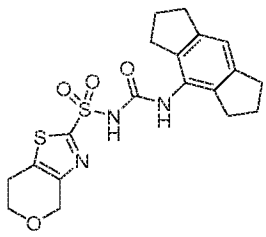
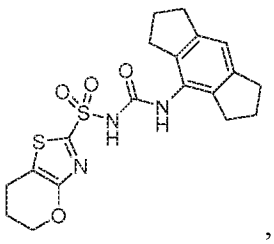
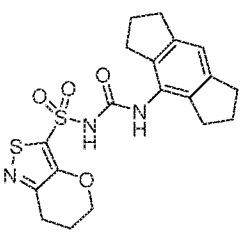
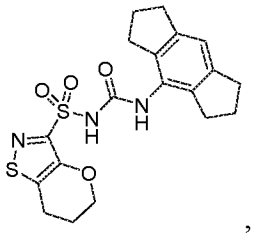
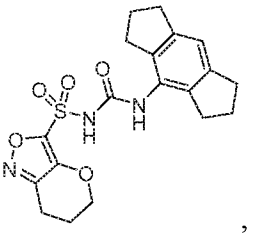
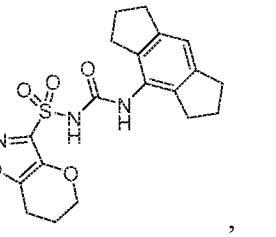
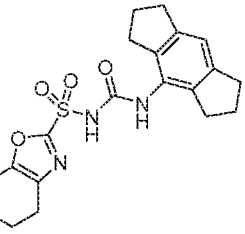
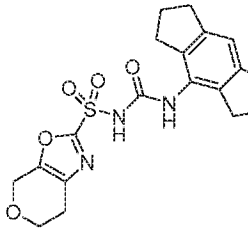
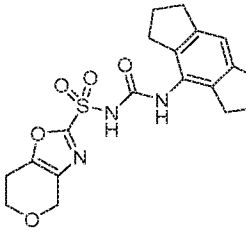
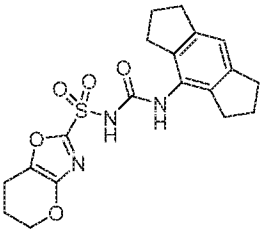
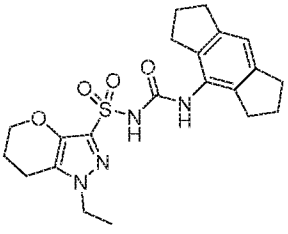
,

,

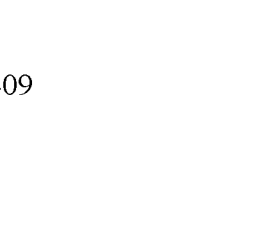

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

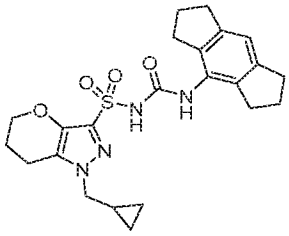
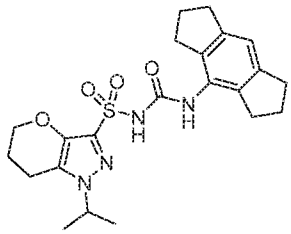
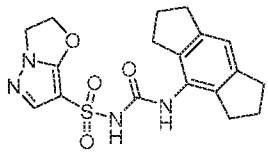
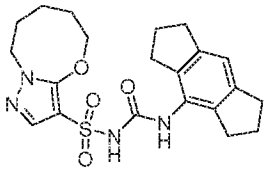
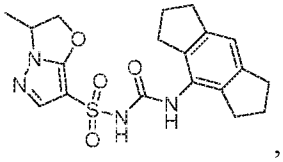
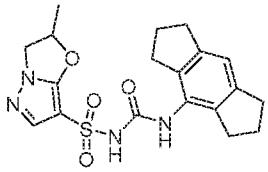
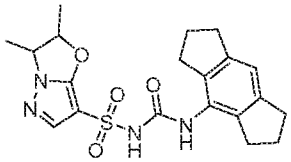
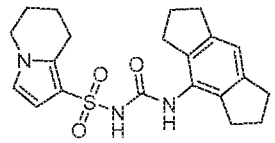
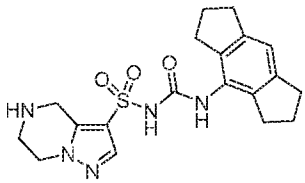
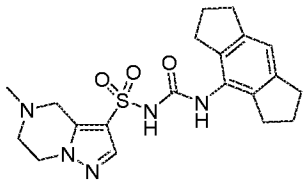
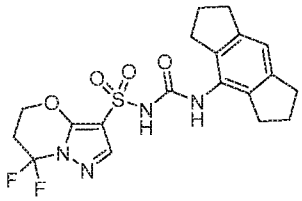
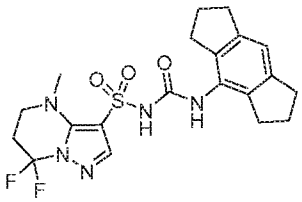
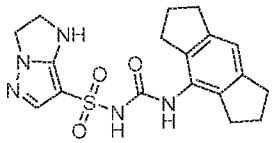
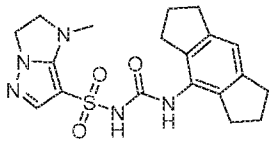
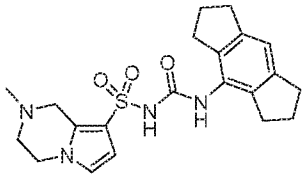
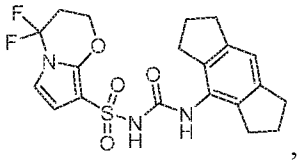
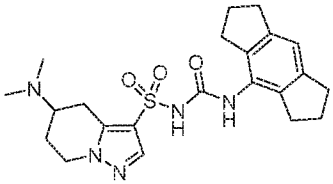
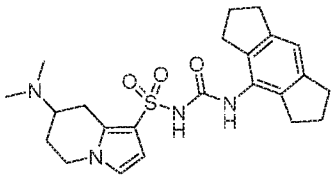
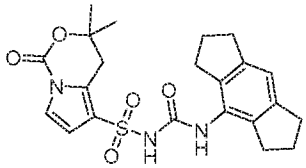
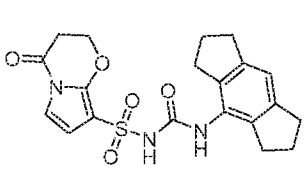
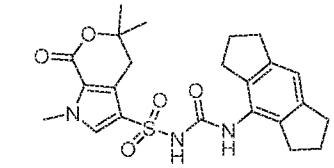
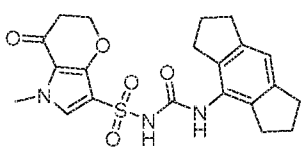
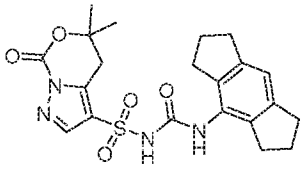
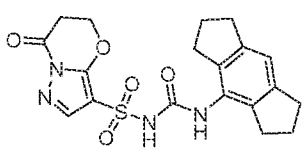
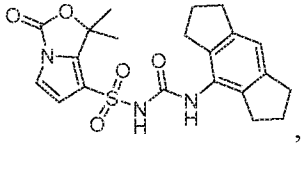
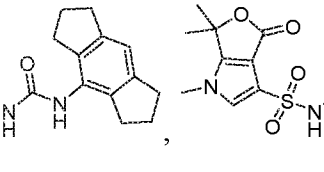
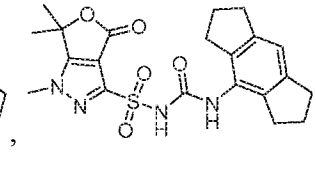

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

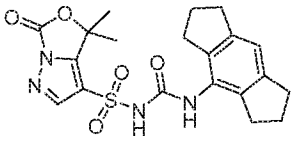
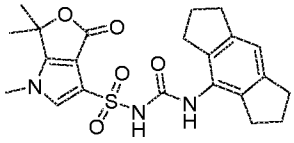

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

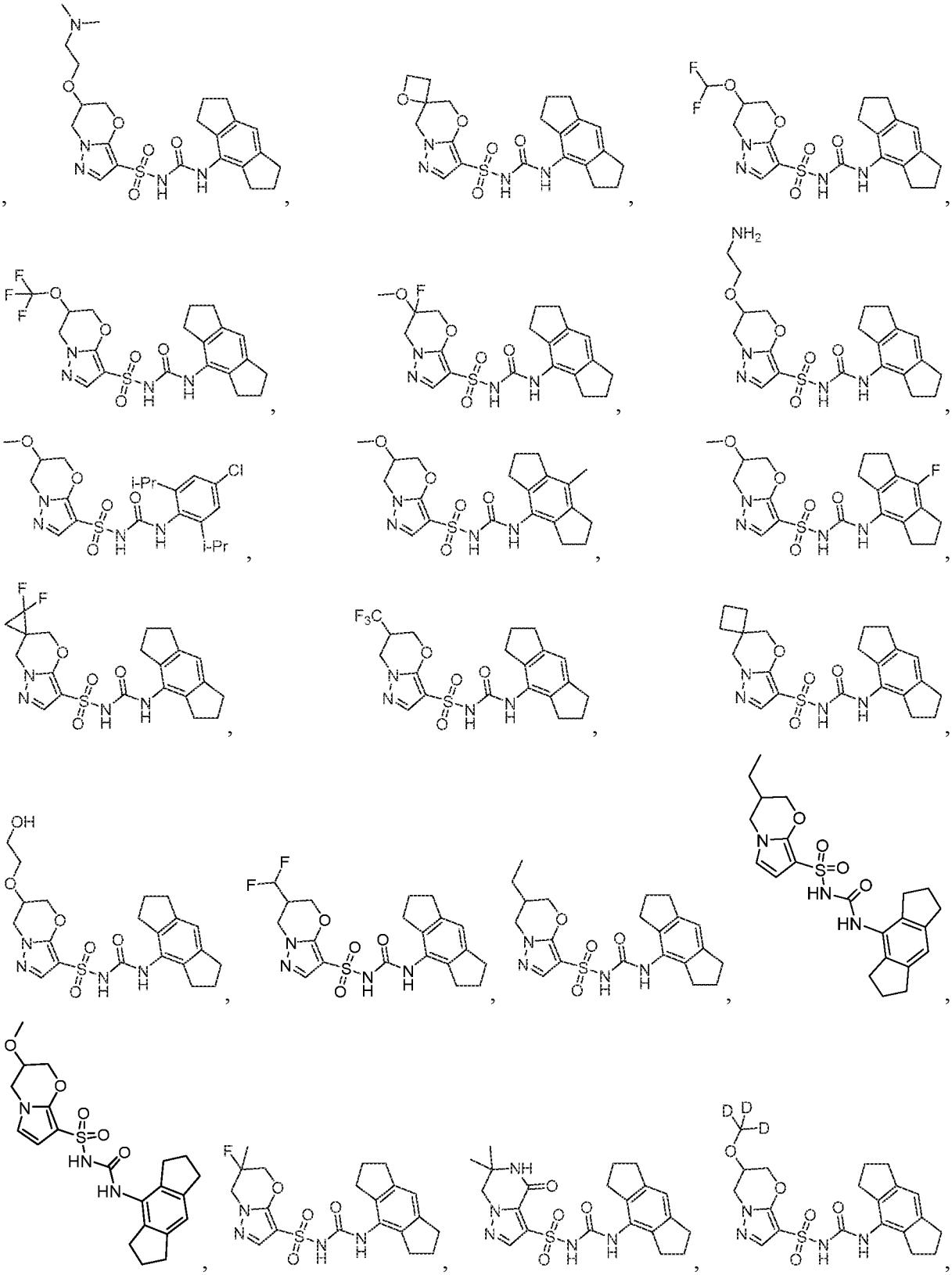
,

,

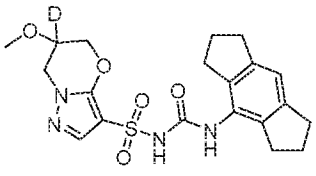
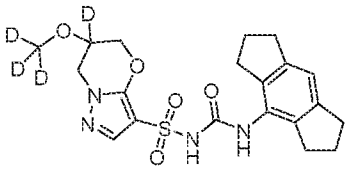
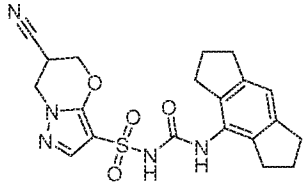
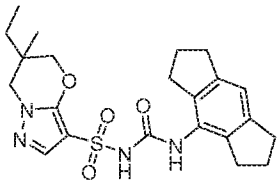
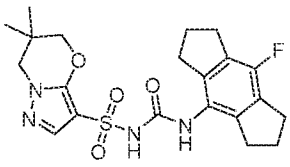
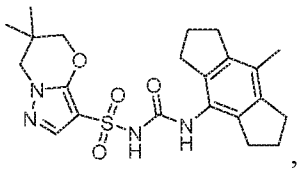
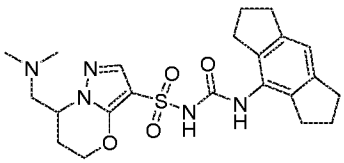
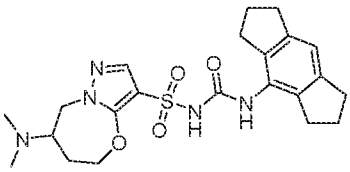
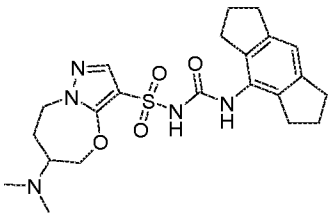
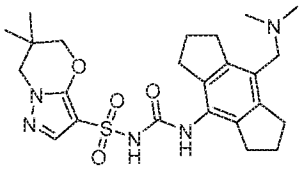
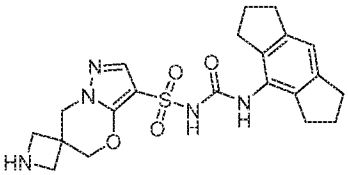
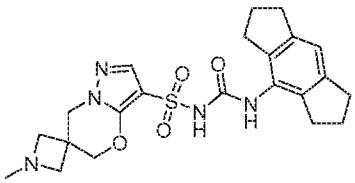
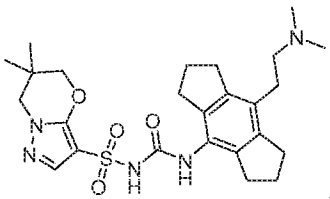
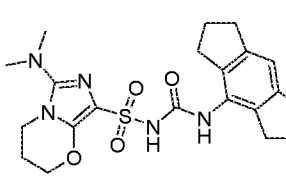
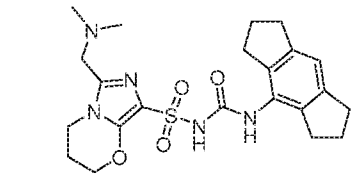
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

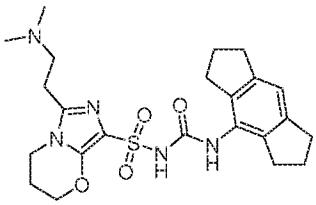
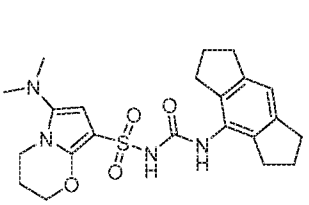
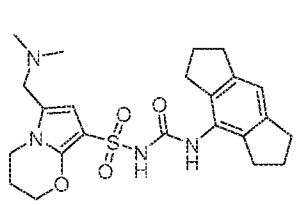
,




,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

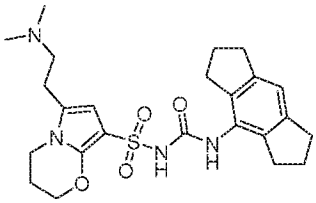
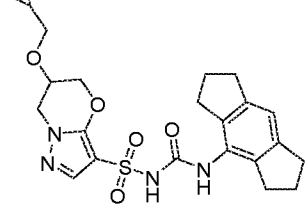
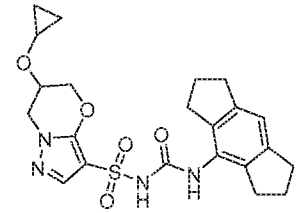
,

,

,

,

,

,

,

,

,

,

,

,

,

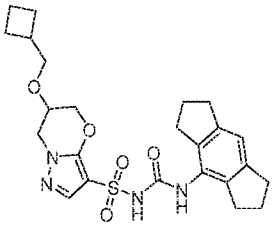
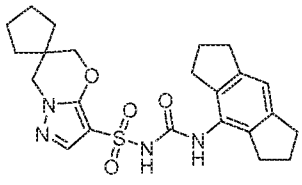
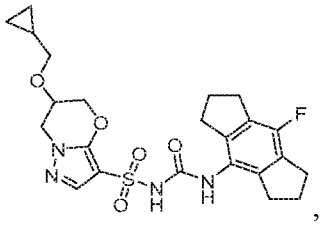
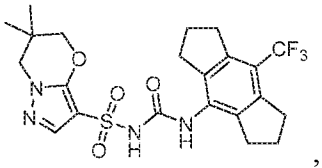
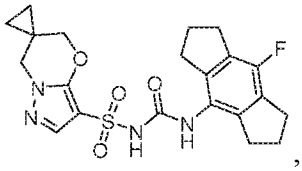
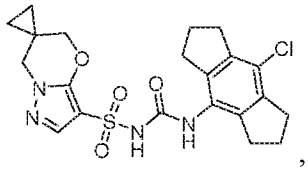
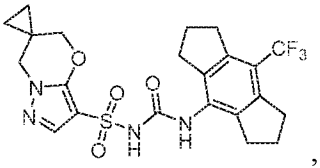
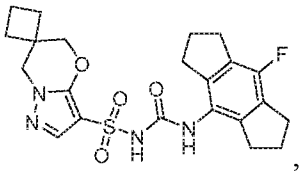
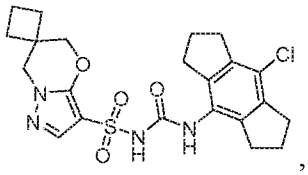
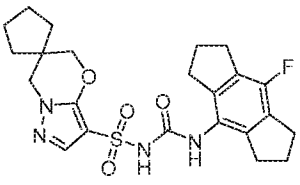
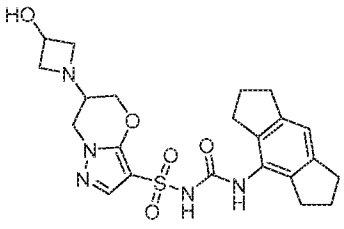
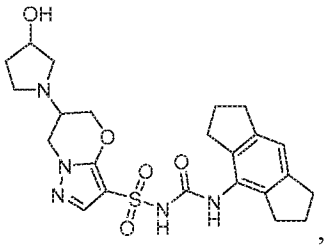
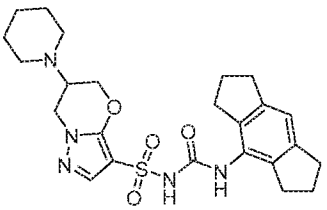
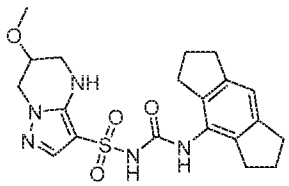
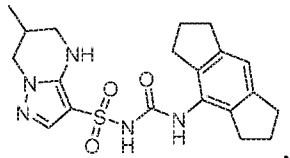
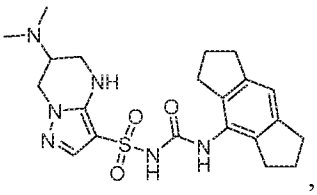
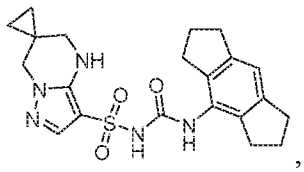
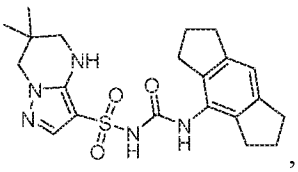
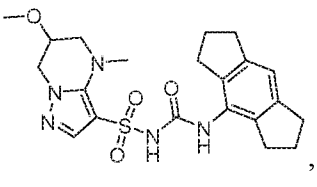
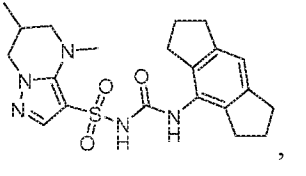
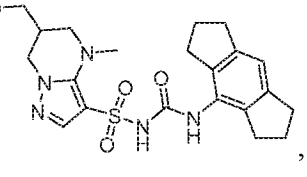
,

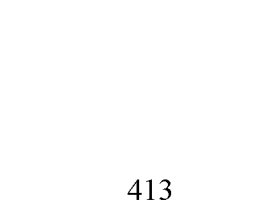
,

,

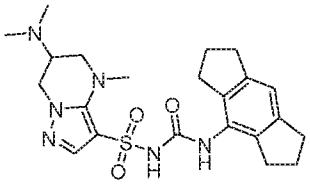
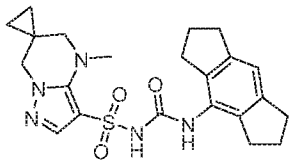
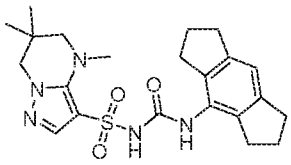
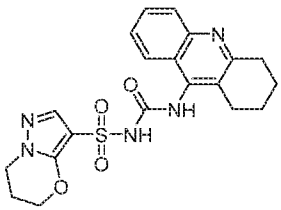
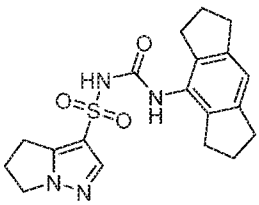
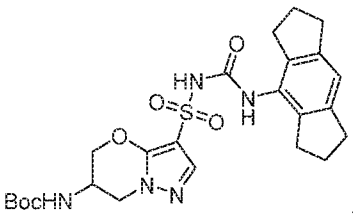
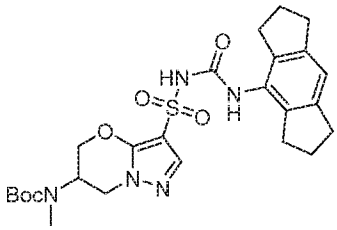
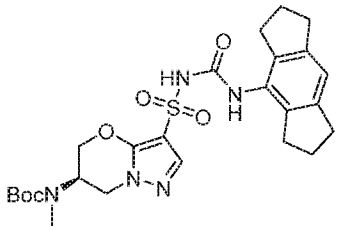
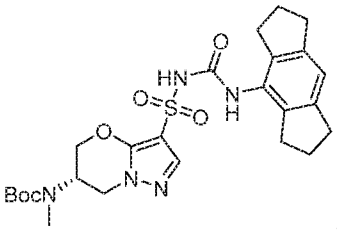
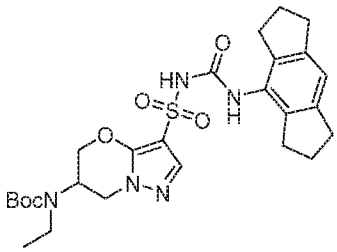
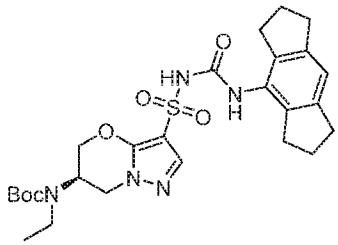
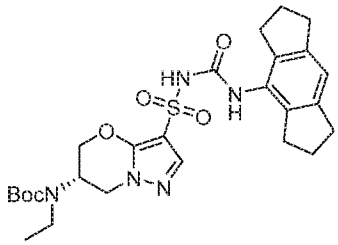
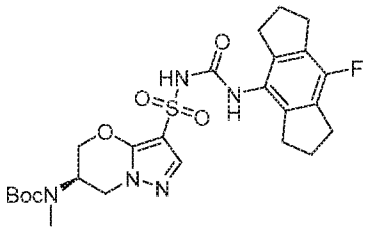
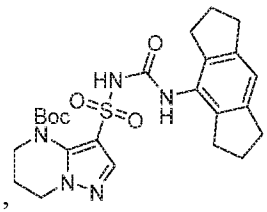
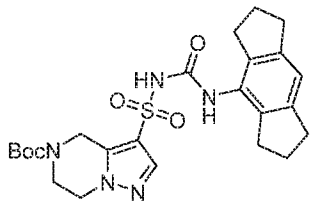
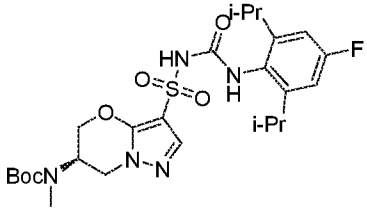
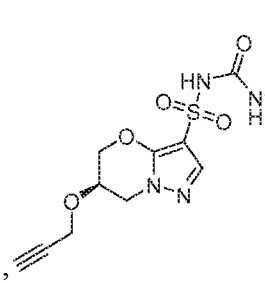
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

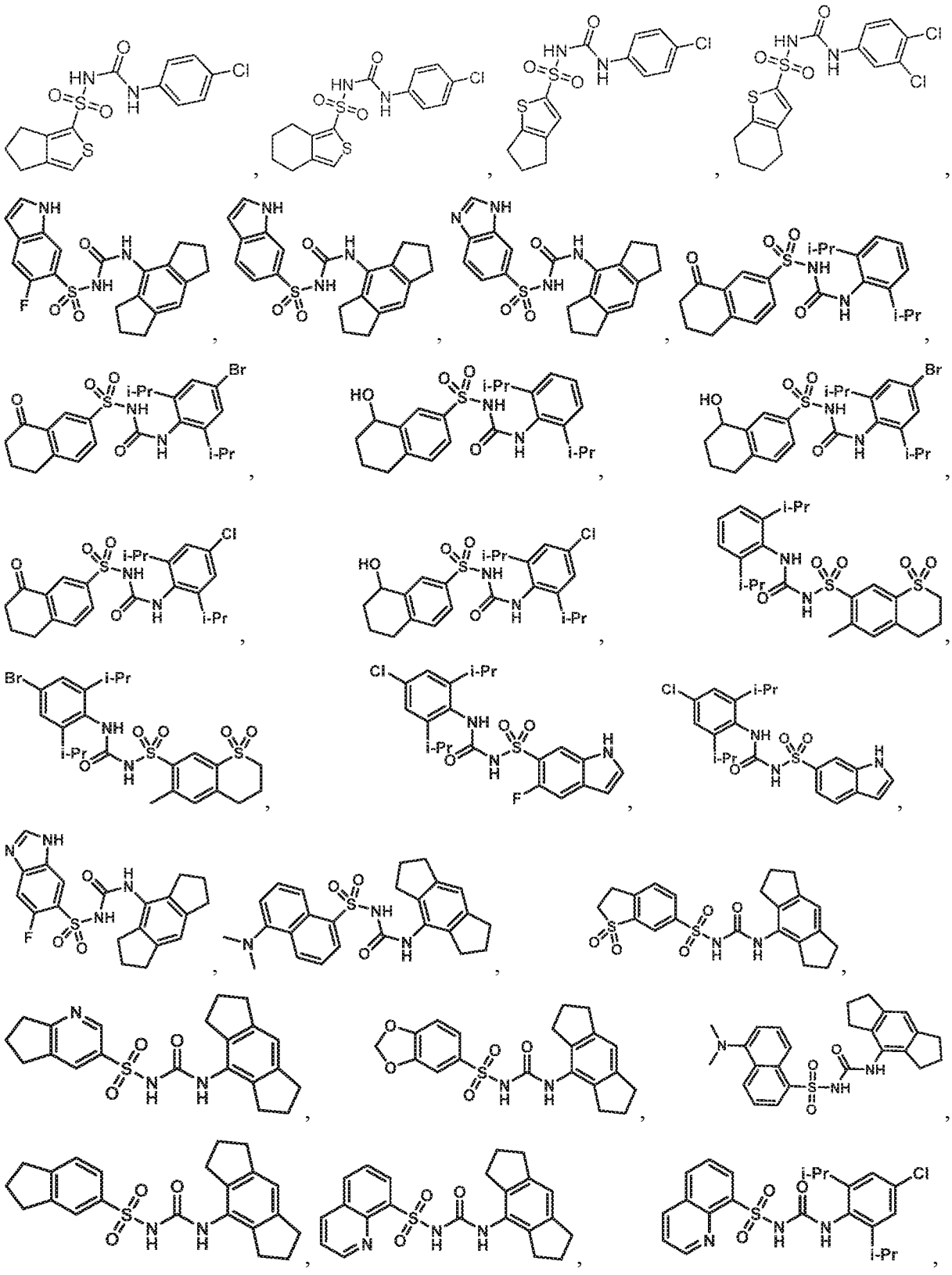

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

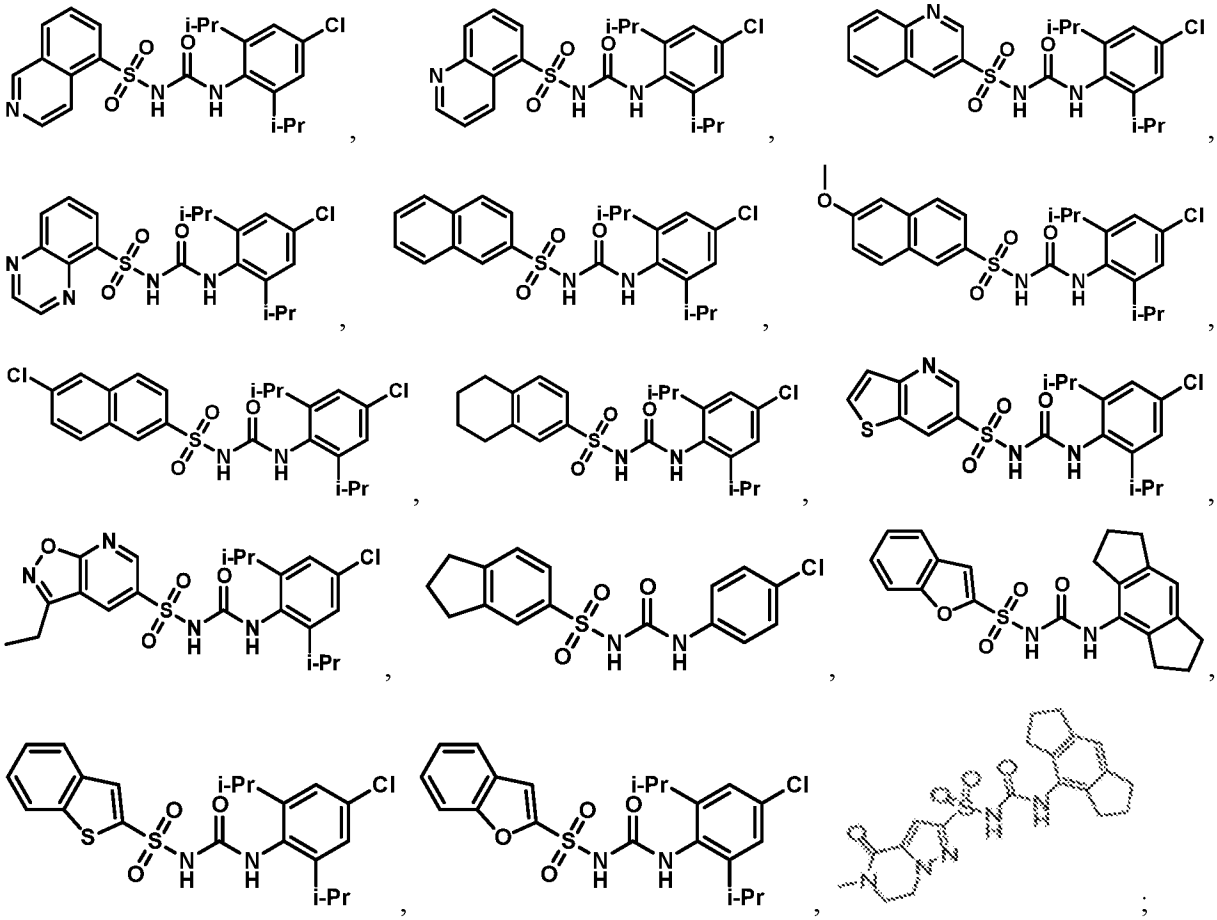
,

,

,

,





or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein X^4 is other than $-X^5-X^6-$; from two to four of R^1, R^2, R^3, and R^4 are present; and wherein at least two of the two to four R^1, R^2, R^3, and R^4 are on adjacent atoms, and taken together with the atoms connecting them, independently form a ring selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}, and

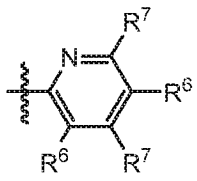
(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

3. The compound of any one of claims 1-2, wherein when one of X^1 and X^4 is N; the other of X^1 and X^4 is other than O.
4. The compound of any one of claims 1-3, wherein X^1 is CR^1.
5. The compound of any one of claims 1-4, wherein X^2 is NR^2.
6. The compound of any one of claims 1-5, wherein X^3 is N.
7. The compound of any one of claims 1-6, wherein X^4 is CR^4.
8. The compound of any one of claims 1-3, wherein X^1 is CR^1; X^2 is NR^2; X^3 is N; and X^4 is CR^4.
9. The compound of any one of claims 5-8, wherein R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.
10. The compound of any one of claims 5-9, wherein R^1 and R^2, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.
11. The compound of any one of claims 5-8, wherein R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic 5-to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
12. The compound of any one of claims 5-8 and 11, wherein R^1 and R^2, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
13. The compound of claim 12, wherein the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.
14. The compound of any one of claims 7-13, wherein R^4 is H or CH_3 (e.g., H).
15. The compound of any one of claims 1-3, wherein X^1 is N.

16. The compound of any one of claims 1-3 and 15, wherein X^2 is NR^2.
17. The compound of any one of claims 1-3 and 15-16, wherein X^3 is CR^3.
18. The compound of any one of claims 1-3 and 15-17, wherein X^4 is CR^4.
19. The compound of any one of claims 1-3, wherein X^1 is N; X^2 is NR^2; X^3 is CR^3; and X^4 is CR^4.
20. The compound of any one of claims 17-19, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.
21. The compound of any one of claims 17-20, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.
22. The compound of any one of claims 17-19, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
23. The compound of any one of claims 17-19 and 22, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
24. The compound of claim 23, wherein the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.
25. The compound of any one of claims 18-24, wherein R^4 is H or CH_3.
26. The compound of any one of claims 1-3, wherein X^1 is S.
27. The compound of any one of claims 1-3 and 26, wherein X^2 is CR^2.
28. The compound of any one of claims 1-3 and 26-27, wherein X^3 is CR^3.
29. The compound of any one of claims 1-3 and 26-28, wherein X^4 is CR^4.

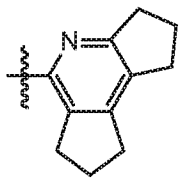
30. The compound of claim 29, wherein R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.
31. The compound of any one of claims 29-30, wherein R^3 and R^4, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.
32. The compound of claim 29, wherein R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
33. The compound of any one of claims 29 and 32, wherein R^3 and R^4, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, N, NH, and NR^{13} (e.g., O, N, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
34. The compound of claim 33, wherein the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.
35. The compound of any one of claims 27-34, wherein R^2 is H or CH_3.
36. The compound of any one of claims 1-3, wherein X^1 is S; and X^4 is other than CR^4.
37. The compound of any one of claims 1-3 and 36, wherein X^2 is CR^2.
38. The compound of any one of claims 1-3 and 36-37, wherein X^3 is CR^3.
39. The compound of any one of claims 1-3 and 36-38, wherein X^4 is N.
40. The compound of any one of claims 1-3, wherein X^1 is S; X^2 is CR^2; X^3 is CR^3; and X^4 is N.
41. The compound of any one of claims 1-3 and 36-40, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

42. The compound of any one of claims 1-3 and 36-41, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.
43. The compound of any one of claims 1-3 and 36-40, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
44. The compound of any one of claims 1-3, 36-40, and 43, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
45. The compound of claim 44, wherein the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.
46. The compound of any one of claims 1-45, wherein each R^{20} is independently selected from the group consisting of: hydroxy, halo (e.g., fluoro), oxo, C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}, C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}, NR^8R^9, 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}, or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom, wherein the ring is optionally substituted with $OS(O)_2Ph$.
47. The compound of any one of claims 1-46, wherein R^{21} is selected from the group consisting of halo (e.g., fluoro), NR^8R^9, C_2-C_6 alkynyl (e.g., ethynyl), and C_1-C_6 alkoxy (e.g., methoxy).
48. The compound of any one of claims 1-47, wherein o is 2 and p is 2.
49. The compound of any one of claims 1-48, wherein B is pyridyl.
50. The compound of claim 49, wherein B is 2-pyridyl.



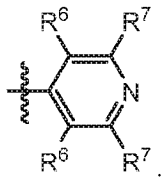
51. The compound of claim 50, wherein the optionally substituted ring B is .

52. The compound of claim 51, wherein two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form a C_4-C_8 carbocyclic ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.



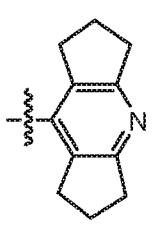
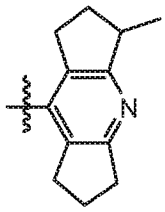
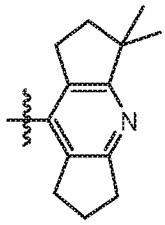
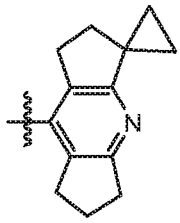
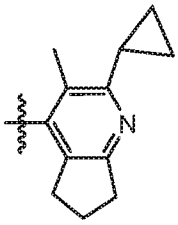
53. The compound of claim 52, wherein the optionally substituted ring B is .

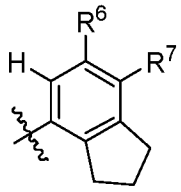
54. The compound of claim 49, wherein B is 4-pyridyl.



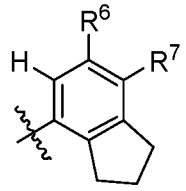
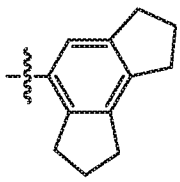
55. The compound of claim 54, wherein the optionally substituted ring B is .

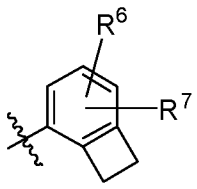
56. The compound of claim 55, wherein at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

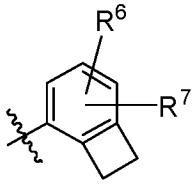
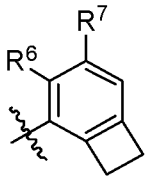
57. The compound of claim 56, wherein the optionally substituted ring B is selected from the group consisting of:  ,  ,  ,  , and  .

58. The compound of any one of claims 1-47, wherein, the optionally substituted ring B is  .

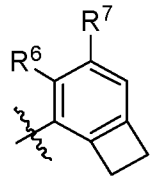
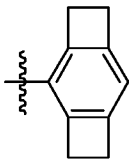
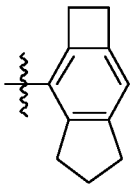
59. The compound of claim 58, wherein R^6 and R^7, taken together with the atoms connecting them, independently form one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

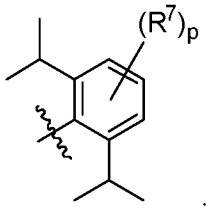
60. The compound of any one of claims 58-59, wherein  is  .

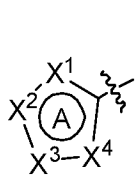
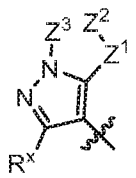
61. The compound of any one of claims 1-47, wherein the optionally substituted ring B is  .

62. The compound of claim 61, wherein  is  .

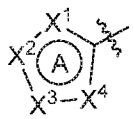
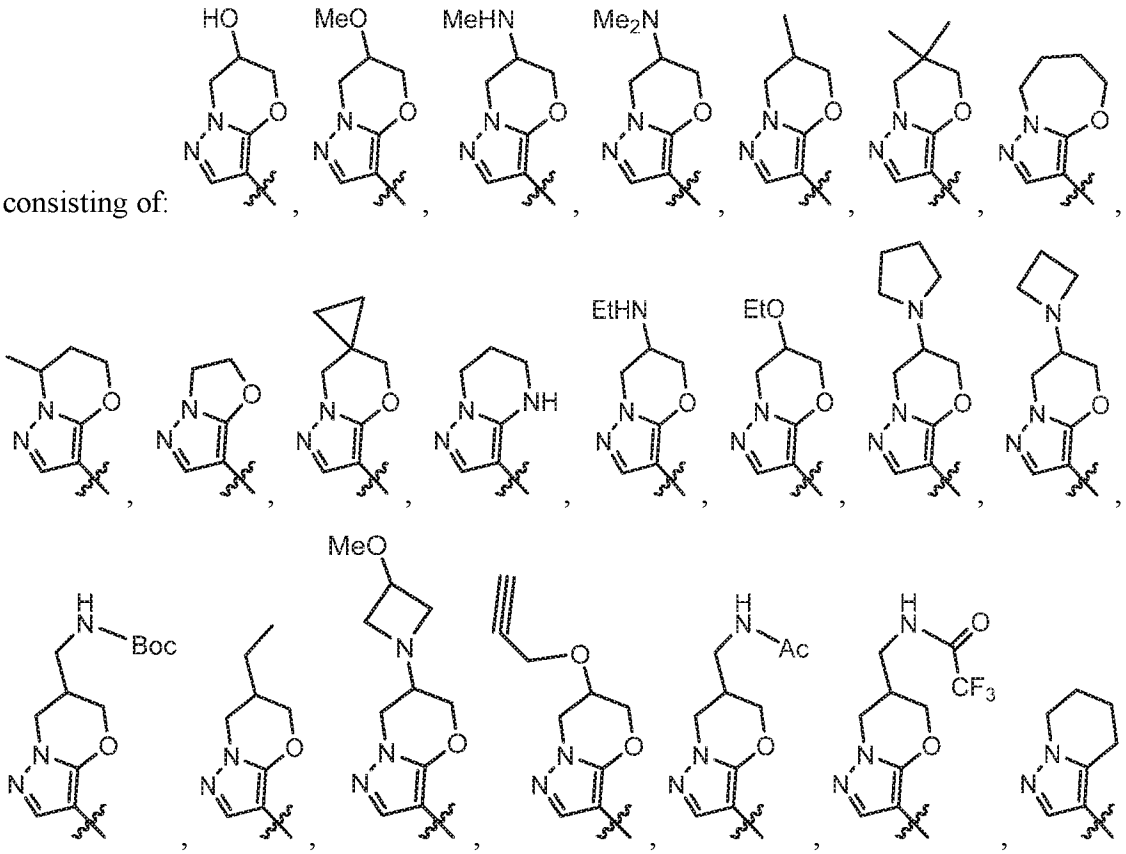
63. The compound of any one of claims 61-62, wherein R^6 and R^7, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

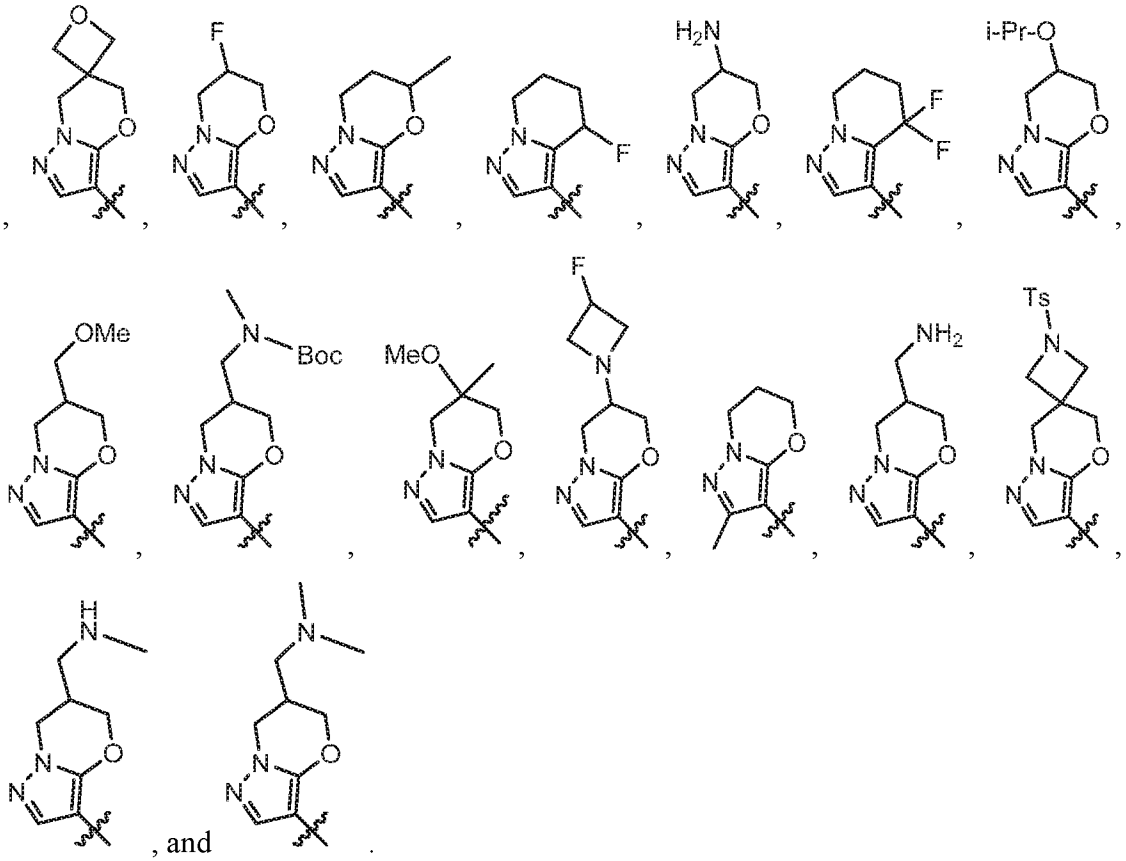
64. The compound of any one of claims 62-63, wherein  is selected from  and  .

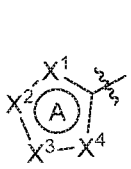
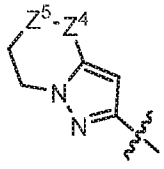
65. The compound of any one of claims 1-47, wherein the optionally substituted ring B is  .

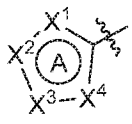
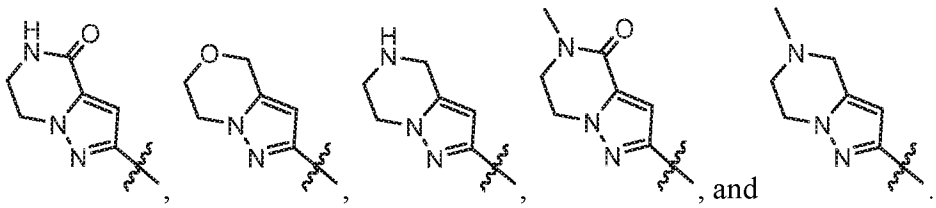
66. The compound of any one of claims 1 and 48-65, wherein  is  , wherein R^x is selected from the group consisting of H and C_1-C_6 alkyl (e.g., methyl); Z^1 is selected from the group consisting of O, NH, and -CH_2- optionally substituted with 1-2 R^{20}; Z^2 is selected from the group consisting of NH and -CH_2- optionally substituted with 1-2 R^{20}; Z^3 is selected from the group consisting of -CH_2- optionally substituted with 1-2 R^{20}, -CH_2CH_2- optionally substituted with 1-2 R^{20}, and -$CH_2CH_2CH_2$- optionally

substituted with 1-2 R^{20}; R^{20} is selected from the group consisting of hydroxy, halo (e.g., fluoro), oxo, C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}, C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}, NR^8R^9, 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}, or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom wherein the ring is optionally substituted with $OS(O)_2Ph$; R^{21} is selected from the group consisting of halo (e.g., fluoro), NR^8R^9, C_2-C_6 alkynyl (e.g., ethynyl), and C_1-C_6 alkoxy (e.g., methoxy); R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl (e.g., methyl or ethyl), COR^{13}, and CO_2R^{13}; R^{13} is selected from the group consisting of: C_1-C_6 alkyl (e.g., methyl or *t*-butyl) and C_1-C_6 haloalkyl (e.g., trifluoromethyl).

67. The compound of any one of claims 48-65, wherein  is selected from the group consisting of: 



68. The compound of any one of claims 48-65, wherein  is  , wherein Z^4 is selected from the group consisting of $–CH_2-$, –C(O)-, and NH; Z^5 is selected from the group consisting of O, NH, $N-CH_3$, and $–CH_2-$.

69. The compound of any one of claims 48-65, wherein  is selected from the group consisting of:  .

70. The compound of any one of claims 1-3 and 48-65, wherein X^1 is S.

71. The compound of any one of claims 1-3, 48-65, and 70, wherein X^2 is CR^2.

72. The compound of any one of claims 1-3, 48-65, and 70-71, wherein X^3 is CR^3.

73. The compound of any one of claims 1-3, 48-65, and 70-72, wherein X^4 is CR^4.

74. The compound of any one of claims 72-73, wherein R^3 and R^4 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-12 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

75. The compound of any one of claims 72-74, wherein R^3 and R^4 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20} and

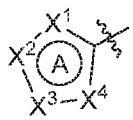
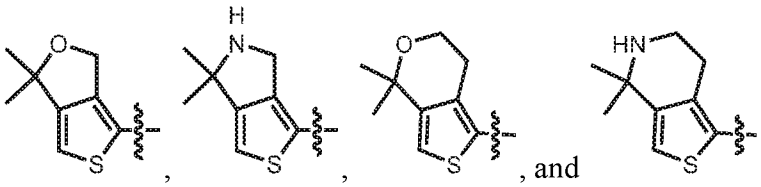
(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

76. The compound of claim 75, wherein R^3 and R^4 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20} and

(ii) a monocyclic 5- to 6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

77. The compound of any one of claims 72-75, wherein R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.
78. The compound of any one of claims 72-75 and 77, wherein R^3 and R^4, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.
79. The compound of any one of claims 72-75, wherein R^3 and R^4, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
80. The compound of any one of claims 72-75 and 79, wherein R^3 and R^4, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.
81. The compound of any one of claims 72-75 and 79-81, wherein the ring is a monocyclic 5-6-membered heterocycloalkyl ring containing one heteroatom or heteroatomic group independently selected from O or NH, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^3 and X^4.
82. The compound of any one of claims 71-81, wherein R^2 is H or CH_3 (e.g., H).
83. The compound of any one of claims 80-81, wherein the ring is substituted with two independently selected R^{20}.
84. The compound of any one of claims 80-83, wherein R^{20} is C_1-C_6 alkyl (e.g., methyl).

85. The compound of any one of claims 79-84, wherein  is selected from the group consisting of:  .

86. The compound of any one of claims 70-73, wherein R^2 and R^3 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

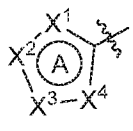
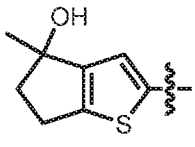
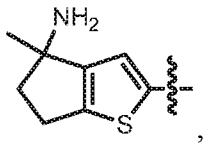
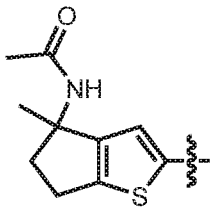
(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

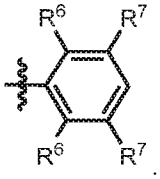
87. The compound of claim 86, wherein the ring is a monocyclic 5-6 membered cycloalkyl ring optionally substituted with one or more R^{20}, or a monocyclic 5-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S (e.g., O and NH), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

88. The compound of claim 86, wherein the ring is a monocyclic 5-6 membered cycloalkyl ring optionally substituted with one or more R^{20}.

89. The compound of any one of claims 86-88, wherein each R^{20} is independently selected from hydroxy, C_1-C_6 alkyl (e.g., methyl), and NR^8R^9.

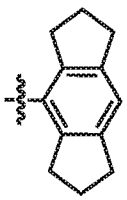
90. The compound of any one of claims 86-89, wherein  is selected from the group consisting of:  ,  , and  .

91. The compound of any one of claims 70-90, where o is 2 and p is 2.

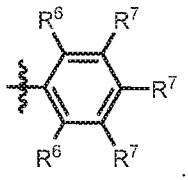
92. The compound of any one of claims 70-91, wherein the optionally substituted ring B is  .

93. The compound of claim 92, wherein two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic ring or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

94. The compound of any one of claims 91-93, wherein two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings each optionally independently substituted with one or more R^{27}.

95. The compound of any one of claims 91-94, wherein the optionally substituted ring B is  .

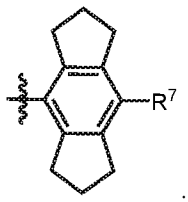
96. The compound of any one of claims 70-90, wherein the optionally substituted ring B is



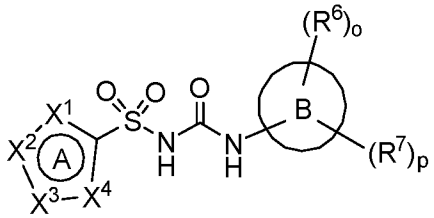
97. The compound of claim 96, wherein two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic ring or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

98. The compound of any one of claims 96-97, wherein two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings each optionally independently substituted with one or more R^{27}.

99. The compound of any one of claims 96-98, wherein the optionally substituted ring B is

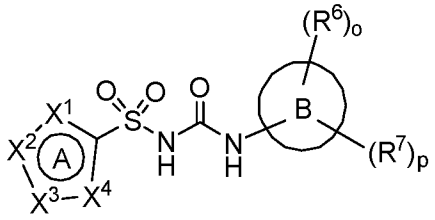


100. A compound of Formula AA

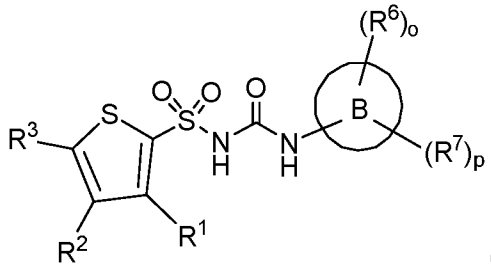


Formula AA

wherein the compound of Formula AA is selected from



(Formula AA-1)



(Formula AA-2)

wherein

A is aromatic and charge neutral;

X^1 is O, S, N, CR^1, or NR^1;

X^2 is O, S, N, CR^2, or NR^2;

X^3 is O, S, N, CR^3, or NR^3;

X^4 is O, S, N, CR^4, NR^4, or $–X^5$-X^6-;

X^5 is N or CR^5;

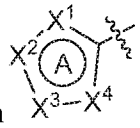
X^6 is N or CR^6;

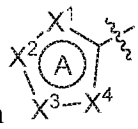
wherein when X^4 is -X^5-X^6, then:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

when X^4 is other than -X^5-X^6-, then  comprises at least one of CR^1, CR^2, CR^3, and CR^4;

when X^4 is -X^5-X^6-, then  comprises at least two of CR^1, CR^2, CR^3, CR^5, and CR^6;

wherein when X^1 is S, X^4 is other than CR^4;
wherein when X^4 is S, X^1 is other than CR^1;

wherein when the compound of Formula AA is a compound of Formula AA-1, from two to four of R^1, R^2, R^3, and R^4 are present or from two to five of R^1, R^2, R^3, R^5, and R^6 are present; and wherein at least two of the two to four R^1, R^2, R^3, and R^4 or at least of two to five R^1, R^2, R^3, R^5, and R^6 are on adjacent atoms;

wherein when the compound of Formula AA is a compound of Formula AA-1, any two adjacent R^1, R^2, R^3, and R^4 or any two adjacent R^1, R^2, R^3, R^5, and R^6 are taken together with the atoms connecting them to form a ring; and wherein when the compound of Formula AA is a compound of Formula AA-2, any two adjacent R^1, R^2, and R^3 are taken together with the atoms connecting them to form a ring; wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4 when the compound of Formula AA is a compound of Formula AA-1, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4 when the compound of Formula AA is a compound of Formula AA-1, and wherein the heteroaryl ring is optionally substituted with one or more R^{20};

R^{20} is selected from the group consisting of: hydroxy, halo, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{21}, C_2-C_6 alkenyl optionally substituted with one or more R^{21}, C_2-C_6 alkynyl

optionally substituted with one or more R^{21}, C_1-C_6 alkoxy optionally substituted with one or more R^{21}, OC_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{21}, $S(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, $OS(O_2)C_6$-C_{10} aryl optionally substituted with one or more R^{21}, C_6-C_{10} aryl optionally substituted with one or more R^{21}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{21}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{21}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{21}, and $CONR^8R^9$;

or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring or at least one monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, and S, wherein the cycloalkyl ring or heterocycloalkyl ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$;

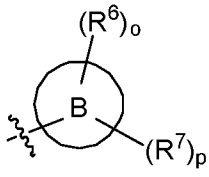
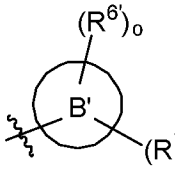
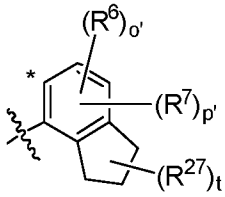
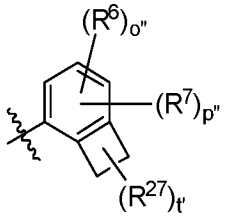
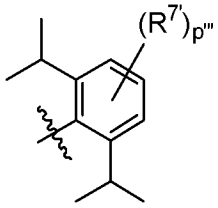
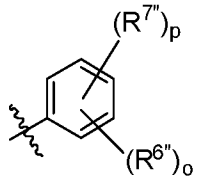
R^{21} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

wherein the remaining R^1, R^2, R^3, and R^4, when present, are each independently selected from H, C_1-C_6 alkyl optionally substituted with one or more R^{22}, C_1-C_6 haloalkyl optionally substituted with one or more R^{22}, C_1-C_6 alkoxy optionally substituted with one or more R^{22}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{22}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{22}, CO-C_6-C_{10} aryl optionally substituted with one or more R^{22}, CO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{22}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{22}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, C_6-C_{10} aryl optionally substituted with one or more R^{22}, 5- to 10-membered heteroaryl

optionally substituted with one or more R^{22}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{22}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{22}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{22}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{22}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{22}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{22}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{22}, $NHCOOCC_1$-C_6 alkyl optionally substituted with one or more R^{22}, NH-$(C=NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl optionally substituted with one or more R^{22}, C_3-C_7 cycloalkyl optionally substituted with one or more R^{22}, and 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{22};

R^{22} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{23}, C_1-C_6 alkoxy optionally substituted with one or more R^{23}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{23}, C_6-C_{10} aryl optionally substituted with one or more R^{24}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{24}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{23}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{24}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{24}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{23}, and $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{23};

R^{23} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, OC_1-C_6 alkyl, and oxo;
R^{24} at each occurrence is independently selected from the group consisting of: hydroxy, halo, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

wherein when the compound is a compound of Formula AA-1,  is selected from the group consisting of:  ,  ,  ,  ,  ,

wherein * denotes that the ring position the * is closest to is unsubstituted;

B is a 5-10-membered heteroaryl or C_6-C_{10} aryl;

B' is a 5-6-membered heteroaryl, wherein when the 5-6 membered heteroaryl contains two or three nitrogen ring members, the 5-6-membered heteroaryl additionally contains one or more non-nitrogen heteroatom or heteroatomic group ring members; 5-pyrimidinyl; 6-pyrimidinyl; pyridazinyl; pyrazinyl; 1,2,3-triazinyl; 1,2,4-triazinyl; tetrazinyl; imidazolyl; pyrazolyl; 1,2,3-triazolyl; tetrazolyl; or C_7-C_{10} aryl;

o = 1 or 2;

p = 0, 1, 2, or 3;

o' = 0 or 1;

p' = 0 or 1;

o'' = 0 or 1;

p'' = 0, 1, or 2;

p''' = 1, 2, or 3;

t is 0, 1, 2, 3, 4, 5, or 6;

t' is 0, 1, 2, 3, or 4;

R^6 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

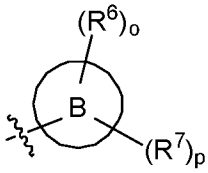
$R^{6'}$ at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

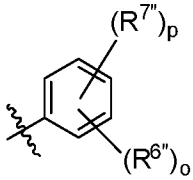
R^7 at each occurrence is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

$R^{7'}$, at each occurrence, is independently selected from C_1-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, I, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_3-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered

heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25},

each occurrence of $R^{6''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, F, Br, I, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

wherein when 

is 

, at least one $R^{6''}$ is *ortho* to the bond connecting the B ring to the NH(CO) group of Formula AA;

each occurrence of $R^{7''}$ is independently selected from C_1-C_2 alkyl, C_4-C_6 alkyl optionally substituted with one or more R^{25}, C_1-C_6 haloalkyl optionally substituted with one or more R^{25}, C_1-C_6 alkoxy optionally substituted with one or more R^{25}, C_1-C_6 haloalkoxy optionally substituted with one or more R^{25}, halo, CN, NO_2, COC_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_1-C_6 alkyl optionally substituted with one or more R^{25}, CO_2C_3-C_8 cycloalkyl optionally substituted with one or more R^{25}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{25}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{25}, OCO(5- to 10-membered heteroaryl)

optionally substituted with one or more R^{25}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{25}, C_6-C_{10} aryl optionally substituted with one or more R^{25}, 5- to 10-membered heteroaryl optionally substituted with one or more R^{25}, NH_2, NHC_1-C_6 alkyl optionally substituted with one or more R^{25}, $N(C_1$-C_6 alkyl$)_2$ optionally substituted with one or more R^{25}, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl optionally substituted with one or more R^{25}, $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{25}, C_4-C_{10} cycloalkyl optionally substituted with one or more R^{25}, 3- to 10-membered heterocycloalkyl optionally substituted with one or more R^{25}, and C_2-C_6 alkenyl optionally substituted with one or more R^{25};

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

or at least one pair of $R^{6'}$ and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 cycloalkyl ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27};

or at least one pair of $R^{6''}$ and $R^{7''}$ on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4 or C_6-C_8 carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more R^{27};

R^{25} at each occurrence is independently selected from the group consisting of: hydroxy, halo, CN, oxo, C_1-C_6 alkyl optionally substituted with one or more R^{26}, C_1-C_6 alkoxy optionally substituted with one or more R^{26}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl optionally substituted with one or more R^{26}, C_6-C_{10} aryl optionally substituted with one or more R^{26}, 5- to 10-membered heteroaryl optionally

substituted with one or more R^{26}, $OCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $OCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, OCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, OCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_1$-C_6 alkyl optionally substituted with one or more R^{26}, $NHCOC_6$-C_{10} aryl optionally substituted with one or more R^{26}, NHCO(5- to 10-membered heteroaryl) optionally substituted with one or more R^{26}, NHCO(3- to 7-membered heterocycloalkyl) optionally substituted with one or more R^{26}, $NHCOC_2$-C_6 alkynyl optionally substituted with one or more R^{26}, C_6-C_{10} aryloxy optionally substituted with one or more R^{26}, and $S(O_2)C_1$-C_6 alkyl optionally substituted with one or more R^{26};

R^{26} at each occurrence is independently selected from the group consisting of: hydroxy, halo, C_6-C_{10} aryl, NR^8R^9, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

R^{27}, at each occurrence, is independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;
each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms and/or heteroatomic groups in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl; and
each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

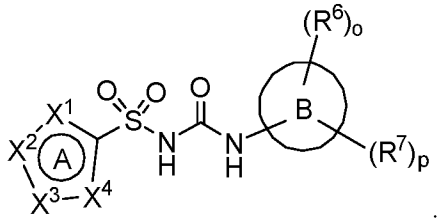
or a pharmaceutically acceptable salt thereof.

101. The compound of claim 100, wherein when the compound of Formula AA is a compound of Formula AA-1, X^4 is other than $–X^5$-X^6- and any two adjacent R^1, R^2, R^3, and R^4 are taken together with the atoms connecting them to form a ring; and wherein when the compound of Formula AA is a compound of Formula AA-2, any two adjacent R^1, R^2, and R^3 are taken together with the atoms connecting them to form a ring; wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}, and

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1, X^2, X^3, and X^4, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

102. The compound of any one of claims 100-101, wherein when one of X^1 and X^4 is N; the other of X^1 and X^4 is other than O.

103. The compound of any one of claims 100-102, wherein the compound of Formula AA is a compound of Formula AA-1: 

.

104. The compound of claim any one of claims 100-103, when one of X^1 and X^4 is N; the other of X^1 and X^4 is other than O.

105. The compound of any one of claims 100-104, wherein X^1 is CR^1.

106. The compound of any one of claims 100-105, wherein X^2 is NR^2.

107. The compound of any one of claims 100-106, wherein X^3 is N.

108. The compound of any one of claims 100-107, wherein X^4 is CR^4.

109. The compound of any one of claims 100-104, wherein X^1 is CR^1; X^2 is NR^2; X^3 is N; and X^4 is CR^4.

110. The compound of any one of claims 106-109, wherein R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

111. The compound of any one of claims 106-110, wherein R^1 and R^2, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

112. The compound of any one of claims 106-109, wherein R^1 and R^2, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

113. The compound of any one of claims 106-109 and 112, wherein R^1 and R^2, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^1 and X^2, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

114. The compound of claim 113, wherein the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

115. The compound of any one of claims 108-114, wherein R^4 is H or CH_3.

116. The compound of any one of claims 100-104, wherein X^1 is N.

117. The compound of any one of claims 100-104 and 116, wherein X^2 is NR^2.

118. The compound of any one of claims 100-104 and 116-117, wherein X^3 is CR^3.

119. The compound of any one of claims 100-104 and 116-118, wherein X^4 is CR^4.

120. The compound of any one of claims 100-104, wherein X^1 is N; X^2 is NR^2; X^3 is CR^3; and X^4 is CR^4.

121. The compound of any one of claims 118-120, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or

heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

122. The compound of any one of claims 118-121, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, and NR^{13} and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with from 1-2 R^{20}.

123. The compound of any one of claims 118-122, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

124. The compound of any one of claims 118-123, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

125. The compound of claim 124, wherein the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 O atom.

126. The compound of any one of claims 119-125, wherein R^4 is H or CH_3.

127. The compound any one of claims 100-104, wherein X^1 is S.

128. The compound any one of claims 100-104 and 127, wherein X^2 is CR^2.

129. The compound any one of claims 100-104 and 127-128, wherein X^3 is CR^3.

130. The compound any one of claims 100-104 and 127-129, wherein X^4 is N.

131. The compound any one of claims 100-104, wherein X^1 is S; X^2 is CR^2; X^3 is CR^3; and X^4 is N.

132. The compound of any one of claims 128-131, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20}.

133. The compound of any one of claims 128-132, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic C_5-C_6 cycloalkyl ring optionally substituted with one or more R^{20}.

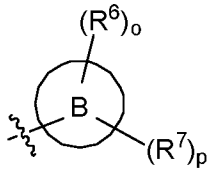
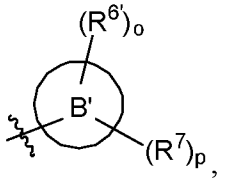
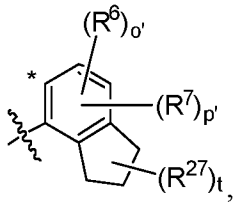
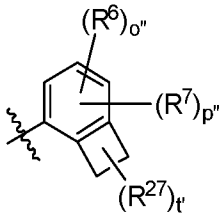
134. The compound of any one of claims 128-131, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

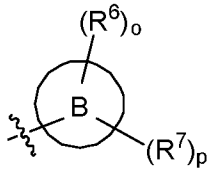
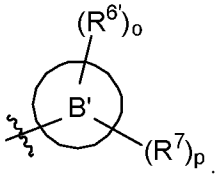
135. The compound of any one of claims 128-131 and 134, wherein R^2 and R^3, taken together with the atoms connecting them, form a monocyclic 5- to-6-membered heterocycloalkyl ring containing 1 heteroatom or heteroatomic group selected from O, NH, and NR^{13} (e.g., O, NH, or NCH_3), wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3, and wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

136. The compound of claim 135, wherein the monocyclic 5- to-6-membered heterocycloalkyl ring contains 1 heteroatom or heteroatomic group selected from O and NH, wherein the heteroatom or heteroatomic group is cumulative with the values selected for X^2 and X^3.

137. The compound of any one of claims 100-136, wherein R^{20} is selected from the group consisting of: hydroxy, halo (e.g., fluoro), oxo, C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}, C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}, NR^8R^9, 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}, or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic 3- to 4-membered heterocycloalkyl ring containing 1 O atom, wherein the ring is optionally substituted with $OS(O)_2Ph$.

138. The compound of claim 137, wherein R^{21} is selected from the group consisting of halo (e.g., fluoro), NR^8R^9, C_2-C_6 alkynyl (e.g., ethynyl), and C_1-C_6 alkoxy (e.g., methoxy).

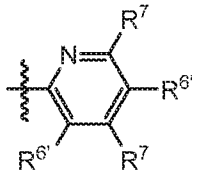
139. The compound of any one of claims 100-138, wherein  is selected from the group consisting of:  ,  , and  .

140. The compound of any one of claims 100-139, wherein  is  .

141. The compound of claim 140, wherein o is 2 and p is 2.

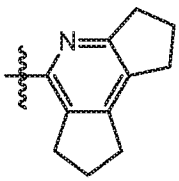
142. The compound of any one of claims 140-141, wherein B' is pyridyl.

143. The compound of any one of claims 140-142, wherein B' is 2-pyridyl.

144. The compound of any one of claims 140-143, wherein the optionally substituted ring B' is  .

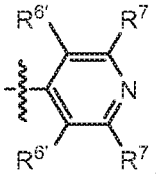
145. The compound of claim 144, wherein two pairs of $R^{6'}$ and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form a C_4-C_8 cycloalkyl ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

146. The compound of claim 144, wherein the optionally substituted ring B' is

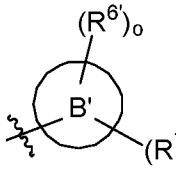
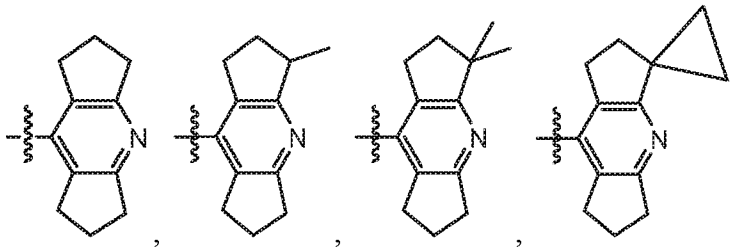
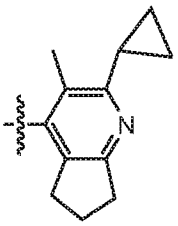


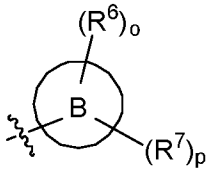
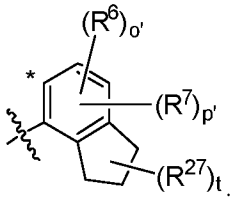
.

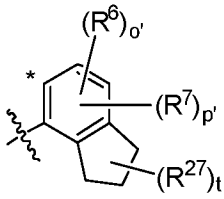
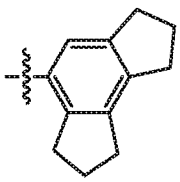
147. The compound of any one of claims 140-142, wherein B' is 4-pyridyl.

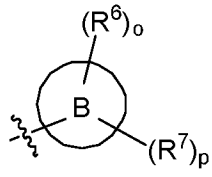
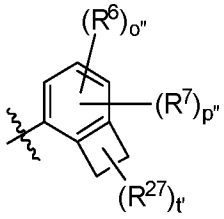
148. The compound of any one of claims 140-142 and 147, wherein the optionally substituted ring B' is  .

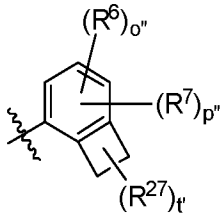
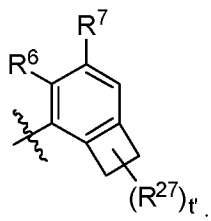
149. The compound of claim 148, wherein at least one pair of $R^{6'}$ and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 cycloalkyl ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the cycloalkyl ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

150. The compound of any one of claims 147-149, wherein  is selected from the group consisting of:  ,  and .

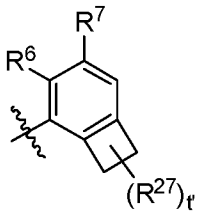
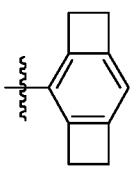
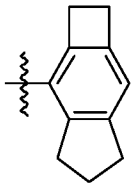
151. The compound of any one of claims 100-139, wherein  is  .

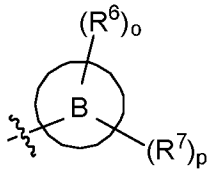
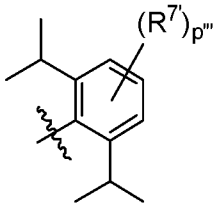
152. The compound of any one of claims 100-139 and 151, wherein  is  .

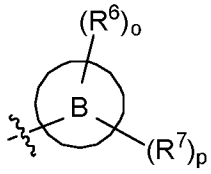
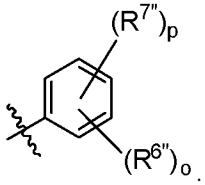
153. The compound of any one of claims 100-139, wherein  is  .

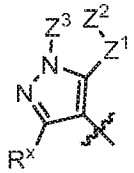
154. The compound of claim 153, wherein  is  .

155. The compound of any one of claims 153-154, wherein R^6 and R^7, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more R^{27}.

156. The compound of any one of claims 154-155, wherein  is selected from  and  .

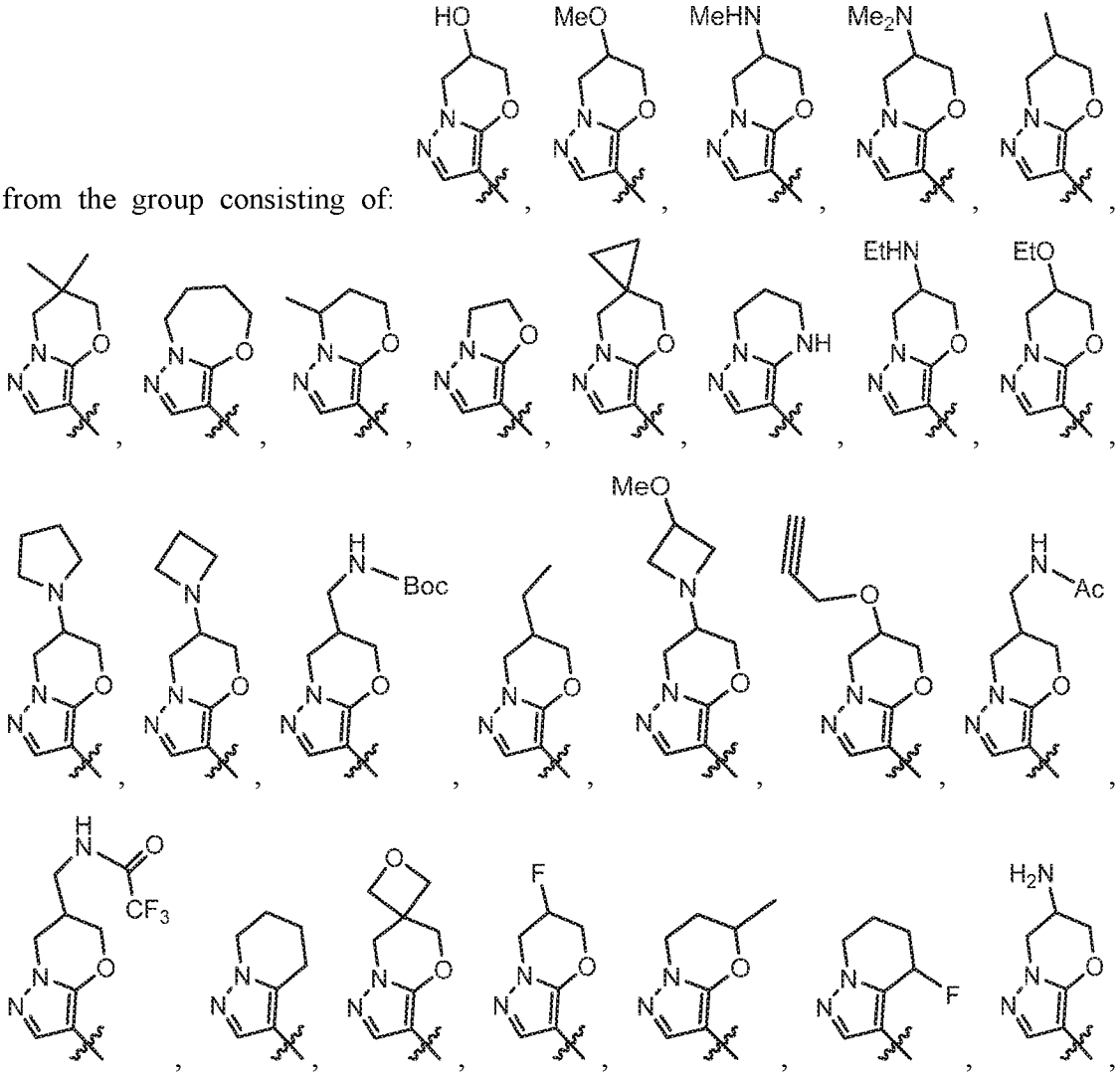
157. The compound of any one of claims 100-139, wherein ,  is  .

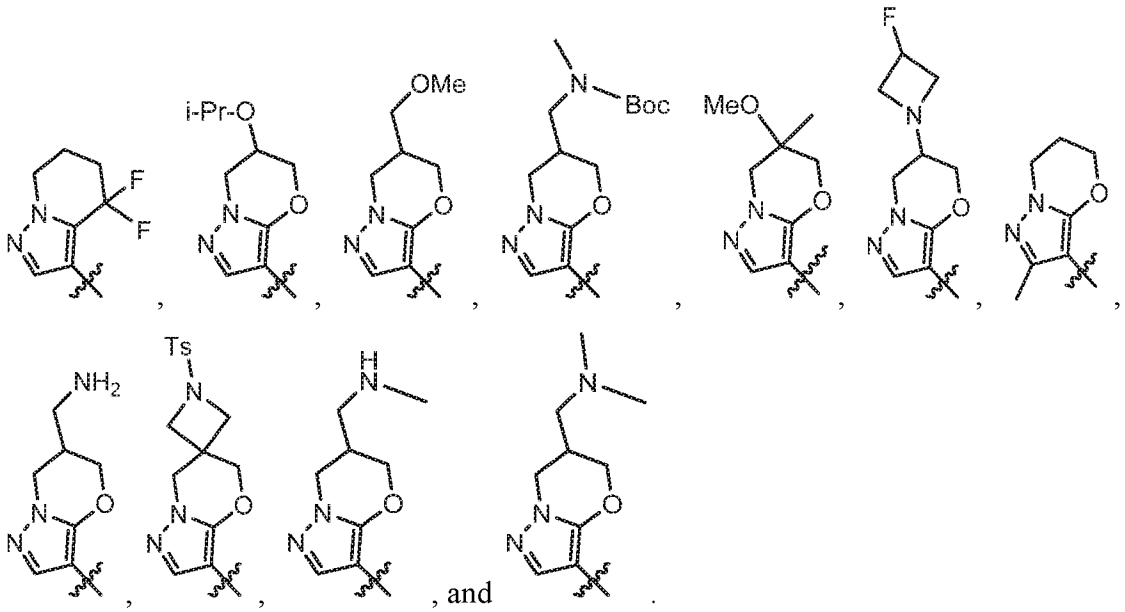
158. The compound of any one of claims 100-139, wherein ,  is  .

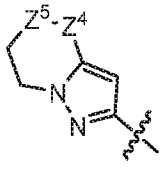
159. The compound of any one of claims 100-104 and 139-158, wherein A is  , wherein R^x is selected from the group consisting of H and C_1-C_6 alkyl (e.g., methyl); Z^1 is selected from the group consisting of O, NH, and -CH_2- optionally substituted with 1-2 R^{20}; Z^2 is selected from the group consisting of NH and -CH_2- optionally substituted with 1-2 R^{20}; Z^3 is selected from the group consisting of -CH_2- optionally substituted with 1-2 R^{20}, -CH_2CH_2- optionally substituted with 1-2 R^{20}, and -$CH_2CH_2CH_2$- optionally substituted with 1-2 R^{20}; R^{20} is selected from the group consisting of hydroxy, halo (e.g., fluoro), oxo, C_1-C_6 alkyl (e.g., methyl or ethyl) optionally substituted with one R^{21}, C_1-C_6 alkoxy (e.g., methoxy, ethoxy, or isopropoxy) optionally substituted with one R^{21}, NR^8R^9, 3- to 10-membered heterocycloalkyl (e.g., azetidinyl or pyrrolidinyl) optionally substituted with one R^{21}, or at least one pair of R^{20} on the same atom, taken together with the atom connecting them, independently forms a monocyclic C_3-C_4 cycloalkyl ring or a monocyclic

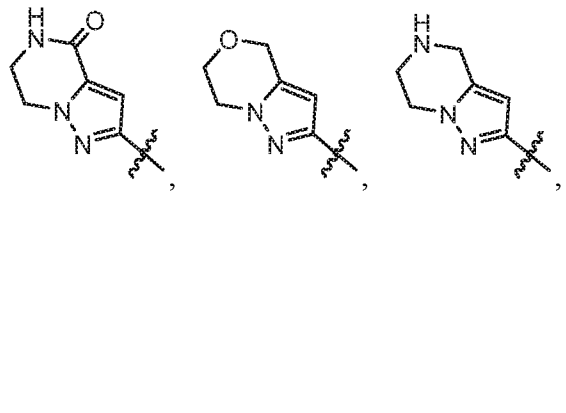
3- to 4-membered heterocycloalkyl ring containing 1 O atom optionally substituted with $OS(O)_2Ph$; R^{21} is selected from the group consisting of halo (e.g., fluoro), NR^8R^9, C_2-C_6 alkynyl (e.g., ethynyl), and C_1-C_6 alkoxy (e.g., methoxy); R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl (e.g., methyl or ethyl), COR^{13}, and CO_2R^{13}; R^{13} is selected from the group consisting of: C_1-C_6 alkyl (e.g., methyl or *t*-butyl) and C_1-C_6 haloalkyl (e.g., trifluoromethyl).

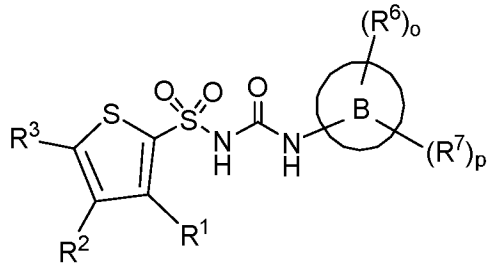
160. The compound of any one of claims 100-104 and 139-159, wherein A is selected from the group consisting of:





161. The compound of any one of claims 100-104 and 139-158, wherein A is  , wherein Z^4 is selected from the group consisting of –CH_2-, –C(O)-, and NH; Z^5 is selected from the group consisting of O, NH, N-CH_3, and –CH_2-.

162. The compound of any one of claims 100-104, 139-158, and 161, wherein A is selected from the group consisting of: 

163. The compound of any one of claims 100-102, wherein the compound of Formula AA is a compound of Formula AA-2:  .

164. The compound of claim 163, wherein R^1 and R^2 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

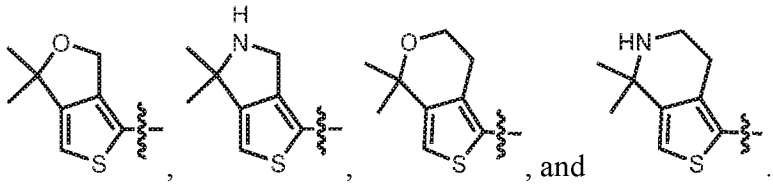
(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

165. The compound of claim 164, wherein the ring is a monocyclic 5-6 membered cycloalkyl ring optionally substituted with one or more R^{20}, or a monocyclic 5-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, or NH, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

166. The compound of any one of claims 164-165, wherein the ring is a monocyclic 5-6-membered heterocycloalkyl ring containing one heteroatom or heteroatomic group independently selected from O, or NH, wherein the heterocycloalkyl ring is optionally substituted with one or more (e.g., two) R^{20}.

167. The compound of any one of claims 164-165, wherein R^{20} is C_1-C_6 alkyl (e.g., methyl).

168. The compound of any one of claims 164-167, wherein A is selected from the group consisting of:  , and .

169. The compound of claim 163, wherein R^2 and R^3 are taken together with the atoms connecting them to form a ring, wherein the ring is selected from the group consisting of:

(i) a monocyclic or bicyclic C_4-C_{12} cycloalkyl ring optionally substituted with one or more R^{20},

(ii) a monocyclic or bicyclic 5- to-12-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20},

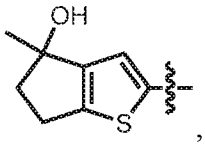
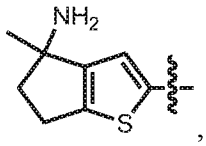
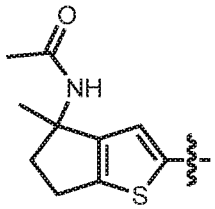
(iii) a monocyclic or bicyclic C_6-C_{10} aryl ring optionally substituted with one or more R^{20}, and

(iv) a monocyclic or bicyclic 5-10 membered heteroaryl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the heteroaryl ring is optionally substituted with one or more R^{20}.

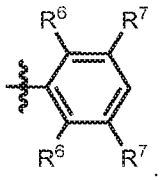
170. The compound of claim 169, wherein the ring is a monocyclic 5-6 membered cycloalkyl ring optionally substituted with one or more R^{20}, or a monocyclic 5-6-membered heterocycloalkyl ring containing 1-3 heteroatoms and/or heteroatomic groups independently selected from O, or NH, wherein the heterocycloalkyl ring is optionally substituted with one or more R^{20}.

171. The compound of any one of claims 169-170, wherein the ring is a monocyclic 5-6-membered heterocycloalkyl ring containing one heteroatom or heteroatomic group independently selected from O or NH, wherein the heterocycloalkyl ring is optionally substituted with one or more (e.g., two) R^{20}.

172. The compound of any one of claims 169-171, wherein R^{20} is selected from hydroxy, C_1-C_6 alkyl (e.g., methyl), and NR^8R^9.

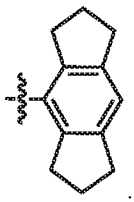
173. The compound of any one of claims 169-172, wherein A is selected from the group consisting of:  ,  , and  .

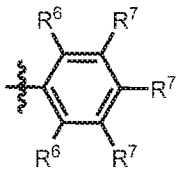
174. The compound of any one of claims 163-173, where o is 2 and p is 2.

175. The compound of any one of claims 163-174, wherein the optionally substituted ring B is  .

176. The compound of claim 175, wherein two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic rings or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

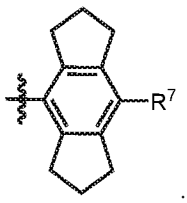
177. The compound of any one of claims 175-176, wherein two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings optionally independently substituted with one or more R^{27}.

178. The compound of any one of claims 174-176, wherein the optionally substituted ring B is  .

179. The compound of any one of claims 163-173, wherein the optionally substituted ring B is  .

180. The compound of claim 179, wherein two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_4-C_8 carbocyclic ring or two 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms and/or heteroatomic groups independently selected from O, N, NH, NR^{13}, and S, wherein the carbocyclic rings or heterocyclic rings are optionally independently substituted with one or more R^{27}.

181. The compound of any one of claims 179-180, wherein two pairs of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form two C_5 carbocyclic rings optionally independently substituted with one or more R^{27}.

182. The compound of any one of claims 179-179, wherein the optionally substituted ring B is  .

183. A compound selected from the compounds in Table 1A, Table 1B, Table 1C, and pharmaceutically acceptable salts thereof.

184. A pharmaceutical composition comprising a compound or salt as claimed in any one of claims 1-183 and one or more pharmaceutically acceptable excipients.

185. A method for modulating NLRP3 activity, the method comprising contacting NLRP3 with an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

186. The method of claim 185, wherein the modulating comprises antagonizing NLRP3.

187. The method of any one of claims 185 and 186, which is carried out *in vitro*.

188. The method of any one of claims 185-187, wherein the method comprises contacting a sample comprising one or more cells comprising NLRP3 with the compound.

189. The method of any one of claims 185-186 and 188, which is carried out *in vivo*.

190. The method of claim 189, wherein the method comprises administering the compound to a subject having a disease in which NLRP3 signaling contributes to the pathology and/or symptoms and/or progression of the disease.

191. The method of claim 190, wherein the subject is a human.

192. A method of treating a disease, disorder or condition that is a metabolic disorder, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

193. The method of claim 192, wherein the metabolic disorder is Type 2 diabetes, atherosclerosis, obesity or gout.

194. A method of treating a disease, disorder or condition that is a disease of the central nervous system, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

195. The method of claim 194, wherein the disease of the central nervous system is Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis or Parkinson's disease.

196. A method of treating a disease, disorder or condition that is lung disease, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

197. The method of claim 196, wherein the lung disease is asthma, COPD or pulmonary idiopathic fibrosis.

198. A method of treating a disease, disorder or condition that is liver disease, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

199. The method of claim 198, wherein the liver disease is NASH syndrome, viral hepatitis or cirrhosis.

200. A method of treating a disease, disorder or condition that is pancreatic disease, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

201. The method of claim 200, wherein the pancreatic disease is acute pancreatitis or chronic pancreatitis.

202. A method of treating a disease, disorder or condition that is kidney disease, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

203. The method of claim 202, wherein the kidney disease is acute kidney injury or chronic kidney injury.

204. A method of treating a disease, disorder or condition that is intestinal disease, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

205. The method of claim 204, wherein the intestinal disease is Crohn's disease or Ulcerative Colitis.

206. A method of treating a disease, disorder or condition that is skin disease, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

207. The method of claim 206, wherein the skin disease is psoriasis.

208. A method of treating a disease, disorder or condition that is musculoskeletal disease, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

209. The method of claim 208, wherein the musculoskeletal disease is scleroderma.

210. A method of treating a disease, disorder or condition that is a vessel disorder, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

211. The method of claim 210, wherein the vessel disorder is giant cell arteritis.

212. A method of treating a disease, disorder or condition that is a disorder of the bones, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

213. The method of claim 212, wherein the disorder of the bones is osteoarthritis, osteoporosis or osteopetrosis disorders.

214. A method of treating a disease, disorder or condition that is eye disease, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

215. The method of claim 214, wherein the eye disease is glaucoma or macular degeneration.

216. A method of treating a disease, disorder or condition that is a disease caused by viral infection, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

217. The method of claim 216, wherein the diseases caused by viral infection is HIV or AIDS.

218. A method of treating a disease, disorder or condition that is an autoimmune disease, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

219. The method of claim 218, wherein the autoimmune disease is Rheumatoid Arthritis, Systemic Lupus Erythematosus, Autoimmune Thyroiditis, Addison's disease, or pernicious anemia.

220. A method of treating a disease, disorder or condition that is cancer or aging, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

221. A method of treating a disease, disorder or condition that is a cancer selected from: myelodysplastic syndromes (MDS); non-small cell lung cancer, such as non-small cell lung cancer in patients carrying mutation or overexpression of NLRP3; acute lymphoblastic leukemia (ALL), such as ALL in patients resistant to glucocorticoids treatment; Langerhan's cell histiocytosis (LCH); multiple myeloma; promyelocytic leukemia; acute myeloid leukemia (AML); chronic myeloid leukemia (CML); gastric cancer; and lung cancer metastasis, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-183 or a pharmaceutical composition as claimed in claim 184.

222. The method of claim 221, wherein the cancer is MDS.

223. The method of claim 221, wherein the cancer is non-small lung cancer.

224. The method of claim 221, wherein the cancer is acute lymphoblastic leukemia.

225. The method of claim 221, wherein the cancer is LCH.

226. The method of claim 221, wherein the cancer is multiple myeloma.

227. The method of claim 221, wherein the cancer is promyelocytic leukemia.

228. The method of claim 221, wherein the cancer is acute myeloid leukemia (AML).

229. The method of claim 221, wherein the cancer is chronic myeloid leukemia (CML).

230. The method of claim 221, wherein the cancer is gastric cancer.

231. The method of claim 221, wherein the cancer is lung cancer metastasis.

232. The method of any one of claims 190-231, further comprising administering a therapeutically effective amount of an anti-TNFα agent to the subject.

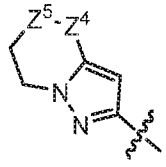
233. The method of claim 232, wherein the NLRP3 antagonist is administered to the subject prior to administration of the anti-TNFα agent to the subject.

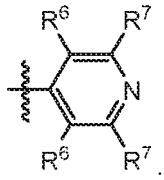
234. The method of claim 232, wherein the anti-TNFα agent is administered to the subject prior to the administration of the NLRP3 antagonist to the subject.

235. The method of claim 232, wherein the NLRP3 antagonist and the anti-TNFα agent are administered to the subject at substantially the same time.

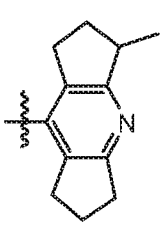
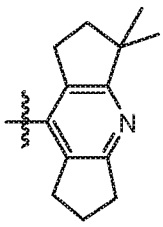
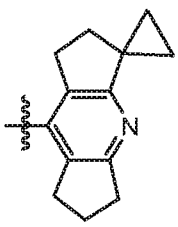
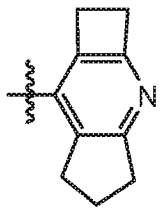
236. The method of claim 232, wherein the NLRP3 antagonist and the anti-TNFα agent are formulated together in a single dosage form.

237. The compound of claim 1, wherein

A is  , wherein Z^4 is selected from the group consisting of $–CH_2-$, –C(O)-, and NH; Z^5 is selected from the group consisting of O, NH, N-CH_3, and $–CH_2-$; and

the B is  .

238. The compoud of claim 237, wherein the B is selected from the group consisting of:

 ,  ,  ,  .

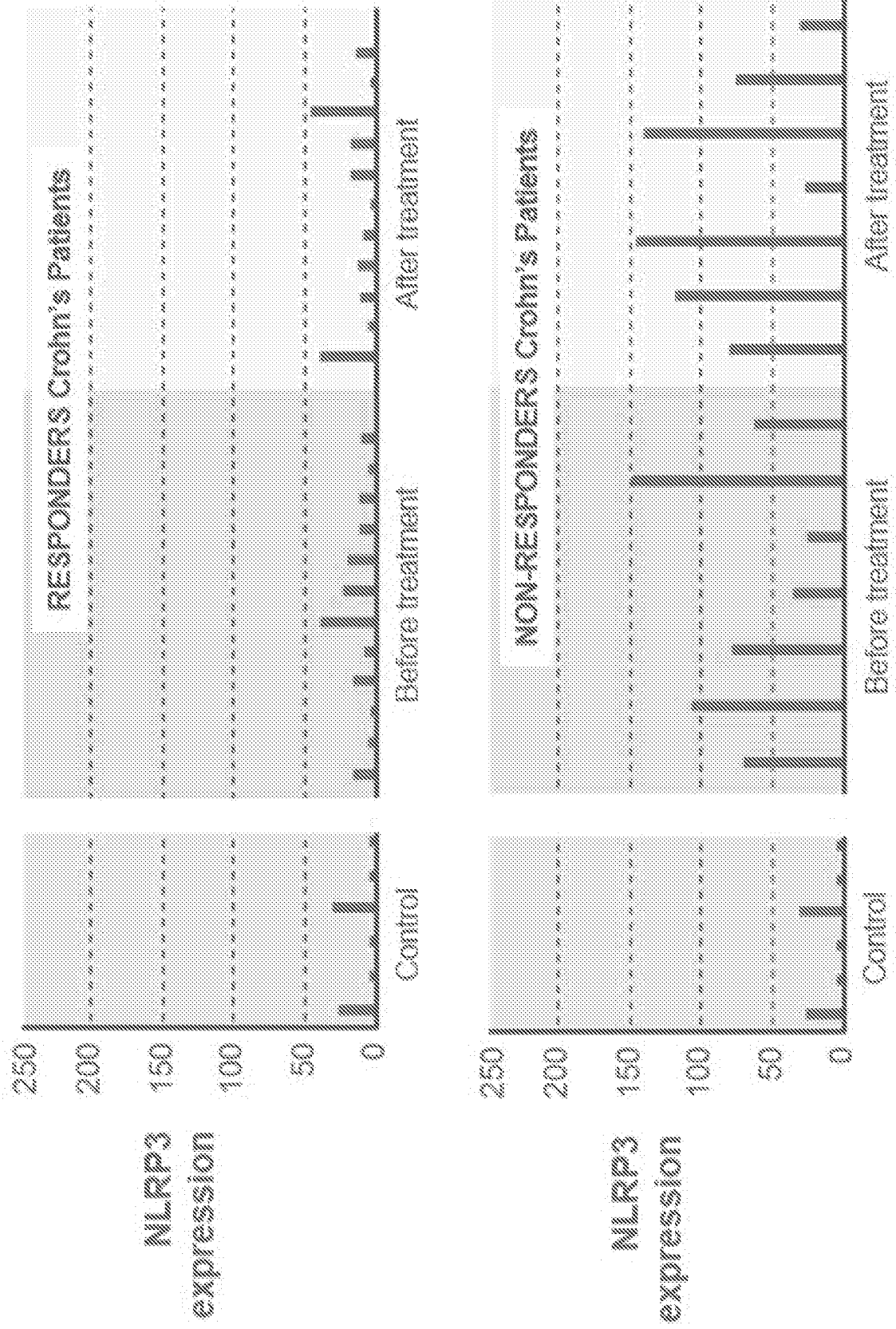

RESPONDERS Crohn's Patients
NON-RESPONDERS Crohn's Patients
NLRP3 expression
250
200
150
100
50
0
Control
Before treatment
After treatment

FIGURE 1

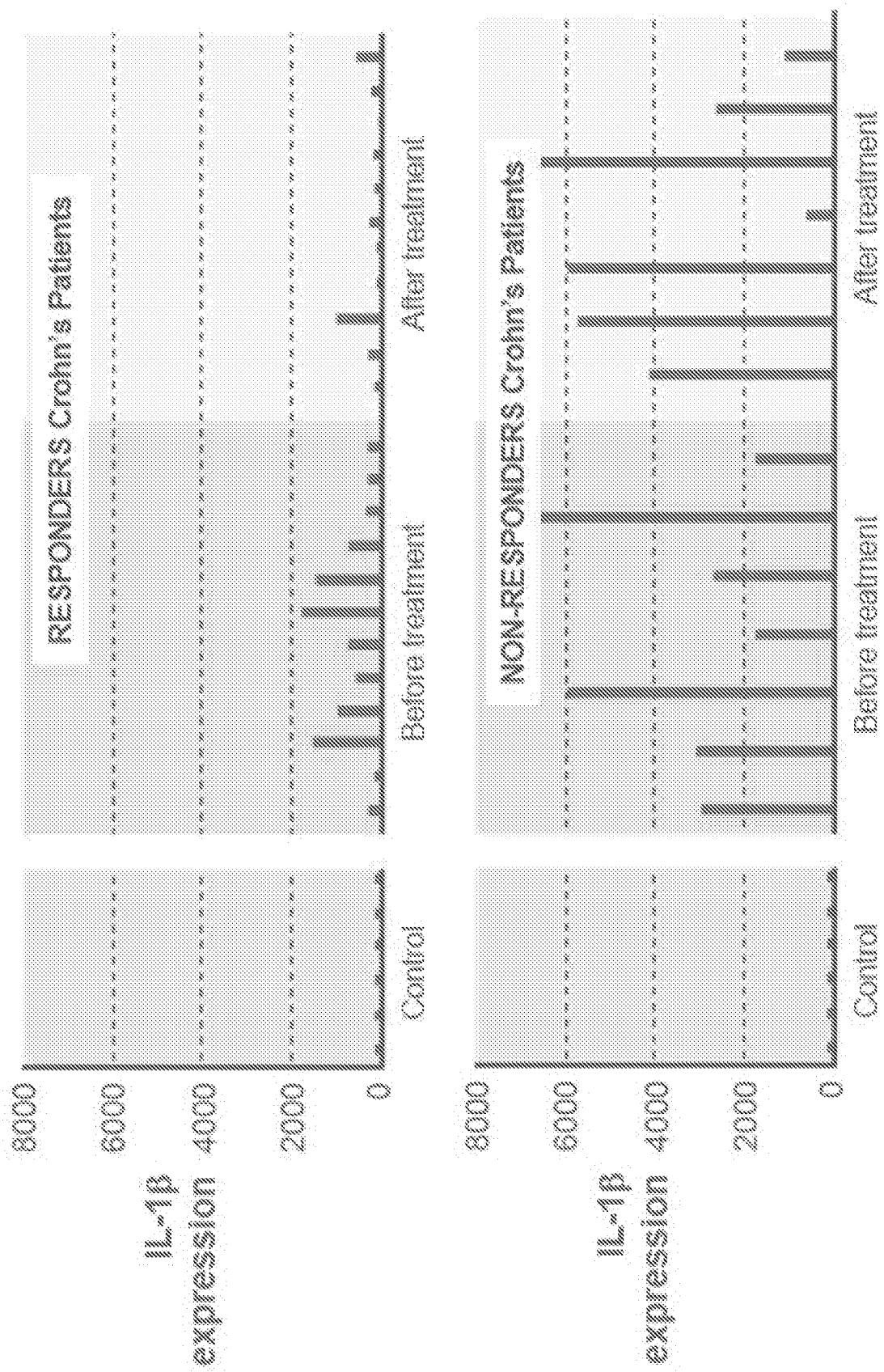

RESPONDERS Crohn's Patients
NON-RESPONDERS Crohn's Patients
IL-1β expression
8000
6000
4000
2000
0
Control
Before treatment
After treatment

FIGURE 2

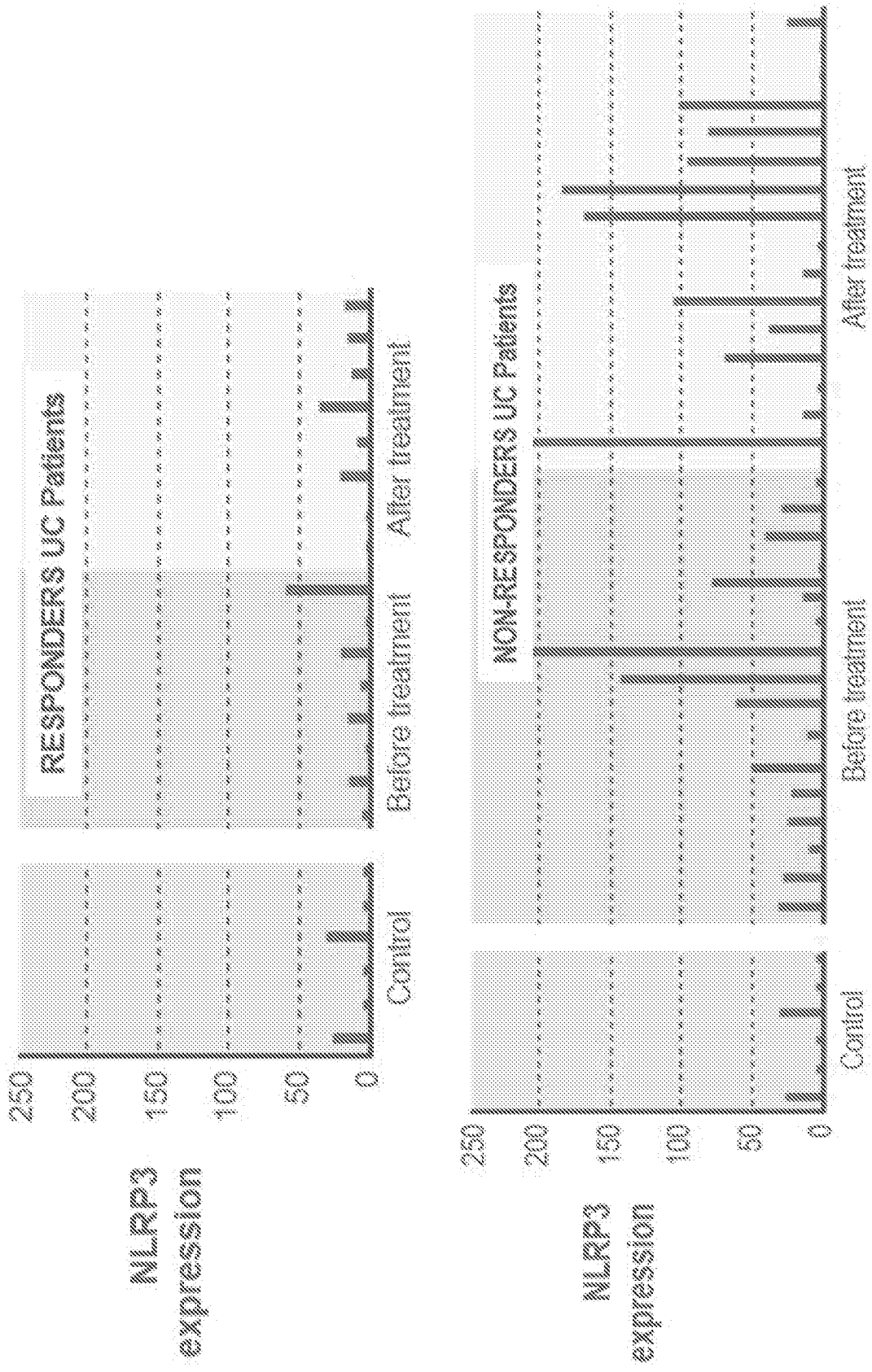

RESPONDERS UC Patients
NON-RESPONDERS UC Patients
NLRP3 expression
250
200
150
100
50
0
Control
Before treatment
After treatment

FIGURE 3

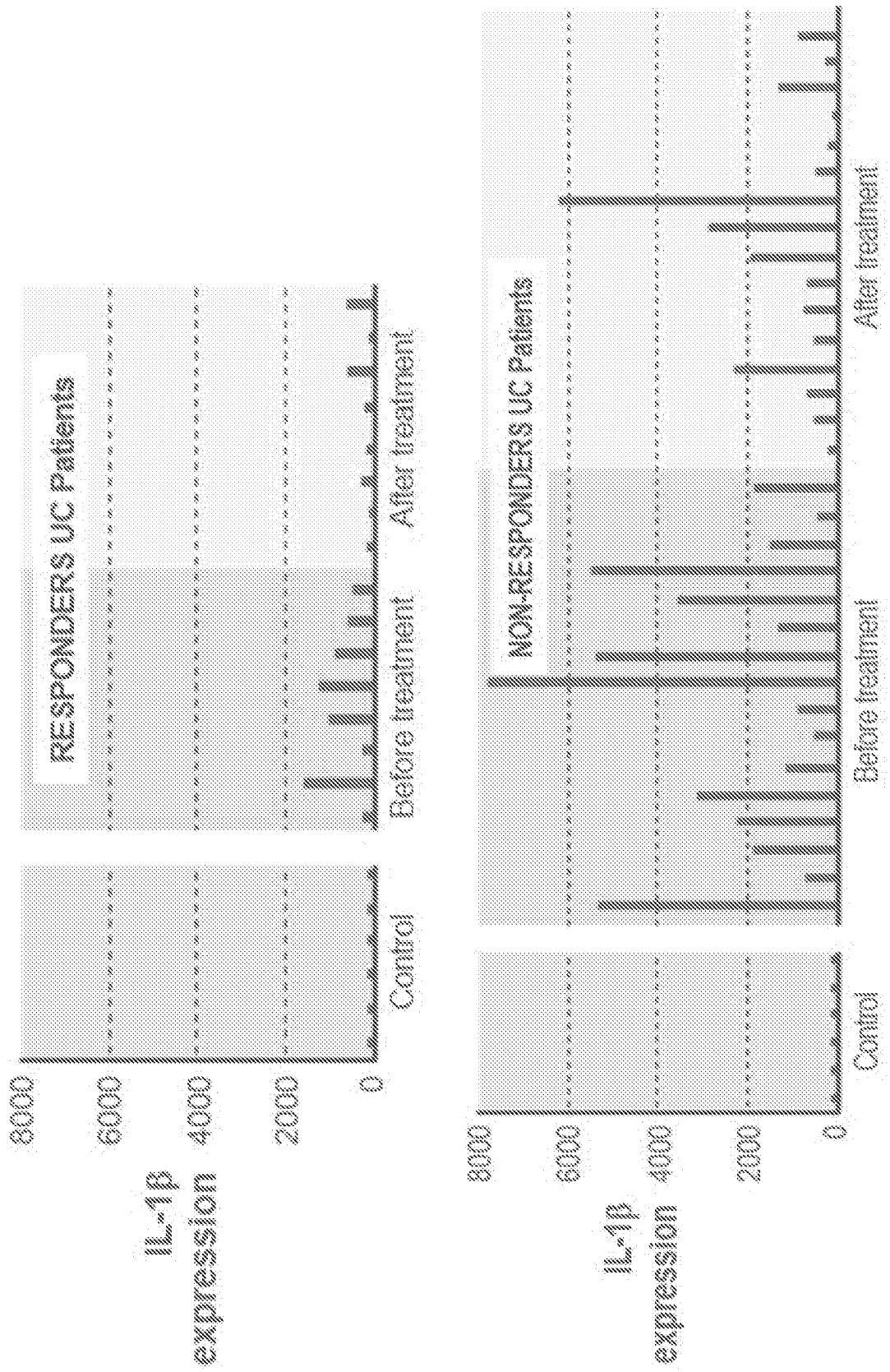

RESPONDERS UC Patients
NON-RESPONDERS UC Patients
IL-1β expression
8000
6000
4000
2000
0
Control
Before treatment
After treatment

FIGURE 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/057682

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D207/333 C07D231/18 C07D277/36 C07D277/60 C07D307/64
C07D333/50 C07D401/04 C07D405/04 C07D471/04 C07D487/04
C07D495/04 C07D498/04 C07D498/20 C07D513/04 A61P1/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/131098 A1 (UNIV QUEENSLAND [AU] ET AL.) 25 August 2016 (2016-08-25) cited in the application the whole document in particular page 255 and claim 36 -----	1-238
X	WO 2018/136890 A1 (JECURE THERAPEUTICS INC [US]) 26 July 2018 (2018-07-26) cited in the application the whole document -----	1-238
X	WO 2017/184624 A1 (IFM THERAPEUTICS INC [US]) 26 October 2017 (2017-10-26) the whole document in particular compounds 176, 178, 199, 200, 202, 210, 215, 216, 223, 224, 225 and 232 -----	1-238

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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
24 February 2020	06/03/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Papathoma, Sofia

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/057682

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/015445 A1 (NODTHERA LTD [GB]) 25 January 2018 (2018-01-25) cited in the application the whole document in particular compounds 10 an 1R -----	1-238
X,P	WO 2019/034690 A1 (INFLAZOME LTD [IE]) 21 February 2019 (2019-02-21) cited in the application the whole document in particular examples 5, 10 and 80 and claim 21 -----	1-238

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/057682

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

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

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

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

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

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

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

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

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

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

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

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/057682

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016131098 A1	25-08-2016	AU 2016222278 A1	10-08-2017
		BR 112017017610 A2	08-05-2018
		CA 2975192 A1	25-08-2016
		CL 2017002097 A1	27-04-2018
		CL 2019000060 A1	03-05-2019
		CN 107428696 A	01-12-2017
		EP 3259253 A1	27-12-2017
		EP 3578547 A1	11-12-2019
		JP 2018510207 A	12-04-2018
		KR 20170109678 A	29-09-2017
		PE 20180160 A1	18-01-2018
		RU 2017128287 A	18-03-2019
		SG 11201706664Q A	28-09-2017
		US 2018044287 A1	15-02-2018
		US 2019359564 A1	28-11-2019
		WO 2016131098 A1	25-08-2016
WO 2018136890 A1	26-07-2018	AU 2018210525 A1	25-07-2019
		CA 3047336 A1	26-07-2018
		CL 2019001988 A1	29-11-2019
		CN 110366549 A	22-10-2019
		CO 2019009036 A2	17-01-2020
		CR 20190356 A	20-11-2019
		EP 3571187 A1	27-11-2019
		KR 20190111068 A	01-10-2019
		PH 12019501611 A1	04-11-2019
		SG 11201906373V A	27-08-2019
		TW 201837021 A	16-10-2018
		US 2019337965 A1	07-11-2019
		WO 2018136890 A1	26-07-2018
WO 2017184624 A1	26-10-2017	AU 2017254522 A1	01-11-2018
		AU 2017254523 A1	01-11-2018
		EP 3445756 A1	27-02-2019
		EP 3445757 A1	27-02-2019
		JP 2019515952 A	13-06-2019
		JP 2019518071 A	27-06-2019
		US 2019119203 A1	25-04-2019
		US 2019119224 A1	25-04-2019
		WO 2017184623 A1	26-10-2017
		WO 2017184624 A1	26-10-2017
WO 2018015445 A1	25-01-2018	EP 3272739 A1	24-01-2018
		WO 2018015445 A1	25-01-2018
WO 2019034690 A1	21-02-2019	AU 2018317798 A1	13-02-2020
		CA 3071150 A1	21-02-2019
		TW 201910316 A	16-03-2019
		UY 37847 A	29-03-2019
		WO 2019034690 A1	21-02-2019