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(71) Applicant: **FGH BIOTECH INC.** [US/US]; 414 Thamer Circle, Houston, Texas 77024-6918 (US).

(72) Inventor: **ABU-ELHEIGA, Lutfi**; c/o FGH Biotech, Inc., 414 Thamer Circle, Houston, Texas 77024-6918 (US).

(74) Agent: **NOSON, Kevin** et al.; Squire Patton Boggs (US) LLP, 275 Battery Street, Suite 2600, San Francisco, California 94111 (US).

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(54) Title: METHODS OF USING INHIBITORS OF SREBP IN COMBINATION WITH NICLOSAMIDE AND ANALOGS THEREOF

(57) Abstract: Provided herein are methods of using SREBP inhibitors in combination with niclosamide and analogs thereof in the treatment of treating a condition, disease, or disorder associated with activation (in some embodiments abnormal activation) of the SREBP pathway and/or of one or more target genes that are essential for proliferation, including cancer and nonalcoholic fatty liver disease (NAFLD).

METHODS OF USING INHIBITORS OF SREBP IN COMBINATION WITH NICLOSAMIDE AND ANALOGS THEREOF

FIELD

[0001] Provided herein are methods of using SREBP inhibitors in combination with niclosamide and analogs thereof for treating a condition, disease, or disorder associated with activation of the SREBP pathway and/or one or more target genes that are essential for proliferation, including cancer and nonalcoholic fatty liver disease (NAFLD).

BACKGROUND

[0002] Niclosamide has been used in the clinic for the treatment of intestinal parasite infections, and recent studies identified niclosamide as a potential anticancer agent (Li *et al. Cancer Lett*. **2014**, *349(1)*, 8–14). It has been reported that niclosamide inhibits several important pathways involved in a number of cancers, including the Wnt/β-catenin, mTORC1, STAT3, NF-κB and Notch signaling pathways (*id.*). It also induces cell cycle arrest, growth inhibition, and apoptosis, by targeting mitochondria in cancer cells (*id.*). A number of studies showed niclosamide has anticancer activities in *in vitro* models (human breast cancer: see Lu *et al. PloS one* **2011,** 6:e29290; Balgi *et al. PloS one* **2009,** 4:e7124; Kim *et al. Cell Signal* **2013,** *25,* 961–969; Wang *et al. PloS one* **2013,** 8:e74538; prostate cancer: see Lu *et al. PloS one* **2011**, 6:e29290; Ren *et al. ACS Med Chem Lett.* **2010,** *1,* 454–459; colon cancer: see Osada *et al. Cancer Res.* **2011,** *71*, 4172– 4182; Sack *et al. J Natl Cancer Inst.* **2011,** *103*, 1018–1036). Liu *et al.* reports in vivo animal studies, using castration resistant prostate cancer (CPRC) mouse models, which show that niclosamide sensitizes the tumor for abiraterone, by inhibiting ARV-7 (Liu *et al. Oncotarget* **2016,** *7(22),* 32210-32220). Other *in vivo* studies show that niclosamide inhibited the growth of colorectal cancer cells in NOD/SCID mice by down-regulating Dvl2 and 3-catenin expression (Osada *et al.*). Wang *et al.* report that niclosamide was able to inhibit the tumor growth of breast cancer stem-like cell subpopulations *in vivo*. Other studies show that niclosamide significantly reduced liver metastasis formation in mice bearing xenografted intrasplenic colon tumors (Sack *et al.*). Thus, niclosamide has demonstrated anti-cancer activity.

[0003] Sterol regulatory element-binding proteins (SREBPs) are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC. SREB proteins are indirectly required for metabolic activites such as cholesterol biosynthesis and uptake, triglyceride biosynthesis, and fatty acid biosynthesis. Emerging evidence indicates that sterol regulatory element-binding protein 1 (SREBP-1), a master transcription factor that controls

lipid metabolism, is a critical link between oncogenic signaling and tumor metabolism. (Bell *et al.;* Gabitova *et al. Clin Cancer Res.* **2014,** *20(1)*, 28). Oncogenic growth signaling regulates glucose, glutamine and lipid metabolism to meet the bioenergetics and biosynthetic demands of rapidly proliferating tumor cells. (Bell *et al. Curr Pharm Des* **2014,** *20(15)*, 2619-26.) It has been shown that, contrary to normal cells, various tumor cells are very active in *de novo* fatty acid biosynthesis, irrespective of the extracellular lipids, and that *de novo* fatty acids accounted for all fatty acid esterification in the tumor cells (Medes *et al. Cancer Research* **1953**, *13*, 27; Menendez *et al. Nat. Rev. Cancer* **2007**, *7*, 763) Another major hallmark of tumor cells is increased metabolic activities such as glucose consumption, protein and nucleic acid synthesis (Menendex *et al.*).

[0004] Pharmacological and RNAi knockdown approaches against acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) have been reported (Brusselmans *et al. Cancer Research* **2005**, *65*, 6719-6725; Kuhajda *et al. Proceedings of the National Academy of Sciences of the United States of America* **2000**, *97*, 3450-3454; Menendez, *et al. Int J Cancer* **2005**, *115*, 19-35). These studies showed, that inhibiting these enzymes, induced growth inhibition and an apoptotic effect against breast and prostate cancer cells. In this regard, SREBP-1 and 2 as master regulators of lipid biosynthesis play a major role in tumor growth. In support of the role of SREBP in cancer, several studies have shown that inhibition of SREBP activation using RNAi and a small molecule resulted in significant growth inhibition. On the other hand it was recently reported that glucose-mediated N-glycolsylation of SCAP resulted in its stabilization and activation of SREBP-1 to promote tumor growth in glioblastoma (Cheng *et al.* 2015). These findings suggest that targeting the SCAP/SREBP complex is a promising approach for treating cancer.

[0005] SREBP inhibitors such as fatostatin and fatostatin derivatives (e.g. FGH10019) bind specifically to SCAP at a distinct site from the sterol-binding domain. As a result of FGH10019 action, SREBPs are retained in the ER, blocking their transportation to the Golgi apparatus, where they are processed by proteases to produce the nuclear active form bHLH. Recently several studies showed that fatostatin derivatives inhibited cell growth in cells and animal models for breast and prostate cancer, thus is validating the potential use of these compounds to treat cancer (Li *et al. Mol. Cancer. Ther.* **2014**, *13(4)*, 855; Li *et al. Oncotarget.* **2015**, *6(38)*, 41018). Thus, SREBP inhibitors are useful as anti-cancer agents.

[0006] SREBPs are also involved in the pathogenesis of NAFLD (Moslehi *et al. J of Clin and Translat Hepatol* **2018,** *6*, 332–3382018) which is a condition that is caused by excess of fat accumulation in the liver of patients without a history of alcohol abuse. NAFLD is the

liver manifestation of metabolic syndrome and has been increasing worldwide in line with the epidemic increase in obesity, type 2 diabetes, and dyslipidemia (Takahashi Y, Fukusato T. Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol.* 2014 Nov 14;20(42):15539-48). NAFLD can be a simple steatosis (triglyceride accumulation in liver) due to shift in *de novo* fatty acid metabolism to net lipogenesis from lipolysis, or the more serious nonalcoholic steatohepatitis (NASH). NASH is considered the major chronic liver disease, with serious damage to liver such as interlobular inflammation, hepatocellular ballooning and fibrosis and it may lead to liver cirrhosis and hepatocellular carcinoma (Schreuder *et al. World J Gastroenterol* **2008,** *14(16),* 2474). Currently, treatment for NASH is limited to substantial weight loss by methods such as bariatric surgery, insulin sensitizing agents and Vitamin E supplements, in addition to life style modification by diet and exercise.

[0007] There still remains a need for treatments of diseases such as cancer and NAFLD.

SUMMARY OF THE INVENTION

[0008] Provided herein are methods of using SREBP inhibitors in combination with niclosamide and analogs thereof for treating a condition, disease, or disorder associated with activation (in some embodiments abnormal activation) of the SREBP pathway and/or one or more target genes that are essential for proliferation, including cancer and nonalcoholic fatty liver disease (NAFLD).

[0009] In one aspect, provided herein is a method of treating a condition, disease, or disorder comprising a) administering a therapeutically effective amount of an SREBP inhibitor or a pharmaceutically acceptable salt thereof, in combination with niclosamide or a niclosamide analog; or b) administering a therapeutically effective amount of a composition comprising an SREBP inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier thereof; in combination with niclosamide or a niclosamide analog or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier thereof.

[0010] In another aspect, provided herein is a method of treating a condition, disease, or disorder associated with activation of the SREBP pathway and/or of one or more target genes that are essential for proliferation comprising a) administering a therapeutically effective amount of an SREBP inhibitor or a pharmaceutically acceptable salt thereof, in combination with niclosamide or a niclosamide analog; or b) administering a therapeutically effective amount of a composition comprising an SREBP inhibitor, or a pharmaceutically acceptable

salt thereof, and a pharmaceutically acceptable carrier thereof; in combination with niclosamide or a niclosamide analog or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier thereof. In some or any embodiments, the activation is abnormal activation. In some or any embodiments, the one or more target gene(s) are selected from ACC, FAS, SCD1, and others considered as targets for therapy of cancer diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1 provides representative western blots of androgen receptor (AR) and androgen receptor variant 7 (AR-V7) extracts from control and treated 22Rv1 cancer cells, according to Biological Example 4.

[0012] Figure 2 and 3 provide relative mRNA levels in 22rv1 cells, as obtained using the procedure in Example 5.

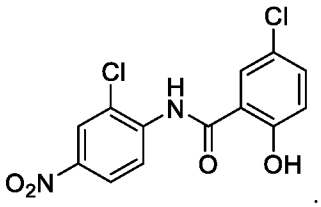
DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0013] In some or any embodiments, the condition, disease, or disorder is cancer or NAFLD. In some or any embodiments, the condition, disease, or disorder is NAFLD. In some or any embodiments, the condition, disease, or disorder is cancer. In some or any embodiments, the cancer is selected from the group consisting of hepatocellular carcinoma – not amenable to surgical or locoregional therapy, glioblastoma multiforme, prostate cancer, breast cancer, post-menopausal breast carcinoma, pancreatic adenocarcinoma, ovarian cancer, B cell lymphoma, lung cancer, a digestive and gastrointestinal cancer, gastrointestinal stromal tumor, gastrointestinal carcinoid tumor, colon cancer, rectal cancer, anal cancer, bile duct cancer, small intestine cancer, stomach (gastric) cancer, esophageal cancer, gall bladder cancer, liver cancer, pancreatic cancer, cancer of the appendix, breast cancer, ovarian cancer, renal cancer, cancer of the central nervous system, skin cancer, a lymphoma, choriocarcinoma, head and neck cancer, osteogenic sarcoma, and a blood cancer (including leukemia, acute lymphoblastic leukemia, and multiple myeloma). In some or any embodiments, the cancer is selected from the group consisting of breast cancer, prostate cancer (including castration-resistant prostate cancer), colorectal cancer, colorectal adenocarcinoma, gastric carcinoma, multiple myeloma, melanoma, hepatic adenocarcinoma, glioblastoma, and liver cancer.

[0014] In some or any embodiments, the SREBP inhibitor is in the form of a pharmaceutical composition or dosage form, as described elsewhere herein. In some or any

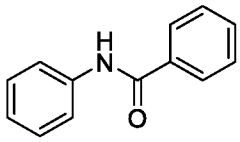
embodiments, the niclosamide or niclosamide analog is in the form of a pharmaceutical composition or dosage form, as described elsewhere herein.

[0015] Niclosamide has the following structure:



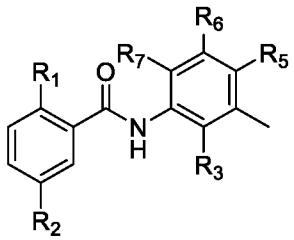
[0016] In some or any embodiments, the niclosamide or niclosamide analog is niclosamide.

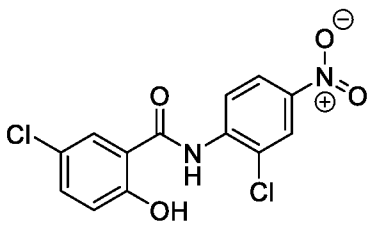
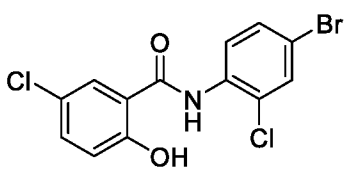
[0017] In some embodiments, niclosamide analog, as used herein, means a compound comprising the following structure:

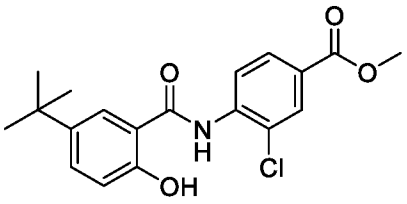
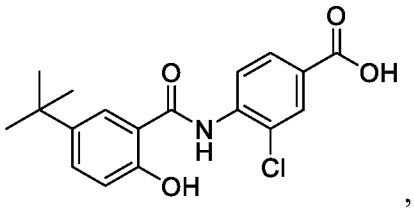
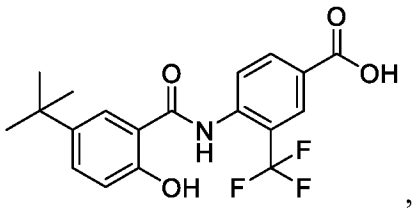
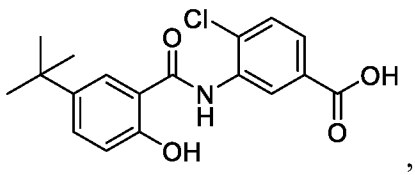
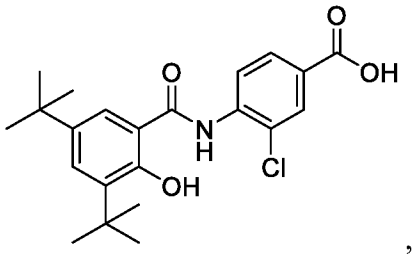
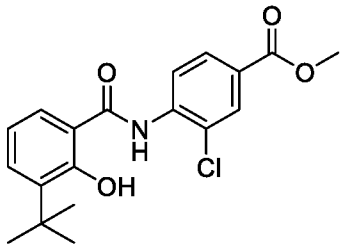
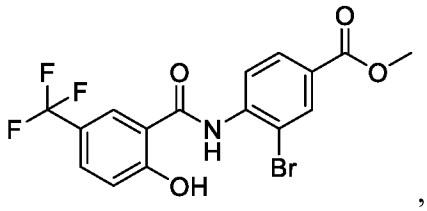
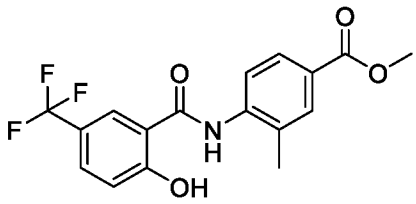
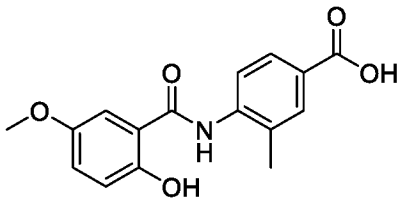


where each of the phenyl groups is independently optionally substituted. In some or any embodiments, the niclosamide analog has similar or improved anti-cancer activity to that of niclosamide. In some or any embodiments, the niclosamide analog has similar anti-cancer activity to that of niclosamide. In some or any embodiments, the niclosamide analog has improved anti-cancer activity to that of niclosamide.

[0018] In some or any embodiments, the niclosamide or niclosamide analog is a niclosamide analog. In some or any embodiments, the niclosamide analog is



where R_1 is OH, R_2 is Cl, R_3 is H, R_4 is H, R_5 is CF_3, R_6 is H, and R_7 is H, or where R_1 is $OONH_2$, R_2 is Cl, R_3 is Cl, R_4 is H, R_5 is NO_2, R_6 is H, and R_7 is H (Arend *et al.* Oncotarget **2016**, *7(52)*, 86803–86815); or is , ,

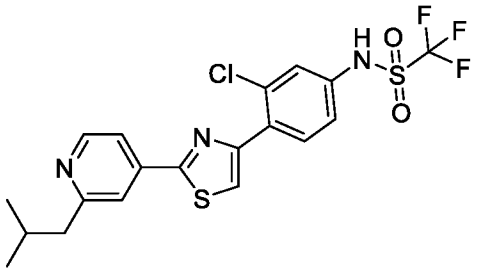

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(PLOS ONE, October 25, 2018, at https://doi.org/10.1371/journal.pone.0204605).

[0019] Any of the embodiments for niclosamide and niclosamide analogs can be combined with any of the SREBP inhibitors selected from Genus A, Genus B, Genus C, SREBP inhibitors disclosed in US 2015-0065519, and SREBP inhibitors disclosed in US 2018-0051013, and additional embodiments of compounds of Genus A, Genus B, and Genus C as provided herein.

[0020] In some or any embodiments, the SREBP inhibitor is selected from Genus A, Genus B, and Genus C, and additional embodiments of compounds of Genus A, Genus B, and Genus C, as provided herein.

[0021] In some or any embodiments, the SREBP inhibitor is selected from SREBP inhibitors disclosed in US 2015-0065519 and US 2018-0051013, each of which are incorporated herein by reference in their entireties. In some or any embodiments, the SREBP inhibitor is selected from SREBP inhibitors disclosed in US 2015-0065519. In some or any embodiments, the SREBP inhibitor is selected from SREBP inhibitors disclosed in US 2018-

0051013. In some or any embodiments, the SREBP inhibitor is



, or a pharmaceutically acceptable salt thereof.

[0022] "Compound" as used throughout is an SREBP inhibitor, unless specified otherwise, or unless clear from the context in which the term is used that a different meaning is intended.

[0023] The use of the term "in combination" does not restrict the order in which the therapies are administered to a subject with a disorder. A first therapy administering the SREBP inhibitor (in some embodiments, as described herein) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of the niclosamide or niclosamide analog (in some embodiments, as described herein) to a subject with a disorder.

[0024] As used herein, the term "synergistic" includes a combination of an SREBP inhibitor (in some embodiments, as described herein) and the niclosamide or niclosamide analog (in some embodiments, as described herein) which has been or is currently being used to prevent, manage, or treat a disorder, which is more effective than the additive effects of the therapies. A synergistic effect of a combination of therapies permits the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject with a disorder. The ability to utilize lower dosages and/or to administer said therapy less frequently reduces the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention or treatment of a disorder). In addition, a synergistic effect can result in improved efficacy of agents in the prevention or treatment of a disorder. Finally, a synergistic effect of a combination of therapies may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

[0025] In the combination therapy provided, effective dosages of the SREBP inhibitor (in some embodiments, as described herein) and the niclosamide or niclosamide analog (in some embodiments, as described herein) are administered together, whereas in alternation or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. The dosages given will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition, disease, or disorder, associated with activation (in some embodiments abnormal activation) of the SREBP pathway and/or of one or more target genes that are essential for proliferation, to be treated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

[0026] "Patient" or "subject" includes humans and other animals, particularly mammals, and other organisms. Thus, the methods are applicable to both human therapy and veterinary applications. In some embodiments, the patient is a mammal, and in other embodiments, the patient is human.

[0027] A "pharmaceutically acceptable salt" of a compound, niclosamide, or niclosamide analog means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent, neutral compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference, or S. M. Berge *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.* **1977**;*66*, 1-19 which is also incorporated herein by reference. It is also understood that the compound can have one or more pharmaceutically acceptable salts associated with it.

[0028] Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, 3-(4-hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic

acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0029] Examples of a pharmaceutically acceptable base addition salts include those formed when an acidic proton present in the parent, neutral compound is replaced by a metal ion, such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum, as salts, and the like. Preferable salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, tromethamine, *N*-methylglucamine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

[0030] The term "substantially free of" or "substantially in the absence of" stereoisomers with respect to a composition refers to a composition that includes at least 85 or 90% by weight, in certain embodiments 95%, 98 %, 99%, or 100% by weight, of a designated stereoisomer of a compound in the composition. In certain embodiments, in the methods and compounds provided herein, the compounds are substantially free of stereoisomers.

[0031] Similarly, the term "isolated" with respect to a composition refers to a composition that includes at least 85%, 90%, 95%, 98%, 99% to 100% by weight, of a specified compound, the remainder comprising other chemical species or stereoisomers.

[0032] The term "solvate," as used herein, and unless otherwise specified, refers to a compound provided herein, or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. In one embodiment, where the solvent is water, the solvate is a hydrate.

[0033] The term "isotopic composition," as used herein, and unless otherwise specified, refers to the amount of each isotope present for a given atom, and "natural isotopic composition" refers to the naturally occurring isotopic composition or abundance for a given

atom. Atoms containing their natural isotopic composition may also be referred to herein as "non-enriched" atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as "H" or "hydrogen," the position is understood to have hydrogen at its natural isotopic composition.

[0034] The term "isotopic enrichment," as used herein, and unless otherwise specified, refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the place of that atom's natural isotopic abundance. In certain embodiments, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The isotopic enrichment of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0035] The term "isotopically enriched," as used herein, and unless otherwise specified, refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom.

[0036] As used herein, "alkyl," "cycloalkyl," "aryl," "alkoxy," "heterocycloalkyl," "heterocyclic," and "heteroaryl," groups optionally comprise deuterium at one or more positions where hydrogen atoms are present, and wherein the deuterium composition of the atom or atoms is other than the natural isotopic composition.

[0037] Also as used herein, "alkyl," "cycloalkyl," "aryl," "alkoxy," "heterocycloalkyl," "heterocyclic," and "heteroaryl," groups optionally comprise carbon-13 at an amount other than the natural isotopic composition.

[0038] As used herein, the terms "subject" and "patient" are used interchangeably. The terms "subject" and "subjects" refer to an animal, such as a mammal including a non-primate (*e.g.*, a cow, pig, horse, cat, dog, rat, and mouse) and a primate (*e.g.*, a monkey such as a cynomolgous monkey, a chimpanzee, and a human), and in certain embodiments, a human. In certain embodiments, the subject is a farm animal (*e.g.*, a horse, a cow, a pig, etc.) or a pet (*e.g.*, a dog or a cat). In certain embodiments, the subject is a human.

[0039] "Administration" and variants thereof (e.g., in some embodiments, "administering" a compound, niclosamide, or niclosamide analog) means introducing the

compound or a prodrug thereof, niclosamide, or niclosamide analog into systemic circulation of the animal in need of treatment. When a compound or prodrug thereof, as described herein, is provided in combination with niclosamide, or niclosamide analog, "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and the niclosamide or niclosamide analog.

[0040] "Therapeutically effective amount" is an amount of a compound, composition, niclosamide, or niclosamide analog that when administered to a patient, is sufficient to effect such treatment for the condition, disease, or disorder, e.g., to ameliorate a symptom of the disease. The amount of a compound, niclosamide, or niclosamide analog which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art in view of their knowledge and this disclosure.

[0041] As used herein, the terms "therapeutic agent" and "therapeutic agents" refer to any agent(s) which can be used in the treatment or prevention of a disorder or one or more symptoms thereof. In certain embodiments, the term "therapeutic agent" includes a compound, niclosamide, or niclosamide analog provided herein. In certain embodiments, a therapeutic agent is an agent that is known to be useful for, or has been or is currently being used for the treatment or prevention of a disorder or one or more symptoms thereof.

[0042] "Treating" or "treatment" of a disease, disorder, or syndrome, as used herein, includes (i) preventing the disease, disorder, or syndrome from occurring in a human, i.e., causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome, but does not yet experience or display symptoms of the disease, disorder, or syndrome; (ii) inhibiting the disease, disorder, or syndrome, *i.e.*, arresting its development; and (iii) relieving the disease, disorder, or syndrome, *e.g.*, relieving or reducing a symptom thereof, and/or causing regression of the disease, disorder, or syndrome. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition, disease, or disorder may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art. "Treating" or "treatment" of any condition, disease, or disorder refers, in certain embodiments, to ameliorating a condition, disease, or disorder that exists in a subject. In another embodiment, "treating" or "treatment" includes ameliorating at least one physical parameter, which may be indiscernible by the subject. In yet another embodiment, "treating"

or "treatment" includes modulating the condition, disease, or disorder, either physically (*e.g.,* stabilization of a discernible symptom) or physiologically (*e.g.,* stabilization of a physical parameter) or both. In yet another embodiment, "treating" or "treatment" includes delaying the onset of the condition, disease, or disorder.

[0043] As used herein, the terms "prophylactic agent" and "prophylactic agents" refer to any agent(s) which can be used in the prevention of a condition, disease, or disorder, or one or more symptoms thereof. In certain embodiments, the term "prophylactic agent" includes a compound, niclosamide, or niclosamide analog provided herein. In certain other embodiments, the term "prophylactic agent" does not refer to a compound provided herein. In certain embodiments, a prophylactic agent can be an agent that is known to be useful for, or has been or is currently being used to prevent or impede the onset, development, progression, and/or severity of a condition, disease, or disorder.

[0044] As used herein, the phrase "prophylactically effective amount" refers to the amount of a therapy (*e.g.*, prophylactic agent) which is sufficient to result in the prevention or reduction of the development, recurrence, or onset of one or more symptoms associated with a condition, disease, or disorder, or to enhance or improve the prophylactic effect(s) of another therapy (*e.g.*, another prophylactic agent).

Optically Active Compounds

[0045] It is appreciated that compounds provided herein may have one or more chiral centers and may exist in and be isolated in optically active and racemic forms. It is to be understood that any racemic, optically-active, diastereomeric, tautomeric, or stereoisomeric form, or mixtures thereof, of a compound provided herein, which possess the useful properties described herein is within the scope of this disclosure. It is well known in the art how to prepare optically active forms (e.g., in certain embodiments, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

[0046] In certain embodiments, methods to obtain optically active materials are known in the art, and include at least the following:

i) physical separation of crystals - a technique whereby macroscopic crystals of the individual stereoisomers are manually separated. This technique can be used if crystals of the separate stereoisomers exist, *i.e.*, the material is a conglomerate, and the crystals are visually distinct;

ii) simultaneous crystallization - a technique whereby the individual stereoisomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;

iii) enzymatic resolutions - a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the stereoisomers with an enzyme;

iv) enzymatic asymmetric synthesis - a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain a stereoisomerically pure or enriched synthetic precursor of the desired stereoisomer;

v) chemical asymmetric synthesis - a synthetic technique whereby the desired stereoisomer is synthesized from an achiral precursor under conditions that produce asymmetry (*i.e.*, chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;

vi) diastereomer separations - a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary is later removed to obtain the desired enantiomer;

vii) first- and second-order asymmetric transformations - a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

viii) kinetic resolutions - this technique refers to the achievement of partial or complete resolution of a racemate (or further resolution of a partially resolved compound) by virtue of unequal reaction rates of the stereoisomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

ix) stereospecific synthesis from non-racemic precursors - a synthetic technique whereby the desired stereoisomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

x) chiral liquid chromatography - a technique whereby the stereoisomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a

stationary phase. The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

xi) chiral gas chromatography - a technique whereby the racemate is volatilized and stereoisomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

xii) extraction with chiral solvents - a technique whereby the stereoisomers are separated by virtue of preferential dissolution of one stereoisomer into a particular chiral solvent; and

xiii) transport across chiral membranes - a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic or chiral nature of the membrane which allows only one stereoisomer of the racemate to pass through.

Isotopically Enriched Compounds

[0047] Also provided herein are isotopically enriched compounds, including but not limited to isotopically enriched di-substituted pyrazoles.

[0048] Isotopic enrichment (in certain embodiments, deuteration) of pharmaceuticals to improve pharmacokinetics ("PK"), pharmacodynamics ("PD"), and toxicity profiles, has been demonstrated previously with some classes of drugs. See, for example, Lijinsky *et al.* Food Cosmet. Toxicol., 20: 393 (1982); Lijinsky *et al.* J. Nat. Cancer Inst., 69: 1127 (1982); Mangold *et al.* Mutation Res. 308: 33 (1994); Gordon *et al.* Drug Metab. Dispos., 15: 589 (1987); Zello *et. al.* Metabolism, 43: 487 (1994); Gately *et. al.* J. Nucl. Med., 27: 388 (1986); Wade D, Chem. Biol. Interact. 117: 191 (1999).

[0049] Isotopic enrichment of a drug can be used, in certain embodiments, to (1) reduce or eliminate unwanted metabolites, (2) increase the half-life of the parent drug, (3) decrease the number of doses needed to achieve a desired effect, (4) decrease the amount of a dose necessary to achieve a desired effect, (5) increase the formation of active metabolites, if any are formed, and/or (6) decrease the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for combination therapy, whether the combination therapy is intentional or not.

[0050] Replacement of an atom for one of its isotopes often will result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect ("KIE"). For example, if a C–H bond is broken during a rate-determining step in a chemical

reaction (i.e., the step with the highest transition state energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect ("DKIE"). See, *e.g.,* Foster *et al.* Adv. Drug Res., vol. 14, pp. 1-36 (1985); Kushner *et al.* Can. J. Physiol. Pharmacol., vol. 77, pp. 79-88 (1999).

[0051] The magnitude of the DKIE can be expressed as the ratio between the rates of a given reaction in which a C–H bond is broken, and the same reaction where deuterium is substituted for hydrogen. The DKIE can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. High DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small mass of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. Because deuterium has more mass than hydrogen, it statistically has a much lower probability of undergoing this phenomenon.

[0052] Tritium ("T") is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators, and radiopharmaceuticals. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T_2O. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level. Substitution of tritium ("T") for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects. Similarly, substitution of isotopes for other elements, including, but not limited to, ^{13}C or ^{14}C for carbon, ^{33}S, ^{34}S, or ^{36}S for sulfur, ^{15}N for nitrogen, and ^{17}O or ^{18}O for oxygen, may lead to a similar kinetic isotope effect.

[0053] For example, the DKIE was used to decrease the hepatotoxicity of halothane by presumably limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example, deuterium incorporation can lead to metabolic switching. The concept of metabolic switching asserts that xenogens, when sequestered by Phase I enzymes, may bind transiently and re-bind in a variety of conformations prior to the chemical reaction (e.g., oxidation). This hypothesis is supported by the relatively vast size of binding pockets in many Phase I enzymes and the

promiscuous nature of many metabolic reactions. Metabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity.

[0054] The animal body expresses a variety of enzymes for the purpose of eliminating foreign substances, such as therapeutic agents, from its circulation system. In certain embodiments, such enzymes include the cytochrome P450 enzymes ("CYPs"), esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C–H) bond to either a carbon-oxygen (C–O) or carbon-carbon (C–C) pi-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For many drugs, such oxidations are rapid. These drugs therefore often require the administration of multiple or high daily doses.

[0055] Therefore, isotopic enrichment at certain positions of a compound provided herein will produce a detectable KIE that will affect the pharmacokinetic, pharmacologic, and/or toxicological profiles of a compound provided herein in comparison with a similar compound having a natural isotopic composition.

Pharmaceutical Compositions and Methods of Administration

[0056] The compounds provided herein can be formulated into pharmaceutical compositions using methods available in the art and those disclosed herein. Any of the compounds disclosed herein can be provided in the appropriate pharmaceutical composition and be administered by a suitable route of administration.

[0057] The methods provided herein encompass administering pharmaceutical compositions containing at least one compound as described herein, if appropriate in a salt form, either used alone or in the form of a combination with one or more compatible and pharmaceutically acceptable carriers, such as diluents or adjuvants, or with another agent for the treatment of a condition, disease, or disorder associated with activation (in some embodiments abnormal activation) of the SREBP pathway and/or of one or more target genes that are essential for proliferation.

[0058] In certain embodiments, the niclosamide or niclosamide analog can be formulated or packaged with the compound provided herein. Of course, the niclosamide or niclosamide analog will only be formulated with the compound provided herein when, according to the

judgment of those of skill in the art, such co-formulation should not interfere with the activity of either agent or the method of administration. In certain embodiments, the compound provided herein and the niclosamide or niclosamide analog are formulated separately. They can be packaged together, or packaged separately, for the convenience of the practitioner of skill in the art.

[0059] In clinical practice the active agents provided herein may be administered by any conventional route, in particular orally, parenterally, rectally, or by inhalation (*e.g.* in the form of aerosols). In certain embodiments, the compound provided herein is administered orally.

[0060] Use may be made, as solid compositions for oral administration, of tablets, pills, hard gelatin capsules, powders, or granules. In these compositions, the active product is mixed with one or more inert diluents or adjuvants, such as sucrose, lactose, or starch.

[0061] These compositions can comprise substances other than diluents, for example, a lubricant, such as magnesium stearate, or a coating intended for controlled release.

[0062] Use may be made, as liquid compositions for oral administration, of solutions which are pharmaceutically acceptable, suspensions, emulsions, syrups, and elixirs containing inert diluents, such as water or liquid paraffin. These compositions can also comprise substances other than diluents, in certain embodiments, wetting, sweetening, or flavoring products.

[0063] The compositions for parenteral administration can be emulsions or sterile solutions. Use may be made, as solvent or vehicle, of propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, or injectable organic esters, in certain embodiments, ethyl oleate. These compositions can also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing, and stabilizing agents. Sterilization can be carried out in several ways, in certain embodiments, using a bacteriological filter, by radiation or by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other injectable sterile medium.

[0064] The compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active principle, excipients such as cocoa butter, semi-synthetic glycerides, or polyethylene glycols.

[0065] The compositions can also be aerosols. For use in the form of liquid aerosols, the compositions can be stable sterile solutions or solid compositions dissolved at the time of use in apyrogenic sterile water, in saline or any other pharmaceutically acceptable vehicle. For

use in the form of dry aerosols intended to be directly inhaled, the active principle is finely divided and combined with a water-soluble solid diluent or vehicle, in certain embodiments, dextran, mannitol, or lactose.

[0066] In certain embodiments, a composition provided herein is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and single unit dosage forms provided herein comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (*e.g.*, a compound provided herein, or other prophylactic or therapeutic agent), and typically one or more pharmaceutically acceptable carriers. In a specific embodiment and in this context, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" includes a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered, and any embodiment described for "excipient." Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water can be used as a carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Examples of suitable pharmaceutical carriers are described in Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[0067] Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well-known to those skilled in the art of pharmacy, and in certain embodiments, suitable excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol, and the like. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a subject and the specific active ingredients in the dosage form. The composition or single unit dosage form, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[0068] Lactose free compositions provided herein can comprise excipients that are well known in the art and are listed, in certain embodiments, in the U.S. Pharmacopeia (USP 36–NF 31 S2). In general, lactose free compositions comprise an active ingredient, a

binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Exemplary lactose free dosage forms comprise an active ingredient, microcrystalline cellulose, pre gelatinized starch, and magnesium stearate.

[0069] Further encompassed herein are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long term storage in order to determine characteristics such as shelf life or the stability of formulations over time. See, *e.g.*, Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, New York, 1995, pp. 379 80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[0070] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine can be anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[0071] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. In certain embodiments, suitable packaging includes, but is not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

[0072] Further provided are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as “stabilizers,” include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[0073] The pharmaceutical compositions and single unit dosage forms can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations, and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such compositions and dosage forms will contain a

prophylactically or therapeutically effective amount of a prophylactic or therapeutic agent, in certain embodiments, in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the subject. The formulation should suit the mode of administration. In one embodiment, the pharmaceutical compositions or single unit dosage forms are sterile and in suitable form for administration to a subject, in certain embodiments, an animal subject, such as a mammalian subject, in certain embodiments, a human subject.

[0074] A pharmaceutical composition is formulated to be compatible with its intended route of administration. In certain embodiments, routes of administration include, but are not limited to, parenteral, *e.g.*, intravenous, intradermal, subcutaneous, intramuscular, subcutaneous, oral, buccal, sublingual, inhalation, intranasal, transdermal, topical, transmucosal, intra-tumoral, intra-synovial, and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical administration to human beings. In an embodiment, a pharmaceutical composition is formulated in accordance with routine procedures for subcutaneous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocamne to ease pain at the site of the injection.

[0075] In certain embodiments, dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a subject, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil in water emulsions, or a water in oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a subject; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a subject.

[0076] The composition, shape, and type of dosage forms provided herein will typically vary depending on their use. In certain embodiments, a dosage form used in the initial treatment of viral infection may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the maintenance treatment of the same infection. Similarly, a parenteral dosage form may contain smaller amounts of one or more of

the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed herein will vary from one another will be readily apparent to those skilled in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[0077] Generally, the ingredients of compositions are supplied either separately or mixed together in unit dosage form, in certain embodiments, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachet indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0078] Typical dosage forms comprise a compound provided herein, or a pharmaceutically acceptable salt, solvate, or hydrate thereof lie within the range of from about 0.1 mg to about 1000 mg per day, given as a single once-a-day dose in the morning or as divided doses throughout the day taken with food. Particular dosage forms can have about 0.1, 0.2, 0.3, 0.4, 0.5, 1.0, 2.0, 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 100, 200, 250, 500 or 1000 mg of the active compound.

Oral Dosage Forms

[0079] Pharmaceutical compositions that are suitable for oral administration can be presented as discrete dosage forms, such as, but not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[0080] In certain embodiments, the oral dosage forms are solid and prepared under anhydrous conditions with anhydrous ingredients, as described in detail herein. However, the scope of the compositions provided herein extends beyond anhydrous, solid oral dosage forms. As such, further forms are described herein.

[0081] Typical oral dosage forms are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. In certain embodiments, excipients suitable for use

in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. In certain embodiments, excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0082] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or non-aqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[0083] In certain embodiments, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0084] In certain embodiments, excipients that can be used in oral dosage forms include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[0085] In certain embodiments, fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[0086] In certain embodiments, suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL PH 101, AVICEL PH 103, AVICEL RC

581, AVICEL PH 105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC 581. Suitable anhydrous or low moisture excipients or additives include AVICEL PH 103™ and Starch 1500 LM.

[0087] Disintegrants are used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

[0088] Disintegrants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

[0089] Lubricants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, in certain embodiments, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB O SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Delayed Release Dosage Forms

[0090] Active ingredients such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill

in the art, in certain embodiments, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500; each of which is incorporated herein by reference in its entirety. Such dosage forms can be used to provide slow or controlled release of one or more active ingredients using, in certain embodiments, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients provided herein. Thus, encompassed herein are single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gel caps, and caplets that are adapted for controlled release.

[0091] All controlled release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition, disease, or disorder in a minimum amount of time. Advantages of controlled release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[0092] Most controlled release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[0093] In certain embodiments, the drug may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In certain embodiments, a pump may be used (*see,* Sefton, *CRC Crit. Ref.*

Biomed. Eng. 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in a subject at an appropriate site determined by a practitioner of skill, *i.e.*, thus requiring only a fraction of the systemic dose (*see, e.g.*, Goodson, *Medical Applications of Controlled Release*, vol. 2, pp. 115-138 (1984)). Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)). The active ingredient can be dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

Parenteral Dosage Forms

[0094] In certain embodiments, provided are parenteral dosage forms. Parenteral dosage forms can be administered to subjects by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intra-arterial. Because their administration typically bypasses subjects' natural defenses against contaminants, parenteral dosage forms are typically sterile or capable of being sterilized prior to administration to a subject. In certain embodiments, parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

[0095] Suitable vehicles that can be used to provide parenteral dosage forms are well known to those skilled in the art. In certain embodiments, suitable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[0096] Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms.

Transdermal, Topical & Mucosal Dosage Forms

[0097] Also provided are transdermal, topical, and mucosal dosage forms. Transdermal, topical, and mucosal dosage forms include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

[0098] Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed herein are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane 1,3 diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels, or ointments, which are nontoxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[0099] Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients provided. In certain embodiments, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl alcohol, and tetrahydrofuryl alcohol; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[00100] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery enhancing or penetration enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Dosage and Unit Dosage Forms

[00101] In human therapeutics, the doctor will determine the posology which s/he considers most appropriate according to a preventive or curative treatment and according to the age, weight, stage of the infection and other factors specific to the subject to be treated. In certain embodiments, doses are from about 1 to about 1000 mg per day for an adult, or from about 5 to about 250 mg per day or from about 10 to 50 mg per day for an adult. In certain embodiments, doses are from about 5 to about 400 mg per day or 25 to 200 mg per day per adult. In certain embodiments, dose rates of from about 50 to about 500 mg per day are also contemplated.

[00102] The amount of the compound or composition which will be effective in the treatment of a disorder or one or more symptoms thereof will vary with the nature and severity of the condition, disease, or disorder, and the route by which the active ingredient is administered. The frequency and dosage will also vary according to factors specific for each subject depending on the specific therapy (*e.g.*, therapeutic or prophylactic agents)

administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the subject. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[00103] In certain embodiments, exemplary doses of a composition include milligram or microgram amounts of the active compound per kilogram of subject or sample weight (*e.g.*, about 10 micrograms per kilogram to about 50 milligrams per kilogram, about 100 micrograms per kilogram to about 25 milligrams per kilogram, or about 100 microgram per kilogram to about 10 milligrams per kilogram). For compositions provided herein, in certain embodiments, the dosage administered to a subject is 0.140 mg/kg to 3 mg/kg of the subject's body weight, based on weight of the active compound. In certain embodiments, the dosage administered to a subject is between 0.20 mg/kg and 2.00 mg/kg, or between 0.30 mg/kg and 1.50 mg/kg of the subject's body weight.

[00104] In certain embodiments, the recommended daily dose range of a composition provided herein for the condition, disease, or disorder described herein lie within the range of from about 0.1 mg to about 1000 mg per day, given as a single once-a-day dose or as divided doses throughout a day. In certain embodiments, the daily dose is administered twice daily in equally divided doses. In certain embodiments, a daily dose range should be from about 10 mg to about 200 mg per day, in other embodiments, between about 10 mg and about 150 mg per day, in further embodiments, between about 25 and about 100 mg per day. It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with subject response.

[00105] Different therapeutically effective amounts may be applicable for different conditions, diseases, or disorders, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat, or ameliorate such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the composition provided herein are also encompassed by the herein described dosage amounts and dose frequency schedules. Further, when a subject is administered multiple dosages of a composition provided herein, not all of the dosages need be the same. In certain embodiments, the dosage administered to the subject may be increased to improve the prophylactic or therapeutic effect of the composition or it may be decreased to reduce one or more side effects that a particular subject is experiencing.

[00106] In certain embodiments, the daily dosage of the composition provided herein, based on weight of the active compound, administered to prevent, treat, manage, or ameliorate a condition, disorder, disease, or one or more symptoms thereof in a subject is about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg, about 90 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 225 mg/kg, about 250 mg/kg, about 275 mg/kg, about 300 mg/kg, about 325 mg/kg, bout 350 mg/kg, about 375 mg/kg, about 400 mg/kg, about 425 mg/kg, about 450 mg/kg, about 475 mg/kg, about 500 mg/kg, or about 600 mg/kg. In certain embodiments, the daily dosage of the composition provided herein, based on weight of the active compound, administered to prevent, treat, manage, or ameliorate a condition, disorder, disease, or one or more symptoms thereof in a subject is between (inclusive) about 1-10 mg/kg, about 10 mg/kg, about 25-50 mg/kg, about 50-100 mg/kg, about 50-150 mg/kg, about 100-150 mg/kg, about 100-200 mg/kg, about 150-200 mg/kg, about 150-250 mg/kg, about 250-300 mg/kg, about 300-350 mg.kg, about 300-400 mg/kg, about 200-400 mg/kg, about 100-300 mg/kg, or about 400-500 mg/kg.

[00107] In certain embodiment, the twice daily dosage of the composition provided herein, based on weight of the active compound, administered to prevent, treat, manage, or ameliorate a condition, disorder, disease, or one or more symptoms thereof in a subject is about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg, about 90 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 225 mg/kg, about 250 mg/kg, about 275 mg/kg, or about 300 mg/kg. In certain embodiments, the twice daily dosage of the composition provided herein, based on weight of the active compound, administered to prevent, treat, manage, or ameliorate a condition, disorder, disease, or one or more symptoms thereof in a subject is between (inclusive) about 1-10 mg/kg, about 10 mg/kg, about 25-50 mg/kg, about 50-100 mg/kg, about 50-150 mg/kg, about 100-150 mg/kg, about 100-200 mg/kg, about 150-200 mg/kg, or about 150-250 mg/kg.

[00108] In certain embodiments, administration of the same composition may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the

administration may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

[00109] In certain aspects, provided herein are unit dosages comprising a compound, or a pharmaceutically acceptable salt thereof, in a form suitable for administration. Such forms are described in detail herein. In certain embodiments, the unit dosage comprises 1 to 1000 mg, 5 to 250 mg or 10 to 50 mg active ingredient. In particular embodiments, the unit dosages comprise about 1, 5, 10, 25, 50, 100, 125, 250, 500, or 1000 mg active ingredient. Such unit dosages can be prepared according to techniques familiar to those of skill in the art.

[00110] In certain embodiments, dosages of the niclosamide or niclosamide analog to be used in a combination therapy are provided herein. In certain embodiments, the compound, Niclosamide, or niclosamide analog dosages lower than those which have been or are currently being used to treat a condition, disease, or disorder associated with activation (in some embodiments abnormal activation) of the SREBP pathway and/or of one or more target genes that are essential for proliferation are used in the combination therapies provided herein. The recommended dosages of the niclosamide or niclosamide analog can be obtained from the knowledge of those of skill in the art. For those niclosamide or niclosamide analogs that are approved for clinical use, recommended dosages are described in, for example, Hardman *et al.*, eds., 1996, Goodman & Gilman's The Pharmacological Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York; and Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, NJ; each of which are incorporated herein by reference in their entirety.

[00111] In various embodiments, the therapies (*e.g.*, a compound provided herein and the niclosamide or niclosamide analog) are administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, about 1 hour apart, about 1 to about 2 hours apart, about 2 hours to about 3 hours apart, about 3 hours to about 4 hours apart, about 4 hours to about 5 hours apart, about 5 hours to about 6 hours apart, about 6 hours to about 7 hours apart, about 7 hours to about 8 hours apart, about 8 hours to about 9 hours apart, about 9 hours to about 10 hours apart, about 10 hours to about 11 hours apart, about 11 hours to about 12 hours apart, about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart. In various embodiments, the therapies are administered no more than 24 hours apart or no more than 48 hours apart. In certain embodiments, two or more therapies are administered

within the same patient visit. In other embodiments, the compound provided herein and the niclosamide or niclosamide analog are administered concurrently.

[00112] In other embodiments, the compound provided herein and the niclosamide or niclosamide analog are administered at about 2 to 4 days apart, at about 4 to 6 days apart, at about 1 week part, at about 1 to 2 weeks apart, or more than 2 weeks apart.

[00113] In certain embodiments, administration of the same agent may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same agent may be repeated and the administration may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

[00114] In certain embodiments, a compound provided herein and the niclosamide or niclosamide analog are administered to a patient, in certain embodiments, a mammal, such as a human, in a sequence and within a time interval such that the compound provided herein can act together with the niclosamide or niclosamide analog to provide an increased benefit than if they were administered otherwise. In certain embodiments, the niclosamide or niclosamide analog can be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. In certain embodiments, the compound provided herein and the niclosamide or niclosamide analog exert their effect at times which overlap. Each niclosamide or niclosamide analog can be administered separately, in any appropriate form and by any suitable route. In other embodiments, the compound provided herein is administered before, concurrently or after administration of the niclosamide or niclosamide analog.

[00115] In certain embodiments, the compound provided herein and the niclosamide or niclosamide analog are cyclically administered to a patient. Cycling therapy involves the administration of a first agent (*e.g.*, a first prophylactic or therapeutic agent) for a period of time, followed by the administration of the niclosamide or niclosamide analog for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

[00116] In certain embodiments, the compound provided herein and the niclosamide or niclosamide analog are administered in a cycle of less than about 3 weeks, about once every two weeks, about once every 10 days or about once every week. One cycle can comprise the

administration of a compound provided herein and the niclosamide or niclosamide analog by infusion over about 90 minutes every cycle, about 1 hour every cycle, and about 45 minutes every cycle. Each cycle can comprise at least 1 week of rest, at least 2 weeks of rest, at least 3 weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

[00117] In other embodiments, courses of treatment are administered concurrently to a patient, *i.e.*, individual doses of the niclosamide or niclosamide analog are administered separately yet within a time interval such that the compound provided herein can work together with the second active agent. In certain embodiments, one component can be administered once per week in combination with the other components that can be administered once every two weeks or once every three weeks. In other words, the dosing regimens are carried out concurrently even if the therapeutics are not administered simultaneously or during the same day.

[00118] The niclosamide or niclosamide analog can act additively or synergistically with the compound provided herein. In certain embodiments, the compound provided herein is administered concurrently with one or more niclosamide or niclosamide analogs in the same pharmaceutical composition. In another embodiment, a compound provided herein is administered concurrently with one or more niclosamide or niclosamide analogs in separate pharmaceutical compositions. In still another embodiment, a compound provided herein is administered prior to or subsequent to administration of a niclosamide or niclosamide analog. Also contemplated are administration of a compound provided herein and a niclosamide or niclosamide analog by the same or different routes of administration, *e.g.*, oral and parenteral. In certain embodiments, when the compound provided herein is administered concurrently with a niclosamide or niclosamide analog that potentially produces adverse side effects including, but not limited to, toxicity, the second active agent can advantageously be administered at a dose that falls below the threshold that the adverse side effect is elicited.

Kits

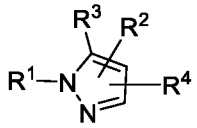
[00119] Also provided are kits for use in methods of treatment of a condition, disease, or disorder associated with activation (in some embodiments abnormal activation) of the SREBP pathway and/or of one or more target genes that are essential for proliferation. The kits can include a compound or composition provided herein, a niclosamide or niclosamide analog or composition, and instructions providing information to a health care provider regarding usage for treating a condition, disease, or disorder associated with activation (in some embodiments abnormal activation) of the SREBP pathway and/or of one or more target

genes that are essential for proliferation. Instructions may be provided in printed form or in the form of an electronic medium such as a floppy disc, CD, or DVD, or in the form of a website address where such instructions may be obtained. A unit dose of a compound or composition provided herein, or a niclosamide or niclosamide analog or composition, can include a dosage such that when administered to a subject, a therapeutically or prophylactically effective plasma level of the compound or composition can be maintained in the subject for at least 1 day. In some embodiments, a compound or composition can be included as a sterile aqueous pharmaceutical composition or dry powder (*e.g.,* lyophilized) composition.

[00120] In some embodiments, suitable packaging is provided. As used herein, "packaging" includes a solid matrix or material customarily used in a system and capable of holding within fixed limits a compound provided herein and/or a niclosamide or niclosamide analog suitable for administration to a subject. Such materials include glass and plastic (*e.g.,* polyethylene, polypropylene, and polycarbonate) bottles, vials, paper, plastic, and plastic-foil laminated envelopes and the like. If e-beam sterilization techniques are employed, the packaging should have sufficiently low density to permit sterilization of the contents.

GENUS A

[00121] Summary of Genus A Formula (I): In some or any embodiments, the SREBP inhibitor is according to a Compound of Formula (I):



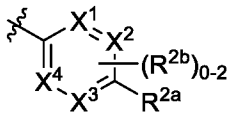
(I)

where

R^1 is phenyl, pyridinonyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl; where the phenyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl rings are optionally substituted with 1, 2, or 3 R^{1a} and where the pyridinonyl is substituted on the nitrogen with R^{1b} and is additionally optionally substituted with 1, 2, or 3 R^{1a};

each R^{1a} is independently halo, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{1b} is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are carbon;

R^{2a} is–$NR^{5a}S(O)_2R^{5b}$ or –$NR^{6a}R^{6b}$;

each R^{2b} is independently halo, alkyl, haloalkyl, -NO_2, or cyano;

R^3 is hydrogen, halo, alkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl, or haloalkyl;

R^{5a} and R^{6a} are independently hydrogen or alkyl; and

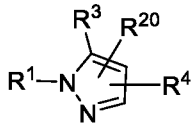
R^{5b} and R^{6b} are independently alkyl; haloalkyl; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; heterocycloalkylalkyl; and

wherein each cycloalkyl, either alone or as part of another group, is independently optionally substituted with one or two groups independently selected from the group consisting of alkyl, halo, and haloalkyl; or

a pharmaceutically acceptable salt thereof;

provided that the compound is not N-methyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; N-ethyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; or N-propyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine.

[00122] Summary of Genus A Formula (II): In some or any embodiments, the SREBP inhibitor is according to a Compound according to Genus A Formula (II):



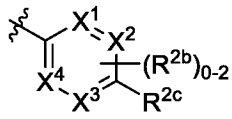
(II)

where

R^1 is phenyl, pyridinonyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl; where the R^1 phenyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl rings are substituted with one R^{1a} and additionally optionally substituted with a second R^{1a} and additionally optionally substituted with a third R^{1a}, and where the pyridinonyl is substituted on the nitrogen with R^{1b} and is additionally optionally substituted with 1, 2, or 3 R^{1a};

each R^{1a} is independently halo, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{1b} is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{20} is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are carbon;

each R^{2b} is independently halo, alkyl, haloalkyl, -NO_2, or cyano;

R^{2c} is –NO_2 or –NH_2;

R^3 is hydrogen or alkyl;

R^4 is hydrogen or alkyl;

R^{5a} and R^{6a} are independently hydrogen or alkyl; and

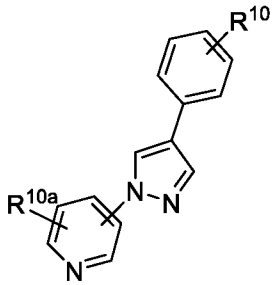
R^{5b} and R^{6b} are independently alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl; and

wherein each cycloalkyl, either alone or as part of another group, is independently optionally substituted with one or two groups independently selected from the group consisting of alkyl, halo, and haloalkyl; or

a pharmaceutically acceptable salt thereof;

provided that the compound is not 4-(1-(3-methylpyridin-4-yl)-1H-pyrazol-4-yl)aniline; 4-(1-(2-methylpyridin-4-yl)-1H-pyrazol-4-yl)aniline; or 4-(1-(3-chloropyridin-4-yl)-1H-pyrazol-4-yl)aniline.

[00123] Summary of Genus A Formula (IV): In some or any embodiments, the SREBP inhibitor is according to a Compound of Formula (IV):



(IV)

wherein R^{10a} is ethyl, n-propyl, isopropyl, -O-C_{1-3} alkyl, -O-C_{1-3} alkoxy, pyrrolidine, or morpholine; R^{10} is H, halogen, -OH, -O-C_{1-3} alkyl, -O-C_{1-3} alkoxy, -OC(O)R^{10d}, or –$NR^{10b}R^{10c}$; R^{10d} is C_1-C_3 alkyl or aryl; R^{10b} is H, C_1-C_3 alkyl, -alkyl-cyclopropane, cyclohexyl, benzyl, or -SO_2-R^{10e}; R^{10c} is H, C_1-C_3 alkyl, or -SO_2-R^{10e}; and R^{10e} is alkyl or cycloalkyl.

[00124] In some or any embodiments, the SREBP inhibitor is provided as a pharmaceutical composition, single unit dosage form, and kit suitable for use in treating disorders associated with activation (in some embodiments abnormal activation) of the

SREBP pathway and/or of one or more target genes that are essential for proliferation which comprise a therapeutically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments, of Genus A Formula (I)-(Im), (100), (200), and (Ia-1)-(Im-1) and specific compounds 1-130, and a pharmaceutically acceptable carrier thereof.

Genus A Definitions

[00125] When referring to the compounds provided herein, the following terms have the following meanings unless indicated otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise. Unless specified otherwise, where a term is defined as being unsubstituted or substituted, the groups in the list of substituents are themselves unsubstituted. For example, a substituted alkyl group can be substituted, for example, with a cycloalkyl group, and the cycloalkyl group is not further substituted unless specified otherwise.

[00126] "-O-C_{1-3} Alkoxy" means an –OR group where R is C_{1-3} alkyl substituted with C_{1-3} alkoxy, as defined herein.

[00127] "Alkenyl" means a straight or branched hydrocarbon radical having from 2 to 8 carbon atoms and at least one double bond, and in some embodiments, includes ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl, and the like. "Lower alkenyl" means an alkenyl group having one to six carbon atoms.

[00128] "Alkyl" means a linear or branched hydrocarbon group having one to eight carbon atoms. "Lower alkyl" means an alkyl group having one to six carbon atoms. In some embodiments, lower alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl, and the like. A "C_0" alkyl (as in "C_0-C_6-alkyl") is a covalent bond. "C_6 alkyl" refers to, for example, *n*-hexyl, *iso*-hexyl, and the like.

[00129] "Alkylamino" means a -NHR radical where R is alkyl as defined herein, or an N-oxide derivative thereof. In some embodiments, alkylamino includes methylamino, ethylamino, *n*- or *iso*-propylamino, *n*-, *iso*-, or *tert*-butylamino, and methylamino-N-oxide, and the like.

[00130] "Amino" means a -NH_2.

[00131] "Aryl" means a monovalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring is aromatic. In some embodiments, aryl is phenyl, naphthyl, or indanyl, and the like.

[00132] "Cycloalkyl" means a monocyclic or polycyclic hydrocarbon radical having three to thirteen carbon atoms. The cycloalkyl can be saturated or partially unsaturated, but cannot contain an aromatic ring. In some embodiments, cycloalkyl includes fused, bridged, and spiro ring systems. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[00133] "Cycloalkylalkyl" means alkyl group substituted with one or two cycloalkyl group(s), as defined herein. In some embodiments, cycloalkylalkyl includes cyclopropylmethyl, 2-cyclobutyl-ethyl, and the like.

[00134] "Dialkylamino" means a -NRR' radical where R and R' are independently alkyl as defined herein, and an N-oxide thereof. In some embodiments, dialkylamino includes dimethylamino, diethylamino, *N,N*-methylpropylamino and *N,N*-methylethylamino, and the like.

[00135] "Haloalkyl" means an alkyl group, as defined herein, substituted with one or more halogens, for example, one, two, three, four, or five halo atoms. In some embodiments, haloalkyl includes 2,2-difluoroethyl, trifluoromethyl, 2-chloro-1-fluoroethyl, and the like.

[00136] "Heteroaryl" means a monocyclic, monovalent aromatic radical of 5 or 6 ring atoms containing one or more heteroatoms, for example one, two, or three ring heteroatoms, independently selected from oxygen, nitrogen, and sulfur and the remaining ring atoms being carbon. Unless stated otherwise, the point of attachment may be located on any atom of any ring of the heteroaryl group, valency rules permitting. In some embodiments, the term heteroaryl includes, but is not limited to, 1,2,4-triazolyl, 1,3,5-triazolyl, pyridinyl, pyrrolyl, imidazolyl, thienyl, furanyl, tetrazoyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, and an N-oxide thereof.

[00137] "Heterocycloalkyl" means a saturated or partially unsaturated (but not aromatic) monovalent monocyclic group of 3 to 9 ring atoms or a saturated or partially unsaturated (but not aromatic) monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more heteroatoms are present, for example, one, two, three, or four ring heteroatoms, independently selected from -O-, $-S(O)_n-$ (n is 0, 1, or 2), -N=, $-N(R^y)-$ (where R^y is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl), and the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the point of attachment of the group may be located on any atom of any ring within the radical, valency rules permitting. In particular, when the point of attachment is located on a nitrogen

atom, R^y is absent. In some embodiments, the term heterocycloalkyl includes, but is not limited to, azetidinyl, pyrrolidinyl, 2-oxopyrrolidinyl, 2,5-dihydro-1*H*-pyrrolyl, piperidinyl, 4-piperidonyl, morpholinyl, piperazinyl, 2-oxopiperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, thiomorpholinyl, thiamorpholinyl, perhydroazepinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, oxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, thiazolidinyl, quinuclidinyl, isothiazolidinyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, tetrahydrofuryl, and tetrahydropyranyl, and an N-oxide thereof. In some embodiments, the heterocycloalkyl is substituted on the nitrogen with R^y where R^y is alkyl.

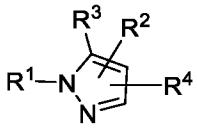
[00138] "Heterocycloalkylalkyl" means an alkyl group, as defined herein, substituted with one or two heterocycloalkyl group(s), as defined herein.

Genus A Compounds

[00139] The embodiments described herein include the recited compounds as well as a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, tautomer, or mixture thereof.

[00140] In some or any embodiments, the SREBP inhibitor is according to the Genus A Compound (e.g., of Genus A Formula (I), (100), (Ia), (Ib), and (Ih), and any embodiments thereof).

[00141] In some or any embodiments, the SREBP inhibitor is according to a Genus A Compound of Formula (100):



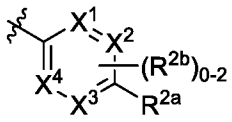
(100)

where

R^1 is phenyl, pyridinonyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl; where the phenyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl rings are optionally substituted with 1 or 2 R^{1a} and where the pyridinonyl is substituted on the nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a};

each R^{1a} is independently halo, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{1b} is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are carbon;

R^{2a} is–$NR^{5a}S(O)_2R^{5b}$ or –$NR^{6a}R^{6b}$;

each R^{2b} is independently halo, alkyl, haloalkyl, -NO_2, or cyano;

R^3 is hydrogen, halo, alkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl, or haloalkyl;

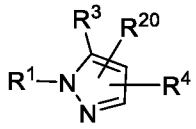
R^{5a} and R^{6a} are independently hydrogen or alkyl; and

R^{5b} and R^{6b} are independently alkyl; haloalkyl; cycloalkyl, where the cycloalkyl is optionally substituted with 1 or 2 alkyl groups; cycloalkylalkyl; heterocycloalkyl; heterocycloalkylalkyl; or

a pharmaceutically acceptable salt thereof;

provided that the compound is not N-methyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; N-ethyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; or N-propyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine.

[00142] In some or any embodiments, the SREBP inhibitor is according to a Genus A Compound according to Genus A Formula (200)



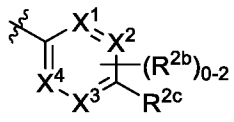
(200)

where

R^1 is phenyl, pyridinonyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl; where the R^1 phenyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl rings are substituted with one R^{1a} and additionally optionally substituted with a second R^{1a}, and where the pyridinonyl is substituted on the nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a};

each R^{1a} is independently halo, alkyl, haloalkyl, or heterocycloalkyl;

R^{1b} is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, or heterocycloalkyl;

R^{20} is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are carbon;

each R^{2b} is independently halo, alkyl, haloalkyl, -NO_2, or cyano;

R^{2c} is –NO_2 or –NH_2;

R^3 is hydrogen or alkyl;

R^4 is hydrogen or alkyl;

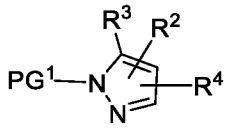
R^{5a} and R^{6a} are independently hydrogen or alkyl; and

R^{5b} and R^{6b} are independently alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

a pharmaceutically acceptable salt thereof;

provided that the compound is not 4-(1-(3-methylpyridin-4-yl)-1H-pyrazol-4-yl)aniline; 4-(1-(2-methylpyridin-4-yl)-1H-pyrazol-4-yl)aniline; or 4-(1-(3-chloropyridin-4-yl)-1H-pyrazol-4-yl)aniline.

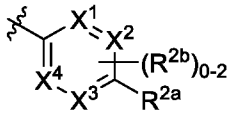
[00143] In some or any embodiments, the SREBP inhibitor is according to a Genus A Compound according to Genus A Formula (300)



(300)

where

PG^1 is a nitrogen protecting group;

R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are carbon;

R^{2a} is $–NR^{5a}S(O)_2R^{5b}$, or $–NR^{6a}R^{6b}$;

each R^{2b} is independently halo, alkyl, haloalkyl, $-NO_2$, or cyano;

R^3 is hydrogen or alkyl;

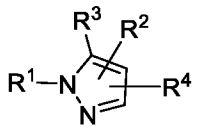
R^4 is hydrogen or alkyl;

R^{5a} and R^{6a} are independently hydrogen or alkyl;

R^{5b} and R^{6b} are independently alkyl; haloalkyl; cycloalkyl; cycloalkylalkyl, where the cycloalkyl is optionally substituted with 1 or 2 alkyl groups; heterocycloalkyl; or heterocycloalkylalkyl; or

a pharmaceutically acceptable salt thereof.

[00144] In some or any embodiments, the SREBP inhibitor is according to a Genus A Compound of Genus A Formula (I):



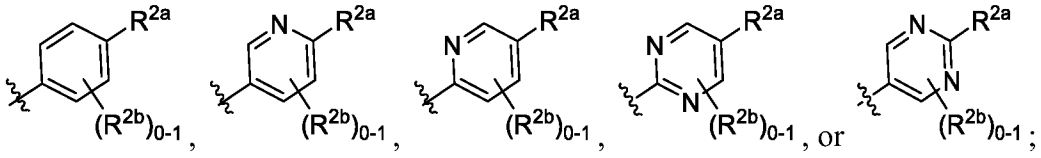
(I)

where

R^1 is phenyl, pyridinonyl, or pyridinyl; where the phenyl, pyridinonyl, and pyridinyl rings are optionally substituted with 1 R^{1a} and where the pyridinonyl is substituted on the nitrogen with R^{1b};

R^{1a} is alkyl, haloalkyl, or heterocycloalkyl;

R^{1b} is alkyl, haloalkyl, or cycloalkylalkyl;

R^2 is ;

R^{2a} is $–NR^{5a}S(O)_2R^{5b}$ or $–NR^{6a}R^{6b}$;

R^{2b} is halo, alkyl, haloalkyl, or cyano;

R^3 is hydrogen or alkyl;

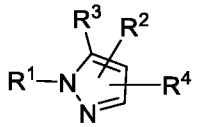
R^4 is hydrogen or alkyl;

R^{5a} and R^{6a} are hydrogen; and

R^{5b} and R^{6b} are independently alkyl; haloalkyl; cycloalkyl, where the cycloalkyl is optionally substituted with 1 or 2 alkyl groups; cycloalkylalkyl; or heterocycloalkyl; or

a pharmaceutically acceptable salt thereof.

[00145] In some or any embodiments, the SREBP inhibitor is according to a Genus A Compound of Formula (I):



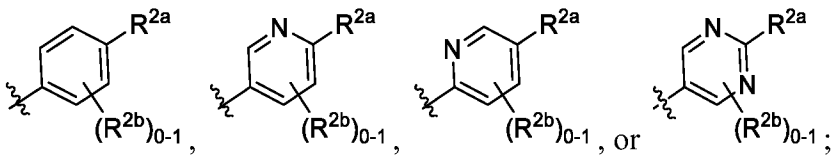
(I)

where

R^1 is phenyl, pyridinonyl, or pyridinyl; where the phenyl, pyridinonyl, and pyridinyl rings are optionally substituted with 1 R^{1a} and where the pyridinonyl is substituted on the nitrogen with R^{1b};

R^{1a} is alkyl, haloalkyl, or heterocycloalkyl;

R^{1b} is alkyl;

R^2 is ;

R^{2a} is–$NR^{5a}S(O)_2R^{5b}$ or –$NR^{6a}R^{6b}$;

R^{2b} is halo, alkyl, haloalkyl, or cyano;

R^3 is hydrogen or alkyl;

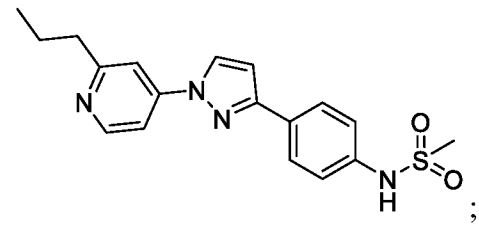
R^4 is hydrogen or alkyl;

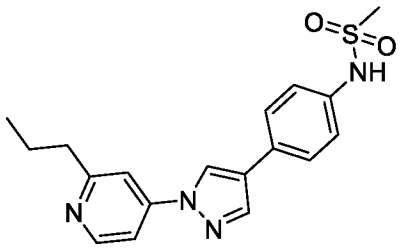
R^{5a} and R^{6a} are hydrogen; and

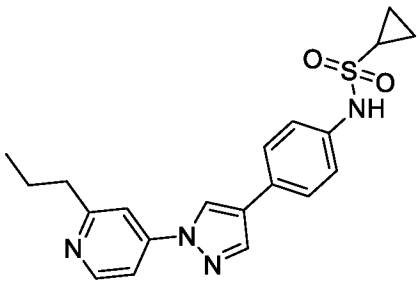
R^{5b} and R^{6b} are independently alkyl; haloalkyl; cycloalkyl; cycloalkylalkyl; or heterocycloalkyl; or

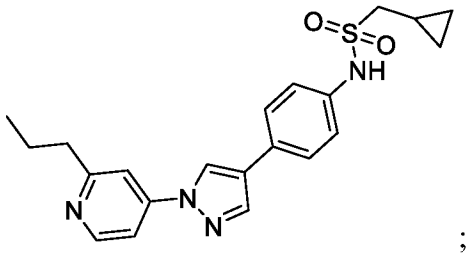
a pharmaceutically acceptable salt thereof.

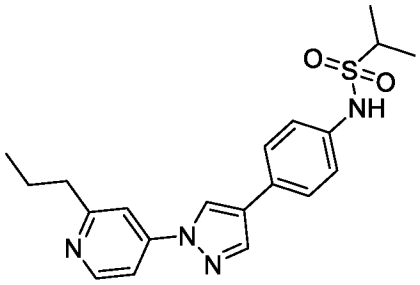
[00146] In some or any embodiments, the SREBP inhibitor according to a Genus A Compound (e.g., of Genus A Formula (I), (100), (Ia), (Ic), (Ie), (If), (Ia-1), (Ic-1), and (Ie-1), and any embodiments thereof) is not

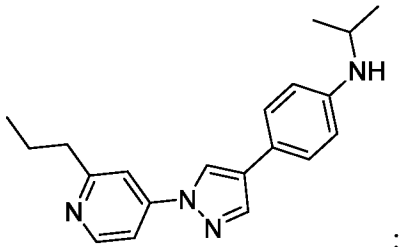

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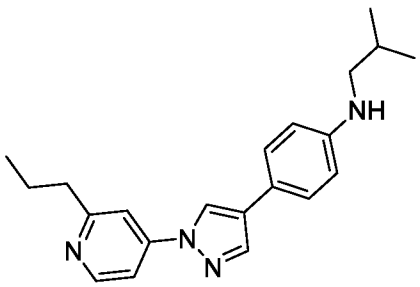

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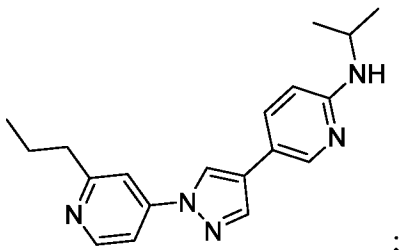

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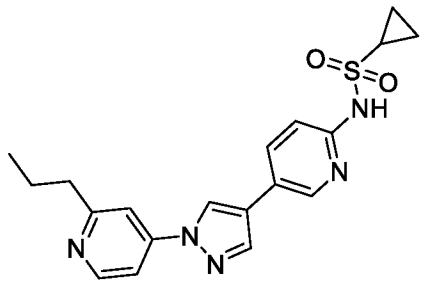

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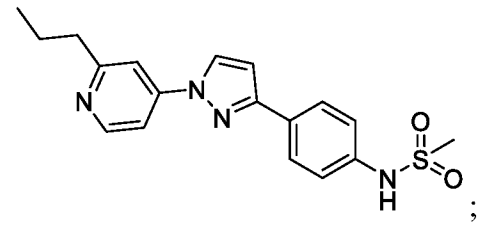

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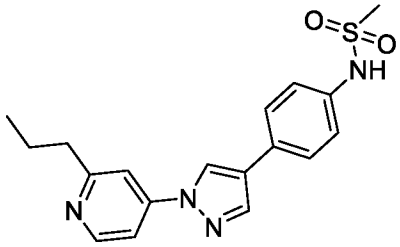
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In some or any embodiments, the Genus A Compound (e.g., of Genus A Formula (I), (100), (Ia), (Ic), (Ie), (If), (Ia-1), (Ic-1), and (Ie-1), and any embodiments thereof) is not a pharmaceutically acceptable salt of one of the specific compounds in this paragraph.

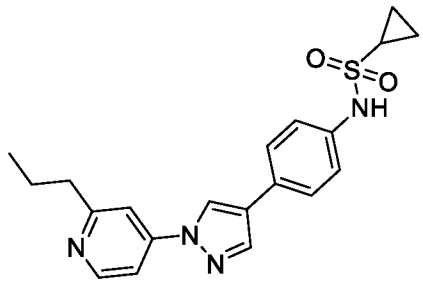
[00147] In some or any embodiments, the Genus A Compound (e.g., of Formula (I), (100), (Ia), (Ib), (Ic), (Ie), (If), (Ih), (Ia-1), (Ic-1), and (Ie-1), and any embodiments thereof) is not N-methyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; N-ethyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; or N-propyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; and not



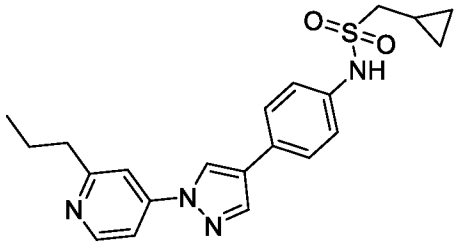
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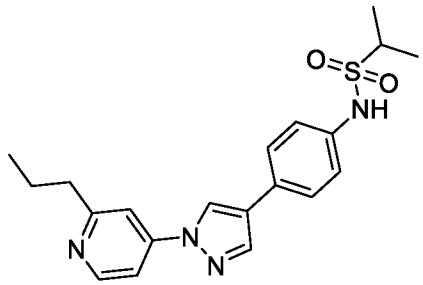
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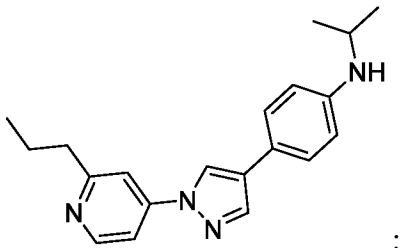
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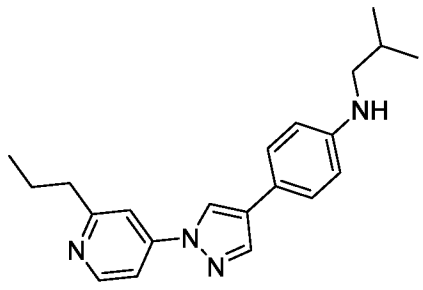
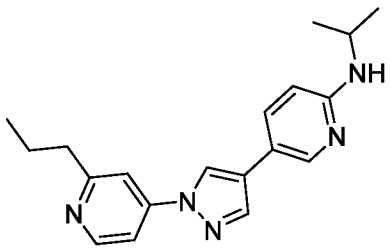
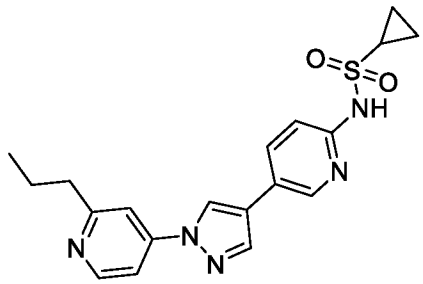
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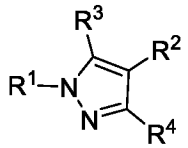


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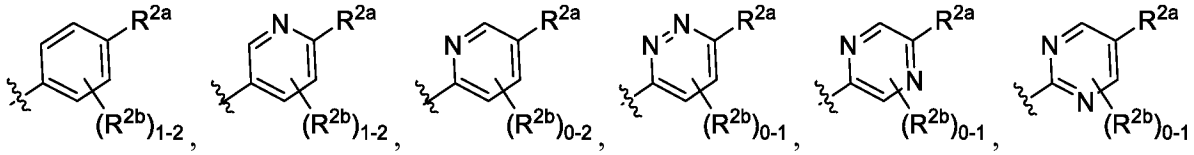
In some embodiments, the Genus A Compound (e.g., of Formula (I), (100), (Ia), (Ib), (Ic), (Ie), (If), (Ih), (Ia-1), (Ic-1), and (Ie-1), and any embodiments thereof) is not a pharmaceutically acceptable salt of one of the specific compounds in this paragraph.

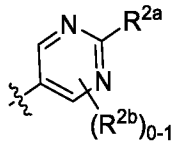
[00148] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Ia):



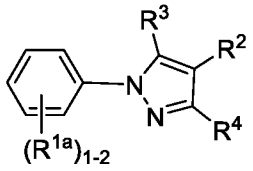
(Ia);

where R^1, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Ia) is that where R^2 is

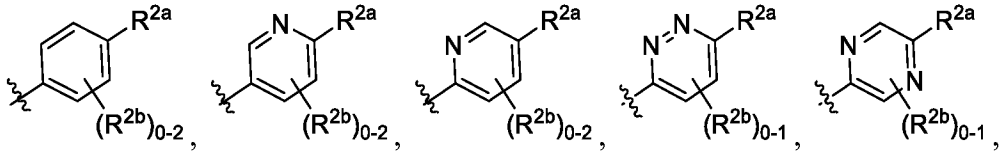


, or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Summary of Genus A Formula (Ia) is that where R^3 and R^4 are hydrogen.

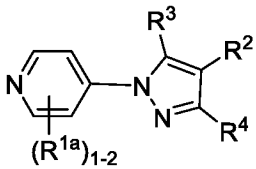
[00149] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Ib):



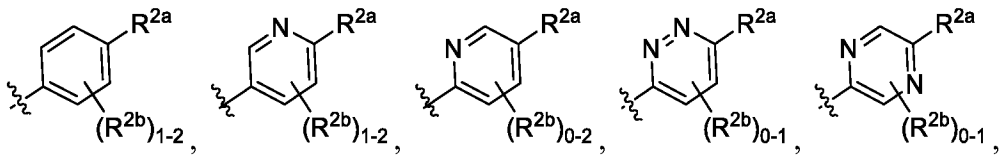
(Ib);

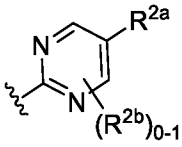
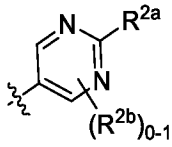
where R^{1a}, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Ib) is that where R^2 is ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Ib) is that where R^3 and R^4 are hydrogen.

[00150] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Ic):

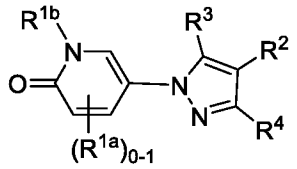


(Ic);

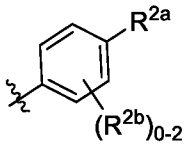
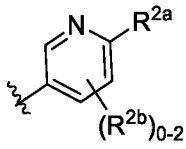
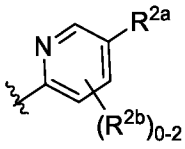
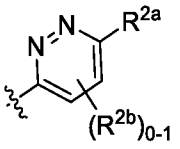
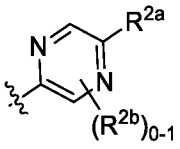
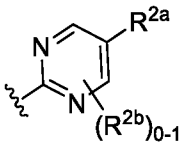
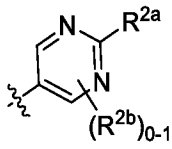
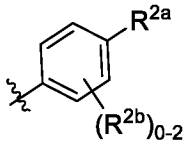
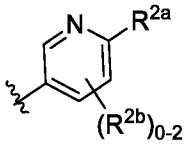
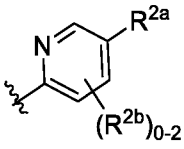
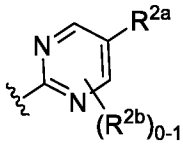
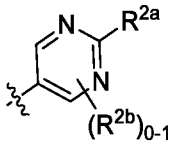
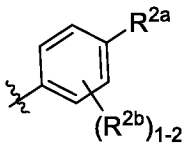
where R^{1a}, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Ic) is that where R^2 is 

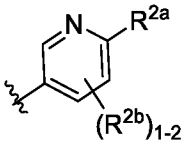
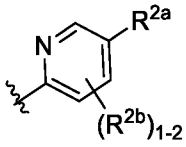
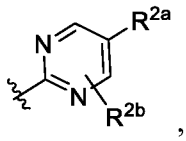

, or 
; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Ic) is that where R^3 and R^4 are hydrogen.

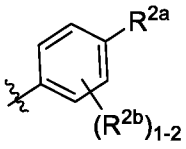
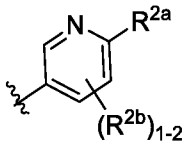
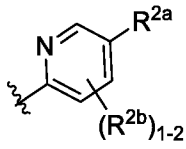
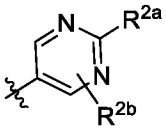
[00151] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Id):

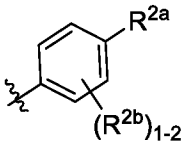
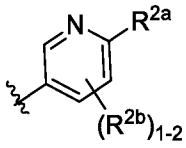
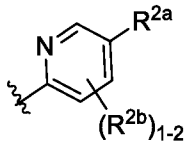
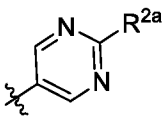


(Id);

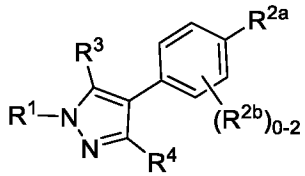
where R^{1a}, R^{1b}, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Id) is that where R^2 is 
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, 
, or 
; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Id) is that where R^2 is 
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, 
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, or 
; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Id) is that where R^2 is 
,




, or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Id) is that where R^2 is




, or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Id) is that where R^2 is

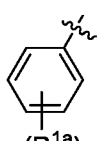
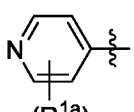
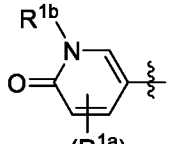



, or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Formula (Id) is that where R^3 and R^4 are hydrogen.

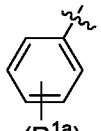
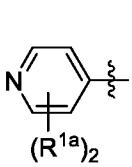
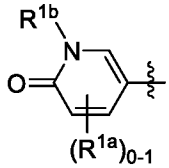
[00152] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Ie):



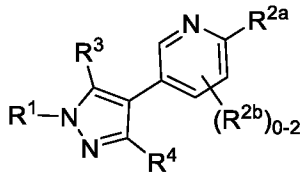
(Ie);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Ie) is that

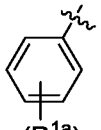
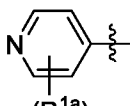
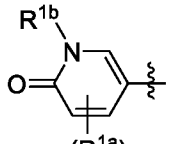
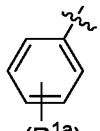
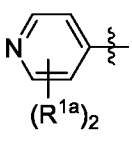
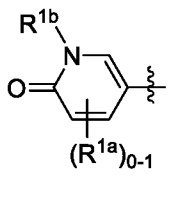
wherein R^1 is 

, or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any

embodiments, the Genus A Compound of Formula (Ie) is that wherein R^1 is , , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Formula (Ie) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Genus A Compound of Formula (Ie) is that where one R^{2b} is present.

[00153] In some or any embodiments, the Genus A Compound is according to Genus A Formula (If):

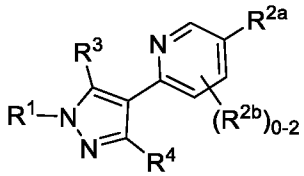


(If);

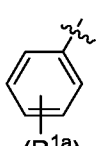
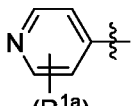
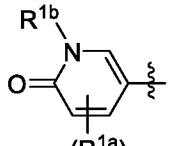
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (If) is that wherein R^1 is , , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (If) is that wherein R^1 is , , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus

A Compound of Formula (If) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Formula (If) is that where one R^{2b} is present.

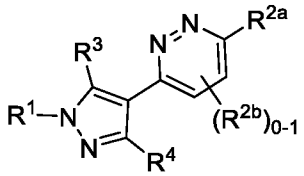
[00154] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Ig):



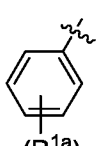
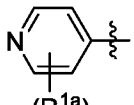
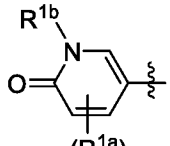
(Ig);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Ig) is that wherein R^1 is , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Ig) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Formula (Ig) is that where one R^{2b} is present.

[00155] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Ih):

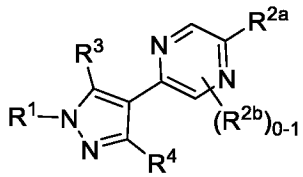


(Ih);

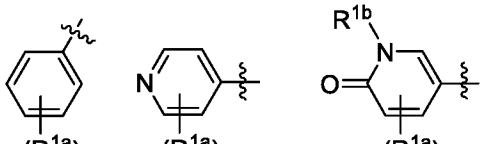
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Ih) is that wherein R^1 is , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any

embodiments, the Genus A Compound of Formula (Ih) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Genus A Compound of Formula (Ih) is that where one R^{2b} is present.

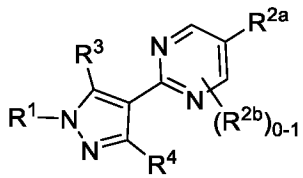
[00156] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Ij):



(Ij);

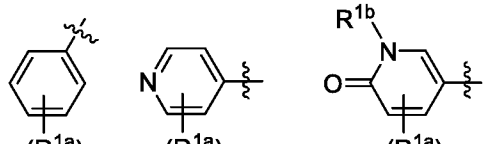
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Ij) is that wherein R^1 is ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Ij) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Genus A Compound of Formula (Ij) is that where one R^{2b} is present.

[00157] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Ik):

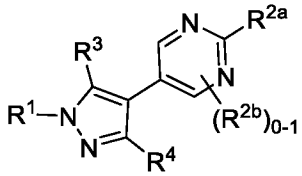


(Ik);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Ik) is that

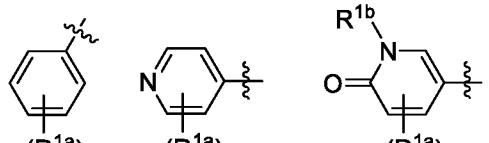
wherein R^1 is ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Ik) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Genus A Compound of Formula (Ik) is that where one R^{2b} is present.

[00158] In some or any embodiments, the Genus A Compound is according to Genus A Formula (Im):



(Im);

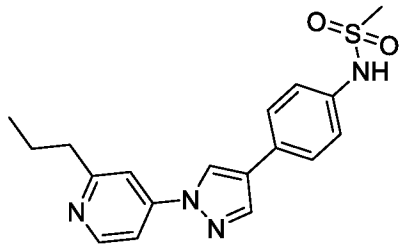
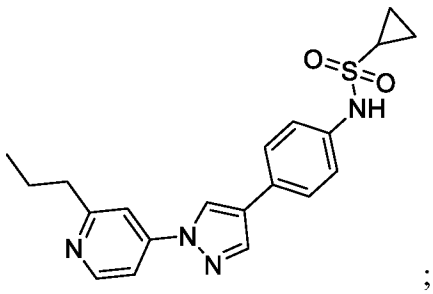
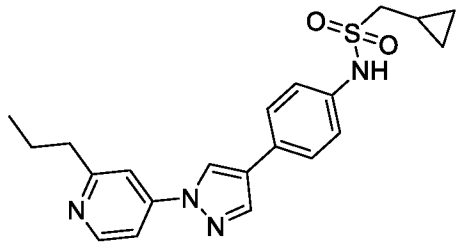
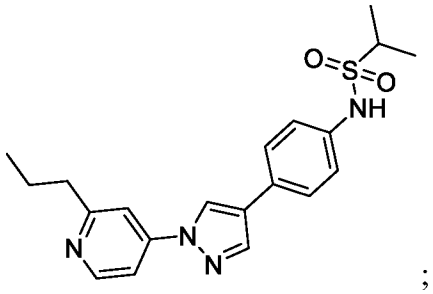
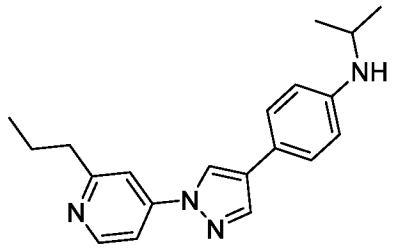
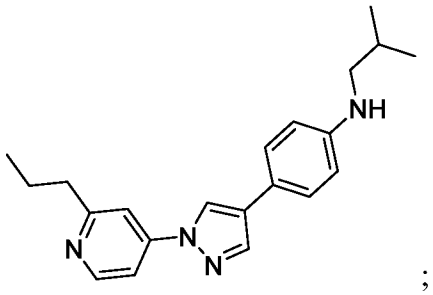
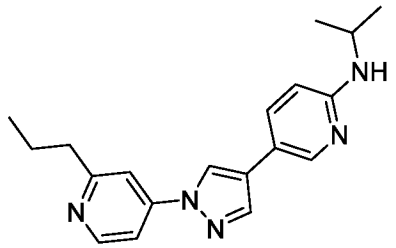
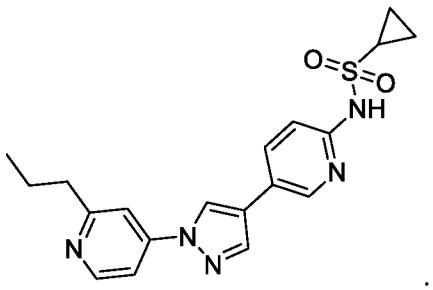
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus A Compound of Formula (Im) is that

wherein R^1 is ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (Im) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Genus A Compound of Formula (Im) is that where one R^{2b} is present. In some or any embodiments, the Genus A Compound of Formula (Im) is that where no R^{2b} is present.

[00159] In some or any embodiments, the Genus A Compound of Formula (I), (100), (Ia), (Ib), or (Ih) is not N-methyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; N-ethyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; or N-propyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine.

[00160] In some or any embodiments, the Genus A Compound of Formula (I), (100), (Ia), (Ib), (Ic), (Ie), (If), or (Ih) is not N-methyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine;

N-ethyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; or N-propyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; and not


;

;

;

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;

;

; or

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In some or any embodiments, the Genus A Compound (e.g., of Genus A Formula (I), (100), (Ia), (Ib), (Ic), (Ie), (If), or (Ih), and any embodiments thereof) is not a pharmaceutically acceptable salt of one of the specific compounds in this paragraph.

[00161] In some or any embodiments, the Genus A Compound of Genus A Formula (I)-(Im), (100), or (Ia-1)-(Im-1) is that where R^3 and R^4 are hydrogen; R^3 and R^4 are alkyl; or one of R^3 and R^4 is hydrogen and the other is alkyl; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (I)-(Im), (100), or (Ia-1)-(Im-1) is that where R^3 and R^4 are hydrogen; R^3 and R^4 are methyl; R^3 is hydrogen and R^4 is methyl; or R^3

is methyl and R^4 is hydrogen; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Genus A Compound of Formula (I)-(Im), (100), or (Ia-1)-(Im-1) is that where R^3 and R^4 are hydrogen; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

[00162] In some or any embodiments, the Genus A Compound of Genus A Formula (I), (Ia), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) is that where R^1 is phenyl, pyridinonyl, or pyridinyl; where the phenyl and pyridinyl rings are optionally substituted with 1 or 2 R^{1a} and where the pyridinonyl is substituted on the nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a}; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

[00163] In some or any embodiments, the Genus A Compound of Genus A Formula (I), (Ia), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) is that where R^1 is pyridinonyl substituted on the nitrogen with R^{1b} and additionally optionally substituted with 1 R^{1a}; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

[00164] In some or any embodiments, the Genus A Compound of Genus A Formula (I), (Ia), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) is that where R^1 is phenyl optionally substituted with 1 or 2 R^{1a}; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

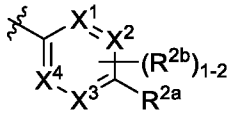
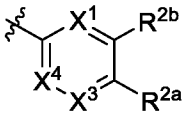
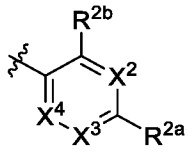
[00165] In some or any embodiments, the Genus A Compound of Genus A Formula (I), (Ia), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) is that where R^1 is pyridinyl optionally substituted with 1 or 2 R^{1a}; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

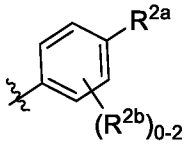
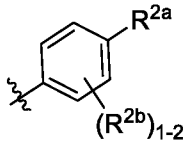
[00166] In some or any embodiments, the Genus A Compound of Genus A Formula (I), (Ia), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) is that where R^1 is pyrimidinyl optionally substituted with 1 or 2 R^{1a}; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

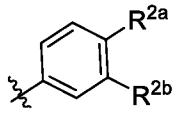
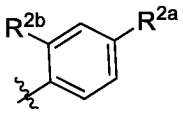
[00167] In some or any embodiments, the Genus A Compound of Genus A Formula (I), (Ia), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1),

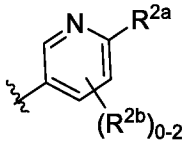
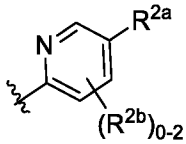
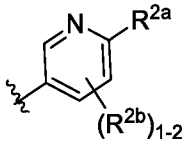
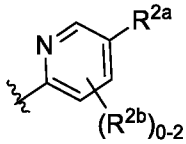
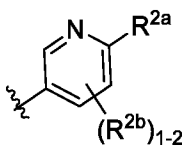
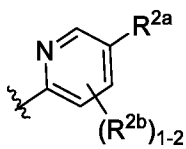
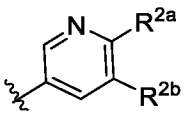
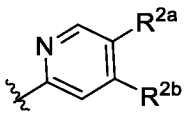
or (Im-1) is that where R^1 is pyridazinyl optionally substituted with 1 or 2 R^{1a}; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

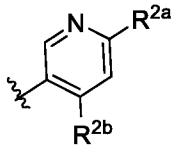
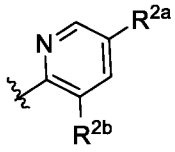
[00168] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) is that where R^1 is pyrazinyl optionally substituted with 1 or 2 R^{1a}; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

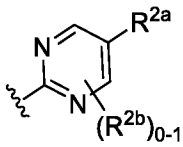
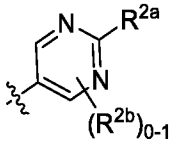
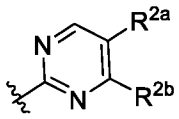
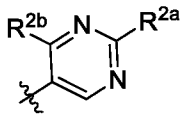
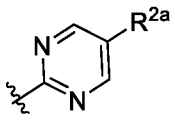
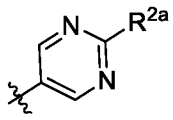
[00169] In some or any embodiments, the Genus A Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are carbon; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiment, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  where 0, 1, or 2 of X^1, X^3, and X^4 are nitrogen and the remaining are carbon; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiment, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  where 0, 1, or 2 of X^2, X^3, and X^4 are nitrogen and the remaining are carbon; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

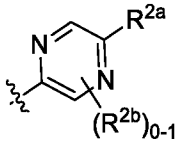
[00170] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all

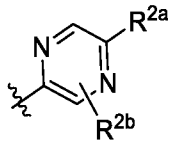
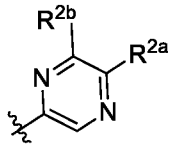
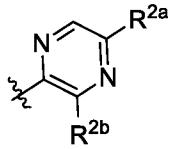
other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

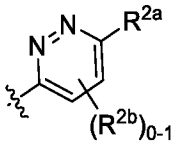
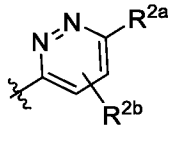
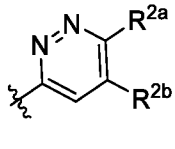
[00171] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  or ; and all other

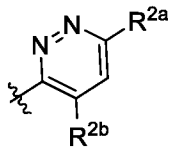
groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

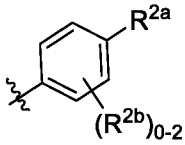
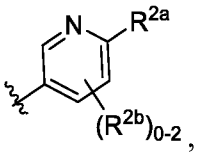
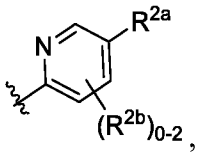
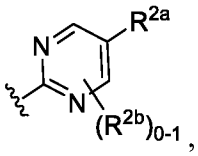
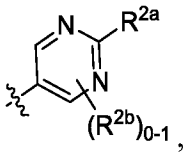
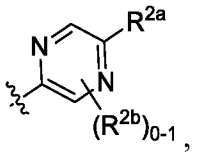
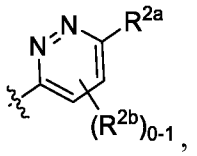
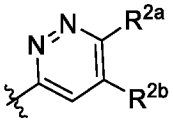
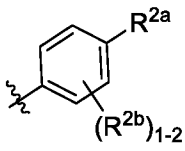
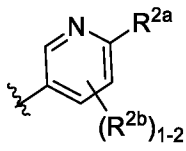
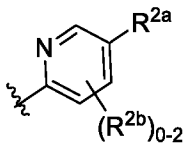
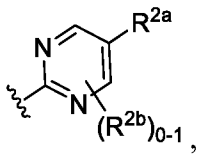
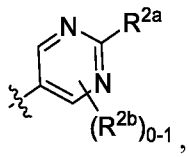
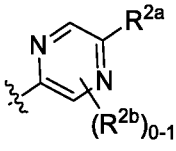
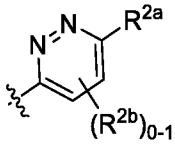
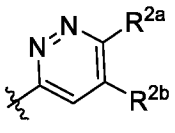
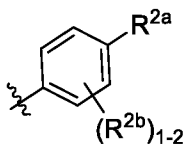
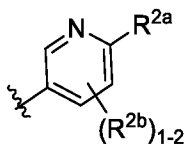
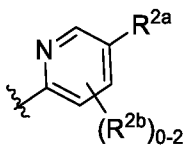
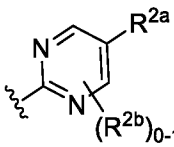
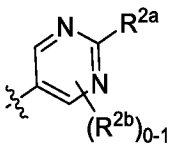
[00172] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

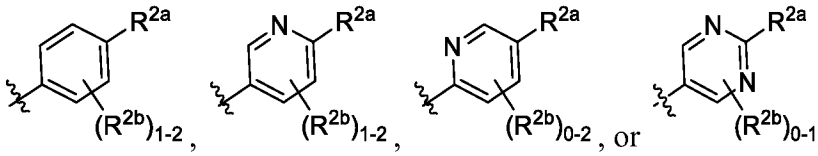
[00173] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia),

(Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

[00174] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia),

(Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

[00175] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is , , , , , , ,  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is , , , , , , , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is , , , ,  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments,

the Compound of Genus A Formula (I), (Ia), (Ib), (Ic), (Id), (100), (Ia-1), (Ib-1), (Ic-1), or (Id-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

[00176] In some or any embodiments, the Compound of Genus A Formula (I)-(Im), (100), or (Ia-1)-(Im-1) is that where R^{2a} is $-NR^{5a}S(O)_2R^{5b}$; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I)-(Im), (100), or (Ia-1)-(Im-1) is that where R^{2a} is $-NHS(O)_2R^{5b}$; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

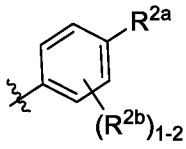
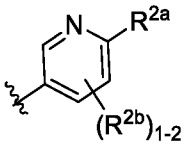
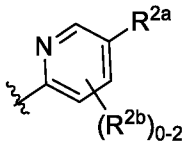
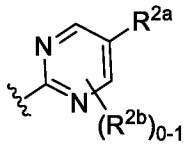
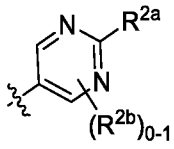
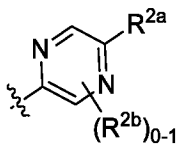
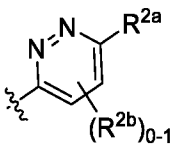
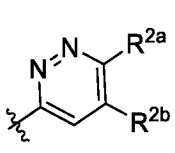
[00177] In some or any embodiments, the Compound of Genus A Formula (I)-(Im), (100), or (Ia-1)-(Im-1) is that where R^{2a} is $-NR^{6a}R^{6b}$; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (I)-(Im), (100), or (Ia-1)-(Im-1) is that where R^{2a} is $-NHR^{6b}$; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

[00178] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) is that where R^1 is phenyl, pyridinonyl, or pyridinyl; where the phenyl and pyridinyl rings are optionally substituted with 1 or 2 R^{1a} and where the pyridinonyl is substituted on the nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a}; R^3 and R^4 are hydrogen; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

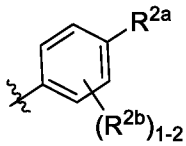
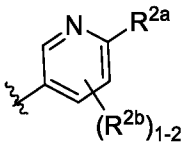
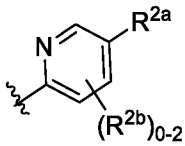
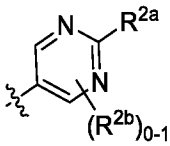
[00179] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) is that where R^1 is phenyl, pyridinonyl, or pyridinyl; where the phenyl and pyridinyl rings are substituted with 1 or 2 R^{1a} and where the pyridinonyl is substituted on the nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a}; R^3 and R^4 are hydrogen; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

[00180] In some or any embodiments, the Compound of Genus A Formula (I), (Ia), (Id), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Id-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) is that where R^1 is pyridinonyl substituted on the nitrogen with R^{1b} and additionally optionally substituted with 1 R^{1a}; and R^{1b} is alkyl, haloalkyl, cycloalkylalkyl, or heterocycloalkylalkyl where the heterocycloalkyl ring is substituted with R^y where R^y is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

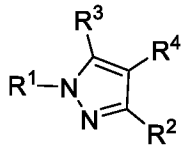
[00181] In some or any embodiments, provided is a Compound of Formula (I), (Ia), (Id), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Id-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) where R^{1b} is additionally optionally substituted with 1 R^{1a}; and R^{1b} is alkyl, haloalkyl, cycloalkylalkyl, or heterocycloalkylalkyl where the heterocycloalkyl ring is substituted with R^y where R^y is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, provided is a Compound of Formula (I), (Ia), (Id), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im), (100), (Ia-1), (Id-1), (Ie-1), (If-1), (Ig-1), (Ih-1), (Ij-1), (Ik-1), or (Im-1) where R^{1b} is additionally optionally substituted with 1 R^{1a}; and R^{1b} is alkyl, haloalkyl, cycloalkylalkyl, or heterocycloalkylalkyl where the heterocycloalkyl ring is substituted with alkyl; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

[00182] In some or any embodiments, the Compound of Genus A Formula (I), (100), (Ia), or (Ia-1) is that where R^1 is phenyl, pyridinonyl, or pyridinyl; where the phenyl and pyridinyl rings are optionally substituted with 1 or 2 R^{1a} and where the pyridinonyl is substituted on the nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a}; R^3 and R^4 are hydrogen; R^2 is , , , , , , or ; ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

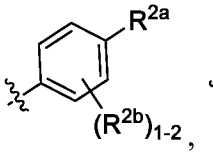
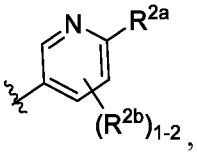
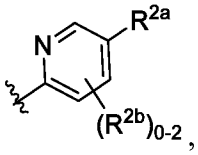
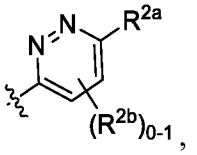
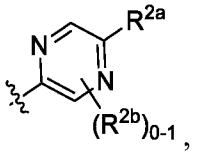
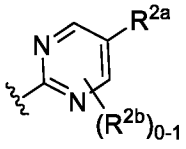
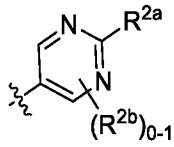
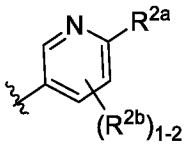
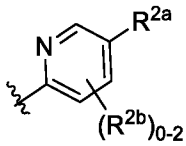
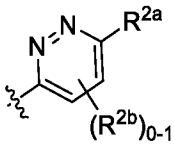
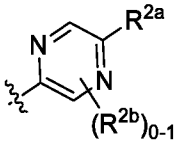
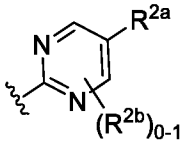
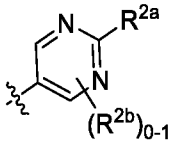
[00183] In some or any embodiments, the Compound of Genus A Formula (I), (100), (Ia), or (Ia-1) is that where R^1 is phenyl, pyridinonyl, or pyridinyl; where the phenyl and pyridinyl rings are optionally substituted with 1 or 2 R^{1a} and where the pyridinonyl is substituted on the

nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a}; R^3 and R^4 are hydrogen; R^2 is , , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein.

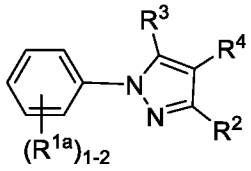
[00184] In some or any embodiments, the Compound according to Genus A Formula (Ia-1):



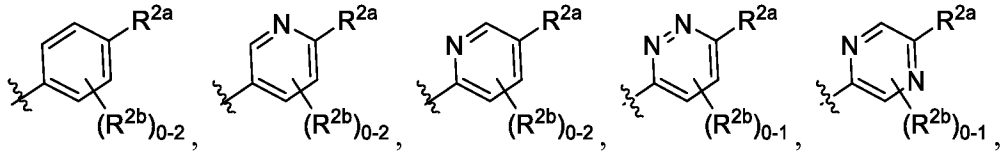
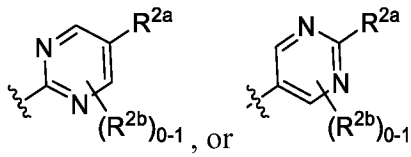
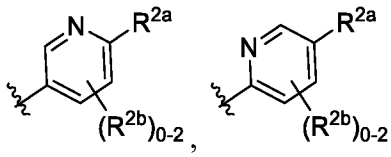
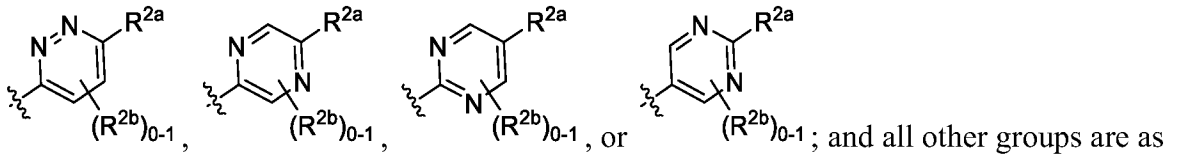
(Ia-1);

where R^1, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Ia-1) is that where R^2 is , , , , , , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ia-1) is that where R^2 is , , , , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ia-1) is that where R^3 and R^4 are hydrogen.

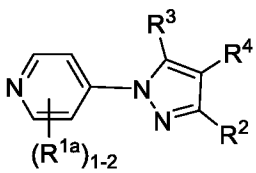
[00185] In some or any embodiments, the Compound is according to Genus A Formula (Ib-1):



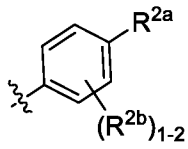
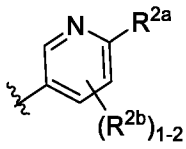
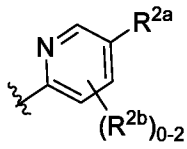
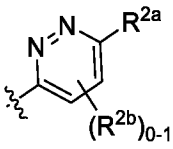
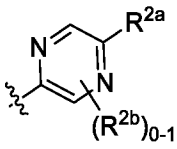
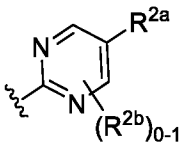
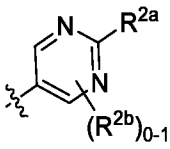
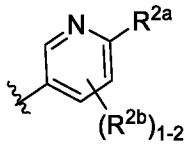
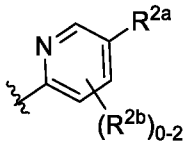
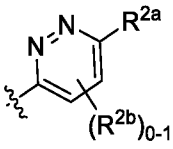
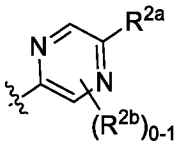
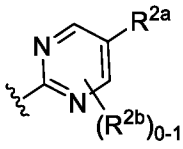
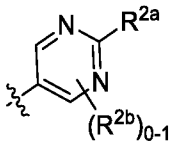
(Ib-1);

where R^{1a}, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Ib-1) is that where R^2 is , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ib-1) is that where R^2 is , ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ib-1) is that where R^3 and R^4 are hydrogen.

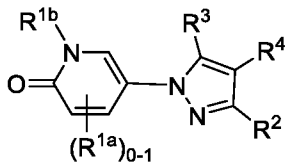
[00186] In some or any embodiments, the Compound is according to Genus A Formula (Ic-1):



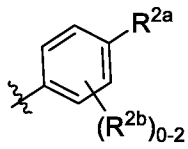
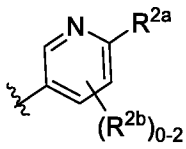
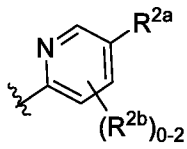
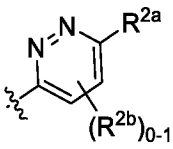
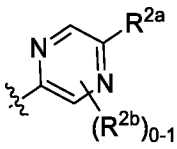
(Ic-1);

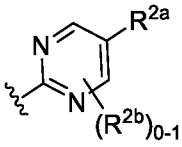
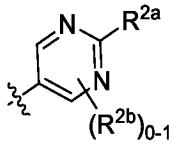
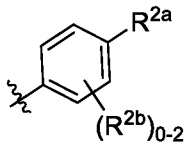
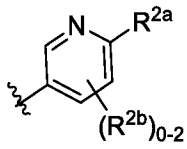
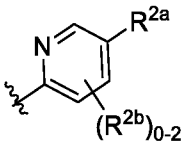
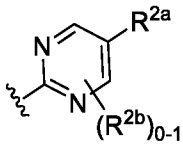
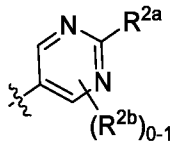
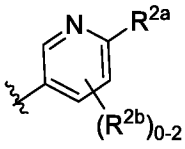
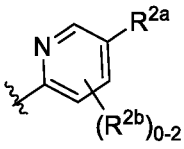
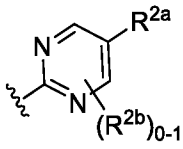
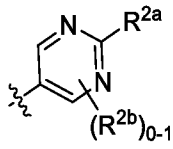
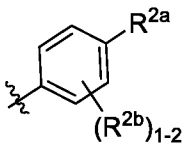
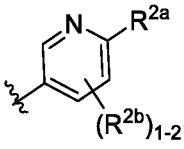
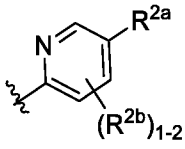
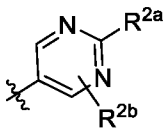
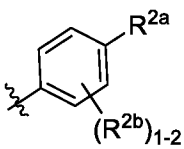
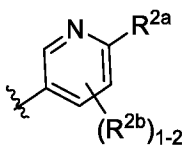
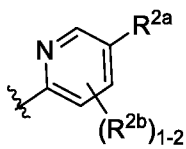
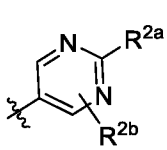
where R^{1a}, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Ic-1) is that where R^2 is , , , , , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ic-1) is that where R^2 is , , , , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ic-1) is that where R^3 and R^4 are hydrogen.

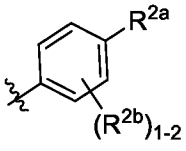
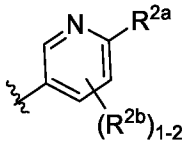
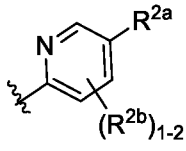
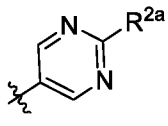
[00187] In some or any embodiments, the Compound is according to Genus A Formula (Id-1):



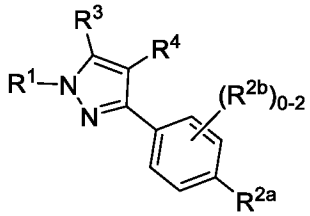
(Id-1);

where R^{1a}, R^{1b}, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Id-1) is that where R^2 is , , , , ,

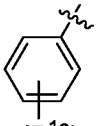
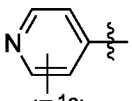
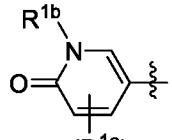
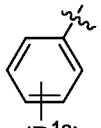
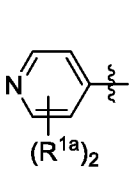
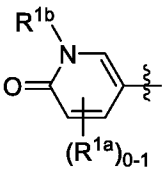

, or 
; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Id-1) is that where R^2 is 
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, or 
; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Id-1) is that where R^2 is 
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, or 
; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Id-1) is that where R^2 is 
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, or 
; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Id-1) is that where R^2 is 
, 
, 
, or 
; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Id-1) is that where R^2 is





; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Id-1) is that where R^3 and R^4 are hydrogen.

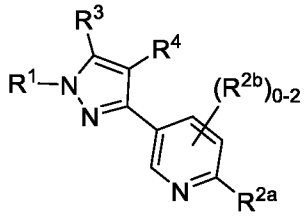
[00188] In some or any embodiments, the Compound is according to Genus A Formula (Ie-1):



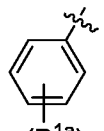
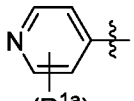
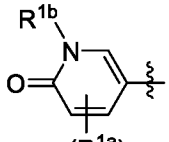
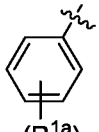
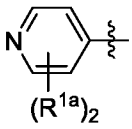
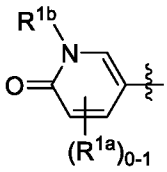
(Ie-1);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Ie-1) is that wherein R^1 is , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ie-1) is that wherein R^1 is , , or ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ie-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus A Formula (Ie-1) is that where one R^{2b} is present.

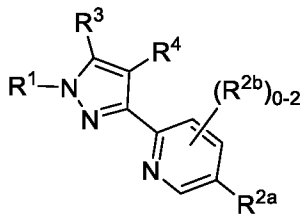
[00189] In some or any embodiments, the Compound is according to Genus A Formula (If-1):



(If-1);

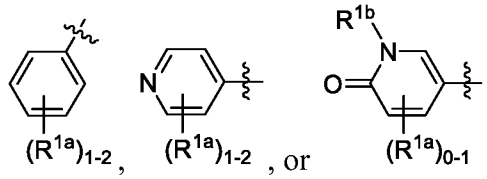
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (If-1) is that wherein R^1 is , , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (If-1) is that wherein R^1 is , , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (If-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus A Formula (If-1) is that where one R^{2b} is present.

[00190] In some or any embodiments, the Compound is according to Genus A Formula (Ig-1):



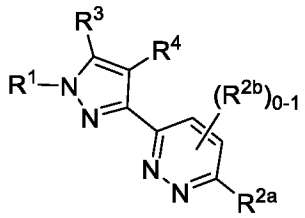
(Ig-1);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Ig-1) is that



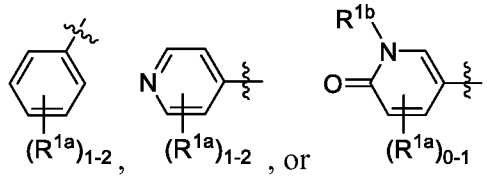
wherein R^1 is $(R^{1a})_{1-2}$, $(R^{1a})_{1-2}$, or $(R^{1a})_{0-1}$; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ig-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus A Formula (Ig-1) is that where one R^{2b} is present.

[00191] In some or any embodiments, the Compound is according to Genus A Formula (Ih-1):



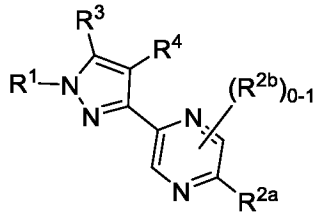
(Ih-1);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Ih-1) is that

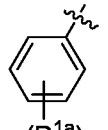
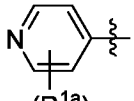
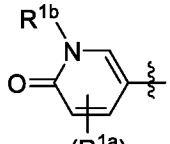


wherein R^1 is $(R^{1a})_{1-2}$, $(R^{1a})_{1-2}$, or $(R^{1a})_{0-1}$; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ih-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus A Formula (Ih-1) is that where one R^{2b} is present.

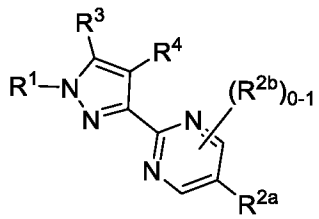
[00192] In some or any embodiments, the Compound is according to Genus A Formula (Ij-1):



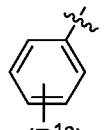
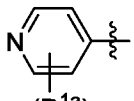
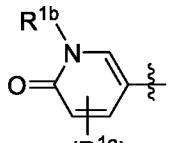
(Ij-1);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Ij-1) is that wherein R^1 is , , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Ij-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus A Formula (Ij-1) is that where one R^{2b} is present.

[00193] In some or any embodiments, the Compound is according to Genus A Formula (Ik-1):

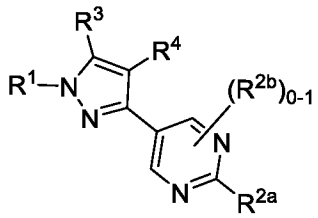


(Ik-1);

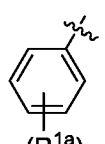
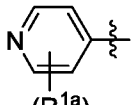
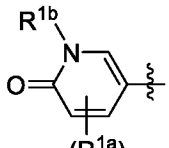
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Ik-1) is that wherein R^1 is , , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any

embodiments, the Compound of Genus A Formula (Ik-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus A Formula (Ik-1) is that where one R^{2b} is present.

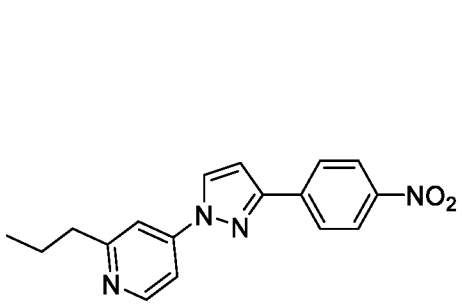
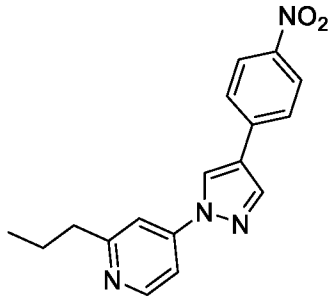
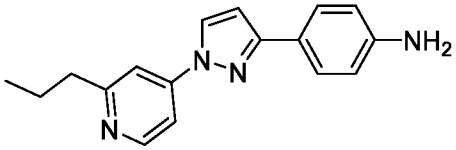
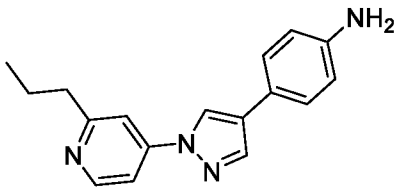
[00194] In some or any embodiments, the Compound is according to Genus A Formula (Im-1):



(Im-1);

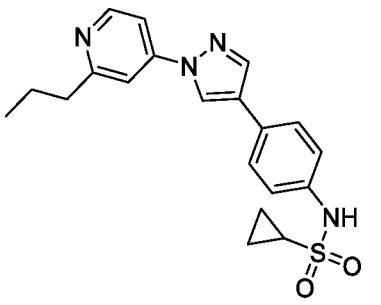
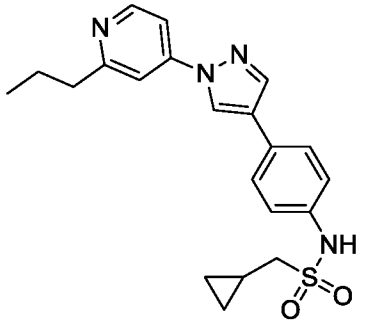
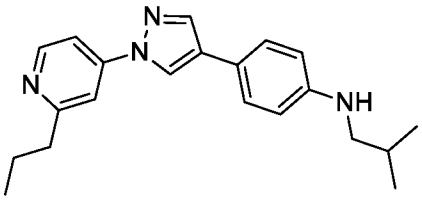
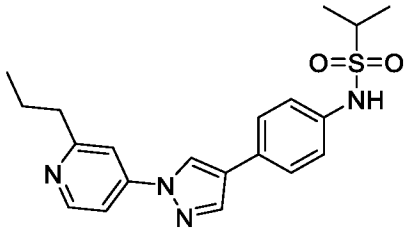
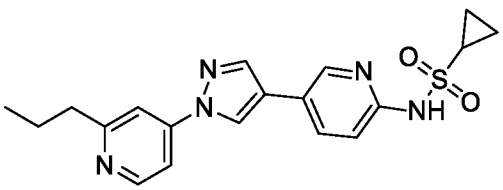
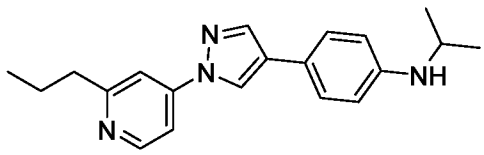
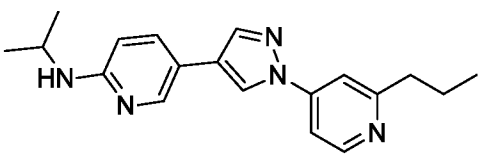
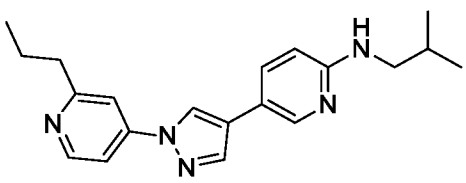
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus A Formula (Im-1) is that wherein R^1 is , , or  ; and all other groups are as defined in the Summary of Genus A Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus A Formula (Im-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus A Formula (Im-1) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus A Formula (Im-1) is that where no R^{2b} is present.

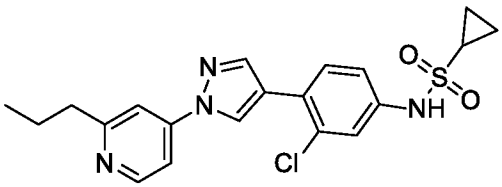
[00195] In some or any embodiments, the Compound of Genus A Formula (II) or (200) is not

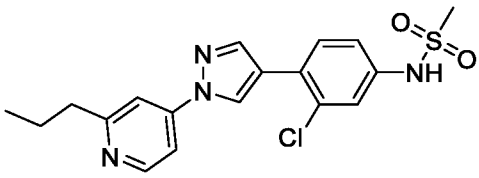

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, or

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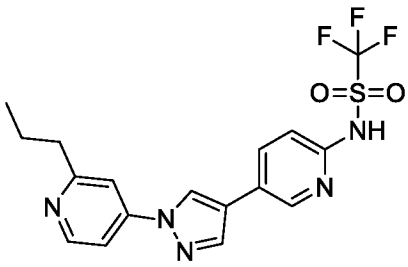
In some or any embodiments, the Compound (e.g., of Genus A Formula (II) and (200), and any embodiments thereof) is not a pharmaceutically acceptable salt of one of the specific compounds in this paragraph.

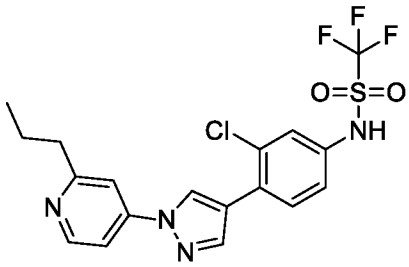
[00196] In some or any embodiments, provided is a Genus A Compound according to any of the following formula, which were prepared as described in WO2017/190086:

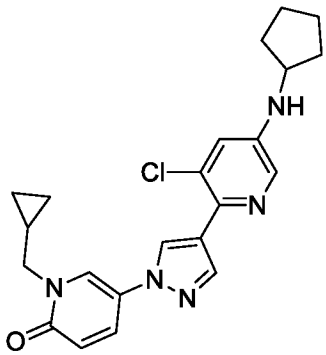









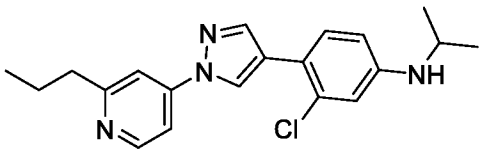


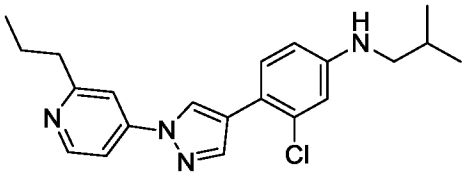


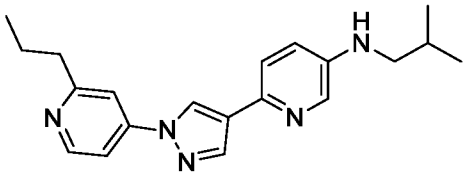


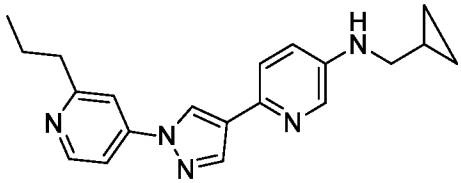


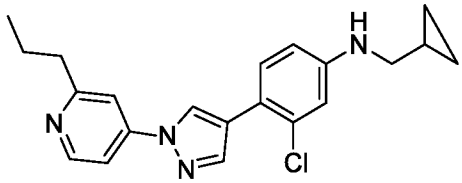


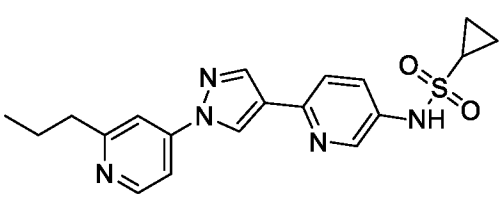


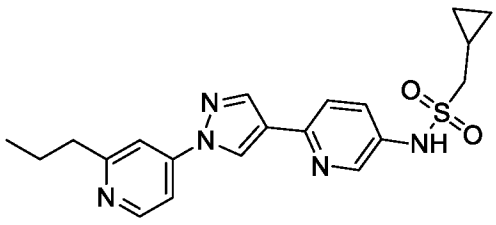


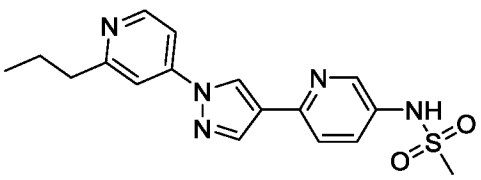


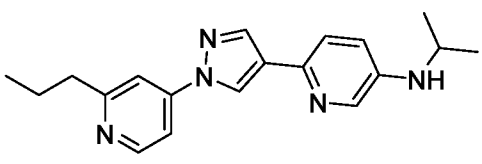


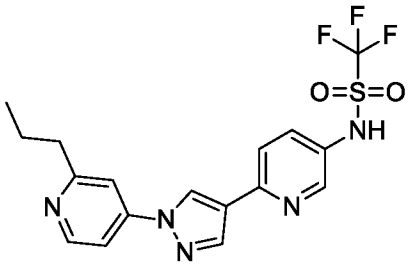


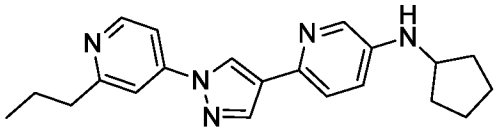


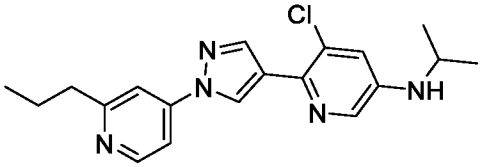


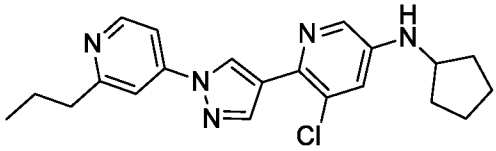


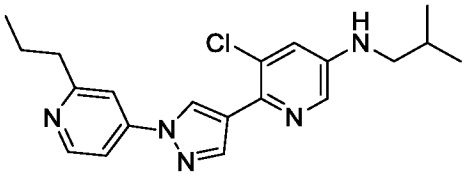


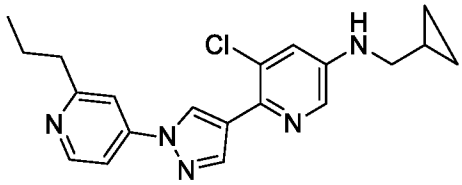


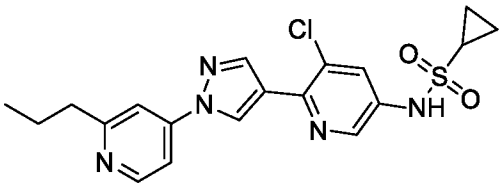


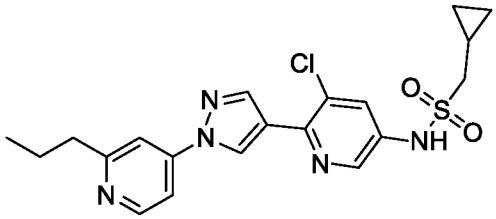


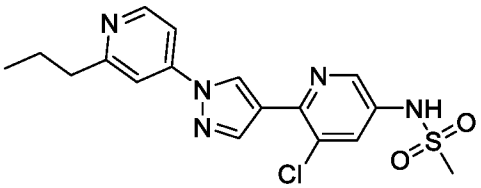


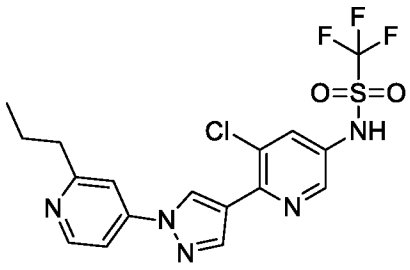


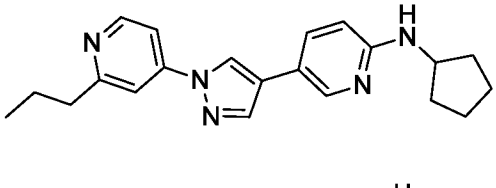


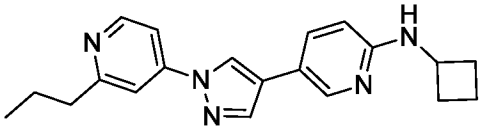


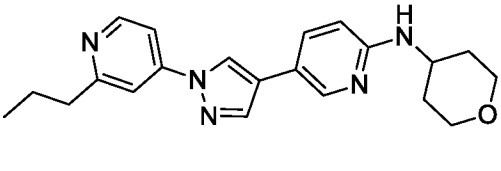


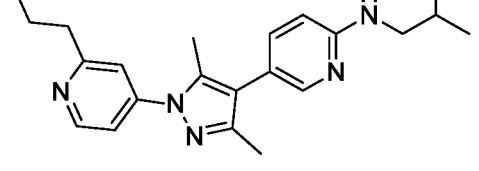


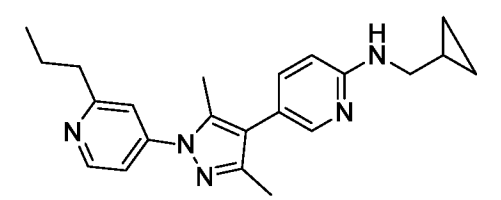


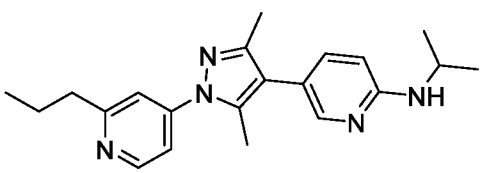


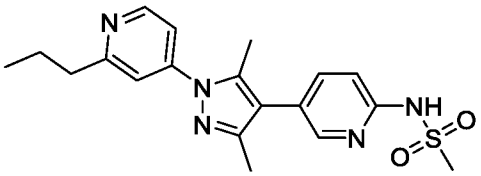


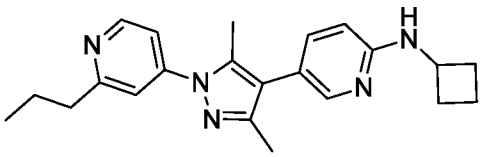


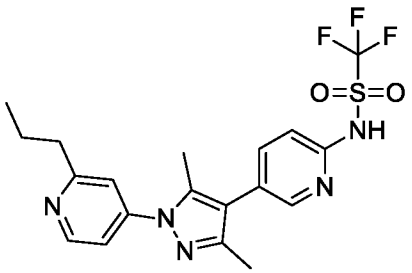


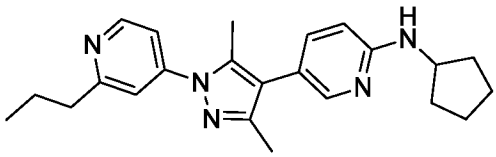


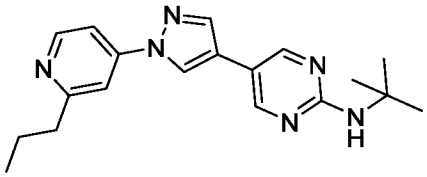


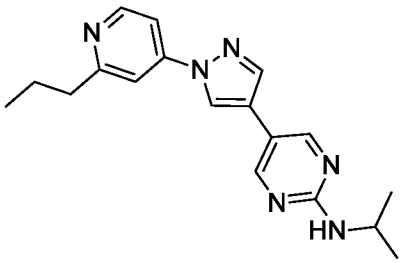


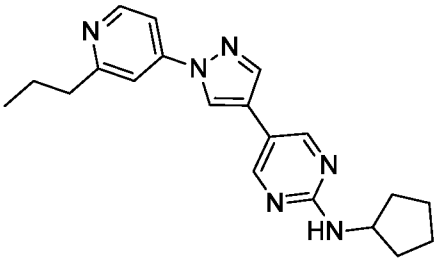


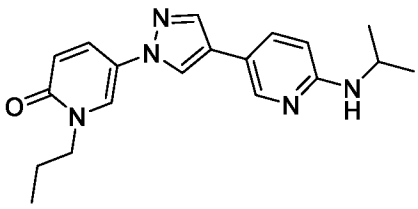


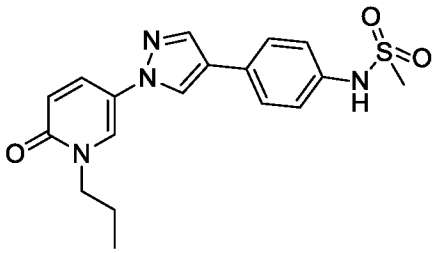


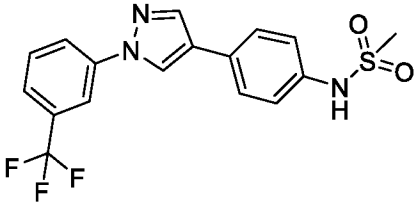


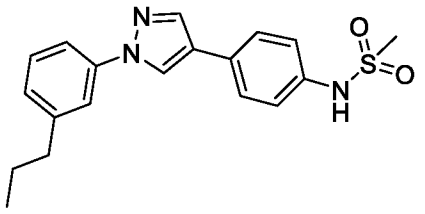


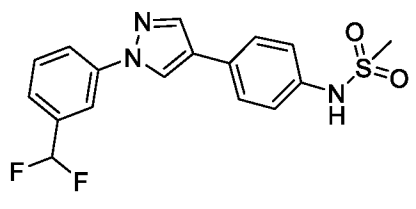


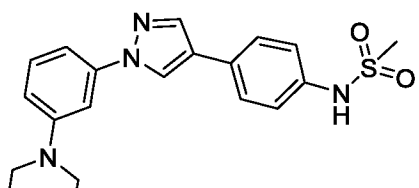


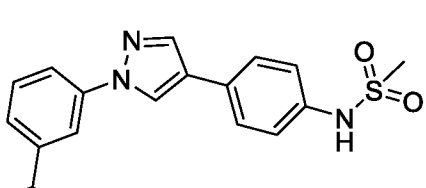


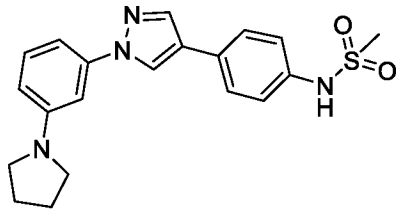


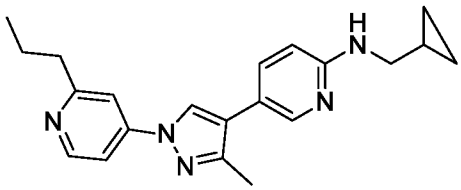


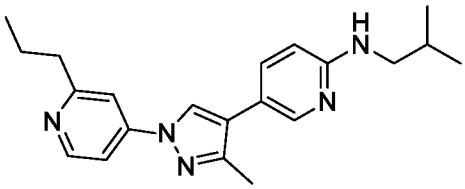


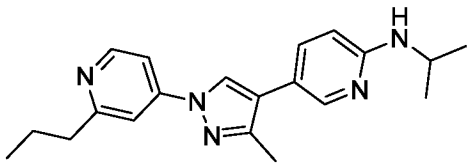


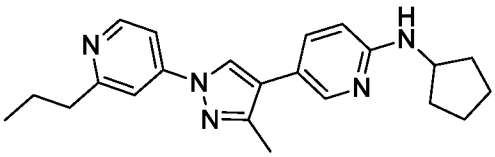


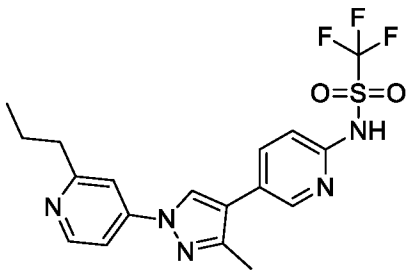


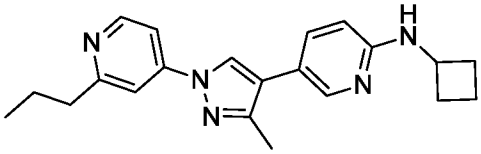


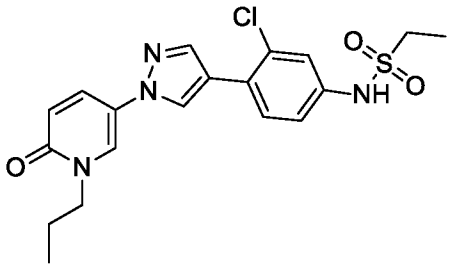


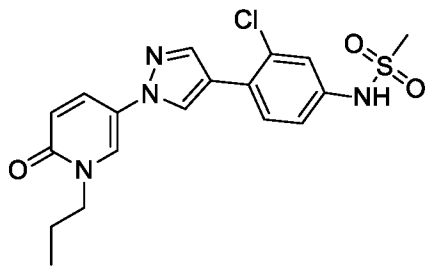


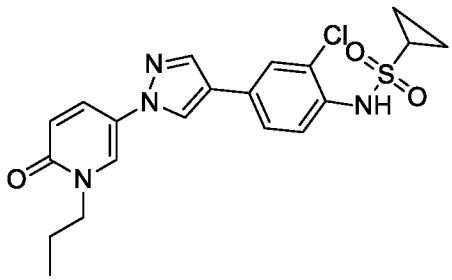


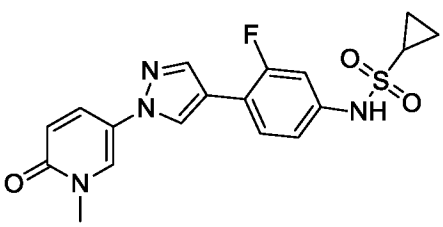


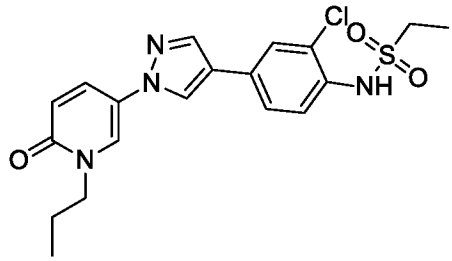


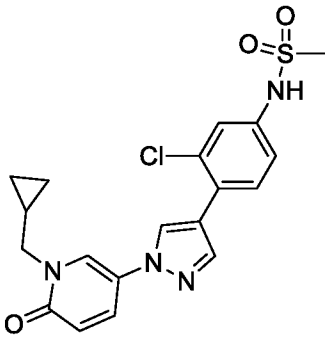


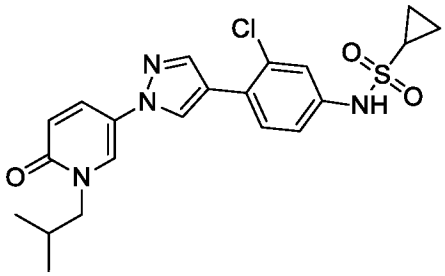


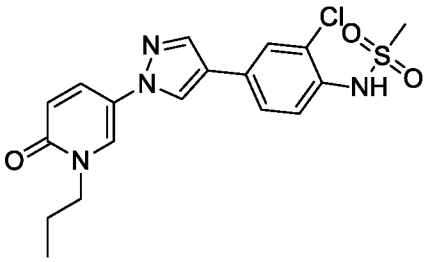


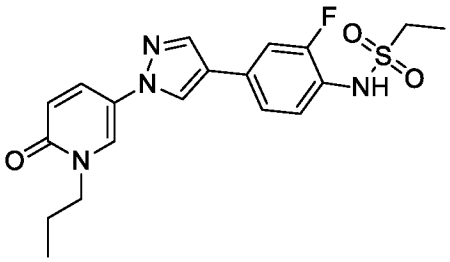


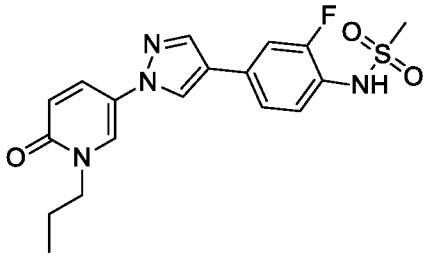


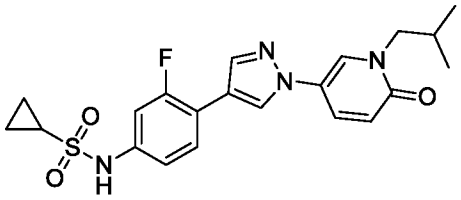


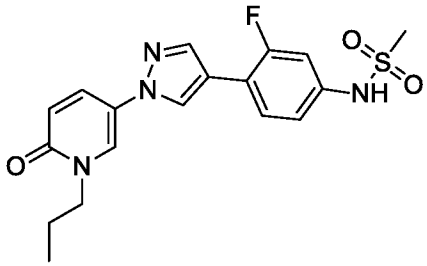


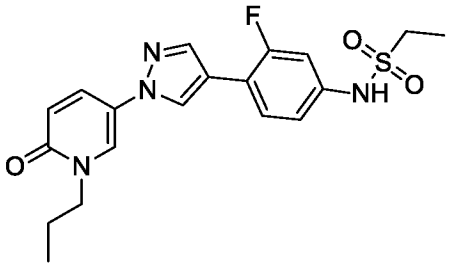


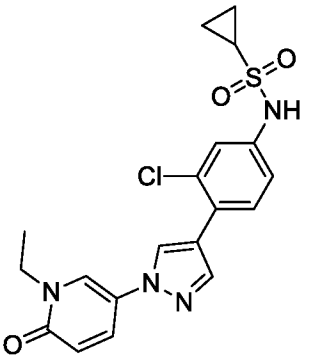


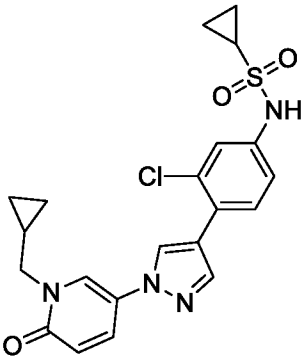


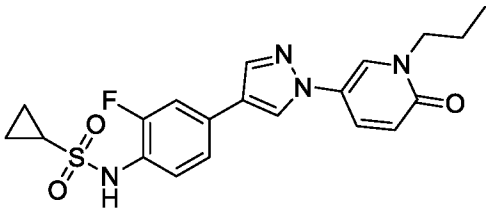


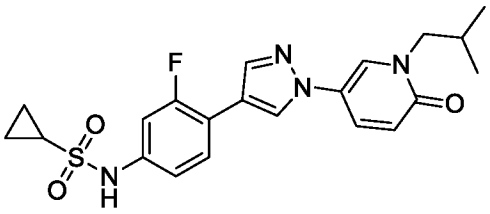


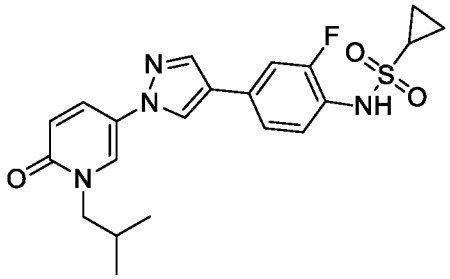


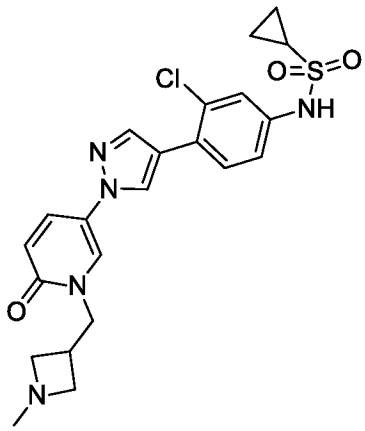


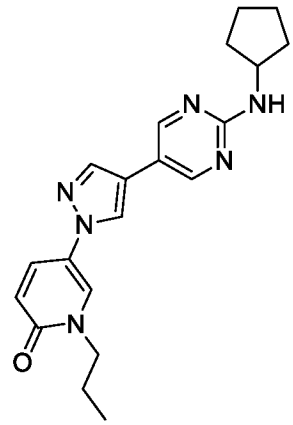


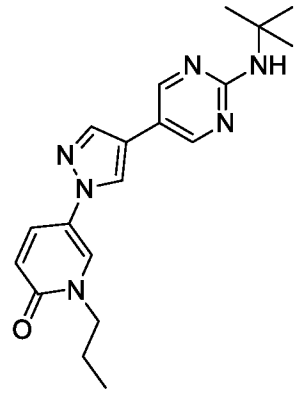


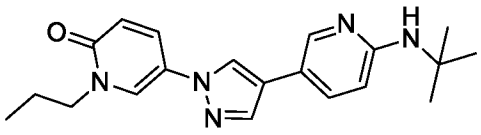


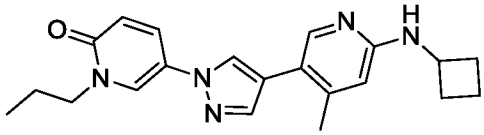


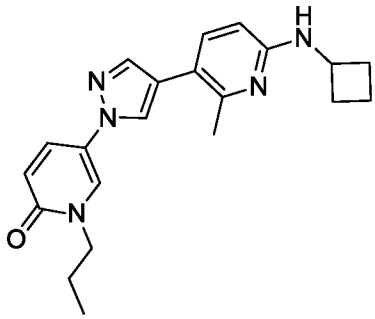


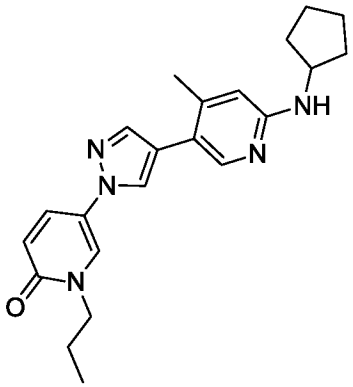


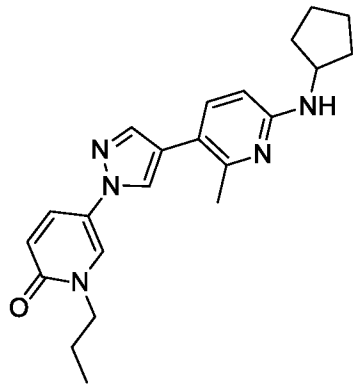


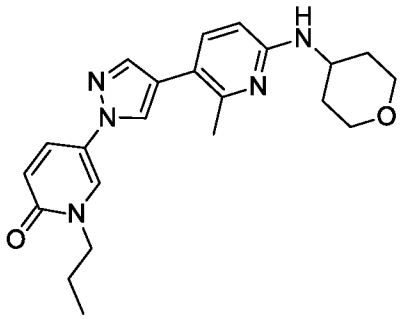


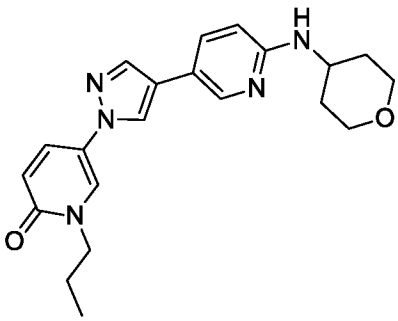


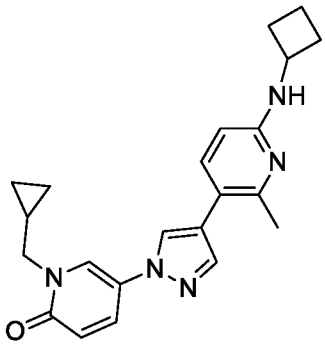


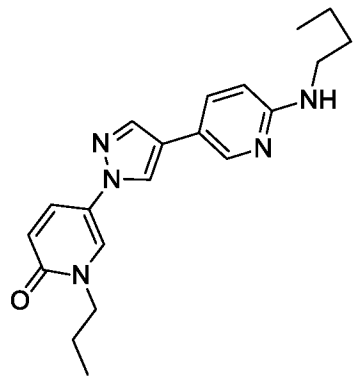


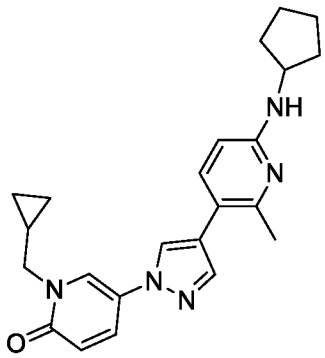


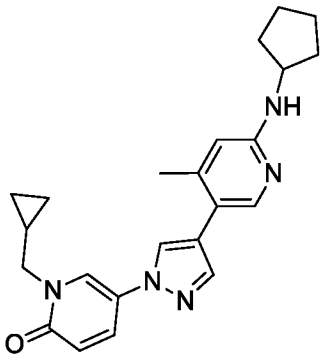


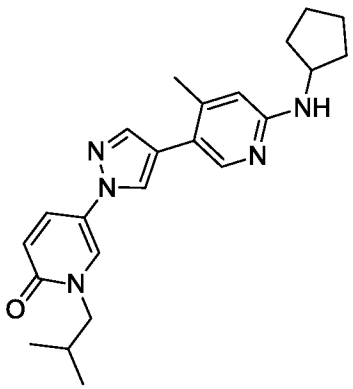


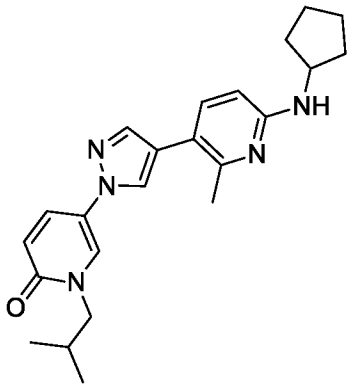


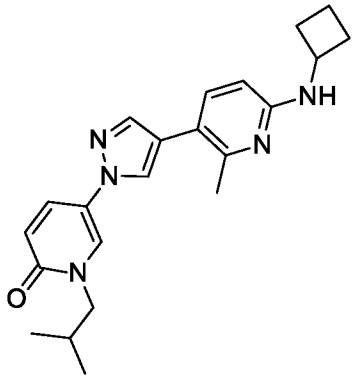


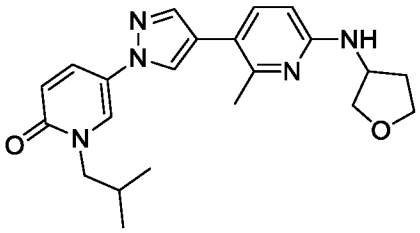


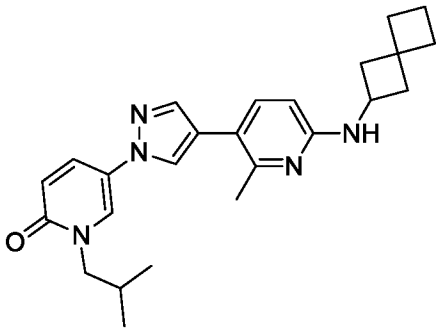


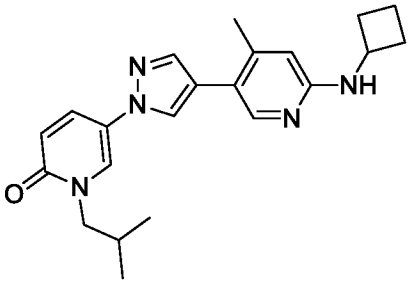


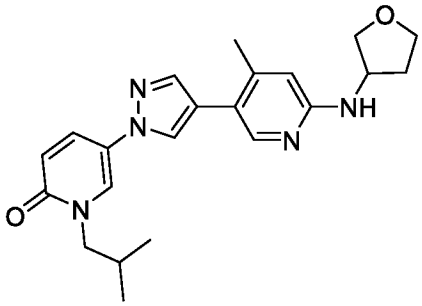


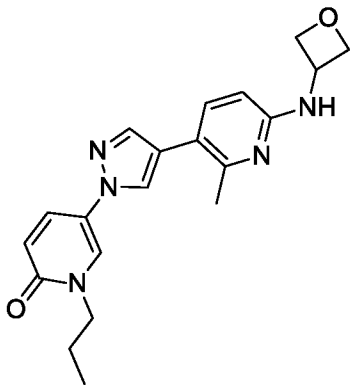


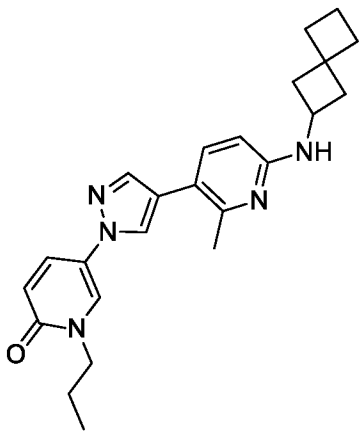


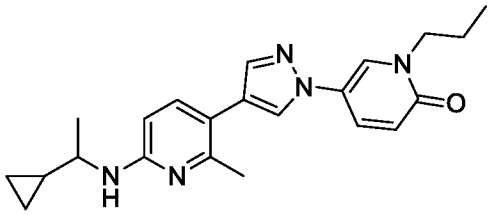


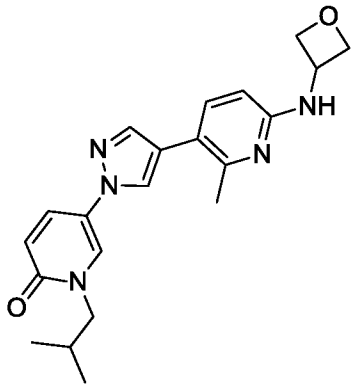


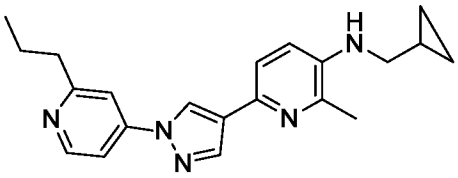


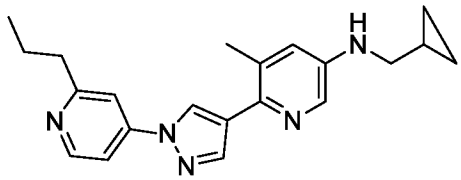


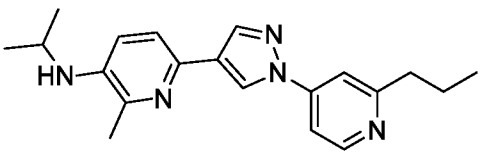


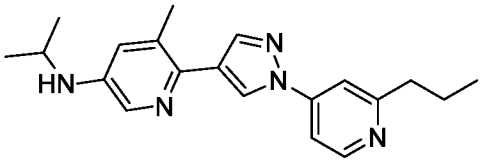


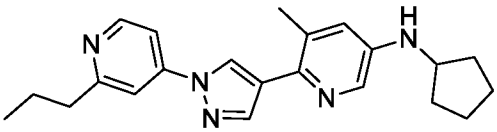


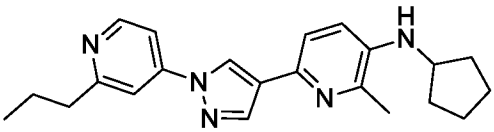


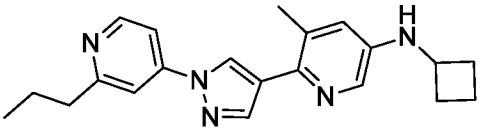


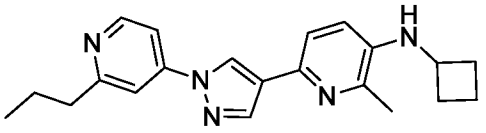


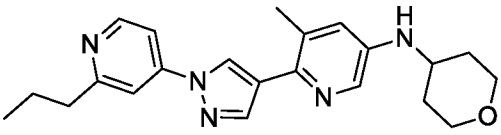


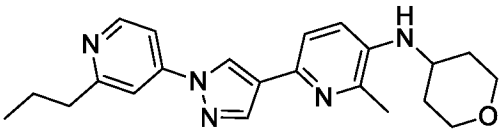


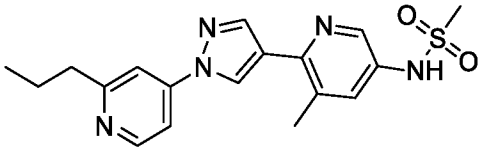


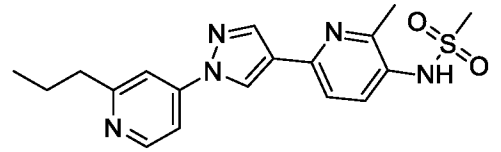


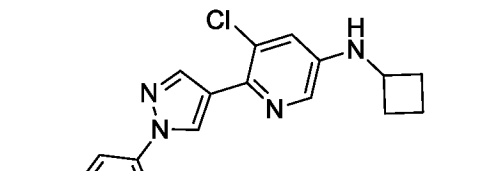


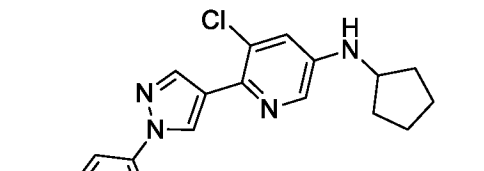






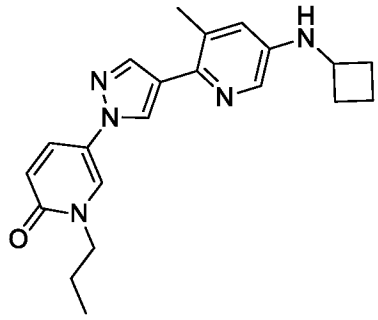


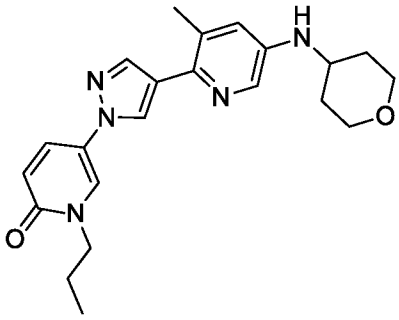


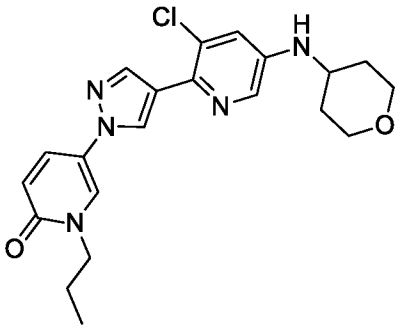


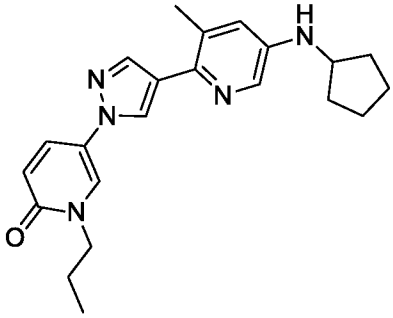


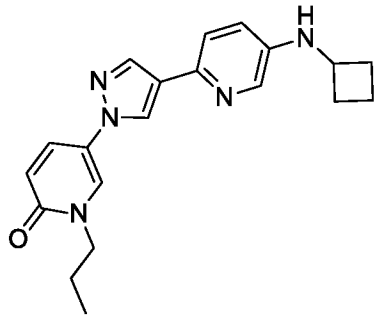


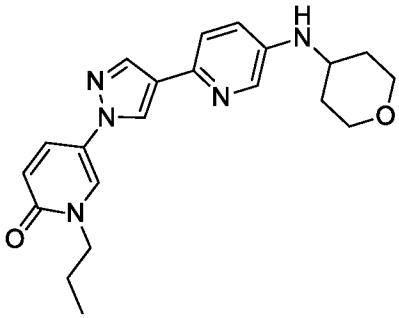


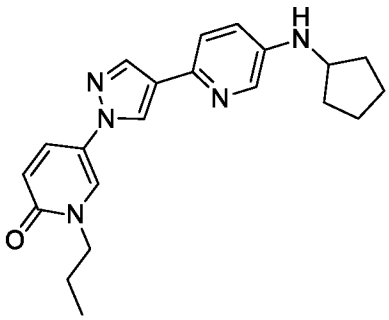


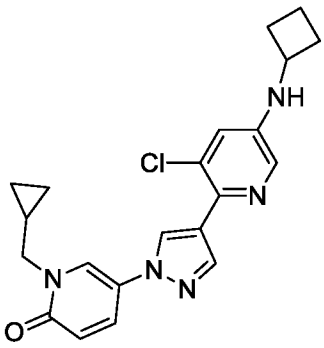


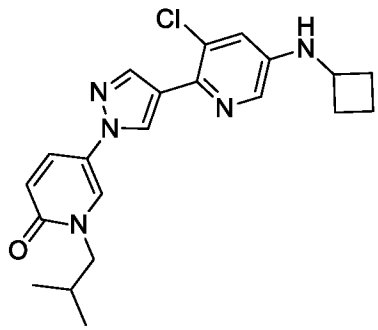


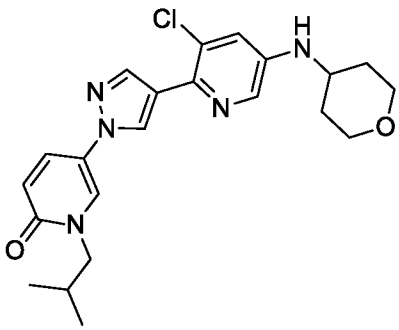






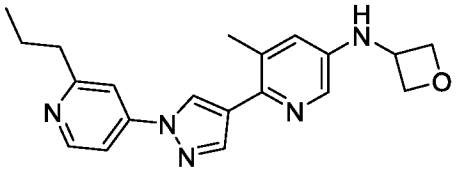


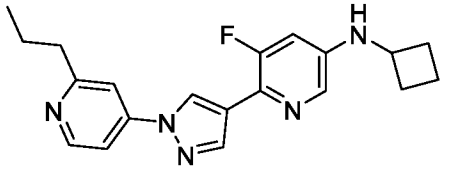




[00197] Additional compounds described herein (Genus A Embodiment A) include the following:

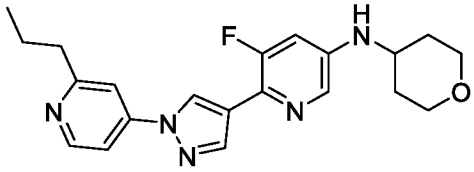
Genus A Embodiment A

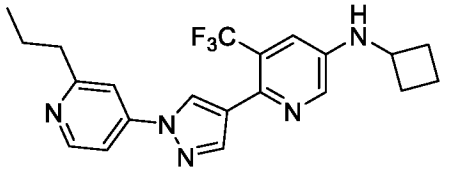


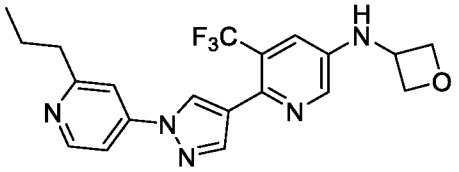


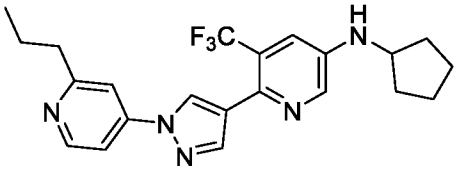


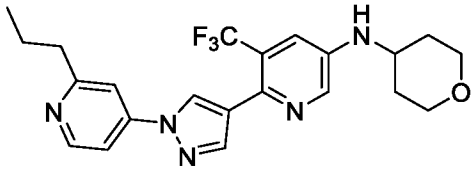


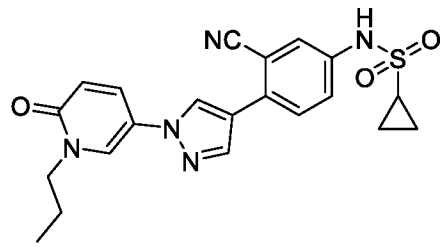


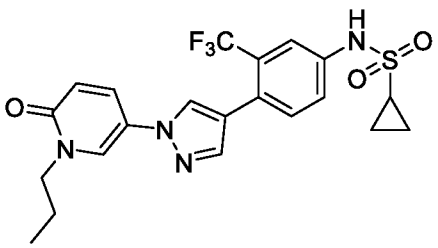


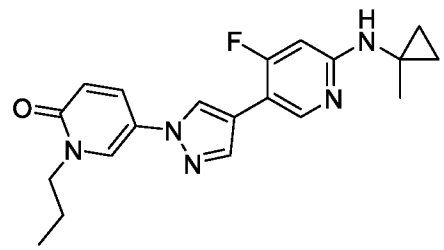


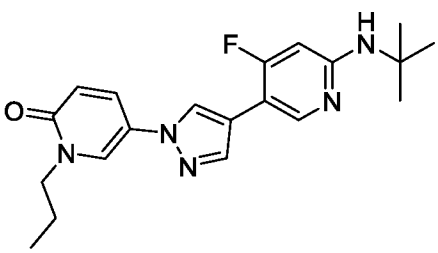


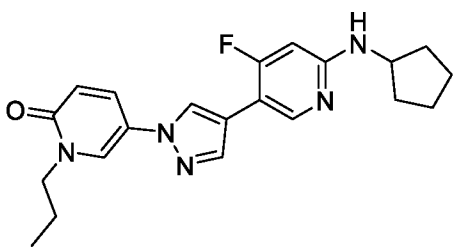




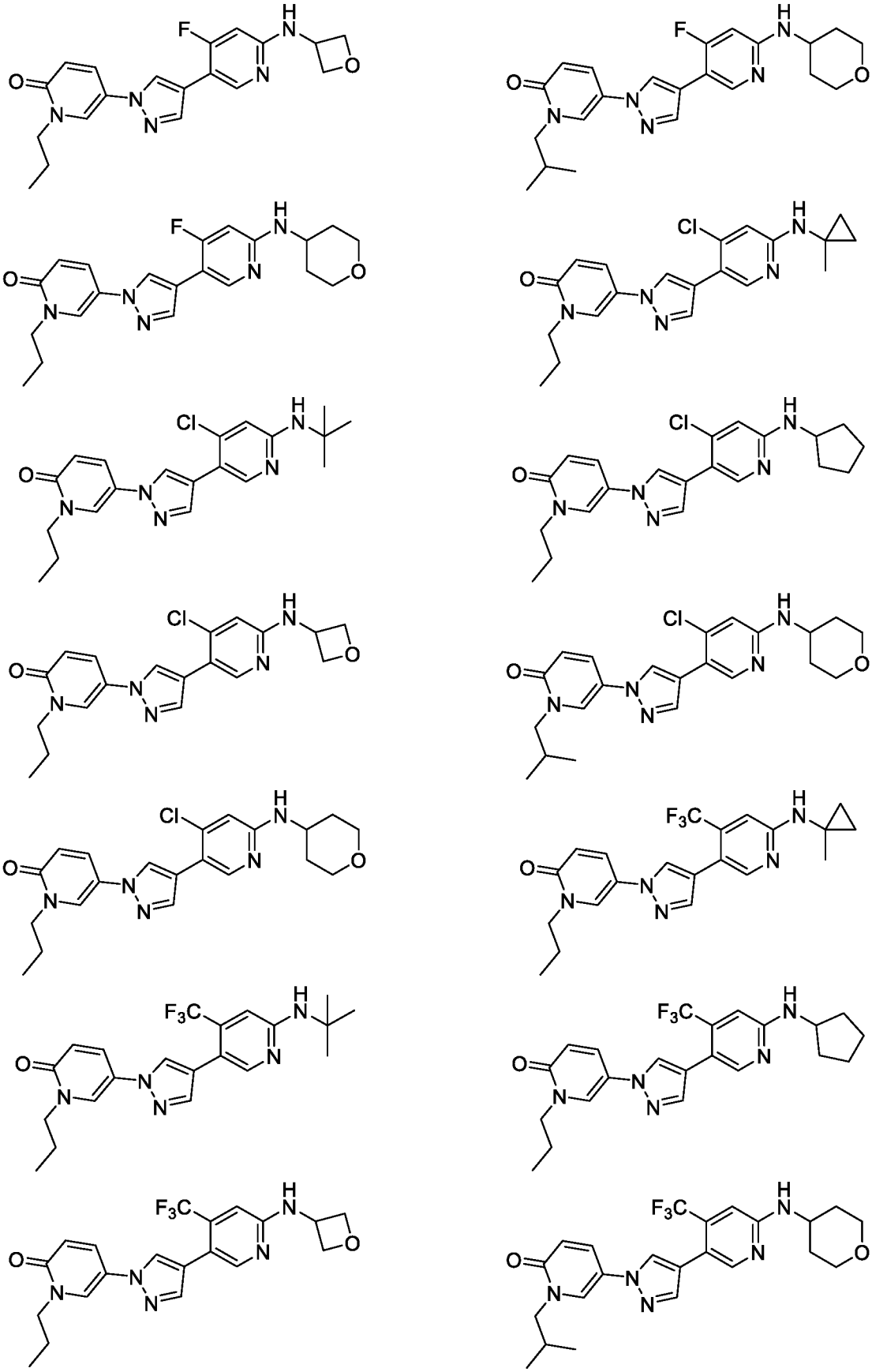




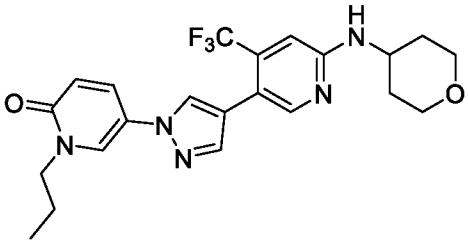


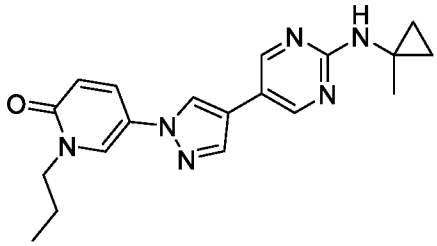


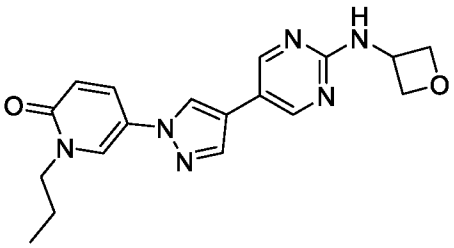
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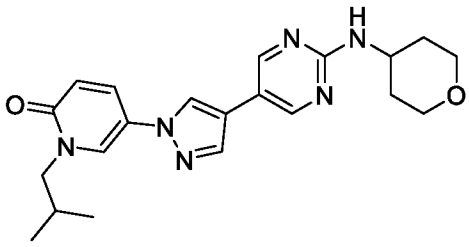


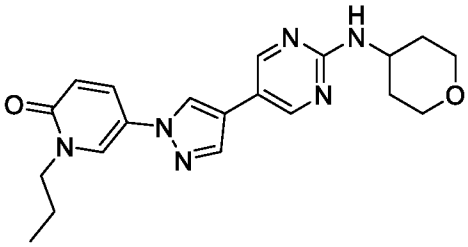
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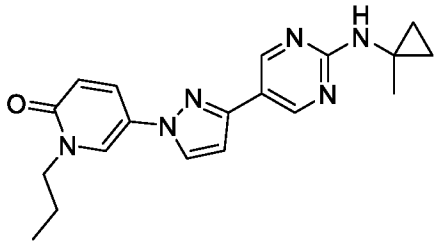


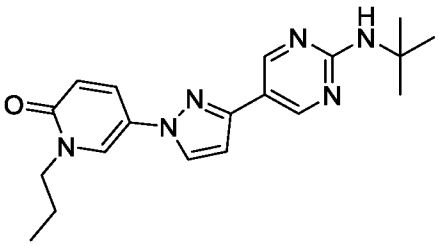


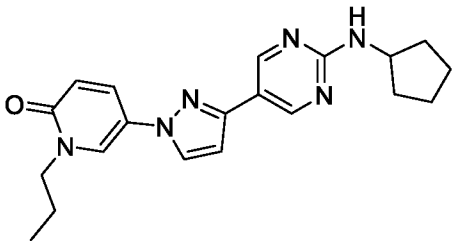


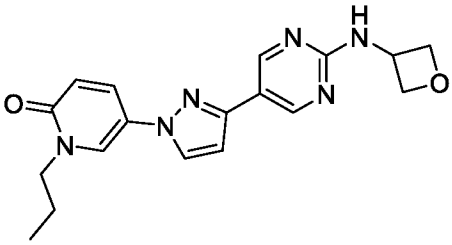


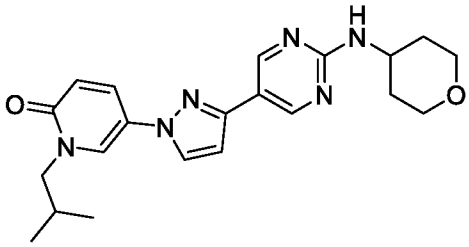


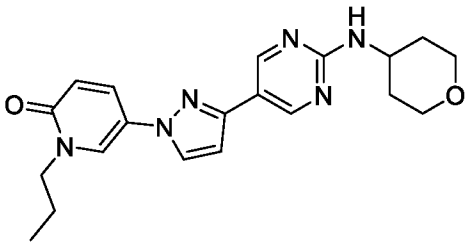


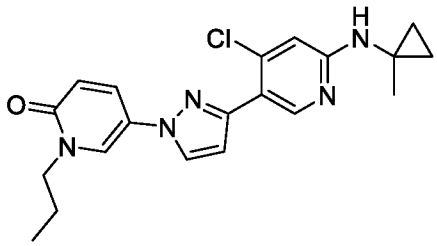


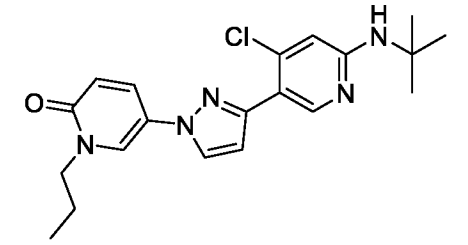


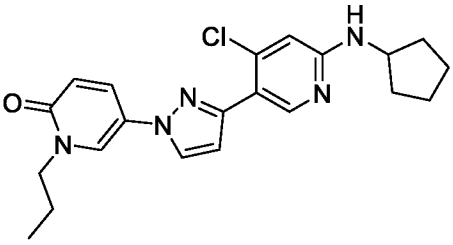




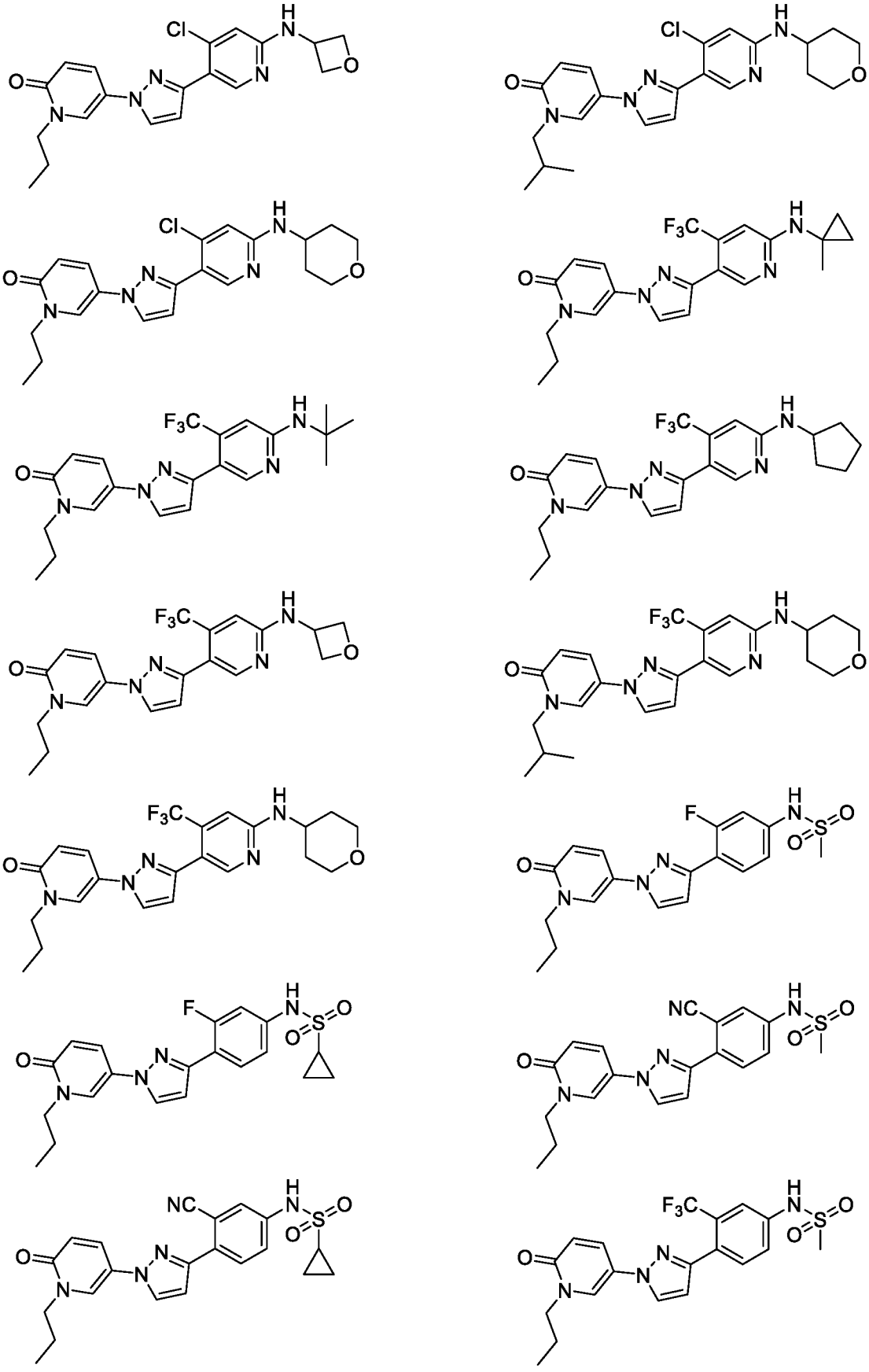




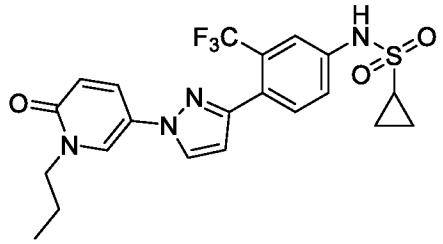


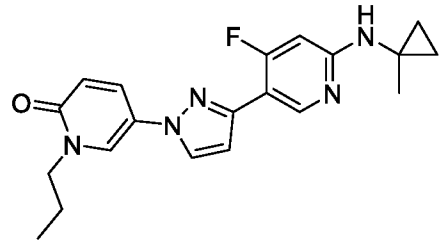


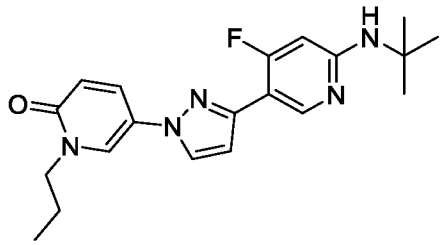
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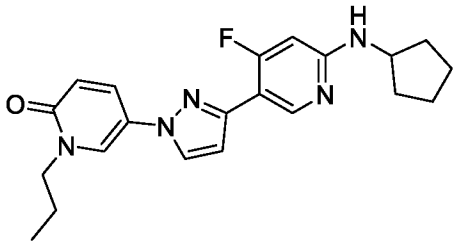


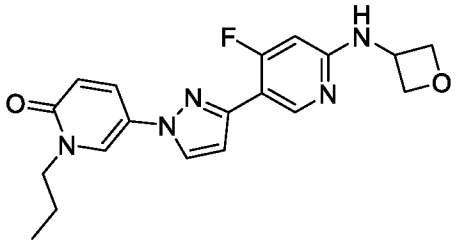
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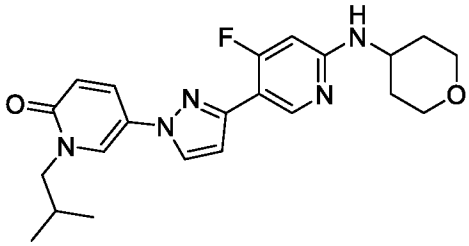


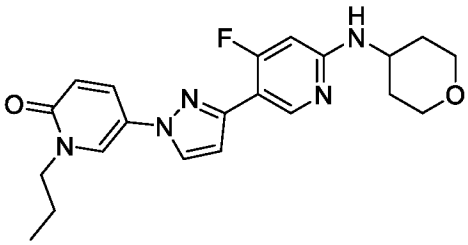


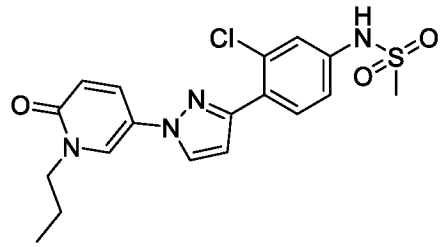


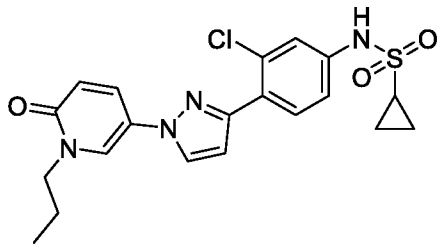


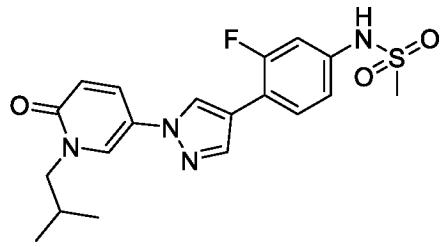


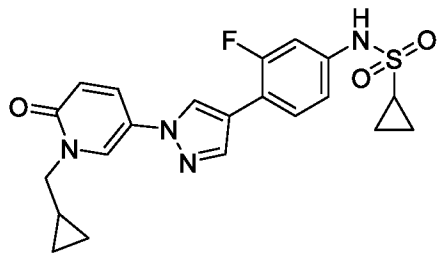


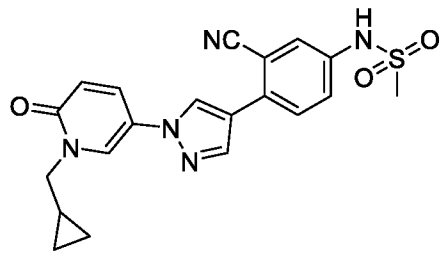


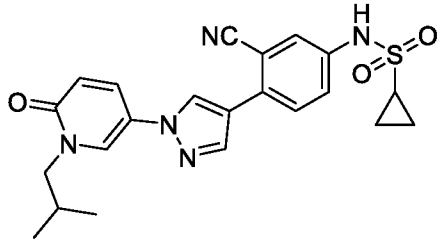


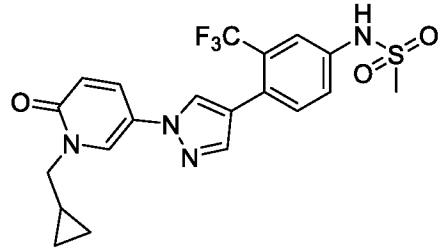




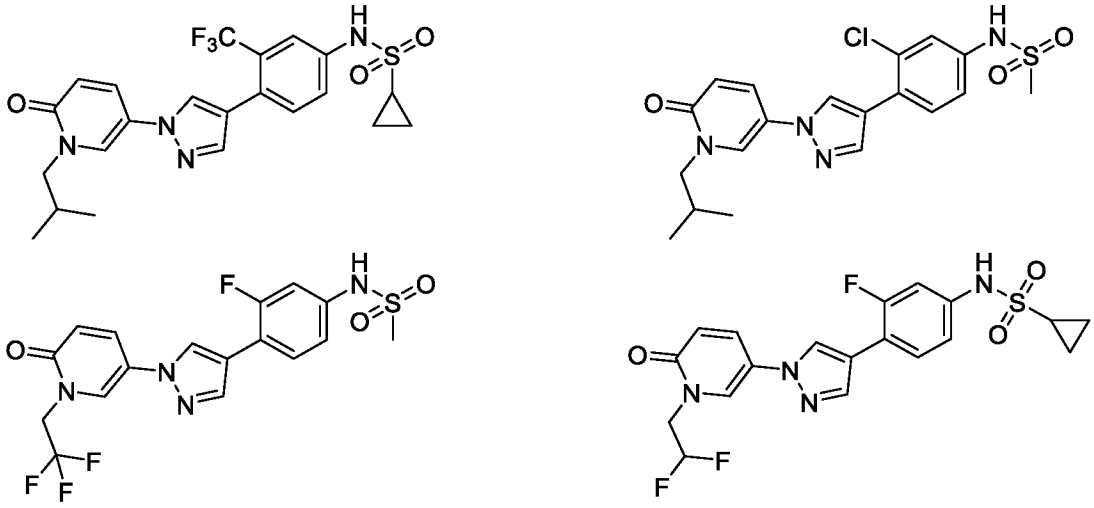








Genus A Embodiment A

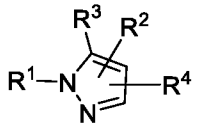


Preparation of Genus A Compounds

[00198] The compounds provided herein can be prepared, isolated, or obtained by any method apparent to those of skill in the art, including those disclosed in WO2017/190086, which is incorporated herein by reference in its entirety. Reaction conditions, steps, and reactants not provided in WO2017/190086 would be apparent to, and known by, those skilled in the art.

GENUS B

[00199] Summary of Genus B Formula (I): In some or any embodiments, the SREBP inhibitor is according to a Genus B Compound of Formula (I):



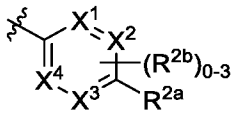
(I)

where

R^1 is pyridinonyl, where the pyridinonyl is substituted on its nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a};

R^{1a}, when present, is halo, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{1b} is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are CH or CR^{2b};

R^{2a} is $-OR^5$, $-S(O)R^6$, or $-S(O)_2R^7$;

each R^{2b}, when present, is independently halo, alkyl, haloalkyl, $-NO_2$, or cyano;

R^3 is hydrogen, halo, alkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl, or haloalkyl; and

R^5, R^6, and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl, alone or as part of cycloalkylalkyl, and heterocycloalkyl, alone or as part of heterocycloalkylalkyl, are optionally substituted with 1, 2, or 3 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; or

a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[00200] In some or any embodiments, the SREBP inhibitor is provided as a pharmaceutical composition, single unit dosage form, and kit suitable for use in treating disorders associated with activation (in some embodiments abnormal activation) of the SREBP pathway and/or of one or more target genes that are essential for proliferation which comprise a therapeutically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments, of Genus B Formula (I)-(Ij), (Ia-1)-(Ij-1), and specific compounds, and a pharmaceutically acceptable carrier thereof.

Genus B Definitions

[00201] When referring to the compounds provided herein, the following terms have the following meanings unless indicated otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise. Unless specified otherwise, where a term is defined as being unsubstituted or substituted, the groups in the list of substituents are themselves unsubstituted. For example, a substituted alkyl group can be substituted, for example, with a cycloalkyl group, and the cycloalkyl group is not further substituted unless specified otherwise.

[00202] "Acyl" means a –C(O)R group where R is alkyl, as defined herein.

[00203] "Alkoxy" means an –OR group where R is an alkyl group as defined herein.

[00204] "Alkenyl" means a straight or branched hydrocarbon radical having from 2 to 8 carbon atoms and at least one double bond and in some embodiments, includes ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like. "Lower alkenyl" means an alkenyl group having one to six carbon atoms. Alkenyl is not substituted unless stated otherwise.

[00205] "Alkyl" means a linear or branched hydrocarbon group having one to eight carbon atoms. "Lower alkyl" means an alkyl group having one to six carbon atoms. In some embodiments, lower alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl, and the like. A "C_0" alkyl (as in "C_0-C_6-alkyl") is a covalent bond. "C_6 alkyl" refers to, for example, *n*-hexyl, *iso*-hexyl, and the like.

[00206] "Alkylsulfonyl" means a $-S(O)_2R$ group where R is an alkyl group as defined herein.

[00207] "Cycloalkyl" means a monocyclic or polycyclic hydrocarbon radical having three to thirteen carbon atoms. The cycloalkyl can be saturated or partially unsaturated, but cannot contain an aromatic ring. In some embodiments, cycloalkyl includes fused, bridged, and spiro ring systems. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[00208] "Cycloalkylalkyl" means alkyl group substituted with one or two cycloalkyl group(s), as defined herein. In some embodiments, cycloalkylalkyl includes cyclopropylmethyl, 2-cyclobutyl-ethyl, and the like.

[00209] "Haloalkyl" means an alkyl group, as defined herein, substituted with one or more halogens, for example one, two, three, four, or five halo atoms. In some embodiments, haloalkyl includes 2,2-difluoroethyl, trifluoromethyl, and 2-chloro-1-fluoroethyl, and the like.

[00210] "Heterocycloalkyl" means a saturated or partially unsaturated (but not aromatic) monovalent monocyclic group of 3 to 9 ring atoms or a saturated or partially unsaturated (but not aromatic) monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more heteroatoms are present, for example, one, two, three, or four ring heteroatoms, independently selected from -O-, $-S(O)_n-$ (n is 0, 1, or 2), -N=, $-N(R^y)-$ (where R^y is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl), and the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the point of attachment of the group may be located on any atom of any ring within the radical, valency rules permitting. In particular, when the point of attachment is located on a nitrogen atom, R^y is absent. In some embodiments, the term heterocycloalkyl includes, but is not

limited to, azetidinyl, pyrrolidinyl, 2-oxopyrrolidinyl, 2,5-dihydro-1*H*-pyrrolyl, piperidinyl, 4-piperidonyl, morpholinyl, piperazinyl, 2-oxopiperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, thiomorpholinyl, thiamorpholinyl, perhydroazepinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, oxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, thiazolidinyl, quinuclidinyl, isothiazolidinyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, tetrahydrofuryl, and tetrahydropyranyl, and an N-oxide thereof.

[00211] "Heterocycloalkylalkyl" means an alkyl group, as defined herein, substituted with one or two heterocycloalkyl group(s), as defined herein.

[00212] "Hydroxyalkyl" means an alkyl group, as defined herein, substituted with at least one, in some embodiments one, two, or three, hydroxy group(s), provided that if two hydroxy groups are present they are not both on the same carbon atom. In some embodiments, hydroxyalkyl includes, but is not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl, 2-(hydroxymethyl)-3-hydroxypropyl, 2-hydroxyethyl, 2,3-dihydroxypropyl, or 1-(hydroxymethyl)-2-hydroxyethyl, and the like.

Genus B Compounds

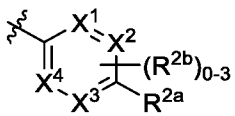
[00213] In some or any embodiments, the Compound is according to Genus B Formula (I)-(Ij). In some or any embodiments, the pharmaceutical composition comprises a Compound according to Genus B Formula (I)-(Ij). In some or any embodiments, the method of treating comprises administering a Compound according to Genus B Formula (I)-(Ij).

[00214] In one embodiment is a Compound of Genus B Formula (I) where

R^1 is pyridinonyl, where the pyridinonyl is substituted on its nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a};

R^{1a}, when present, is halo, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{1b} is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are CH or CR^{2b};

R^{2a} is $-OR^5$, $-S(O)R^6$, or $-S(O)_2R^7$;

each R^{2b}, when present, is independently halo, alkyl, haloalkyl, -NO_2, or cyano;

R^3 is hydrogen, halo, alkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl, or haloalkyl; and

R^5, R^6, and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl and heterocycloalkyl, alone or as part of another group, are optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, and hydroxyalkyl; or

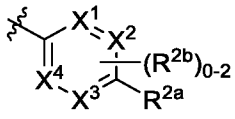
a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[00215] In one embodiment is a Compound of Genus B Formula (I) where

R^1 is pyridinonyl, where the pyridinonyl is substituted on its nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a};

R^{1a}, when present, is halo, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{1b} is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are CH or CR^{2b};

R^{2a} is –OR^5, –S(O)R^6, or –$S(O)_2R^7$;

each R^{2b}, when present, is independently halo, alkyl, haloalkyl, -NO_2, or cyano;

R^3 is hydrogen, halo, alkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl, or haloalkyl; and

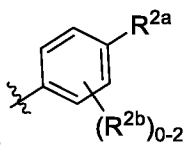
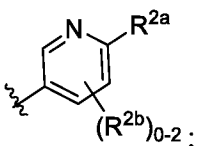
R^5, R^6, and R^7 are independently alkyl; haloalkyl; cycloalkyl, where the cycloalkyl is optionally substituted with 1 or 2 alkyl groups; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; or

a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[00216] In one embodiment, provided is a Compound of Genus B Formula (I) where

R^1 is pyridinonyl, where the pyridinonyl is substituted on its nitrogen with R^{1b};

R^{1b} is alkyl;

R^2 is  or ;

R^{2a} is –OR^5 or –$S(O)_2R^7$;

each R^{2b}, when present, is halo or alkyl;

R^3 is hydrogen;

R^4 is hydrogen;

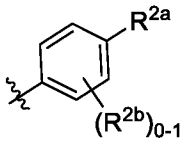
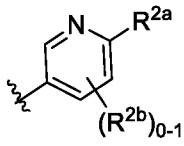
R^5 and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl, alone or as part of cycloalkylalkyl, and heterocycloalkyl, alone or as part of heterocycloalkylalkyl, are optionally substituted with 1, 2, or 3 groups independently selected from hydroxy, halo, and hydroxyalkyl; or

a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[00217] In one embodiment, provided is a Compound of Genus B Formula (I) where

R^1 is pyridinonyl, where the pyridinonyl is substituted on its nitrogen with R^{1b};

R^{1b} is alkyl;

R^2 is  or ;

R^{2a} is $-OR^5$ or $-S(O)_2R^7$;

R^{2b}, when present, is halo or alkyl;

R^3 is hydrogen;

R^4 is hydrogen; and

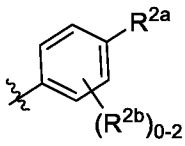
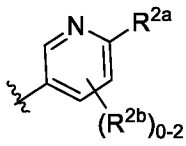
R^5 and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl, alone or as part of cycloalkylalkyl, and heterocycloalkyl, alone or as part of heterocycloalkylalkyl, are optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; or

a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[00218] In one embodiment, provided is a Compound of Genus B Formula (I) where

R^1 is pyridinonyl, where the pyridinonyl is substituted on its nitrogen with R^{1b};

R^{1b} is alkyl;

R^2 is  or ;

R^{2a} is $-OR^5$ or $-S(O)_2R^7$;

each R^{2b}, when present, is halo or alkyl;

R^3 is hydrogen;

R^4 is hydrogen;

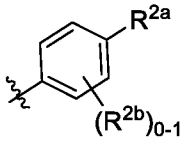
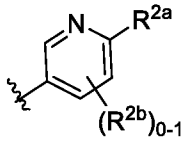
R^5 and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; cycloalkyl; cycloalkylalkyl, or heterocycloalkylalkyl; where the cycloalkyl, alone or as part of cycloalkylalkyl, and heterocycloalkyl, alone or as part of heterocycloalkylalkyl, are optionally substituted with 1 or 2 groups independently selected from one hydroxy and hydroxyalkyl; or

a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[00219] In one embodiment, provided is a Compound of Genus B Formula (I) where

R^1 is pyridinonyl, where the pyridinonyl is substituted on its nitrogen with R^{1b};

R^{1b} is alkyl;

R^2 is  or ;

R^{2a} is $-OR^5$ or $-S(O)_2R^7$;

R^{2b}, when present, is halo or alkyl;

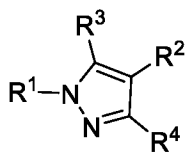
R^3 is hydrogen;

R^4 is hydrogen; and

R^5 and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; cycloalkyl; cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, where the cycloalkyl, alone or as part of cycloalkylalkyl, and heterocycloalkyl, alone or as part of heterocycloalkylalkyl, are optionally substituted with one hydroxy or hydroxyalkyl; or

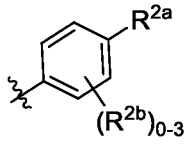
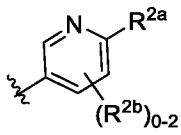
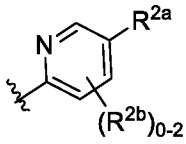
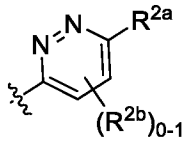
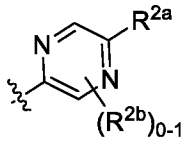
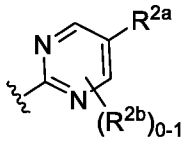
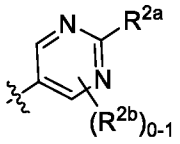
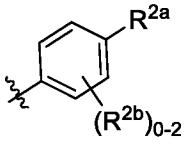
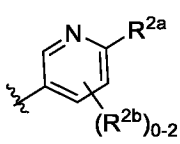
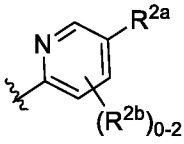
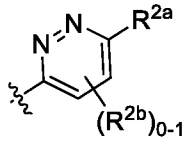
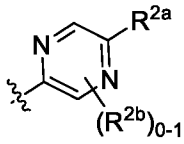
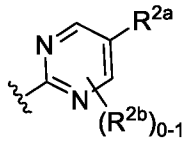
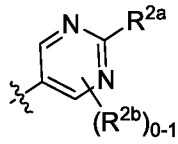
a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[00220] In some or any embodiments, the Compound according to Genus B Formula (Ia) is:

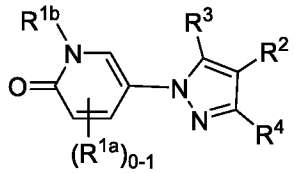


(Ia);

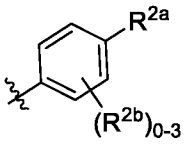
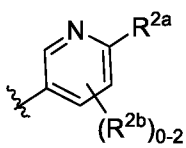
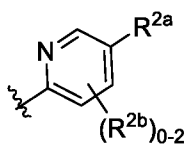
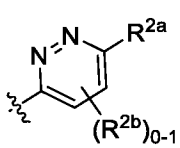
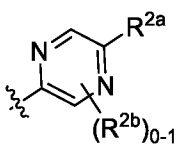
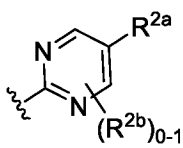
where R^1, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the

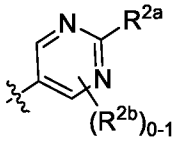
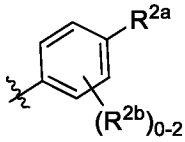
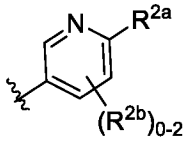
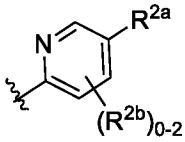
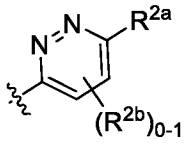
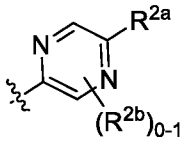
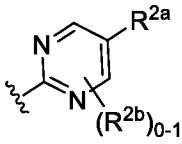
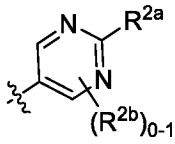
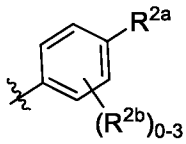
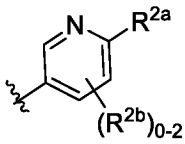
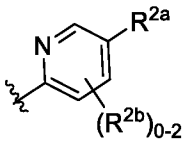
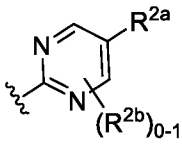
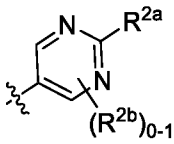
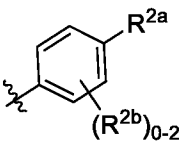
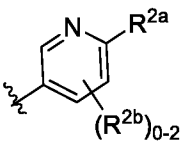
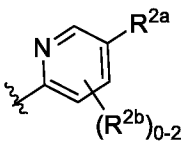
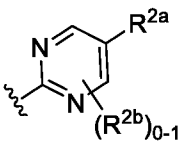
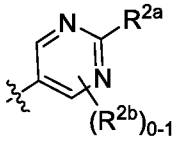
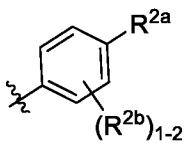
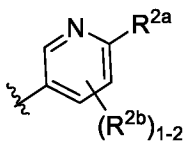
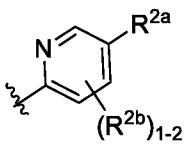
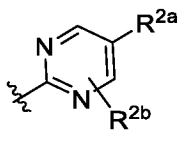
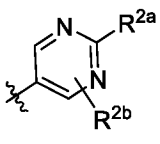
Compound of Genus B Formula (Ia) is that where R^2 is , , , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ia) is that where R^2 is , , , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ia) is that where R^3 and R^4 are hydrogen.

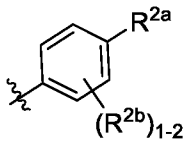
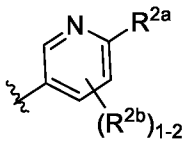
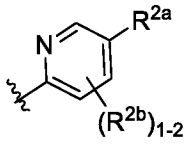
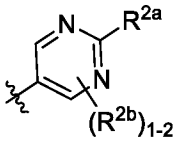
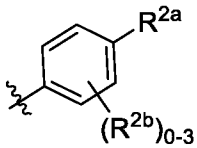
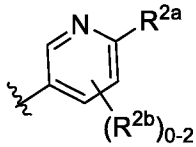
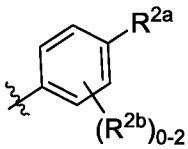
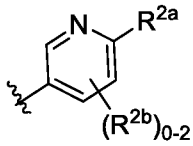
[00221] In some or any embodiments, the Compound is according to Genus B Formula (Ib):



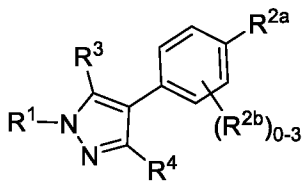
(Ib);

where R^{1a}, R^{1b}, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ib) is that where R^2 is , , , , , , or


; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib) is that where R^2 is , , , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib) is that where R^2 is , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib) is that where R^2 is , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib) is that where R^2 is , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the

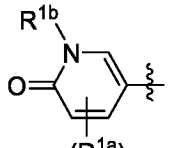
Compound of Genus B Formula (Ib) is that where R^2 is , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib) is that where R^2 is  or ; and all other groups are as defined in the Summary. In some or any embodiments, the Compound of Genus B Formula (Ib) is that where R^2 is  or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib) is that where R^3 and R^4 are hydrogen.

[00222] In some or any embodiments, the Compound is according to Genus B Formula (Ic):

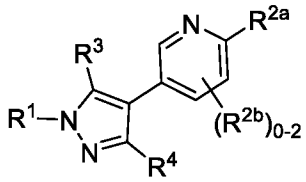


(Ic);

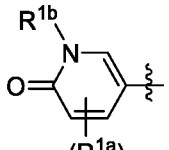
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ic) is that wherein there are 0-2 R^{2b}; and

all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ic) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ic) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ic) is that where two R^{2b} are present. In some or any embodiments, the Compound of Genus B Formula (Ic) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (Ic) is that where no R^{2b} is present.

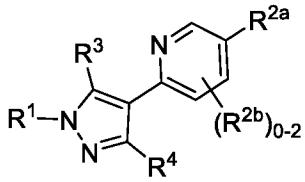
[00223] In some or any embodiments, the Compound is according to Genus B Formula (Id):



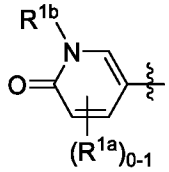
(Id);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Id) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Id) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Id) is that where one R^{2b} is present.

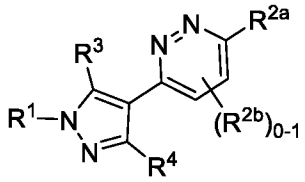
[00224] In some or any embodiments, the Compound is according to Genus B Formula (Ie):



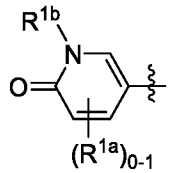
(Ie);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ie) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ie) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ie) is that where one R^{2b} is present.

[00225] In some or any embodiments, the Compound is according to Genus B Formula (If):

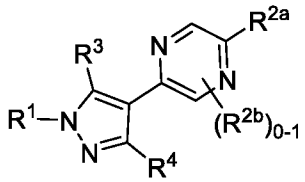


(If);

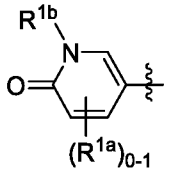
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (If) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (If) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the

Compound of Genus B Formula (If) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (If) is that where no R^{2b} is present.

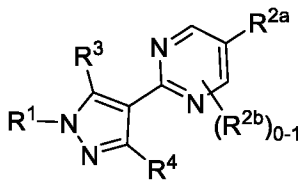
[00226] In some or any embodiments, the Compound is according to Genus B Formula (Ig):



(Ig);

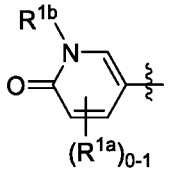
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ig) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ig) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ig) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (Ig) is that where no R^{2b} is present.

[00227] In some or any embodiments, the Compound is according to Genus B Formula (Ih):



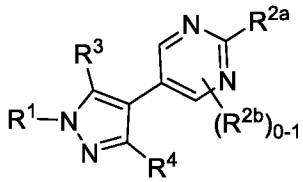
(Ih);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any



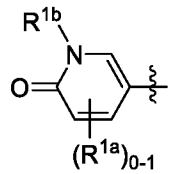
embodiments, the Compound of Genus B Formula (Ih) is that wherein R^1 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ih) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ih) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (Ih) is that where no R^{2b} is present.

[00228] In some or any embodiments, the Compound is according to Genus B Formula (Ij):



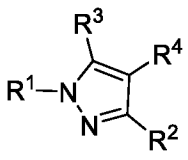
(Ij);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any

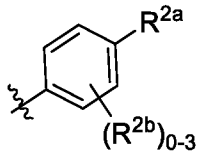
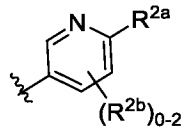
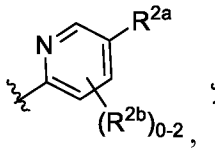
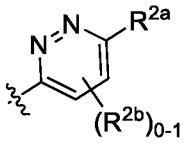
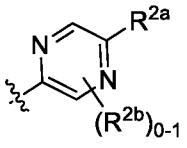
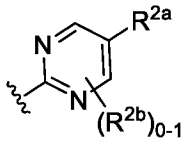
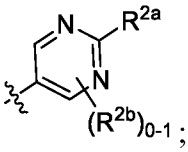
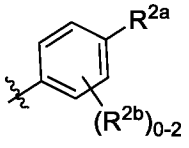
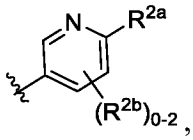
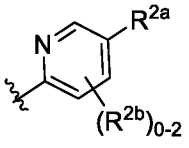
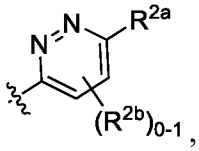
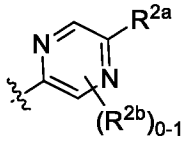
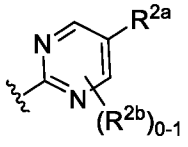
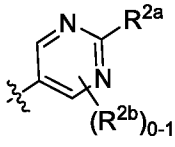
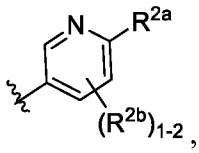
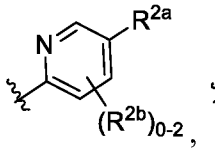
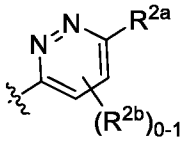
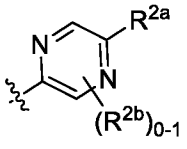
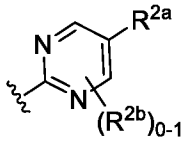
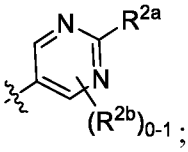


embodiments, the Compound of Genus B Formula (Ij) is that wherein R^1 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ij) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ij) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (Ij) is that where no R^{2b} is present.

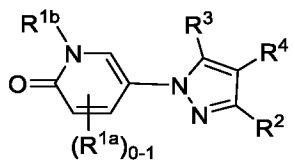
[00229] In some or any embodiments, the Compound is according to Genus B Formula (Ia-1):



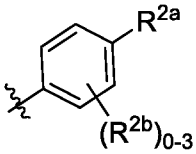
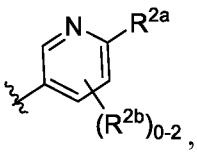
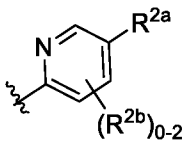
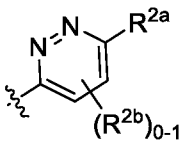
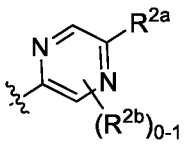
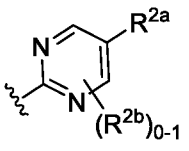
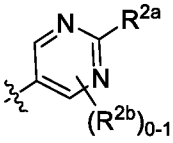
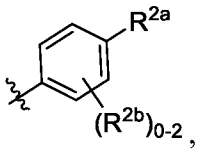
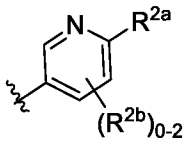
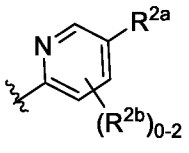
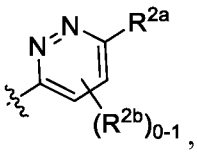
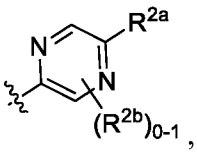
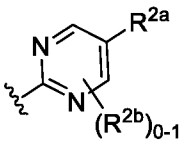
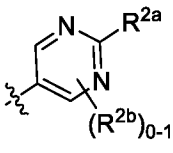
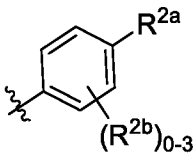
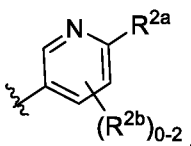
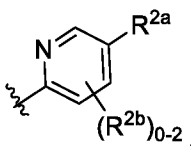
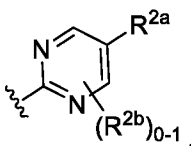
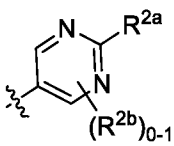
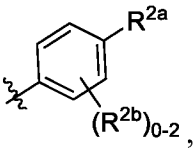
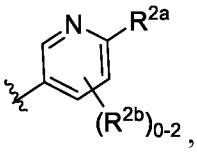
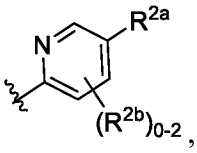
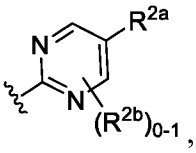
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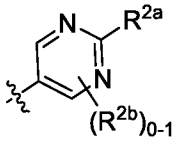
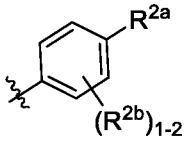
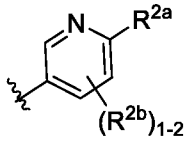
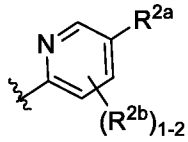
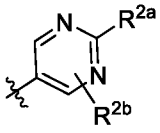
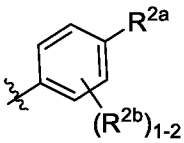
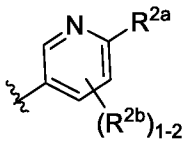
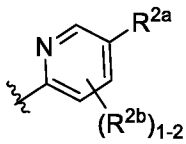
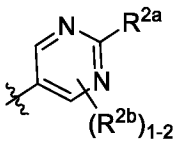
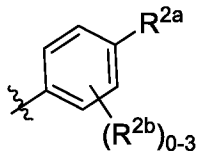
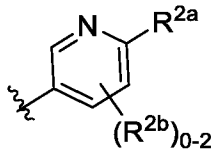
where R^1, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ia-1) is that where R^2 is , , , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ia-1) is that where R^2 is , , , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ia-1) is that where R^2 is , , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ia-1) is that where R^3 and R^4 are hydrogen.

[00230] In some or any embodiments, the Compound is according to Genus B Formula (Ib-1):

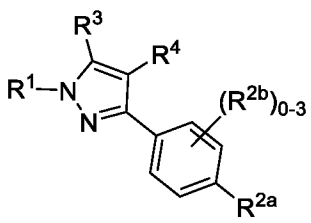


(Ib-1);

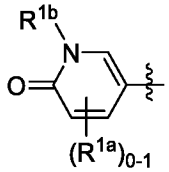
where R^{1a}, R^{1b}, R^2, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ib-1) is that where R^2 is , , , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib-1) is that where R^2 is , , , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib-1) is that where R^2 is , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib-1) is that where R^2 is , , , , or


; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib-1) is that where R^2 is , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib-1) is that where R^2 is , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib-1) is that where R^2 is  or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ib-1) is that where R^3 and R^4 are hydrogen.

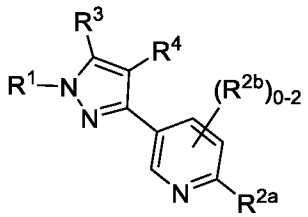
[00231] In some or any embodiments, the Compound is according to Genus B Formula (Ic-1):



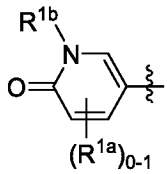
(Ic-1);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ic-1) is that wherein there are 0-2 R^{2b}; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ic-1) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ic-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ic-1) is that where two R^{2b} are present. In some or any embodiments, the Compound of Genus B Formula (Ic-1) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (Ic-1) is that where no R^{2b} is present.

[00232] In some or any embodiments, the Compound is according to Genus B Formula (Id-1):

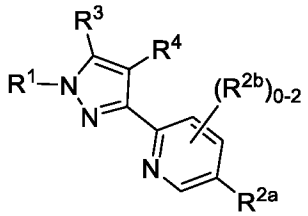


(Id-1);

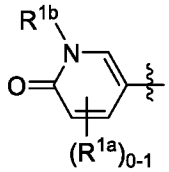
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Id-1) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B

Formula (Id-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Id-1) is that where one R^{2b} is present.

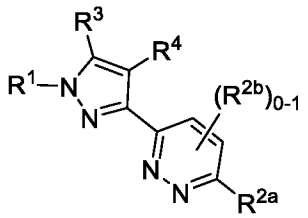
[00233] In some or any embodiments, the Compound is according to Genus B Formula (Ie-1):



(Ie-1);

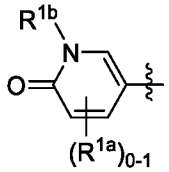
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ie-1) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ie-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ie-1) is that where one R^{2b} is present.

[00234] In some or any embodiments, the Compound is according to Genus B Formula (If-1):



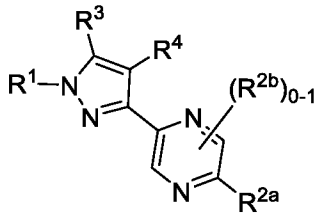
(If-1);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any



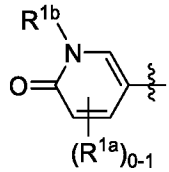
embodiments, the Compound of Genus B Formula (If-1) is that wherein R^1 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (If-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (If-1) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (If-1) is that where no R^{2b} is present.

[00235] In some or any embodiments, the Compound is according to Genus B Formula (Ig-1):



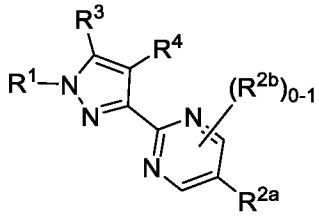
(Ig-1);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any

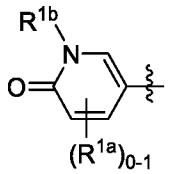


embodiments, the Compound of Genus B Formula (Ig-1) is that wherein R^1 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ig-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ig-1) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (Ig-1) is that where no R^{2b} is present.

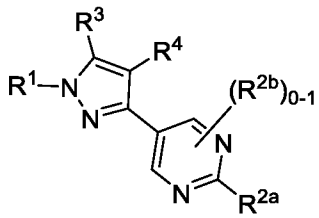
[00236] In some or any embodiments, the Compound is according to Genus B Formula (Ih-1):



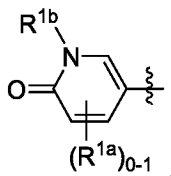
(Ih-1);

where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ih-1) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (Ih-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ih-1) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (Ih-1) is that where no R^{2b} is present.

[00237] In some or any embodiments, the Compound is according to Genus B Formula (Ij-1):



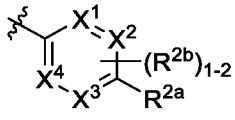
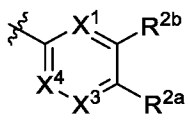
(Ij-1);

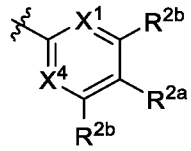
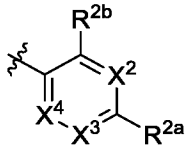
where R^1, R^{2a}, R^{2b}, R^3, R^4, and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Compound of Genus B Formula (Ij-1) is that wherein R^1 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B

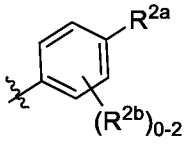
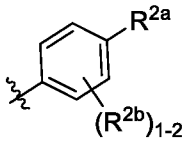
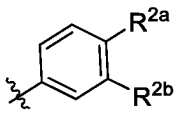
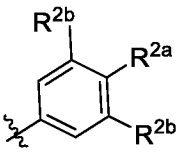
Formula (Ij-1) is that where R^3 and R^4 are hydrogen. In some or any embodiments, the Compound of Genus B Formula (Ij-1) is that where one R^{2b} is present. In some or any embodiments, the Compound of Genus B Formula (Ij-1) is that where no R^{2b} is present.

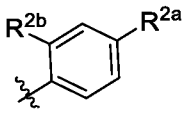
[00238] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^3 and R^4 are hydrogen; R^3 and R^4 are alkyl; or one of R^3 and R^4 is hydrogen and the other is alkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^3 and R^4 are hydrogen; R^3 and R^4 are methyl; R^3 is hydrogen and R^4 is methyl; or R^3 is methyl and R^4 is hydrogen; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^3 and R^4 are hydrogen; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

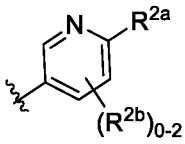
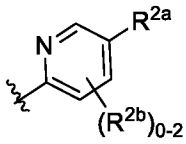
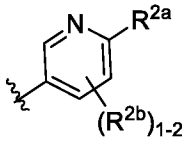
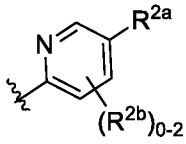
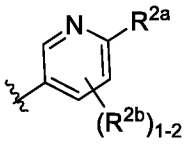
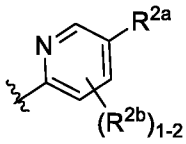
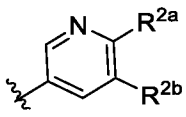
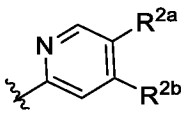
[00239] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij), (Ia-1)-(Ij-1) is that where R^1 is pyridinonyl substituted on its nitrogen with R^{1b} and additionally optionally substituted with 1 R^{1a}; R^{1b} is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij), (Ia-1)-(Ij-1) is that where R^1 is pyridinonyl substituted on its nitrogen with R^{1b} and additionally optionally substituted with 1 R^{1a}; R^{1b} is alkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

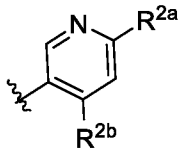
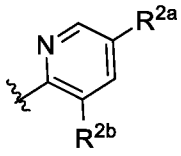
[00240] In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are CH or CR^{2b}; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiment, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  where 0, 1, or 2 of X^1, X^3, and X^4 are nitrogen and the remaining are CH or CR^{2b}; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiment, the Compound of Genus B

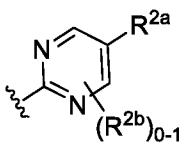
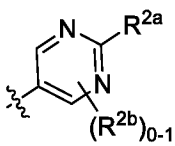
Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  where 0, 1, or 2 of X^1, X^3, and X^4 are nitrogen and the remaining are CH or CR^{2b}; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiment, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  where 0, 1, or 2 of X^2, X^3, and X^4 are nitrogen and the remaining are CH or CR^{2b}; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

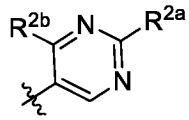
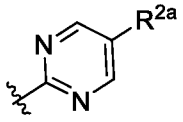
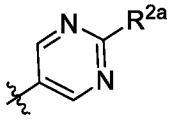
[00241] In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that

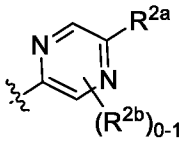
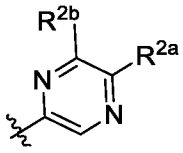
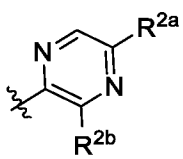
where R^2 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

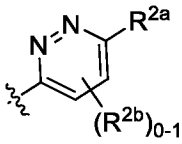
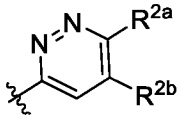
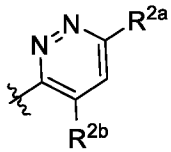
[00242] In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  or  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  or  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  or  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  or  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is

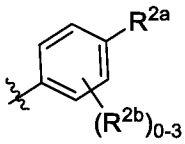
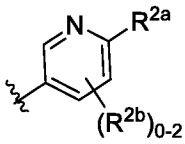
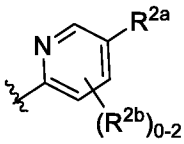
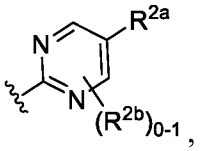
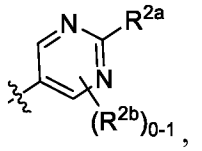
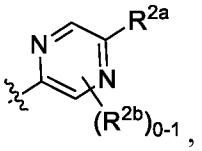
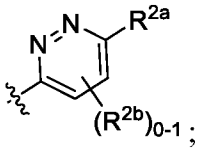
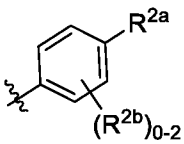
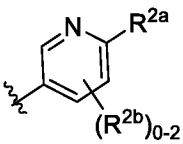
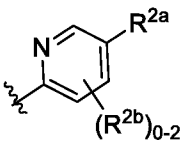
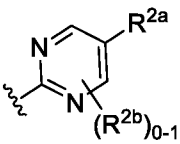
 or  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

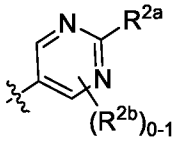
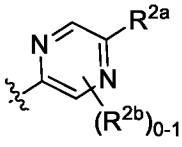
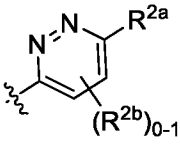
[00243] In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  , or  ; and all other groups are

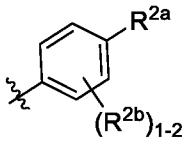
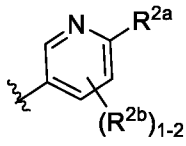
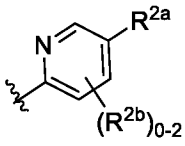
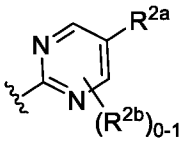
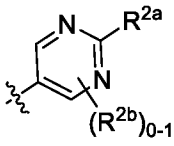
as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is , or  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is , or  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

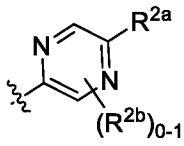
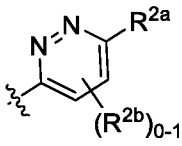
[00244] In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is  ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

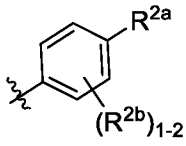
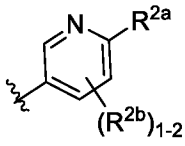
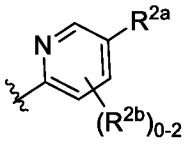
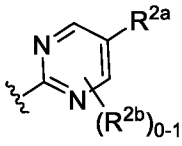
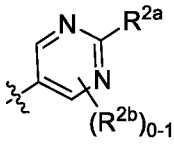
[00245] In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

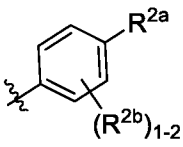
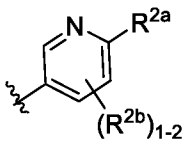
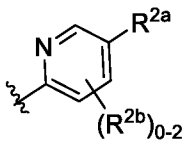
[00246] In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is , , , , , , or ; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is , , , ,

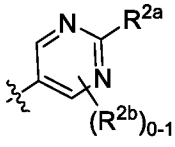



; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where

R^2 is 







; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is






; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I), (Ia), (Ib), (Ia-1), or (Ib-1) is that where R^2 is




, or


; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00247] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl in R^5, alone or as part of cycloalkylalkyl, and heterocycloalkyl in R^5, alone or as part of heterocycloalkylalkyl, are optionally substituted with 1, 2, or 3 groups independently selected

from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; or heterocycloalkylalkyl; where the cycloalkyl in R^5, alone or as part of cycloalkylalkyl, and heterocycloalkyl in R^5, as part of heterocycloalkylalkyl, are optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00248] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is alkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is haloalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is haloalkyl further substituted with 1 or 2 hydroxy; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is cycloalkyl which is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is cycloalkylalkyl where the cycloalkyl is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is heterocycloalkylalkyl where the heterocycloalkyl is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00249] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00250] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is C_4-C_8-alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl where the cycloalkyl is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, and hydroxyalkyl groups; cycloalkylalkyl where the cycloalkyl ring is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, and hydroxyalkyl groups; heterocycloalkyl where the heterocycloalkyl is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, and hydroxyalkyl groups; or heterocycloalkylalkyl where the heterocycloalkyl ring is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, and hydroxyalkyl groups; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is C_4-C_8-alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl and heterocycloalkyl are optionally substituted with 1 or 2 groups which are independently hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is C_4-C_8-alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; or heterocycloalkylalkyl; where the cycloalkyl and heterocycloalkyl ring are optionally substituted with 1 or 2 groups which are independently hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00251] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $–OR^5$; R^5 is C_4-C_8-alkyl; haloalkyl; cycloalkyl, where the cycloalkyl is optionally substituted with 1 or 2 alkyl groups; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is C_4-C_8-alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$; R^5 is C_4-C_8-alkyl; haloalkyl; cycloalkyl; or cycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00252] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $–S(O)R^6$; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)R^6$ and R^6 is alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl (alone or as part of cycloalkylalkyl) and heterocycloalkyl (alone or as part of heterocycloalkylalkyl) are optionally substituted with 1 or 2 groups which are independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $–S(O)R^6$ and R^6 is alkyl; haloalkyl; hydroxyalkyl; cycloalkyl; cycloalkylalkyl; or heterocycloalkyl; where the cycloalkyl and heterocycloalkyl are optionally substituted with 1 or 2 groups which are independently hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $–S(O)R^6$ and R^6 is alkyl or haloalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $–S(O)R^6$ and R^6 is alkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B

Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)R^6$ and R^6 is hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00253] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)R^6$; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is -$S(O)R^6$ and R^6 is alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)R^6$ and R^6 is alkyl; haloalkyl; cycloalkyl; cycloalkylalkyl; or heterocycloalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00254] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl, alone or as part of cycloalkylalkyl, and heterocycloalkyl, alone or as part of heterocycloalkylalkyl, are optionally substituted with 1, 2, or 3 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is alkyl; haloalkyl; hydroxyalkyl; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl (alone or as part of cycloalkylalkyl) and heterocycloalkyl, alone or as part of heterocycloalkylalkyl, are optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is alkyl or haloalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00255] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is alkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is cycloalkyl which is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is cycloalkylalkyl where the cycloalkyl ring is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is heterocycloalkyl which is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00256] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is alkyl; haloalkyl; cycloalkyl; cycloalkylalkyl; or heterocycloalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is alkyl or haloalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is alkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-S(O)_2R^7$ and R^7 is

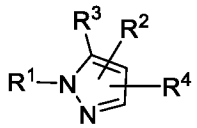
cycloalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is -$S(O)_2R^7$ and R^7 is cycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is –$S(O)_2R^7$ and R^7 is heterocycloalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00257] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is –OR^5, –$S(O)R^6$, or –$S(O)_2R^7$; R^5 is C_4-C_8-alkyl; hydroxyalkyl; haloalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl where the cycloalkyl is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; cycloalkylalkyl where the cycloalkyl ring is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; heterocycloalkyl where the heterocycloalkyl is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; or heterocycloalkylalkyl where the heterocycloalkyl ring is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and R^6 and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl where the cycloalkyl is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; cycloalkylalkyl where the cycloalkyl ring is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; heterocycloalkyl where the heterocycloalkyl is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; or heterocycloalkylalkyl where the heterocycloalkyl ring is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is -OR^5, -$S(O)R^6$, or –$S(O)_2R^7$; R^5 is C_4-C_8-alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and R^6 and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is -OR^5, -$S(O)R^6$, or –$S(O)_2R^7$; R^5 is C_4-C_8-alkyl; haloalkyl;

hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; or heterocycloalkylalkyl; and R^6 and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; cycloalkyl; cycloalkylalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00258] In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $–OR^5$, $–S(O)R^6$, or $–S(O)_2R^7$; R^5 is C_4-C_8-alkyl; haloalkyl; cycloalkyl where the cycloalkyl is optionally substituted with 1 or 2 alkyl groups; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and R^6 and R^7 are independently alkyl; haloalkyl; cycloalkyl where the cycloalkyl is optionally substituted with 1 or 2 alkyl groups; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$, $-S(O)R^6$, or $–S(O)_2R^7$; R^5 is C_4-C_8-alkyl; haloalkyl; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and R^6 and R^7 are independently alkyl; haloalkyl; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein. In some or any embodiments, the Compound of Genus B Formula (I)-(Ij) or (Ia-1)-(Ij-1) is that where R^{2a} is $-OR^5$, $-S(O)R^6$, or $–S(O)_2R^7$; R^5 is C_4-C_8-alkyl; haloalkyl; cycloalkyl; or cycloalkylalkyl; and R^6 and R^7 are independently alkyl; haloalkyl; cycloalkyl; or cycloalkylalkyl; and all other groups are as defined in the Summary of Genus B Formula (I) or in any embodiments described herein.

[00259] Embodiment 1. Provided is a Compound of Genus B Formula (I):



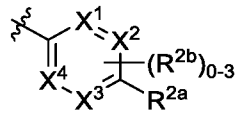
(I)

where

R^1 is pyridinonyl, where the pyridinonyl is substituted on its nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a};

R^{1a}, when present, is halo, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{1b} is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are CH or CR^{2b};

R^{2a} is $-OR^5$, $-S(O)R^6$, or $-S(O)_2R^7$;

each R^{2b}, when present, is independently halo, alkyl, haloalkyl, $-NO_2$, or cyano;

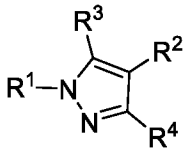
R^3 is hydrogen, halo, alkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl, or haloalkyl; and

R^5, R^6, and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl, alone or as part of cycloalkylalkyl, and heterocycloalkyl, alone or as part of heterocycloalkylalkyl, are optionally substituted with 1, 2, or 3 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; or

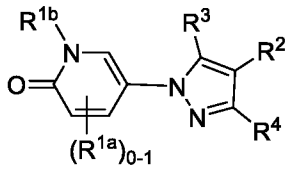
a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[00260] Embodiment 2. Provided is the Compound of Embodiment 1 according to Genus B Formula (Ia):



(Ia).

[00261] Embodiment 3. Provided is the Compound of Embodiment 1 or 2 according to Genus B Formula (Ib):



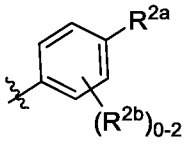
(Ib).

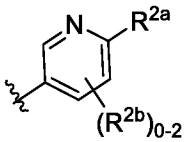
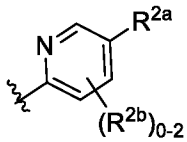
[00262] Embodiment 4. Provided is the Compound of Embodiment 1, 2, or 3 where R^3 and R^4 are hydrogen.

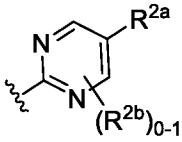
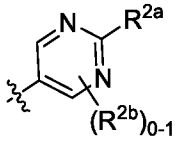
[00263] Embodiment 5. Provided is the Compound of Embodiment 1, 2, or 3 where R^3 and R^4 are methyl.

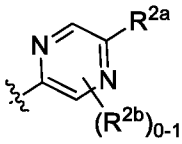
[00264] Embodiment 6. Provided is the Compound of Embodiment 1, 2, or 3 where R^3 is hydrogen and R^4 is methyl.

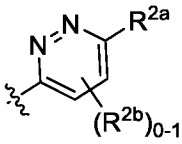
[00265] Embodiment 7. Provided is the Compound of Embodiment 1, 2, or 3 where R^3 is methyl and R^4 is hydrogen.

[00266] Embodiment 8. Provided is the Compound of any one of Embodiments 1-7 where R^2 is .

[00267] Embodiment 9. Provided is the Compound of any one of Embodiments 1-7 where R^2 is  or .

[00268] Embodiment 10. Provided is the Compound of any one of Embodiments 1-7 where R^2 is  or .

[00269] Embodiment 11. Provided is the Compound of any one of Embodiments 1-7 where R^2 is .

[00270] Embodiment 12. Provided is the Compound of any one of Embodiments 1-7 where R^2 is .

[00271] Embodiment 13. Provided is the Compound of any one of Embodiments 1-12 where the R^2 ring is substituted with a first R^{2b}.

[00272] Embodiment 14. Provided is the Compound of any one of Embodiments 1-13 where the first R^{2b}, when present, is halo.

[00273] Embodiment 15. Provided is the Compound of any one of Embodiments 1-14 where the first R^{2b}, when present, is chloro.

[00274] Embodiment 16. Provided is the Compound of any one of Embodiments 1-14 where the first R^{2b}, when present, is fluoro.

[00275] Embodiment 17. Provided is the Compound of any one of Embodiments 1-13 where the first R^{2b}, when present, is -CN.

[00276] Embodiment 18. Provided is the Compound of any one of Embodiments 1-13 where the first R^{2b}, when present, is $-CH_3$.

[00277] Embodiment 19. Provided is the Compound of any one of Embodiments 1-13 where the first R^{2b}, when present, is $-CF_3$.

[00278] Embodiment 20. Provided is the Compound of any one of Embodiments 1-19 where the R^2 ring is substituted with a second R^{2b}.

[00279] Embodiment 21. Provided is the Compound of any one of Embodiments 1-20 where the second R^{2b}, when present, is halo.

[00280] Embodiment 22. Provided is the Compound of any one of Embodiments 1-21 where the second R^{2b}, when present, is chloro.

[00281] Embodiment 23. Provided is the Compound of any one of Embodiments 1-21 where the second R^{2b}, when present, is fluoro.

[00282] Embodiment 24. Provided is the Compound of any one of Embodiments 1-20 where the second R^{2b}, when present, is -CN.

[00283] Embodiment 25. Provided is the Compound of any one of Embodiments 1-20 where the second R^{2b}, when present, is $-CH_3$.

[00284] Embodiment 26. Provided is the Compound of any one of Embodiments 1-20 where the second R^{2b}, when present, is $-CF_3$.

[00285] Embodiment 27. Provided is the Compound of any one of Embodiments 1-26 where R^{2a} is $-S(O)_2R^7$.

[00286] Embodiment 28. Provided is the Compound of any one of Embodiments 1-26 where R^{2a} is $-S(O)R^6$.

[00287] Embodiment 29. Provided is the Compound of any one of Embodiments 1-26 where R^{2a} is $-OR^5$.

[00288] Embodiment 30. Provided is the Compound of any one of Embodiments 1-29 where R^5, R^6, and R^7 are independently alkyl.

[00289] Embodiment 31. Provided is the Compound of any one of Embodiments 1-29 where R^5, R^6, and R^7 are independently haloalkyl.

[00290] Embodiment 31. Provided is the Compound of any one of Embodiments 1-29 where R^5, R^6, and R^7 are independently cycloalkyl where the cycloalkyl is optionally substituted with 1 or 2 groups that are independently hydroxyalkyl.

[00291] Embodiment 32. Provided is the Compound of any one of Embodiments 1-29 where R^5, R^6, and R^7 are independently cycloalkylalkyl where the cycloalkyl ring is optionally substituted with 1 or 2 groups that are independently hydroxyalkyl.

[00292] Embodiment 33. Provided is the Compound of any one of Embodiments 1-29 where R^5, R^6, and R^7 are independently hydroxyalkyl.

[00293] Embodiment 34. Provided is the Compound of any one of Embodiments 1-29 where R^5, R^6, and R^7 are independently heterocycloalkylalkyl where the heterocycloalkyl, alone or as part of heterocycloalkylalkyl is optionally substituted with 1 or 2 groups that are independently hydroxyalkyl.

[00294] Embodiment 35. Provided is the Compound of any one of Embodiments 1-29 where R^5, R^6, and R^7 are independently heterocycloalkyl which is optionally substituted with 1 or 2 groups that are independently halo.

[00295] Embodiment 36. Provided is the Compound of any one of Embodiments 1-29 where R^5, R^6, and R^7 are independently haloalkyl further substituted with 1 or 2 hydroxy.

[00296] Embodiment 37. Provided is the Compound of any one of Embodiments 1-30 where R^5 is C_4-C_8-alkyl.

[00297] Embodiment 38. Provided is the Compound of any one of Embodiments 1-37 where R^1 is substituted with one R^{1a}.

[00298] Embodiment 39. Provided is the Compound of any one of Embodiments 1-38 where R^{1a}, when present, is alkyl.

[00299] Embodiment 40. Provided is the Compound of any one of Embodiments 1-39 where R^{1b} is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl.

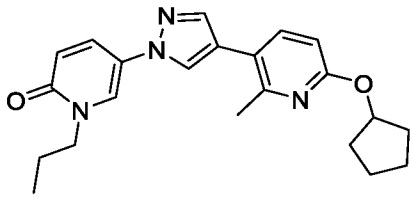
[00300] Embodiment 41. Provided is the compound of any one of Embodiments 1-40 where R^{1b} is alkyl.

[00301] Embodiment 42. Provided is the compound of Embodiment 1 selected from Embodiment B; or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

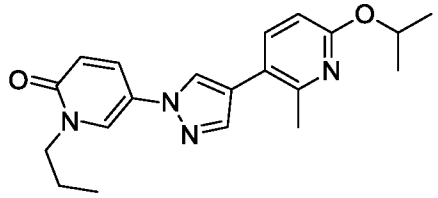
[00302] Embodiment 43. Provided is a pharmaceutical composition comprising a Compound of any one of Embodiments 1-42 or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[00303] **Embodiment B**: In some or any embodiments, provided is a Genus B Compound according to any of the following formulae, which were prepared as described in WO2018/049080:

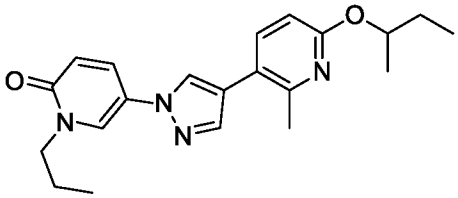
Genus B Embodiment B



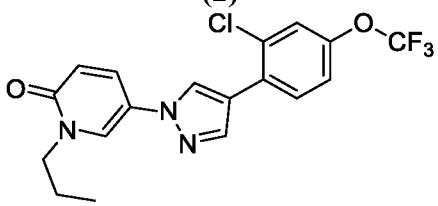
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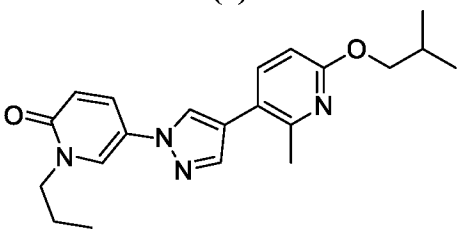
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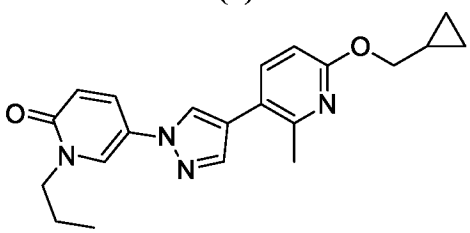
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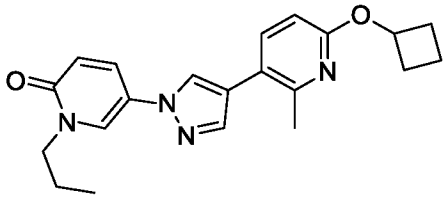
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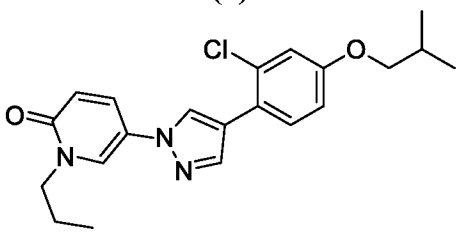
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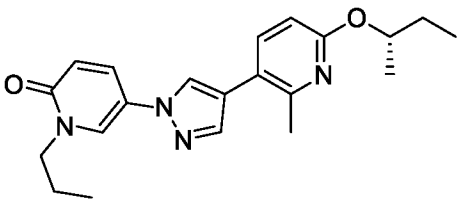
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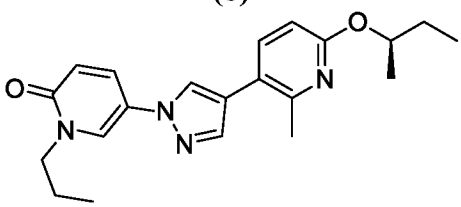
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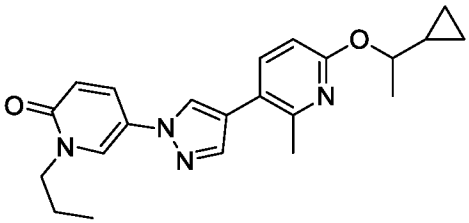
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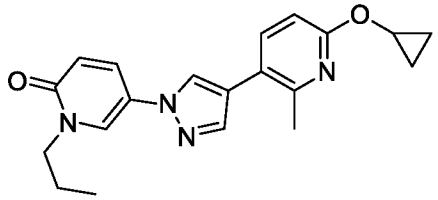
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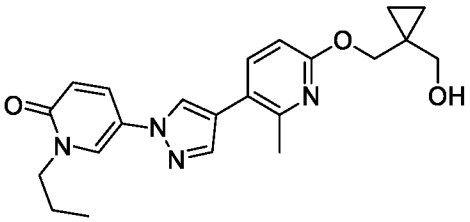


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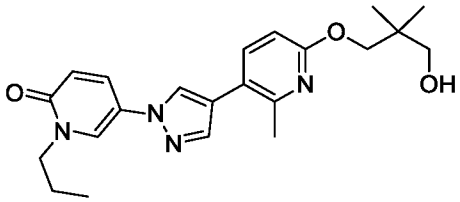


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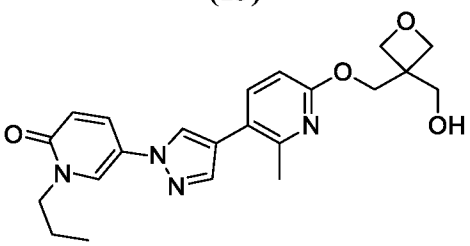
Genus B Embodiment B



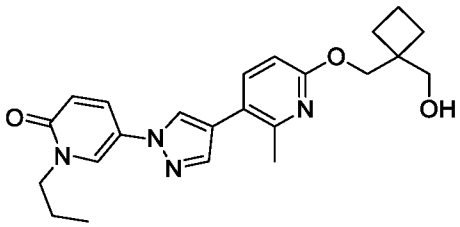
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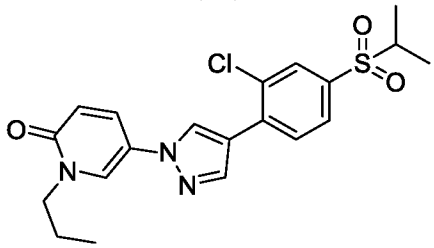
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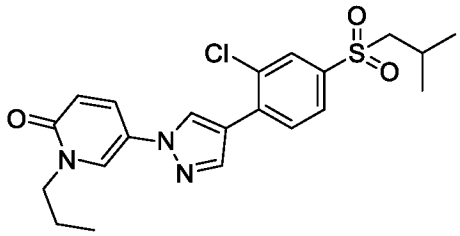
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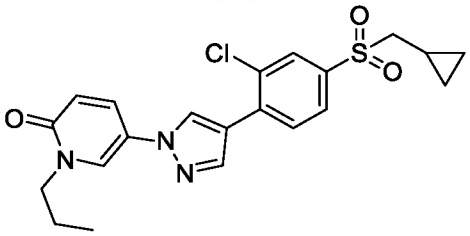
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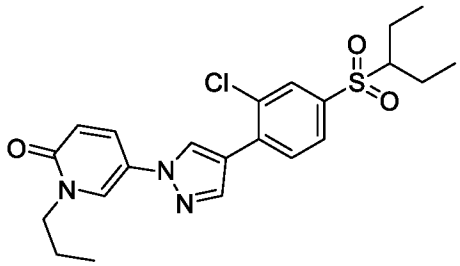
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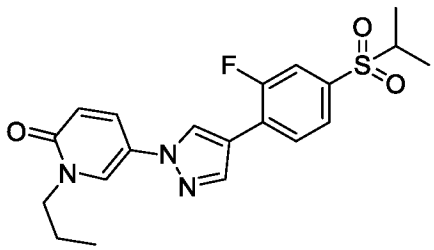
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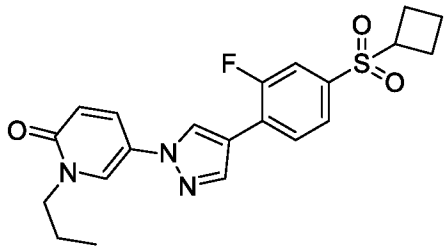
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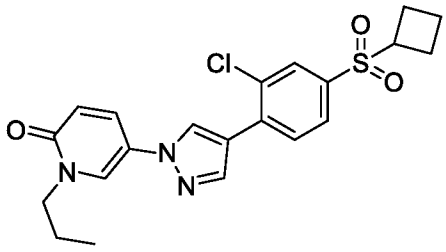
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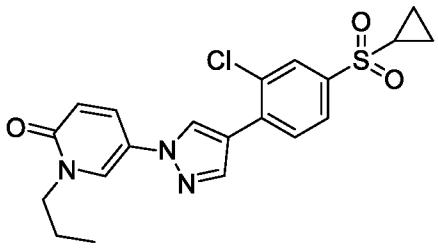
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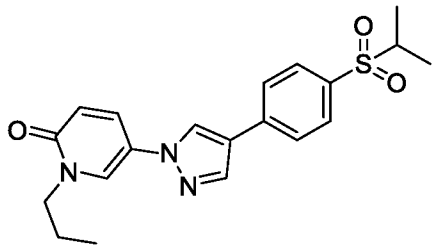


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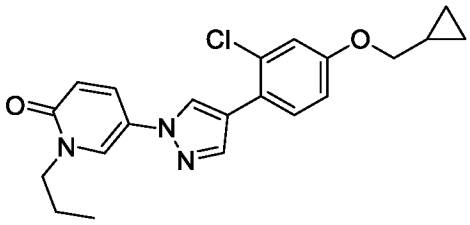


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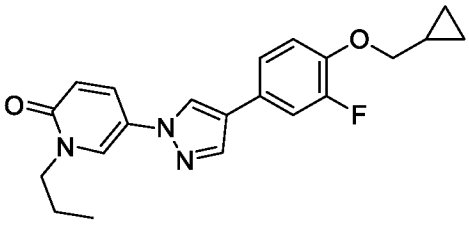
Genus B Embodiment B



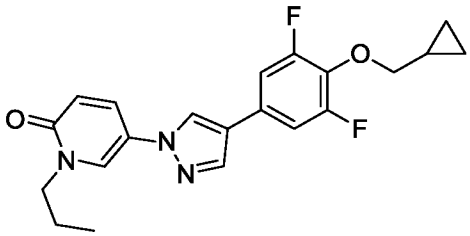
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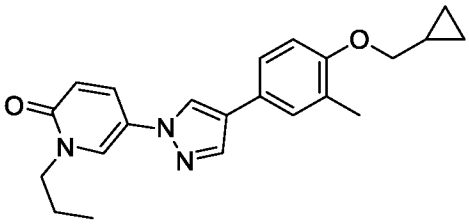
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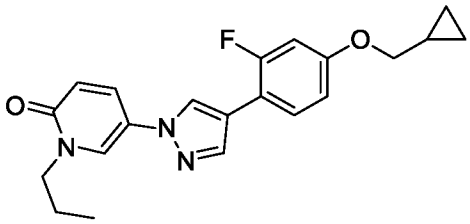
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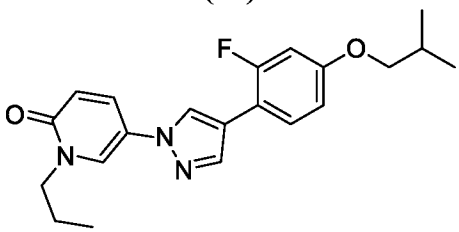
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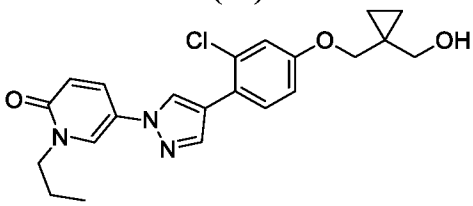
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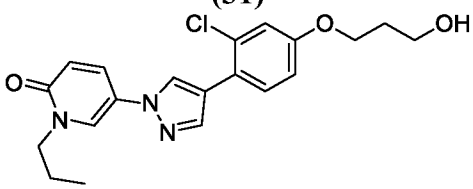
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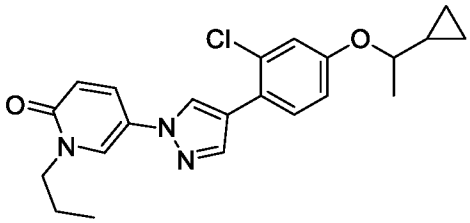
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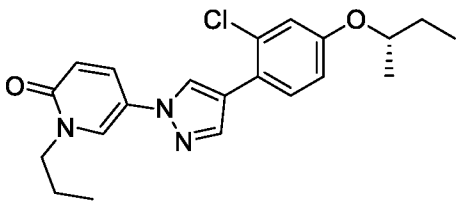
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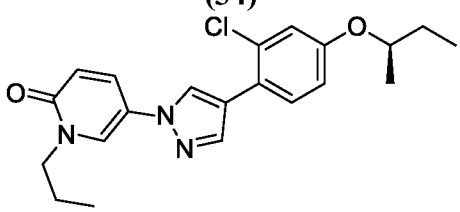
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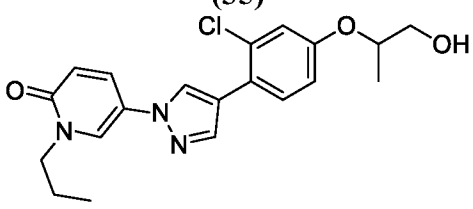
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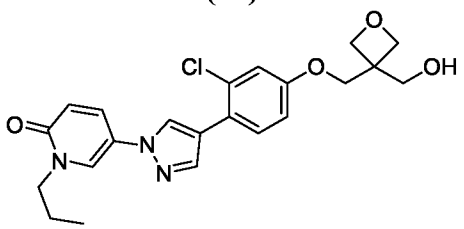


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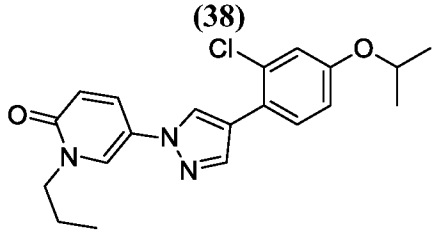


Genus B Embodiment B

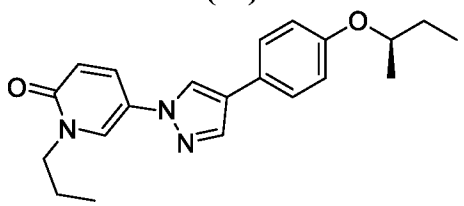
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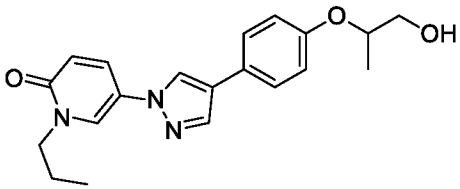
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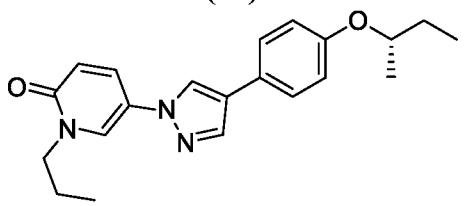
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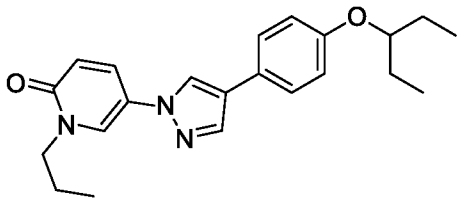
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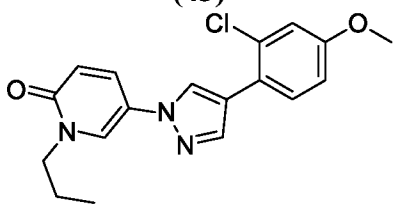
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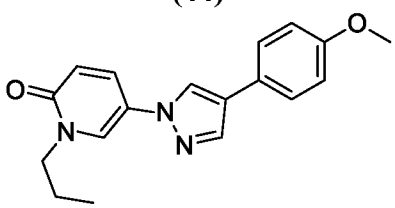
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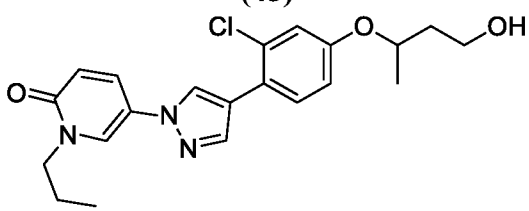
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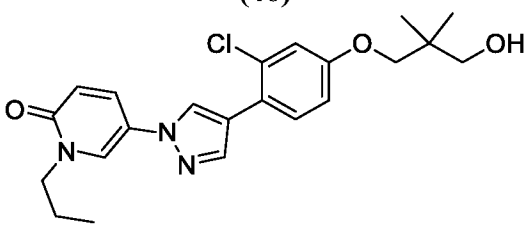
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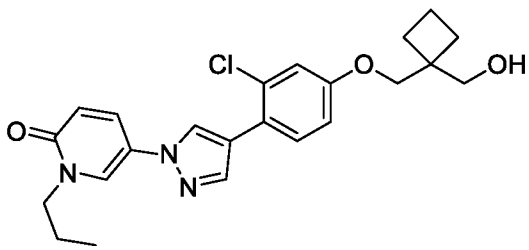
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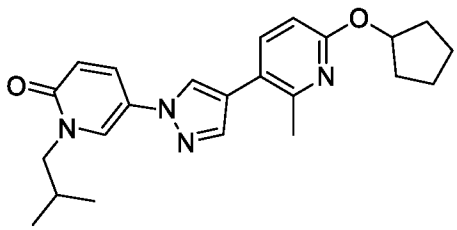


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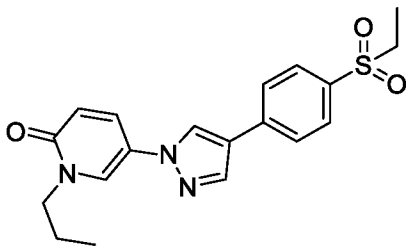


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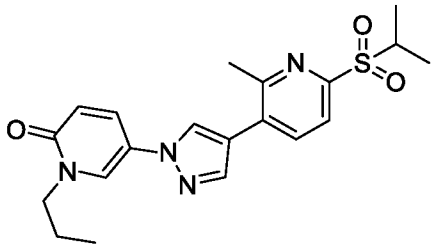
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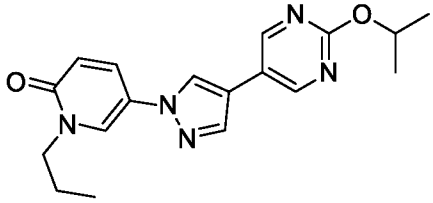
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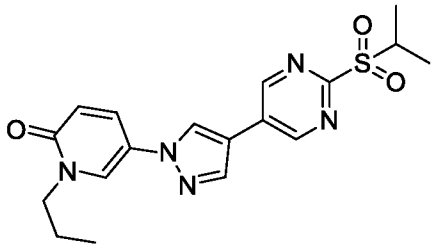
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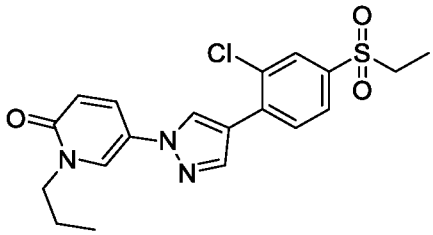
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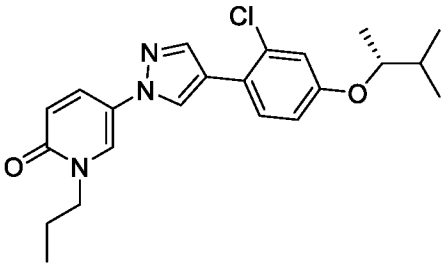
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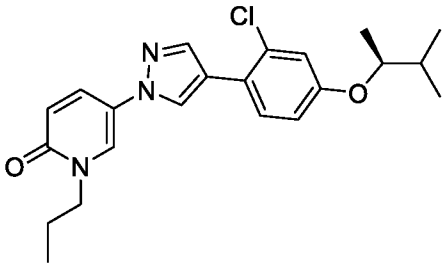
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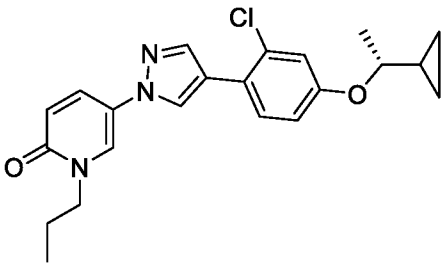
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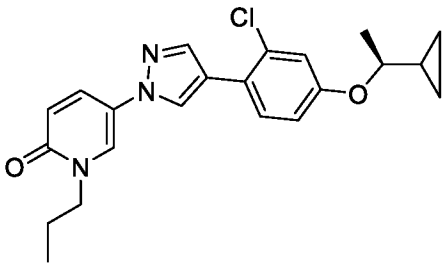
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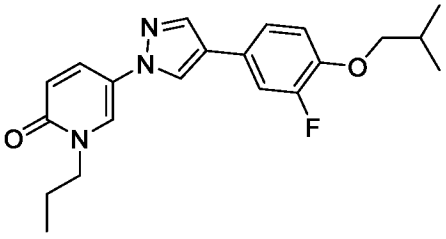
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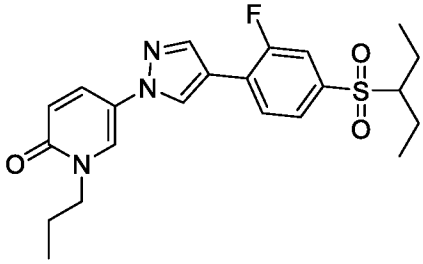
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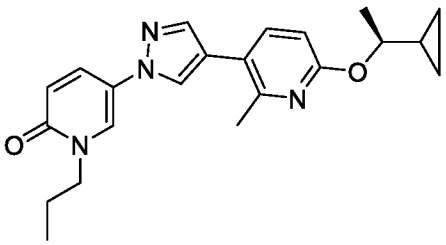
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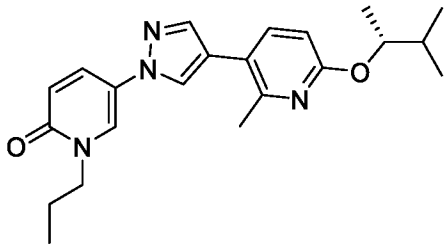
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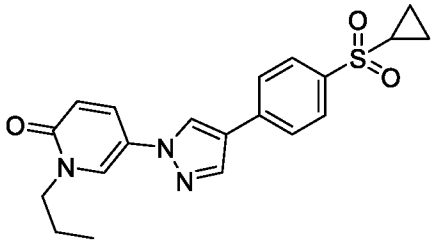
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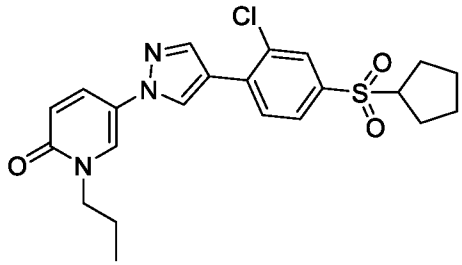
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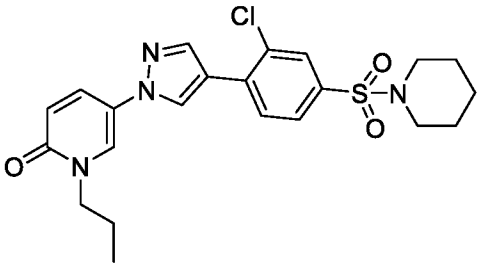
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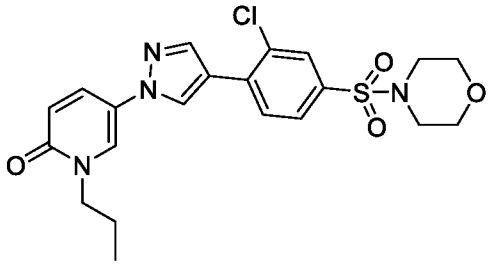
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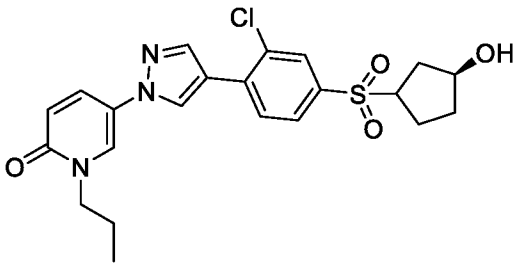
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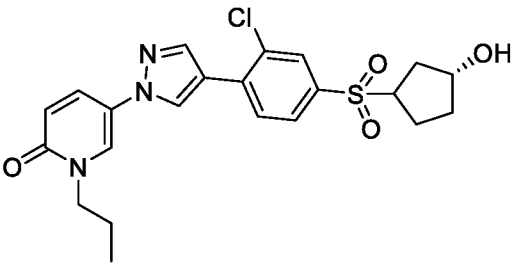
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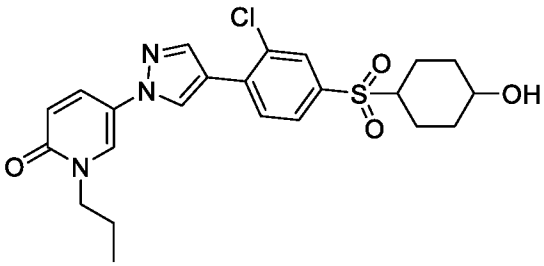
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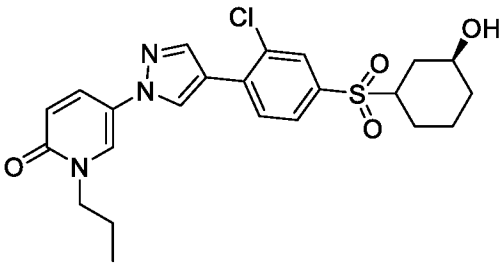
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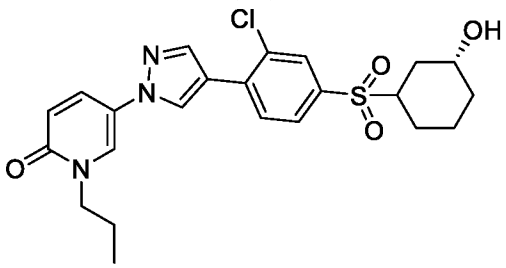
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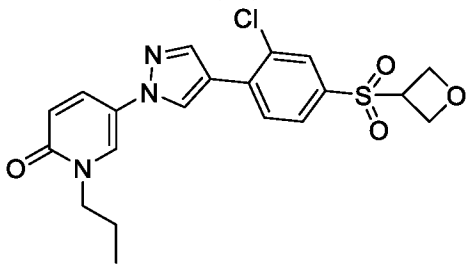
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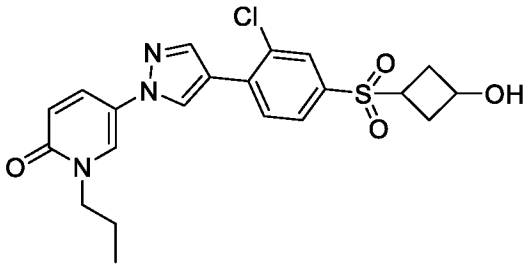
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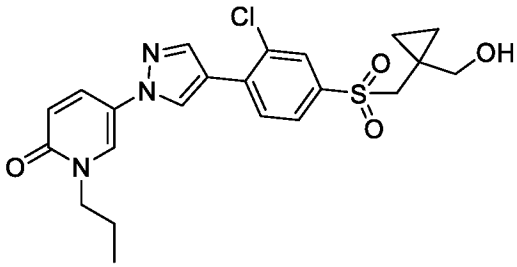
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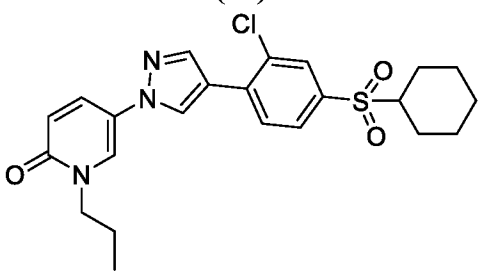
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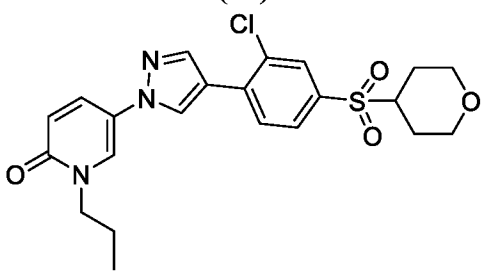
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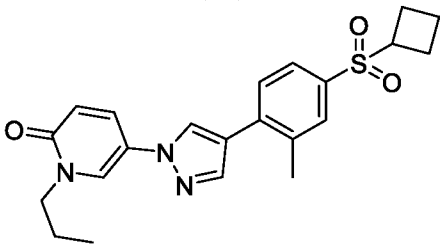
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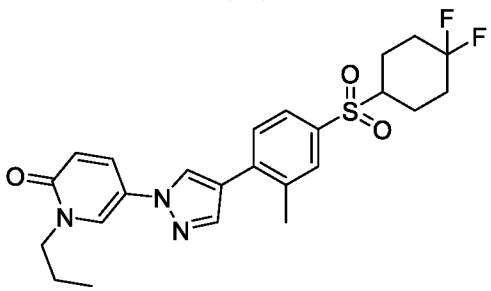
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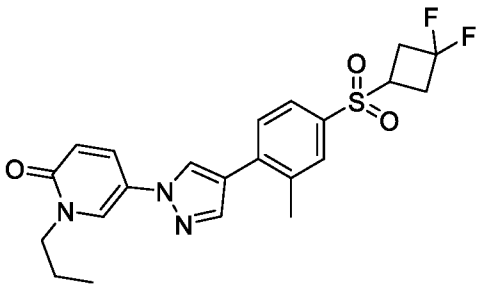
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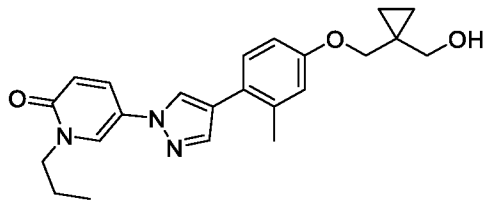
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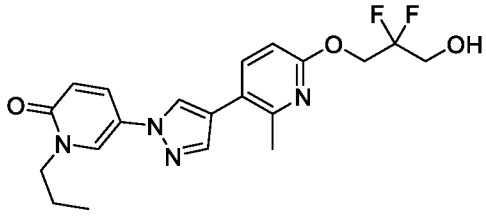
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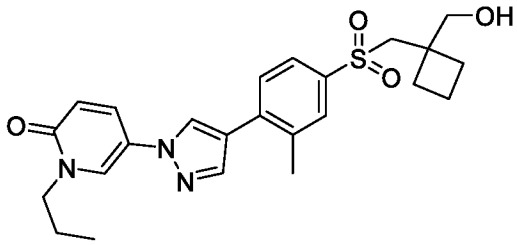
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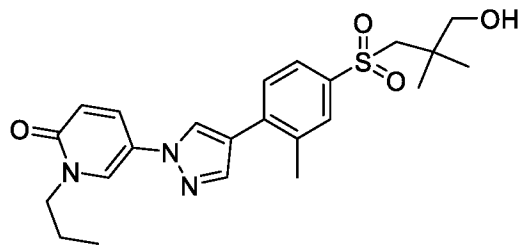
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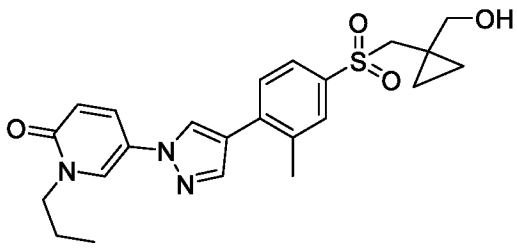
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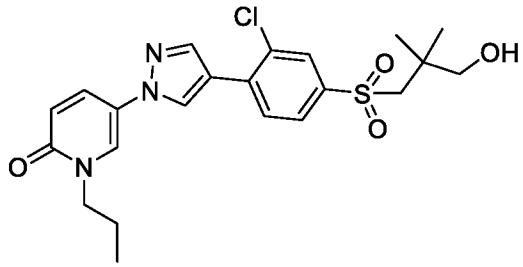
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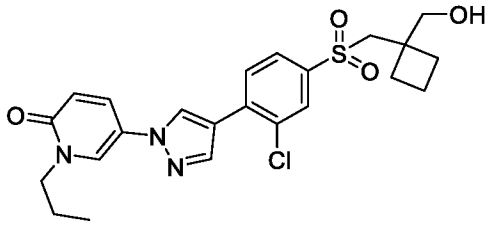
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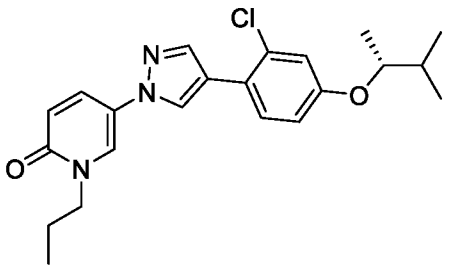


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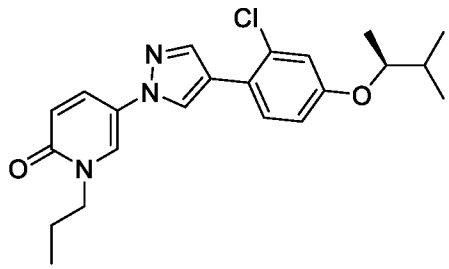
or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[00304] Additional compounds disclosed herein (Genus B Embodiment A), which can be prepared using methods disclosed herein and known to one of ordinary skill in the art using readily-obtainable or commercially-available starting materials, include the following:

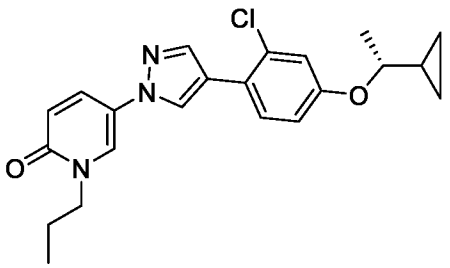
Genus B Embodiment A



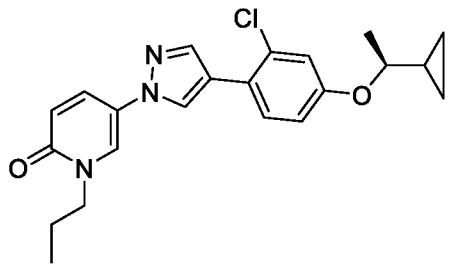
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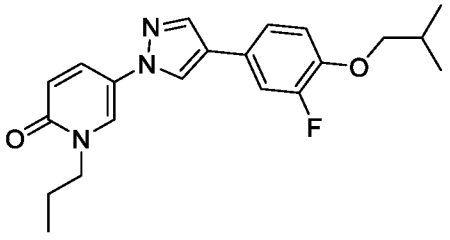
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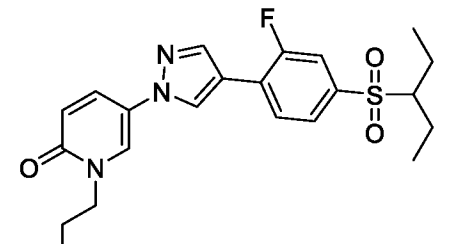
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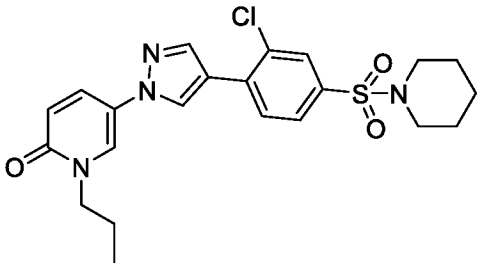
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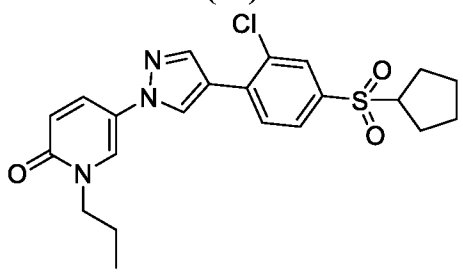
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Genus B Embodiment A

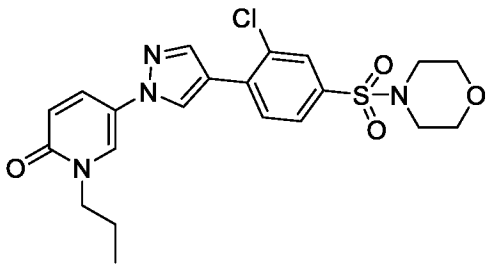
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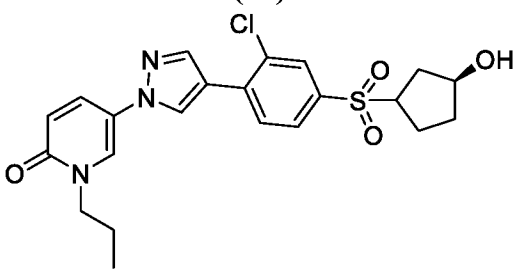
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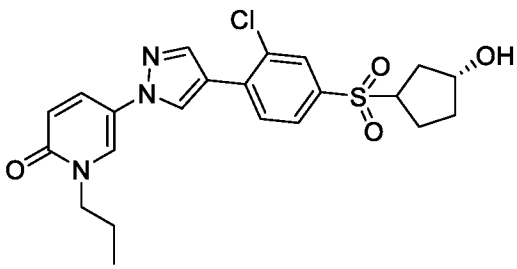
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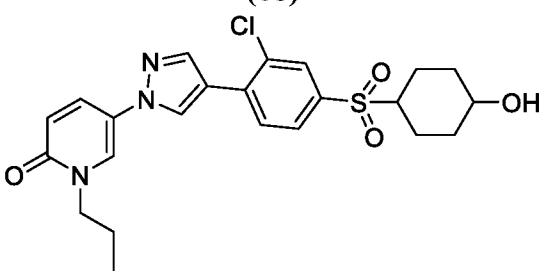
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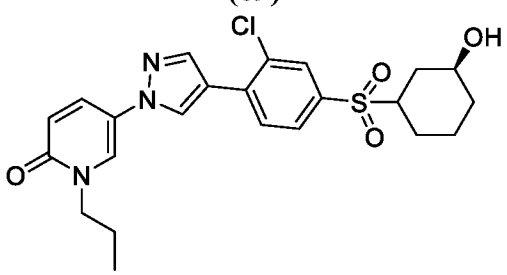
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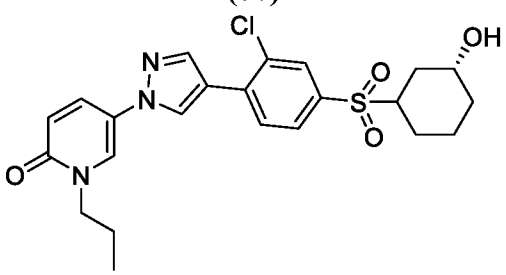
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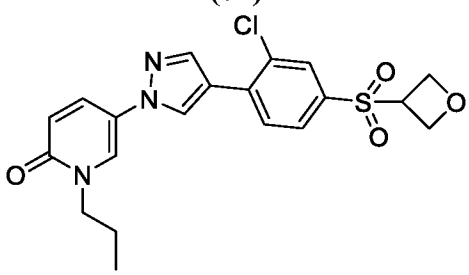
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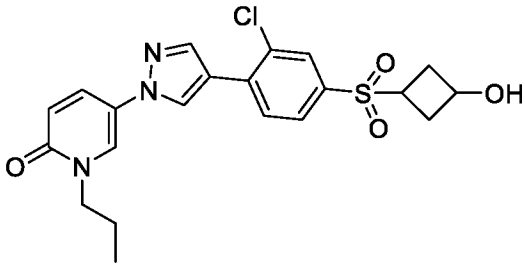
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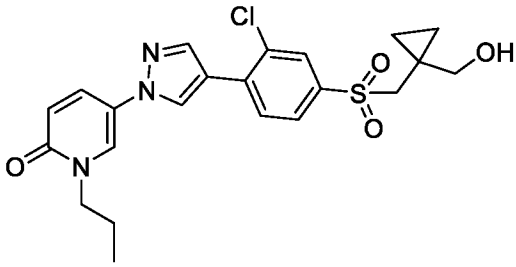
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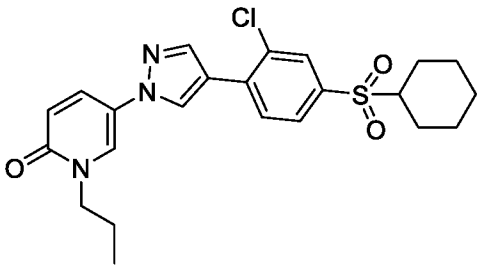
Genus B Embodiment A



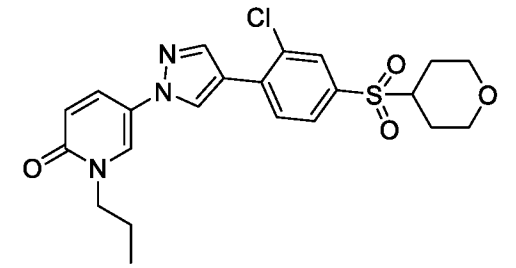
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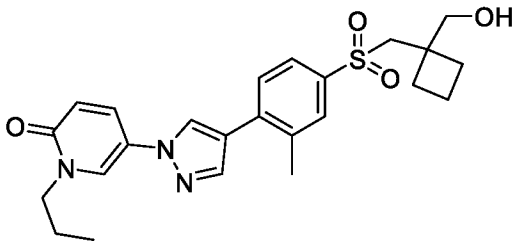
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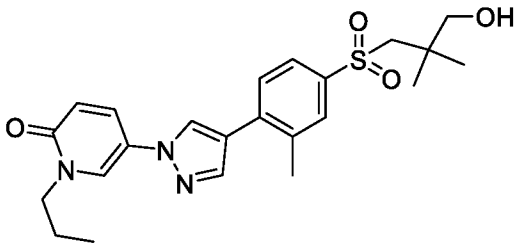
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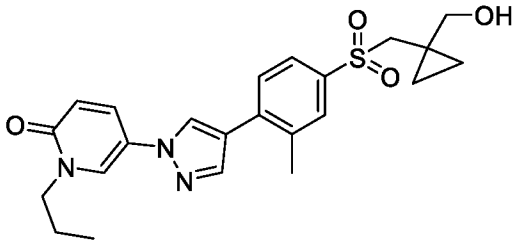
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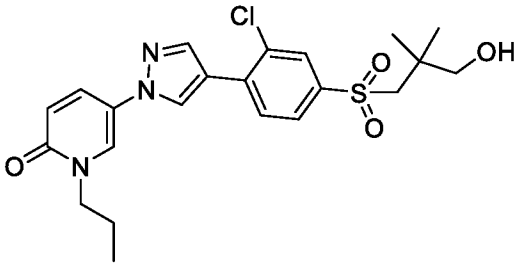
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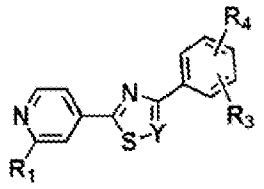
or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

Preparation of Genus B Compounds

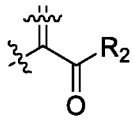
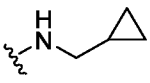
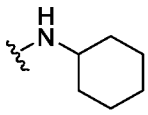
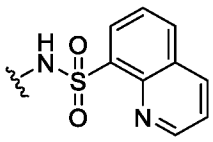
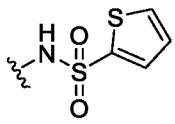
[00305] The compounds provided herein can be prepared, isolated, or obtained by any method apparent to those of skill in the art, including those disclosed in WO2018/049080, which is incorporated herein by reference in its entirety. Reaction conditions, steps, and reactants not provided in WO2018/049080 would be apparent to, and known by, those skilled in the art.

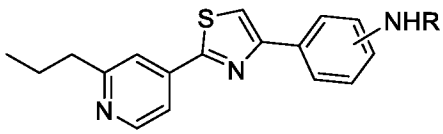
GENUS C

[00306] In some or any embodiments, the SREBP inhibitor is according to a Genus C Compound according to Genus C Formula (X):



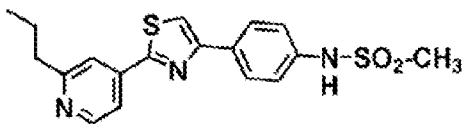
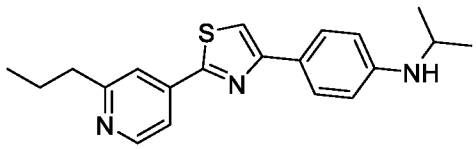
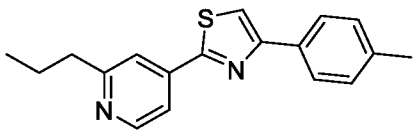
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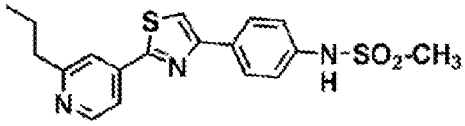
wherein R_1 is H, ethyl, –OMe, or n-propyl; Y is CH or  ; and R_2 is –OH, -OMe, or –NH-i-Pr; R_3 is H, F, or Cl; and R_4 is H, Me, Cl, Br, F, –OH, –OBz, -$OCH_2C(O)OMe$, –$OCH_2C(O)OH$, $–NH_2$, –NH-i-Pr, –NHC(O)Me, $–NHS(O)_2Me$, –NHBn,  , –OMe, –NHBoc,  , –NHTs,  , or  ; or a pharmaceutically acceptable salt or stereoisomer thereof or a combination thereof. In some or any embodiments, the SREBP inhibitor is according to a Genus C Compound according to Genus C Formula (X-1):



(X-1)

wherein R is H, isopropyl, benzyl, cyclohexyl, cyclopropylmethyl, –C(O)Me, tert-butyloxycarbonyl, or methylsulfonyl; or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus C SREBP inhibitor is

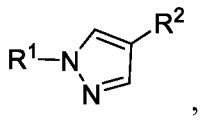
 ,  , or  ;

or a pharmaceutically acceptable salt thereof. In some or any embodiments, the Genus C SREBP inhibitor is  or a pharmaceutically acceptable salt thereof.

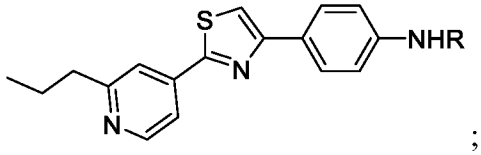
Preparation of Genus C Compounds

[00307] The compounds provided herein can be prepared, isolated, or obtained by any method apparent to those of skill in the art, including those disclosed in US 8,207,196, which is incorporated herein by reference in its entirety. Reaction conditions, steps, and reactants not provided in US 8,207,196 would be apparent to, and known by, those skilled in the art.

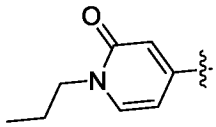
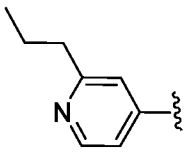
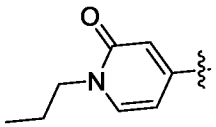
[00308] In some or any embodiments, the SREBP inhibitor is selected from the compound of Genus A or B which is according to

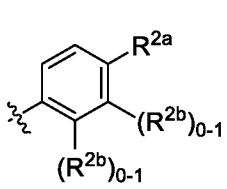
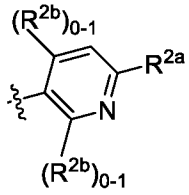
,

and the compound of Genus C which is according to

;

wherein

R^1 of the compound of Genus A is  or ; R^1 of the compound of Genus B is ;

R^2 in the compound of Genus A or B is  or , preferably where one R^{2b} group is absent and one R^{2b} group is present;

R^{2a} in the compound of Genus A is $–NHS(O)_2R^{5b}$ or $–NHR^{6b}$; R^{2a} in the compound of Genus B is $-OR^5$ or $–S(O)_2R^7$;

R^{5b} and R^{6b} in the compound of Genus A are alkyl, haloalkyl, or cycloalkyl, preferably alkyl or cycloalkyl; R^5 in the compound of Genus B is a) alkyl, b) hydroxyalkyl, c) haloalkyl further substituted with 1 or 2 hydroxy, or d) cycloalkylalkyl wherein the cycloalkyl ring is optionally substituted with 1, 2, or 3 groups (preferably one group) independently selected from alkyl, hydroxy, halo, and hydroxyalkyl (preferably one group which is alkyl, hydroxy, or hydroxyalkyl); R^7 in the compound of Genus B is alkyl or cycloalkyl;

R in the compound of Genus C is isopropyl, cyclohexyl, cyclopropylmethyl, –C(O)Me, or methylsulfonyl, preferably cyclopropylmethyl or methylsulfonyl; and

each R^{2b} in the compound of Genus A and B is independently halo or methyl, preferably fluoro, chloro, or methyl.

Compounds A-N, which were tested in various cell lines, fall within the scope of the compounds provided in this paragraph.

Biological Examples and Methods

Assay Methods

[00309] SREBP inhibitors in combination with niclosamide and analogs thereof can be assayed for efficacy in treating a condition, disease, or disorder associated with activation (in some embodiments abnormal activation) of the SREBP pathway and/or of one or more target genes that are essential for proliferation according to any assay known to those of skill in the art. Exemplary assay methods are provided below and in WO2017/190086 and WO2018/049080, each of which are incorporated herein by reference in their entireties.

Biological Example 1

Quantitative PCR (qPCR)

[00310] For Genus A compounds, data for percent inhibition of SCD1 expression are provided in Biological Examples 1 and 2 of WO2017/190086, which is incorporated herein by reference in its entirety. These data demonstrate activity of Genus A compounds for inhibition of the SREBP pathway.

[00311] For Genus B compounds, data for percent inhibition data of SCD1 expression, data for percent inhibition data of PCSK9 expression, and PCKS9 IC_{50} data are provided in Biological Examples 1a and 1b of WO2018/049080, which is incorporated herein by

reference in its entirety. These data demonstrate activity of Genus B componds for inhibition of the SREBP pathway.

[00312] For Genus C compounds, including 2-(2-propylpyridin-4-yl)-4-(p-tolyl)thiazole (fatostation), *N*-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide, and *N*-isopropyl-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)aniline, see US 8,207,196 for data on their inhibition of the SREBP pathway.

Biological Example 2

Cell viability assay

Compounds of Genuses A, B, and C

[00313] For Genus A compounds, data in a cell viability assay for growth inhibition in liver cancer cell lines (HepG2, Huh7, Hep3B2.1-7, and SK-HEP-1), human prostate cancer cells LNCaP and 22Rv1, colorectal adenocarcinoma (HCT-15), gastric carcinoma (NCI-N87), and leukemia cell lines (MOLT4 and RPMI8226) are provided in Biological Example 3 of WO2017/190086, which is incorporated herein by reference in its entirety.

[00314] For Genus B compounds, IC_{50} data in a cell viability assay in a liver cancer cell line (HepG2) are provided in Biological Example 2 of WO2018/049080, which is incorporated herein by reference in its entirety. The assay(s) provided in WO2018/049080 can be followed for determining activity in Huh7 (liver cancer), MDA-MB-231 (breast cancer), T47D (breast cancer), MCF7 (breast cancer), and DU145 (prostate cancer) cells.

[00315] For Genus C compounds *N*-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide and *N*-isopropyl-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)aniline, see US 9,187,485 for data on growth inhibition of human acute lymphoblastic leukemia MOLT-4 cells and human multiple myeloma RPMI8226 cells. For Genus C compound *N*-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide, see US 9,187,485 for data on growth inhibition of human breast cancer SUM 159 cells and human liver cancer HepG2 cells.

[00316] The following method can be used to determine growth inhibition activity. Colorectal cell lines HCT-15 and HCT116 are cultured in cell medium (RPMI-1640 for HCT-15, McCoy's 5A for HCT116) containing 5% FBS and antibiotic-antimycotic and are grown in a humidified incubator at 37 °C with 5% CO_2. For the assay, 2,000 colorectal cell lines HCT-15 and HCT116 cells are seeded into each well of 96-well plates. After one day (24 h) in culture, cells are treated with a test compound at concentrations of 0, 1, 10, 32, 100, 320, 1000, 3,000, 3200, 10,000, 20,000 nM for 48 and 72 hr. The cell viability is assessed

using Thiazolyl Blue Tetrazolium Bromide (MTT) assay (n=3 for each dose). 5 mg/mL MTT is added in an amount equal to 10% of the culture medium volume after 48- and 72-hr treatment with the test compound. After the plates are incubated at 37 °C for 3.5 hours, the medium is removed and formazan crystals are dissolved in isopropanol. The absorbance is measured on a Cytation 5 epi-fluorescence microscope at a wavelength of 550 nm and 690 nm. The absorbance at 690 nm is subtracted from the absorbance at 550 nm and the result is used for graphing.

Effect of Compound A and Niclosamide Combination on Cell Viability of Different Cancer Cell Lines

[00317] Prostate cancer cells 22Rv1, colon cancer cells HCT-15, and stomach cancer cells NCI-N87 were cultured in RPMI-1640 containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. Hepatocellular carcinoma cells HepG2 were cultured in DMEM containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. HCT116 colorectal cancer cells were cultured in McCoy's 5A containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. DU145 prostate cancer cells were cultured in DMEM containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. MCF7 breast cancer cells were cultured in DMEM containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. MDA-MB-231 breast cancer cells were cultured in DMEM containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. RPMI8226 multiple myeloma cells were cultured in RPMI-1640 containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. SK-HEP-1 hepatic adenocarcinoma cells were cultured in DMEM containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. SNU-475 liver cancer cells were cultured in RPMI-1640 containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. HT144 melanoma cells were cultured in McCoy's 5A containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. LNCaP prostate cancer cells were cultured in RPMI-1640 containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2. PC3 prostate cancer cells were cultured in DMEM/F12 containing 5% FBS and were grown in a humidified incubator at 37 °C with 5% CO_2.

[00318] For the assay, 2,000 cells of 22Rv1 /HCT-15 /NCI-N87, or 1,000 cells of HepG2 were seeded into each well of 96-well plates. After one day (24 h) in culture, cells (where cell types are indicated in the tables below) were treated with 1) test Compound A, B, or C alone, at concentrations of 0, 0.01, 0.032, 0.1, 0.32, 1, 3.2, 10 or 20 μM; or test Compound A, B, or C at the foregoing doses in combination with 0.1, 0.25, or 0.5 μM Niclosamide (Nic).

Compounds A, C, and E are compounds from Genus A. Compounds F-N are compounds from genus B. Compounds B and D are compounds from Genus C. Cells were treated for 72 hr. The cell viability was assessed using Thiazolyl Blue Tetrazolium Bromide (MTT) assay (n=3 for each dose). 5 mg/mL MTT was added in an amount equal to 10% of the culture medium volume after 72-hr treatment with the test compound. After the plates were incubated at 37 °C for 3 hours, the medium was removed and formazan crystals were dissolved in DMSO. The absorbance was measured on a FLUOstar Omega microplate reader (BMG LABTECH) at a wavelength of 550 nm and 690 nm. The absorbance at 690 nm was subtracted from the absorbance at 550 nm and the result was used for graphing.

[00319] IC_{50} (μM) of Compound A in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table. IC_{50} of Niclosamide alone in the NCI-N87 assay was 0.47 μM. IC_{50} of Niclosamide alone in the HCT116 assay was 0.41 μM. IC_{50} of Niclosamide alone in the DU145 assay was 1.4 μM. IC_{50} of Niclosamide alone in the MCF7 assay was 1.0 μM. IC_{50} of Niclosamide alone in the MDA-MB-231 assay was ~2.9 μM. IC_{50} of Niclosamide alone in the RPMI8226 assay was 0.29 μM. IC_{50} of Niclosamide alone in the SK-HEP-1 assay was 0.81 μM. IC_{50} of Niclosamide alone in the SNU-475 assay was not tested. IC_{50} of Niclosamide alone in the HT144 assay was 0.82 μM. IC_{50} of Niclosamide alone in the LNCaP assay was 0.36 μM. IC_{50} of Niclosamide alone in the PC3 assay was 0.55 μM.

Cancer cell line	**Niclosamide (μM)**			
	0	**0.1**	**0.25**	**0.5**
22Rv1	1.6	0.90	0.31	0.055
HepG2	0.23	0.13	0.047	0.039
HCT-15	6.0	2.7	1.1	0.39
NCI-N87	2.1	1.8	0.42	0.26
HCT116	21.9	0.49	0.1	0.22
DU145	37.9	10.6	3.4	1.2
MCF7	2.1	2.2	1.2	0.53
MDA-MB-231	11.5	15	11.1	5.4
RPMI8226	3.4	1.4	0.33	0.23
SK-HEP-1	4.0	2.5	1.1	0.45
SNU-475	62.5	31.3	52.9	63.9
HT144	1.5	Not tested	0.47	Not tested
LNCaP	0.51	Not tested	0.13	Not tested
PC3	2.6	Not tested	0.46	Not tested

[00320] As demonstrated by the above data, niclosamide has the effect of synergistically increasing Compound A's efficacy many fold when the two are administered together.

[00321] IC_{50} (μM) of Compound B in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table.

Cancer cell line	**Niclosamide (μM)**

	0	0.5
22Rv1	6.5	2.6
HepG2	8	2.3

[00322] As demonstrated by the above data, at 0.5 μM has the effect of synergistically increasing Compound B's efficacy many fold when the two are administered together.

[00323] IC_{50} (μM) of Compound C in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table. IC_{50} of Niclosamide alone in the NCI-N87 assay was 0.47 μM. IC_{50} of Niclosamide alone in the HCT116 assay was 0.41 μM.

Cancer cell line	Niclosamide (μM)			
	0	**0.1**	**0.25**	**0.5**
22Rv1	1.8	1.3	0.23	0.038
NCI-N87	0.96	2.0	0.55	0.092
HCT116	11.2	0.54	0.098	

[00324] As demonstrated by the above data, niclosamide at least 0.25 μM has the effect of synergistically increasing Compound C's efficacy many fold when the two are administered together.

[00325] IC_{50} (μM) of Compound D in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table.

Cancer cell line	Niclosamide (μM)			
	0	**0.1**	**0.25**	**0.5**
22Rv1	11.4	7.4	5.1	2.7
HepG2	13.6	7.6	5.5	5.8

[00326] As demonstrated by the above data, niclosamide has the effect of synergistically increasing Compound D's efficacy when the two are administered together.

[00327] IC_{50} (μM) of Compound E in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table.

Cancer cell line	Niclosamide (μM)			
	0	**0.1**	**0.25**	**0.5**
22Rv1	3.0	1.0	0.26	0.036
HepG2	0.54	0.13	0.036	

[00328] As demonstrated by the above data, niclosamide at 0.25 μM has the effect of synergistically increasing Compound E's efficacy many fold when the two are administered together.

[00329] IC_{50} (μM) of Compound F in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table.

Cancer cell line	Niclosamide (μM)			
	0	**0.1**	**0.25**	**0.5**
22Rv1	8.4	4.8	1.0	0.30

HepG2	2.6	1.1	0.34	

[00330] As demonstrated by the above data, niclosamide at 0.25 μM has the effect of synergistically increasing Compound F's efficacy many fold when the two are administered together.

[00331] IC_{50} (μM) of Compound G in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table.

Cancer cell line	**Niclosamide (μM)**			
	0	**0.1**	**0.25**	**0.5**
22Rv1	3.8		0.35	

[00332] As demonstrated by the above data, niclosamide at 0.25 μM has the effect of synergistically increasing Compound G's efficacy many fold when the two are administered together.

[00333] IC_{50} (μM) of Compound H in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table. IC_{50} of Niclosamide alone in the 22Rv1 assay was 0.70 μM. IC_{50} of Niclosamide alone in the HT144 assay was 0.82 μM. IC_{50} of Niclosamide alone in the LNCaP assay was 0.36 μM. IC_{50} of Niclosamide alone in the PC3 assay was 0.55 μM.

Cancer cell line	**Niclosamide (μM)**	
	0	**0.25**
22Rv1	4.0	0.44
HT144	3.6	0.62
LNCaP	0.92	0.13
PC3	7.2	0.42

[00334] As demonstrated by the above data, Niclosamide at 0.25 μM has the effect of synergistically increasing Compound H's efficacy many fold when the two are administered together.

[00335] IC_{50} (μM) of Compound HH in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table. IC_{50} of Niclosamide alone in the 22Rv1 assay was 0.70 μM. IC_{50} of Niclosamide alone in the HT144 assay was 0.82 μM. IC_{50} of Niclosamide alone in the LNCaP assay was 0.36 μM. IC_{50} of Niclosamide alone in the PC3 assay was 0.55 μM.

Cancer cell line	**Niclosamide (μM)**	
	0	**0.25**
22Rv1	4.5	0.51
HT144	3.4	1.0
LNCaP	0.78	0.10
PC3	3.2	0.55

[00336] As demonstrated by the above data, niclosamide at 0.25 μM has the effect of synergistically increasing Compound HH's efficacy many fold when the two are administered together.

[00337] IC_{50} (μM) of Compound J in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table. IC_{50} of Niclosamide alone in the 22Rv1 assay was 0.70 μM. IC_{50} of Niclosamide alone in the HT144 assay was 0.82 μM. IC_{50} of Niclosamide alone in the LNCaP assay was 0.36 μM. IC_{50} of Niclosamide alone in the PC3 assay was 0.55 μM.

Cancer cell line	**Niclosamide (μM)**	
	0	**0.25**
22Rv1	2.4	0.24
HT144	1.7	0.47
LNCaP	0.35	0.084
PC3	2.6	0.48

[00338] As demonstrated by the above data, niclosamide at 0.25 μM has the effect of synergistically increasing Compound J's efficacy many fold when the two are administered together.

[00339] IC_{50} (μM) of Compound K in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table. IC_{50} of Niclosamide alone in the 22Rv1 assay was 0.70 μM. IC_{50} of Niclosamide alone in the HT144 assay was 0.82 μM. IC_{50} of Niclosamide alone in the LNCaP assay was 0.36 μM. IC_{50} of Niclosamide alone in the PC3 assay was 0.55 μM.

Cancer cell line	**Niclosamide (μM)**	
	0	**0.25**
22Rv1	3.0	0.49
HT144	6.1	0.96
LNCaP	0.67	0.12
PC3	5.2	0.75

[00340] As demonstrated by the above data, niclosamide at 0.25 μM has the effect of synergistically increasing Compound K's efficacy many fold when the two are administered together.

[00341] IC_{50} (μM) of Compound L in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table.

Cancer cell line	**Niclosamide (μM)**	
	0	**0.25**
22Rv1	4.3	0.17

[00342] As demonstrated by the above data, niclosamide at 0.25 μM has the effect of synergistically increasing Compound L's efficacy many fold when the two are administered together.

[00343] IC_{50} (μM) of Compound M in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table. IC_{50} of Niclosamide alone in the 22Rv1 assay was 0.70 μM. IC_{50} of Niclosamide alone in the HT144 assay was 0.82 μM. IC_{50} of Niclosamide alone in the LNCaP assay was 0.36 μM. IC_{50} of Niclosamide alone in the PC3 assay was 0.55 μM.

Cancer cell line	Niclosamide (μM)	
	0	0.25
22Rv1	4.2	0.22
HT144	5.4	0.96
LNCaP	0.78	0.13
PC3	6.0	0.47

[00344] As demonstrated by the above data, niclosamide at 0.25 μM has the effect of synergistically increasing Compound M's efficacy many fold when the two are administered together.

[00345] IC_{50} (μM) of Compound N in the dose-response MTT studies with Niclosamide at different doses in different cancer cell lines are presented in the following table. IC_{50} of Niclosamide alone in the 22Rv1 assay was 0.70 μM. IC_{50} of Niclosamide alone in the HT144 assay was 0.82 μM. IC_{50} of Niclosamide alone in the LNCaP assay was 0.36 μM. IC_{50} of Niclosamide alone in the PC3 assay was 0.55 μM.

Cancer cell line	Niclosamide (μM)	
	0	0.25
22Rv1	4.6	0.18
HT144	4.6	0.61
LNCaP	0.91	0.10
PC3	4.9	2.2

[00346] As demonstrated by the above data, niclosamide at 0.25 μM has the effect of synergistically increasing Compound N's efficacy many fold when the two are administered together.

Biological Example 3

[00347] Effect of Genus B Compounds on protein levels of PCSK9 and LDL receptor (LDLR) in HePG2 cells are provided in Example 4 of WO2018/049080, which is incorporated herein by reference in its entirety.

Biological Example 4

Western blots of androgen receptor (AR) and androgen receptor variant 7 (AR-V7) extracts from control and treated 22Rv1 cancer cells

[00348] 30 μg protein crude extracts of 22Rv1 treated for 24 hours with Compound A at a concentration of 0.1 or 0.32 μM alone or in combination with 0.5 μM niclosamide and control cells were subjected to 4-20% Tris-Glycine electrophoresis gel separation. Proteins were transferred onto PVDF membrane and were detected with commercial antibodies' against AR, AR-V7 (Cat#:133273, Abcam) or actin using Odyssey Fc Imaging system (LI-COR). Intensity of the correspondent bands was quantified using actin as internal control and using Image Studio Lite Ver 5.2 software. Lanes: 1,2 (control DMSO); 3, 4 (0.1 μM Compound A alone); 5,6 (0.32 μM Compound A alone); 7,8 (0.1 μM Compound A + 0.5 μM niclosamide); 9, 10 (0.32 μM Compound A + 0.5 μM niclosamide); 11, 12 (0.5 μM niclosamide alone). See Figure 1. As shown from the intensity of the bands, combination of 0.1 or 0.32 μM of Compound A with 0.5 μM niclosamide reduced the AR and AR-V7 by about 40% and 60%, respectively compared to controls. Cells treated with Compound A or niclosamide alone did not significantly affect the protein levels of these protein receptors.

Biological Example 5

Change in mRNA levels in cells treated with Compound A alone or in combination with niclosamide.

[00349] mRNA levels of proprotein convertase subtilisin/kexin type 9 (PCSK9), protein specific antigen (PSA), and mevalonate decarboxylase (MVD) in 22Rv1 cells were determined using Quantitative PCR (qPCR). 22Rv1 cells were grown in RPMI-1640 supplemented with 5 % FBS in a 5% CO_2 incubator at 37 ºC. For the assay the cells were plated in 24 well plates at a concentration of 200,000 cells/well in RPMI-1640 with 5% FBS. The compounds at the indicated doses were added to the growth medium. After 24 hours of incubation with compounds, the RNA was isolated from the cells using the illustra RNAspin Mini kit (GE Healthcare). For the quantitative PCR, the RNA was analyzed using the Power SYBR® Green PCR Master Mix (Thermo Fisher Scientific) and gene specific primers. The reaction was run on a StepOnePlus Real-Time PCR System (Thermo Fisher Scientific), and the instrument software was used to determine the Ct values. The fold change of mRNA expression relative to the vehicle control was calculated. Results are provided in Figures 2 and 3.

[00350] All publications, patents, and patent applications cited in this specification are herein incorporated by reference as if each individual publication, patent, or patent application were specifically and individually indicated to be incorporated by reference. While the claimed subject matter has been described in terms of various embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the claimed subject matter is limited solely by the scope of the following claims, including equivalents thereof.

WHAT IS CLAIMED IS:

1. A method of treating a condition, disease, or disorder comprising a) administering a therapeutically effective amount of an SREBP inhibitor or a pharmaceutically acceptable salt thereof, in combination with niclosamide or a niclosamide analog; or b) administering a therapeutically effective amount of a composition comprising an SREBP inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier thereof; in combination with niclosamide or a niclosamide analog or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier thereof.

2. The method of claim 1, wherein the condition, disease, or disorder is associated with activation of the SREBP pathway and/or one or more target genes that are essential for proliferation.

3. The method of claim 1 or 2, wherein the condition, disease, or disorder is cancer or NAFLD.

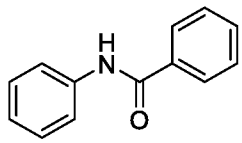
4. The method of claim 1 or 2, wherein the condition, disease, or disorder is cancer.

5. The method of any one of claims 1-5, wherein the condition, disease, or disorder is cancer and the cancer is selected from breast cancer, prostate cancer, castration-resistant prostate cancer, colorectal cancer, colorectal adenocarcinoma, gastric carcinoma, multiple myeloma, melanoma, hepatic adenocarcinoma, glioblastoma, and liver cancer.

6. The method of claim 1 or 2, wherein the condition, disease, or disorder is NAFLD.

7. The method of any one of claims 1-6, wherein the niclosamide or a niclosamide analog is a niclosamide analog.

8. The method of any one of claims 1-7, wherein the niclosamide or a niclosamide analog is a niclosamide analog comprising the following structure:

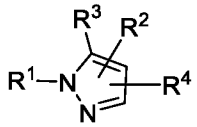


where each of the phenyl groups is independently optionally substituted.

9. The method of any one of claims 1-6, wherein the niclosamide or a niclosamide analog is niclosamide.

10. The method of any one of claims 1-9, wherein the SREBP inhibitor is a compound according to Genus A, Genus B, or Genus C,

wherein the Compound of Genus A is according to:



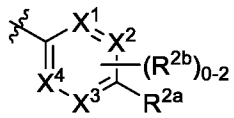
(I)

where

R^1 is phenyl, pyridinonyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl; where the phenyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl rings are optionally substituted with 1, 2, or 3 R^{1a} and where the pyridinonyl is substituted on the nitrogen with R^{1b} and is additionally optionally substituted with 1, 2, or 3 R^{1a};

each R^{1a} is independently halo, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{1b} is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are carbon;

R^{2a} is $-NR^{5a}S(O)_2R^{5b}$ or $-NR^{6a}R^{6b}$;

each R^{2b} is independently halo, alkyl, haloalkyl, $-NO_2$, or cyano;

R^3 is hydrogen, halo, alkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl, or haloalkyl;

R^{5a} and R^{6a} are independently hydrogen or alkyl; and

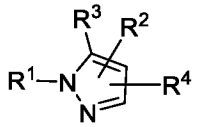
R^{5b} and R^{6b} are independently alkyl; haloalkyl; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; heterocycloalkylalkyl; and

wherein each cycloalkyl, either alone or as part of another group, is independently optionally substituted with one or two groups independently selected from the group consisting of alkyl, halo, and haloalkyl; or

a pharmaceutically acceptable salt thereof;

provided that the compound is not N-methyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; N-ethyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine; or N-propyl-6-(1-phenyl-1H-pyrazol-4-yl)pyridazin-3-amine;

wherein the Compound of Genus B is according to:



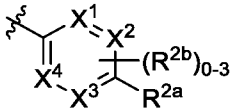
(I)

where

R^1 is pyridinonyl, where the pyridinonyl is substituted on its nitrogen with R^{1b} and is additionally optionally substituted with 1 R^{1a};

R^{1a}, when present, is halo, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^{1b} is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

R^2 is  where 0, 1, or 2 of X^1-X^4 are nitrogen and the remaining are CH or CR^{2b};

R^{2a} is $-OR^5$, $-S(O)R^6$, or $-S(O)_2R^7$;

each R^{2b}, when present, is independently halo, alkyl, haloalkyl, $-NO_2$, or cyano;

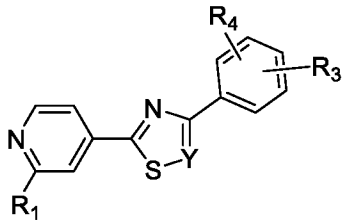
R^3 is hydrogen, halo, alkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl, or haloalkyl; and

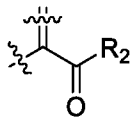
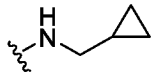
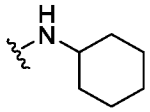
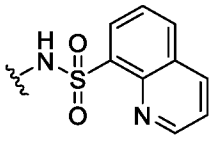
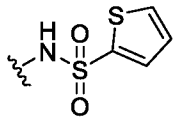
R^5, R^6, and R^7 are independently alkyl; haloalkyl; hydroxyalkyl; haloalkyl further substituted with 1 or 2 hydroxy; cycloalkyl; cycloalkylalkyl; heterocycloalkyl; or heterocycloalkylalkyl; where the cycloalkyl, alone or as part of cycloalkylalkyl, and heterocycloalkyl, alone or as part of heterocycloalkylalkyl, are optionally substituted with 1, 2, or 3 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; or

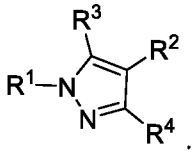
a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof; and

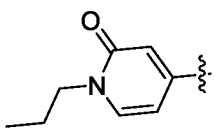
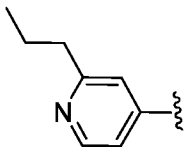
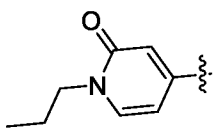
wherein the Compound of Genus C is according to:



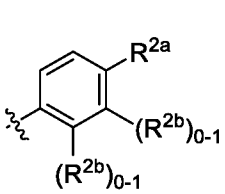
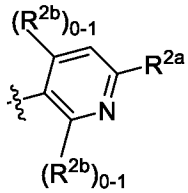
(X)

wherein R_1 is H, ethyl, –OMe, or n-propyl; Y is CH or  ; and R_2 is –OH, -OMe, or -NH-i-Pr; R_3 is H, F, or Cl; and R_4 is H, Me, Cl, Br, F, –OH, –OBz, -$OCH_2C(O)OMe$, –$OCH_2C(O)OH$, –NH_2, –NH-i-Pr, –NHC(O)Me, –$NHS(O)_2Me$, –NHBn, , –OMe, –NHBoc, , –NHTs, , or  ; or a pharmaceutically acceptable salt or stereoisomer thereof or a combination thereof.

11. The method of any one of claims 1-10, wherein the compound of Genus A or Genus B is according to .

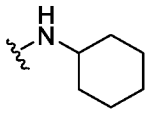
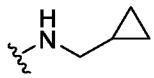
12. The method of any one of claims 1-11, wherein R^1 of the compound of Genus A is  or ; R^1 of the compound of Genus B is  ; and R_1 of Genus C is n-propyl.

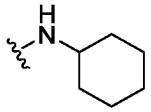
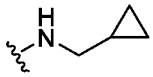
13. The method of any one of claims 1-12, wherein R^3 and R^4 of the compound of Genus A are each hydrogen; R^3 and R^4 of the compound of Genus B are each hydrogen; and in the compound of Genus C, Y is CH and R_3 is H.

14. The method of any one of claims 1-13, wherein R^2 in the compound of Genus A or B is  or  ; and where R_4 in the compound of Genus C is attached at the para-position of the phenyl with respect to the point of of attachment to the rest of the molecule.

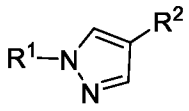
15. The method of any one of claims 1-14, wherein each R^{2b} in the compound of Genus A or B is independently halo or methyl.

16. The method of any one of claims 1-15, wherein R^{2a} in the compound of Genus A is –$NHS(O)_2R^{5b}$ or –NHR^{6b}; R^{2a} in the compound of Genus B is -OR^5 or –$S(O)_2R^7$; and R_4 in

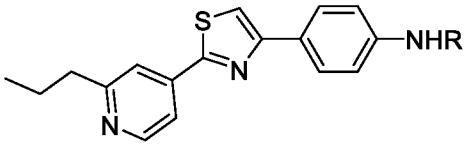
the compound of Genus C is –NH-i-Pr, , , –NHC(O)Me, or –$NHS(O)_2Me$.

17. The method of any one of claims 1-15, wherein R^{5b} and R^{6b} in the compound of Genus A are alkyl, haloalkyl, or cycloalkyl; R^5 in the compound of Genus B is a) alkyl, b) hydroxyalkyl, c) haloalkyl further substituted with 1 or 2 hydroxy, or d) cycloalkylalkyl wherein the cycloalkyl ring is optionally substituted with 1, 2, or 3 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; R^7 in the compound of Genus B is alkyl or cycloalkyl; and R_4 in the compound of Genus C is –NH-i-Pr, , , –NHC(O)Me , or –$NHS(O)_2Me$.

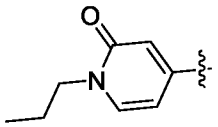
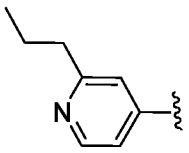
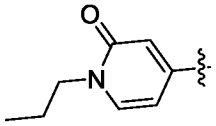
18. The method of any one of claims 1-10, wherein the compound of Genus A or B is according to

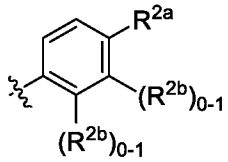
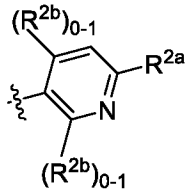
,

and the compound of Genus C is according to

;

and wherein

R^1 of the compound of Genus A is  or ; R^1 of the compound of Genus B is ;

R^2 in the compound of Genus A or B is  or  ; and

R^{2a} in the compound of Genus A is $–NHS(O)_2R^{5b}$ or $–NHR^{6b}$; R^{2a} in the compound of Genus B is $-OR^5$ or $–S(O)_2R^7$;

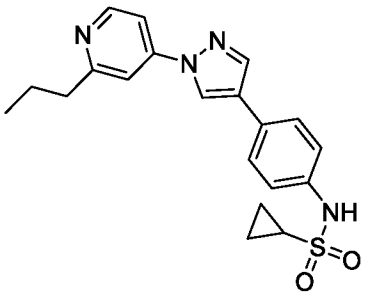
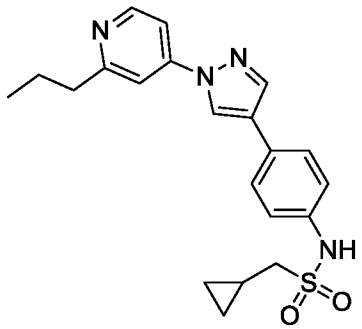
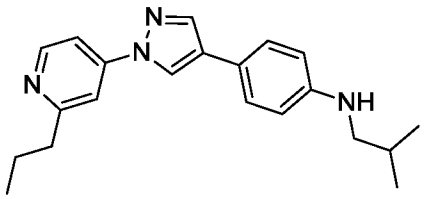
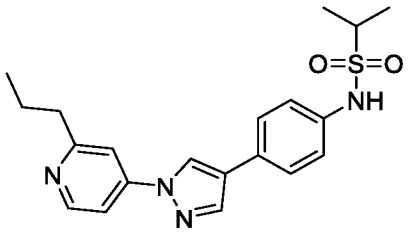
R^{5b} and R^{6b} in the compound of Genus A are alkyl, haloalkyl, or cycloalkyl; R^5 in the compound of Genus B is a) alkyl, b) hydroxyalkyl, c) haloalkyl further substituted with 1 or 2 hydroxy, or d) cycloalkylalkyl wherein the cycloalkyl ring is optionally substituted with 1, 2, or 3 groups independently selected from alkyl, hydroxy, halo, and hydroxyalkyl; R^7 in the compound of Genus B is alkyl or cycloalkyl;

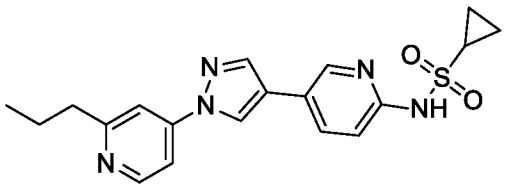
R in the compound of Genus C is isopropyl, cyclohexyl, cyclopropylmethyl, –C(O)Me, or methylsulfonyl; and

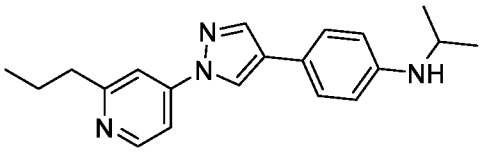
each R^{2b} in the compound of Genus A and B is independently halo or methyl, preferably fluoro, chloro, or methyl.

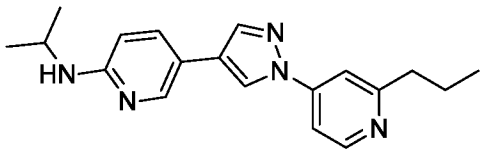
19. The method of any one of claims 1-18, wherein the SREBP inhibitor is selected from Genus A.

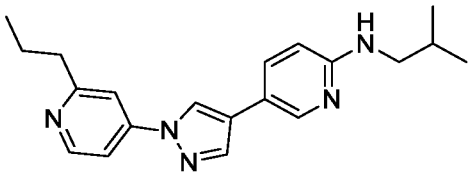
20. The method of any one of claims 1-13, wherein the SREBP inhibitor is selected from Genus A compounds:

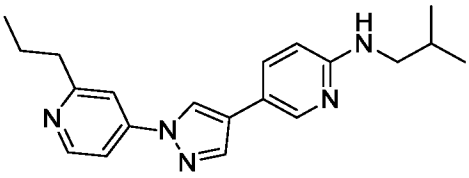





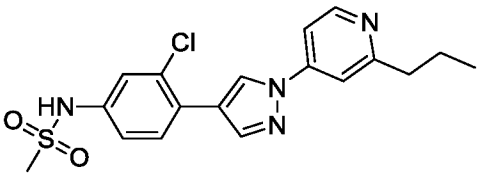


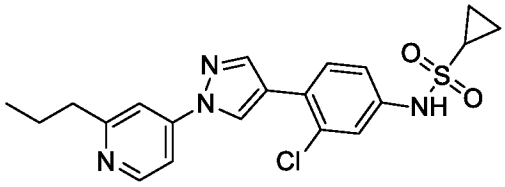


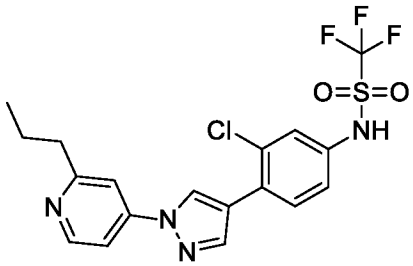


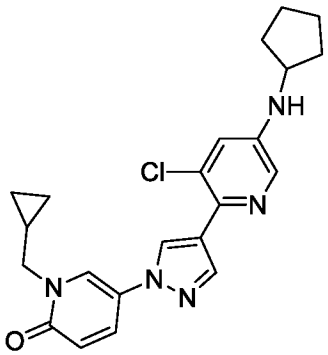


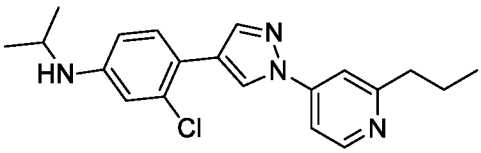


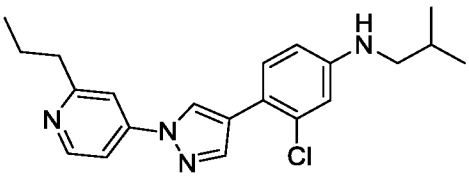


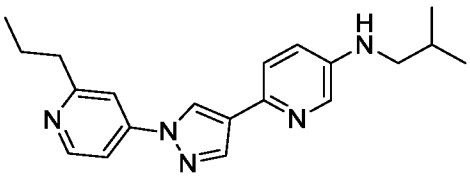


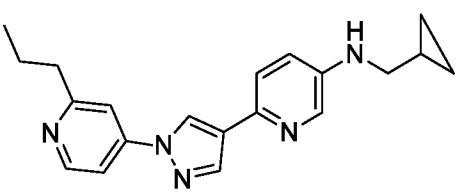


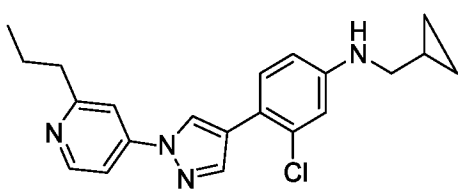


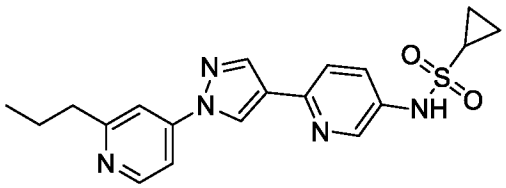
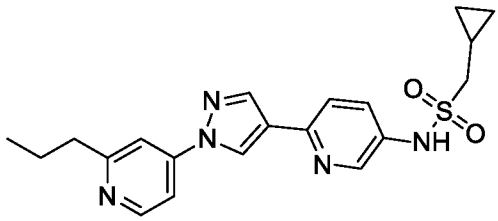
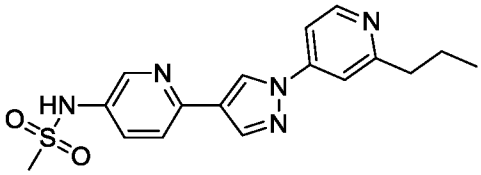
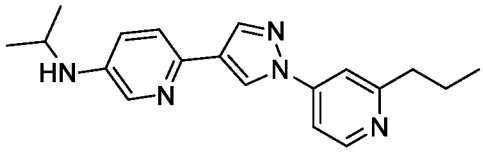
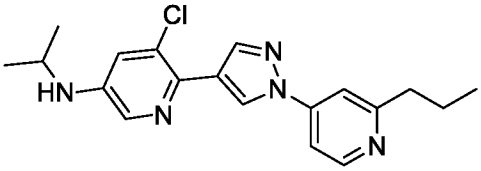
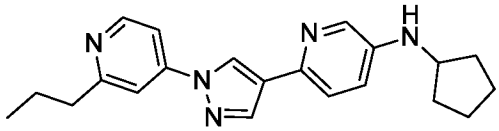
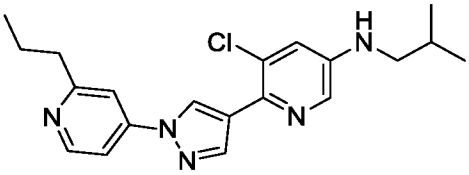
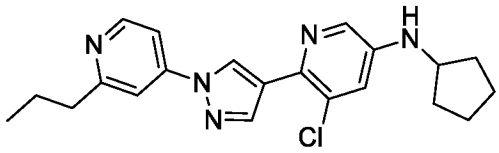
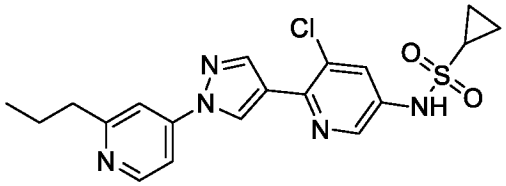
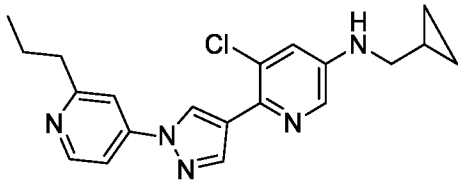
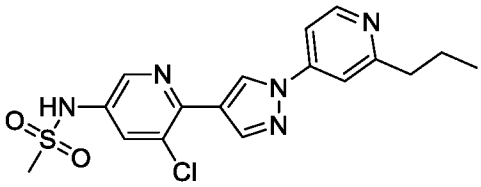
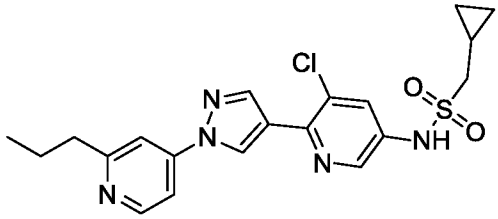
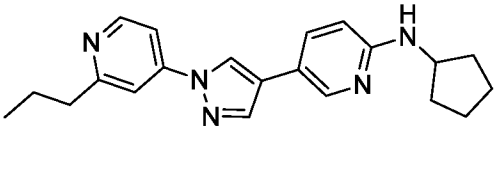
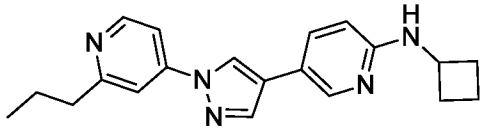
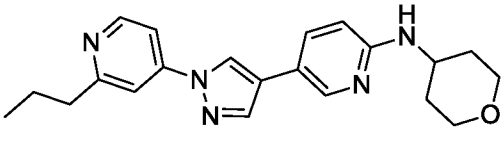
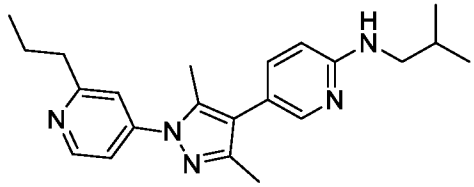
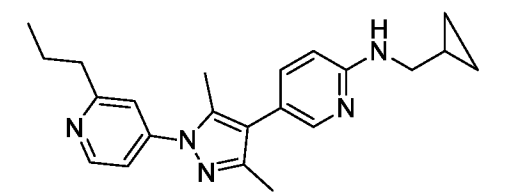


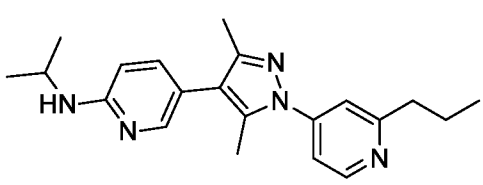


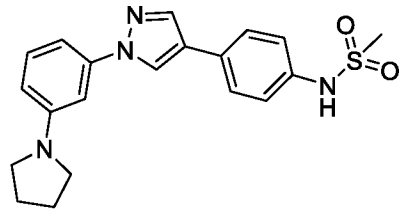


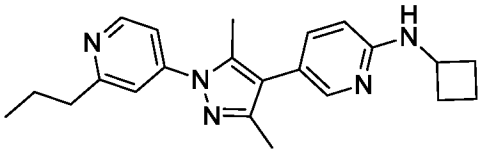


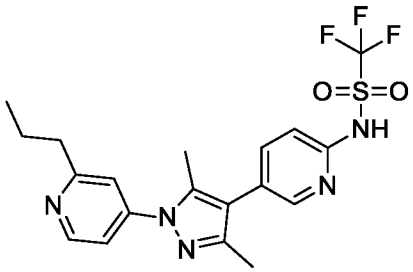


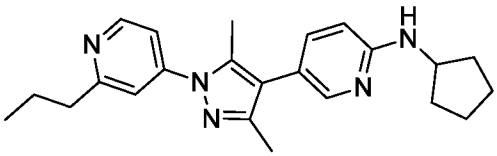


















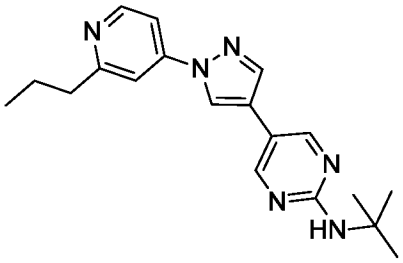


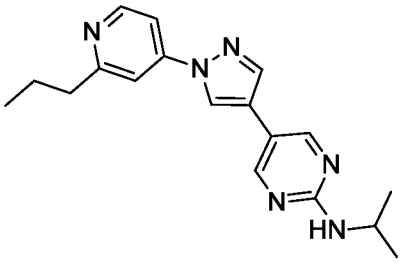


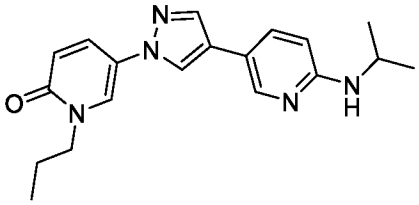


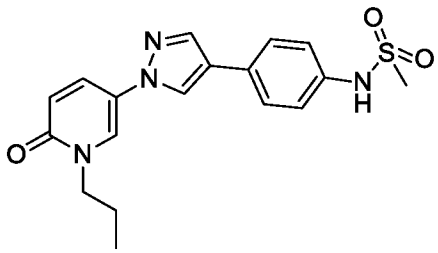


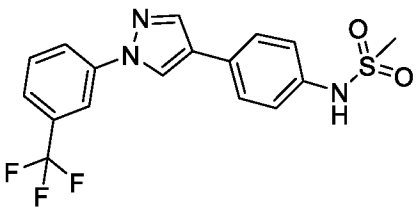


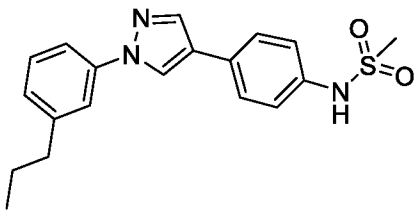


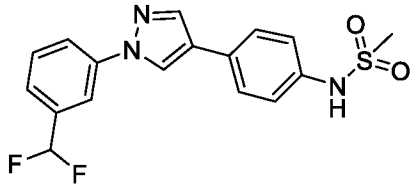


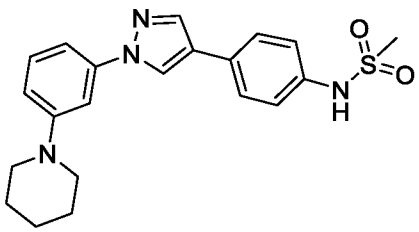


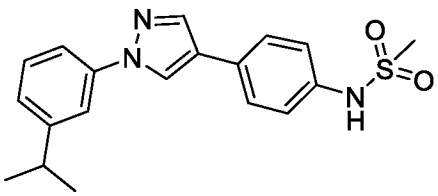


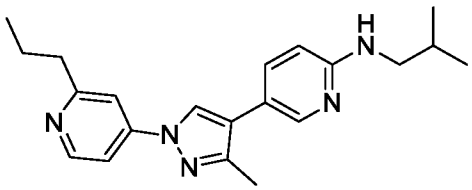


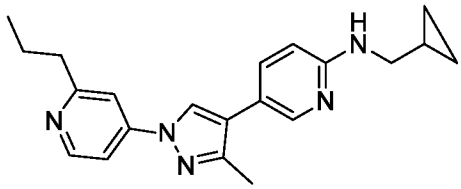


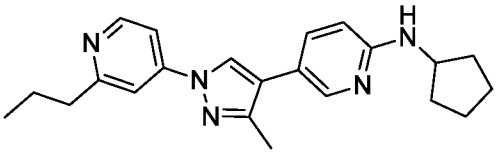


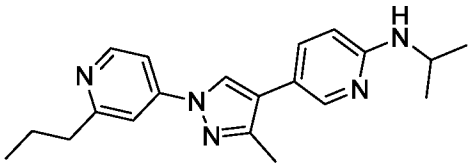


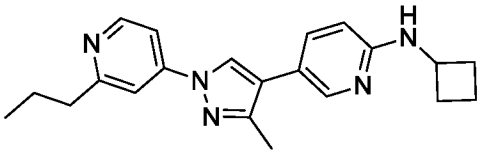


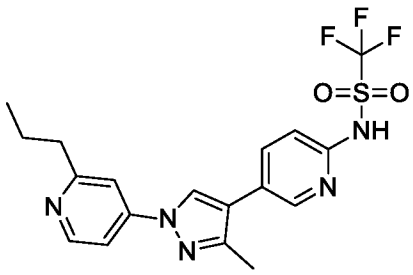


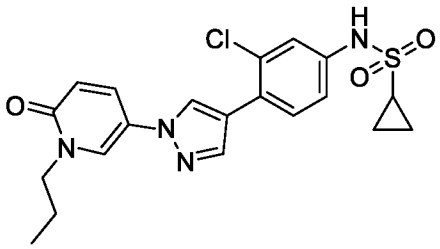


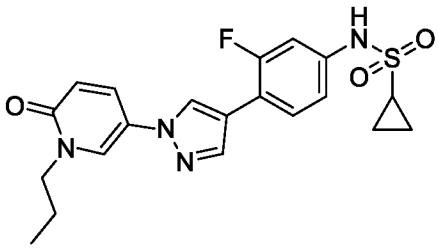


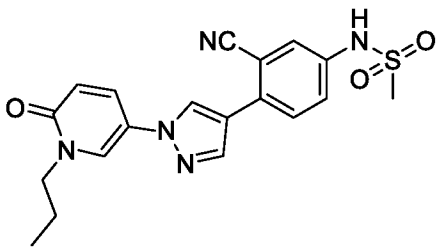


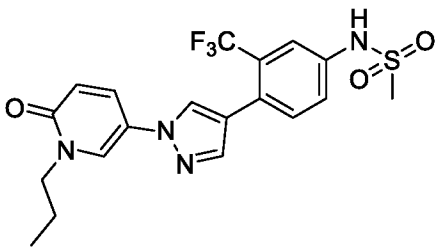


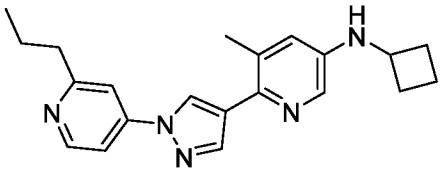


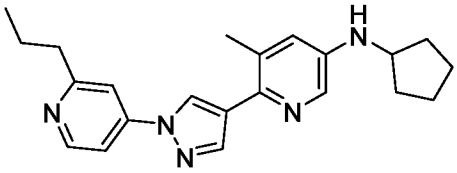


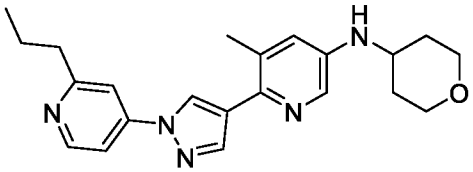


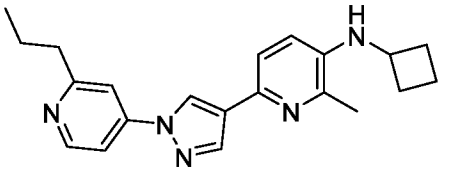


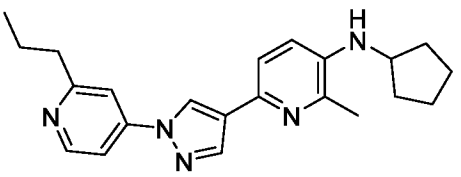


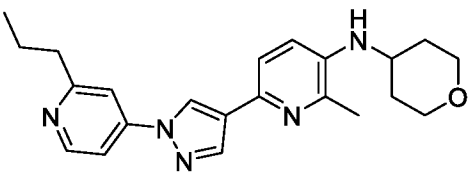


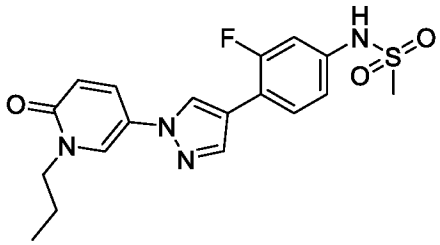


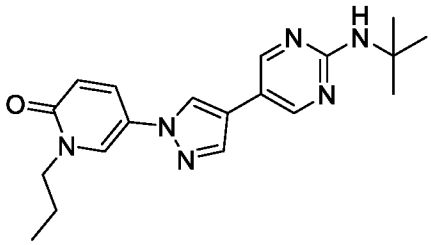


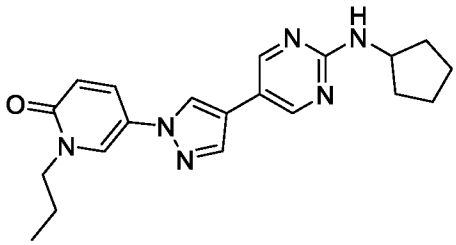


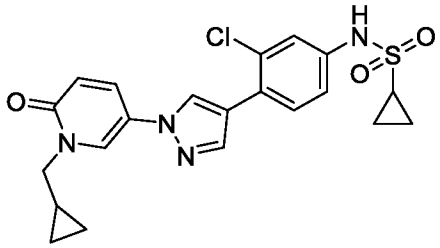


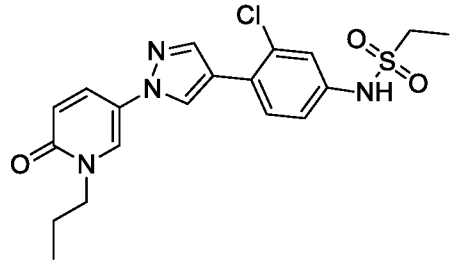


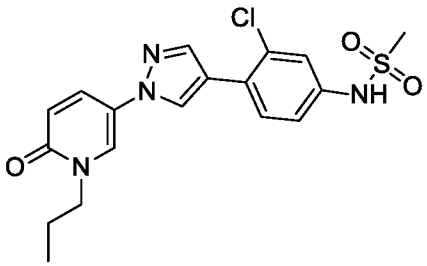


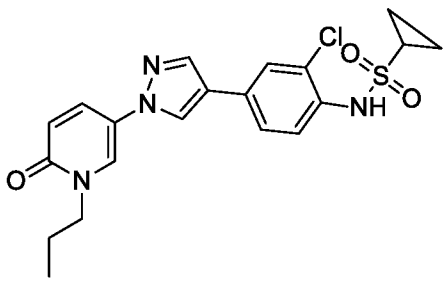


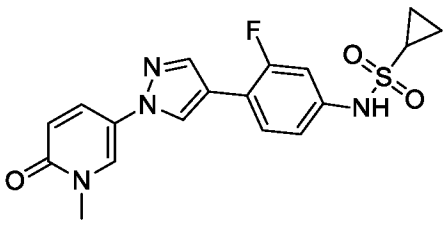


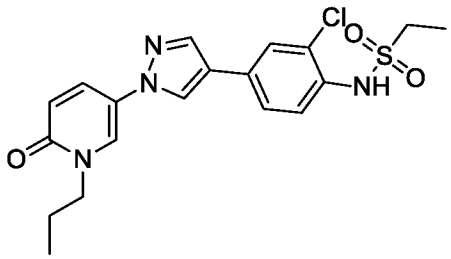


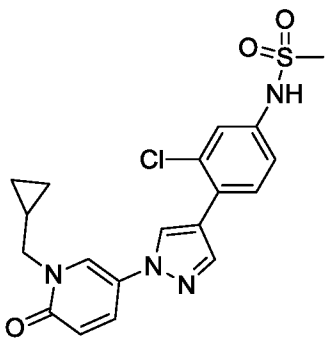


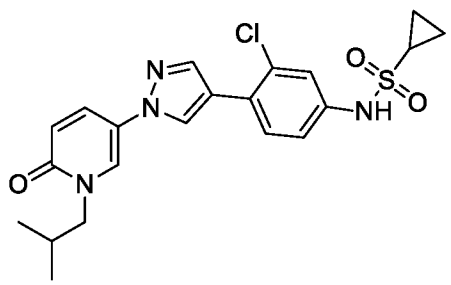


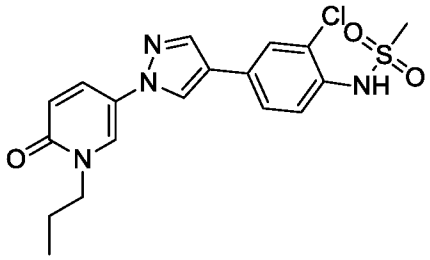


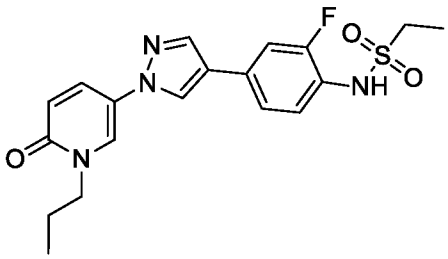


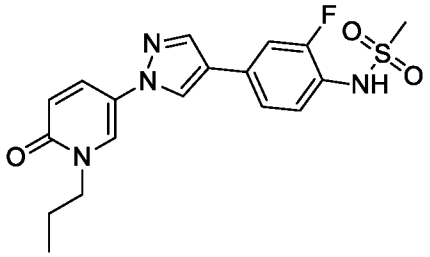


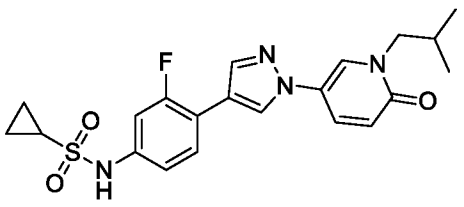


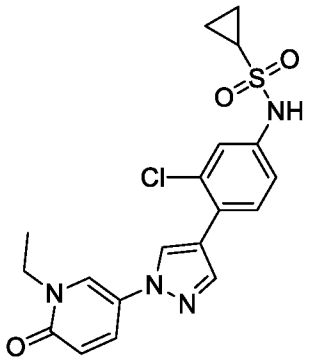


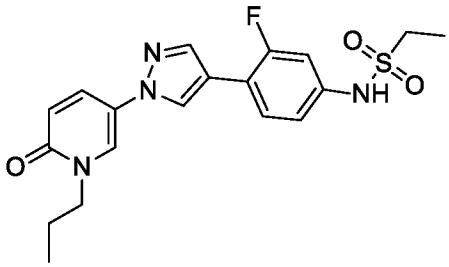


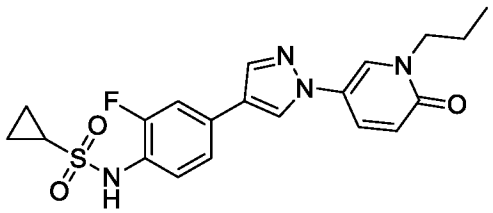


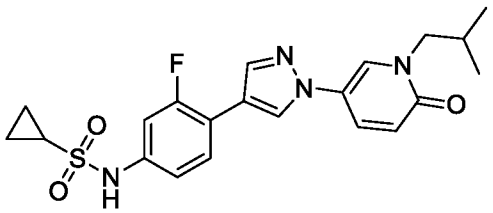


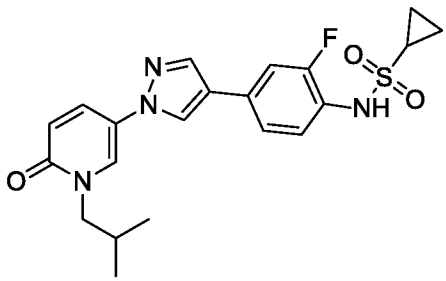


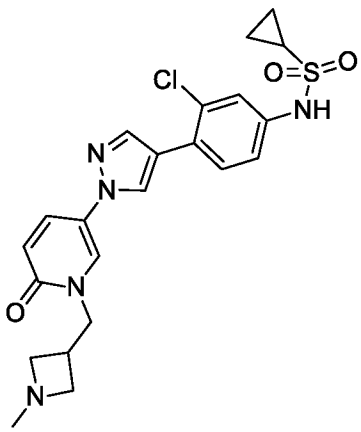


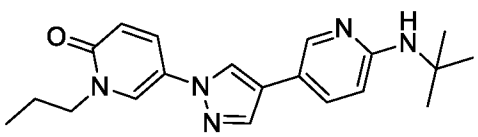


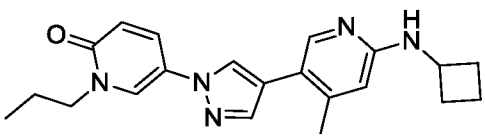


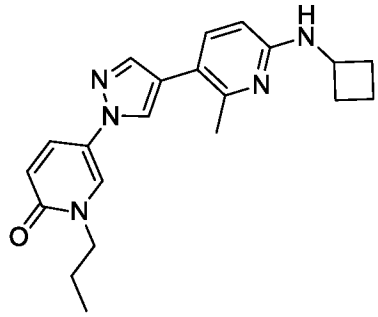


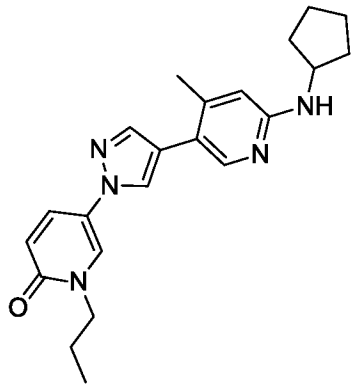


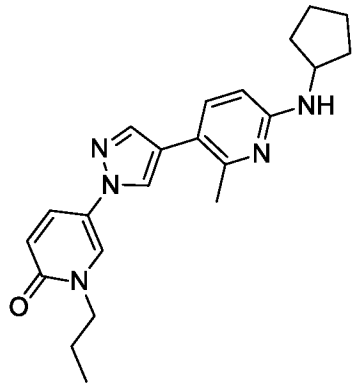


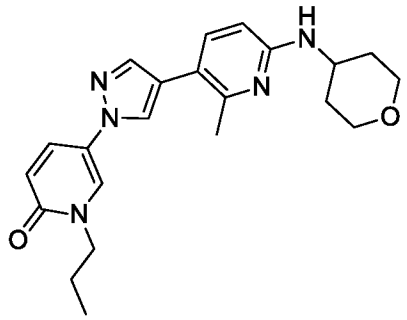


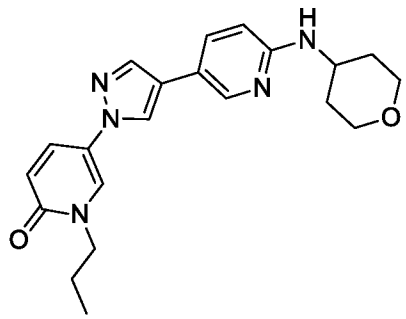


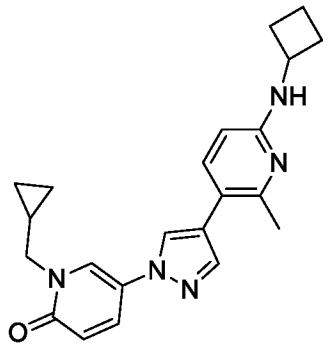


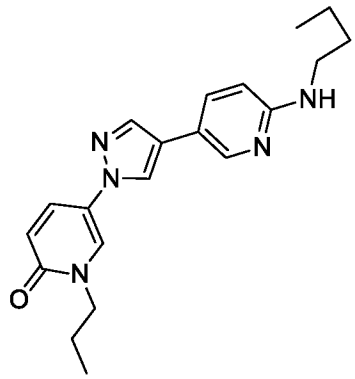


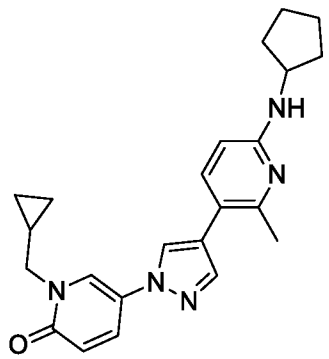


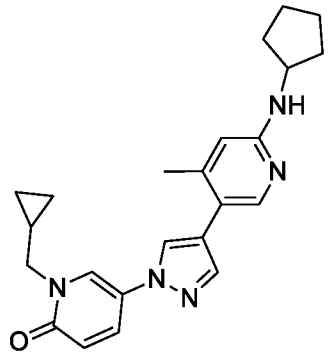


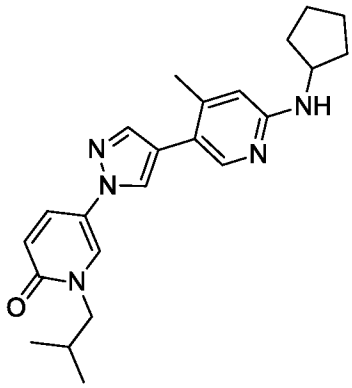


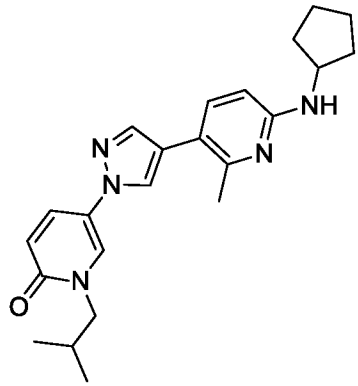


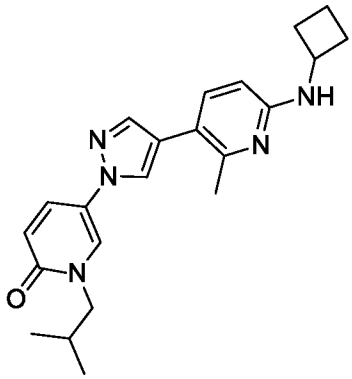


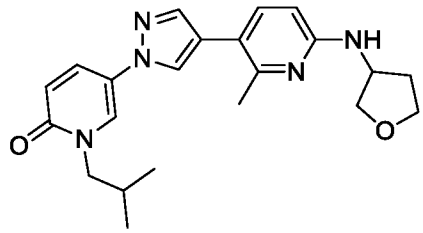


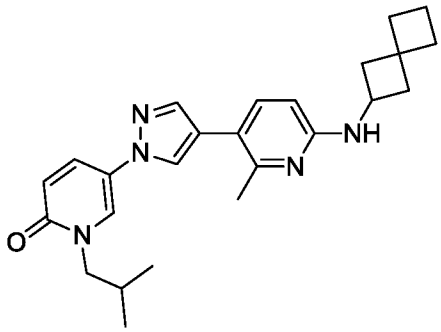


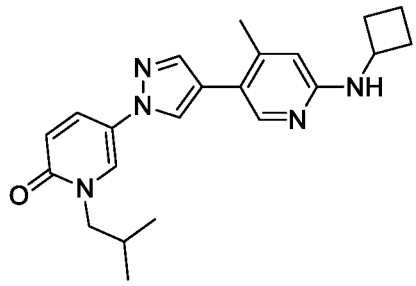


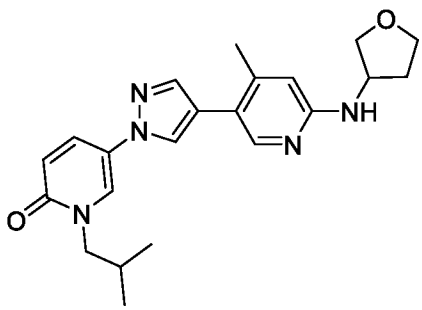


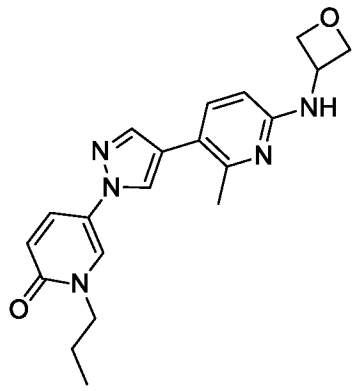


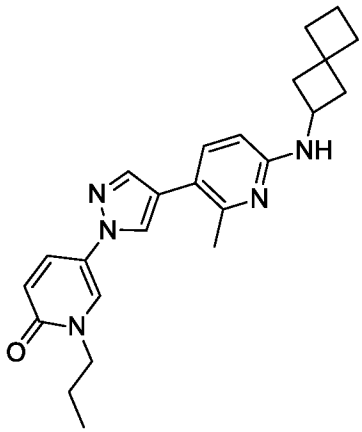


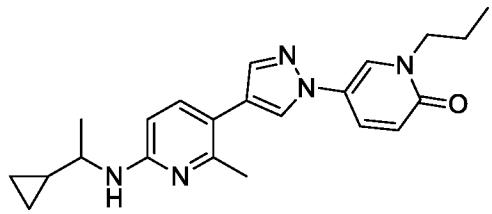


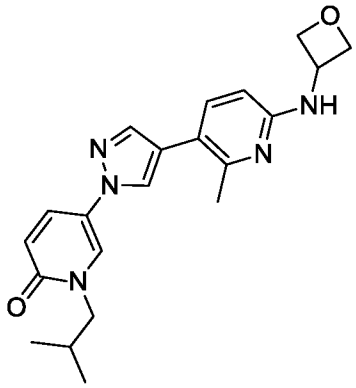


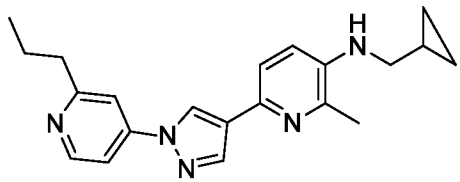


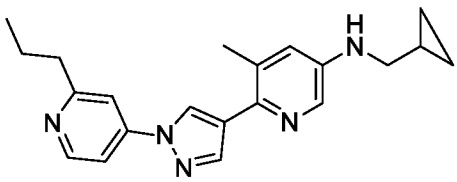


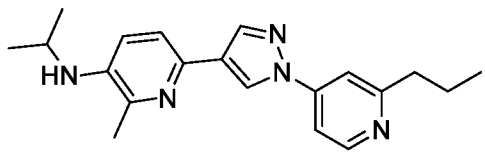


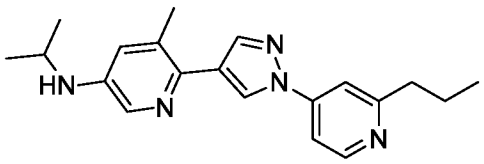


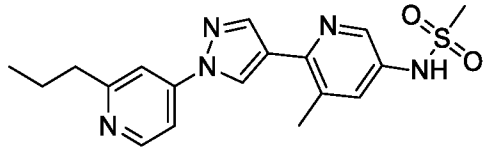


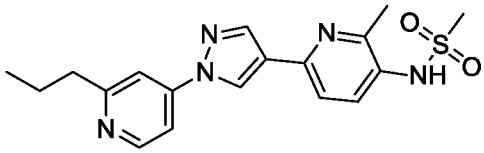


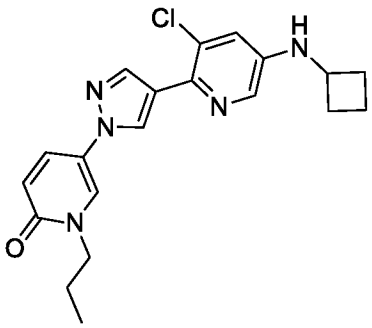


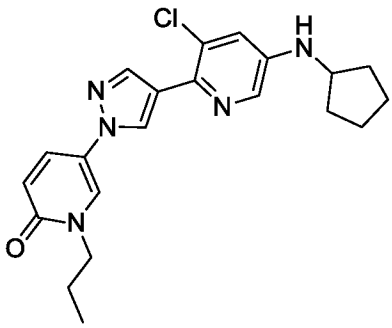


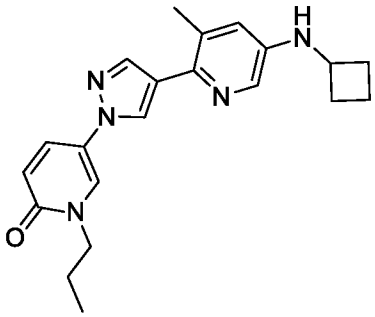


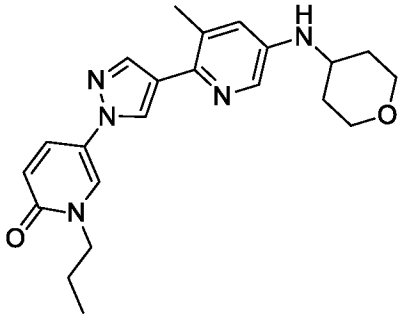


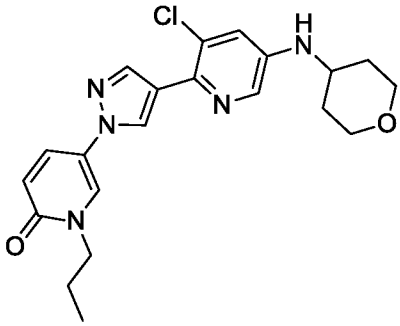


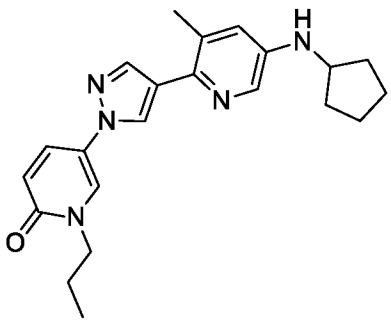


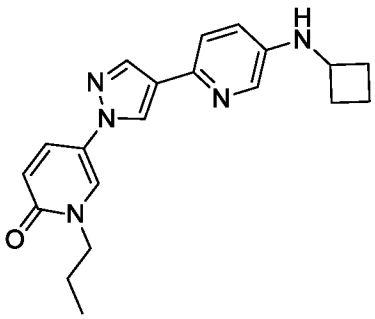


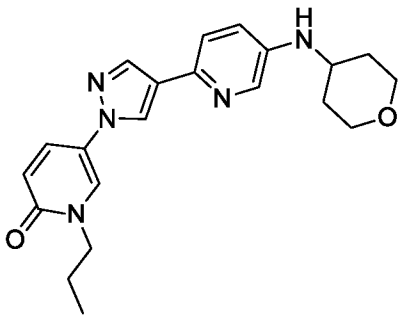


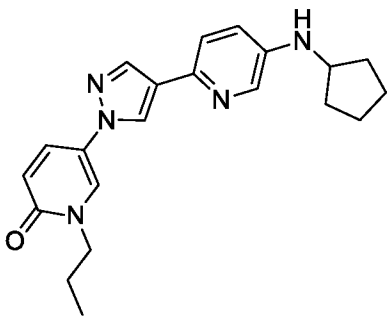


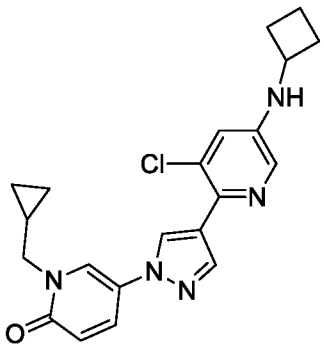


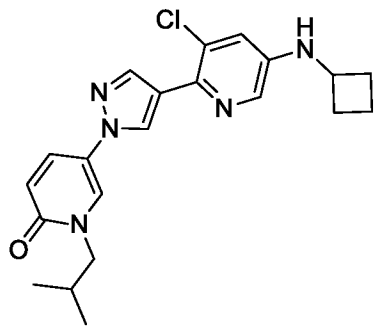


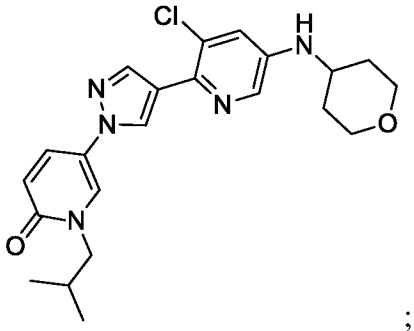








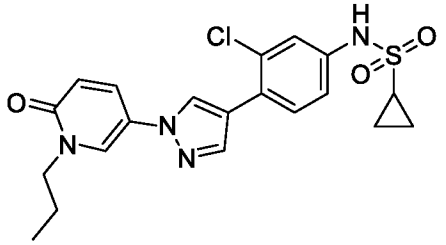


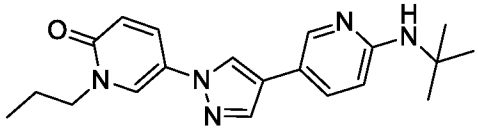


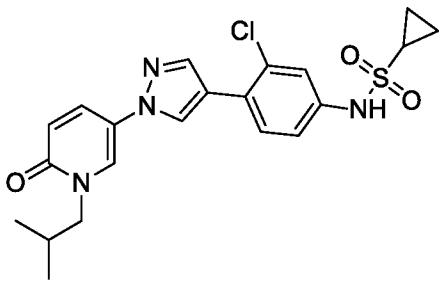
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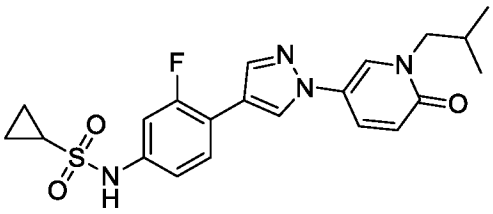
or a pharmaceutically acceptable salt thereof.

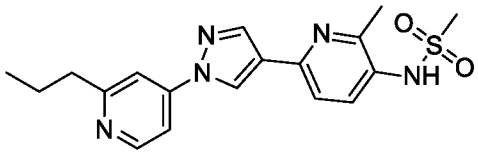
19. The method of any one of claims 1-13, wherein the SREBP inhibitor is selected from Genus A compounds:

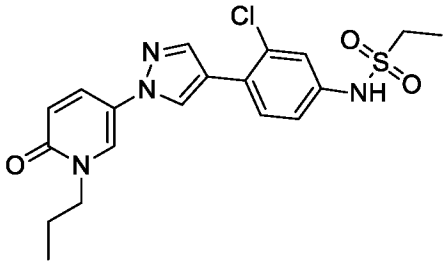


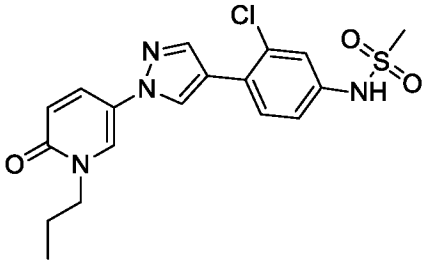


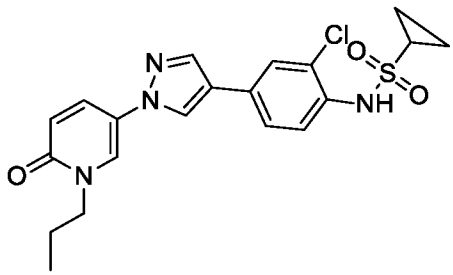


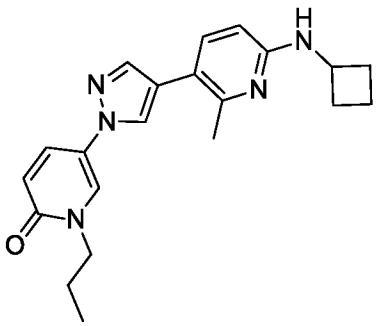


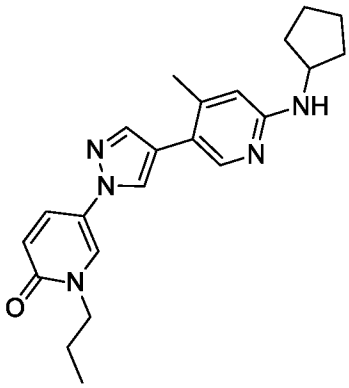


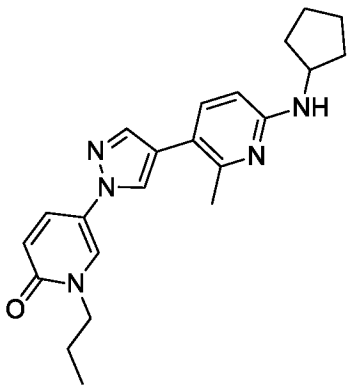


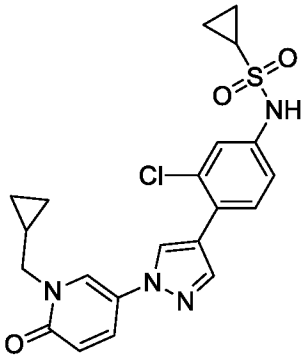


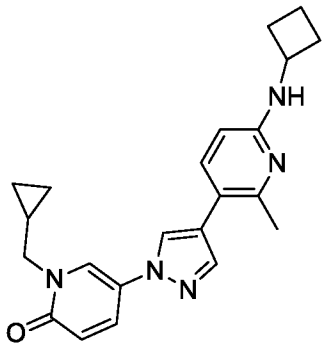


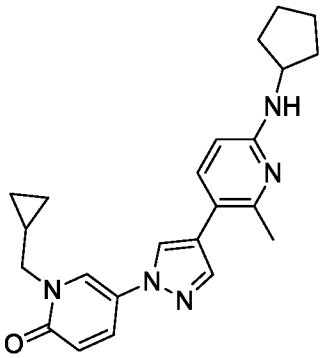


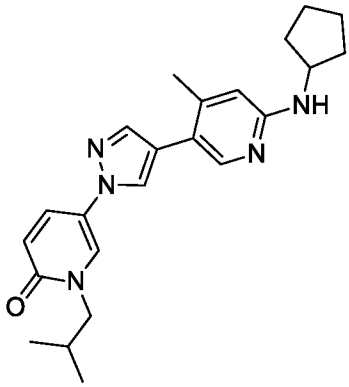


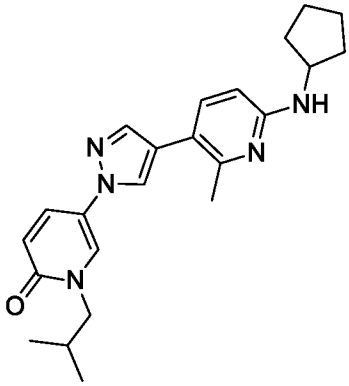


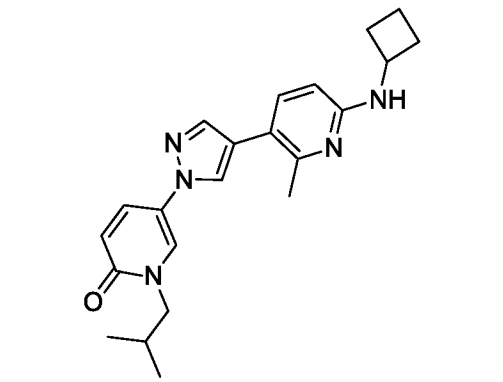


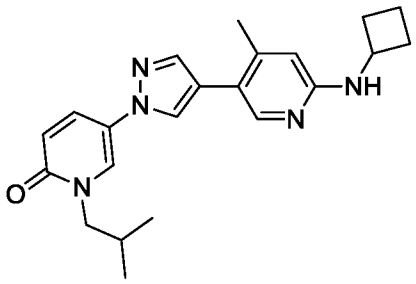


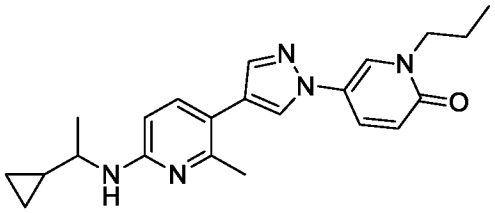










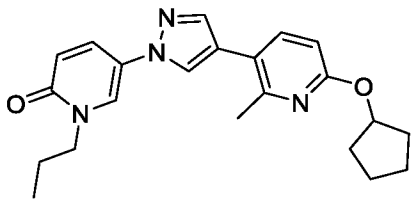


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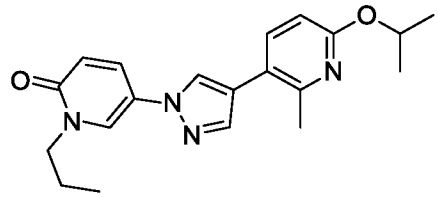
or a pharmaceutically acceptable salt thereof.

22. The method of any one of claims 1-18, wherein the SREBP inhibitor is selected from Genus B.

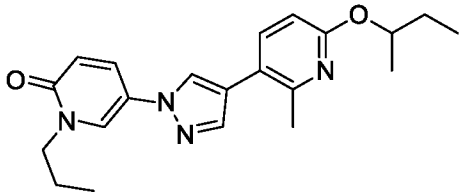
23. The method of any one of claims 1-13, wherein the SREBP inhibitor is selected from Genus B compounds:



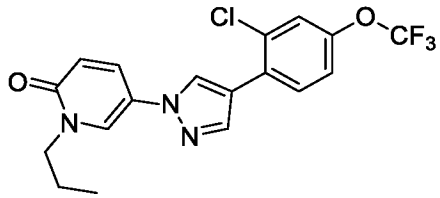
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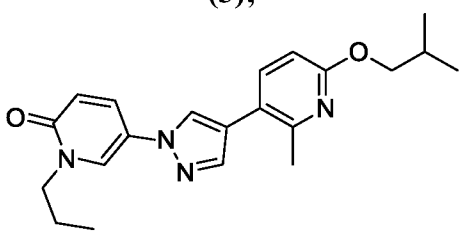
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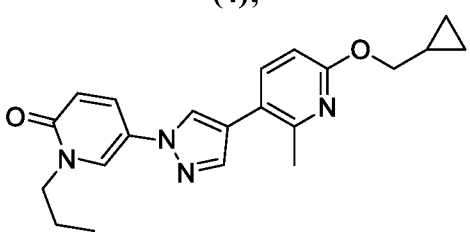
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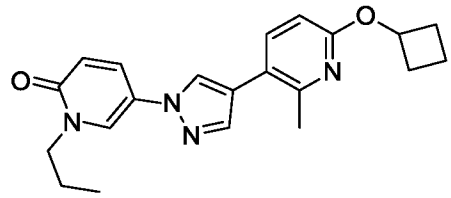
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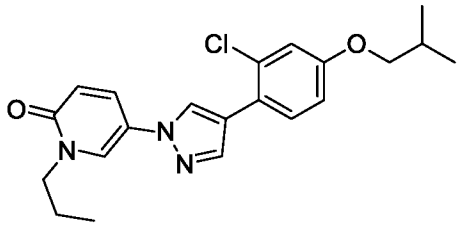
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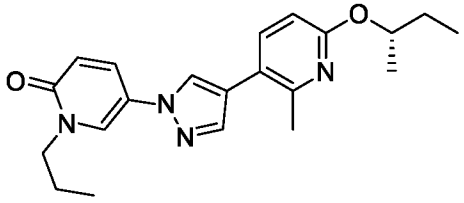
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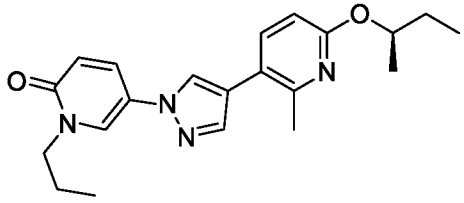
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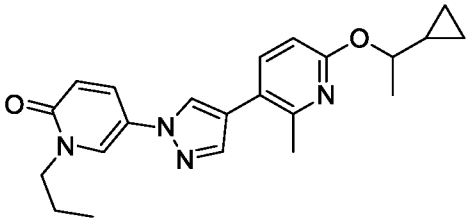
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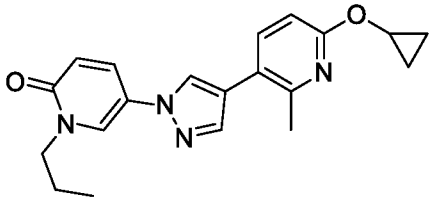
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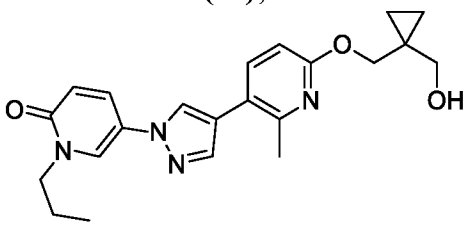
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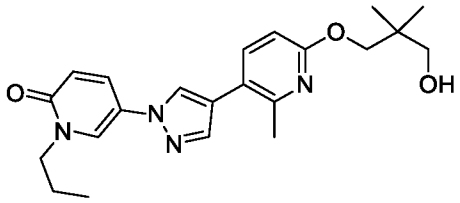
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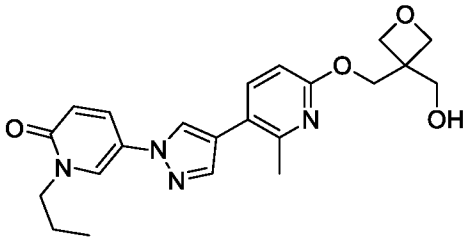
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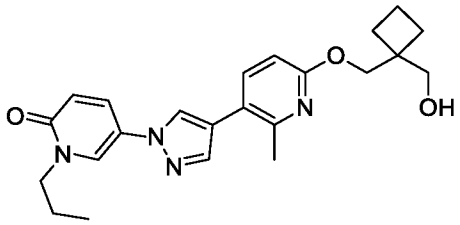
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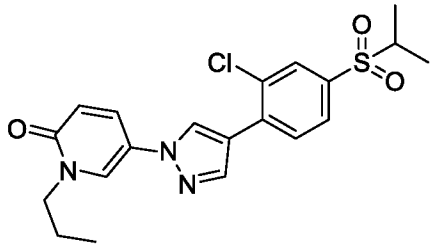
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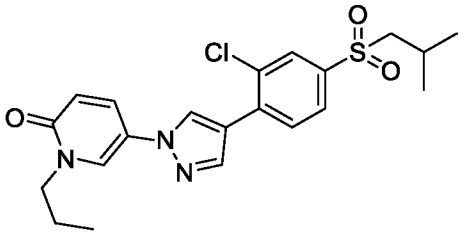
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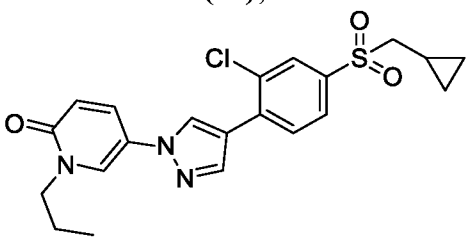
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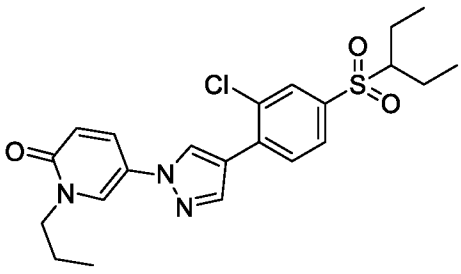
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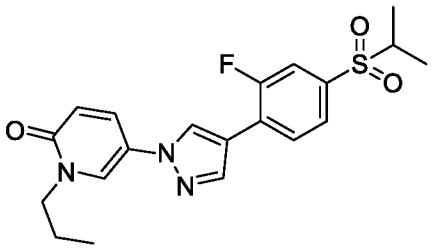


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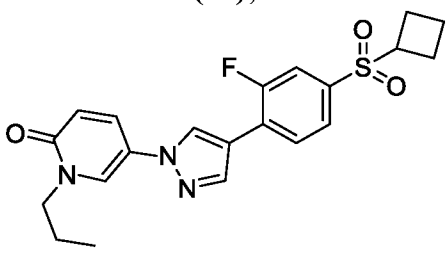


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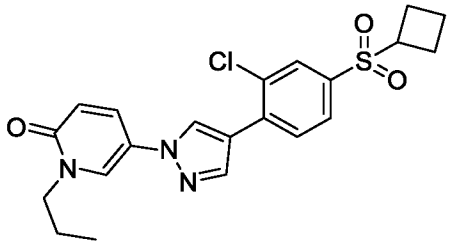




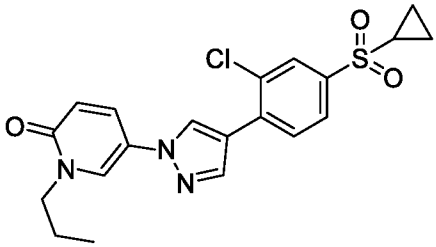
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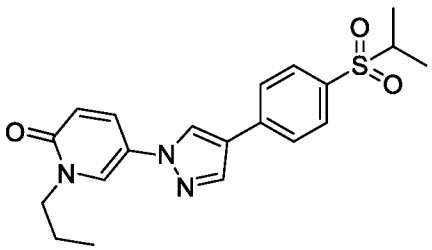
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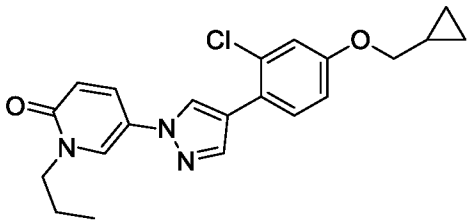
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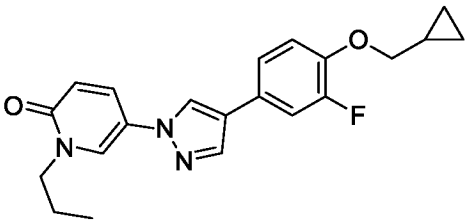
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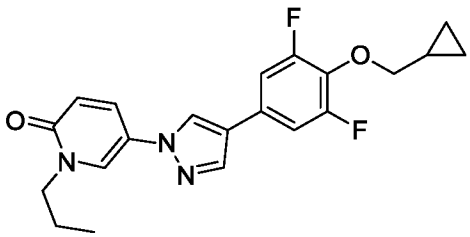
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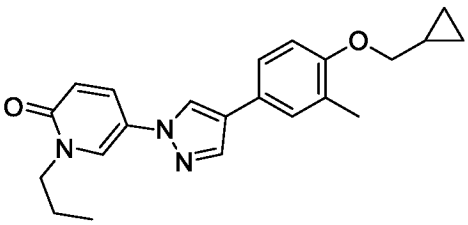
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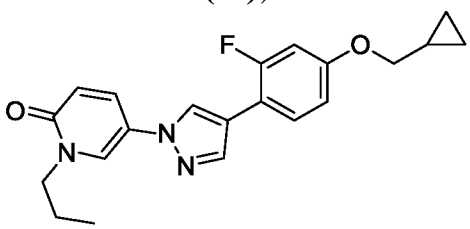
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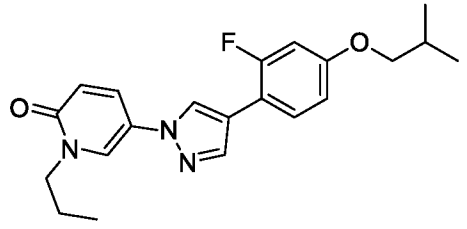
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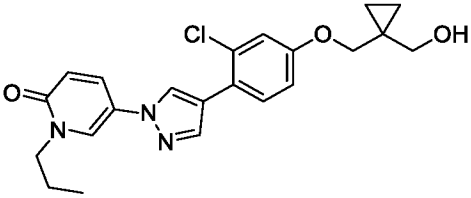
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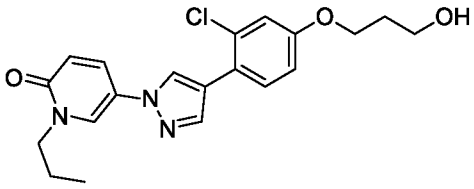


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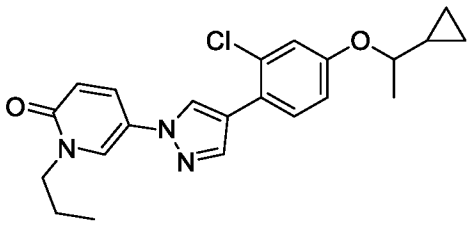


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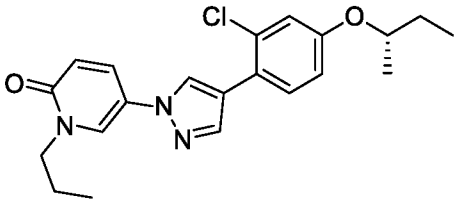
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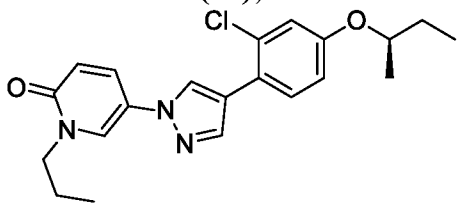
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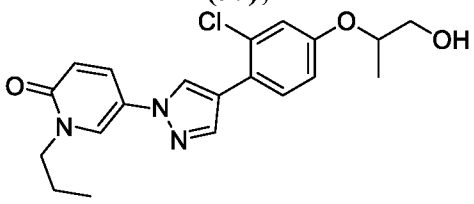
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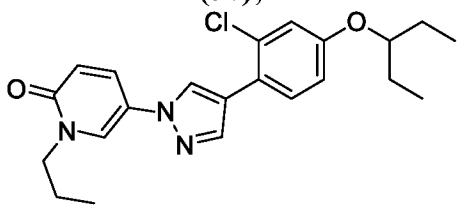
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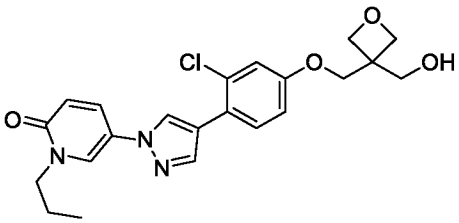
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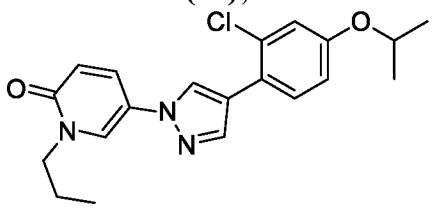
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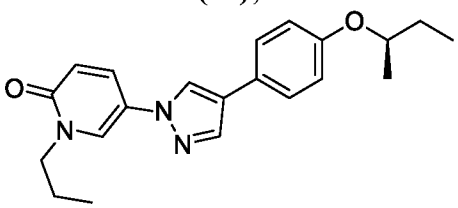
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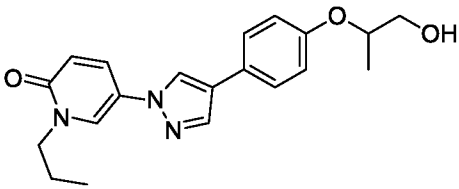
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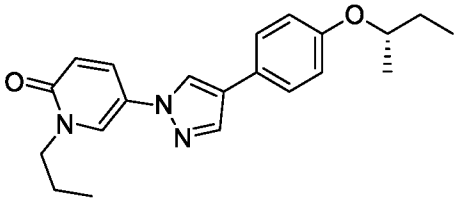
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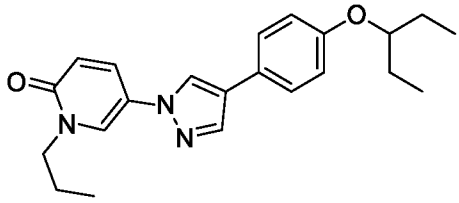
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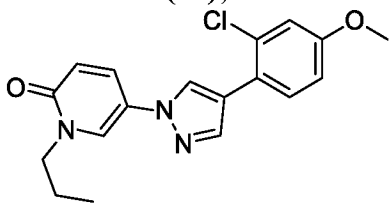
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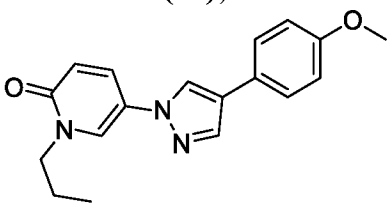
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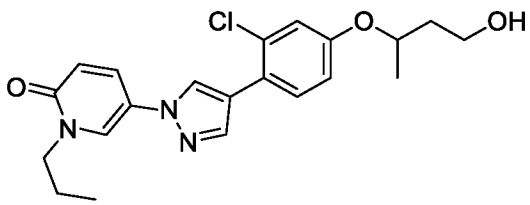
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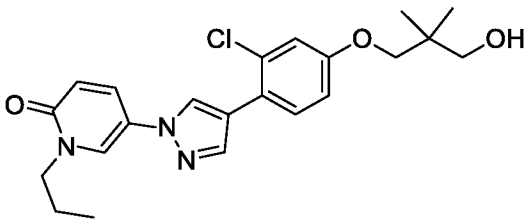
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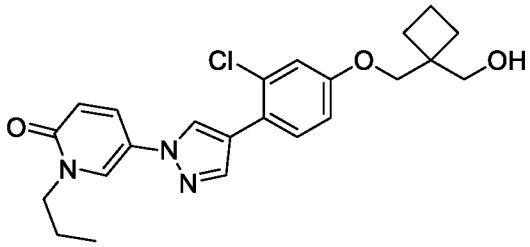
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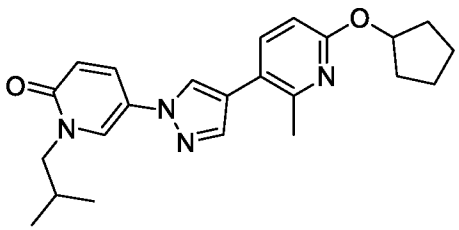
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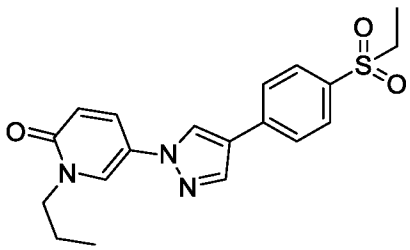
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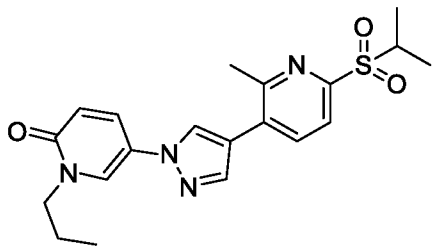
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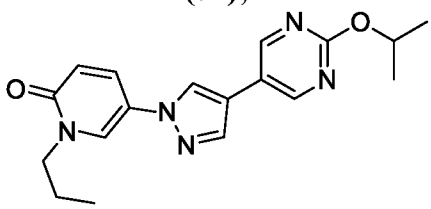
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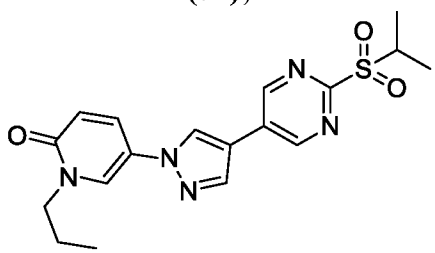
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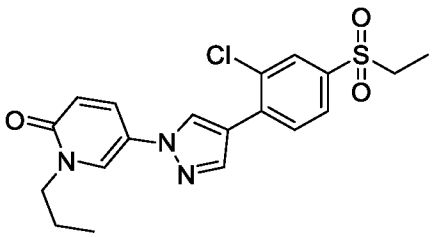
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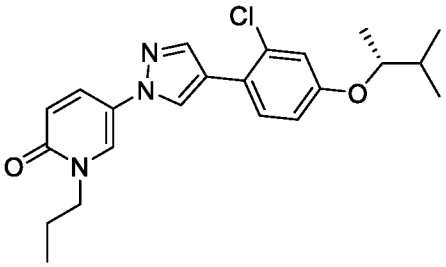
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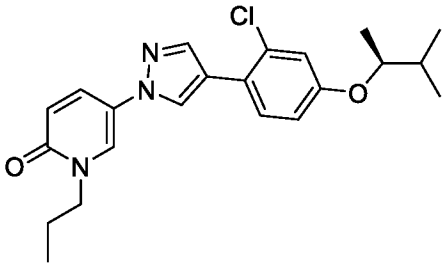
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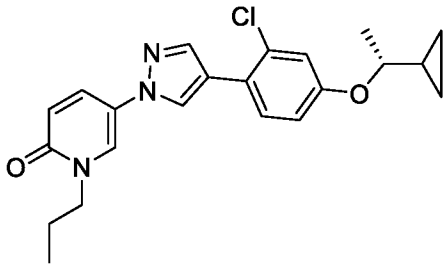
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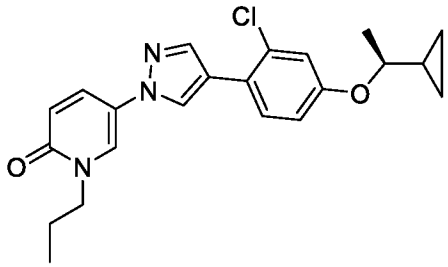
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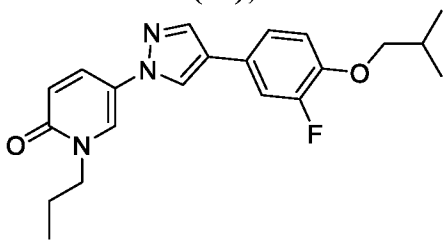
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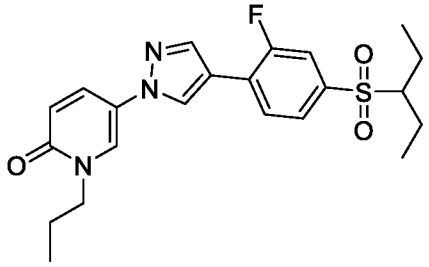
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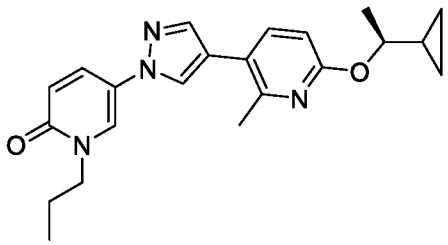
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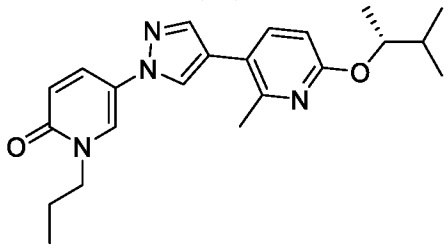
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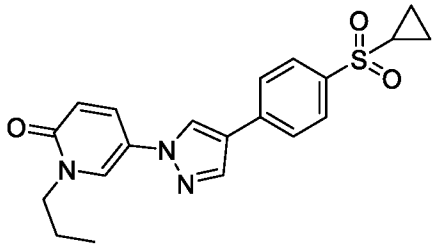
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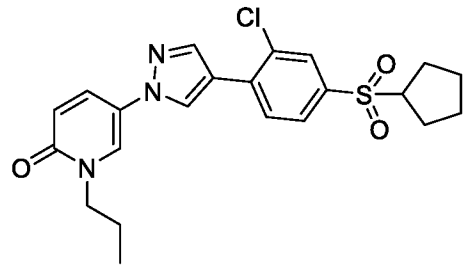
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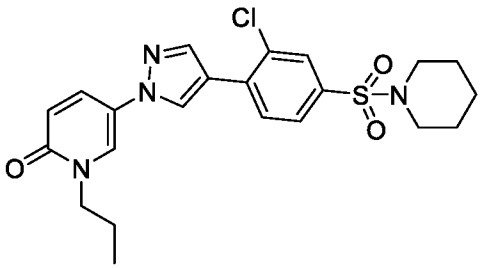
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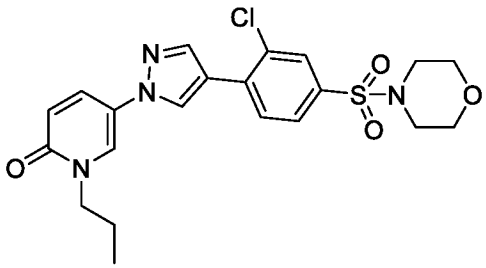
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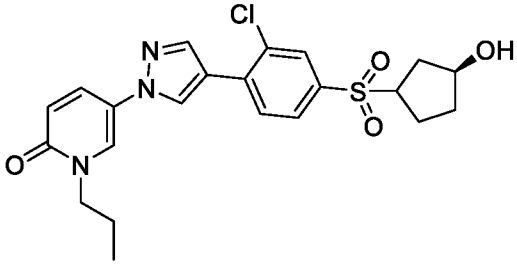
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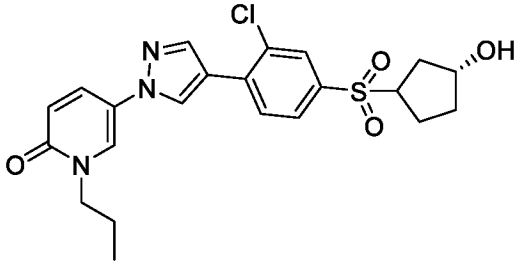
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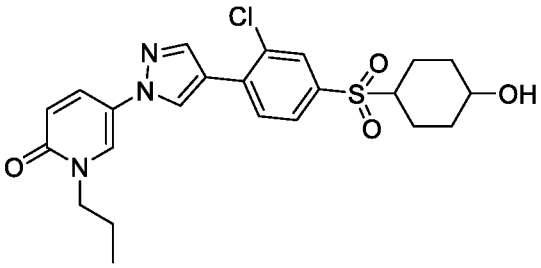
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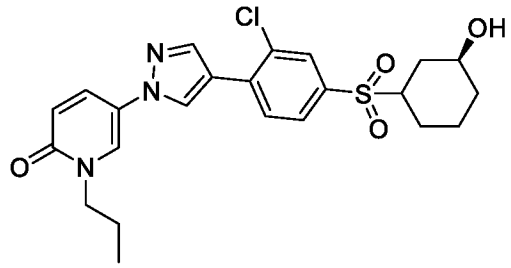
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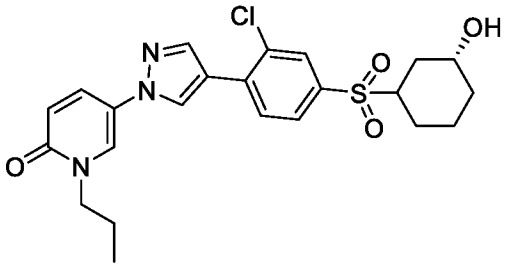
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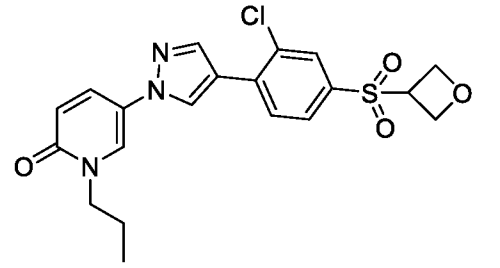
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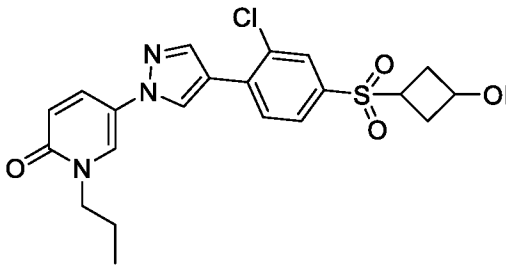
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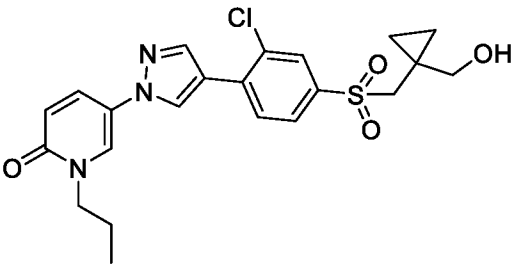
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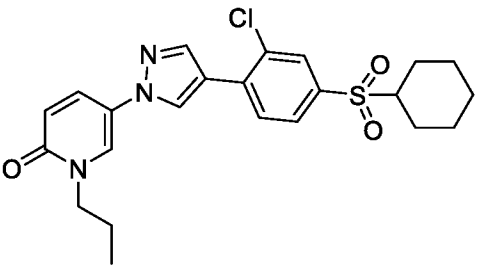
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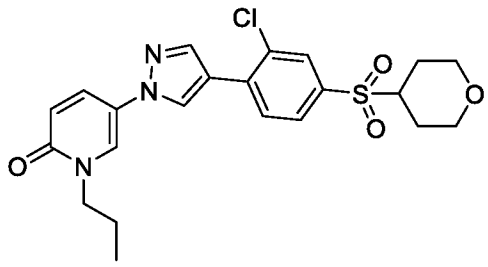
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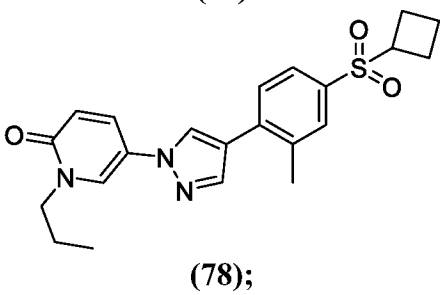
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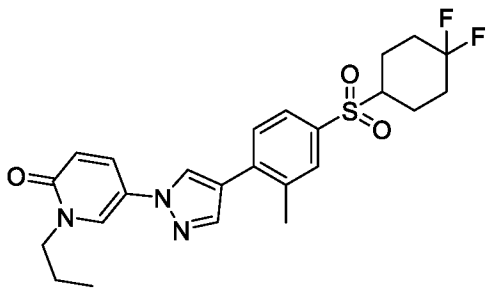
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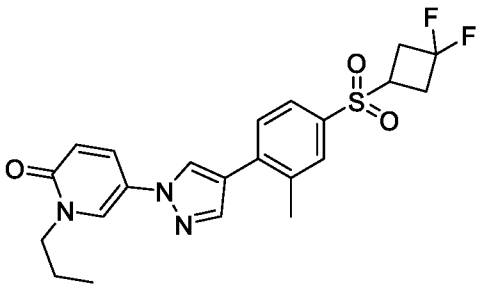
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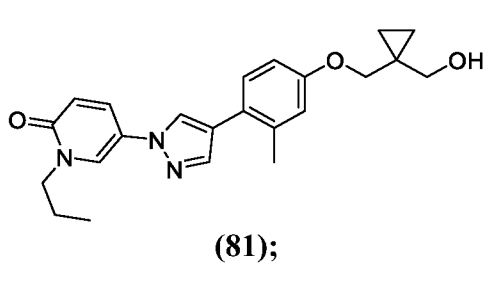


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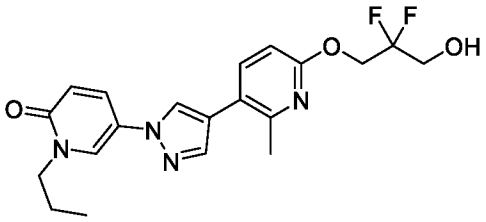
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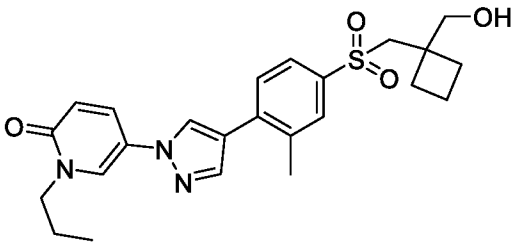




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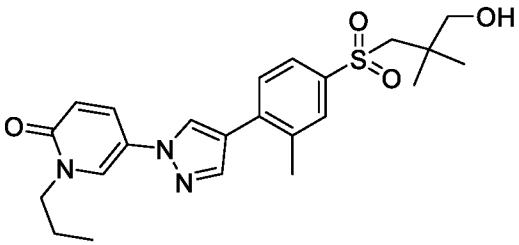
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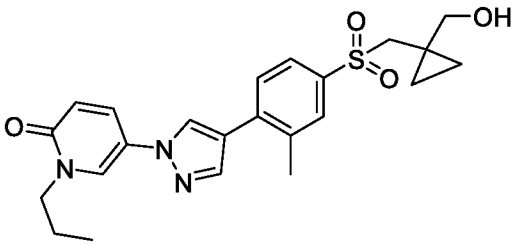




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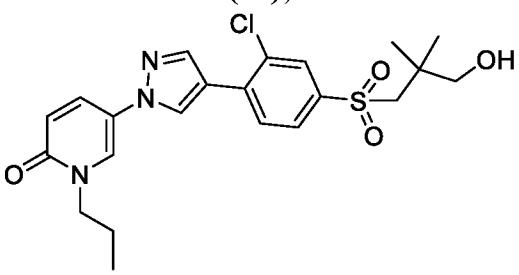
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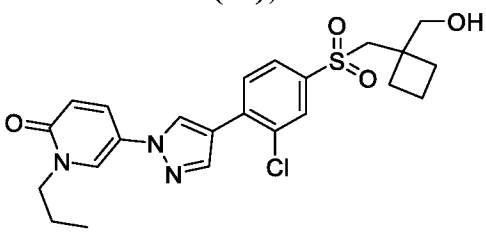




(84);

(85);



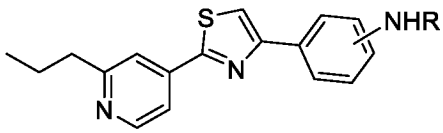


(86); and

(87);

or a stereoisomer, a mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

24. The method of any one of claims 1-13, wherein the SREBP inhibitor is selected from Genus C Formula (X-1):

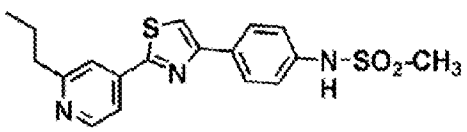


(X-1)

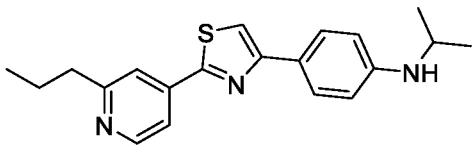
wherein R is H, isopropyl, benzyl, cyclohexyl, cyclopropylmethyl, –C(O)Me, tert-butyloxycarbonyl, or methylsulfonyl; or a pharmaceutically acceptable salt thereof.

25. The method of any one of claims 1-18, wherein the SREBP inhibitor is selected from Genus C.

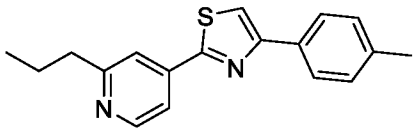
26. The method of any one of claims 1-13, wherein the SREBP inhibitor is selected from Genus C compounds:



,



, or



; or a pharmaceutically acceptable salt thereof.

27. The method of any one of claims 1-26, wherein the SREBP inhibitor and the niclosamide or niclosamide analog is administered sequentially in any order.

28. The method of any one of claims 1-26, wherein the SREBP inhibitor and the niclosamide or niclosamide analog is administered concurrently.

Fig. 1

Representative Western blots of androgen receptor (AR) and androgen receptor variant 7 (AR-V7) extracts from control and treated 22Rv1 cancer cells.

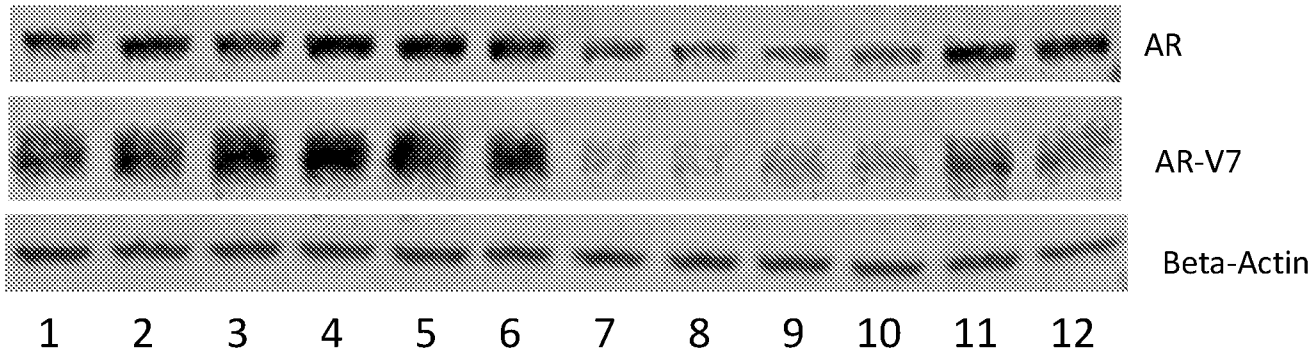
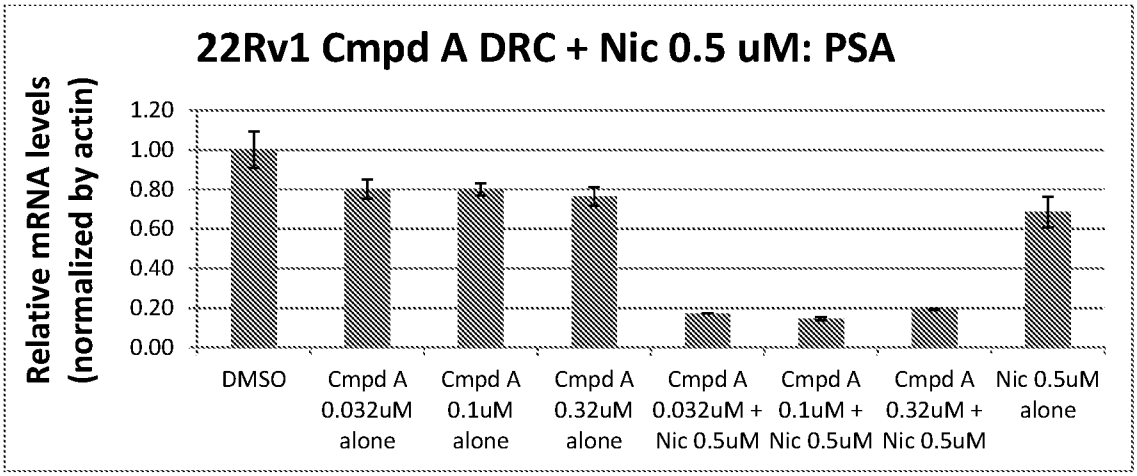


Fig. 2

Relative mRNA levels in 22v1 Cells



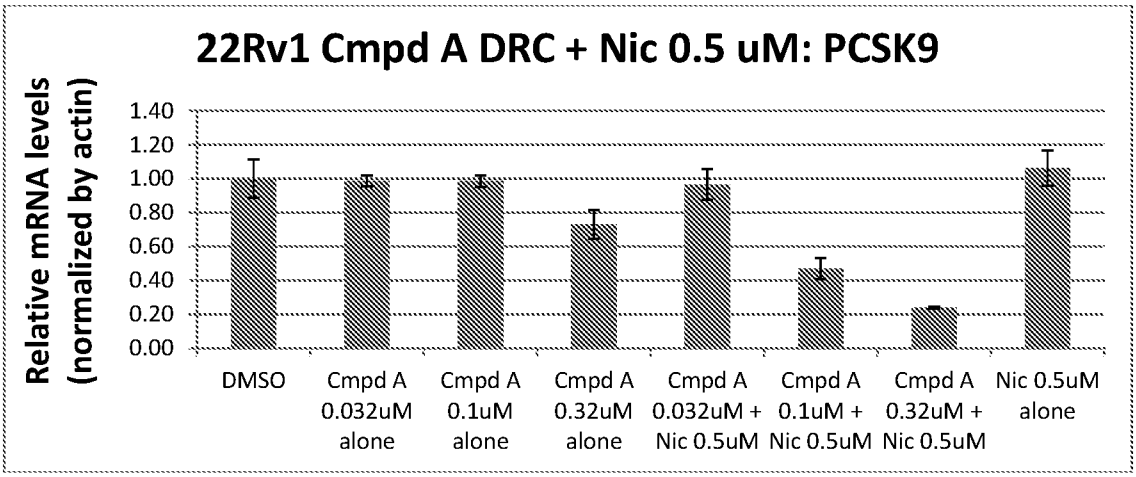
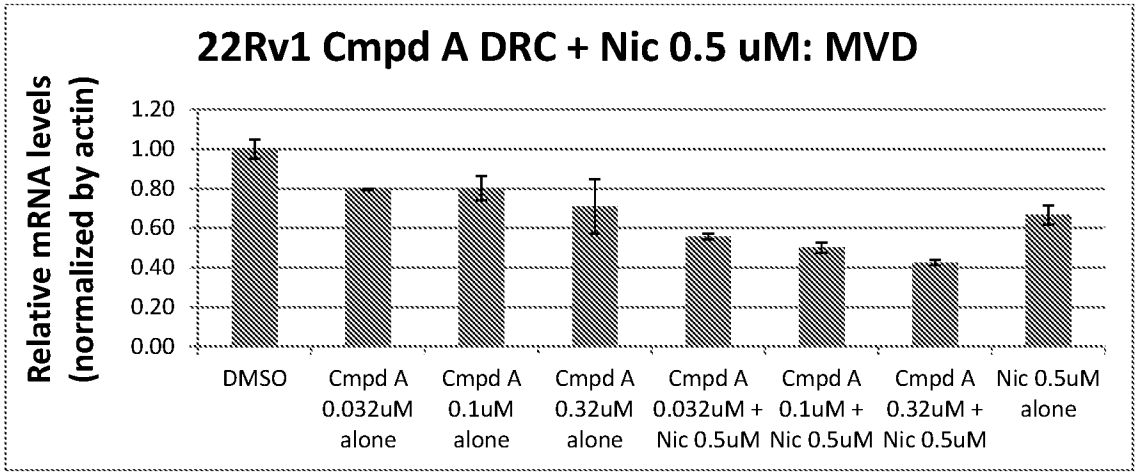


Fig. 3

Relative mRNA levels in 22v1 Cells



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/068445

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/167 A61K31/4025 A61K31/4155 A61K31/4439 A61K31/5025
A61K31/506 A61K31/5377 A61P3/00 A61P3/04 A61P9/10
A61P35/00

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)
A61K A61P

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2017/190086 A1 (FGH BIOTECH INC [US]) 2 November 2017 (2017-11-02) cited in the application claim all; example all	1-28
Y	WO 2018/049080 A1 (FGH BIOTECH INC [US]; UESUGI MOTONARI [JP]; KINCAID JOHN [US]) 15 March 2018 (2018-03-15) cited in the application claim all; example all	1-28
Y	WO 2008/097835 A2 (BAYLOR COLLEGE MEDICINE [US]; UESUGI MOTONARI [US] ET AL.) 14 August 2008 (2008-08-14) claim all; example all	1-28

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[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

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"O" document referring to an oral disclosure, use, exhibition or other means

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2020	03/04/2020

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	Bareyt, Sébastian

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LI YONGHE ET AL: "Multi-targeted therapy of cancer by niclosamide: A new application for an old drug", CANCER LETTERS, NEW YORK, NY, US, vol. 349, no. 1, 13 April 2014 (2014-04-13), pages 8-14, XP029026967, ISSN: 0304-3835, DOI: 10.1016/J.CANLET.2014.04.003 the whole document	1-28
Y	HIRAL A. BHAGAT ET AL: "N-substituted phenylbenzamides of the niclosamide chemotype attenuate obesity related changes in high fat diet fed mice", PLOS ONE, vol. 13, no. 10, 25 October 2018 (2018-10-25), page e0204605, XP055679714, DOI: 10.1371/journal.pone.0204605 the whole document	1-28
Y	C. LIU ET AL: "Niclosamide Inhibits Androgen Receptor Variants Expression and Overcomes Enzalutamide Resistance in Castration-Resistant Prostate Cancer", CLINICAL CANCER RESEARCH, vol. 20, no. 12, 16 April 2014 (2014-04-16), pages 1-21, XP055248432, US ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-13-3296 the whole document	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/068445

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