

MODULATORS OF NLRP3 INFLAMMASOME
AND RELATED PRODUCTS AND METHODS

BACKGROUND

Technical Field

5 The invention relates to modulators of NLRP3 inflammasome, to products containing the same, as well as to methods of their use and preparation.

Description of the Related Art

 The NOD-like receptor protein 3 (NLRP3) is a key protein that interacts with, apoptosis-associated speck-like protein (ASC) and procaspase-1 to form the NLRP3
10 inflammasome. The activation of the NLRP3 inflammasome produces inflammatory mediators, such as interleukin-1 β (IL-1 β) and interleukin-18 (IL-18), thereby contributing to the activation of the innate immune system. The dysregulation of innate immunity contributes to various diseases.

 The innate immune response protects the host from invading microorganisms.
15 The formation of the NLRP3 inflammasome activates caspase-1, which leads to the maturation and secretion of IL-1 β and IL-18, cleavage of gasdermin-D and, finally the initiation of cell death via pyroptosis. The system is alerted to the presence of the invading microorganism by cytokine release and is working to resolve the inflammation by eliminating the infected cells.

 However, nonmicrobial compounds of either endogenous or exogenous origin
20 are also effective inducers of NLRP3 inflammation, allergic responses, or other forms of inflammation. For example, NLRP3 may be implicated in Parkinson's disease and/or Alzheimer's disease, suggesting that misfolded proteins form aggregates that lead to the activation of the NLRP3 inflammasome. Environmental particulates such as inhaled asbestos and silica also activate the NLRP3 inflammasome, and the high levels of IL-1 β are involved in the development
25 of asbestosis and silicosis, two progressive pulmonary diseases leading to fibrosis.

Emerging studies have revealed the involvement of increased production of IL-1 β and IL-18 by the NLRP3 inflammasome can contribute to the onset and progression of various diseases such as neuroinflammation-related disorders, for example, brain infection, acute injury, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and other neurodegenerative diseases; cardiovascular diseases, cardiovascular risk reduction, atherosclerosis, type I and type II diabetes and related complications, inflammatory skin diseases, acne, hidradenitis suppurativa, asthma, age-related macular degeneration, or cancer related diseases. Those disorders that are immune or inflammatory in nature are usually difficult to diagnose or treat efficiently.

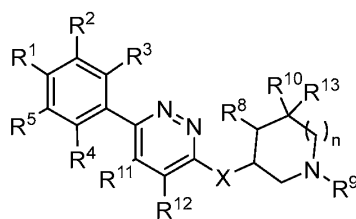
Accordingly, there is a need in the art for compounds that modulate the NLRP3 inflammasome for the purpose of treating diseases in which blockade of the NLRP3 inflammasome would be beneficial.

Additionally, there is a need for compounds that modulate the NLRP3 inflammasome and have low risk of off target effects. For example, human ether-a-go-go related gene (hERG) potassium channels are essential for normal electrical activity in the heart. hERG channels are involved in cardiac action potential repolarization, and reduced function of hERG lengthens ventricular action potentials, prolongs the QT interval in an electrocardiogram, and increases the risk for potentially fatal ventricular arrhythmias. In order to reduce the risk of investing resources in a drug candidate that fails preclinical safety studies because of QT prolongation, it is important to screen compounds for off target activity on hERG channels early in the lead optimization process. Thus, it is advantageous to develop compounds that modulate the NLRP3 inflammasome while displaying little to no hERG activity and, therefore, a reduced potential of cardiotoxicity.

The present invention fulfills these needs and provides other advantages as evident from the following description.

BRIEF SUMMARY

In an embodiment a compound is provided having structure (I):



(I)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein X, R¹, R², R³, R⁴, R⁵, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, and n are as defined herein.

5 In another embodiment, pharmaceutical compositions are provided comprising a carrier or excipient and a compound having structure (I), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

In a further embodiment, a method is provided for treating a NLRP3 inflammasome-dependent condition by administering to a subject in need thereof an effective
 10 amount of a compounds of structure (I), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, or a pharmaceutical composition comprising the same. In some embodiments, the NLRP3 inflammasome-dependent condition is a neuroinflammation-related disorder or a neurodegenerative disease. In some embodiments, NLRP3 inflammasome activity is modulated such that there is no cardiotoxicity risk at physiologically relevant exposures for
 15 NLRP modulatory effect.

DETAILED DESCRIPTION

Definitions

As used herein, the following terms have the meaning defined below, unless the context indicates otherwise.

20 “Modulating” NLRP3 inflammasome means that the compound interacts with NLRP3 in a manner such that it blocks its ATPase function and the downstream formation of the NLRP3 inflammasome complex. In the above context, the compound acts to inhibit, or block, activation of the NLRP3 inflammasome and therefore the compound can also be described as an inhibitor.

NLRP3 refers to NOD-Like Receptor Protein 3. NLRP3 is a protein-coding gene, and an exemplary sequence may be found at <https://www.uniprot.org/uniprot/Q96P20>. NLRP3 functions as an ATPase that is auto-inhibited under normal conditions. NLRP3, unlike other inflammasomes, requires a two step activation process, which can be triggered by a variety of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). The first step primes the NLRP3 inflammasome via recognition of PAMPs, DAMPs, or pathological species via pattern recognition receptors (PRRs) (e.g. Toll-like receptors). Priming increases NLRP3, pro-IL1 β , and pro-IL18 expression. Activation of NLRP3 is triggered by a second signal, such as ATP, K⁺ efflux, other cellular stress, or pathological species, which leads to ATP hydrolysis and activation of the enzyme. This activation leads to oligomerization of the inflammasome complex, resulting in auto-cleavage and activation of caspase-1. Active caspase-1 then cleaves pro-IL1 β and pro-IL18. Active IL1 β and IL18 then are released from the cell through a gasdermin D pore, and release of such cytokines triggers a downstream inflammatory response and cell death via pyroptosis.

“hERG” refers to the human ether-a-go-go-related gene (hERG) that encodes the pore-forming subunit of the rapidly activating delayed rectifier potassium channel (I_{Kr}), which is important for cardiac repolarization. Reduced function of hERG lengthens ventricular action potentials, prolongs the QT interval in an electrocardiogram, and increases the risk for potentially fatal ventricular arrhythmias.

“Effective amount” refers to a quantity of a specified agent sufficient to achieve a desired effect in a subject being treated with that agent. Ideally, an effective amount of an agent is an amount sufficient to inhibit or treat the disease without causing substantial toxicity in the subject. The effective amount of an agent will be dependent on the subject being treated, the severity of the affliction, and the manner of administration of the pharmaceutical composition. Methods of determining an effective amount of the disclosed compound sufficient to achieve a desired effect in a subject will be understood by those of skill in the art in light of this disclosure.

“Alkyl” means a saturated or unsaturated straight chain or branched alkyl group having from 1 to 8 carbon atoms, in some embodiments from 1 to 6 carbon atoms, in some embodiments from 1 to 4 carbon atoms, and in some embodiments from 1 to 3 carbon atoms.

Examples of saturated straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl-, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups.

5 "Halo" or "halogen" refers to fluorine, chlorine, bromine, and iodine.

"Hydroxyl" refers to -OH.

"Cyano" refers to -CN.

"Carboxyl" or "carboxy" refers to -CO₂H.

"Oxo" refers to the =O substituent.

10 "Haloalkyl" refers to alkyl as defined above with one or more hydrogen atoms replaced with halogen. Examples of haloalkyl groups include, but are not limited to, -CF₃, -CHF₂, -CH₂CF₃, -CH₂CHF₂, and the like.

"Alkoxy" refers to alkyl as defined above joined by way of an oxygen atom (i.e., -O-alkyl). Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, n-
15 propoxy, n-butoxy, isopropoxy, sec-butoxy, tert-butoxy, and the like.

"Haloalkoxy" refers to haloalkyl as defined above joined by way of an oxygen atom (i.e., -O-haloalkyl). Examples of haloalkoxy groups include, but are not limited to, -OCF₃, and the like.

"Aminyl" refers to -NH₂, -NHalkyl or N(alkyl)₂, wherein alkyl is as defined above.
20 Examples of amino or aminyl include, but are not limited to - NH₂ , -NHCH₃, -N(CH₃)₂, and the like.

"Cycloalkyl" refers to non-aromatic ring moieties containing 3 or more ring members. In some embodiments, cycloalkyl includes 3 to 8 ring members. In some embodiments, cycloalkyl includes 3 to 5 ring members. For example, cycloalkyl includes
25 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

"Heterocycle" refers to aromatic and non-aromatic ring moieties containing 3 or more ring members, of which one or more is a heteroatom such as, but not limited to, N, O,

S, or P. In some embodiments, heterocyclyl include 3 to 20 ring members, whereas other such groups have 3 to 15 ring members. At least one ring contains a heteroatom, but every ring in a polycyclic system need not contain a heteroatom. For example, a dioxolanyl ring and a benzodioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. For example, heterocyclic rings include dioxane, tetrahydrofuran, 5 tetrahydropyran, pyrrolidine, piperidine, and the like.

Heterocyclyl groups also include fused ring species including those having fused aromatic and non-aromatic groups. A heterocyclyl group also includes polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl, and also includes heterocyclyl 10 groups that have substituents, including but not limited to alkyl, halo, amino, hydroxy, cyano, carboxy, nitro, thio, or alkoxy groups, bonded to one of the ring members. A heterocyclyl group as defined herein can be a heteroaryl group or a partially or completely saturated cyclic group including at least one ring heteroatom. Heterocyclyl groups include, but are not limited to, pyrrolidinyl, furanyl, tetrahydrofuranyl, dioxolanyl, piperidinyl, piperazinyl, morpholinyl, 15 pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, dihydrobenzofuranyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

20 “Isomer” is used herein to encompass all chiral, diastereomeric or racemic forms of a structure (also referred to as a stereoisomer, as opposed to a structural or positional isomer), unless a particular stereochemistry or isomeric form is specifically indicated. Such compounds can be enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric 25 mixtures, as well as the individual optical isomers can be synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of certain embodiments of the invention. The isomers resulting from the presence of a chiral center comprise a pair of nonsuperimposable-isomers that are called “enantiomers.” Single enantiomers of a pure compound are optically active (i.e., they are capable of rotating the plane 30 of plane polarized light and designated R or S).

“Isolated optical isomer” means a compound which has been substantially purified from the corresponding optical isomer(s) of the same formula. For example, the isolated isomer may be at least about 80%, at least 80% or at least 85% pure by weight. In other embodiments, the isolated isomer is at least 90% pure or at least 98% pure, or at least 99% pure by weight.

“Substantially enantiomerically or diastereomerically” pure means a level of enantiomeric or diastereomeric enrichment of one enantiomer with respect to the other enantiomer or diastereomer of at least about 80%, and more specifically in excess of 80%, 85%, 90%, 95%, 98%, 99%, 99.5% or 99.9%.

The terms “racemate” and “racemic mixture” refer to an equal mixture of two enantiomers. A racemate is labeled “(±)” because it is not optically active (i.e., will not rotate plane-polarized light in either direction since its constituent enantiomers cancel each other out). All compounds with an asterisk (*) adjacent to a tertiary or quaternary carbon are optically active isomers, which may be purified from the respective racemate and/or synthesized by appropriate chiral synthesis.

A “hydrate” is a compound that exists in combination with water molecules. The combination can include water in stoichiometric quantities, such as a monohydrate or a dihydrate, or can include water in random amounts. As the term is used herein a “hydrate” refers to a solid form; that is, a compound in a water solution, while it may be hydrated, is not a hydrate as the term is used herein.

A “solvate” is similar to a hydrate except that a solvent other than water is present. For example, methanol or ethanol can form an “alcoholate”, which can again be stoichiometric or non-stoichiometric. As the term is used herein a “solvate” refers to a solid form; that is, a compound in a solvent solution, while it may be solvated, is not a solvate as the term is used herein.

“Isotope” refers to atoms with the same number of protons but a different number of neutrons, and an isotope of a compound of structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), includes any such compound wherein one or more atoms are replaced by an isotope of that atom. For example,

carbon 12, the most common form of carbon, has six protons and six neutrons, whereas carbon 13 has six protons and seven neutrons, and carbon 14 has six protons and eight neutrons. Hydrogen has two stable isotopes, deuterium (one proton and one neutron) and tritium (one proton and two neutrons). While fluorine has a number of isotopes, fluorine-19 is longest-lived.

5 Thus, an isotope of a compound having the structure of structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), includes, but not limited to, compounds of structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), wherein one or more carbon 12 atoms are replaced by carbon-13 and/or carbon-14 atoms, wherein one or more hydrogen atoms are

10 replaced with deuterium and/or tritium, and/or wherein one or more fluorine atoms are replaced by fluorine-19.

"Salt" generally refers to an organic compound, such as a carboxylic acid or an amine, in ionic form, in combination with a counter ion. For example, salts formed between acids in their anionic form and cations are referred to as "acid addition salts". Conversely, salts

15 formed between bases in the cationic form and anions are referred to as "base addition salts."

The term "pharmaceutically acceptable" refers an agent that has been approved for human consumption and is generally non-toxic. For example, the term "pharmaceutically acceptable salt" refers to nontoxic inorganic or organic acid and/or base addition salts (see, e.g., Lit et al., Salt Selection for Basic Drugs, Int. J. Pharm., 33, 201-217, 1986)

20 (incorporated by reference herein).

Pharmaceutically acceptable base addition salts of compounds of the invention include, for example, metallic salts including alkali metal, alkaline earth metal, and transition metal salts such as, for example, calcium, magnesium, potassium, sodium, and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic

25 amines such as, for example, *N,N*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine.

Pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic

acids may be selected from aliphatic, cycloaliphatic, aromatic, aromatic aliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, hippuric, malonic, oxalic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, panthothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric, and galacturonic acid.

The compounds of the disclosure (*i.e.*, compounds of structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), and embodiments thereof), or their pharmaceutically acceptable salts may contain one or more centers of geometric asymmetry and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids. Embodiments thus include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers. Likewise, all tautomeric forms are also included.

Although pharmaceutically unacceptable salts are not generally useful as medicaments, such salts may be useful, for example as intermediates in the synthesis of compounds having the structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), , for example in their purification by recrystallization.

As used herein, the phrase "NLRP3 inflammasome dependent condition" means a condition wherein modulating NLRP3 provides a medical benefit to the patient or subject.

In some embodiments, the NLRP3 inflammasome dependent condition is inflammation, an inflammatory disease, an immune disease, cancer, infections including viral infections; central nervous system diseases, metabolic diseases, cardiovascular diseases, respiratory diseases, liver diseases, renal diseases, ocular diseases, skin diseases, psychological diseases or blood diseases.

In one embodiment, the NLRP3 inflammasome dependent condition is neuroinflammation-related disorders or neurodegenerative diseases.

In one embodiment, the invention provides a method for inhibiting NLRP3 inflammasome with an effective amount of a pharmaceutical composition as described herein.

10 In one embodiment, the pharmaceutical composition is selective for modulating NLRP3 inflammasome activity over hERG activity. In certain embodiments, the selectivity for NLRP3 inflammasome activity is $\geq 1,000$ -fold over hERG activity. In certain embodiments, the selectivity for NLRP3 inflammasome activity is ≥ 10 -fold over hERG activity. In certain embodiments, the selectivity for NLRP3 inflammasome activity is ≥ 100 -fold over hERG activity.

15 In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition by administering to a subject in need thereof an effective amount of a pharmaceutical composition as described herein. In certain embodiments, the NLRP3 inflammasome dependent condition is a neuroinflammation-related disorder(s) or a neurodegenerative disease(s).

20 As used herein the phrase "inflammation" refers to inflammation, including inflammation occurring as a result of an inflammatory disorder, e.g. an autoinflammatory disease, inflammation occurring as a symptom of a non-inflammatory disorder, inflammation occurring as a result of infection, or inflammation secondary to trauma, injury or autoimmunity. Examples of inflammation that may be treated or prevented include inflammatory responses

25 occurring in connection with, or as a result of:

(a) a skin condition such as contact hypersensitivity, bullous pemphigoid, sunburn, psoriasis, atopic dermatitis, contact dermatitis, allergic contact dermatitis, seborrheoetic dermatitis, lichen planus, scleroderma, pemphigus, epidermolysis bullosa, urticaria, erythemas, or alopecia;

(b) a joint condition such as osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis, rheumatoid arthritis, juvenile chronic arthritis, crystal induced arthropathy (e.g. pseudo-gout, gout), or a seronegative spondyloarthropathy (e.g. ankylosing spondylitis, psoriatic arthritis or Reiter's disease);

5 (c) a muscular condition such as polymyositis or myasthenia gravis;

(d) a gastrointestinal tract condition such as inflammatory bowel disease (including Crohn's disease and ulcerative colitis), gastric ulcer, coeliac disease, proctitis, pancreatitis, eosinophilic gastro-enteritis, mastocytosis, antiphospholipid syndrome, or a food-related allergy which may have effects remote from the gut (e.g., migraine, rhinitis or eczema);

10 (e) a respiratory system condition such as chronic obstructive pulmonary disease (COPD), asthma (including bronchial, allergic, intrinsic, extrinsic or dust asthma, and particularly chronic or inveterate asthma, such as late asthma and airways hyper-responsiveness), bronchitis, rhinitis (including acute rhinitis, allergic rhinitis, atrophic rhinitis, chronic rhinitis, rhinitis caseosa, hypertrophic rhinitis, rhinitis pum lenta, rhinitis sicca, rhinitis
15 medicamentosa, membranous rhinitis, seasonal rhinitis e.g. hay fever, and vasomotor rhinitis), sinusitis, idiopathic pulmonary fibrosis (IPF), sarcoidosis, farmer's lung, silicosis, asbestosis, adult respiratory distress syndrome, hypersensitivity pneumonitis, or idiopathic interstitial pneumonia;

(f) a vascular condition such as atherosclerosis, Behcet's disease, vasculitides,
20 or Wegener's granulomatosis;

(g) an immune condition, e.g. autoimmune condition, such as systemic lupus erythematosus (SLE), Sjogren's syndrome, systemic sclerosis, Hashimoto's thyroiditis, type I diabetes, idiopathic thrombocytopenia purpura, or Graves disease;

(h) an ocular condition such as uveitis, allergic conjunctivitis, or vernal
25 conjunctivitis;

(i) a nervous system condition such as multiple sclerosis or encephalomyelitis;

(j) an infection or infection-related condition, such as Acquired Immunodeficiency Syndrome (AIDS), acute or chronic bacterial infection, acute or chronic

parasitic infection, acute or chronic viral infection, acute or chronic fungal infection, meningitis, hepatitis (A, B or C, or other viral hepatitis), peritonitis, pneumonia, epiglottitis, malaria, dengue hemorrhagic fever, leishmaniasis, streptococcal myositis, Mycobacterium tuberculosis, Mycobacterium avium intracellulare, Pneumocystis carinii pneumonia, orchitis/epididymitis,
5 legionella, Lyme disease, influenza A, epstein-barr virus, viral encephalitis/aseptic meningitis, or pelvic inflammatory disease;

(k) a renal condition such as mesangial proliferative glomerulonephritis, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, uremia, or nephritic syndrome;

10 (l) a lymphatic condition such as Castleman's disease;

(m) a condition of, or involving, the immune system, such as hyper IgE syndrome, lepromatous leprosy, familial hemophagocytic lymphohistiocytosis, or graft versus host disease;

(n) a hepatic condition such as chronic active hepatitis, non-alcoholic
15 steatohepatitis (NASH), alcohol-induced hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease (AFLD), alcoholic steatohepatitis (ASH) or primary biliary cirrhosis;

(o) a cancer, including those cancers listed herein below;

(p) a burn, wound, trauma, haemorrhage or stroke;

(q) radiation exposure; and/or

20 (r) obesity;

(s) pain such as inflammatory hyperalgesia; and/or

(t) neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, or amyotrophic lateral sclerosis.

As used herein the phrase "an inflammatory disease" means for example,
25 inflammation occurring as a result of an inflammatory disorder, e.g. an autoinflammatory disease, such as cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), familial Mediterranean fever (FMF),

neonatal onset multisystem inflammatory disease (NOMID), Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), adult-onset Still's disease (AOSD), haploinsufficiency of A20 (HA20), pediatric granulomatous arthritis (PGA), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), PLCG2-associated autoinflammatory, 5 antibody deficiency and immune dysregulation (APLAID), or sideroblastic anaemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD).

As used herein the phrase "an immune disease" means for example, autoimmune diseases, such as acute disseminated encephalitis, Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome (APS), anti-synthetase syndrome, aplastic 10 anemia, autoimmune adrenalitis, autoimmune hepatitis, autoimmune oophoritis, autoimmune polyglandular failure, autoimmune thyroiditis, Coeliac disease, Crohn's disease, type 1 diabetes (T1D), Goodpasture's syndrome, Graves' disease, Guillain-Barre syndrome (GBS), Hashimoto's disease, idiopathic thrombocytopenic purpura, Kawasaki's disease, lupus erythematosus including systemic lupus erythematosus (SLE), multiple sclerosis (MS) including primary 15 progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS) and relapsing remitting multiple sclerosis (RRMS), myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, pemphigus, pernicious anaemia, polyarthritis, primary biliary cirrhosis, rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis or Still's disease, refractory gouty arthritis, Reiter's syndrome, Sjogren's syndrome, systemic 20 sclerosis a systemic connective tissue disorder, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis, Beliefs disease, Chagas' disease, dysautonomia, endometriosis, hidradenitis suppurativa (HS), interstitial cystitis, neuromyotonia, psoriasis, sarcoidosis, scleroderma, ulcerative colitis, Schnitzler syndrome, macrophage activation syndrome, Blau syndrome, giant cell arteritis, 25 vitiligo or vulvodynia.

As used herein the phrase "cancer" means for example, lung cancer, renal cell carcinoma, non-small cell lung carcinoma (NSCLC), Langerhans cell histiocytosis (LCH), myeloproliferative neoplasms (MPN), pancreatic cancer, gastric cancer, myelodysplastic syndrome (MDS), leukaemia including acute lymphocytic leukaemia (ALL) and acute myeloid 30 leukaemia (AML), promyelocytic leukemia (APML, or APL), adrenal cancer, anal cancer, basal

and squamous cell skin cancer, bile duct cancer, bladder cancer, bone cancer, brain and spinal cord tumours, breast cancer, cervical cancer, chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), chronic myelomonocytic leukaemia (CMML), colorectal cancer, endometrial cancer, oesophagus cancer, Ewing family of tumours, eye cancer, gallbladder cancer, gastrointestinal carcinoid tumours, gastrointestinal stromal tumour (GIST), gestational trophoblastic disease, glioma, Hodgkin lymphoma, Kaposi sarcoma, kidney cancer, laryngeal and hypopharyngeal cancer, liver cancer, lung carcinoid tumour, lymphoma including cutaneous T cell lymphoma, malignant mesothelioma, melanoma skin cancer, Merkel cell skin cancer, multiple myeloma, nasal cavity and paranasal sinuses cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, penile cancer, pituitary tumours, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, stomach cancer, testicular cancer, thymus cancer, thyroid cancer including anaplastic thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumour.

As used herein the phrase “infections including viral infections” means for example, viral infections (e.g. from influenza virus, human immunodeficiency virus (HIV), alphavirus (such as Chikungunya and Ross River virus), flaviviruses (such as Dengue virus and Zika virus), herpes viruses (such as Epstein Barr Virus, cytomegalovirus, Varicella-zoster virus, and KSHV), poxyviruses (such as vaccinia virus (Modified vaccinia virus Ankara) and Myxoma virus), adenoviruses (such as Adenovirus 5), or papillomavirus), bacterial infections (e.g. from *Staphylococcus aureus*, *Helicobacter pylori*, *Bacillus anthracis*, *Bordetella pertussis*, *Burkholderia pseudomallei*, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Clostridium botulinum*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Listeria monocytogenes*, *Hemophilus influenzae*, *Pasteurella multocida*, *Shigella dysenteriae*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycoplasma pneumoniae*, *Mycoplasma hominis*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Rickettsia rickettsii*, *Legionella pneumophila*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Propionibacterium acnes*, *Treponema pallidum*, *Chlamydia trachomatis*, *Vibrio cholerae*, *Salmonella typhimurium*, *Salmonella typhi*, *Borrelia burgdorferi* or *Yersinia pestis*), fungal infections (e.g. from *Candida* or *Aspergillus* species),

protozoan infections (e.g. from Plasmodium, Babesia, Giardia, Entamoeba, Leishmania or Trypanosomes), helminth infections (e.g. from schistosoma, roundworms, tapeworms or flukes), and prion infections.

As used herein the phrase “central nervous system diseases” means for example, Parkinson's disease, Alzheimer's disease, Frontotemporal dementia, dementia, motor neuron disease, Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis, intracranial aneurysms, traumatic brain injury, multiple sclerosis, and amyotrophic lateral sclerosis.

As used herein the phrase “neuroinflammation-related diseases” means for example, multiple sclerosis, brain infection, acute injury, neurodegenerative disease, Parkinson's disease or Alzheimer's disease.

As used herein the phrase “neurodegenerative disease” means for example, Alzheimer's disease, Parkinson's disease, multiple sclerosis, or amyotrophic lateral sclerosis.

In one embodiment, neurodegenerative diseases are characterized by deep involvement of cell mediating neuroinflammatory processes.

As used herein the phrase “metabolic diseases” means for example, type 2 diabetes (T2D), atherosclerosis, obesity, gout, and pseudo-gout.

As used herein the phrase “cardiovascular diseases” means for example, hypertension, ischaemia, reperfusion injury including post-MI ischemic reperfusion injury, stroke including ischemic stroke, transient ischemic attack, myocardial infarction including recurrent myocardial infarction, heart failure including congestive heart failure and heart failure with preserved ejection fraction, embolism, aneurysms including abdominal aortic aneurysm, cardiovascular risk reduction (CvRR), and pericarditis including Dressler's syndrome.

As used herein the phrase “respiratory diseases” means for example, chronic obstructive pulmonary disorder (COPD), asthma such as allergic asthma and steroid-resistant asthma, asbestosis, silicosis, nanoparticle induced inflammation, cystic fibrosis, and idiopathic pulmonary fibrosis.

As used herein the phrase “liver diseases” means for example, non-alcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) including advanced fibrosis stages F3 and F4, alcoholic fatty liver disease (AFLD), and alcoholic steatohepatitis (ASH).

As used herein the phrase “renal diseases” means for example, acute kidney
5 disease, hyperoxaluria, chronic kidney disease, oxalate nephropathy, nephrocalcinosis, glomerulonephritis, and diabetic nephropathy;

As used herein the phrase “ocular diseases” means for example, diseases of the ocular epithelium, age-related macular degeneration (AMD) (dry and wet), uveitis, corneal infection, diabetic retinopathy, optic nerve damage, dry eye, and glaucoma.

10 As used herein the phrase “skin diseases” means for example, dermatitis such as contact dermatitis and atopic dermatitis, contact hypersensitivity, sunburn, skin lesions, hidradenitis suppurativa (HS), other cyst-causing skin diseases, and acne conglobate.

As used herein the phrase “psychological diseases” means for example, depression, and psychological stress.

15 As used herein the phrase “blood diseases” means for example, sickle cell disease.

As used herein, the term “administration” refers to providing a compound, or a pharmaceutical composition comprising the compound as described herein. The compound or composition can be administered by another person to the subject or it can be self-administered
20 by the subject. Non-limiting examples of routes of administration are oral, parenteral (*e.g.*, intravenous), or topical.

As used herein, the term “treatment” refers to an intervention that ameliorates a sign or symptom of a disease or pathological condition. As used herein, the terms “treatment”, “treat” and “treating,” with reference to a disease, pathological condition or symptom, also
25 refers to any observable beneficial effect of the treatment. The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the disease in a susceptible subject, a reduction in severity of some or all clinical symptoms of the disease, a slower progression of the disease, a reduction in the number of relapses of the disease, an

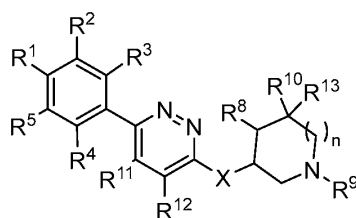
improvement in the overall health or well-being of the subject, or by other parameters well known in the art that are specific to the particular disease. A prophylactic treatment is a treatment administered to a subject who does not exhibit signs of a disease or exhibits only early signs, for the purpose of decreasing the risk of developing pathology. A therapeutic
 5 treatment is a treatment administered to a subject after signs and symptoms of the disease have developed.

As used herein, the term “subject” refers to an animal (*e.g.*, a mammal, such as a human). A subject to be treated according to the methods described herein may be one who has been diagnosed with a NLRP3 inflammasome dependent condition, such as inflammation,
 10 an inflammatory disease, an immune disease, cancer, infections including viral infections; central nervous system diseases, metabolic diseases, cardiovascular diseases, respiratory diseases, liver diseases, renal diseases, ocular diseases, skin diseases, psychological diseases or blood diseases.

Diagnosis may be performed by any method or technique known in the art. One
 15 skilled in the art will understand that a subject to be treated according to the present disclosure may have been subjected to standard tests or may have been identified, without examination, as one at risk due to the presence of one or more risk factors associated with the disease or condition. The term “patient” may be used interchangeably with the term “subject.” A subject may refer to an adult or pediatric subject.

20 Compounds

As detailed above, the present disclosure provides compounds showing significant activity as NLRP3 inflammasome antagonists (*i.e.*, as NLRP3 inflammasome inhibitors). Accordingly, one embodiment a compound is provided having structure (I):



(I)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

(1) when X is CR_aR_b;

wherein R_a and R_b are each, independently, H or C₁₋₆ alkyl;

R¹ is H, OH, CF₃, C₁₋₆ alkyl, C₃₋₅ cycloalkyl, CN, halo, OC₁₋₆ alkyl or OCF₃;

5 R² and R⁵ are independently H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

one of R³ or R⁴ is OH and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or
OC₁₋₆ alkyl;

R⁸ is H or halo;

R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

10 R^{9'} is OH, F or C₃₋₅ cycloalkyl;

R¹⁰ and R¹³ are independently H or halo;

R¹¹ and R¹² are each, independently, is H, halo, CF₃, C₁₋₆ alkyl, CN or OC₁₋₆ alkyl;

n is 0, 1 or 2; or

15 (2) when X is NR_a or O;

wherein R_a and R_b are each, independently, H or C₁₋₆ alkyl;

R¹ is H, OH, CF₃, C₁₋₆ alkyl, C₃₋₅ cycloalkyl, CN, halo, OC₁₋₆ alkyl or OCF₃;

R² and R⁵ are independently H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

20 one of R³ or R⁴ is OH and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or
OC₁₋₆ alkyl;

R⁸ is H or halo;

R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

R^{9'} is OH, F or C₃₋₅ cycloalkyl;

R^{10} and R^{13} are independently H or halo;

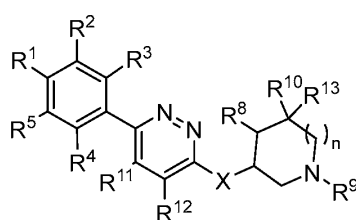
R^{11} and R^{12} are each, independently, is H, halo, CF_3 , C_{1-6} alkyl, CN or OC_{1-6} alkyl;

n is 0, 1 or 2; and

wherein if X is NR_a or O and R^1 is Cl, CH_3 , CF_3 , OCF_3 , or methyl, then one of R^2 and R^5 is not H.

5

In another embodiment, a compound is provided having the following structure (I):



(I)

10 or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

(1) when X is CR_aR_b ;

wherein R_a and R_b are each, independently, H or C_{1-6} alkyl;

R^1 is H, OH, CF_3 , C_{1-6} alkyl, C_{3-5} cycloalkyl, CN, halo, OC_{1-6} alkyl or OCF_3 ;

R^2 and R^5 are independently H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

15 one of R^3 or R^4 is OH and the other is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, F or C_{3-5} cycloalkyl;

20 R^{10} and R^{13} are independently H or halo;

R^{11} and R^{12} are each, independently, is H, halo, CF_3 , C_{1-6} alkyl, CN or OC_{1-6} alkyl;

n is 0, 1 or 2; or

(2) when X is NR_a or O;

wherein R_a and R_b are each, independently, H or C₁₋₆ alkyl; then

- 5 (A) R¹ is H, OH, C₂₋₆ alkyl, C₃₋₅ cycloalkyl, CN, F, Br or OC₁₋₆ alkyl;
- R² and R⁵ are independently H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;
- one of R³ or R⁴ is OH and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;
- 10 R⁸ is H or halo;
- R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};
- R^{9'} is OH, F or C₃₋₅ cycloalkyl;
- R¹⁰ and R¹³ are independently H or halo;
- 15 R¹¹ and R¹² are each, independently, is H, halo, CF₃, C₁₋₆ alkyl, CN or OC₁₋₆ alkyl; and
- n is 0, 1 or 2; or
- (B) R¹ is CF₃, methyl, Cl or OCF₃;
- one of R² and R⁵ is OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl and
- 20 the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;
- one of R³ or R⁴ is OH and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;
- R⁸ is H or halo;

R^9 is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, F or C₃₋₅ cycloalkyl;

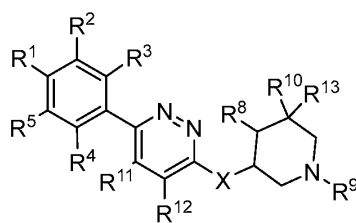
R^{10} and R^{13} are independently H or halo;

5 R^{11} and R^{12} are each, independently, is H, halo, CF₃, C₁₋₆ alkyl, CN or OC₁₋₆ alkyl; and

n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

(I'):



10

(I')

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

X is CR_aR_b, NR_a or O;

wherein R_a and R_b are each, independently, H or C₁₋₆ alkyl;

15 R^1 is H, OH, C₂₋₆ alkyl, C₃₋₅ cycloalkyl, CN, F, Br or OC₁₋₆ alkyl;

R^2 and R^5 are each, independently, H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

one of R^3 or R^4 is OH and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

20 R^8 is H or halo;

R^9 is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, F or C₃₋₅ cycloalkyl;

R^{10} and R^{13} are independently H or halo;

R^{11} and R^{12} are each, independently, is H, halo, CF_3 , C_{1-6} alkyl, CN or OC_{1-6} alkyl;

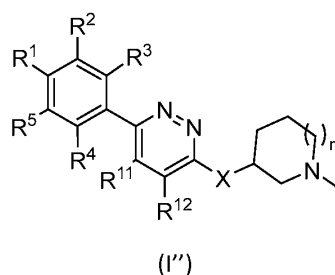
and

n is 0, 1 or 2.

5

In one embodiment, a compound is provided having the following structure

(I''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

10

X is CR_aR_b , NR_a or O ;

wherein R_a and R_b are each, independently, H or C_{1-6} alkyl;

R^1 is H, F, CN, C_{2-6} alkyl or C_{3-5} cycloalkyl;

R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H, OH or C_{1-6} alkyl;

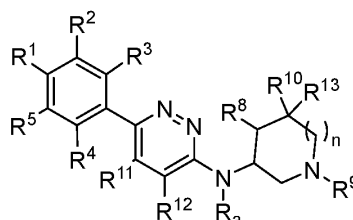
15

R^{11} and R^{12} are each, independently, H, F or C_{1-6} alkyl; and

n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

(Ia):



(Ia)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C₁₋₆ alkyl; and wherein

(A) R¹ is H, OH, C₂₋₆ alkyl, C₃₋₅ cycloalkyl, CN, F, Br or OC₁₋₆ alkyl;

5 R² and R⁵ are independently H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

one of R³ or R⁴ is OH and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

R⁸ is H or halo;

R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

10 R^{9'} is OH, F or C₃₋₅ cycloalkyl;

R¹⁰ and R¹³ are independently H or halo;

R¹¹ and R¹² are each, independently, is H, halo, CF₃, C₁₋₆ alkyl, CN or OC₁₋₆ alkyl;

and

n is 0, 1 or 2; or

15

(B) R¹ is CF₃, methyl, Cl or OCF₃;

one of R² and R⁵ is OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

20 one of R³ or R⁴ is OH and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

R⁸ is H or halo;

R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

R^{9'} is OH, F or C₃₋₅ cycloalkyl;

R¹⁰ and R¹³ are independently H or halo;

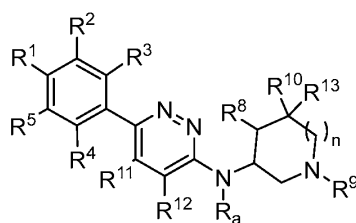
R^{11} and R^{12} are each, independently, is H, halo, CF_3 , C_{1-6} alkyl, CN or OC_{1-6} alkyl;

and

n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

5 (Ia):



(Ia)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C_{1-6} alkyl;

10

R^1 is H, OH, C_{2-6} alkyl, C_{3-5} cycloalkyl, CN, F, Br or OC_{1-6} alkyl;

R^2 and R^5 are each, independently, H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

15

R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, F or C_{3-5} cycloalkyl;

R^{10} and R^{13} are independently H or halo;

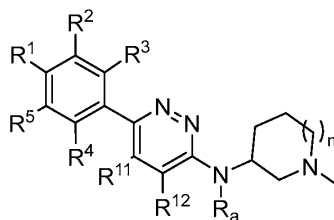
R^{11} and R^{12} are each, independently, is H, halo, CF_3 , C_{1-6} alkyl, CN or OC_{1-6} alkyl;

20 and

n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

(Ia'):



(Ia')

5 or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C_{1-6} alkyl;

R^1 is H, F, CN, C_{2-6} alkyl or C_{3-5} cycloalkyl;

R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

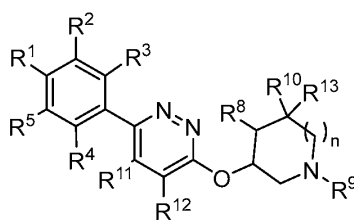
one of R^3 or R^4 is OH and the other is H, OH or C_{1-6} alkyl;

10 R^{11} and R^{12} are each, independently, H, F or C_{1-6} alkyl; and

n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

(Ib):



(Ib)

15

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

(A) R^1 is H, OH, C_{2-6} alkyl, C_{3-5} cycloalkyl, CN, F, Br or OC_{1-6} alkyl;

R^2 and R^5 are independently H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

one of R³ or R⁴ is OH and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

R⁸ is H or halo;

R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

5 R^{9'} is OH, F or C₃₋₅ cycloalkyl;

R¹⁰ and R¹³ are independently H or halo;

R¹¹ and R¹² are each, independently, is H, halo, CF₃, C₁₋₆ alkyl, CN or OC₁₋₆ alkyl;

and

n is 0, 1 or 2; or

10

(B) R¹ is CF₃, methyl, Cl or OCF₃;

one of R² and R⁵ is OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

15 one of R³ or R⁴ is OH and the other is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl;

R⁸ is H or halo;

R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

R^{9'} is OH, F or C₃₋₅ cycloalkyl;

R¹⁰ and R¹³ are independently H or halo;

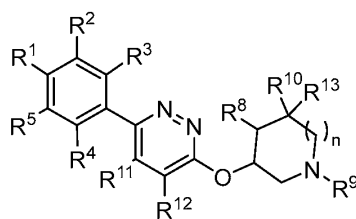
20 R¹¹ and R¹² are each, independently, is H, halo, CF₃, C₁₋₆ alkyl, CN or OC₁₋₆ alkyl;

and

n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

(Ib):



(Ib)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^1 is H, OH, C_{2-6} alkyl, C_{3-5} cycloalkyl, CN, F, Br or OC_{1-6} alkyl;

5 R^2 and R^5 are each, independently, H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

R^8 is H or halo;

10 R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, F or C_{3-5} cycloalkyl;

R^{10} and R^{13} are independently H or halo;

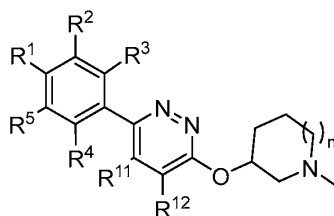
R^{11} and R^{12} are each, independently, is H, halo, CF_3 , C_{1-6} alkyl, CN or OC_{1-6} alkyl;

and

15 n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

(Ib'):



(Ib')

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^1 is H, F, C_{2-6} alkyl or C_{3-5} cycloalkyl;

R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

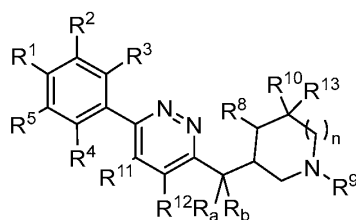
one of R^3 or R^4 is OH and the other is H, OH or C_{1-6} alkyl;

5 R^{11} and R^{12} are each, independently, H or C_{1-6} alkyl; and

n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

(Ic):



10

(Ic)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a and R_b are each, independently, H or C_{1-6} alkyl;

R^1 is H, OH, CF_3 , C_{1-6} alkyl, C_{3-5} cycloalkyl, CN, halo, OC_{1-6} alkyl or OCF_3 ;

R^2 and R^5 are independently H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

15 one of R^3 or R^4 is OH and the other is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, F or C_{3-5} cycloalkyl;

20

R^{10} and R^{13} are independently H or halo;

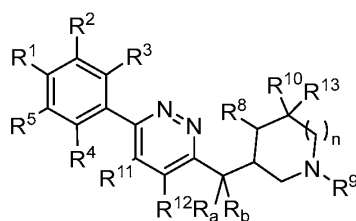
R^{11} and R^{12} are each, independently, is H, halo, CF_3 , C_{1-6} alkyl, CN or OC_{1-6} alkyl;

and

n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

5 (Ic):



(Ic)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a and R_b are each independently, H or C_{1-6} alkyl;

10

R^1 is H, OH, C_{2-6} alkyl, C_{3-5} cycloalkyl, CN, F, Br or OC_{1-6} alkyl;

R^2 and R^5 are each, independently, H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl;

15

R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, F or C_{3-5} cycloalkyl;

R^{10} and R^{13} are independently H or halo;

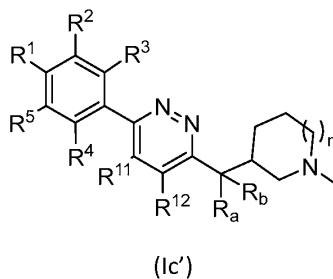
R^{11} and R^{12} are each, independently, is H, halo, CF_3 , C_{1-6} alkyl, CN or OC_{1-6} alkyl;

20 and

n is 0, 1 or 2.

In one embodiment, a compound is provided having the following structure

(Ic'):



5 or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a and R_b are each, independently, H or C_{1-6} alkyl;

R^1 is H, F, C_{2-6} alkyl or C_{3-5} cycloalkyl;

R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H, OH or C_{1-6} alkyl;

10 R^{11} and R^{12} are each, independently, H or C_{1-6} alkyl; and

n is 0, 1 or 2.

In more specific embodiments of each of Structures (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), and (Ic'), as appropriate, such structures include the following more specific embodiments.

15 In one embodiment, X is CR_aR_b .

In another embodiment, X is NR_a .

In yet another embodiment, X is O.

In one embodiment, R^{11} and R^{12} are not H.

In some embodiments, R^{11} is halo, CF_3 , C_{1-6} alkyl, CN, or OC_{1-6} alkyl, and R^{12} is H.

20 In other embodiments, R^{11} is H and R^{12} is halo, CF_3 , C_{1-6} alkyl, CN, or OC_{1-6} alkyl.

In yet other embodiments, both R^{11} and R^{12} are H.

In some embodiments, both R^{11} and R^{12} are not H.

In one embodiment, R^1 is H.

In another embodiment, R^1 is OH.

In other embodiments, R^1 is CF_3 .

5 In yet another embodiment, R^1 is F.

In one embodiment, R^1 is Cl.

In another embodiment, R^1 is Br.

In another embodiment, R^1 is I.

In some embodiments, R^1 is OCF_3 .

10 In one embodiment, R^1 is CN.

In some embodiments, R^1 is C_{1-6} alkyl.

In a certain embodiment, R^1 is methyl.

In other embodiments, R^1 is C_{2-6} alkyl.

In a certain embodiment, R^1 is ethyl.

15 In a certain embodiment, R^1 is isopropyl.

In one embodiment, R^1 is OC_{1-6} alkyl.

In a certain embodiment, R^1 is OCH_3 .

In one embodiment, R^1 is C_{3-5} cycloalkyl.

In a certain embodiment, R^1 is cyclopropyl.

20 In a certain embodiment, R^1 is cyclobutyl.

In one embodiment, R^2 and R^5 are independently H, C_{1-6} alkyl, F, Cl, CF_3 or CN.

In another embodiment, R^2 is OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl,

and R^5 is H.

In some embodiments, R^2 is H and R^5 is OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl.

In one embodiment, R^2 is H.

In another embodiment, R^2 is OH.

5 In some embodiments, R^2 is CF_3 .

In other embodiments, R^2 is C_{1-6} alkyl.

In certain embodiments, R^2 is methyl.

In other embodiments, R^2 is ethyl.

In yet other embodiments, R^2 is isopropyl.

10 In another embodiment, R^2 is CN.

In some embodiments, R^2 is F.

In yet another embodiment, R^2 is Cl.

In some embodiments, R^2 is Br.

In another embodiment, R^2 is I.

15 In one embodiment, R^2 is OCF_3 .

In yet other embodiments, R^2 is OC_{1-6} alkyl.

In one embodiment, R^2 is OCH_3 .

In some embodiments, R^5 is H.

In one embodiment, R^5 is OH.

20 In some embodiments, R^5 is CF_3 .

In other embodiments, R^5 is C_{1-6} alkyl.

In yet other embodiments, R^5 is methyl.

In certain embodiments, R^5 is ethyl.

- In other embodiments, R⁵ is isopropyl.
- In yet other embodiments, R⁵ is CN.
- In one embodiment, R⁵ is F.
- In some embodiments, R⁵ is Cl.
- 5 In another embodiment, R⁵ is Cl.
- In other embodiments, R⁵ is Br.
- In another embodiment, R⁵ is I.
- In one embodiment, R⁵ is OCF₃.
- In yet other embodiments, R⁵ is OC₁₋₆ alkyl.
- 10 In one embodiment, R⁵ is OCH₃.
- In some embodiments, R³ is OH and R⁴ is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl.
- In other embodiments, R⁴ is OH and R³ is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl.
- 15 In one embodiment, R³ is OH and R⁴ is H or C₁₋₆ alkyl.
- In another embodiment, R⁴ is OH and R³ is H or C₁₋₆ alkyl.
- In one embodiment, R³ is OH.
- In other embodiments, R³ is H.
- In another embodiment, R³ is CF₃.
- 20 In some embodiments, R³ is C₁₋₆ alkyl.
- In other embodiments, R³ is methyl.
- In certain embodiments, R³ is ethyl.
- In some embodiments, R³ is isopropyl.

- In other embodiments, R^3 is CN.
- In yet other embodiments, R^3 is F.
- In one embodiment, R^3 is Cl.
- In some embodiments, R^3 is Br.
- 5 In another embodiment, R^3 is I.
- In another embodiment, R^3 is OCF_3 .
- In yet other embodiments, R^3 is OC_{1-6} alkyl.
- In one embodiment, R^3 is OCH_3 .
- In some embodiments, R^4 is OH.
- 10 In one embodiment, R^4 is H.
- In another embodiment, R^4 is CF_3 .
- In yet another embodiment, R^4 is C_{1-6} alkyl.
- In some embodiments, R^4 is methyl.
- In other embodiments, R^4 is ethyl.
- 15 In some embodiments, R^4 is isopropyl.
- In one embodiment, R^4 is CN.
- In another embodiment, R^4 is F.
- In yet another embodiment, R^4 is Cl.
- In yet another embodiment, R^4 is Br.
- 20 In another embodiment, R^4 is I.
- In another embodiment, R^4 is OCF_3 .
- In yet other embodiments, R^4 is OC_{1-6} alkyl.
- In some embodiments, R^4 is OCH_3 .

In one embodiment, R^8 is H.

In another embodiment, R^8 is F.

In yet another embodiment, R^8 is Cl.

In another embodiment, R^8 is Br.

5 In another embodiment, R^8 is I.

In some embodiments, R^9 is H.

In one embodiment, R^9 is not H.

In another embodiment, R^9 is C_{1-6} alkyl.

In some embodiments, R^9 is methyl.

10 In other embodiments, R^9 is ethyl.

In yet other embodiments, R^9 is isopropyl.

In one embodiment, R^9 is C_{1-6} alkyl optionally substituted with one or more F.

In certain embodiments, R^9 is $-CH_2CH_2F$.

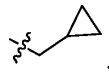
In yet another embodiment, R^9 is $-CH_2CHF_2$.

15 In some embodiments, R^9 is $-CH_2CF_3$.

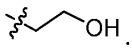
In one embodiment, R^9 is C_{3-5} cycloalkyl.

In certain embodiments, R^9 is cyclopropyl.

In one embodiment, R^9 is C_{1-6} alkyl optionally substituted with one or more C_{3-5} cycloalkyl.

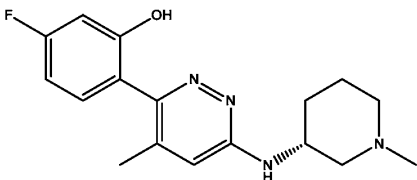
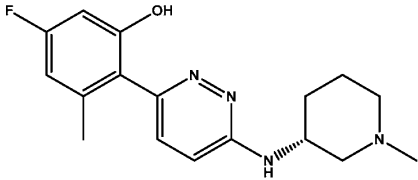
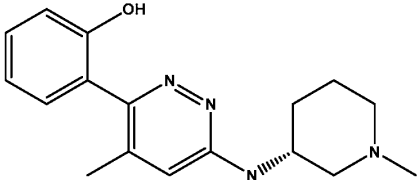
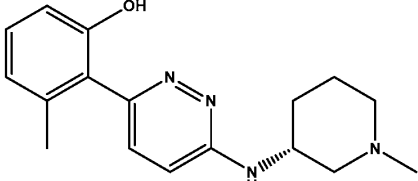
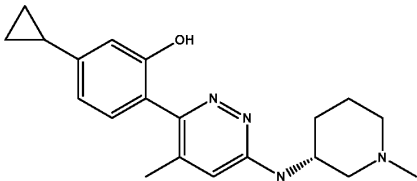
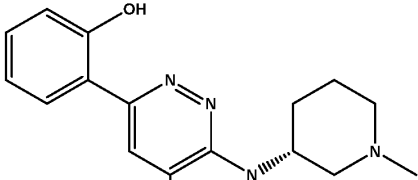
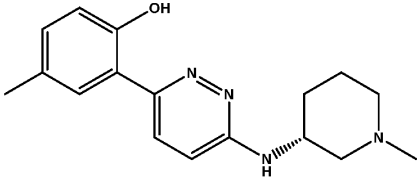
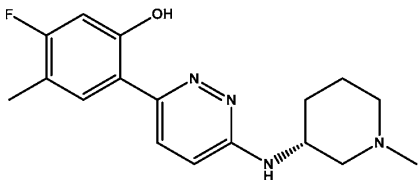
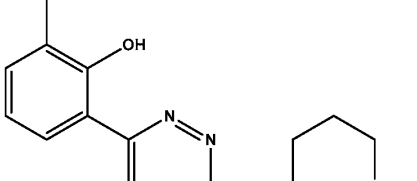
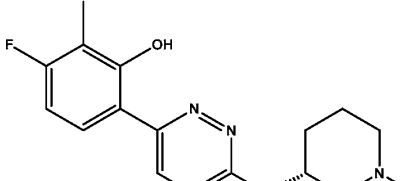
20 In certain embodiments, R^9 is .

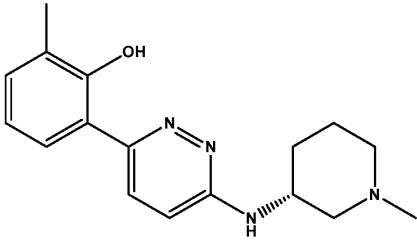
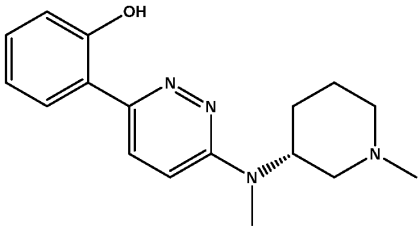
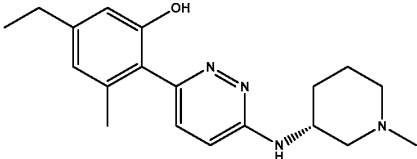
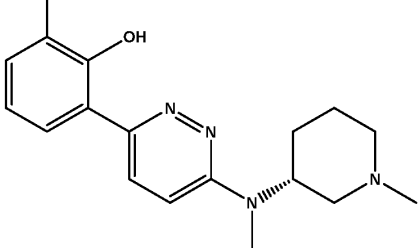
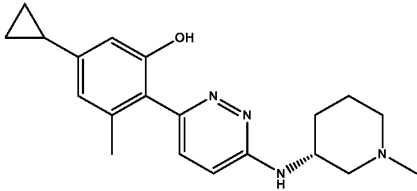
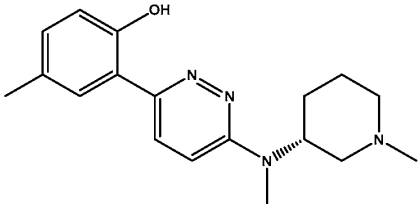
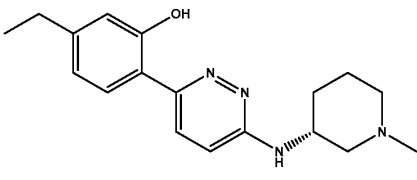
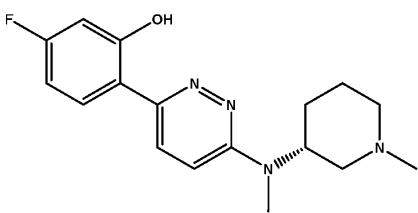
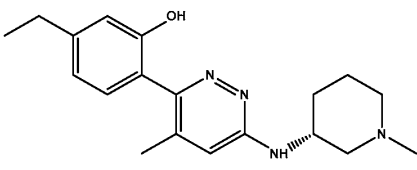
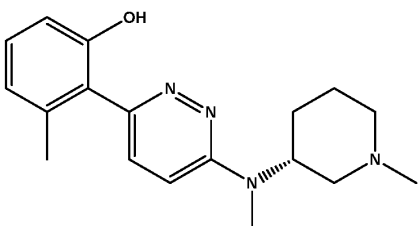
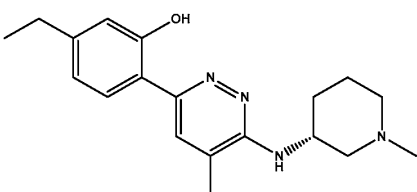
In some embodiments, R^9 is C_{1-6} alkyl optionally substituted with one or more OH.

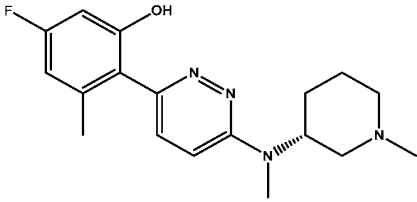
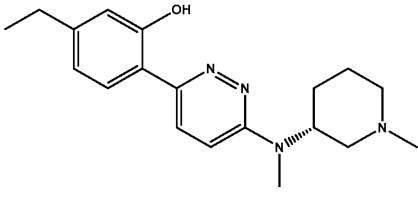
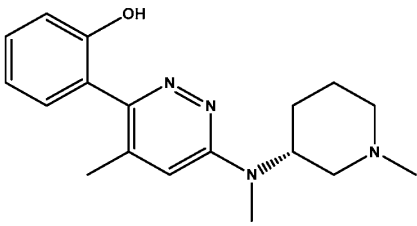
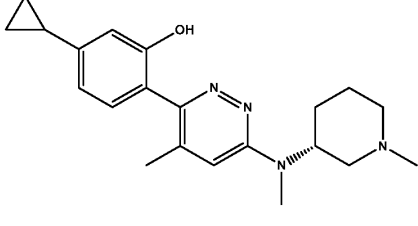
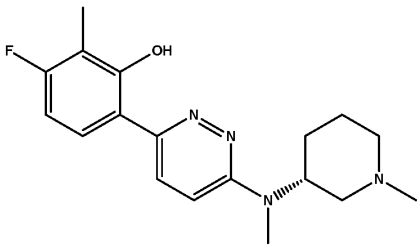
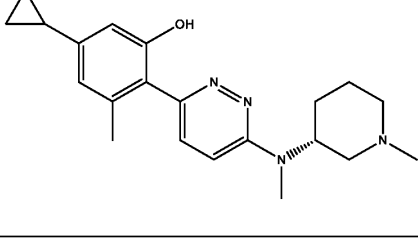
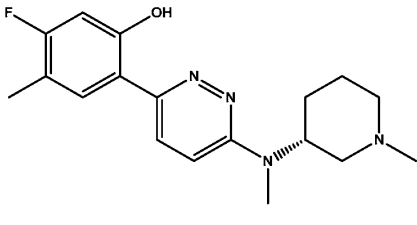
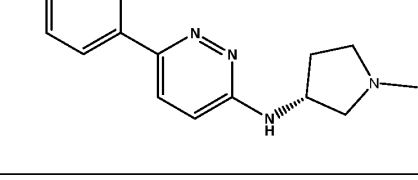
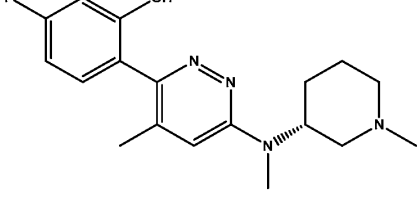
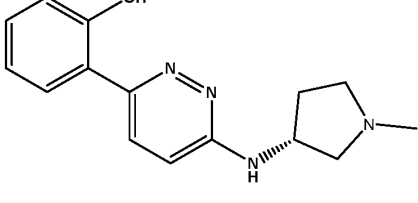
In other embodiments, R^9 is .

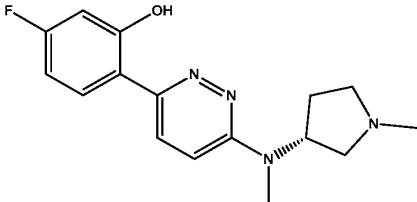
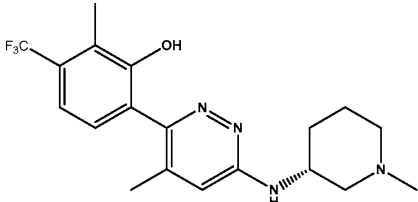
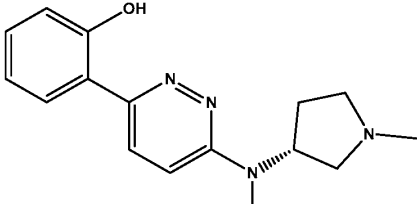
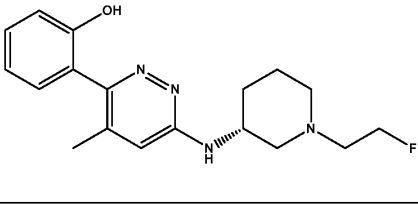
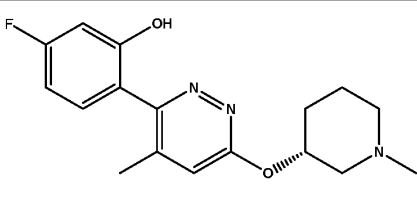
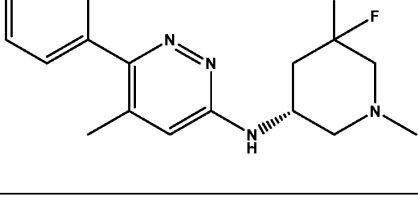
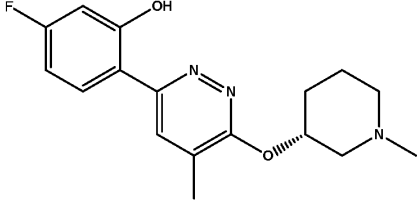
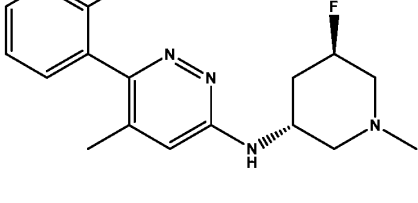
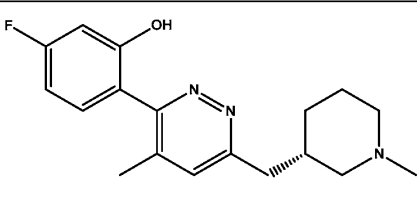
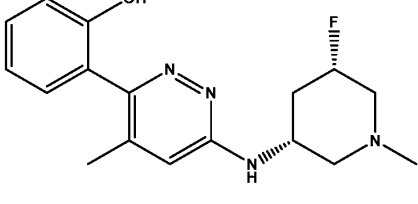
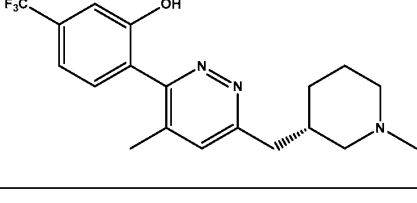
- In another embodiment, R^{10} and R^{13} are both H.
- In one embodiment, R^{10} and R^{13} are both halo.
- In certain embodiments, R^{10} and R^{13} are both F.
- In another embodiment, R^{10} is H and R^{13} is halo.
- 5 In yet another embodiment, R^{10} is H and R^{13} is F.
- In one embodiment, R^{10} is H.
- In another embodiment, R^{10} is F.
- In certain embodiments, R^{10} is Cl.
- In other embodiments, R^{10} is Br.
- 10 In another embodiment, R^{10} is I.
- In one embodiment, R^{13} is H.
- In some embodiments, R^{13} is F.
- In other embodiments, R^{13} is Cl.
- In yet other embodiments, R^{13} is Br.
- 15 In another embodiment, R^{13} is I.
- In some embodiments, n is 0.
- In other embodiments, n is 1.
- In other embodiments, n is 2.
- 20 In one embodiment, a compound is selected from one of the compounds listed in Table 1, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

Table 1
Representative compounds having Structure (I)

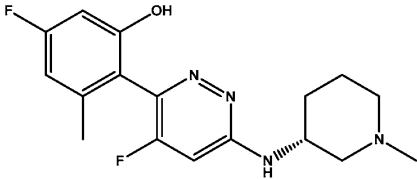
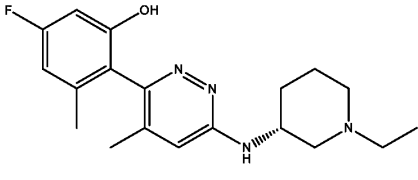
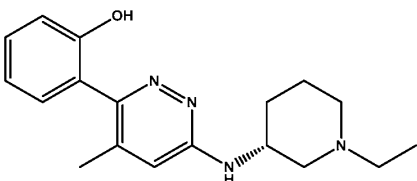
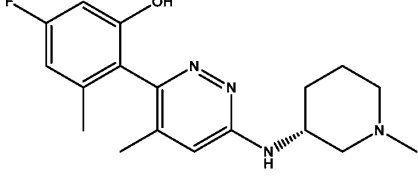
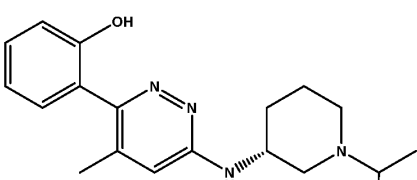
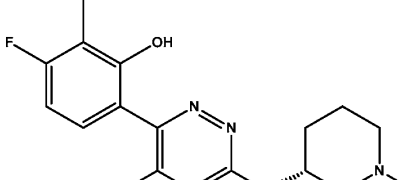
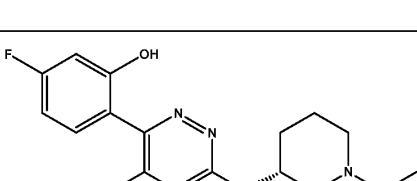
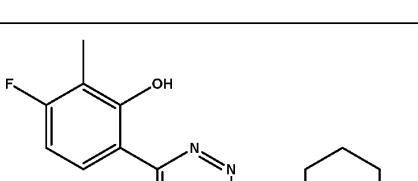
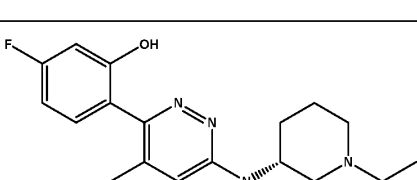
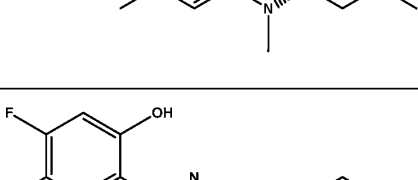
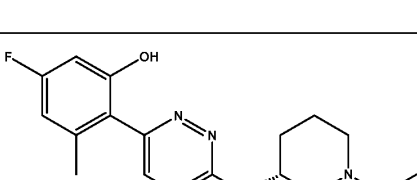
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	2		7
	3		8
	4		9
	5		10

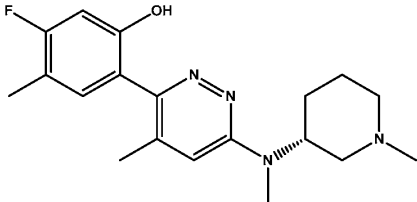
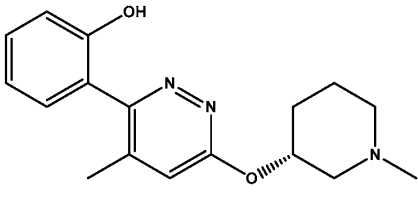
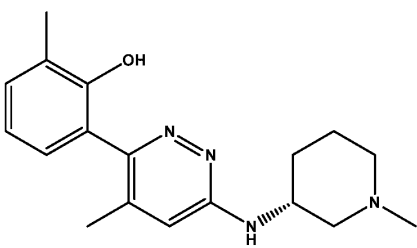
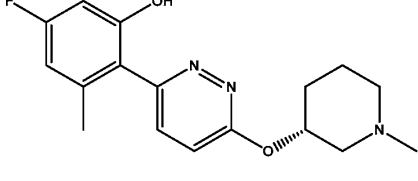
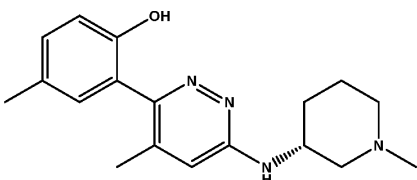
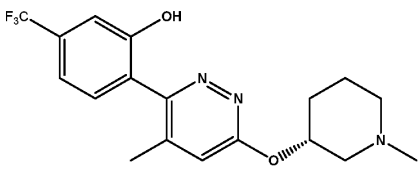
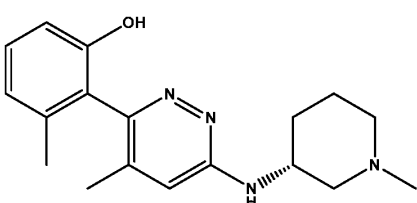
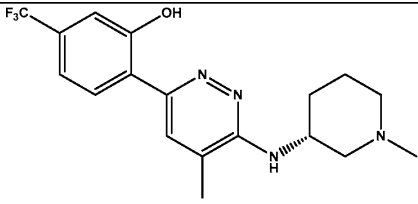
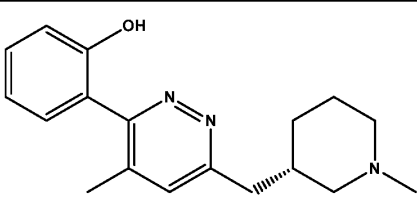
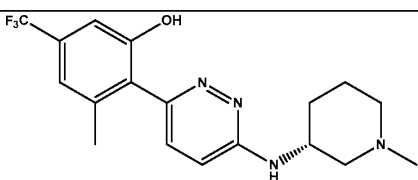
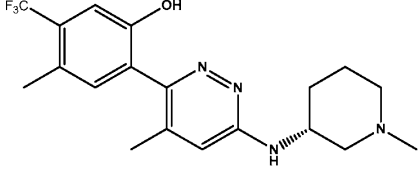
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	12		18
	13		19
	14		20
	15		21
	16		

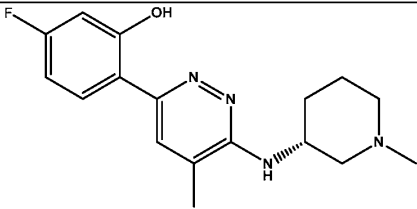
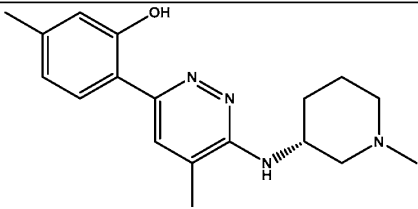
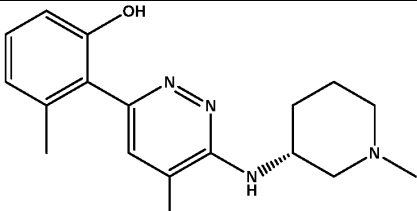
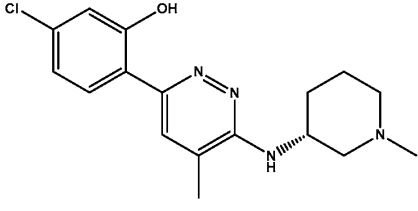
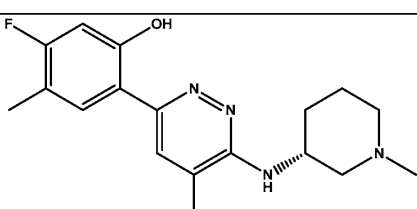
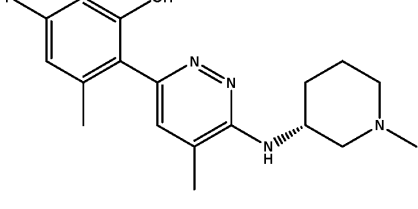
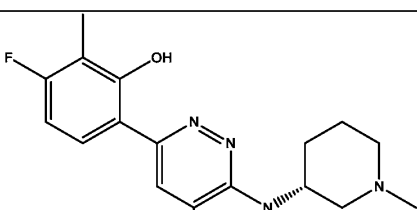
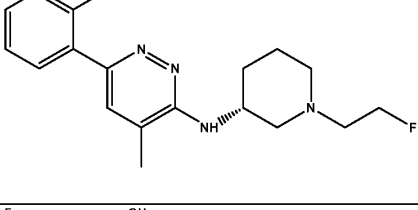
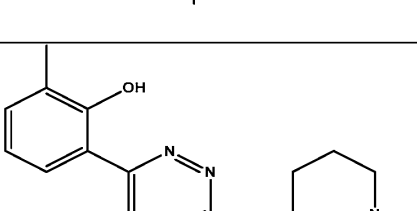
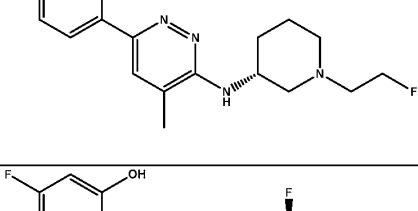
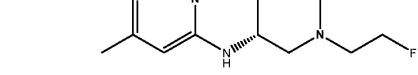
Structure	Cpd No.	Structure	Cpd No.
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	23		28
	24		29
	25		30
	26		31

Structure	Cpd No.	Structure	Cpd No.
	32		38
	33		39
	34		40
	35		41
	36		42
	37		

Structure	Cpd No.	Structure	Cpd No.
	43		49
	44		50
	45		51
	46		52
	47		53
	48		54

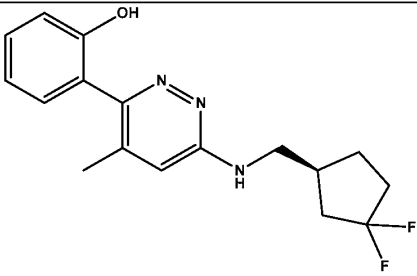
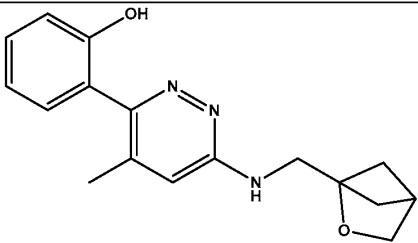
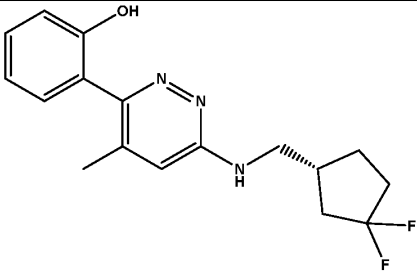
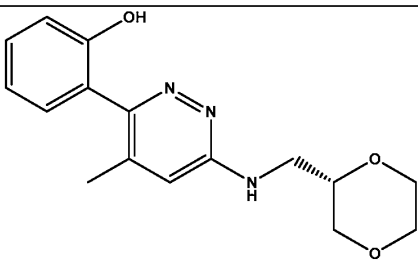
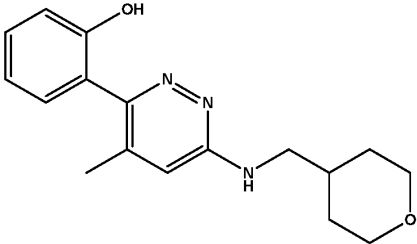
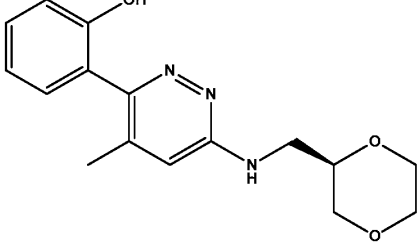
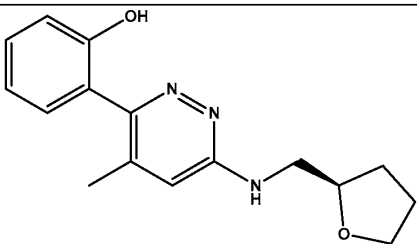
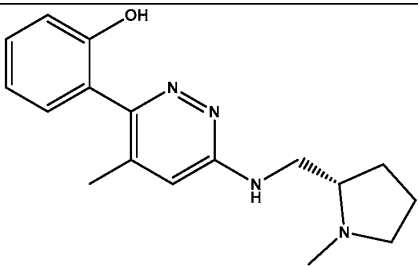
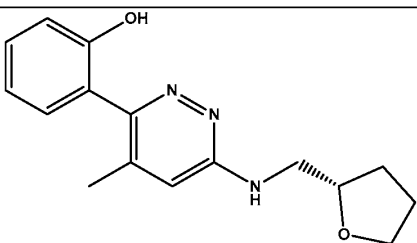
Structure	Cpd No.	Structure	Cpd No.
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	56		62
	57		63
	58		64
	59		65
	60		

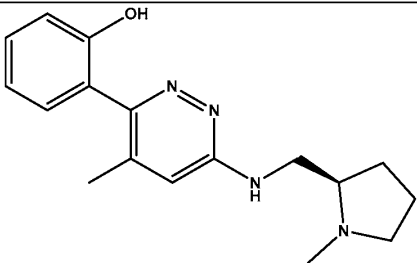
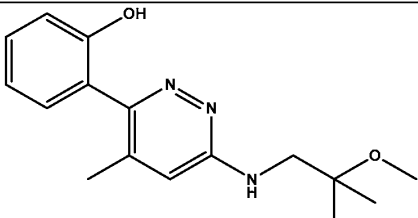
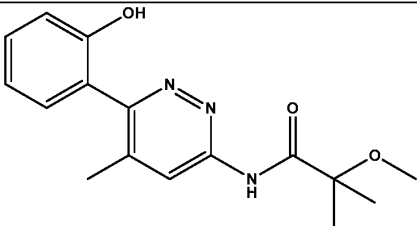
Structure	Cpd No.	Structure	Cpd No.
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	67		72
	68		73
	69		74
	70		75
			76

Structure	Cpd No.	Structure	Cpd No.
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	78		83
	79		84
	80		85
	81		86
			87

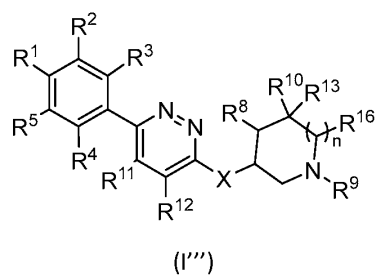
Structure	Cpd No.	Structure	Cpd No.
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	89		95
	90		96
	91		97
	92		98
	93		99

Structure	Cpd No.	Structure	Cpd No.
	100		107
	101		108
	102		109
	103		110
	104		111
	105		112
	106		

Structure	Cpd No.	Structure	Cpd No.
	113		118
	114		119
	115		120
	116		121
	117		

Structure	Cpd No.	Structure	Cpd No.
	122		124
	123		

In one embodiment, a compound is provided having structure (I'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof,
 5 wherein:

X is CR_aR_b, NR_a or O;

R_a and R_b are each, independently, H or C₁₋₆ alkyl;

R¹ is H, F or CN;

R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

5 R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

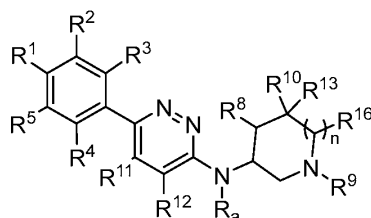
R^{10} and R^{13} are each, independently, H or halo;

10 R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

R^{16} is H or CO_2H ; and

n is 0, 1 or 2.

In another embodiment, a compound is provided having structure (Ia'''):



15 (Ia''')

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C_{1-6} alkyl;

R^1 is H, F or CN;

20 R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

5 $R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

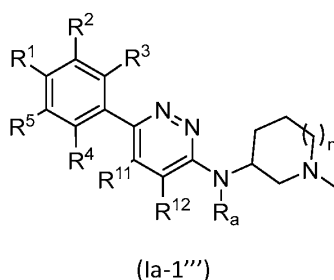
R^{10} and R^{13} are each, independently, H or halo;

R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

R^{16} is H or CO_2H ; and

10 n is 0, 1 or 2.

In another embodiment, a compound is provided having structure (Ia-1'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof,

15 wherein:

R_a is H or C_{1-6} alkyl;

R^1 is H, F or CN;

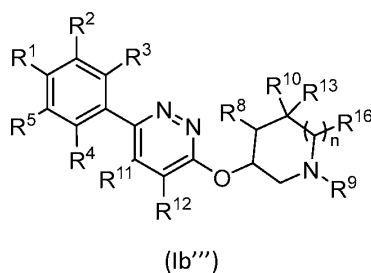
R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H or C_{1-6} alkyl;

20 R^{11} and R^{12} are each, independently, H, F or C_{1-6} alkyl; and

n is 0, 1 or 2.

In another embodiment, a compound is provided having structure (Ib'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof,

5 wherein:

R^1 is H, F or CN;

R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

10 one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

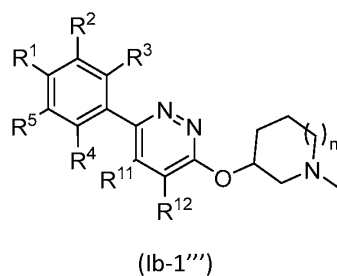
R^{10} and R^{13} are each, independently, H or halo;

15 R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

R^{16} is H or CO_2H ; and

n is 0, 1 or 2.

In another embodiment, a compound is provided having structure (Ib-1'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof,
 5 wherein:

R^1 is H, F or CN;

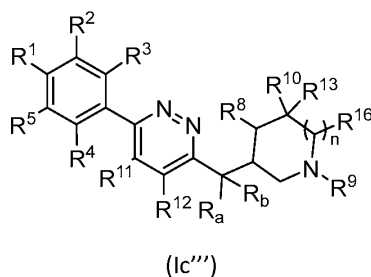
R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H or C_{1-6} alkyl;

R^{11} and R^{12} are each, independently, H or C_{1-6} alkyl; and

10 n is 0, 1 or 2.

In another embodiment, a compound is provided having structure (Ic'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof,
 15 wherein:

R_a and R_b are each, independently, H or C_{1-6} alkyl;

R^1 is H, F or CN;

R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl,
 OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

5 $R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

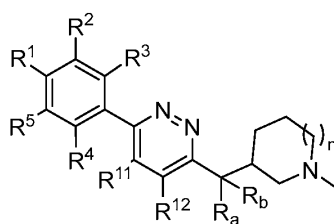
R^{10} and R^{13} are each, independently, H or halo;

R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

R^{16} is H or CO_2H ; and

10 n is 0, 1 or 2.

In another embodiment, a compound is provided having structure (Ic-1'''):



(Ic-1''')

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof,

15 wherein:

R_a and R_b are each, independently, H or C_{1-6} alkyl;

R^1 is H, F or CN;

R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H or C_{1-6} alkyl;

20 R^{11} and R^{12} are each, independently, H or C_{1-6} alkyl; and

n is 0, 1 or 2.

In more specific embodiments of each of Structures (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), and (Ic-1'''), as appropriate, such structures include the following more specific embodiments.

In one embodiment, X is CR_aR_b. In another embodiment, X is NR_a. In yet another
5 embodiment, X is O.

In one embodiment, one of R¹¹ and R¹² is H. In another embodiment, R¹¹ is C₁₋₆ alkyl and R¹² is H. In another embodiment, R¹¹ is H and R¹² is C₁₋₆ alkyl. In another embodiment, both R¹¹ and R¹² are H. In another embodiment, both R¹¹ and R¹² are not H. In some
10 embodiments, R¹¹ is H, halo, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl or OC₁₋₆ alkyl, and R¹² is H. In some
embodiments, R¹¹ is H, F, CN, methyl, CF₃ or OCH₃, and R¹² is H. In other embodiments, R¹¹ is H
and R¹² is H, halo, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl or OC₁₋₆ alkyl. In other embodiments, R¹¹ is H and
R¹² is H, F, CN, methyl, CF₃ or OCH₃.

In one embodiment, wherein R¹ is H. In another embodiment, wherein R¹ is F.
In another embodiment, R¹ is CN.

15 In one embodiment, R² and R⁵ are each, independently, H, C₁₋₆ alkyl, F, Cl, CF₃,
or CN. In another embodiment, R² is OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl, and R⁵ is H.
In another embodiment, R² is H and R⁵ is OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl.

In one embodiment, R² is H. In another embodiment, R² is OH. In additional
embodiments, R² is C₁₋₆ haloalkyl. In some embodiments, R² is CF₃. In additional embodiments,
20 R² is C₁₋₆ alkyl. In a specific embodiment, R² is methyl. In another embodiment, R² is ethyl. In
another embodiment, R² is isopropyl. In yet other embodiments, R² is CN. In one embodiment,
R² is halo. In another embodiment, R² is F. In another embodiment, R² is Cl. In another
embodiment, R² is Br. In another embodiment, R² is OC₁₋₆ haloalkyl. In some embodiments, R² is
OCF₃. In another embodiment, R² is OC₁₋₆ alkyl. In a specific embodiment, R² is OCH₃.

25 In one embodiment, R⁵ is H. In another embodiment, R⁵ is OH. In another
embodiment, R⁵ is C₁₋₆ haloalkyl. In another embodiment, R⁵ is CF₃. In another embodiment, R⁵
is C₁₋₆ alkyl. In another embodiment, R⁵ is methyl. In another embodiment, R⁵ is ethyl. In another
embodiment, R⁵ is isopropyl. In another embodiment, R⁵ is CN. In one embodiment, R⁵ is halo.

In another embodiment, R⁵ is F. In another embodiment, R⁵ is Cl. In another embodiment, R⁵ is Br. In another embodiment, R⁵ is OC₁₋₆ haloalkyl. In another embodiment, R⁵ is OCF₃. In another embodiment, R⁵ is OC₁₋₆ alkyl. In another embodiment, R⁵ is OCH₃.

In one embodiment, R³ is OH and R⁴ is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl. In another embodiment, R⁴ is OH and R³ is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl. In yet other embodiments, R³ is OH and R⁴ is H or C₁₋₆ alkyl. In another embodiment, R⁴ is OH and R³ is H or C₁₋₆ alkyl.

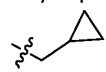
In some embodiments, R³ is OH. In another embodiment, R³ is H. In another embodiment, R³ is C₁₋₆ haloalkyl. In one embodiment, R³ is CF₃. In another embodiment, R³ is C₁₋₆ alkyl. In a specific embodiment, R³ is methyl. In another embodiment, R³ is ethyl. In certain embodiments, R³ is isopropyl. In another embodiment, R³ is CN. In one embodiment, R³ is halo. In some embodiments, R³ is F. In another embodiment, R³ is Cl. In one embodiment, R³ is Br. In another embodiment, R³ is OC₁₋₆ haloalkyl. In another embodiment, R³ is OCF₃. In some embodiments, R³ is OC₁₋₆ alkyl. In certain embodiments, R³ is OCH₃.

In one embodiment, R⁴ is OH. In another embodiment, R⁴ is H. In another embodiment, R⁴ is C₁₋₆ haloalkyl. In yet other embodiments, R⁴ is CF₃. In another embodiment, R⁴ is C₁₋₆ alkyl. In specific embodiments, R⁴ is methyl. In another embodiment, R⁴ is ethyl. In certain embodiments, R⁴ is isopropyl. In another embodiment, R⁴ is CN. In one embodiment, R⁴ is halo. In yet other embodiments, R⁴ is F. In another embodiment, R⁴ is Cl. In additional embodiments, R⁴ is Br. In additional embodiments, R⁴ is I. In another embodiment, R⁴ is OC₁₋₆ haloalkyl. In another embodiment, R⁴ is OCF₃. In other embodiments, R⁴ is OC₁₋₆ alkyl. In certain embodiments, R⁴ is OCH₃.

In one embodiment, R⁸ is H. In another embodiment, R⁸ is F. In another embodiment, R⁸ is Cl. In yet other embodiments, R⁸ is Br. In yet other embodiments, R⁸ is I.

In one embodiment, R⁹ is H. In another embodiment, R⁹ is not H. In some embodiments, R⁹ is C₁₋₆ alkyl. In a specific embodiment, R⁹ is methyl. In some embodiments, R⁹ is ethyl. In certain embodiments, R⁹ is isopropyl. In some embodiments, R⁹ is C₁₋₆ alkyl optionally substituted with one or more F. In another embodiment, R⁹ is -CH₂CH₂F. In certain embodiments, R⁹ is -CH₂CHF₂. In another embodiment, R⁹ is -CH₂CF₃. In one embodiment, R⁹ is

C₃₋₅ cycloalkyl. In a specific embodiment, R⁹ is cyclopropyl. In another embodiment, R⁹ is C₁₋₆ alkyl optionally substituted with one or more C₃₋₅ cycloalkyl. In certain embodiments, R⁹ is



. In another embodiment, R⁹ is C₁₋₆ alkyl optionally substituted with one or more OH.

In some embodiments, R⁹ is .

5 In one embodiment, R^{9'} is OH. In one embodiment, R^{9'} is halo. In yet other embodiments, R^{9'} is F. In another embodiment, R^{9'} is Cl. In additional embodiments, R^{9'} is Br. In additional embodiments, R^{9'} is I. In one embodiment, R^{9'} is C₃₋₅ cycloalkyl. In a specific embodiment, R^{9'} is cyclopropyl.

In one embodiment, R¹⁰ and R¹³ are both H. In another embodiment, R¹⁰ and R¹³
10 are both halo. In yet other embodiments, R¹⁰ is H and R¹³ is halo. In other embodiments, R¹³ is H and R¹⁰ is halo.

In one embodiment, R¹⁰ is H. In one embodiment, R¹⁰ is F. In another embodiment, R¹⁰ is Cl. In yet other embodiments, R¹⁰ is Br.

In one embodiment, R¹³ is H. In one embodiment, R¹³ is F. In another
15 embodiment, R¹³ is Cl. In yet other embodiments, R¹³ is Br.

In one embodiment, R¹⁶ is H. In another embodiment, R¹⁶ is CO₂H.

In one embodiment, Ra is H. In another embodiment, Ra is C₁₋₆ alkyl. In certain embodiments, Ra is methyl.

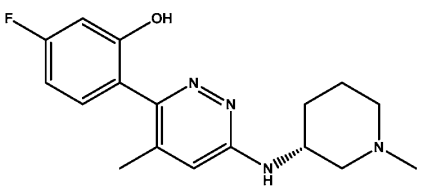
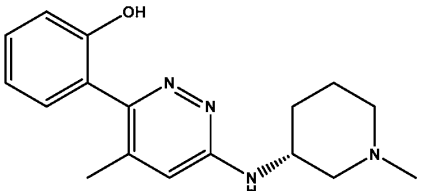
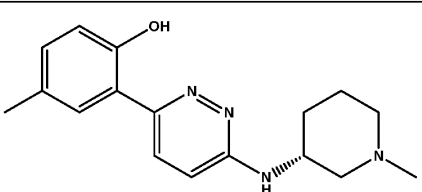
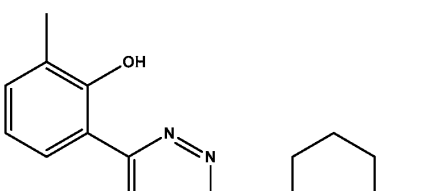
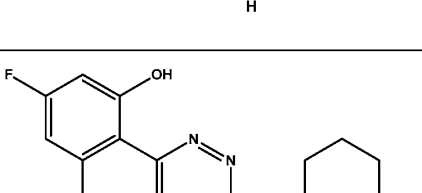
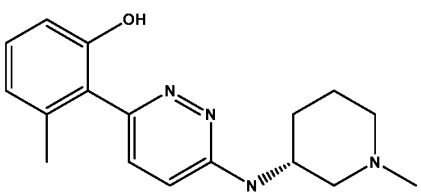
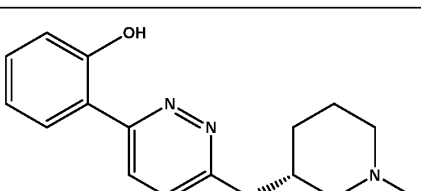
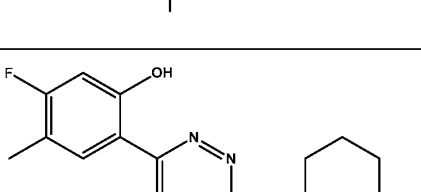
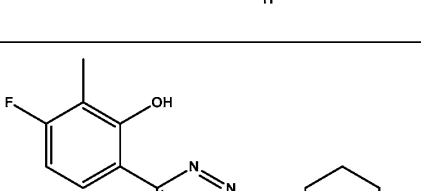
In one embodiment, Rb is H. In another embodiment, Rb is C₁₋₆ alkyl. In certain
20 embodiments, Rb is methyl.

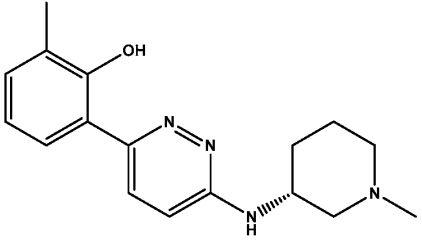
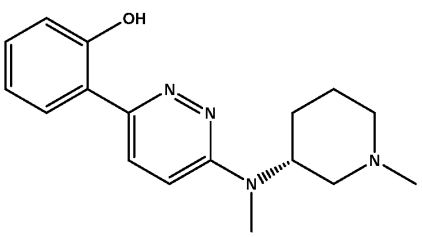
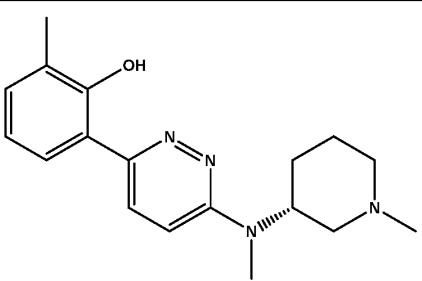
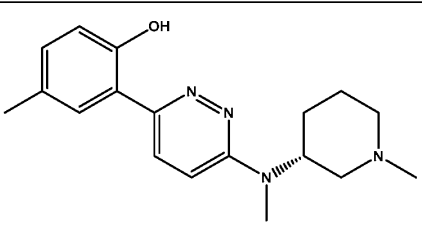
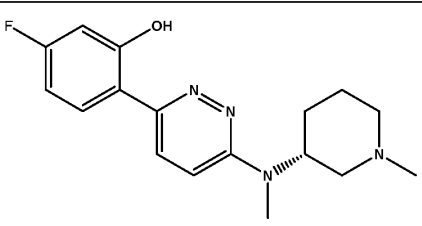
In one embodiment, n is 0-2. In one embodiment, n is 0 or 1. In other embodiments, n is 1 or 2. In yet other embodiments, n is 0 or 2. In some embodiments, n is 0. In other embodiments, n is 1. In other embodiments, n is 2.

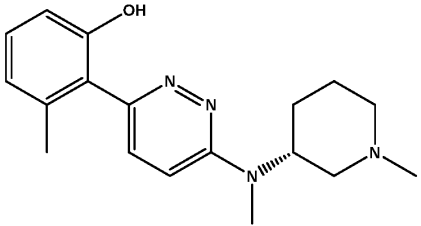
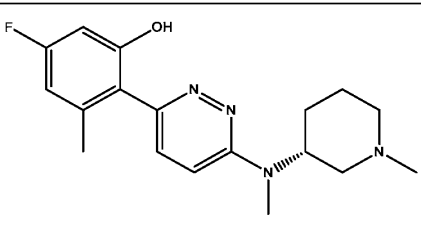
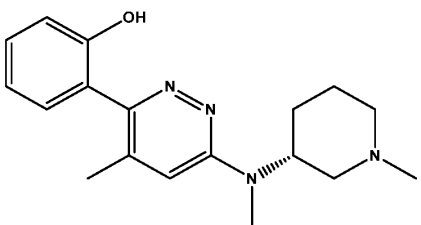
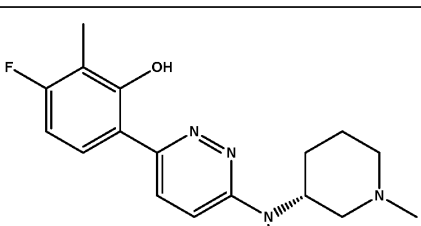
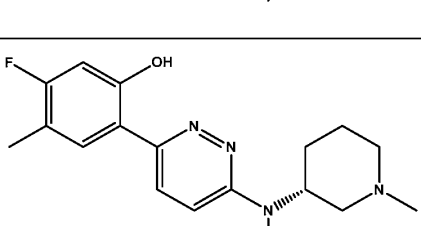
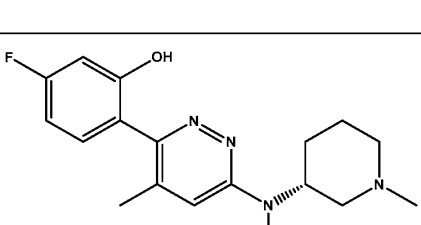
In one embodiment, a compound is selected from one of the compounds listed
25 in Table 2, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

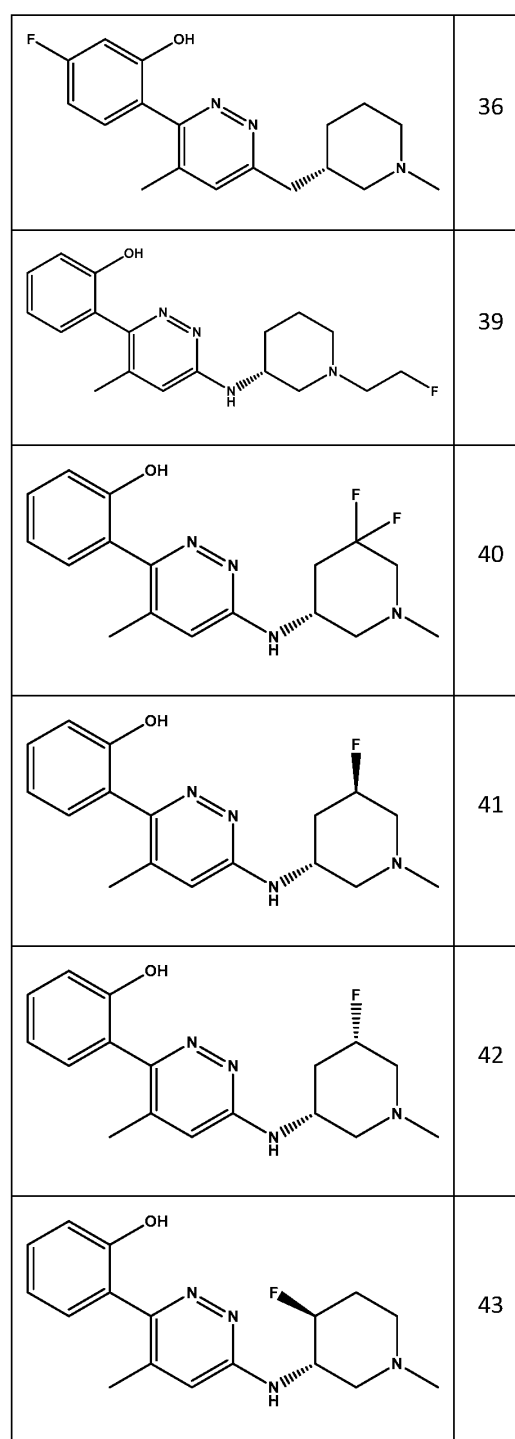
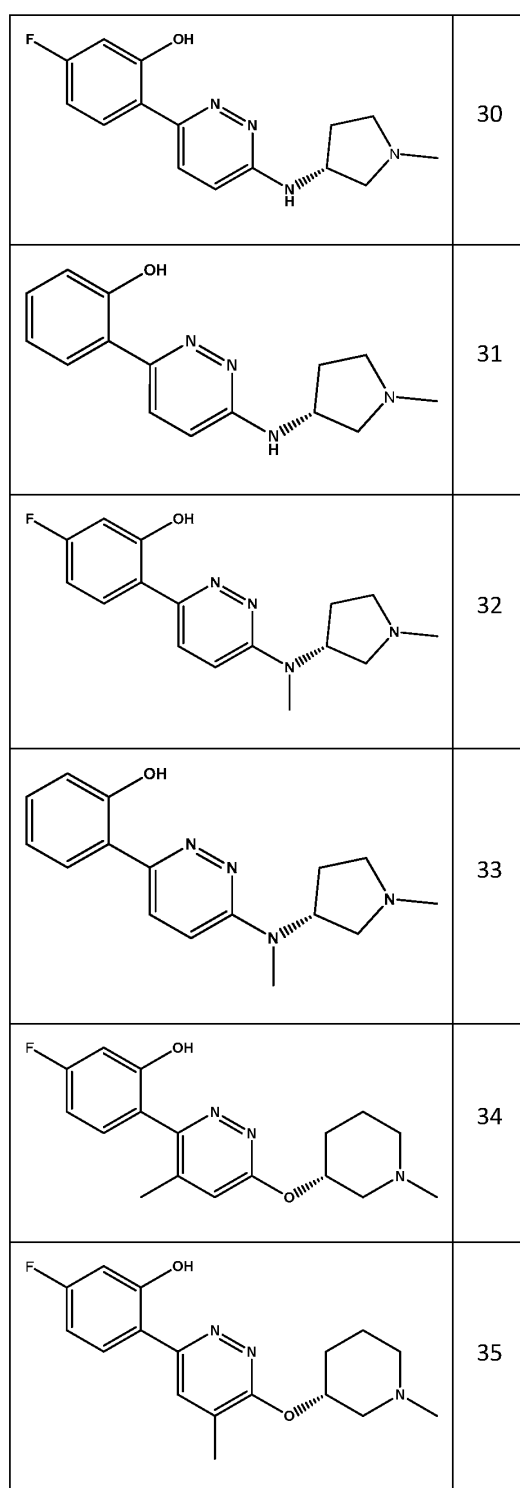
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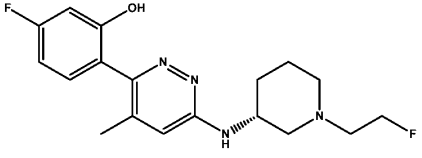
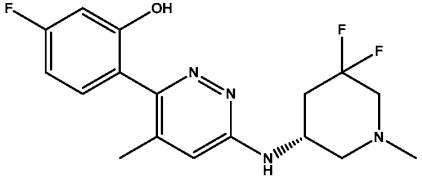
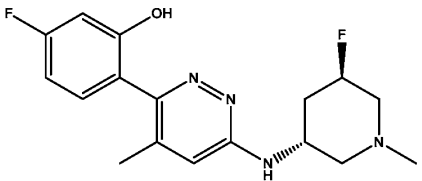
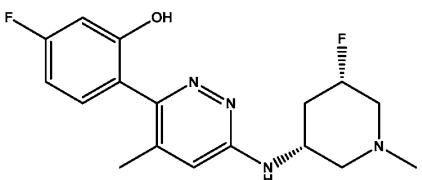
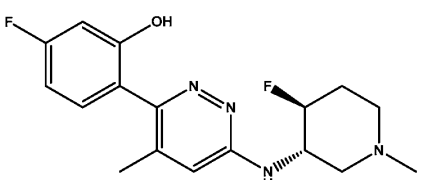
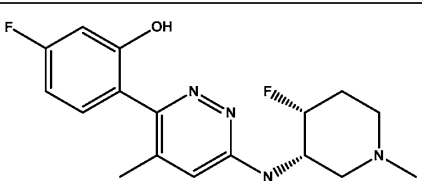
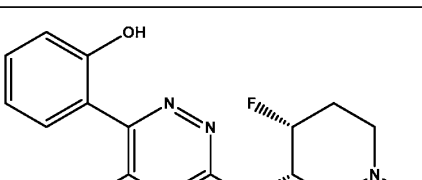
Representative compounds having Structure (I''')

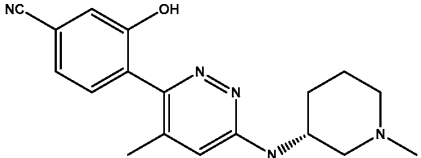
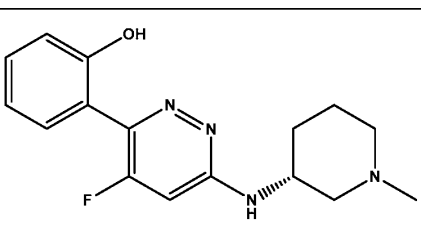
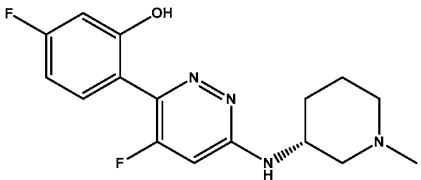
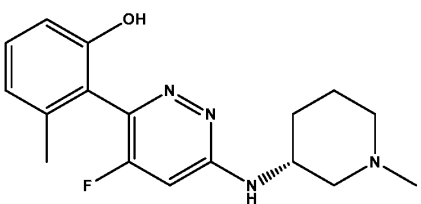
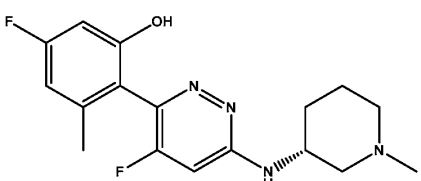
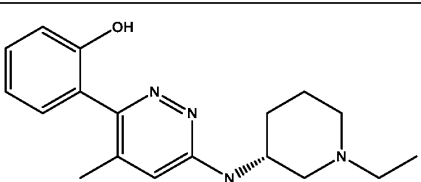
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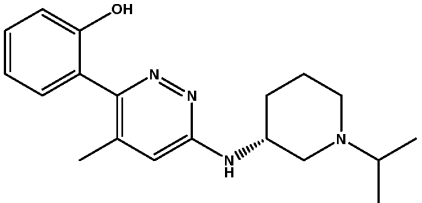
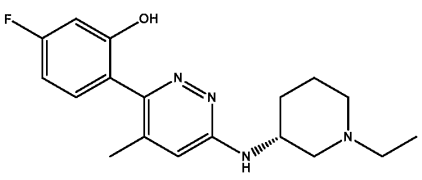
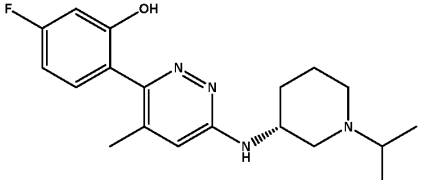
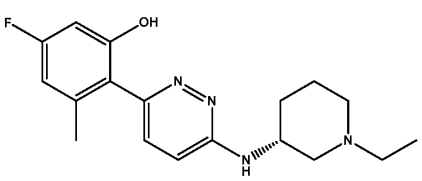
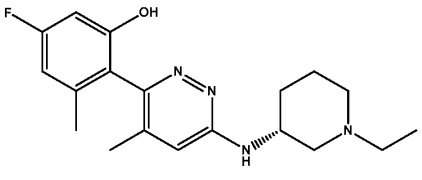
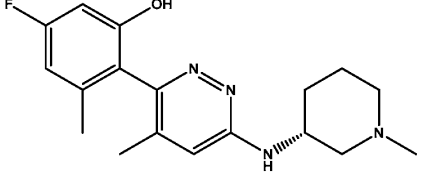
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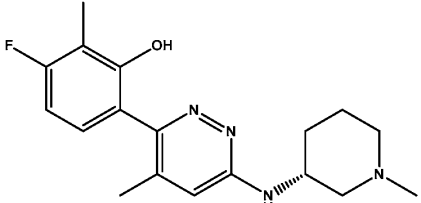
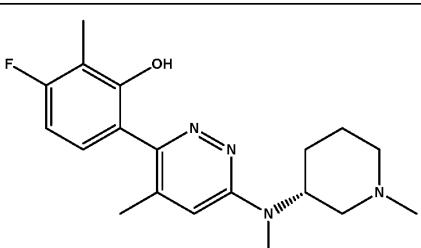
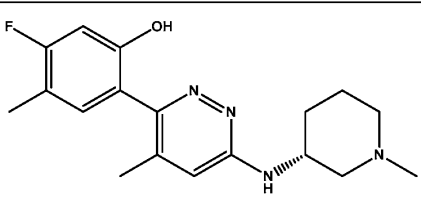
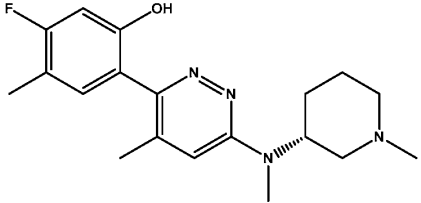
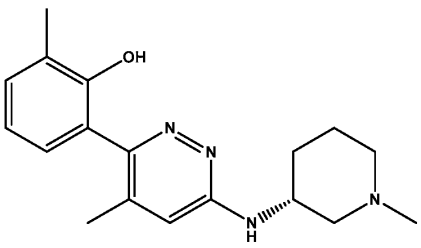
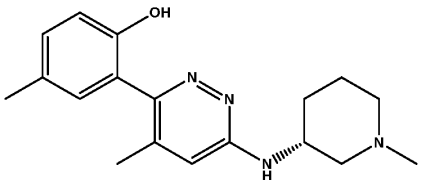
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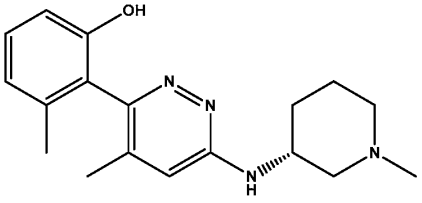
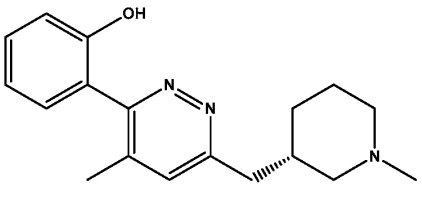
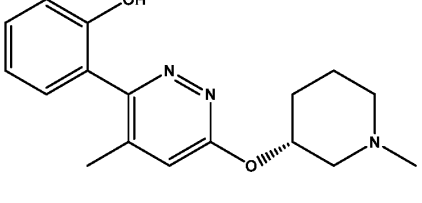
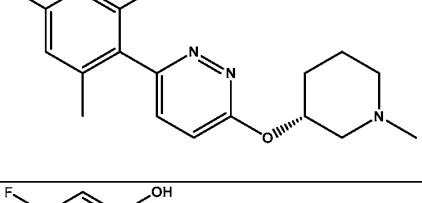
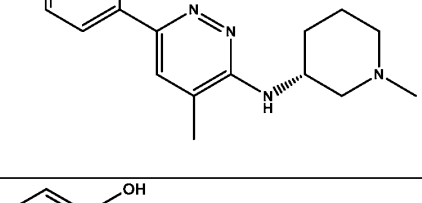
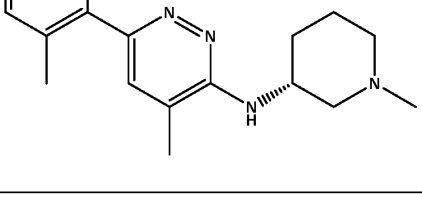


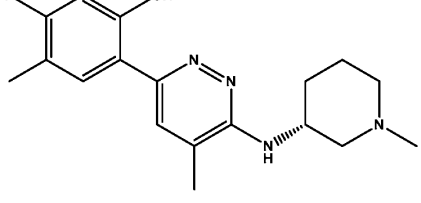
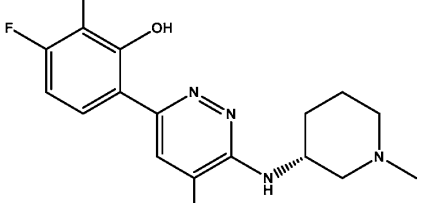
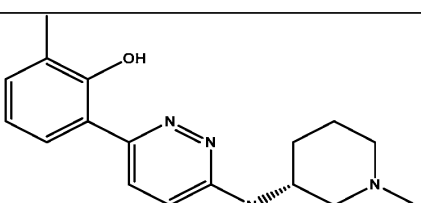
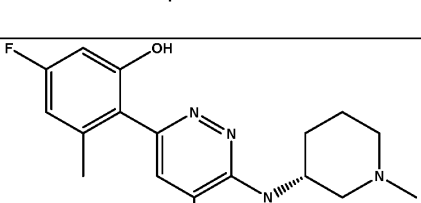
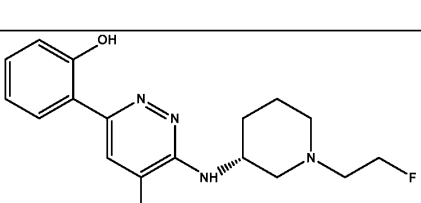
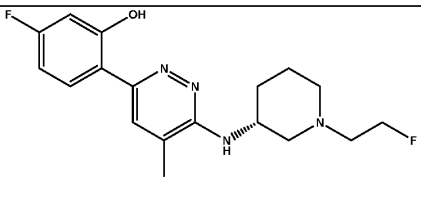
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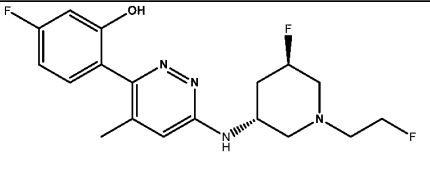
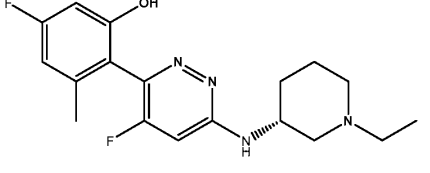
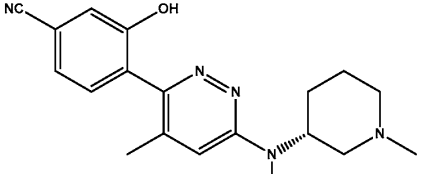
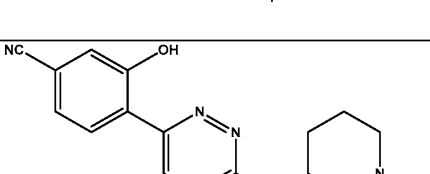
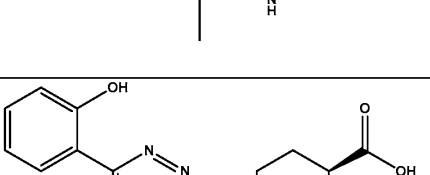
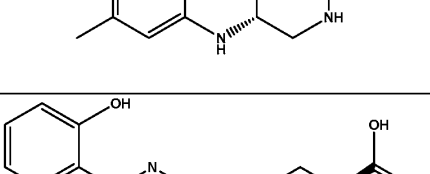
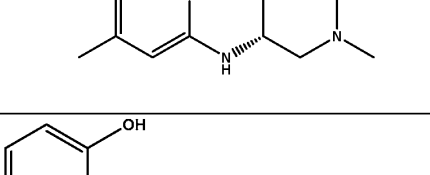
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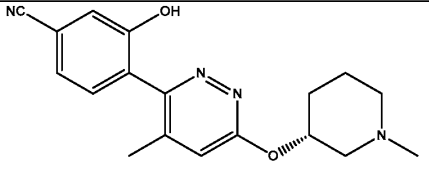
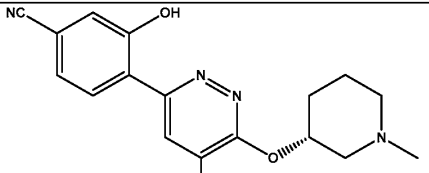
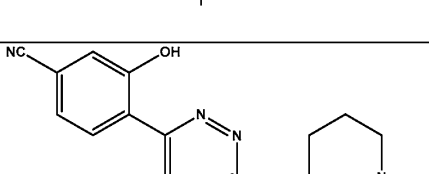
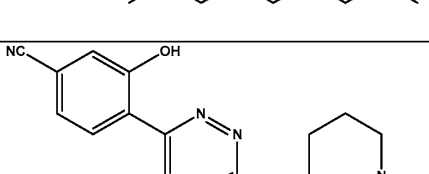
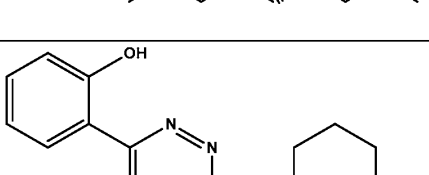
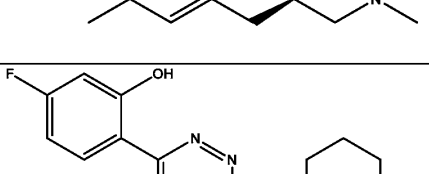
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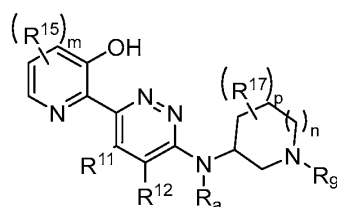
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In another embodiment, a compound is provided having structure (II):



(II)

5 or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C₁₋₆ alkyl;

each R¹⁵ is, independently, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OC₁₋₆ alkyl, OC₁₋₆ haloalkyl or C₃₋₅ cycloalkyl;

10 R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

R^{9'} is OH, halo or C₃₋₅ cycloalkyl;

each R¹⁷ is, independently, halo or CO₂H;

R¹¹ and R¹² are each, independently, is H, halo, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or OC₁₋₆ alkyl; and

15 n is 0-2;

m is 0-3; and

p is 0-9.

In more specific embodiments of Structure (II), as appropriate, such structures include the following more specific embodiments.

20 In one embodiment, one of R¹¹ and R¹² is H. In another embodiment, R¹¹ is C₁₋₆ alkyl and R¹² is H. In another embodiment, R¹¹ is H and R¹² is C₁₋₆ alkyl. In another embodiment, both R¹¹ and R¹² are H. In another embodiment, both R¹¹ and R¹² are not H. In some

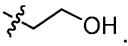
embodiments, R¹¹ is H, halo, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl or OC₁₋₆ alkyl, and R¹² is H. In some embodiments, R¹¹ is H, F, CN, methyl, CF₃ or OCH₃, and R¹² is H. In other embodiments, R¹¹ is H and R¹² is H, halo, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl or OC₁₋₆ alkyl. In other embodiments, R¹¹ is H and R¹² is H, F, CN, methyl, CF₃ or OCH₃.

5 In one embodiment, R¹¹ is H. In another embodiment, R¹¹ is halo. In certain embodiments R¹¹ is F. In other embodiments R¹¹ is Cl. In certain embodiments R¹¹ is Br. In specific embodiments R¹¹ is I. In some embodiments, R¹¹ is C₁₋₆ alkyl. In one embodiment, R¹¹ is methyl. In other embodiments, R¹¹ is ethyl. In additional embodiments, R¹¹ is propyl. In additional embodiments, R¹¹ is propyl. In further embodiments, R¹¹ is isopropyl. In other
10 embodiments, R¹¹ is n-butyl. In further embodiments, R¹¹ is sec-butyl. In some embodiments, R¹¹ is tert-butyl. In some embodiments, R¹¹ is CN. In some embodiments, R¹¹ is C₁₋₆ haloalkyl. In specific embodiments, R¹¹ is CF₃. In some embodiments, R¹¹ is OC₁₋₆ alkyl. In specific embodiments, R¹¹ is OCH₃.

In one embodiment, R¹² is H. In another embodiment, R¹² is halo. In certain
15 embodiments, R¹² is F. In other embodiments, R¹² is Cl. In certain embodiments, R¹² is Br. In specific embodiments, R¹² is I. In some embodiments, R¹² is C₁₋₆ alkyl. In one embodiment, R¹² is methyl. In other embodiments, R¹² is ethyl. In additional embodiments, R¹² is propyl. In additional embodiments, R¹² is propyl. In further embodiments, R¹² is isopropyl. In other
20 embodiments, R¹² is n-butyl. In further embodiments, R¹² is sec-butyl. In some embodiments, R¹² is tert-butyl. In some embodiments, R¹² is CN. In some embodiments, R¹² is C₁₋₆ haloalkyl. In specific embodiments, R¹² is CF₃. In some embodiments, R¹² is OC₁₋₆ alkyl. In specific embodiments, R¹² is OCH₃.

In one embodiment, R¹⁵ is CN, halo, or C₁₋₆ haloalkyl. In one embodiment, R¹⁵ is
CN, F, or CF₃. In one embodiment, R¹⁵ is halo. In certain embodiments, R¹⁵ is F. In other
25 embodiments, R¹⁵ is Cl. In certain embodiments R¹⁵ is Br. In specific embodiments R¹⁵ is I. In some embodiments, R¹⁵ is CN. In other embodiments, R¹⁵ is OH. In some embodiments, R¹⁵ is C₁₋₆ alkyl. In one embodiment, R¹⁵ is methyl. In other embodiments, R¹⁵ is ethyl. In additional
embodiments, R¹⁵ is propyl. In additional embodiments, R¹⁵ is propyl. In further embodiments, R¹⁵ is isopropyl. In other embodiments, R¹⁵ is n-butyl. In further embodiments, R¹⁵ is sec-butyl.
30 In some embodiments, R¹⁵ is tert-butyl. In some embodiments, R¹⁵ is C₁₋₆ haloalkyl. In specific

embodiments, R^{15} is CF_3 . In some embodiments, R^{15} is OC_{1-6} alkyl. In specific embodiments, R^{15} is OCH_3 . In some embodiments, R^{15} is OC_{1-6} haloalkyl. In specific embodiments, R^{15} is OCF_3 . In some embodiments, R^{15} is C_{3-5} cycloalkyl. In specific embodiments, R^{15} is cyclopropyl.

In one embodiment, R^9 is H. In another embodiment, R^9 is not H. In some
 5 embodiments, R^9 is C_{1-6} alkyl. In a specific embodiment, R^9 is methyl. In some embodiments, R^9 is ethyl. In certain embodiments, R^9 is isopropyl. In some embodiments, R^9 is C_{1-6} alkyl optionally substituted with one or more F. In another embodiment, R^9 is $-CH_2CH_2F$. In certain embodiments, R^9 is $-CH_2CHF_2$. In another embodiment, R^9 is $-CH_2CF_3$. In one embodiment, R^9 is C_{3-5} cycloalkyl. In a specific embodiment, R^9 is cyclopropyl. In another embodiment, R^9 is C_{1-6}
 10 alkyl optionally substituted with one or more C_{3-5} cycloalkyl. In certain embodiments, R^9 is . In another embodiment, R^9 is C_{1-6} alkyl optionally substituted with one or more OH. In some embodiments, R^9 is .

In one embodiment, $R^{9'}$ is OH. In one embodiment, $R^{9'}$ is halo. In yet other
 embodiments, $R^{9'}$ is F. In another embodiment, $R^{9'}$ is Cl. In additional embodiments, $R^{9'}$ is Br. In
 15 additional embodiments, $R^{9'}$ is I. In one embodiment, $R^{9'}$ is C_{3-5} cycloalkyl. In a specific
 embodiment, $R^{9'}$ is cyclopropyl.

In one embodiment, R^{17} is halo. In certain embodiments, R^{17} is F. In other
 embodiments, R^{17} is Cl. In certain embodiments R^{17} is Br. In specific embodiments R^{17} is I. In
 some embodiments, R^{17} is CO_2H .

20 In one embodiment, R_a is H. In another embodiment, R_a is C_{1-6} alkyl. In certain
 embodiments, R_a is methyl.

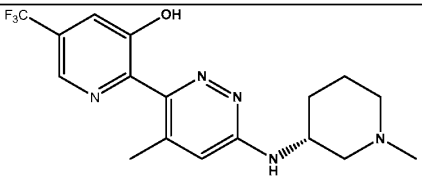
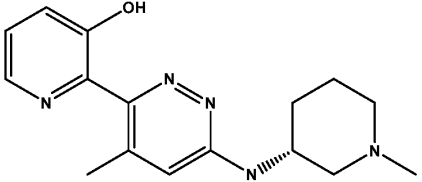
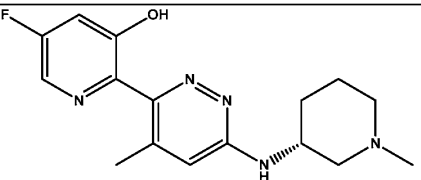
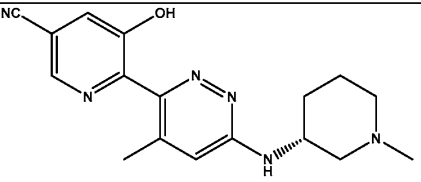
In one embodiment, n is 0-2. In one embodiment, n is 0 or 1. In other
 embodiments, n is 1 or 2. In yet other embodiments, n is 0 or 2. In some embodiments, n is 0.
 In other embodiments, n is 1. In other embodiments, n is 2.

25 In one embodiment, m is 0-3. In one embodiment, m is 0 or 1. In other
 embodiments, m is 1 or 2. In yet other embodiments, m is 0 or 2. In some embodiments, m is 0.
 In other embodiments, m is 1. In other embodiments, m is 2. In other embodiments, m is 3.

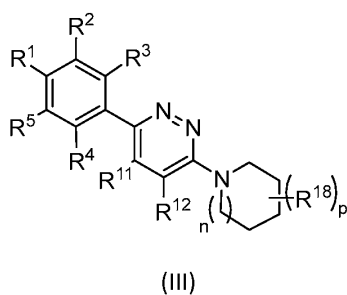
In one embodiment, p is 0-9. In one embodiment, p is 0-3. In one embodiment, p is 0 or 1. In other embodiments, p is 1 or 2. In yet other embodiments, p is 0 or 2. In some embodiments, p is 0. In other embodiments, p is 1. In other embodiments, p is 2. In other embodiments, p is 3.

5 In one embodiment, a compound is selected from one of the compounds listed in Table 3, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

Table 3
Representative compounds having Structure (II)

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In another embodiment, a compound is provided having structure (III):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof,
wherein:

R^1 is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl, OC_{1-6} haloalkyl or C_{3-5} cycloalkyl;

5 R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

10 R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

each R^{18} is halo, CO_2H , aminyl, C_{3-5} cycloalkyl, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

n is 1 or 2; and

15 p is 1-9.

In more specific embodiments of Structure (III), as appropriate, such structures include the following more specific embodiments.

20 In one embodiment, one of R^{11} and R^{12} is H. In another embodiment, R^{11} is C_{1-6} alkyl and R^{12} is H. In another embodiment, R^{11} is H and R^{12} is C_{1-6} alkyl. In another embodiment, both R^{11} and R^{12} are H. In another embodiment, both R^{11} and R^{12} are not H. In some embodiments, R^{11} is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl, and R^{12} is H. In some embodiments, R^{11} is H, F, CN, methyl, CF_3 or OCH_3 , and R^{12} is H. In other embodiments, R^{11} is H and R^{12} is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl. In other embodiments, R^{11} is H and R^{12} is H, F, CN, methyl, CF_3 or OCH_3 .

25 In one embodiment, R^{11} is H. In another embodiment, R^{11} is halo. In certain embodiments R^{11} is F. In other embodiments R^{11} is Cl. In certain embodiments R^{11} is Br. In specific embodiments R^{11} is I. In some embodiments, R^{11} is C_{1-6} alkyl. In one embodiment, R^{11} is

methyl. In other embodiments, R¹¹ is ethyl. In additional embodiments, R¹¹ is propyl. In additional embodiments, R¹¹ is propyl. In further embodiments, R¹¹ is isopropyl. In other embodiments, R¹¹ is n-butyl. In further embodiments, R¹¹ is sec-butyl. In some embodiments, R¹¹ is tert-butyl. In some embodiments, R¹¹ is CN. In some embodiments, R¹¹ is C₁₋₆ haloalkyl. In
5 specific embodiments, R¹¹ is CF₃. In some embodiments, R¹¹ is OC₁₋₆ alkyl. In specific embodiments, R¹¹ is OCH₃.

In one embodiment, R¹² is H. In another embodiment, R¹² is halo. In certain embodiments, R¹² is F. In other embodiments, R¹² is Cl. In certain embodiments, R¹² is Br. In specific embodiments, R¹² is I. In some embodiments, R¹² is C₁₋₆ alkyl. In one embodiment, R¹² is
10 methyl. In other embodiments, R¹² is ethyl. In additional embodiments, R¹² is propyl. In additional embodiments, R¹² is propyl. In further embodiments, R¹² is isopropyl. In other embodiments, R¹² is n-butyl. In further embodiments, R¹² is sec-butyl. In some embodiments, R¹² is tert-butyl. In some embodiments, R¹² is CN. In some embodiments, R¹² is C₁₋₆ haloalkyl. In specific embodiments, R¹² is CF₃. In some embodiments, R¹² is OC₁₋₆ alkyl. In specific
15 embodiments, R¹² is OCH₃.

In one embodiment, R¹ is H or CN. In one embodiment, R¹ is H. In one embodiment, R¹ is halo. In certain embodiments, R¹ is F. In other embodiments, R¹ is Cl. In certain embodiments R¹ is Br. In specific embodiments R¹ is I. In some embodiments, R¹ is CN. In other embodiments, R¹ is OH. In some embodiments, R¹ is C₁₋₆ alkyl. In one embodiment, R¹
20 is methyl. In other embodiments, R¹ is ethyl. In additional embodiments, R¹ is propyl. In additional embodiments, R¹ is propyl. In further embodiments, R¹ is isopropyl. In other embodiments, R¹ is n-butyl. In further embodiments, R¹ is sec-butyl. In some embodiments, R¹ is tert-butyl. In some embodiments, R¹ is C₁₋₆ haloalkyl. In specific embodiments, R¹ is CF₃. In some embodiments, R¹ is OC₁₋₆ alkyl. In specific embodiments, R¹ is OCH₃. In some
25 embodiments, R¹ is OC₁₋₆ haloalkyl. In specific embodiments, R¹ is OCF₃. In some embodiments, R¹ is C₃₋₅ cycloalkyl. In specific embodiments, R¹ is cyclopropyl.

In one embodiment, R² and R⁵ are each, independently, H, C₁₋₆ alkyl, F, Cl, CF₃, or CN. In another embodiment, R² is OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl, and R⁵ is H. In another embodiment, R² is H and R⁵ is OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl.

In one embodiment, R^2 is H. In another embodiment, R^2 is OH. In additional embodiments, R^2 is C_{1-6} haloalkyl. In some embodiments, R^2 is CF_3 . In additional embodiments, R^2 is C_{1-6} alkyl. In a specific embodiment, R^2 is methyl. In another embodiment, R^2 is ethyl. In another embodiment, R^2 is isopropyl. In yet other embodiments, R^2 is CN. In one embodiment, 5 R^2 is halo. In another embodiment, R^2 is F. In another embodiment, R^2 is Cl. In another embodiment, R^2 is Br. In another embodiment, R^2 is OC_{1-6} haloalkyl. In some embodiments, R^2 is OCF_3 . In another embodiment, R^2 is OC_{1-6} alkyl. In a specific embodiment, R^2 is OCH_3 .

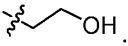
In one embodiment, R^5 is H. In another embodiment, R^5 is OH. In another embodiment, R^5 is C_{1-6} haloalkyl. In another embodiment, R^5 is CF_3 . In another embodiment, R^5 10 is C_{1-6} alkyl. In another embodiment, R^5 is methyl. In another embodiment, R^5 is ethyl. In another embodiment, R^5 is isopropyl. In another embodiment, R^5 is CN. In one embodiment, R^5 is halo. In another embodiment, R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is Br. In another embodiment, R^5 is OC_{1-6} haloalkyl. In another embodiment, R^5 is OCF_3 . In another embodiment, R^5 is OC_{1-6} alkyl. In another embodiment, R^5 is OCH_3 .

15 In one embodiment, R^3 is OH and R^4 is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl. In another embodiment, R^4 is OH and R^3 is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl. In yet other embodiments, R^3 is OH and R^4 is H or C_{1-6} alkyl. In another embodiment, R^4 is OH and R^3 is H or C_{1-6} alkyl.

In some embodiments, R^3 is OH. In another embodiment, R^3 is H. In another embodiment, R^3 is C_{1-6} haloalkyl. In one embodiment, R^3 is CF_3 . In another embodiment, R^3 is C_{1-6} 20 C_{1-6} alkyl. In a specific embodiment, R^3 is methyl. In another embodiment, R^3 is ethyl. In certain embodiments, R^3 is isopropyl. In another embodiment, R^3 is CN. In one embodiment, R^3 is halo. In some embodiments, R^3 is F. In another embodiment, R^3 is Cl. In one embodiment, R^3 is Br. In another embodiment, R^3 is OC_{1-6} haloalkyl. In another embodiment, R^3 is OCF_3 . In some 25 embodiments, R^3 is OC_{1-6} alkyl. In certain embodiments, R^3 is OCH_3 .

In one embodiment, R^4 is OH. In another embodiment, R^4 is H. In another embodiment, R^4 is C_{1-6} haloalkyl. In yet other embodiments, R^4 is CF_3 . In another embodiment, R^4 is C_{1-6} alkyl. In specific embodiments, R^4 is methyl. In another embodiment, R^4 is ethyl. In certain embodiments, R^4 is isopropyl. In another embodiment, R^4 is CN. In one embodiment, R^4

is halo. In yet other embodiments, R^4 is F. In another embodiment, R^4 is Cl. In additional embodiments, R^4 is Br. In another embodiment, R^4 is OC_{1-6} haloalkyl. In another embodiment, R^4 is OCF_3 . In other embodiments, R^4 is OC_{1-6} alkyl. In certain embodiments, R^4 is OCH_3 .

In one embodiment, R^{18} is halo. In certain embodiments, R^{18} is F. In other
 5 embodiments, R^{18} is Cl. In certain embodiments R^{18} is Br. In specific embodiments R^{18} is I. In
 some embodiments, R^{18} is CO_2H . In other embodiments, R^{18} is aminyl. In certain embodiments,
 R^{18} is $N(CH_3)_2$. In certain embodiments, R^{18} is $NH(CH_3)$. In some embodiments, R^{18} is C_{3-5}
 cycloalkyl. In specific embodiments, R^{18} is cyclopropyl. In some embodiments, R^{18} is C_{1-6} alkyl. In
 one embodiment, R^{18} is methyl. In other embodiments, R^{18} is ethyl. In additional embodiments,
 10 R^{18} is propyl. In additional embodiments, R^{18} is propyl. In further embodiments, R^{18} is isopropyl.
 In other embodiments, R^{18} is n-butyl. In further embodiments, R^{18} is sec-butyl. In some
 embodiments, R^{18} is tert-butyl. In some embodiments, R^{18} is C_{1-6} alkyl optionally substituted with
 one or more F. In another embodiment, R^{18} is $-CH_2CH_2F$. In certain embodiments, R^{18} is $-CH_2CHF_2$.
 In another embodiment, R^{18} is $-CH_2CF_3$. In one embodiment, R^{18} is C_{3-5} cycloalkyl. In a specific
 15 embodiment, R^{18} is cyclopropyl. In another embodiment, R^{18} is C_{1-6} alkyl optionally substituted
 with one or more C_{3-5} cycloalkyl. In certain embodiments, R^{18} is . In another
 embodiment, R^{18} is C_{1-6} alkyl optionally substituted with one or more OH. In some embodiments,
 R^{18} is .

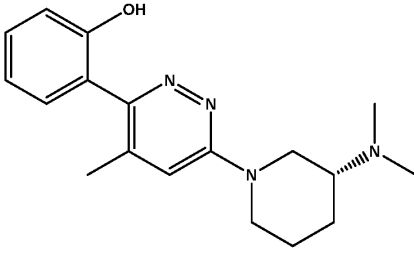
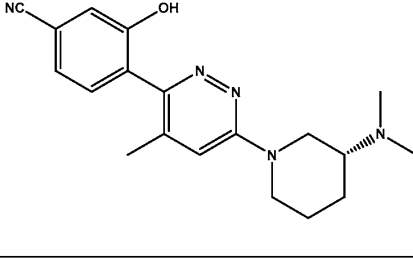
In one embodiment, $R^{9'}$ is OH. In one embodiment, $R^{9'}$ is halo. In yet other
 20 embodiments, $R^{9'}$ is F. In another embodiment, $R^{9'}$ is Cl. In additional embodiments, $R^{9'}$ is Br. In
 additional embodiments, $R^{9'}$ is I. In one embodiment, $R^{9'}$ is C_{3-5} cycloalkyl. In a specific
 embodiment, $R^{9'}$ is cyclopropyl.

In one embodiment, n is 1 or 2. In other embodiments, n is 1. In other
 embodiments, n is 2.

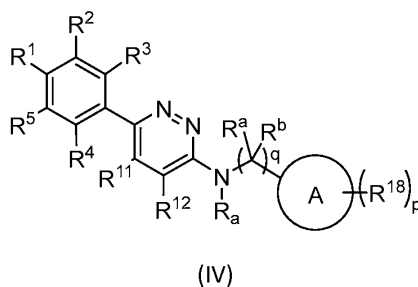
25 In one embodiment, p is 1-9. In one embodiment, p is 1-3. In other
 embodiments, p is 1 or 2. In yet other embodiments, p is 2 or 3. In yet other embodiments, p is
 1 or 3. In other embodiments, p is 1. In other embodiments, p is 2. In other embodiments, p is
 3.

In one embodiment, a compound is selected from one of the compounds listed in Table 4, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

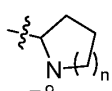
Table 4
Representative compounds having Structure (III)

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In another embodiment, a compound is provided having structure (IV):



5 or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

ring A is C₃₋₈ cycloalkyl,  or a saturated heterocyclic ring wherein the heteroatoms consist of 1-2 oxygen atoms;

each R_a and R_b are each, independently, H or C₁₋₆ alkyl;

R^1 is H, halo, OH, CN, C_{1-6} alkyl, OC_{1-6} alkyl, OC_{1-6} haloalkyl or C_{3-5} cycloalkyl;

R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl,
 5 OC_{1-6} alkyl or OC_{1-6} haloalkyl;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

R^{18} is halo, CO_2H , aminyl, C_{3-5} cycloalkyl, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is
 10 optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

n is 0, 1 or 2;

p is 0-9; and

q is 1-3.

15 provided that when R^1 is H and A is  then R^9 is not unsubstituted ethyl.

In more specific embodiments of Structure (IV), as appropriate, such structures include the following more specific embodiments.

In one embodiment, one of R^{11} and R^{12} is H. In another embodiment, R^{11} is C_{1-6} alkyl and R^{12} is H. In another embodiment, R^{11} is H and R^{12} is C_{1-6} alkyl. In another embodiment, both R^{11} and R^{12} are H. In another embodiment, both R^{11} and R^{12} are not H. In some
 20 embodiments, R^{11} is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl, and R^{12} is H. In some embodiments, R^{11} is H, F, CN, methyl, CF_3 or OCH_3 , and R^{12} is H. In other embodiments, R^{11} is H and R^{12} is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl. In other embodiments, R^{11} is H and
 25 R^{12} is H, F, CN, methyl, CF_3 or OCH_3 .

In one embodiment, R^{11} is H. In another embodiment, R^{11} is halo. In certain embodiments R^{11} is F. In other embodiments R^{11} is Cl. In certain embodiments R^{11} is Br. In specific embodiments R^{11} is I. In some embodiments, R^{11} is C_{1-6} alkyl. In one embodiment, R^{11} is methyl. In other embodiments, R^{11} is ethyl. In additional embodiments, R^{11} is propyl. In 5 additional embodiments, R^{11} is propyl. In further embodiments, R^{11} is isopropyl. In other embodiments, R^{11} is n-butyl. In further embodiments, R^{11} is sec-butyl. In some embodiments, R^{11} is tert-butyl. In some embodiments, R^{11} is CN. In some embodiments, R^{11} is C_{1-6} haloalkyl. In specific embodiments, R^{11} is CF_3 . In some embodiments, R^{11} is OC_{1-6} alkyl. In specific embodiments, R^{11} is OCH_3 .

10 In one embodiment, R^{12} is H. In another embodiment, R^{12} is halo. In certain embodiments, R^{12} is F. In other embodiments, R^{12} is Cl. In certain embodiments, R^{12} is Br. In specific embodiments, R^{12} is I. In some embodiments, R^{12} is C_{1-6} alkyl. In one embodiment, R^{12} is methyl. In other embodiments, R^{12} is ethyl. In additional embodiments, R^{12} is propyl. In additional embodiments, R^{12} is propyl. In further embodiments, R^{12} is isopropyl. In other 15 embodiments, R^{12} is n-butyl. In further embodiments, R^{12} is sec-butyl. In some embodiments, R^{12} is tert-butyl. In some embodiments, R^{12} is CN. In some embodiments, R^{12} is C_{1-6} haloalkyl. In specific embodiments, R^{12} is CF_3 . In some embodiments, R^{12} is OC_{1-6} alkyl. In specific embodiments, R^{12} is OCH_3 .

In one embodiment, R^1 is H. In one embodiment, R^1 is halo. In certain 20 embodiments, R^1 is F. In other embodiments, R^1 is Cl. In certain embodiments R^1 is Br. In specific embodiments R^1 is I. In some embodiments, R^1 is CN. In other embodiments, R^1 is OH. In some embodiments, R^1 is C_{1-6} alkyl. In one embodiment, R^1 is methyl. In other embodiments, R^1 is ethyl. In additional embodiments, R^1 is propyl. In additional embodiments, R^1 is propyl. In further embodiments, R^1 is isopropyl. In other embodiments, R^1 is n-butyl. In further embodiments, R^1 25 is sec-butyl. In some embodiments, R^1 is tert-butyl. In some embodiments, R^1 is OC_{1-6} alkyl. In specific embodiments, R^1 is OCH_3 . In some embodiments, R^1 is OC_{1-6} haloalkyl. In specific embodiments, R^1 is OCF_3 . In some embodiments, R^1 is C_{3-5} cycloalkyl. In specific embodiments, R^1 is cyclopropyl.

In one embodiment, R^2 and R^5 are each, independently, H, C_{1-6} alkyl, F, Cl, CF_3 , or CN. In another embodiment, R^2 is OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl, and R^5 is H. In another embodiment, R^2 is H and R^5 is OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl.

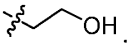
In one embodiment, R^2 is H. In another embodiment, R^2 is OH. In additional
5 embodiments, R^2 is C_{1-6} haloalkyl. In some embodiments, R^2 is CF_3 . In additional embodiments, R^2 is C_{1-6} alkyl. In a specific embodiment, R^2 is methyl. In another embodiment, R^2 is ethyl. In another embodiment, R^2 is isopropyl. In yet other embodiments, R^2 is CN. In one embodiment, R^2 is halo. In another embodiment, R^2 is F. In another embodiment, R^2 is Cl. In another embodiment, R^2 is Br. In another embodiment, R^2 is OC_{1-6} haloalkyl. In some embodiments, R^2 is
10 OCF_3 . In another embodiment, R^2 is OC_{1-6} alkyl. In a specific embodiment, R^2 is OCH_3 .

In one embodiment, R^5 is H. In another embodiment, R^5 is OH. In another embodiment, R^5 is C_{1-6} haloalkyl. In another embodiment, R^5 is CF_3 . In another embodiment, R^5 is C_{1-6} alkyl. In another embodiment, R^5 is methyl. In another embodiment, R^5 is ethyl. In another embodiment, R^5 is isopropyl. In another embodiment, R^5 is CN. In one embodiment, R^5 is halo.
15 In another embodiment, R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is Br. In another embodiment, R^5 is OC_{1-6} haloalkyl. In another embodiment, R^5 is OCF_3 . In another embodiment, R^5 is OC_{1-6} alkyl. In another embodiment, R^5 is OCH_3 .

In one embodiment, R^3 is OH and R^4 is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl. In another embodiment, R^4 is OH and R^3 is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or
20 OC_{1-6} alkyl. In yet other embodiments, R^3 is OH and R^4 is H or C_{1-6} alkyl. In another embodiment, R^4 is OH and R^3 is H or C_{1-6} alkyl.

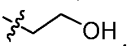
In some embodiments, R^3 is OH. In another embodiment, R^3 is H. In another embodiment, R^3 is C_{1-6} haloalkyl. In one embodiment, R^3 is CF_3 . In another embodiment, R^3 is C_{1-6} alkyl. In a specific embodiment, R^3 is methyl. In another embodiment, R^3 is ethyl. In certain
25 embodiments, R^3 is isopropyl. In another embodiment, R^3 is CN. In one embodiment, R^3 is halo. In some embodiments, R^3 is F. In another embodiment, R^3 is Cl. In one embodiment, R^3 is Br. In another embodiment, R^3 is OC_{1-6} haloalkyl. In another embodiment, R^3 is OCF_3 . In some embodiments, R^3 is OC_{1-6} alkyl. In certain embodiments, R^3 is OCH_3 .

In one embodiment, R^4 is OH. In another embodiment, R^4 is H. In another embodiment, R^4 is C_{1-6} haloalkyl. In yet other embodiments, R^4 is CF_3 . In another embodiment, R^4 is C_{1-6} alkyl. In specific embodiments, R^4 is methyl. In another embodiment, R^4 is ethyl. In certain embodiments, R^4 is isopropyl. In another embodiment, R^4 is CN. In one embodiment, R^4 is halo. In yet other embodiments, R^4 is F. In another embodiment, R^4 is Cl. In additional embodiments, R^4 is Br. In another embodiment, R^4 is OC_{1-6} haloalkyl. In another embodiment, R^4 is OCF_3 . In other embodiments, R^4 is OC_{1-6} alkyl. In certain embodiments, R^4 is OCH_3 .

In one embodiment, R^9 is H. In another embodiment, R^9 is not H. In some embodiments, R^9 is C_{1-6} alkyl. In a specific embodiment, R^9 is methyl. In some embodiments, R^9 is ethyl. In certain embodiments, R^9 is isopropyl. In some embodiments, R^9 is C_{1-6} alkyl optionally substituted with one or more F. In another embodiment, R^9 is $-CH_2CH_2F$. In certain embodiments, R^9 is $-CH_2CHF_2$. In another embodiment, R^9 is $-CH_2CF_3$. In one embodiment, R^9 is C_{3-5} cycloalkyl. In a specific embodiment, R^9 is cyclopropyl. In another embodiment, R^9 is C_{1-6} alkyl optionally substituted with one or more C_{3-5} cycloalkyl. In certain embodiments, R^9 is . In another embodiment, R^9 is C_{1-6} alkyl optionally substituted with one or more OH. In some embodiments, R^9 is .

In one embodiment, $R^{9'}$ is OH. In one embodiment, $R^{9'}$ is halo. In yet other embodiments, $R^{9'}$ is F. In another embodiment, $R^{9'}$ is Cl. In additional embodiments, $R^{9'}$ is Br. In additional embodiments, $R^{9'}$ is I. In one embodiment, $R^{9'}$ is C_{3-5} cycloalkyl. In a specific embodiment, $R^{9'}$ is cyclopropyl.

In one embodiment, R^{18} is halo. In certain embodiments, R^{18} is F. In other embodiments, R^{18} is Cl. In certain embodiments R^{18} is Br. In specific embodiments R^{18} is I. In some embodiments, R^{18} is CO_2H . In other embodiments, R^{18} is aminyl. In certain embodiments, R^{18} is $N(CH_3)_2$. In certain embodiments, R^{18} is $NH(CH_3)$. In some embodiments, R^{18} is C_{3-5} cycloalkyl. In specific embodiments, R^{18} is cyclopropyl. In some embodiments, R^{18} is C_{1-6} alkyl. In one embodiment, R^{18} is methyl. In other embodiments, R^{18} is ethyl. In additional embodiments, R^{18} is propyl. In additional embodiments, R^{18} is propyl. In further embodiments, R^{18} is isopropyl. In other embodiments, R^{18} is n-butyl. In further embodiments, R^{18} is sec-butyl. In some embodiments, R^{18} is tert-butyl. In some embodiments, R^{18} is C_{1-6} alkyl optionally substituted with

one or more F. In another embodiment, R¹⁸ is -CH₂CH₂F. In certain embodiments, R¹⁸ is -CH₂CHF₂. In another embodiment, R¹⁸ is -CH₂CF₃. In one embodiment, R¹⁸ is C₃₋₅ cycloalkyl. In a specific embodiment, R¹⁸ is cyclopropyl. In another embodiment, R¹⁸ is C₁₋₆ alkyl optionally substituted with one or more C₃₋₅ cycloalkyl. In certain embodiments, R¹⁸ is . In another embodiment, R¹⁸ is C₁₋₆ alkyl optionally substituted with one or more OH. In some embodiments, R¹⁸ is .

In one embodiment, R_a is H. In another embodiment, R_a is C₁₋₆ alkyl. In certain embodiments, R_a is methyl.

In one embodiment, R_b is H. In another embodiment, R_b is C₁₋₆ alkyl. In certain embodiments, R_b is methyl.

In one embodiment, n is 0-2. In one embodiment, n is 0 or 1. In other embodiments, n is 1 or 2. In yet other embodiments, n is 0 or 2. In some embodiments, n is 0. In other embodiments, n is 1. In other embodiments, n is 2.

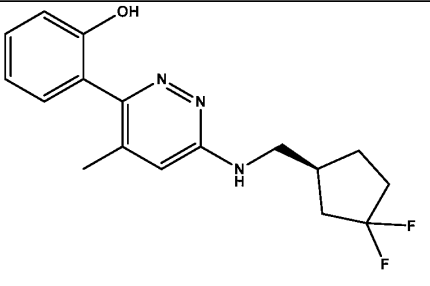
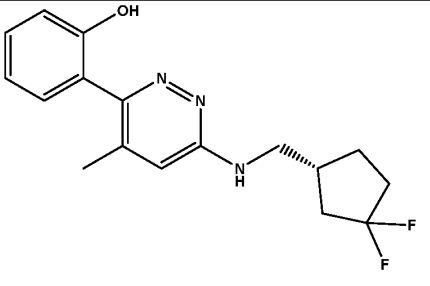
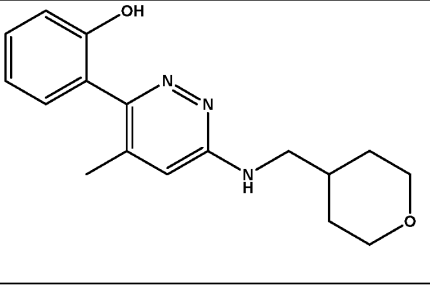
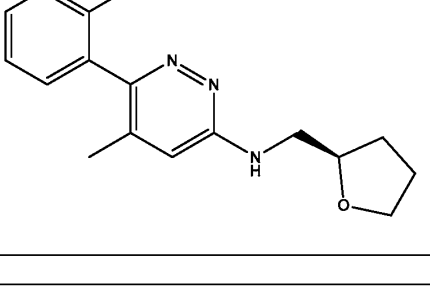
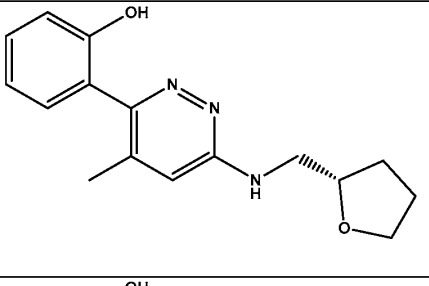
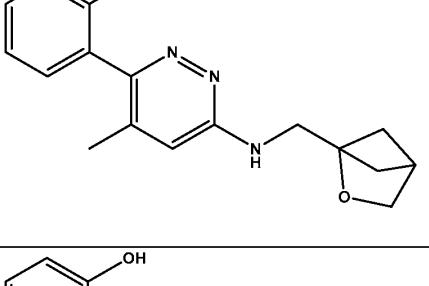
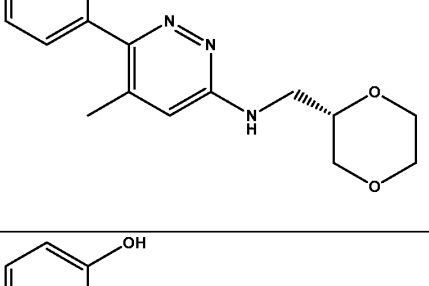
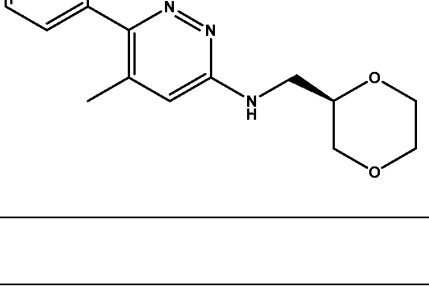
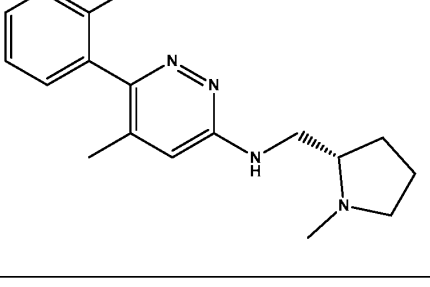
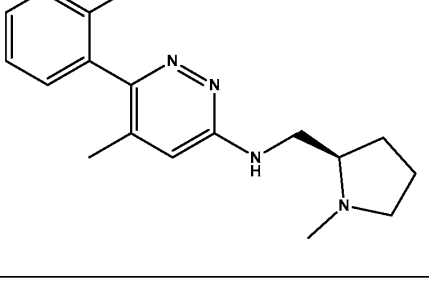
In one embodiment, p is 0-9. In one embodiment, p is 0-3. In one embodiment, p is 0 or 1. In other embodiments, p is 1 or 2. In yet other embodiments, p is 0 or 2. In some embodiments, p is 0. In other embodiments, p is 1. In other embodiments, p is 2. In other embodiments, p is 3.

In one embodiment, q is 1-3. In other embodiments, q is 1 or 2. In yet other embodiments, q is 1 or 3. In some embodiments, q is 2 or 3. In other embodiments, q is 1. In other embodiments, q is 2. In other embodiments, q is 3.

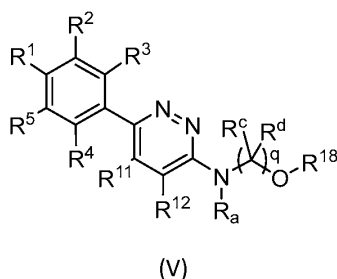
In one embodiment, a compound is selected from one of the compounds listed in Table 5, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

Table 5

Representative compounds having Structure (IV)

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In another embodiment, a compound is provided having structure (V):



5 or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C_{1-6} alkyl;

each R_c and R_d are each, independently, H or C_{1-6} alkyl, or R_c and R_d join together to form oxo;

10 R^1 is H, halo, OH, CN, C_{1-6} alkyl, OC_{1-6} alkyl, OC_{1-6} haloalkyl or C_{3-5} cycloalkyl;

R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

15 R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

R^{18} is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl; and

20 q is 1-3.

In more specific embodiments of Structure (V), as appropriate, such structures include the following more specific embodiments.

In one embodiment, one of R^{11} and R^{12} is H. In another embodiment, R^{11} is C_{1-6} alkyl and R^{12} is H. In another embodiment, R^{11} is H and R^{12} is C_{1-6} alkyl. In another embodiment, both R^{11} and R^{12} are H. In another embodiment, both R^{11} and R^{12} are not H. In some embodiments, R^{11} is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl, and R^{12} is H. In some
5 embodiments, R^{11} is H, F, CN, methyl, CF_3 or OCH_3 , and R^{12} is H. In other embodiments, R^{11} is H and R^{12} is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl. In other embodiments, R^{11} is H and R^{12} is H, F, CN, methyl, CF_3 or OCH_3 .

In one embodiment, R^{11} is H. In another embodiment, R^{11} is halo. In certain embodiments R^{11} is F. In other embodiments R^{11} is Cl. In certain embodiments R^{11} is Br. In
10 specific embodiments R^{11} is I. In some embodiments, R^{11} is C_{1-6} alkyl. In one embodiment, R^{11} is methyl. In other embodiments, R^{11} is ethyl. In additional embodiments, R^{11} is propyl. In additional embodiments, R^{11} is propyl. In further embodiments, R^{11} is isopropyl. In other embodiments, R^{11} is n-butyl. In further embodiments, R^{11} is sec-butyl. In some embodiments, R^{11} is tert-butyl. In some embodiments, R^{11} is CN. In some embodiments, R^{11} is C_{1-6} haloalkyl. In
15 specific embodiments, R^{11} is CF_3 . In some embodiments, R^{11} is OC_{1-6} alkyl. In specific embodiments, R^{11} is OCH_3 .

In one embodiment, R^{12} is H. In another embodiment, R^{12} is halo. In certain embodiments, R^{12} is F. In other embodiments, R^{12} is Cl. In certain embodiments, R^{12} is Br. In
20 specific embodiments, R^{12} is I. In some embodiments, R^{12} is C_{1-6} alkyl. In one embodiment, R^{12} is methyl. In other embodiments, R^{12} is ethyl. In additional embodiments, R^{12} is propyl. In additional embodiments, R^{12} is propyl. In further embodiments, R^{12} is isopropyl. In other embodiments, R^{12} is n-butyl. In further embodiments, R^{12} is sec-butyl. In some embodiments, R^{12} is tert-butyl. In some embodiments, R^{12} is CN. In some embodiments, R^{12} is C_{1-6} haloalkyl. In
25 specific embodiments, R^{12} is CF_3 . In some embodiments, R^{12} is OC_{1-6} alkyl. In specific embodiments, R^{12} is OCH_3 .

In one embodiment, R^1 is H. In one embodiment, R^1 is halo. In certain embodiments, R^1 is F. In other embodiments, R^1 is Cl. In certain embodiments R^1 is Br. In specific
embodiments R^1 is I. In some embodiments, R^1 is CN. In other embodiments, R^1 is OH. In some
embodiments, R^1 is C_{1-6} alkyl. In one embodiment, R^1 is methyl. In other embodiments, R^1 is
30 ethyl. In additional embodiments, R^1 is propyl. In additional embodiments, R^1 is propyl. In further

embodiments, R^1 is isopropyl. In other embodiments, R^1 is n-butyl. In further embodiments, R^1 is sec-butyl. In some embodiments, R^1 is tert-butyl. In some embodiments, R^1 is OC_{1-6} alkyl. In specific embodiments, R^1 is OCH_3 . In some embodiments, R^1 is OC_{1-6} haloalkyl. In specific embodiments, R^1 is OCF_3 . In some embodiments, R^1 is C_{3-5} cycloalkyl. In specific embodiments,
 5 R^1 is cyclopropyl.

In one embodiment, R^2 and R^5 are each, independently, H, C_{1-6} alkyl, F, Cl, CF_3 , or CN. In another embodiment, R^2 is OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl, and R^5 is H. In another embodiment, R^2 is H and R^5 is OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl.

In one embodiment, R^2 is H. In another embodiment, R^2 is OH. In additional
 10 embodiments, R^2 is C_{1-6} haloalkyl. In some embodiments, R^2 is CF_3 . In additional embodiments, R^2 is C_{1-6} alkyl. In a specific embodiment, R^2 is methyl. In another embodiment, R^2 is ethyl. In another embodiment, R^2 is isopropyl. In yet other embodiments, R^2 is CN. In one embodiment, R^2 is halo. In another embodiment, R^2 is F. In another embodiment, R^2 is Cl. In another embodiment, R^2 is Br. In another embodiment, R^2 is OC_{1-6} haloalkyl. In some embodiments, R^2 is
 15 OCF_3 . In another embodiment, R^2 is OC_{1-6} alkyl. In a specific embodiment, R^2 is OCH_3 .

In one embodiment, R^5 is H. In another embodiment, R^5 is OH. In another embodiment, R^5 is C_{1-6} haloalkyl. In another embodiment, R^5 is CF_3 . In another embodiment, R^5 is C_{1-6} alkyl. In another embodiment, R^5 is methyl. In another embodiment, R^5 is ethyl. In another embodiment, R^5 is isopropyl. In another embodiment, R^5 is CN. In one embodiment, R^5 is halo.
 20 In another embodiment, R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is Br. In another embodiment, R^5 is OC_{1-6} haloalkyl. In another embodiment, R^5 is OCF_3 . In another embodiment, R^5 is OC_{1-6} alkyl. In another embodiment, R^5 is OCH_3 .

In one embodiment, R^3 is OH and R^4 is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or OC_{1-6} alkyl. In another embodiment, R^4 is OH and R^3 is H, OH, CF_3 , C_{1-6} alkyl, CN, halo, OCF_3 or
 25 OC_{1-6} alkyl. In yet other embodiments, R^3 is OH and R^4 is H or C_{1-6} alkyl. In another embodiment, R^4 is OH and R^3 is H or C_{1-6} alkyl.

In some embodiments, R^3 is OH. In another embodiment, R^3 is H. In another embodiment, R^3 is C_{1-6} haloalkyl. In one embodiment, R^3 is CF_3 . In another embodiment, R^3 is C_{1-6} alkyl. In a specific embodiment, R^3 is methyl. In another embodiment, R^3 is ethyl. In certain

embodiments, R^3 is isopropyl. In another embodiment, R^3 is CN. In one embodiment, R^3 is halo. In some embodiments, R^3 is F. In another embodiment, R^3 is Cl. In one embodiment, R^3 is Br. In another embodiment, R^3 is OC_{1-6} haloalkyl. In another embodiment, R^3 is OCF_3 . In some embodiments, R^3 is OC_{1-6} alkyl. In certain embodiments, R^3 is OCH_3 .

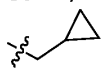
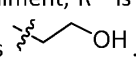
5 In one embodiment, R^4 is OH. In another embodiment, R^4 is H. In another embodiment, R^4 is C_{1-6} haloalkyl. In yet other embodiments, R^4 is CF_3 . In another embodiment, R^4 is C_{1-6} alkyl. In specific embodiments, R^4 is methyl. In another embodiment, R^4 is ethyl. In certain embodiments, R^4 is isopropyl. In another embodiment, R^4 is CN. In one embodiment, R^4 is halo. In yet other embodiments, R^4 is F. In another embodiment, R^4 is Cl. In additional
10 embodiments, R^4 is Br. In another embodiment, R^4 is OC_{1-6} haloalkyl. In another embodiment, R^4 is OCF_3 . In other embodiments, R^4 is OC_{1-6} alkyl. In certain embodiments, R^4 is OCH_3 .

In one embodiment, R_a is H. In another embodiment, R_a is C_{1-6} alkyl. In certain embodiments, R_a is methyl.

In one embodiment, R_c is H. In another embodiment, R_c is C_{1-6} alkyl. In certain
15 embodiments, R_c is methyl.

In one embodiment, R_d is H. In another embodiment, R_d is C_{1-6} alkyl. In certain embodiments, R_d is methyl.

In one embodiment, R_c and R_d join together to form oxo.

In some embodiments, R^{19} is C_{1-6} alkyl. In a specific embodiment, R^{19} is methyl.
20 In some embodiments, R^{19} is ethyl. In certain embodiments, R^{19} is isopropyl. In some embodiments, R^{19} is C_{1-6} alkyl optionally substituted with one or more F. In another embodiment, R^{19} is $-CH_2CH_2F$. In certain embodiments, R^{19} is $-CH_2CHF_2$. In another embodiment, R^{19} is $-CH_2CF_3$. In one embodiment, R^{19} is C_{3-5} cycloalkyl. In a specific embodiment, R^{19} is cyclopropyl. In another embodiment, R^{19} is C_{1-6} alkyl optionally substituted with one or more C_3 -
25 C_5 cycloalkyl. In certain embodiments, R^{19} is . In another embodiment, R^{19} is C_{1-6} alkyl optionally substituted with one or more OH. In some embodiments, R^{19} is .

In one embodiment, $R^{9'}$ is OH. In one embodiment, $R^{9'}$ is halo. In yet other embodiments, $R^{9'}$ is F. In another embodiment, $R^{9'}$ is Cl. In additional embodiments, $R^{9'}$ is Br. In

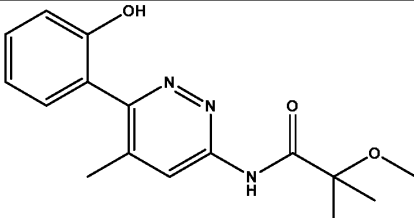
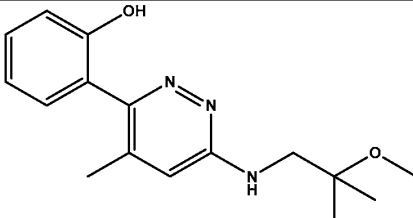
additional embodiments, $R^{9'}$ is H. In one embodiment, $R^{9'}$ is C_{3-5} cycloalkyl. In a specific embodiment, $R^{9'}$ is cyclopropyl.

In one embodiment, q is 1-3. In other embodiments, q is 1 or 2. In yet other embodiments, q is 1 or 3. In some embodiments, q is 2 or 3. In other embodiments, q is 1. In
 5 other embodiments, q is 2. In other embodiments, q is 3.

In one embodiment, a compound is selected from one of the compounds listed in Table 6, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

Table 6

Representative compounds having Structure (V)

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Pharmaceutical Compositions

In certain embodiments, the invention provides a pharmaceutical composition comprising a compound of structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''),
 5 (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, together with at least one pharmaceutically acceptable carrier, diluent, or excipient. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which can be in the form of an ampoule, capsule, sachet, paper, or other container. When the active compound is mixed with

a carrier, or when the carrier serves as a diluent, it can be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid carrier, for example contained in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid, or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose, and polyvinylpyrrolidone. Similarly, the carrier or diluent can include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

As used herein, the term "pharmaceutical composition" refers to a composition containing one or more of the compounds described herein, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, formulated with a pharmaceutically acceptable carrier, which can also include other additives, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); for administration to a pediatric subject (e.g., solution, syrup, suspension, elixir, powder for reconstitution as suspension or solution, dispersible/effervescent tablet, chewable tablet, lollipop, freezer pops, troches, oral thin strips, orally disintegrating tablet, orally disintegrating strip, and sprinkle oral powder or granules); or in any other formulation described herein. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington: The Science and Practice of Pharmacy, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005) and in The United States Pharmacopeia: The National Formulary (USP 36 NF31), published in 2013.

In some embodiments, the pharmaceutical composition comprising a compound of structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-

1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, with at least one pharmaceutically acceptable carrier, diluent, or excipient further comprises a second therapeutic agent.

As used herein, the term "pharmaceutically acceptable carrier" refers to any
5 ingredient other than the disclosed compounds, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof (e.g., a carrier capable of suspending or dissolving the active compound) and having the properties of being nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers
10 (diluent), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin,
15 hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium
20 dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

The formulations can be mixed with auxiliary agents which do not deleteriously react with the active compounds. Such additives can include wetting agents, emulsifying and suspending agents, salt for influencing osmotic pressure, buffers and/or coloring substances, preserving agents, sweetening agents, or flavoring agents. The compositions can also be
25 sterilized if desired.

In another embodiment, there are provided methods of making a composition of a compound described herein including formulating a compound of the invention with a pharmaceutically acceptable carrier or diluent. In some embodiments, the pharmaceutically acceptable carrier or diluent is suitable for oral administration. In some such embodiments, the
30 methods can further include the step of formulating the composition into a tablet or capsule.

In other embodiments, the pharmaceutically acceptable carrier or diluent is suitable for parenteral administration. In some such embodiments, the methods further include the step of lyophilizing the composition to form a lyophilized preparation. In some embodiments, the composition is formulated into a pediatric dosage form suitable for treating a pediatric subject.

5 In certain embodiments, the invention provides a compound having structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof. Such compounds can be synthesized using standard synthetic techniques known to those skilled in the art. For example, compounds of the present invention can be synthesized
10 using appropriately modified synthetic procedures set forth in the following Examples and Reaction Schemes.

 To this end, the reactions, processes, and synthetic methods described herein are not limited to the specific conditions described in the following experimental section, but rather are intended as a guide to one with suitable skill in this field. For example, reactions may
15 be carried out in any suitable solvent, or other reagents to perform the transformation[s] necessary. Generally, suitable solvents are protic or aprotic solvents which are substantially non-reactive with the reactants, the intermediates or products at the temperatures at which the reactions are carried out (i.e., temperatures which may range from the freezing to boiling temperatures). A given reaction may be carried out in one solvent or a mixture of more than
20 one solvent. Depending on the particular reaction, suitable solvents for a particular work-up following the reaction may be employed.

 All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art. The compounds and intermediates
25 produced according to the methods of the invention may require purification. Purification of organic compounds is well known to a person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by
30 chromatography, particularly flash column chromatography, using purpose-made or prepacked

silica gel cartridges and eluents such as gradients of solvents such as heptane, ether, ethyl acetate, acetonitrile, ethanol and the like. In some cases, the compounds may be purified by preparative HPLC using methods as described.

Purification methods as described herein may provide compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt, or, in the case of a compound of the present invention, which is sufficiently acidic, an ammonium salt. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to a person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form of a compound of the present invention as isolated and as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Chemical names were generated using the ChemDraw naming software (Version 17.0.0.206) by PerkinElmer Informatics, Inc. In some cases, generally accepted names of commercially available reagents were used in place of names generated by the naming software.

Methods of Treatment

In some embodiments, the invention provides a method for treating an NLRP3 inflammasome dependent condition, wherein "treatment" refers to an intervention that ameliorates a sign or symptom of a disease or pathological condition. As used herein, the terms "treatment", "treat" and "treating," with reference to a disease, pathological condition or symptom, also refers to any observable beneficial effect of the treatment. The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the disease in a susceptible subject, a reduction in severity of some or all clinical symptoms of the disease, a slower progression of the disease, a reduction in the number of relapses of the disease, an improvement in the overall health or well-being of the subject, or by other parameters well known in the art that are specific to the particular disease. A prophylactic treatment is a treatment administered to a subject who does not exhibit signs of a disease or exhibits only

early signs, for the purpose of decreasing the risk of developing pathology. A therapeutic treatment is a treatment administered to a subject after signs and symptoms of the disease have developed.

In some embodiments, the invention provides a method for treating an NLRP3
5 inflammasome dependent condition in a subject, wherein "subject" refers to an animal (e.g., a mammal, such as a human). A subject to be treated according to the methods described herein may be one who has been diagnosed with a NLRP3 inflammasome dependent condition, such as inflammation, an inflammatory disease, an immune disease, cancer, infections including viral
10 infections; central nervous system diseases, metabolic diseases, cardiovascular diseases, respiratory diseases, liver diseases, renal diseases, ocular diseases, skin diseases, psychological diseases or blood diseases.

Diagnosis may be performed by any method or technique known in the art. One skilled in the art will understand that a subject to be treated according to the present disclosure may have been subjected to standard tests or may have been identified, without examination,
15 as one at risk due to the presence of one or more risk factors associated with the disease or condition. The term "patient" may be used interchangeably with the term "subject." A subject may refer to an adult or pediatric subject.

The route of administration can be any route which effectively transports the active compound of the invention to the appropriate or desired site of action, such as oral, nasal,
20 pulmonary, buccal, subdermal, intradermal, transdermal, or parenteral, including intravenous, subcutaneous and/or intramuscular. In one embodiment, the route of administration is oral. In another embodiment, the route of administration is topical.

Dosage forms can be administered once a day, or more than once a day, such as twice or thrice daily. Alternatively, dosage forms can be administered less frequently than
25 daily, such as every other day, or weekly, if found to be advisable by a prescribing physician or drug's prescribing information. Dosing regimens include, for example, dose titration to the extent necessary or useful for the indication to be treated, thus allowing the patient's body to adapt to the treatment, to minimize or avoid unwanted side effects associated with the treatment, and/or to maximize the therapeutic effect of the present compounds. Other dosage

forms include delayed or controlled-release forms. Suitable dosage regimens and/or forms include those set out, for example, in the latest edition of the Physicians' Desk Reference, incorporated herein by reference.

In one embodiment, the invention provides an oral pharmaceutical composition comprising a compound of structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, together with at least one pharmaceutically acceptable oral carrier, diluent, or excipient. In another embodiment, the invention provides a topical pharmaceutical composition comprising a compound of structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, together with at least one pharmaceutically acceptable topical carrier, diluent, or excipient. In another embodiment, the invention provides an parenteral pharmaceutical composition comprising a compound of structure (I), (I'), (I''), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (I'''), (Ia'''), (Ia-1'''), (Ib'''), (Ib-1'''), (Ic'''), (Ic-1'''), (II), (III), (IV), or (V), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, together with at least one pharmaceutically acceptable topical carrier, diluent, or excipient.

In some embodiments, the invention provides a method for treating an NLRP3 inflammasome dependent condition, wherein modulating NLRP3 provides a medical benefit to the patient or subject.

In some embodiments, the NLRP3 inflammasome dependent condition is inflammation, an inflammatory disease, an immune disease, cancer, infections including viral infections; central nervous system diseases, metabolic diseases, cardiovascular diseases, respiratory diseases, liver diseases, renal diseases, ocular diseases, skin diseases, psychological diseases or blood diseases.

In one embodiment, the NLRP3 inflammasome dependent condition is neuroinflammation-related disorders or neurodegenerative diseases.

In one embodiment, the invention provides a method for inhibiting NLRP3 inflammasome with an effective amount of a pharmaceutical composition as described herein.

In one embodiment, the pharmaceutical composition is selective for modulating NLRP3 inflammasome activity over hERG activity. In certain embodiments, the selectivity for NLRP3 inflammasome activity is $\geq 1,000$ -fold over hERG activity. In certain embodiments, the selectivity for NLRP3 inflammasome activity is ≥ 10 -fold over hERG activity. In certain embodiments, the
5 selectivity for NLRP3 inflammasome activity is ≥ 100 -fold over hERG activity.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition by administering to a subject in need thereof an effective amount of a pharmaceutical composition as described herein. In certain embodiments, the NLRP3 inflammasome dependent condition is a neuroinflammation-related disorder(s) or a
10 neurodegenerative disease(s).

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition including inflammation occurring as a result of an inflammatory disorder, e.g. an autoinflammatory disease, inflammation occurring as a symptom of a non-inflammatory disorder, inflammation occurring as a result of infection, or inflammation
15 secondary to trauma, injury or autoimmunity. Examples of inflammation that may be treated or prevented include inflammatory responses occurring in connection with, or as a result of:

(a) a skin condition such as contact hypersensitivity, bullous pemphigoid, sunburn, psoriasis, atopic dermatitis, contact dermatitis, allergic contact dermatitis, seborrhectic dermatitis, lichen planus, scleroderma, pemphigus, epidermolysis bullosa, urticaria, erythemas, or alopecia;
20

(b) a joint condition such as osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis, rheumatoid arthritis, juvenile chronic arthritis, crystal induced arthropathy (e.g. pseudo-gout, gout), or a seronegative spondyloarthropathy (e.g. ankylosing spondylitis, psoriatic arthritis or Reiter's disease);

25 (c) a muscular condition such as polymyositis or myasthenia gravis;

(d) a gastrointestinal tract condition such as inflammatory bowel disease (including Crohn's disease and ulcerative colitis), gastric ulcer, coeliac disease, proctitis,

pancreatitis, eosinophilic gastro-enteritis, mastocytosis, antiphospholipid syndrome, or a food-related allergy which may have effects remote from the gut (e.g., migraine, rhinitis or eczema);

(e) a respiratory system condition such as chronic obstructive pulmonary disease (COPD), asthma (including bronchial, allergic, intrinsic, extrinsic or dust asthma, and particularly chronic or inveterate asthma, such as late asthma and airways hyper-responsiveness), bronchitis, rhinitis (including acute rhinitis, allergic rhinitis, atrophic rhinitis, chronic rhinitis, rhinitis caseosa, hypertrophic rhinitis, rhinitis pum lenta, rhinitis sicca, rhinitis medicamentosa, membranous rhinitis, seasonal rhinitis e.g. hay fever, and vasomotor rhinitis), sinusitis, idiopathic pulmonary fibrosis (IPF), sarcoidosis, farmer's lung, silicosis, asbestosis, adult respiratory distress syndrome, hypersensitivity pneumonitis, or idiopathic interstitial pneumonia;

(f) a vascular condition such as atherosclerosis, Behcet's disease, vasculitides, or Wegener's granulomatosis;

(g) an immune condition, e.g. autoimmune condition, such as systemic lupus erythematosus (SLE), Sjogren's syndrome, systemic sclerosis, Hashimoto's thyroiditis, type I diabetes, idiopathic thrombocytopenia purpura, or Graves disease;

(h) an ocular condition such as uveitis, allergic conjunctivitis, or vernal conjunctivitis;

(i) a nervous system condition such as multiple sclerosis or encephalomyelitis;

(j) an infection or infection-related condition, such as Acquired Immunodeficiency Syndrome (AIDS), acute or chronic bacterial infection, acute or chronic parasitic infection, acute or chronic viral infection, acute or chronic fungal infection, meningitis, hepatitis (A, B or C, or other viral hepatitis), peritonitis, pneumonia, epiglottitis, malaria, dengue hemorrhagic fever, leishmaniasis, streptococcal myositis, Mycobacterium tuberculosis, Mycobacterium avium intracellulare, Pneumocystis carinii pneumonia, orchitis/epididymitis, legionella, Lyme disease, influenza A, epstein-barr virus, viral encephalitis/aseptic meningitis, or pelvic inflammatory disease;

(k) a renal condition such as mesangial proliferative glomerulonephritis, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, uremia, or nephritic syndrome;

(l) a lymphatic condition such as Castleman's disease;

5 (m) a condition of, or involving, the immune system, such as hyper IgE syndrome, lepromatous leprosy, familial hemophagocytic lymphohistiocytosis, or graft versus host disease;

(n) a hepatic condition such as chronic active hepatitis, non-alcoholic steatohepatitis (NASH), alcohol-induced hepatitis, non-alcoholic fatty liver disease (NAFLD),
10 alcoholic fatty liver disease (AFLD), alcoholic steatohepatitis (ASH) or primary biliary cirrhosis;

(o) a cancer, including those cancers listed herein below;

(p) a burn, wound, trauma, haemorrhage or stroke;

(q) radiation exposure; and/or

(r) obesity;

15 (s) pain such as inflammatory hyperalgesia; and/or

(t) neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, or amyotrophic lateral sclerosis.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as an inflammatory disease. For example,
20 inflammation occurring as a result of an inflammatory disorder, e.g. an autoinflammatory disease, such as cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), familial Mediterranean fever (FMF), neonatal onset multisystem inflammatory disease (NOMID), Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), adult-onset Still's disease (AOSD),
25 haploinsufficiency of A20 (HA20), pediatric granulomatous arthritis (PGA), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), PLCG2-associated autoinflammatory,

antibody deficiency and immune dysregulation (APLAID), or sideroblastic anaemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD).

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as an immune disease. For example, auto-immune diseases, such as acute disseminated encephalitis, Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome (APS), anti-synthetase syndrome, aplastic anemia, autoimmune adrenalitis, autoimmune hepatitis, autoimmune oophoritis, autoimmune polyglandular failure, autoimmune thyroiditis, Coeliac disease, Crohn's disease, type 1 diabetes (T1D), Goodpasture's syndrome, Graves' disease, Guillain-Barre syndrome (GBS), Hashimoto's disease, idiopathic thrombocytopenic purpura, Kawasaki's disease, lupus erythematosus including systemic lupus erythematosus (SLE), multiple sclerosis (MS) including primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS) and relapsing remitting multiple sclerosis (RRMS), myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, pemphigus, pernicious anaemia, polyarthritis, primary biliary cirrhosis, rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis or Still's disease, refractory gouty arthritis, Reiter's syndrome, Sjogren's syndrome, systemic sclerosis a systemic connective tissue disorder, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis, Beliefs disease, Chagas' disease, dysautonomia, endometriosis, hidradenitis suppurativa (HS), interstitial cystitis, neuromyotonia, psoriasis, sarcoidosis, scleroderma, ulcerative colitis, Schnitzler syndrome, macrophage activation syndrome, Blau syndrome, giant cell arteritis, vitiligo or vulvodynia.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as cancer. For example, lung cancer, renal cell carcinoma, non-small cell lung carcinoma (NSCLC), Langerhans cell histiocytosis (LCH), myeloproliferative neoplasms (MPN), pancreatic cancer, gastric cancer, myelodysplastic syndrome (MDS), leukaemia including acute lymphocytic leukaemia (ALL) and acute myeloid leukaemia (AML), promyelocytic leukemia (APML, or APL), adrenal cancer, anal cancer, basal and squamous cell skin cancer, bile duct cancer, bladder cancer, bone cancer, brain and spinal cord tumours, breast cancer, cervical cancer, chronic lymphocytic leukaemia (CLL), chronic

myeloid leukaemia (CML), chronic myelomonocytic leukaemia (CMML), colorectal cancer, endometrial cancer, oesophagus cancer, Ewing family of tumours, eye cancer, gallbladder cancer, gastrointestinal carcinoid tumours, gastrointestinal stromal tumour (GIST), gestational trophoblastic disease, glioma, Hodgkin lymphoma, Kaposi sarcoma, kidney cancer, laryngeal and
 5 hypopharyngeal cancer, liver cancer, lung carcinoid tumour, lymphoma including cutaneous T cell lymphoma, malignant mesothelioma, melanoma skin cancer, Merkel cell skin cancer, multiple myeloma, nasal cavity and paranasal sinuses cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, penile cancer, pituitary tumours, prostate
 10 cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, stomach cancer, testicular cancer, thymus cancer, thyroid cancer including anaplastic thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumour.

In another embodiment, the invention provides a method of treating a NLRP3
 15 inflammasome dependent condition such as an infection, including viral infections. For example, viral infections (e.g. from influenza virus, human immunodeficiency virus (HIV), alphavirus (such as Chikungunya and Ross River virus), flaviviruses (such as Dengue virus and Zika virus), herpes viruses (such as Epstein Barr Virus, cytomegalovirus, Varicella-zoster virus, and KSHV), poxyruses (such as vaccinia virus (Modified vaccinia virus Ankara) and Myxoma virus),
 20 adenoviruses (such as Adenovirus 5), or papillomavirus), bacterial infections (e.g. from Staphylococcus aureus, Helicobacter pylori, Bacillus anthracis, Bordatella pertussis, Burkholderia pseudomallei, Corynebacterium diphtheriae, Clostridium tetani, Clostridium botulinum, Streptococcus pneumoniae, Streptococcus pyogenes, Listeria monocytogenes, Hemophilus influenzae, Pasteurella multocida, Shigella dysenteriae, Mycobacterium
 25 tuberculosis, Mycobacterium leprae, Mycoplasma pneumoniae, Mycoplasma hominis, Neisseria meningitidis, Neisseria gonorrhoeae, Rickettsia rickettsii, Legionella pneumophila, Klebsiella pneumoniae, Pseudomonas aeruginosa, Propionibacterium acnes, Treponema pallidum, Chlamydia trachomatis, Vibrio cholerae, Salmonella typhimurium, Salmonella typhi, Borrelia burgdorferi or Yersinia pestis), fungal infections (e.g. from Candida or Aspergillus species),
 30 protozoan infections (e.g. from Plasmodium, Babesia, Giardia, Entamoeba, Leishmania or

Trypanosomes), helminth infections (e.g. from schistosoma, roundworms, tapeworms or flukes), and prion infections.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a central nervous system disease. For example,
5 Parkinson's disease, Alzheimer's disease, Frontotemporal dementia, dementia, motor neuron disease, Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis, intracranial aneurysms, traumatic brain injury, multiple sclerosis, and amyotrophic lateral sclerosis.

In another embodiment, the invention provides a method of treating a NLRP3
10 inflammasome dependent condition such as a neuroinflammation-related disease. For example, multiple sclerosis, brain infection, acute injury, neurodegenerative disease, Parkinson's disease or Alzheimer's disease.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a neurodegenerative disease. For example,
15 Alzheimer's disease, Parkinson's disease, multiple sclerosis, or amyotrophic lateral sclerosis.

In one embodiment, neurodegenerative diseases are characterized by deep involvement of cell mediating neuroinflammatory processes.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a metabolic disease. For example, type 2 diabetes
20 (T2D), atherosclerosis, obesity, gout, and pseudo-gout.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a cardiovascular disease. For example, hypertension, ischaemia, reperfusion injury including post-MI ischemic reperfusion injury, stroke including ischemic stroke, transient ischemic attack, myocardial infarction including
25 recurrent myocardial infarction, heart failure including congestive heart failure and heart failure with preserved ejection fraction, embolism, aneurysms including abdominal aortic aneurysm, cardiovascular risk reduction (CvRR), and pericarditis including Dressler's syndrome.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a respiratory disease. For example, chronic obstructive pulmonary disorder (COPD), asthma such as allergic asthma and steroid-resistant asthma, asbestosis, silicosis, nanoparticle induced inflammation, cystic fibrosis, and idiopathic pulmonary fibrosis.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a liver disease. For example, non-alcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) including advanced fibrosis stages F3 and F4, alcoholic fatty liver disease (AFLD), and alcoholic steatohepatitis (ASH).

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a renal disease. For example, acute kidney disease, hyperoxaluria, chronic kidney disease, oxalate nephropathy, nephrocalcinosis, glomerulonephritis, and diabetic nephropathy;

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as an ocular disease. For example, diseases of the ocular epithelium, age-related macular degeneration (AMD) (dry and wet), uveitis, corneal infection, diabetic retinopathy, optic nerve damage, dry eye, and glaucoma.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a skin disease. For example, dermatitis such as contact dermatitis and atopic dermatitis, contact hypersensitivity, sunburn, skin lesions, hidradenitis suppurativa (HS), other cyst-causing skin diseases, and acne conglobate.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a psychological disease. For example, depression, and psychological stress.

In another embodiment, the invention provides a method of treating a NLRP3 inflammasome dependent condition such as a blood disease. For example, sickle cell disease.

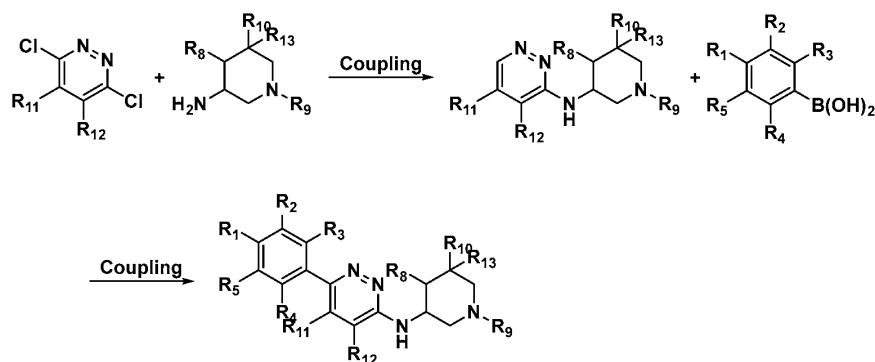
EXAMPLESGeneral Methods

¹H NMR (400 MHz) spectra were obtained in solution of deuteriochloroform (CDCl₃), deuteromethanol (CD₃OD) or dimethyl sulfoxide – D₆ (DMSO). HPLC retention times, purities, and mass spectra (LCMS) were obtained using Shimadzu LCMS 2010 (Shim-pack XR-ODS 3.0*30 mm 2.2 μm) operating in ES (+) ionization mode. Flow Rate: 0.8 mL/min, Acquire Time: 3 min, Wavelength: UV220, Oven, Temp.: 50 °C.

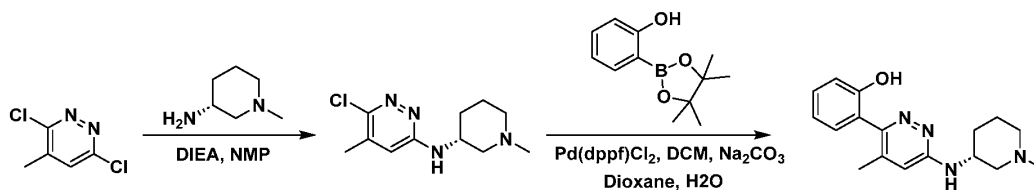
The following additional abbreviations are used: ethyl acetate (EtOAc), *N,N*-diisopropylethylamine (DIEA), water (H₂O), hydrochloridric acid (HCl), methanol (MeOH), dimethyl sulfoxide (DMSO), silica gel (SiO₂), trifluoroacetic acid (TFA), 1-methyl-2-pyrrolidinone (NMP), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl₂), tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄), palladium on carbon (Pd/C), 9-borabicyclo[3.3.1]nonane (9-BBN), sodium carbonate (Na₂CO₃), potassium carbonate (K₂CO₃), sodium sulfate (Na₂SO₄), cesium carbonate (Cs₂CO₃), ammonia (NH₃), tetrahydrofuran (THF), dichloromethane (DCM), acetonitrile (MeCN or ACN), dimethoxyethane (DME), boron tribromide (BBr₃), retention time (RT), molecular weight (MW), room temperature (rt), hour (h), volume/volume (v/v), proton nuclear magnetic resonance (¹HNMR), sodium hydride (NaH), formaldehyde (HCHO), acetic acid (AcOH), (2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (XPhosPdG3), degree Celsius (°C), milligram (mg), gram (g), millimole (mmol), milliliter (mL), polyethylene (PE), molar (M), sodium bicarbonate (NaHCO₃), potential of hydrogen (pH), sodium cyanoborohydride (NaBH₃CN), preparative high-performance liquid chromatography (prep-HPLC), normal (N).

EXAMPLE 1

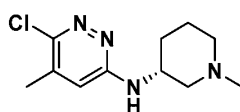
GENERAL SYNTHETIC ROUTE A

General Scheme 1

- 5 Synthesis of 2-[4-methyl-6-[[[(3R)-1-methyl-3-piperidyl]amino]pyridazin-3-yl]phenol
(Compound No. 2)

Synthesis of (R)-6-chloro-5-methyl-N-(1-methylpiperidin-3-yl)pyridazin-3-amine

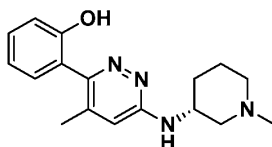
10



- To a solution of 3,6-dichloro-4-methyl-pyridazine (8.56 g, 52.5 mmol) in NMP (50 mL) were added (3R)-1-methylpiperidin-3-amine (5.0 g, 43.8 mmol) and DIEA (11 mL, 65.7 mmol). The resulting mixture was stirred at 110 °C for 14 h under nitrogen atmosphere. The mixture was then poured into water (100 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure

to afford crude residue. The crude was purified by silica gel column chromatography (4.6% MeOH in DCM) to afford desired product (*R*)-6-chloro-5-methyl-*N*-(1-methylpiperidin-3-yl)pyridazin-3-amine (5.30 g) as yellow solid.

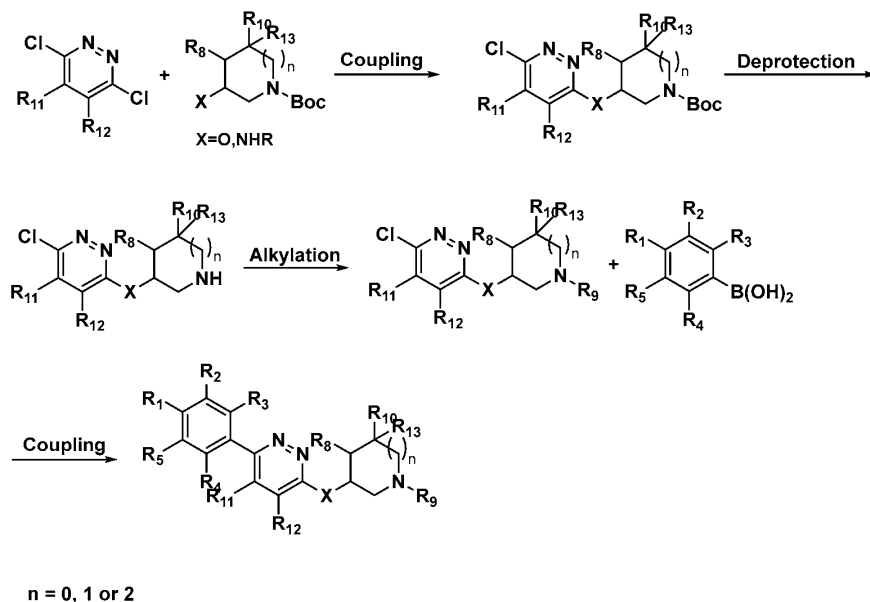
5 Synthesis of 2-[4-methyl-6-[[*(3R)*-1-methyl-3-piperidyl]amino]pyridazin-3-yl]phenol
 (Compound No. 2)



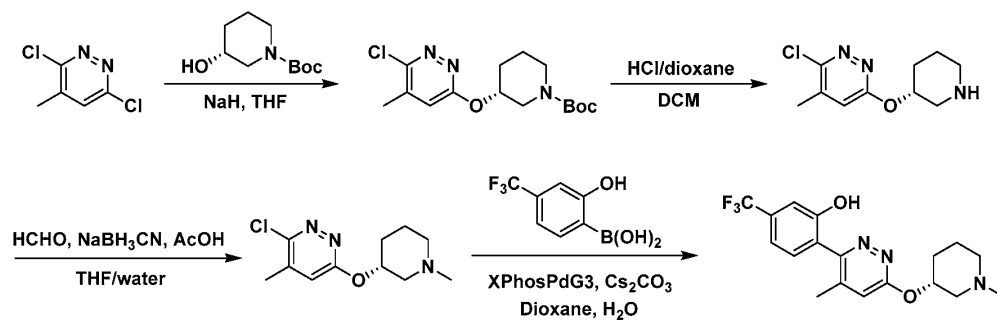
10 To a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (110 mg, 0.498 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) were added (*R*)-6-chloro-5-methyl-*N*-(1-methylpiperidin-3-yl)pyridazin-3-amine (100 mg, 0.415 mmol), Na₂CO₃ (110 mg, 1.04 mmol) and Pd(dppf)Cl₂•DCM (17 mg, 0.021 mmol). The resulting mixture was stirred at 120 °C for 4 h under nitrogen atmosphere. The mixture was then diluted with water (30 mL), acidified with 2 N
15 aqueous HCl to pH ~ 7-8, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (0.05% NH₃.H₂O as additive) to afford the desired product 2-[4-methyl-6-[[*(3R)*-1-methyl-3-piperidyl]amino]pyridazin-3-yl]phenol (**Compound No. 2**, 43 mg, 33% yield) as a white solid.

EXAMPLE 2

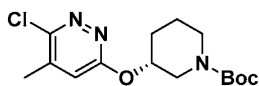
GENERAL SYNTHETIC ROUTE B

General Scheme 2

5 Synthesis of (*R*)-2-(4-methyl-6-((1-methylpiperidin-3-yl)oxy)pyridazin-3-yl)-5-(trifluoromethyl)phenol (Compound No. 73)

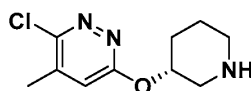


Synthesis of tert-butyl (*R*)-3-((6-chloro-5-methylpyridazin-3-yl)oxy)piperidine-1-carboxylate



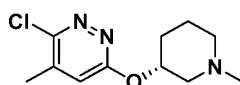
To a mixture of (*R*)-tert-butyl 3-hydroxypiperidine-1-carboxylate (1.00 g, 4.97 mmol) in THF (10 mL) was added NaH (230 mg, 5.85 mmol) (60% in mineral oil) portionwise at 0 °C. The mixture was stirred at 20 °C for 2 h under nitrogen atmosphere. 3,6-dichloro-4-methylpyridazine (830 mg, 5.07 mmol) was then added and the resulting mixture was stirred at 20 °C for an additional 14 h. The mixture was poured into water (30 mL) and was extracted with EtOAc (3 X 30 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford crude residue. The crude residue was purified by silica gel column chromatography (30% EtOAc in PE) to afford desired product tert-butyl (*R*)-3-((6-chloro-5-methylpyridazin-3-yl)oxy)piperidine-1-carboxylate (1.27 g, 78% yield) as a yellow solid.

Synthesis of (*R*)-3-chloro-4-methyl-6-(piperidin-3-yloxy)pyridazine



To a mixture of tert-butyl (*R*)-3-((6-chloro-5-methylpyridazin-3-yl)oxy)piperidine-1-carboxylate (11.6 g, 35.4 mmol) in DCM (110 mL) was added 4 M HCl in dioxane (100 mL). The mixture was stirred at 20 °C for 2 h. Saturated aqueous NaHCO₃ was then added to adjust pH~8-9. The resulting mixture was extracted with EtOAc (3 X 100 mL). The organic layers were combined, washed with brine (2 X 100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford crude product (*R*)-3-chloro-4-methyl-6-(piperidin-3-yloxy)pyridazine as an off-white solid, which was used without further purification.

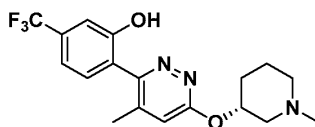
Synthesis of (*R*)-3-chloro-4-methyl-6-((1-methylpiperidin-3-yl)oxy)pyridazine



To a mixture of (*R*)-3-chloro-4-methyl-6-(piperidin-3-yloxy)pyridazine (6.95 g) in THF (50 mL) and water (5 mL) were added HCHO (2.48 g, 30.5 mmol) (37% in water), NaBH₃CN (2.88 g, 45.8 mmol) and AcOH (1.83 g, 30.5 mmol). The mixture was stirred at 50 °C for 2 h under nitrogen atmosphere. The mixture was then poured into water (100 mL) and was extracted with EtOAc (3 X 100 mL). The organic layers were combined, washed with brine (2 X 100 mL), dried

over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford crude product (*R*)-3-chloro-4-methyl-6-((1-methylpiperidin-3-yl)oxy)pyridazine as brown oil which was used without further purification.

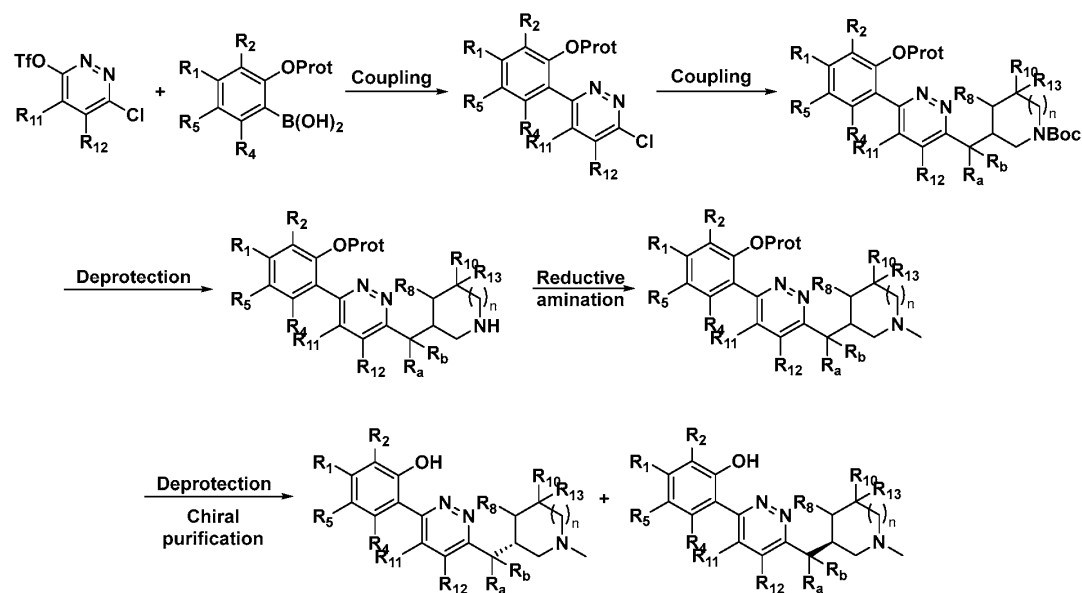
5 Synthesis of (*R*)-2-(4-methyl-6-((1-methylpiperidin-3-yl)oxy)pyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound No. 73**)



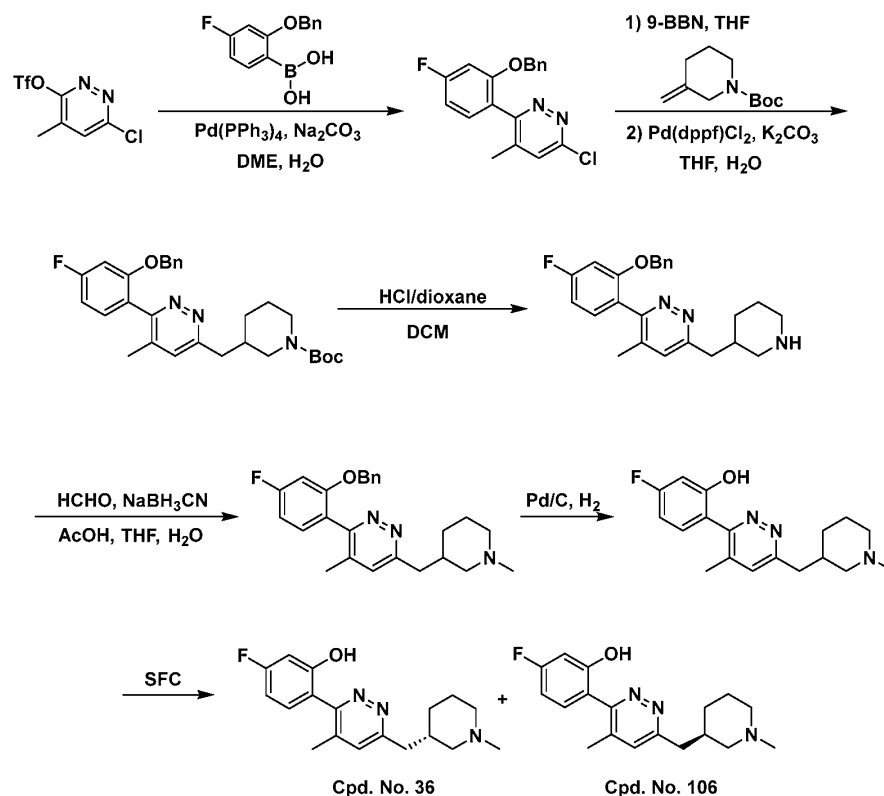
To a mixture of (*R*)-3-chloro-4-methyl-6-((1-methylpiperidin-3-yl)oxy)pyridazine (300 mg) in dioxane (3 mL) and water (0.3 mL) were added [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (307 mg, 1.49 mmol), XPhosPdG3 (53 mg, 0.06 mmol) and Cs₂CO₃ (1.20 g, 3.72 mmol). The mixture was stirred at 100 °C for 16 h under nitrogen atmosphere. The mixture was then poured into water (10 mL) and was extracted with EtOAc (3 X 20 mL). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford crude residue. The crude residue was purified by prep-HPLC (0.05% NH₃.H₂O as additive) to afford desired product (*R*)-2-(4-methyl-6-((1-methylpiperidin-3-yl)oxy)pyridazin-3-yl)-5-(trifluoromethyl)phenol (**Compound No. 73**, 42 mg, 9% yield) as an off-white solid.

EXAMPLE 3

GENERAL SYNTHETIC ROUTE C

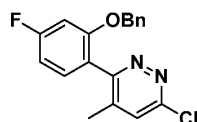
General Scheme 3

Synthesis of (S)-5-fluoro-2-(4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)phenol (Compound No. 36) and (R)-5-fluoro-2-(4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)phenol (Compound No. 106)



5

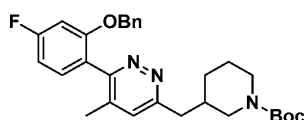
Synthesis of 3-(2-(benzyloxy)-4-fluorophenyl)-6-chloro-4-methylpyridazine



To a solution of 6-chloro-4-methylpyridazin-3-yltrifluoromethanesulfonate (562 mg, 2.03 mmol) and 2-(benzyloxy)-4-fluorophenylboronic acid (500 mg, 2.03 mmol) in DME (7 mL) and H₂O (1 mL) were added Pd(PPh₃)₄ (352 mg, 0.305 mmol) and Na₂CO₃ (843 mg, 6.10 mmol). The resulting mixture was stirred at 90 °C for 16 h under nitrogen atmosphere. The mixture was then poured into water (30 mL) and was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na₂SO₄ and

concentrated under reduced pressure to afford a crude residue. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 3:1) to afford desired product 3-(2-(benzyloxy)-4-fluorophenyl)-6-chloro-4-methylpyridazine (340 mg, 50 % yield) as a white solid.

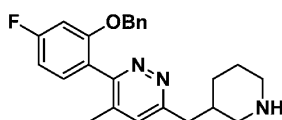
5 Synthesis of *tert*-butyl 3-((6-(2-(benzyloxy)-4-fluorophenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate



To a solution of *tert*-butyl 3-methylenepiperidine-1-carboxylate (300 mg, 1.52 mmol) in THF (10 mL) was added a solution of 1 M 9-BBN in THF (1.52 mL, 1.52 mmol). The mixture was stirred at 65 °C for 12 h under nitrogen atmosphere. To the mixture were then added 3-(2-(benzyloxy)-4-fluorophenyl)-6-chloro-4-methylpyridazine (250 mg, 0.760 mmol), Pd(dppf)Cl₂ (111 mg, 0.152 mmol), K₂CO₃ (315 mg, 2.28 mmol) and H₂O (2 mL) at room temperature. The resulting mixture was stirred at 65 °C for 12 h under nitrogen atmosphere. The mixture was diluted with water (30 mL) and was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford a crude residue. The crude residue was purified by silica gel column chromatography (PE:EtOAc, 2:1) to afford desired product *tert*-butyl 3-((6-(2-(benzyloxy)-4-fluorophenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (90 mg, 24 % yield) as a yellow oil.

20

Synthesis of 3-(2-(benzyloxy)-4-fluorophenyl)-4-methyl-6-(piperidin-3-ylmethyl)pyridazine

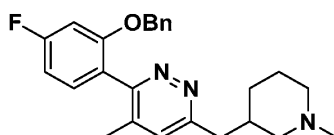


To a solution of *tert*-butyl 3-((6-(2-(benzyloxy)-4-fluorophenyl)-5-methylpyridazin-3-yl)methyl)piperidine-1-carboxylate (90 mg, 0.18 mmol) in DCM (1 mL) was added a solution of 4 M HCl in 1,4-dioxane (10 mL). The resulting mixture was stirred at room temperature for 1 h and was then concentrated under reduced pressure to afford crude product

3-(2-(benzyloxy)-4-fluorophenyl)-4-methyl-6-(piperidin-3-ylmethyl)pyridazine (90 mg) as a yellow oil. The crude product was used in the next step without further purification.

Synthesis of 3-(2-(benzyloxy)-4-fluorophenyl)-4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazine

5

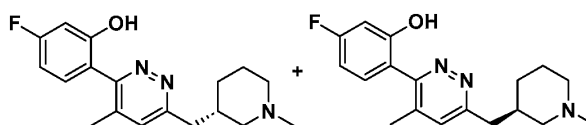


To a solution of 3-(2-(benzyloxy)-4-fluorophenyl)-4-methyl-6-(piperidin-3-ylmethyl)pyridazine (90 mg) in THF (3 mL) and H₂O (0.3 mL) were added 37 % aqueous formaldehyde (20 mg, 0.25 mmol), NaBH₃CN (20 mg, 0.32 mmol) and AcOH (13 mg, 0.21 mmol). The resulting mixture was stirred at 50 °C for 2 h. A saturated aqueous solution of NaHCO₃ was then added to adjust pH to ~7-8 and the mixture was extracted with EtOAc (3 X 100 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford crude product 3-(2-(benzyloxy)-4-fluorophenyl)-4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazine (40 mg) as a yellow oil. The crude product was used in the next step without further purification.

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Synthesis of (S)-5-fluoro-2-(4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)phenol (Compound No. 36) and (R)-5-fluoro-2-(4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)phenol (Compound No. 106)



Cpd. No. 36

Cpd. No. 106

20

To a solution of 3-(2-(benzyloxy)-4-fluorophenyl)-4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazine (40 mg) in MeOH (1 mL) was added Pd/C (10 mg). The mixture was stirred at 30 °C for 14 h under hydrogen atmosphere (15 psi). The resulting mixture was filtered and the filtrate was concentrated under reduced pressure to afford crude product 5-fluoro-2-(4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)phenol (20 mg) as a

25

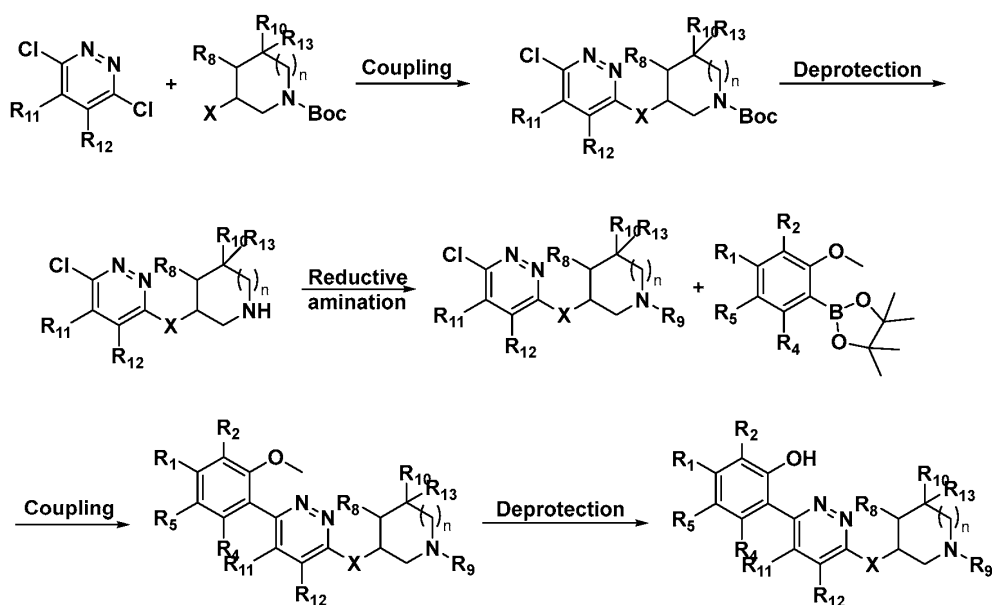
racemic mixture. The crude product was then purified by preparative supercritical fluid chromatography (prep-SFC) (DAICEL CHIRALPAK AS (250 mm*30 mm,10 μ m); mobile phase: [0.1 % $\text{NH}_3\text{H}_2\text{O}$ EtOH]; B %:30 %-30 %, min) to afford desired products (*R*)-5-fluoro-2-(4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)phenol (**Compound No. 106**, 5.6 mg, 43 % yield) and

5 (*S*)-5-fluoro-2-(4-methyl-6-((1-methylpiperidin-3-yl)methyl)pyridazin-3-yl)phenol (**Compound No. 36**, 8.9 mg, 27 % yield) as a white solids.

EXAMPLE 4

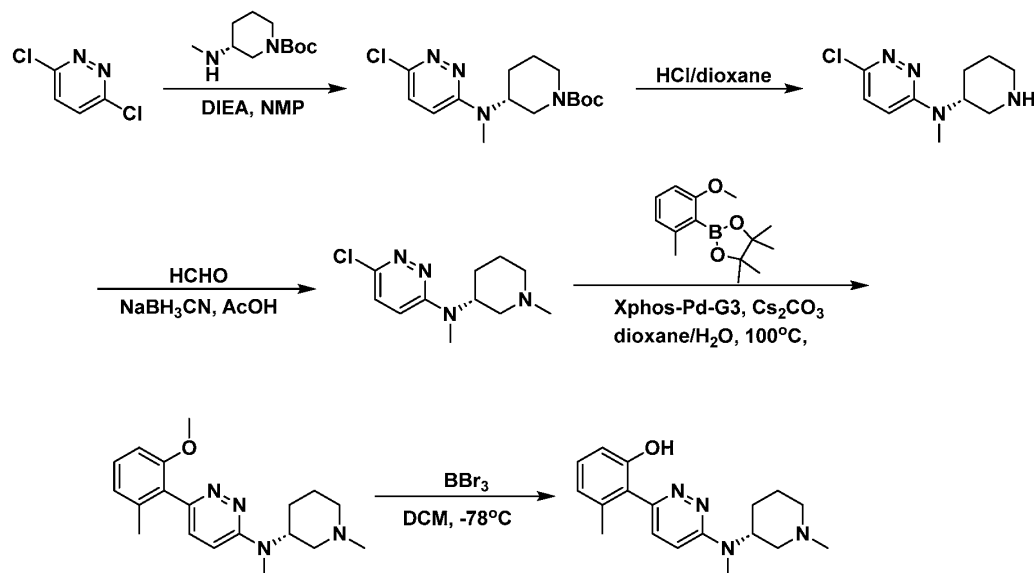
GENERAL SYNTHETIC ROUTE D

General Scheme 4

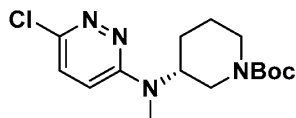


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Synthesis of (*R*)-3-methyl-2-(6-(methyl(1-methylpiperidin-3-yl)amino)pyridazin-3-yl)phenol
(Compound No. 21)

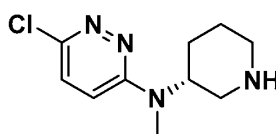


5 Synthesis of *tert*-butyl (*R*)-3-((6-chloropyridazin-3-yl)(methyl)amino)piperidine-1-carboxylate



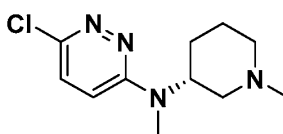
- To a solution of 3,6-dichloropyridazine (1.00 g, 6.71 mmol) and (*R*)-*tert*-butyl 3-(methylamino)piperidine-1-carboxylate (1.51 g, 7.05 mmol) in NMP (8 mL) was added DIEA (2.6 g, 20 mmol). The resulting mixture was stirred at 140 °C for 16 h under nitrogen atmosphere.
- 10 The mixture was then poured into water (100 mL) and extracted with 6:1 DCM:MeOH (3 X 80 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a crude residue. The crude residue was purified by silica gel column chromatography (30 % EtOAc in PE) to afford desired product *tert*-butyl (*R*)-3-((6-chloropyridazin-3-yl)(methyl)amino)piperidine-1-carboxylate (1.88 g, 70 % yield) as a
- 15 yellow solid.

Synthesis of (*R*)-6-chloro-*N*-methyl-*N*-(piperidin-3-yl)pyridazin-3-amine



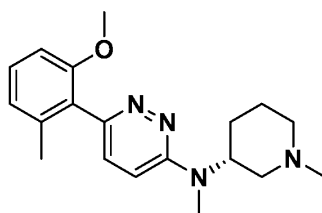
To a solution of *tert*-butyl (*R*)-3-((6-chloropyridazin-3-yl)(methyl)amino)piperidine-1-carboxylate (1.83 g, 5.61 mmol) in DCM (2 mL) was added a solution of 4 M HCl in 1,4-dioxane (15 mL). The resulting mixture was stirred at room temperature for 2 h. A saturated aqueous solution of NaHCO₃ was then added to adjust pH to ~7-8 and the mixture was extracted with 5:1 DCM:MeOH (3 X 50 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford crude product (*R*)-6-chloro-*N*-methyl-*N*-(piperidin-3-yl)pyridazin-3-amine (1.40 g) as a yellow solid. The crude product was used in the next step without further purification.

Synthesis of (*R*)-6-chloro-*N*-methyl-*N*-(1-methylpiperidin-3-yl)pyridazin-3-amine



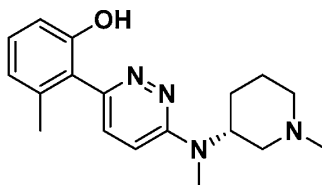
To a solution of (*R*)-6-chloro-*N*-methyl-*N*-(piperidin-3-yl)pyridazin-3-amine (1.40 g, 6.17 mmol) in THF (3 mL) and water (0.3 mL) were added 37 % aqueous formaldehyde (0.60 g, 7.41 mmol), NaBH₃CN (0.58 g, 9.26 mmol) and AcOH (0.37 g, 6.17 mmol). The resulting mixture was stirred at 50 °C for 2 h. A saturated aqueous solution of NaHCO₃ was then added to adjust pH to ~7-8 and the mixture was extracted with 5:1 DCM:MeOH (3 X 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (15 % MeOH in DCM) to afford desired product (*R*)-6-chloro-*N*-methyl-*N*-(1-methylpiperidin-3-yl)pyridazin-3-amine (445 mg, 30 % yield) as a yellow solid.

Synthesis of (*R*)-6-(2-methoxy-6-methylphenyl)-*N*-methyl-*N*-(1-methylpiperidin-3-yl)pyridazin-3-amine



To a solution of (*R*)-6-chloro-*N*-methyl-*N*-(1-methylpiperidin-3-yl)pyridazin-3-amine (100 mg, 0.415 mmol) and 2-(2-methoxy-6-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (113 mg, 0.457 mmol) in 1,4-dioxane (4 mL) and water (1 mL) were added Xphos-
 5 pd-G3 (53 mg, 0.062 mmol) and Cs₂CO₃ (406 mg, 1.25 mmol). The resulting mixture was stirred at 100 °C for 16 h under nitrogen atmosphere. The mixture was then poured into water (30 mL) and was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford a crude residue. The crude residue was purified by silica gel column chromatography (15 % MeOH
 10 in DCM) to afford desired product (*R*)-6-(2-methoxy-6-methylphenyl)-*N*-methyl-*N*-(1-methylpiperidin-3-yl)pyridazin-3-amine (96 mg, 71 % yield) as an off-white solid.

Synthesis of (*R*)-3-methyl-2-(6-(methyl(1-methylpiperidin-3-yl)amino)pyridazin-3-yl)phenol (Compound No. 21)



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To a solution of (*R*)-6-(2-methoxy-6-methylphenyl)-*N*-methyl-*N*-(1-methylpiperidin-3-yl)pyridazin-3-amine (86 mg, 0.26 mmol) in anhydrous DCM (3 mL) was slowly added BBr₃ (0.25 mL, 2.6 mmol) at -78 °C. The resulting mixture was stirred at room temperature for 2 h under nitrogen atmosphere. A saturated aqueous solution of NaHCO₃ was
 20 then added to adjust pH to ~7-8 and the mixture was extracted with 5:1 DCM:MeOH (3 X 50 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford a crude residue. The crude residue was purified by prep-HPLC (0.05 % NH₄HCO₃ as additive) to afford desired product (*R*)-

3-methyl-2-(6-(methyl(1-methylpiperidin-3-yl)amino)pyridazin-3-yl)phenol (**Compound No. 21**, 21.3 mg, 26 % yield) as an off-white solid.

EXAMPLE 5

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SYNTHESIS OF REPRESENTATIVE COMPOUNDS

The Compounds listed in Table 7 below were prepared by procedures similar to the ones described in the representative schemes found in the Examples with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents and reaction conditions. The characterization data of the compounds are also summarized herein in Table 7.

Table 7

Cpd No.	General Synthetic Route	Characterization
1	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.32 (brs, 1H), 7.16-7.21 (m, 1H), 6.66-6.73 (m, 3H), 6.57 (brd, <i>J</i> = 8.0 Hz, 1H), 4.00-4.06 (m, 1H), 2.84-2.88 (m, 1H), 2.55-2.58 (m, 1H), 2.19 (s, 3H), 1.95-2.05 (m, 4H), 1.80-1.87 (m, 2H), 1.68-1.74 (m, 1H), 1.50-1.57 (m, 1H), 1.26-1.30 (m, 1H). LCMS[M+H] ⁺ = 317.1
2	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 7.19 (t, <i>J</i> = 7.6 Hz, 1H), 7.13 (d, <i>J</i> = 7.6 Hz, 1H), 6.88 (d, <i>J</i> = 8.0 Hz, 1H), 6.82 (t, <i>J</i> = 7.6 Hz, 1H), 6.66 (s, 1H), 6.51 (brd, <i>J</i> = 8.0 Hz, 1H), 4.01-4.06 (m, 1H), 2.83-2.87 (m, 1H), 2.52-2.55 (m, 1H), 2.17 (s, 3H), 1.95-2.03 (m, 4H), 1.81-1.85 (m, 2H), 1.69-1.71 (m, 1H), 1.52-1.68 (m, 1H), 1.20-1.31 (m, 1H). LCMS[M+H] ⁺ = 299.1

Cpd No.	General Synthetic Route	Characterization
3	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.80 (brs, 1H), 7.05 (d, <i>J</i> = 8.0 Hz, 1H), 8.66 (s, 1H), 6.56-6.61 (m, 2H), 6.52 (d, <i>J</i> = 8.0 Hz, 1H), 3.95-4.06 (m, 1H), 2.76-2.94 (m, 1H), 2.40-2.48 (m, 1H), 2.17 (s, 3H), 1.99-2.06 (m, 4H), 1.78-1.92 (m, 3H), 1.65-1.74 (m, 1H), 1.46-1.59 (m, 1H), 1.20-1.34 (m, 1H), 0.91-0.98 (m, 2H), 0.61-0.68 (m, 2H). LCMS[M+H] ⁺ = 339.2
4	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.56 (brs, 1H), 8.08 (d, <i>J</i> = 9.6 Hz, 1H), 7.61 (d, <i>J</i> = 1.6 Hz, 1H), 7.03-7.12 (m, 3H), 6.81 (d, <i>J</i> = 8.0 Hz, 1H), 4.01-4.11 (m, 1H), 2.73-2.90 (m, 1H), 2.51-2.54 (m, 1H), 2.27 (s, 3H), 2.18 (s, 3H), 2.01-2.12 (m, 1H), 1.90-2.00 (m, 1H), 1.79-1.87 (m, 1H), 1.68-1.75 (m, 1H), 1.49-1.59 (m, 1H), 1.28-1.39 (m, 1H). LCMS[M+H] ⁺ = 299.1
5	A	¹ H NMR (DMSO- <i>d</i> ₆): δ 14.30 (brs, 1H), 8.11 (d, <i>J</i> = 9.6 Hz, 1H), 7.64 (d, <i>J</i> = 8.0 Hz, 1H), 7.08-7.17 (m, 3H), 6.80 (t, <i>J</i> = 7.6 Hz, 1H), 4.02-4.13 (m, 1H), 2.76-2.88 (m, 1H), 2.51-2.52 (m, 1H), 2.16-2.23 (m, 6H), 2.01-2.12 (m, 1H), 1.90-2.01 (m, 1H), 1.79-1.87 (m, 1H), 1.68-1.75 (m, 1H), 1.50-1.60 (m, 1H), 1.29-1.39 (m, 1H). LCMS[M+H] ⁺ = 299.1
6	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.13 (brs, 1H), 8.10 (dd, <i>J</i> = 8.0 Hz, 2.0 Hz, 1H), 7.65 (d, <i>J</i> = 8.4 Hz, 1H), 5.89-6.02 (m, 1H), 5.54-5.70 (m, 1H), 3.61-3.74 (m, 1H), 3.08-3.21 (m, 1H), 2.64-2.77 (m, 1H), 2.41-2.48 (m, 1H), 2.16 (s, 3H), 2.11 (s, 3H), 1.98-2.08 (m, 1H), 1.84-1.96 (m, 1H), 1.62-1.77 (m, 2H), 1.44-1.57 (m, 1H), 1.21-1.36 (m, 1H). LCMS[M+H] ⁺ = 317.1

Cpd No.	General Synthetic Route	Characterization
7	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.48 (s, 1H), 7.18 (d, <i>J</i> = 9.2 Hz, 1H), 7.07 (t, <i>J</i> = 8.0 Hz, 1H), 6.86 (d, <i>J</i> = 9.2 Hz, 1H), 6.64-6.77 (m, 3H), 4.01-4.12 (m, 1H), 2.82-2.90 (m, 1H), 2.51-2.58 (m, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.97-2.04 (m, 1H), 1.79-1.96 (m, 2H), 1.67-1.75 (m, 1H), 1.49-1.60 (m, 1H), 1.24-1.38 (m, 1H). LCMS[M+H] ⁺ = 299.2
8	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.05 (s, 1H), 8.06 (s, 1H), 7.81-7.89 (m, 1H), 7.21-7.28 (m, 1H), 6.86-6.97 (m, 2H), 6.14 (d, <i>J</i> = 8.0 Hz, 1H), 4.18-4.26 (m, 1H), 2.89-2.95 (m, 1H), 2.62-2.67 (m, 1H), 2.23 (s, 3H), 2.20 (s, 3H), 1.85-1.96 (m, 3H), 1.68-1.75 (m, 1H), 1.52-1.61 (m, 1H), 1.40-1.48 (m, 1H). LCMS[M+H] ⁺ = 299.1
9	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.13 (brs, 1H), 8.06 (d, <i>J</i> = 9.6 Hz, 1H), 7.74 (d, <i>J</i> = 9.2 Hz, 1H), 7.07-7.13 (m, 2H), 6.70 (d, <i>J</i> = 11.2 Hz, 1H), 4.00-4.10 (m, 1H), 2.77-2.85 (m, 1H), 2.51-2.53 (m, 1H), 2.16-2.21 (m, 6H), 1.90-2.12 (m, 2H), 1.79-1.86 (m, 1H), 1.66-1.75 (m, 1H), 1.49-1.59 (m, 1H), 1.28-1.39 (m, 1H). LCMS[M+H] ⁺ = 317.0
10	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.98 (brs, 1H), 8.09 (d, <i>J</i> = 9.6 Hz, 1H), 7.68-7.77 (m, 1H), 7.10-7.17 (m, 2H), 6.72 (t, <i>J</i> = 8.8 Hz, 1H), 3.99-4.12 (m, 1H), 2.76-2.86 (m, 1H), 2.52-2.56 (m, 1H) (overlap with DMSO- <i>d</i> ₆ single), 2.18 (s, 3H), 2.12 (s, 3H), 2.03-2.09 (m, 1H), 1.91-2.02 (m, 1H), 1.78-1.86 (m, 1H), 1.67-1.74 (m, 1H), 1.48-1.61 (m, 1H), 1.29-1.39 (m, 1H). LCMS[M+H] ⁺ = 317.0

Cpd No.	General Synthetic Route	Characterization
11	A	¹ H NMR (DMSO- <i>d</i> ₆): δ 14.30 (brs, 1H), 8.11 (d, <i>J</i> = 9.6 Hz, 1H), 7.64 (d, <i>J</i> = 8.0 Hz, 1H), 7.08-7.17(m, 3H), 6.80 (t, <i>J</i> = 7.6 Hz, 1H), 4.02-4.13 (m, 1H), 2.76-2.88 (m, 1H), 2.51-2.52 (m, 1H), 2.16-2.23 (m, 6H), 2.01-2.12 (m, 1H), 1.90-2.01 (m, 1H), 1.79-1.87 (m, 1H), 1.68-1.75 (m, 1H), 1.50-1.60 (m, 1H), 1.29-1.39 (m, 1H). LCMS[M+H] ⁺ = 299.1
12	A	¹ H NMR (400 MHz, CDCl ₃): δ 10.35-11.51 (m, 1H), 7.44 (d, <i>J</i> = 9.2 Hz, 1H), 6.77-6.82 (m, 2H), 6.66 (s, 1H), 5.25-5.60 (m, 1H), 4.20-4.32 (m, 1H), 2.56-2.64 (m, 4H), 2.40 (s, 3H), 2.15-2.34 (m, 5H), 1.78-1.88 (m, 2H), 1.61-1.72 (m, 2H), 1.22-1.27 (m, 3H). LCMS[M+H] ⁺ = 327.1
13	A	¹ H NMR (400 MHz, CDCl ₃): δ 9.50 (brs, 1H), 7.18 (d, <i>J</i> = 9.2 Hz, 1H), 6.85 (d, <i>J</i> = 9.2 Hz, 1H), 6.67 (d, <i>J</i> = 7.6 Hz, 1H), 6.47 (s, 1H), 6.45 (s, 1H), 4.00-4.10 (m, 1H), 2.82-2.91 (m, 1H), 2.52-2.54 (m, 1H), 2.19 (s, 3H), 2.04 (s, 3H), 1.93-2.02 (m, 1H), 1.83-1.88 (m, 1H), 1.76-1.82 (m, 2H), 1.65-1.73 (m, 1H), 1.51-1.64 (m, 1H), 1.26-1.39 (m, 1H), 0.89-0.96 (m, 2H), 0.59-0.65 (m, 2H). LCMS[M+H] ⁺ = 339.3
14	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.71 (brs, 1H), 8.20 (s, 1H), 8.07 (d, <i>J</i> = 9.6 Hz, 1H), 7.71 (d, <i>J</i> = 8.4 Hz, 1H), 7.06-7.13 (m, 2H), 6.73-6.79 (m, 2H), 4.04-4.13 (m, 1H), 2.82-2.94 (m, 1H), 2.58-2.68 (m, 3H)(overlap with DMSO- <i>d</i> ₆ single), 2.23 (s, 3H), 1.99-2.17 (m, 2H), 1.70-1.88 (m, 2H), 1.50-1.60 (m, 1H), 1.30-1.40(m, 1H), 1.19 (t, <i>J</i> = 7.6 Hz, 3H). LCMS[M+H] ⁺ = 313.2

Cpd No.	General Synthetic Route	Characterization
15	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.81 (brs, 1H), 7.08 (d, <i>J</i> = 7.6 Hz, 1H), 6.69-6.77 (m, 2H), 6.67 (s, 1H), 6.52 (brd, <i>J</i> = 8.0 Hz, 1H), 3.96-4.09 (m, 1H), 2.81-2.90 (m, 1H), 2.55-2.62 (m, 3H), 2.18 (s, 3H), 2.04 (s, 3H), 1.95-2.02 (m, 1H), 1.80-1.90 (m, 2H), 1.65-1.75 (m, 1H), 1.51-1.60 (m, 1H), 1.25-1.30 (m, 1H), 1.20 (t, <i>J</i> = 7.6 Hz, 3H). LCMS[M+H] ⁺ = 327.2
16	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.00 (brs, 1H), 8.01 (s, 1H), 7.75 (d, <i>J</i> = 8.4 Hz, 1H), 6.72-6.79 (m, 2H), 6.09 (brd, <i>J</i> = 8.0 Hz, 1H), 4.14-4.27 (m, 1H), 2.88-2.91 (m, 1H), 2.55-2.63 (m, 3H), 2.18-2.23 (m, 6H), 1.84-1.97 (m, 3H), 1.65-1.75 (m, 1H), 1.51-1.60 (m, 1H), 1.35-1.42 (m, 1H), 1.19 (t, <i>J</i> = 7.6 Hz, 3H). LCMS[M+H] ⁺ = 327.1
17	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.61 (brs, 1H), 8.22 (d, <i>J</i> = 10.0 Hz, 1H), 8.19 (s, 1H), 7.88 (dd, <i>J</i> = 8.0 Hz, 1.2 Hz, 1H), 7.38 (d, <i>J</i> = 9.6 Hz, 1H), 7.23-7.30 (m, 1H), 6.85-7.06 (m, 2H), 4.54-4.66 (m, 1H), 3.01 (s, 3H), 2.75-2.83 (m, 2H), 2.24 (s, 3H), 2.11 (t, <i>J</i> = 10.4 Hz, 1H), 1.86-1.95 (m, 1H), 1.69-1.79 (m, 2H), 1.53-1.69 (m, 2H). LCMS[M+H] ⁺ = 299.2
18	D	¹ H NMR (DMSO- <i>d</i> ₆): δ 14.13 (brs, 1H), 8.22 (d, <i>J</i> = 10.0 Hz, 1H), 7.71 (d, <i>J</i> = 7.6 Hz, 1H), 7.38 (d, <i>J</i> = 9.6 Hz, 1H), 7.15 (d, <i>J</i> = 7.2 Hz, 1H), 6.82 (t, <i>J</i> = 7.6 Hz, 1H), 4.50-4.61 (m, 1H), 3.00 (s, 3H), 2.71-2.79 (m, 2H), 2.18-2.23 (m, 6H), 2.00-2.07 (m, 1H), 1.79-1.88 (m, 1H), 1.54-1.77 (m, 4H). LCMS[M+H] ⁺ = 313.1

Cpd No.	General Synthetic Route	Characterization
19	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.33 (brs, 1H), 8.18 (d, <i>J</i> = 10.0 Hz, 1H), 7.67 (s, 1H), 7.35 (d, <i>J</i> = 10.0 Hz, 1H), 7.06 (d, <i>J</i> = 8.4 Hz, 1H), 6.82 (d, <i>J</i> = 8.4 Hz, 1H), 4.47-4.63 (m, 1H), 3.00 (s, 3H), 2.70-2.78 (m, 2H), 2.28 (s, 3H), 2.20 (s, 3H), 1.99-2.07 (m, 1H), 1.80-1.87 (m, 1H), 1.53-1.76 (m, 4H). LCMS[M+H] ⁺ = 313.0
20	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.23 (s, 1H), 8.18 (d, <i>J</i> = 10.0 Hz, 1H), 7.94 (dd, <i>J</i> = 9.6, 6.8 Hz, 1H), 7.39 (d, <i>J</i> = 10.0 Hz, 1H), 6.70-6.82 (m, 2H), 4.50-4.56 (m, 1H), 3.00 (s, 3H), 2.72-2.78 (m, 2H), 2.20 (s, 3H), 2.04 (t, <i>J</i> = 10.8 Hz, 1H), 1.79-1.89 (m, 1H), 1.68-1.76 (m, 2H), 1.54-1.67 m (m, 2H). LCMS[M+H] ⁺ = 317.2
21	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.47 (brs, 1H), 7.31 (d, <i>J</i> = 9.2 Hz, 1H), 7.04-7.12 (m, 2H), 6.75 (t, <i>J</i> = 8.8 Hz, 2H), 4.55-4.66 (m, 1H), 2.96 (s, 3H), 2.70-2.79 (m, 2H), 2.20 (s, 3H), 2.06 (s, 3H), 1.98-2.04 (m, 1H), 1.78-1.86 (m, 1H), 1.67-1.75 (m, 2H), 1.54-1.67 (m, 2H). LCMS[M+H] ⁺ = 313.0
22	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.00 (brs, 1H), 7.30 (d, <i>J</i> = 9.6 Hz, 1H), 7.08 (d, <i>J</i> = 9.6 Hz, 1H), 6.52-6.62 (m, 2H), 4.54-4.68 (m, 1H), 2.99 (s, 3H), 2.71-2.80 (m, 2H), 2.20 (s, 3H), 2.00-2.09 (m, 4H), 1.79-1.87 (m, 1H), 1.68-1.77 (m, 2H), 1.55-1.66 (m, 2H). LCMS[M+H] ⁺ = 331.0
23	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.73 (brs, 1H), 7.21-7.27 (m, 1H), 7.15-7.20 (m, 1H), 6.86-6.95 (m, 3H), 4.52-4.65 (m, 1H), 2.95 (s, 3H), 2.74 (d, <i>J</i> = 10.4 Hz 2H), 2.20 (s, 3H), 2.10 (s, 3H), 2.02 (t, <i>J</i> = 10.4 Hz 1H), 1.77-1.84 (m, 1H), 1.65-1.76 (m, 2H), 1.43-1.64 (m, 2H). LCMS[M+H] ⁺ = 313.1

Cpd No.	General Synthetic Route	Characterization
24	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.80 (s, 1H), 8.20 (d, <i>J</i> = 10.0 Hz, 1H), 7.76-7.82(m, 1H), 7.40 (d, <i>J</i> = 10.0Hz, 1H), 6.75 (t, <i>J</i> = 8.8 Hz, 1H), 4.48-4.62(m, 1H), 3.00 (s, 3H), 2.71-2.79(m, 2H), 2.21 (s, 3H), 2.14 (s, 3H), 2.01-2.08(m, 1H), 1.81-1.88 (m, 1H), 1.56-1.76 (m, 4H). LCMS[M+H] ⁺ = 331.0
25	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.90 (brs, 1H), 8.17 (d, <i>J</i> = 10.0 Hz, 1H), 7.82 (d, <i>J</i> = 8.8Hz, 1H), 7.38 (d, <i>J</i> = 10.0 Hz, 1H), 6.71 (d, <i>J</i> = 11.2Hz, 1H), 4.49-4.60 (m, 1H), 2.99 (s, 3H), 2.71-2.77(m, 2H), 2.17-2.22(m, 6H), 2.00-2.06(m, 1H), 1.79-1.87 (m, 1H), 1.55-1.75(m, 4H). LCMS[M+H] ⁺ = 331.0
26	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.25(brs, 1H), 7.22(dd, <i>J</i> = 8.8, 2.0 Hz, 1H), 6.95 (s, 1H), 6.70-6.75 (m, 2H), 4.59-4.67 (m, 1H), 2.95 (s, 3H), 2.72-2.83(m, 2H), 2.22 (s, 3H), 2.09 (s, 3H), 2.01-2.07 (m, 1H), 1.81-1.88 (m, 1H), 1.67-1.76 (m, 2H), 1.56-1.65 (m, 2H). LCMS[M+H] ⁺ = 331.2
27	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.59 (brs, 1H), 8.17 (d, <i>J</i> = 10.0 Hz, 1H), 7.77 (d, <i>J</i> = 8.8 Hz, 1H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 6.75-6.79 (m, 2H), 4.50-4.65 (m, 1H), 3.00 (s, 3H), 2.59-2.78 (m, 2H), 2.50-2.57 (m, 2H), 2.26 (s, 3H), 2.03-2.19 (m, 1H), 1.71-1.72 (m, 1H), 1.63-1.70 (m, 2H), 1.53-4.62 (m, 2H), 1.19 (t, <i>J</i> = 7.6 Hz, 3H). LCMS[M+H] ⁺ = 327.2

Cpd No.	General Synthetic Route	Characterization
28	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.76 (s, 1H), 7.07 (d, <i>J</i> = 7.6 Hz, 1H), 6.93 (s, 1H), 6.57-6.71 (m, 2H), 4.53-4.68 (m, 1H), 2.94 (s, 3H), 2.74-2.76 (m, 2H), 2.20 (s, 3H), 2.11 (s, 3H), 1.98-2.05 (m, 1H), 1.86-1.92 (m, 1H), 1.77-1.84 (m, 1H), 1.63-1.78 (m, 3H), 1.55-1.60 (m, 1H), 0.93-1.00 (m, 2H), 0.63-0.70 (m, 2H). LCMS[M+H] ⁺ = 353.1
29	A	LCMS[M+H] ⁺ = 352.2 (calc.)
30	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 14.50 (brs, 1H), 8.08 (d, <i>J</i> = 9.6 Hz, 1H), 7.80-7.91 (m, 1H), 7.42 (d, <i>J</i> = 6.4 Hz, 1H), 7.08 (d, <i>J</i> = 9.6 Hz, 1H), 6.68-6.80 (m, 2H), 4.30-4.49 (m, 1H), 2.59-2.76 (m, 2H), 2.44-2.48 (m, 1H), 2.23-2.40 (m, 5H), 1.53-1.73 (m, 1H). LCMS[M+H] ⁺ = 289.0
31	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.85 (brs, 1H), 8.20 (s, 1H), 8.12 (d, <i>J</i> = 9.6 Hz, 1H), 7.81 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.49 (d, <i>J</i> = 6.8 Hz, 1H), 7.19-7.30 (m, 1H), 7.07 (d, <i>J</i> = 9.6 Hz, 1H), 6.86-6.95 (m, 2H), 4.42-4.49 (m, 1H), 2.75-2.90 (m, 2H), 2.54-2.65 (m, 1H), 2.24-2.40 (m, 5H), 1.60-1.78 (m, 1H). LCMS[M+H] ⁺ = 271.1
32	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, <i>J</i> = 9.6 Hz, 1H), 7.92 (s, 1H), 7.40 (d, <i>J</i> = 9.6 Hz, 1H), 6.75 (m, 2H), 5.21 (m, 1H), 3.05 (s, 3H), 2.67-2.86 (m, 2H), 2.39-2.48 (m, 1H) (overlap with DMSO- <i>d</i> ₆ singal), 2.14-2.30 (m, 5H), 1.74 (s, 1H). LCMS[M+H] ⁺ = 303.2

Cpd No.	General Synthetic Route	Characterization
33	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.18 (d, <i>J</i> = 9.2 Hz, 1H), 7.86 (d, <i>J</i> = 7.2 Hz, 1H), 7.17-7.46 (m, 2H), 6.92 (m, 2H), 5.23 (m, 1H), 3.05 (s, 3H), 2.66-2.88 (m, 2H), 2.41-2.47 (m, 1H) (overlap with DMSO- <i>d</i> ₆ singal), 2.15-2.31 (m, 5H), 1.74 (m, 1H). LCMS[M+H] ⁺ = 285.2
34	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.16 (brs, 1H), 7.21 (t, <i>J</i> = 7.2 Hz 1H), 7.06 (s, 1H), 6.70-6.78 (m, 2H), 5.20-5.25 (m, 1H), 2.85-2.95 (m, 1H), 1.95-2.25 (m, 10H), 1.71-1.76 (m, 1H), 1.40-1.58 (m, 2H). LCMS[M+H] ⁺ = 271.1
35	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.75 (brs, 1H), 8.35 (s, 1H), 7.98 (t, <i>J</i> = 7.2 Hz 1H), 6.80-6.84 (m, 2H), 5.15-5.35 (m, 1H), 2.90-2.95 (m, 1H), 2.15-2.25 (m, 7H), 2.00-2.12 (m, 3H), 1.71-1.75 (m, 1H), 1.48-1.60 (m, 2H). LCMS[M+H] ⁺ = 271.1
36	C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.39 (brs, 1H), 7.45 (s, 1H), 7.23-7.30 (m, 1H), 6.71-6.81 (m, 2H), 2.78 (d, <i>J</i> = 7.6 Hz, 2H), 2.57-2.72 (m, 2H), 2.09-2.19 (m, 6H), 1.98-2.06 (m, 1H), 1.82-1.92 (m, 1H), 1.53-1.75 (m, 3H), 1.42-1.48 (m, 1H), 0.94-1.03 (m, 1H). LCMS[M+H] ⁺ = 316.0
37	C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.51-11.21 (m, 1H), 7.38-7.56 (m, 2H), 7.20-7.33 (m, 2H), 2.77-2.81 (m, 2H), 2.64-2.68 (m, 2H), 2.12-2.18 (m, 6H), 1.98-2.05 (m, 1H), 1.83-1.92 (m, 1H), 1.71-1.75 (m, 1H), 1.59-1.63 (m, 2H), 1.43-1.48 (m, 1H), 0.91-1.12 (m, 1H). LCMS[M+H] ⁺ = 366.0

Cpd No.	General Synthetic Route	Characterization
38	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.19 (s, 1H), 7.34 (d, <i>J</i> = 8.0 Hz, 1H), 7.23 (d, <i>J</i> = 8.4 Hz, 1H), 6.87 (d, <i>J</i> = 8.0 Hz, 1H), 6.80 (s, 1H), 4.02-4.13 (m, 1H), 2.84-2.98 (m, 1H), 2.57-2.66 (m, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 2.08-2.17 (m, 4H), 1.94-2.05 (m, 1H), 1.80-1.90 (m, 1H), 1.70-1.78 (m, 1H), 1.51-1.63 (m, 1H), 1.26-1.41 (m, 1H). LCMS[M+H] ⁺ = 381.2
39	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.77 (brs, 1H), 7.20-7.26 (m, 1H), 7.14-7.18 (m, 1H), 6.85-6.93 (m, 2H), 6.67 (s, 1H), 6.54 (d, <i>J</i> = 8.0 Hz, 1H), 4.50 (dt, <i>J</i> = 48.0, 4.8 Hz, 2H), 3.96-4.07 (m, 1H), 3.01-3.07 (m, 1H), 2.71-2.77 (m, 1H), 2.67-2.70 (m, 1H), 2.60-2.63 (m, 1H), 2.08-2.14 (m, 1H), 2.03 (s, 3H), 1.94-2.01 (m, 1H), 1.85-1.91 (m, 1H), 1.68-1.75 (m, 1H), 1.51-1.59 (m, 1H), 1.24-1.34 (m, 1H). LCMS[M+H] ⁺ = 331.2
40	A	¹ H NMR (DMSO- <i>d</i> ₆): δ 9.03-10.52 (m, 1H), 8.23 (s, 0.55H), 7.23-7.33 (m, 1H), 7.15-7.21 (m, 1H), 6.84-6.98 (m, 2H), 6.70 (s, 1H), 6.66 (d, <i>J</i> = 8.0 Hz, 1H), 4.23-4.46 (m, 1H), 2.88-3.10 (m, 2H), 2.36-2.47 (m, 2H), 2.38 (s, 3H), 1.95-2.07 (m, 4H), 1.74-1.95 (m, 1H). LCMS[M+H] ⁺ = 335.3
41	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.73 (brs, 1H), 7.20-7.26 (m, 1H), 7.12-7.18 (m, 1H), 6.83-6.94 (m, 2H), 6.64-6.68 (m, 1H), 6.61 (brd, <i>J</i> = 8.0 Hz, 1H), 4.82-5.02 (m, 1H), 4.27-4.39 (m, 1H), 2.86-2.93 (m, 1H), 2.70-2.82 (m, 1H), 2.14-2.27 (m, 4H), 2.08 (m, 4H), 1.89-1.96 (m, 1H), 1.55-1.74 (m, 1H). LCMS[M+H] ⁺ = 317.2

Cpd No.	General Synthetic Route	Characterization
42	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.73 (brs, 1H), 7.21-7.26 (m, 1H), 7.14-7.18 (m, 1H), 6.85-6.94 (m, 2H), 6.67 (s, 1H), 6.60 (d, <i>J</i> = 8.0 Hz, 1H), 4.63-4.83 (m, 1H), 4.07-4.16 (m, 1H), 2.90-3.01 (m, 2H), 2.29-2.36 (m, 1H), 2.26 (s, 3H), 2.00-2.10 (m, 4H), 1.80-1.88 (m, 1H), 1.45-1.54 (m, 1H). LCMS[M+H] ⁺ = 317.0
43	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.73 (brs, 1H), 7.21-7.27 (m, 1H), 7.13-7.17 (m, 1H), 6.85-6.93 (m, 2H), 6.80 (d, <i>J</i> = 8.0 Hz, 1H), 6.75 (s, 1H), 4.46-4.66 (m, 1H), 4.26-4.34 (m, 1H), 2.83-2.91 (m, 1H), 2.56-2.62 (m, 1H), 2.14-2.22 (m, 4H), 2.05-2.11 (m, 2H), 2.03 (s, 3H), 1.73-1.84 (m, 1H). LCMS[M+H] ⁺ = 317.2
44	A	¹ H NMR (400 MHz, CDCl ₃): δ 7.28-7.35 (m, 1H), 6.72 (dd, <i>J</i> = 10.4, 2.4, 1H), 6.60 (s, 1H), 6.53-6.58 (m, 1H), 5.24-5.28 (m, 1H), 4.59 (dt, <i>J</i> = 48.0, 4.8, 2H), 4.10-4.14 (m, 1H), 2.58 – 2.70 (m, 5H), 2.26 - 2.40 (m, 4 H), 1.66 – 1.75 (m, 2H), 1.55 – 1.65 (m, 2 H). LCMS[M+H] ⁺ = 349.0
45	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.28 (brs, 1H), 7.10-7.27 (m, 1H), 6.63-6.81 (m, 4H), 4.21-4.38 (m, 1H), 2.85-3.06 (m, 2H), 2.35-2.46 (m, 2H), 2.31 (s, 3H), 1.98-2.09 (m, 4H), 1.76-1.95 (m, 1H). LCMS[M+H] ⁺ = 353.3
46	A	LCMS[M+H] ⁺ = 334.2 (calc.)

Cpd No.	General Synthetic Route	Characterization
47	A	¹ H NMR (400 MHz, CDCl ₃): δ 7.40 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 6.80 (dd, <i>J</i> = 10.4, 8.0 Hz, 1H), 6.67 (s, 1H), 6.62-6.65 (m, 1H), 5.36-5.51 (m, 1H), 4.82-5.00 (m, 1H), 4.47-4.57 (m, 1H), 3.04-3.16 (m, 1H), 2.91-3.01 (m, 1H), 2.43 (s, 3H), 2.35 (s, 3H), 2.20-2.35 (m, 2H), 2.03-2.10 (m, 1H), 1.85-1.95 (m, 1H), 1.71-1.79 (m, 1H). LCMS[M+H] ⁺ = 334.9
48	A	¹ H NMR (400 MHz, CDCl ₃): δ 7.28-7.34 (m, 1H), 6.70-6.76 (m, 1H), 6.63-6.68 (m, 1H), 6.53-6.58 (m, 1H), 4.62-4.85 (m, 1H), 4.22-4.49 (m, 1H), 2.76-2.89 (m, 1H), 2.43-2.71 (m, 3H), 2.25-2.40 (m, 6H), 1.81-1.99 (m, 2H). LCMS[M+H] ⁺ = 335.3
49	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.28 (s, 1H), 7.15-7.21 (m, 1H), 6.79 (s, 1H), 6.68-6.76 (m, 3H), 4.81-4.99 (m, 1H), 4.26-4.46 (m, 1H), 2.69-2.77 (m, 1H), 2.52-2.58 (m, 1H), 2.22 (s, 3H), 2.10-2.19 (m, 2H), 2.01 (s, 3H), 1.76-1.98 (m, 2H). LCMS[M+H] ⁺ = 335.0
50	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.73 (brs, 1H), 7.19-7.26 (m, 1H), 7.12-7.17 (m, 1H), 6.84-6.92 (m, 2H), 6.79 (s, 1H), 6.72 (brd, <i>J</i> = 8.4 Hz, 1H), 4.80-4.98 (m, 1H), 4.27-4.46 (m, 1H), 2.70-2.76 (m, 1H), 2.54-2.59 (m, 1H), 2.22 (s, 3H), 2.10-2.19 (m, 2H), 2.02 (s, 3H), 1.98-1.75 (m, 2H). LCMS[M+H] ⁺ = 317.0
51	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.62 (brs, 1H), 7.29-7.41 (m, 2H), 7.25 (d, <i>J</i> = 1.2 Hz, 1H), 6.64-6.75 (m, 2H), 3.96-4.10 (m, 1H), 2.77-2.84 (m, 1H), 2.52-2.61 (m, 1H), 2.18 (s, 3H), 1.95-2.05 (m, 4H), 1.78-1.94 (m, 2H), 1.65-1.75 (m, 1H), 1.48-1.60 (m, 1H), 1.23-1.35 (m, 1H). LCMS[M+H] ⁺ = 324.1

Cpd No.	General Synthetic Route	Characterization
52	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.69 (brs, 1H), 7.39-7.45 (m, 1H), 7.25-7.30 (m, 1H), 7.09 (d, <i>J</i> = 8.0 Hz, 1H), 6.87-6.98 (m, 2H), 6.78 (brd, <i>J</i> = 13.2 Hz, 1H), 4.03-4.12 (m, 1H), 2.75-2.83 (m, 1H), 1.98-2.21 (m, 6H), 1.77-1.84 (m, 1H), 1.68-1.74 (m, 1H), 1.50-1.57 (m, 1H), 1.31-1.40 (m, 1H). LCMS[M+H] ⁺ = 303.2
53	A	LCMS[M+H] ⁺ = 320.1 (calc.)
54	A	LCMS[M+H] ⁺ = 316.2 (calc.)
55	A	LCMS[M+H] ⁺ = 334.2 (calc.)
56	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.76 (brs, 1H), 7.20-7.25 (m, 1H), 7.13-7.17 (m, 1H), 6.83-6.94 (m, 2H), 6.66 (s, 1H), 6.66 (s, 1H), 6.52 (brd, <i>J</i> = 8.0 Hz, 1H), 3.96-4.06 (m, 1H), 3.28-3.33 (m, 1H), 2.92-3.01 (m, 1H), 2.62-2.71 (m, 1H), 2.32-2.38 (m, 2H), 1.94-2.06 (m, 4H), 1.82-1.93 (m, 2H), 1.68-1.72 (m, 1H), 1.47-1.57 (m, 1H), 1.23-1.34 (m, 1H), 1.00 (t, <i>J</i> = 7.2 Hz, 3H). LCMS[M+H] ⁺ = 313.2
57	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.76 (brs, 1H), 7.20-7.26 (m, 1H), 7.16 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 6.84-6.93 (m, 2H), 6.66 (s, 1H), 6.47 (brd, <i>J</i> = 8.0 Hz, 1H), 3.88-4.01 (m, 1H), 2.91-2.98 (m, 1H), 2.69-2.76 (m, 1H), 2.59-2.66 (m, 1H), 2.13-2.25 (m, 1H), 1.98-2.08 (m, 4H), 1.81-1.91 (m, 1H), 1.65-1.75 (m, 1H), 1.42-1.56 (m, 1H), 1.23-1.35 (m, 1H), 0.82-1.03 (m, 6H). LCMS[M+H] ⁺ = 327.3

Cpd No.	General Synthetic Route	Characterization
58	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.32 (brs, 1H), 7.11-7.26 (m, 1H), 6.64-6.75 (m, 3H), 6.55 (brd, <i>J</i> = 7.6 Hz, 1H), 3.95-4.07 (m, 1H), 2.85-3.00 (m, 1H), 2.62-2.73 (m, 1H), 2.34 (q, <i>J</i> = 7.2 Hz, 2H), 1.95-2.01 (m, 4H), 1.80-1.91 (m, 2H), 1.65-1.75 (m, 1H), 1.47-1.57 (m, 1H), 1.22-1.35 (m, 1H), 0.99 (t, <i>J</i> = 7.0 Hz, 3H). LCMS[M+H] ⁺ = 331.2
59	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.35 (brs, 1H), 7.15-7.21 (m, 1H), 6.65-6.72 (m, 3H), 6.50 (brd, <i>J</i> = 8.0 Hz, 1H), 3.85-4.07 (m, 1H), 2.89-2.97 (m, 1H), 2.71-2.75 (m, 1H), 2.60-2.69 (m, 1H), 2.14-2.24 (m, 1H), 1.97-2.07 (m, 4H), 1.82-1.87 (m, 1H), 1.65-1.75 (m, 1H), 1.41-1.55 (m, 1H), 1.22-1.36 (m, 1H), 0.80-1.02 (m, 6H). LCMS[M+H] ⁺ = 345.3
60	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.26 (s, 1H), 7.20 (d, <i>J</i> = 9.2 Hz, 1H), 6.83-6.91 (m, 2H), 6.54-6.61 (m, 2H), 4.10-4.20 (m, 1H), 3.12-3.23 (m, 1H), 2.84-2.93 (m, 1H), 2.62 (dd, <i>J</i> = 14.4, 7.2, 2H), 2.28-2.38 (m, 1H), 2.18-2.27 (m, 1H), 2.06 (s, 3H), 1.90-1.98 (m, 1H), 1.76-1.85 (m, 1H), 1.57-1.68 (m, 1H), 1.35-1.48 (m, 1H), 1.08 (t, <i>J</i> = 7.2 Hz, 3H). LCMS[M+H] ⁺ = 331.0
61	A	LCMS[M+H] ⁺ = 344.2 (calc.)
62	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.75-9.83 (m, 1H), 6.69 (d, <i>J</i> = 4.4 Hz, 1H), 6.60 (d, <i>J</i> = 10.0 Hz, 1H), 6.50-6.56 (m, 2H), 4.00-4.06 (m, 1H), 2.84-2.89 (m, 1H), 2.57-2.59 (m, 1H), 2.19 (s, 3H), 1.95-2.09 (m, 2H), 1.83-1.91 (m, 7H), 1.68-1.73 (m, 1H), 1.51-1.58 (m, 1H), 1.27-1.34 (m, 1H). LCMS[M+H] ⁺ = 331.3

Cpd No.	General Synthetic Route	Characterization
63	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.23 (brs, 1H), 7.14-7.20(m, 1H), 6.86 (brd, J= 7.6 Hz, 1H), 6.67-6.80 (m, 2H), 4.02-4.19 (m, 1H), 2.95-3.06(m, 1H), 2.68-2.75 (m, 1H), 2.05-2.41 (m, 11H), 1.72-1.93 (m, 2H), 1.52-1.67 (m, 1H), 1.28-1.47(m, 1H). LCMS[M+H] ⁺ = 331.1
64	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.14-8.21(m, 1H), 7.18 (t, J= 8.4Hz, 1H), 7.06 (s, 1H), 6.74 (t, J= 8.8Hz, 1H), 4.59-4.65(m,1H), 2.97 (s, 3H), 2.76-2.84 (m, 2H), 2.23-2.30 (m, 3H), 2.20 (s, 3H), 2.14(s, 3H), 2.03-2.12 (m, 1H), 1.86-1.99 (m, 1H), 1.59-1.79 (m, 4H). LCMS[M+H] ⁺ = 345.2
65	A	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 9.99 (brs, 1H), 7.6 (d, J = 9.2 Hz, 1 H), 6.62-6.69 (m, 2H), 6.54 (d, J = 8.0 Hz, 1H), 3.96-4.06 (m, 1H), 2.86-2.92 (m, 1H), 2.55-2.60 (m, 1H), 2.15-2.20 (m, 6H), 1.98-2.05 (m, 4H), 1.77-1.90 (m, 2H), 1.67-1.75 (m, 1H), 1.50-1.60 (m, 1H), 1.25-1.34 (m, 1H). LCMS[M+H] ⁺ = 331.0
66	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.0 (brs, 1H), 7.07 (d, J = 9.2 Hz, 1H), 6.93 (s, 1H), 6.66 (d, J = 11.2 Hz, 1H), 4.55-4.65 (m, 1H), 2.95 (s, 3H), 2.71-2.78 (m, 2H), 2.15-2.22 (m, 6H), 2.10 (s, 3H), 1.99-2.01 (m, 1H), 1.78-1.85 (m, 1H), 1.55-1.75 (m, 4H). LCMS[M+H] ⁺ = 345.1
67	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.1 (brs, 1H), 7.13 (dd, J = 7.2, 2.4 Hz, 2H), 6.76-6.86 (m, 2H), 6.69 (d, J = 8.0 Hz, 1H), 3.99-4.09 (m, 1H), 2.80-2.89 (m, 1H), 2.54-2.58 (m, 1H), 2.12-2.24 (m, 9H), 1.98-2.06 (m, 1H), 1.80-1.94 (m, 2H), 1.69-1.75 (m, 1H), 1.50-1.61 (m, 1H), 1.25-1.35 (m, 1H). LCMS[M+H] ⁺ = 313.4

Cpd No.	General Synthetic Route	Characterization
68	A	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 9.48 (brs, 1H), 7.02 (d, J = 8.0 Hz, 1 H), 6.95 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.66 (s, 1H), 6.52 (d, J = 7.6 Hz, 1H), 3.96-4.07 (m, 1H), 2.81-2.90 (m, 1H), 2.57-2.65 (m, 1H, overlap with DMSO singal), 2.23 (m, 3H), 2.17 (s, 3H), 1.94-2.04 (m, 4H), 1.78-1.90 (m, 2H), 1.66-1.74 (m, 2H), 1.49-1.59 (m, 2H), 1.20-1.32 (m, 1H). LCMS[M+H] ⁺ = 313.1
69	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.01-9.59(m, 1H), 8.32 (brs, 1H), 7.09 (t, J= 7.6 Hz, 1H), 6.70-6.76(m, 2H), 6.66-6.70 (m, 1H), 6.48 (brd, J= 8.0Hz, 1H), 3.99-4.05 (m, 1H), 2.82-2.91 (m, 1H), 2.53-2.59(m, 1H), 2.18 (s, 3H), 1.99-2.06 (m, 1H), 1.80-1.91 (m, 8H), 1.67-1.74 (m, 1H), 1.50-1.59(m, 1H), 1.25-1.33(m, 1H). LCMS[M+H] ⁺ = 313.1
70	C	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 9.79 (brs, 1H), 7.43 (s, 1H), 7.27-7.33 (m, 1H), 7.18-7.23 (m, 1H), 6.90-6.99 (m, 2H), 2.75-2.80 (m, 2H), 2.55-2.59 (m, 2H, overlap with DMSO signal), 2.15 (s, 3H), 2.12 (s, 3H), 1.97-2.05 (m, 1H), 1.80-1.91 (m, 1H), 1.57-1.69 (m, 3H), 1.41-1.50 (m, 1H), 0.93-1.04 (m, 1H). LCMS[M+H] ⁺ = 298.2
71	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.75 (brs, 1H), 7.24-7.33 (m, 1H), 7.14-7.22 (m, 1H), 7.05 (s, 1H), 6.87-6.97 (m, 2H), 5.19-5.31 (m, 1H), 2.89-2.98 (m, 1H), 2.52-2.58 (m, 1H, overlapped with DMSO peak), 2.15-2.23 (m, 4H), 2.07-2.14 (m, 4H), 2.00-2.06 (m, 1H), 1.70-1.82 (m, 1H), 1.45-1.62 (m, 2H). LCMS[M+H] ⁺ = 330.2

Cpd No.	General Synthetic Route	Characterization
72	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.08 (brs, 1H), 7.54 (d, <i>J</i> = 9.2 Hz, 1H), 7.18 (d, <i>J</i> = 9.2 Hz, 1H), 6.56-6.64 (m, 2H), 5.24-5.31 (m, 1H), 2.91-2.97 (m, 1H), 2.54-2.57 (m, 1H), 2.19-2.23 (m, 4H), 2.09-2.13 (m, 1H), 2.02-2.07 (m, 4H), 1.74-1.80 (m, 1H), 1.50-1.63 (m, 2H). LCMS[M+H] ⁺ = 318.0
73	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.53 (brs, 1H), 7.42 (d, <i>J</i> = 7.6 Hz, 1H), 7.19-7.32 (m, 2H), 7.10 (s, 1H), 5.21-5.31 (m, 1H), 2.93-2.95 (m, 1H), 2.02-2.20 (m, 10H), 1.75-1.78 (m, 1H), 1.41-1.61 (m, 2H). LCMS[M+H] ⁺ = 368.1
74	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.47 (br s, 1H), 7.39 (d, <i>J</i> = 7.6 Hz, 1H), 7.22 (d, <i>J</i> = 8.0 Hz, 1H), 7.19 (s, 1H), 6.70 (s, 1H), 6.66 (d, <i>J</i> = 8.0 Hz, 1H), 3.97-4.08 (m, 1H), 3.43-3.49 (m, 1H), 2.86 (d, <i>J</i> = 8.0 Hz, 1H), 2.18 (s, 3H), 1.90-2.05 (m, 4H), 1.77-1.93 (m, 2H), 1.64-1.76 (m, 1H), 1.46-1.60 (m, 1H), 1.22-1.35 (m, 1H). LCMS[M+H] ⁺ = 367.2
75	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.14 (brs, 1H), 7.21 (d, <i>J</i> = 9.2 Hz, 1H), 7.10 (s, 1H), 7.04 (s, 1H), 6.89 (d, <i>J</i> = 9.2 Hz, 1H), 6.78 (d, <i>J</i> = 7.6 Hz, 1H), 4.03-4.14 (m, 1H), 2.79-2.92 (m, 1H), 2.52-2.56 (m, 1H), 2.18 (s, 3H), 2.13 (s, 3H), 1.98-2.08 (m, 1H), 1.89-1.97 (m, 1H), 1.79-1.88 (m, 1H), 1.67-1.79 (m, 1H), 1.49-1.61 (m, 1H), 1.25-1.38 (m, 1H). LCMS[M+H] ⁺ = 367.1
76	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.95-10.42 (m, 1H), 7.22 (s, 1H), 7.19 (s, 1H), 6.69 (s, 1H), 6.63 (d, <i>J</i> = 8.0 Hz, 1H), 3.98-4.01 (m, 1H), 2.85 (d, <i>J</i> = 9.2 Hz, 1H), 2.52-2.58 (m, 1H), 2.35 (s, 3H), 2.17 (s, 3H), 2.01 (s, 4H), 1.78-1.93 (m, 2H), 1.64-1.76 (m, 1H), 1.48-1.60 (m, 1H), 1.20-1.36 (m, 1H). LCMS[M+H] ⁺ = 381.2

Cpd No.	General Synthetic Route	Characterization
77	A	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 8.19 (brs, 1H), 8.04 (s, 1 H), 7.87-7.93 (m, 1H), 6.71-6.79 (m, 2H), 6.21 (d, <i>J</i> = 8.0 Hz), 4.15-4.32 (m, 1H), 2.94-2.99 (m, 1H), 2.66-2.71 (m, 1H), 2.21-2.25 (m, 6H), 1.99-2.10 (m, 2H), 1.84-1.90 (m, 1H), 1.70-1.75 (m, 1H), 1.50-1.60 (m, 1H), 1.34-1.42 (m, 1H). LCMS[M+H] ⁺ = 317.0
78	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.94-9.62 (m, 1H), 8.26 (brs, 1H), 7.09 (t, <i>J</i> = 7.6 Hz, 1H), 6.71-6.77(m, 2H), 6.66-6.70(m, 1H), 6.50 (brd, <i>J</i> = 7.6Hz, 1H), 4.00-4.06(m, 1H), 2.87-2.96 (m, 1H), 2.54-2.61(m, 1H), 2.20 (s, 3H), 1.98-2.06(m, 1H), 1.80-1.93 (m, 8H), 1.68-1.75(m, 1H), 1.50-1.60(m, 1H), 1.25-1.32(m, 1H). LCMS[M+H] ⁺ = 313.1
79	A	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 14.35 (brs, 1H), 8.02 (s, 1 H), 7.79 (d, <i>J</i> = 8.8 Hz, 1H), 6.69 (d, <i>J</i> = 11.8 Hz, 1H), 6.14 (d, <i>J</i> = 8.0 Hz, 1H), 4.15-4.25 (m, 1H), 2.91-2.99 (m, 1H), 2.60-2.67 (m, 1H), 2.18-2.25 (m, 9H), 1.85-1.97 (m, 3H), 1.65-1.75 (m, 1H), 1.52-1.62 (m, 1H), 1.38-1.47 (m, 1H). LCMS[M+H] ⁺ = 331.1
80	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.23 (d, <i>J</i> = 5.6Hz, 1H), 8.04 (s, 1H), 7.75 (t, <i>J</i> = 7.6 Hz, 1H), 6.73 (t, <i>J</i> = 8.8Hz, 1H), 6.12-6.20 (m, 1H), 4.19-4.27 (m, 1H), 2.80-2.96(m, 1H), 2.57-2.65(m, 1H), 2.20-2.24 (m, 6H), 2.13 (s, 3H), 1.90-2.01(m, 2H), 1.80-1.90(m, 1H), 1.65-1.72(m, 1H), 1.54-1.60 (m, 1H), 1.41-1.47(m, 1H). LCMS[M+H] ⁺ = 331.1

Cpd No.	General Synthetic Route	Characterization
81	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.44 (s, 1H), 8.05 (s, 1H), 7.69 (d, <i>J</i> = 7.6 Hz, 1H), 7.14 (d, <i>J</i> = 7.2 Hz, 1H), 6.80 (t, <i>J</i> = 7.6 Hz, 1H), 6.13 (d, <i>J</i> = 7.6 Hz, 1H), 4.16-4.30 (m, 1H), 2.85-2.95 (m, 1H), 2.59-2.65 (m, 1H), 2.17-2.28 (m, 9H), 1.84-1.99 (m, 3H), 1.67-1.75 (m, 1H), 1.52-1.62 (m, 1H), 1.39-1.50 (m, 1H). LCMS[M+H] ⁺ = 313.3
82	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.21 (brs, 1H), 8.01 (s, 1H), 7.72 (d, <i>J</i> = 8.0 Hz, 1H), 6.68-6.73 (m, 2H), 6.15 (d, <i>J</i> = 7.6 Hz, 1H), 4.20-4.30 (m, 1H), 2.96-3.08 (m, 1H), 2.66-2.83 (m, 1H), 2.24-2.30 (m, 6H), 2.22 (s, 3H), 2.01-2.12 (m, 2H), 1.83-1.92 (m, 1H), 1.69-1.78 (m, 1H), 1.53-1.65 (m, 1H), 1.41-1.52 (m, 1H). LCMS[M+H] ⁺ = 313.1
83	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.57 (brs, 1H), 8.05 (s, 1H), 7.87 (d, <i>J</i> = 8.8 Hz, 1H), 6.88-7.04 (m, 2H), 6.21 (d, <i>J</i> = 7.6 Hz, 1H), 4.17-4.26 (m, 1H), 2.87-2.94 (m, 1H), 2.54-2.57 (m, 1H), 2.22 (s, 3H), 2.19 (s, 3H), 1.84-1.96 (m, 3H), 1.66-1.73 (m, 1H), 1.51-1.59 (m, 1H), 1.40-1.47 (m, 1H). LCMS[M+H] ⁺ = 333.1
84	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.95-10.02 (m, 1H), 7.09 (s, 1H), 6.53-6.61 (m, 2H), 5.70-5.79 (m, 1H), 4.24-4.35 (m, 1H), 2.96-3.01 (m, 1H), 2.54-2.56 (m, 1H), 2.25 (s, 3H), 2.11 (s, 3H), 1.98-2.07 (m, 5H), 1.86-1.91 (m, 1H), 1.71-1.76 (m, 1H), 1.55-1.62 (m, 1H), 1.41-1.49 (m, 1H). LCMS[M+H] ⁺ = 331.3
85	A	¹ H NMR (400 MHz, CDCl ₃): δ 13.46-14.04 (m, 1H), 7.57-7.65 (m, 2H), 7.23-7.27 (m, 1H), 7.03-7.08 (m, 1H), 6.87-6.93 (m, 1H), 5.22-5.40 (m, 1H), 4.63 (m, 1H), 4.47-4.57 (m, 2H), 2.58-2.87 (m, 5H), 2.30-2.40 (m, 1H), 2.25 (s, 3H), 1.89-2.03 (m, 1H), 1.71-1.84 (m, 1H), 1.60-1.67 (m, 2H). LCMS[M+H] ⁺ = 331.2

Cpd No.	General Synthetic Route	Characterization
86	A	¹ H NMR (400 MHz, CDCl ₃): δ 8.28 (s, 1H), 7.44-7.51 (m, 2H), 6.64-6.72 (m, 1H), 6.52-6.57 (m, 1H), 5.78-5.81 (m, 1H), 4.68-4.72 (m, 1H), 4.56-4.65 (m, 2H), 3.11-3.20 (m, 2H), 2.98 (dd, <i>J</i> = 28.4, 4.4, 2H), 2.75 – 2.84 (m, 1H), 2.45 - 2.55 (m, 1 H), 2.22 (s, 3 H), 1.85 - 2.05 (m, 2H), 1.55 – 1.69 (m, 2 H). LCMS[M+H] ⁺ = 349.1
87	A	LCMS[M+H] ⁺ = 366.2 (calc.)
88	A	LCMS[M+H] ⁺ = 348.2 (calc.)
89	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.46 (brs, 1H), 7.42 (d, <i>J</i> = 8.0 Hz, 1H), 7.19-7.29 (m, 2H), 6.97 (s, 1H), 4.57-4.71 (m, 1H), 2.96 (s, 3H), 2.70-2.78 (m, 2H), 2.20 (s, 3H), 2.10 (s, 3H), 1.99-2.03 (m, 1H), 1.78-1.87 (m, 1H), 1.55-1.76 (m, 4H). LCMS[M+H] ⁺ = 381.3
90	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ: 10.56 (brs, 1H), 7.33-7.40 (m, 2H), 7.25 (d, <i>J</i> = 1.2 Hz, 1H), 6.96 (s, 1H), 4.56-4.67 (m, 1H), 2.95 (s, 3H), 2.70-2.76 (m, 2H), 2.19 (s, 3H), 2.08 (s, 3H), 1.99-2.05 (m, 1H), 1.78-1.85 (m, 1H), 1.57-1.74 (m, 4H). LCMS[M+H] ⁺ = 338.0
91	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.63 (brs, 1H), 8.16 (s, 1H), 8.06 (d, <i>J</i> = 8.4 Hz, 1H), 7.31-7.39 (m, 2H), 6.37 (d, <i>J</i> = 7.6 Hz, 1H), 4.20-4.30 (m, 1H), 2.89-2.95 (m, 1H), 2.60-2.67 (m, 1H), 2.24 (s, 3H), 2.20 (s, 3H), 1.84-1.97 (m, 3H), 1.67-1.75 (m, 1H), 1.52-1.61 (m, 1H), 1.38-1.49 (m, 1H). LCMS[M+H] ⁺ = 323.9

Cpd No.	General Synthetic Route	Characterization
92	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.11 (brs, 1H), 7.51 (s, 1H), 7.45 (d, <i>J</i> = 8.0 Hz, 1H), 7.25 (d, <i>J</i> = 8.0 Hz, 1H), 6.69 (s, 1H), 6.63 (d, <i>J</i> = 8.0 Hz, 1H), 4.00-4.07 (m, 1H), 2.85-2.90 (m, 1H), 2.57-2.60 (m, 1H), 2.19 (s, 3H), 1.99-2.04 (m, 4H), 1.89-1.94 (m, 1H), 1.81-1.86 (m, 1H), 1.69-1.74 (m, 1H), 1.53-1.59 (m, 1H), 1.27-1.34 (m, 1H). LCMS[M+H] ⁺ = 342.9
93	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 14.08 (brs, 1H), 8.11 (s, 1H), 7.94 (d, <i>J</i> = 8.0 Hz, 1H), 7.41-7.46 (m, 2H), 6.26 (d, <i>J</i> = 7.6 Hz, 1H), 4.22-4.28 (m, 1H), 2.91-2.95 (m, 1H), 2.64-2.67 (m, 1H), 2.23 (s, 3H), 2.20 (s, 3H), 1.94-1.99 (m, 2H), 1.86-1.90 (m, 1H), 1.69-1.73 (m, 1H), 1.55-1.60 (m, 1H), 1.42-1.47 (m, 1H). LCMS[M+H] ⁺ = 342.9
94	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.05-10.17 (m, 1H), 7.23 (t, <i>J</i> = 7.6 Hz, 1H), 7.14 (d, <i>J</i> = 7.2 Hz, 1H), 6.92 (d, <i>J</i> = 8.0 Hz, 1H), 6.88 (d, <i>J</i> = 7.2 Hz, 1H), 6.73 (brd, <i>J</i> = 7.2 Hz, 1H), 6.66 (s, 1H), 4.07-4.22 (m, 1H), 3.40-3.41 (m, 2H, overlapped with water peak single), 2.92-3.33 (m, 1H), 2.57-2.63 (m, 1H), 2.16-2.25 (m, 1H), 1.99-2.13 (m, 4H), 1.44-1.63 (m, 2H). LCMS[M+H] ⁺ = 329.0
95	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.77 (brs, 1H), 7.20-7.27 (m, 1H), 7.12-7.20 (m, 1H), 6.82-6.96 (m, 2H), 6.57-6.74 (m, 2H), 4.05-4.14 (m, 1H), 3.21-3.25 (m, 1H, overlapped with water peak single), 2.77-2.83 (m, 1H), 2.44 (s, 3H), 2.17-2.27 (m, 1H), 1.95-2.06 (m, 5H), 1.56-1.65 (m, 1H), 1.33-1.42 (m, 1H). LCMS[M+H] ⁺ = 343.1

Cpd No.	General Synthetic Route	Characterization
96	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 7.39 (d, <i>J</i> = 7.2 Hz, 1H), 7.18-7.25 (m, 2H), 6.90-7.02 (m, 1H), 6.67 (s, 1H), 4.26-4.53 (m, 1H), 2.70-2.93 (m, 1H), 2.52-2.56 (m, 3H) (overlap with DMSO- <i>d</i> ₆ signal), 2.17-2.31 (m, 4H), 2.02 (s, 3H), 1.59-1.71 (m, 1H). LCMS[M+H] ⁺ = 353.2
97	D	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 10.06 (brs, 1H), 7.40 (d, <i>J</i> = 7.6 Hz, 1H), 7.17-7.29 (m, 2H), 6.99 (s, 1H), 5.24-5.42 (m, 1H), 3.02 (s, 3H), 2.76-2.85 (m, 1H), 2.67-2.71 (m, 1H), 2.14-2.31 (m, 6H), 2.08 (s, 3H), 1.70-1.80 (m, 1H). LCMS[M+H] ⁺ = 367.3
98	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.32 (brs, 1H), 8.36 (s, 1H), 8.11 (d, <i>J</i> = 8.4 Hz, 1H), 7.21-7.35 (m, 2H), 5.22-5.33 (m, 1H), 2.82-3.04 (m, 1H), 1.92-2.42 (m, 10H), 1.70-1.82 (m, 1H), 1.42-1.70 (m, 2H). LCMS[M+H] ⁺ = 368.1
99	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.76 (brs, 1H), 7.26-7.32 (m, 1H), 7.17 (d, <i>J</i> = 7.2 Hz, 1H), 7.05 (s, 1H), 6.89-6.97 (m, 2H), 5.20-5.31 (m, 1H), 2.90-2.96 (m, 1H), 2.53-2.57 (m, 1H), 2.24-2.29 (m, 4H), 2.01-2.21 (m, 4H), 1.95-2.00 (m, 1H), 1.65-1.81 (m, 1H), 1.45-1.58 (m, 2H). LCMS[M+H] ⁺ = 330.2
100	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 7.35 (d, <i>J</i> = 8.0 Hz, 1H), 7.25 (d, <i>J</i> = 7.6 Hz, 1H), 7.18 (d, <i>J</i> = 1.2 Hz, 1H), 7.07 (s, 1H), 5.21-5.27 (m, 1H), 2.89-2.95 (m, 1H), 2.52-2.58 (m, 1H), 2.19 (s, 3H), 1.98-2.16 (m, 6H), 1.72-1.78 (m, 1H), 1.43-1.62 (m, 2H). LCMS[M+H] ⁺ = 325.3

Cpd No.	General Synthetic Route	Characterization
101	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.41 (brs, 1H), 8.39 (s, 1H), 8.10 (d, <i>J</i> = 8.0 Hz, 1H), 7.39-7.44 (m, 2H), 5.25-5.33 (m, 1H), 2.88-2.98 (m, 1H), 2.52-2.56 (m, 1H), 2.27 (s, 3H), 2.21 (s, 3H), 1.98-2.17 (m, 3H), 1.75-1.81 (m, 1H), 1.48-1.65 (m, 2H). LCMS[M+H] ⁺ = 325.3
102	C	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 7.48 (s, 1H), 7.36-7.39 (m, 2H), 7.29 (s, 1H), 2.75-2.83 (m, 2H), 2.63-2.66 (m, 2H), 2.12-2.15 (m, 6H), 1.96-2.06 (m, 1H), 1.82-1.88 (m, 1H), 1.66-1.70 (m, 1H), 1.55-1.65 (m, 2H), 1.38-1.50 (m, 1H), 0.91-1.03 (m, 1H). LCMS[M+H] ⁺ = 323.0
103	C	LCMS[M+H] ⁺ = 322.2 (calc.)
104	C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 7.13-7.51 (m, 4H), 2.79 (d, <i>J</i> = 7.2 Hz, 2H), 2.60-2.68 (m, 2H), 2.12-2.18 (m, 6H), 1.98-2.05 (m, 1H), 1.83-1.92 (m, 1H), 1.71-1.75 (m, 1H), 1.59-1.63 (m, 2H), 1.43-1.48 (m, 1H), 0.91-1.12 (m, 1H). LCMS[M+H] ⁺ = 366.0
105	C	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) 9.78 (brs, 1H), 7.43 (s, 1H), 7.27-7.33 (m, 1H), 7.18-7.23 (m, 1H), 6.90-6.99 (m, 2H), 2.75-2.80 (m, 2H), 2.54-2.56 (m, 2H, overlap with DMSO signal), 2.15 (s, 3H), 2.12 (s, 3H), 1.95-2.07 (m, 1H), 1.79-1.92 (m, 1H), 1.56-1.75 (m, 3H), 1.37-1.52 (m, 1H), 0.89-1.04 (m, 1H). LCMS[M+H] ⁺ = 298.2
106	C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.84-10.74 (m, 1H), 7.44 (s, 1H), 7.19-7.32 (m, 1H), 6.70-6.84 (m, 2H), 2.78 (d, <i>J</i> = 7.2 Hz, 2H), 2.63-2.70 (m, 2H), 2.10-2.16 (m, 6H), 1.97-2.08 (m, 1H), 1.78-1.90 (m, 1H), 1.58-1.73 (m, 3H), 1.40-1.49 (m, 1H), 0.92-1.04 (m, 1H). LCMS[M+H] ⁺ = 316.0

Cpd No.	General Synthetic Route	Characterization
107	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 14.04 (brs, 1H), 8.47-8.50 (m, 1H), 7.66 (d, <i>J</i> = 1.6 Hz, 1H), 7.25 (d, <i>J</i> = 7.6 Hz, 1H), 6.93 (s, 1H), 3.98-4.16 (m, 1H), 2.75-2.93 (m, 1H), 2.52-2.53 (m, 4H), 2.19 (s, 3H), 1.91-2.10 (m, 2H), 1.68-1.89 (m, 2H), 1.48-1.62 (m, 1H), 1.28-1.42 (m, 1H). LCMS[M+H] ⁺ = 368.0
108	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.55 (brs, 1H), 8.12-8.16 (m, 1H), 7.31-7.35 (m, 1H), 7.23-7.28 (m, 1H), 7.06 (d, <i>J</i> = 8.0 Hz, 1H), 6.88 (s, 1H), 4.01-4.11 (m, 1H), 2.78-2.87 (m, 1H), 2.51-2.55 (m, 4H), 2.18 (s, 3H), 1.81-2.05 (m, 3H), 1.67-1.76 (m, 1H), 1.51-1.58 (m, 1H), 1.27-1.37 (m, 1H). LCMS[M+H] ⁺ = 300.3
109	A	¹ H NMR (400 MHz, CDCl ₃) δ 8.03 (d, <i>J</i> = 2.4 Hz, 1H), 7.06 (dd, <i>J</i> = 2.8, 10.0 Hz, 1H), 6.68 (s, 1H), 5.28-5.47 (m, 1H), 4.17-4.24 (m, 1H), 2.75 (s, 3H), 2.51-2.62 (m, 3H), 2.30 (s, 3H), 2.22-2.28 (m, 1H), 1.74-1.86 (m, 3H), 0.76-0.95 (m, 1H). LCMS[M+H] ⁺ = 318.3
110	A	LCMS[M+H] ⁺ = 324.2 (calc.)
111	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.74 (brs, 1H), 7.22-7.30 (m, 1H), 7.18 (dd, <i>J</i> = 7.2, 1.6 Hz, 1H), 7.13 (s, 1H), 6.85-6.95 (m, 2H), 4.48 (d, <i>J</i> = 12.4 Hz, 1H), 4.24 (d, <i>J</i> = 12.8 Hz, 1H), 2.80-2.91 (m, 2H), 2.20-2.29 (m, 7H), 2.10 (s, 3H), 1.90-1.98 (m, 1H), 1.75-1.83 (m, 1H), 1.40-1.52 (m, 2H). LCMS[M+H] ⁺ = 313.1

Cpd No.	General Synthetic Route	Characterization
112	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ: 10.59 (brs, 1H), 7.33-7.40 (m, 2H), 7.26 (d, <i>J</i> = 1.2 Hz, 1H), 7.16 (s, 1H), 4.45-4.51 (m, 1H), 4.24 (brd, <i>J</i> = 12.8 Hz, 1H), 2.83-2.91 (m, 2H), 2.26 (s, 6H), 2.17-2.23 (m, 1H), 2.07 (s, 3H), 1.90-1.97 (m, 1H), 1.74-1.82 (m, 1H), 1.42-1.49 (m, 2H). LCMS[M+H] ⁺ = 338.0
113	A	¹ H NMR (400 MHz, CDCl ₃): δ 7.42 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.26-7.30 (m, 1H, overlap with CDCl ₃ signal), 7.12 (dd, <i>J</i> = 8.0, 0.8 Hz, 1H), 6.92-6.96 (m, 1H), 6.68 (s, 1H), 4.93 (brs, 1H), 3.51 (t, <i>J</i> = 6.4 Hz, 2H), 2.55-2.59 (m, 1H), 2.47 (s, 3H), 2.31-2.40 (m, 1H), 2.19-2.30 (m, 1H), 2.05-2.15 (m, 2H), 1.84-1.93 (m, 1H), 1.57-1.64 (m, 1H). LCMS[M+H] ⁺ = 320.0
114	A	¹ H NMR (400 MHz, CDCl ₃): δ 7.42 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.26-7.30 (m, 1H, overlap with CDCl ₃ signal), 7.12 (d, <i>J</i> = 8.4 Hz, 1H), 6.94 (d, <i>J</i> = 7.6 Hz, 1H), 6.68 (s, 1H), 4.93 (brs, 1H), 3.51 (t, <i>J</i> = 6.4 Hz, 2H), 2.55-2.59 (m, 1H), 2.47 (s, 3H), 2.31-2.40 (m, 1H), 2.19-2.30 (m, 1H), 2.05-2.15 (m, 2H), 1.84-1.93 (m, 1H), 1.57-1.64 (m, 1H). LCMS[M+H] ⁺ = 320.0
115	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.86 (brs, 1H), 7.23-7.34 (m, 2H), 6.87-7.01 (m, 3H), 6.76 (s, 1H), 3.92-3.98 (m, 2H), 3.30-3.38 (m, 4H, overlap with water signal), 2.12 (s, 3H), 1.93-1.99 (m, 1H), 1.72-1.78 (m, 2H), 1.28-1.34 (m, 2H). LCMS[M+H] ⁺ = 300.0
116	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.77 (brs, 1H), 7.19-7.26 (m, 1H), 7.16 (d, <i>J</i> = 7.2 Hz, 1H), 6.84-6.94 (m, 2H), 6.69-6.80 (m, 2H), 4.00-4.08 (m, 1H), 3.76-3.84 (m, 1H), 3.61-3.69 (m, 1H), 3.40-3.49 (m, 2H), 2.03 (s, 3H), 1.91-1.99 (m, 1H), 1.76-1.89 (m, 2H), 1.54-1.64 (m, 1H). LCMS[M+H] ⁺ = 286.0

Cpd No.	General Synthetic Route	Characterization
117	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.77 (brs, 1H), 7.11-7.27 (m, 2H), 6.82-6.98 (m, 2H), 6.62-6.81 (m, 2H), 3.99-4.10 (m, 1H), 3.77-3.84 (m, 1H), 3.60-3.68 (m, 1H), 3.35-3.52 (m, 2H), 2.02 (s, 3H), 1.78-1.98 (m, 3H), 1.54-1.64 (m, 1H). LCMS[M+H] ⁺ = 286.0
118	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.78 (brs, 1H), 7.13-7.24 (m, 2H), 6.83-6.94 (m, 2H), 6.75 (s, 1H), 6.63-6.68 (m, 1H), 3.67-3.73 (m, 4H), 2.87 (s, 1H), 2.03 (s, 3H), 1.74-1.79 (m, 2H), 1.33-1.44 (m, 2H). LCMS[M+H] ⁺ = 298.0
119	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.76 (brs, 1H), 7.19-7.26 (m, 1H), 7.15 (dd, <i>J</i> = 7.20, 1.20 Hz, 1H), 6.83-6.94 (m, 2H), 6.75-6.83 (m, 1H), 6.70 (s, 1H), 3.70-3.83 (m, 3H), 3.42-3.69 (m, 4H), 3.24-3.31 (m, 2H), 2.02 (s, 3H). LCMS[M+H] ⁺ = 302.0
120	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.75 (brs, 1H), 7.20-7.27 (m, 1H), 7.15 (dd, <i>J</i> = 7.20, 1.20 Hz, 1H), 6.84-6.94 (m, 2H), 6.78 (t, <i>J</i> = 6.0 Hz, 1H), 6.70 (s, 1H), 3.70-3.83 (m, 3H), 3.54-3.68 (m, 2H), 3.40-3.52 (m, 2H), 3.23-3.32 (m, 2H), 2.02 (s, 3H). LCMS[M+H] ⁺ = 302.0
121	A	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 9.77 (brs, 1H), 7.19-7.26 (m, 1H), 7.12-7.17 (m, 1H), 6.84-6.93 (m, 2H), 6.72 (s, 1H), 6.47-6.56 (m, 1H), 3.58-3.69 (m, 1H), 3.13-3.22 (m, 1H), 2.94-3.02 (m, 1H), 2.36-2.44 (m, 1H), 2.32 (s, 3H), 2.10-2.21 (m, 1H), 2.02 (s, 3H), 1.83-1.95 (m, 1H), 1.55-1.70 (m, 3H). LCMS[M+H] ⁺ = 299.0

Cpd No.	General Synthetic Route	Characterization
122	A	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 9.77 (brs, 1H), 7.19-7.26 (m, 1H), 7.12-7.17 (m, 1H), 6.84-6.93 (m, 2H), 6.72 (s, 1H), 6.47-6.56 (m, 1H), 3.58-3.69 (m, 1H), 3.13-3.22 (m, 1H), 2.94-3.02 (m, 1H), 2.36-2.44 (m, 1H), 2.32 (s, 3H), 2.10-2.21 (m, 1H), 2.02 (s, 3H), 1.83-1.95 (m, 1H), 1.55-1.70 (m, 3H). LCMS[M+H] ⁺ = 299.1
123	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.63-10.20 (m, 2H), 8.17 (s, 1H), 7.14-7.36 (m, 2H), 6.86-7.04 (m, 2H), 3.30-3.32 (m, 3H, overlapped with water peak single), 2.19 (s, 3H), 1.42 (s, 6H). LCMS[M+H] ⁺ = 302.0
124	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.79 (brs, 1H), 7.10-7.28 (m, 2H), 6.77-6.97 (m, 3H), 6.43 (s, 1H), 3.40-3.45 (m, 2H), 3.16 (s, 3H), 2.02 (s, 3H), 1.17 (s, 6H). LCMS[M+H] ⁺ = 288.0

EXAMPLE 6

NLRP3 INFLAMMASOME ACTIVATION AND CELL VIABILITY ASSESSMENT

IN THP1 MACROPHAGES

5 THP1 – Human acute monocytic leukemia cells were cultured (ATCC, cat # TIB-202) in Gibco RPMI-1640 medium (ThermoFisher cat # 72400054) supplemented with 10% Heat Inactivated FBS at density between 3-8 x10⁵ viable cells/ml. The cells were then subcultured when the cell concentration reached 8 x10⁵ cells/mL (every 2-3 days).

To determine the compounds' IC₅₀, 1.75x10⁴ cells/well were plated in CELLSTAR
 10 384 well plates (Greiner cat # 781091) in 50ul /well DMEM (ThermoFisher, cat # 10393021), 10% FBS, 1x GlutaMax (ThermoFisher, cat # 35050038) + 20 nM PMA (Sigma, cat # P1585) and only

the inner 224 wells of a 384 well plate were used. The paremetier wells were filled with 50 ul PBS and incubated at 37°C, 5% CO₂ for 48 hrs.

After 48 hrs incubation, the PMA containg media was removed, and changed for 40 ul/well of fresh DMEM, 10% FBS, 1x GlutMax and incubated at 37°C, 5% CO₂ for 24 hrs.

5 The following day the cells were primed with LPS (*E.coli*) (Sigma, cat # L3129) at 20 ng/ml in DMEM, 10%FBS, 1x GlutMax for 3 hrs at 37°C, 5% CO₂.

Following the LPS priming step, the cells were treated with compounds at 10 uM top final concentration, 1:4 dilution, 8 times: (10 uM, 2.5 uM, 0.625 uM, 0.156 uM, 0.039 uM, 0.0097 uM, 0.0024 uM, 0.0006 uM). DMSO was used as a vehicle control, and MCC950
10 (InvivGen, cat # inh-mcc) was used at 1 uM as a postive control, and incubated for 1 hrs at 37°C, 5% CO₂.

Following the 1 hr compound incubation, the NLRP3 inflammasome activation step was conducted by treateing cells with Nigericin (InvivoGen, cat # tlr1-nig) at 6.7 uM final concentration for 3 hrs at 37°C, 5% CO₂.

15 Thereafter, 30 ul samples of cells' supernatants were collected for cytokine analysis which was conducted on Hu IL-1 β AlphaLISA (Perkin Elemer, cat # AL220C) and Hu IL-6 AlphaLISA (Perkin Elemer, cat # AL220C). The cells' viability was assessed by perfoming CellTiter-Glo Luminescent Assay (Promega, cat #G7572) according to the manufacturer's protocol.

Cell viability assessment for select NLRP3 inflammasome modulators is
20 displayed in Tables 8 and 9.

For Table 8 - The activity ranges are as follows: "+++++" denotes IL-1 β activity of ≤ 1 nM; "++++" denotes IL-1 β activity of >1 nM and ≤ 10 nM; "+++" denotes IL-1 β activity of >10 nM and ≤ 100 nM; "++" denotes IL-1 β activity of >100 nM and ≤ 500 nM; "+" denotes IL-1 β activity of >500 nM and $\leq 1,000$ nM; "+" denotes IL-1 β activity of $>1,000$ nM; and "*" denotes
25 not yet tested.

For Table 4 – The activity ranges are as follows: "++++" denotes IL-6 activity of ≤ 1 μ M; "+++" denotes IL-6 activity of >1 μ M and ≤ 5 μ M; "++" denotes IL-6 activity of >5 μ M and ≤ 10 μ M; "+" denotes IL-6 activity of >10 μ M; and "*" denotes not yet tested.

Table 8

Cpd No.	IL-1 β Activity (nM)
1	+++++
2	+++++
3	+++++
4	+++
5	+++++
6	+++++
7	+++++
8	+++++

Cpd No.	IL-1 β Activity (nM)
9	+++
10	++++
11	+++++
12	+++++
13	+++++
14	++++
15	+++++
16	+++++

Cpd No.	IL-1 β Activity (nM)
17	+
18	+
19	+
20	+
21	++++
22	++++
23	++++
24	++++

Cpd No.	IL-1 β Activity (nM)
25	+
26	+++++
27	++++
28	++++++
29	*
30	+
31	+
32	+

Cpd No.	IL-1 β Activity (nM)
33	+
34	++++
35	++++
36	++++
37	++
38	+++++
39	++++
40	++

Cpd No.	IL-1 β Activity (nM)
41	++++
42	++++
43	++++
44	+++++
45	+++
46	*
47	++++
48	++++

Cpd No.	IL-1 β Activity (nM)
49	++++
50	++++
51	+++++
52	+++++
53	*
54	*
55	*
56	+++++

Cpd No.	IL-1 β Activity (nM)
57	+++++
58	+++++
59	+++++
60	+++++
61	*
62	+++++
63	+++++
64	+++++

Cpd No.	IL-1 β Activity (nM)
65	+++++
66	+++
67	+++++
68	++++
69	+++++
70	++++
71	++++
72	++++

Cpd No.	IL-1 β Activity (nM)
73	+
74	+++++
75	+++++
76	+++++
77	++++
78	+++++
79	+++
80	+++++

Cpd No.	IL-1 β Activity (nM)
81	+++++
82	++++
83	+++++
84	+++++
85	+
86	++
87	*
88	*

Cpd No.	IL-1 β Activity (nM)
89	*
90	+++++
91	++++
92	++++
93	+
94	+
95	+
96	+++++

Cpd No.	IL-1 β Activity (nM)
97	++++
98	+++
99	+
100	+++
101	+
102	+++
103	*
104	+++++

Cpd No.	IL-1 β Activity (nM)
105	+
106	+
107	++++++
108	+++
109	+++
110	*
111	+++
112	+

Cpd No.	IL-1 β Activity (nM)
113	+
114	+
115	+
116	+
117	++
118	+
119	+
120	+

Cpd No.	IL-1 β Activity (nM)
121	+
122	+

Cpd No.	IL-1 β Activity (nM)
123	+
124	+

5

Table 9

Cpd No.	IL-6 Activity (μ M)
1	++++
2	++

Cpd No.	IL-6 Activity (μ M)
3	++
4	+

Cpd No.	IL-6 Activity (μ M)
5	+
6	++

Cpd No.	IL-6 Activity (μ M)
7	+++
8	+
9	+
10	++
11	+
12	+
13	+
14	+

Cpd No.	IL-6 Activity (μ M)
15	*
16	*
17	+
18	++
19	++
20	++
21	++
22	+

Cpd No.	IL-6 Activity (μ M)
23	+
24	+++
25	+++
26	+
27	+
28	++++
29	*
30	+

Cpd No.	IL-6 Activity (μ M)
31	+
32	+
33	+
34	+
35	++
36	+
37	+
38	+++

Cpd No.	IL-6 Activity (μ M)
39	+
40	+
41	*
42	+
43	+
44	+
45	+
46	*

Cpd No.	IL-6 Activity (μ M)
47	+
48	+
49	+
50	+
51	++
52	+
53	*
54	*

Cpd No.	IL-6 Activity (μ M)
55	*
56	+
57	++
58	++
59	++
60	+
61	*
62	+

Cpd No.	IL-6 Activity (μ M)
63	+
64	+
65	+
66	++
67	++
68	+
69	++
70	+

Cpd No.	IL-6 Activity (μ M)
71	+
72	+
73	+
74	+
75	+
76	++
77	+
78	+

Cpd No.	IL-6 Activity (μ M)
79	++++
80	++
81	+
82	++++
83	*
84	+
85	+
86	+

Cpd No.	IL-6 Activity (μ M)
87	*
88	*
89	*
90	+
91	+
92	+
93	+
94	+

Cpd No.	IL-6 Activity (μ M)
95	+
96	+
97	+
98	+
99	+
100	+
101	+
102	+

Cpd No.	IL-6 Activity (μ M)
103	*
104	+
105	+
106	+
107	+
108	+
109	++
110	*

Cpd No.	IL-6 Activity (μ M)
111	+
112	+
113	+
114	+
115	+
116	+
117	+
118	+

Cpd No.	IL-6 Activity (μ M)
119	*
120	+
121	+
122	+
123	+
124	+

EXAMPLE 7

HERG ASSAY PROTOCOL

IN CHO-HERG CELLS

CHO-hERG cells (Sophion Biosciences (Ballerup, Denmark), subcultured and
5 frozen in WuXi AppTec (Suzhou) Co., Ltd.), stored in liquid nitrogen, were tested and determined
to be free from mycoplasma contamination. Cells were not used after the 30th passage. CHO-
hERG cells were cultured in a humidified incubator of 5% CO₂ (4% to 8%) in air at 37°C (±2°C).
The cells were recovered with recovery medium (F12 medium with 10% fetal bovine serum),
subcultured in complete medium (F12 medium, supplemented with 10% fetal bovine serum, 1%
10 Geneticin® selective antibiotic (G418), 89 µg/mL Hygromycin B (HB)), and the culture medium
was switched to recovery medium in the last subculture before patch-clamp experiment.

To determine the compounds' IC₅₀, select compounds ("test articles") were
dissolved into DMSO, and then diluted with ECS to get working solutions. Five concentrations of
0.3, 1, 3, 10, and 30 µM were tested. Two replicate cells for each concentration were tested.

15 Exponentially growing CHO-hERG cells were collected and suspended in
extracellular solution for use. The hERG current was recorded at physiological temperature (33.0
°C to 37.0 °C) using whole-cell patch-clamp techniques. Output signals from the patch-clamp
amplifier were digitized and low-pass filtered at 2.9 KHz. The recording was controlled with
Patchmaster Pro software. The recording chamber with seeded cells was mounted on an
20 inverted microscope stage. A cell in the recording chamber was randomly selected for testing.
The cell was continuously perfused from the perfusion system. A micropipette filled with ICS
was used as recording electrode in the manual patch-clamp study. The micropipette was
prepared on the day of the patch-clamp experiment using glass capillaries (BF150-117-10,
SUTTER INSTRUMENT USA). The pipette resistance (Rp) was within 2 to 5 MΩ with ICS filled.
25 From the holding potential of -80 mV, the voltage was increased to +60 mV for 850 ms to open
the hERG channels. After that, the voltage was decreased to -50 mV for 1275 ms, causing a
"rebound" or tail current, the peak tail current was measured and collected for data analysis.
Finally, the voltage was decreased to the holding potential (-80 mV). This command voltage
protocol was repeated every 15s continuously during the test article application.

During the initial recording period with vehicle control working solution, the peak tail current amplitude was monitored until it had been stable for at least 3 sweeps. Cells were then perfused with test article/positive control working solutions until the peak tail current amplitude reached steady state. Steady state was considered reached when three consecutive
5 super-imposable peak tail currents were collected. At this point, cells were once again perfused with next concentration of test article. One or more test articles/positive control or different concentrations of the same test article were tested on each cell with vehicle control washout until the current amplitude returned to values at least 80% of those measured before application of test article. 100 nM cisapride was tested as the positive control to evaluate the
10 reliability of the test system. At least 2 replicate cells for each concentration were tested. According to scientific literature, 100 nM cisapride inhibits hERG current more than 50%. (Milnes, J.T., et al.)

Seal criteria: When acquiring whole-cell configuration, a holding potential (e.g., -80 mV) was applied while membrane parameters were collected (Cm, Rm and Rs). A “good”
15 whole-cell recording was generally defined as: series resistance (Rs) was less than 10 MΩ; membrane resistance (Rm) was more than 500 MΩ and membrane capacitance (Cm) was less than 100 pF. Current amplitude: The peak current amplitude must be between 400 pA and 5000 pA before the test article/positive control application; otherwise the cell was discarded. Leak criteria: At -80 mV holding potential, the absolute leak current value must be less than 200 pA.
20 The amplitude of current was adjusted with leak current at -80 mV. The sweeps which absolute leak current value was more than 200 pA was not used in data analysis.

Activity assessment for select compounds is displayed in Table 10.

For Table 10 – The activity ranges are as follows: “+++++” denotes hERG activity $\leq 1 \mu\text{M}$; “++++” denotes hERG activity of $>1 \mu\text{M}$ and $\leq 3 \mu\text{M}$; “+++” denotes hERG activity of $>3 \mu\text{M}$ and $\leq 10 \mu\text{M}$; “++” denotes hERG activity of $>10 \mu\text{M}$ and $\leq 20 \mu\text{M}$; “+” denotes hERG activity of $>20 \mu\text{M}$ and $\leq 30 \mu\text{M}$; “+” denotes hERG activity of $> 30 \mu\text{M}$; and “*” denotes not yet tested.
25

Table 10

Cpd No.	hERG Activity (μ M)
1	++
2	+
3	++++
4	*
5	*
6	*
7	+
8	*

Cpd No.	hERG Activity (μ M)
9	*
10	*
11	*
12	*
13	*
14	*
15	++++
16	*

Cpd No.	hERG Activity (μ M)
17	*
18	*
19	*
20	*
21	+
22	+
23	*
24	*

Cpd No.	hERG Activity (μ M)
25	*
26	*
27	*
28	*
29	*
30	*
31	*
32	*

Cpd No.	hERG Activity (μ M)
33	*
34	+
35	*
36	*
37	*
38	*
39	*
40	*

Cpd No.	hERG Activity (μ M)
41	*
42	*
43	*
44	*
45	*
46	*
47	*
48	*

Cpd No.	hERG Activity (μ M)
49	*
50	*
51	+
52	*
53	*
54	*
55	*
56	*

Cpd No.	hERG Activity (μ M)
57	*
58	*
59	*
60	*
61	*
62	*
63	*
64	*

Cpd No.	hERG Activity (μ M)
65	*
66	*
67	+++
68	*
69	*
70	*
71	*
72	*

Cpd No.	hERG Activity (μ M)
73	*
74	*
75	*
76	*
77	*
78	*
79	*
80	*

Cpd No.	hERG Activity (μ M)
81	*
82	*
83	*
84	*
85	*
86	*
87	*
88	*

Cpd No.	hERG Activity (μ M)
89	*
90	*
91	*
92	*
93	*
94	*
95	*
96	*

Cpd No.	hERG Activity (μ M)
97	*
98	*
99	*
100	*
101	*
102	*
103	*
104	*

Cpd No.	hERG Activity (μ M)
105	*
106	*
107	*
108	*
109	*
110	*
111	*
112	*

Cpd No.	hERG Activity (μ M)
113	*
114	*
115	*
116	*
117	*
118	*
119	*
120	*

Cpd No.	hERG Activity (μM)	Cpd No.	hERG Activity (μM)
121	*	123	*
122	*	124	*

EXAMPLE 8

5 COMPARATIVE ASSAY DATA

Inhibition of hERG channels and associated QT prolongation in the electrocardiograph (ECG) associated with NLRP3 inflammasome modulators represents a recognized human cardiovascular safety risk (Hancox *et al.*, *Molecular Pharmacology* 2008, 73:1592-1595, incorporated here by reference). QT prolongation can lead to torsades de pointes
10 (TdP) cardiac arrhythmia which can degenerate into ventricular tachycardia and sudden death. As such, there is a need for NLRP3 inflammasome modulators that overcome hERG safety liabilities.

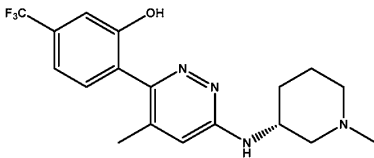
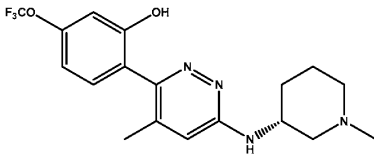
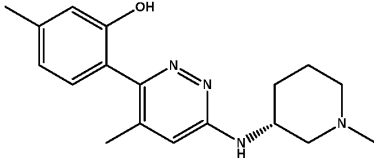
Provided are NLRP3 modulators which have surprising and unexpected technical advantages with regard to cardiac ion channel (e.g., hERG) activity. For example,
15 compounds 2, 21, 22, and 51 (and similar analogs thereof) of the present invention exhibit potent IL-1β and IL-6 activity, while possessing unexpectedly low hERG inhibition. By comparison, compounds A, B, C, D, and compounds 3 and 15 as shown in Table 6 below, while exhibiting potent IL-1β activity, possess high hERG inhibition. These data show that chemical

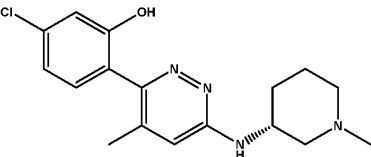
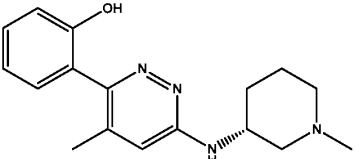
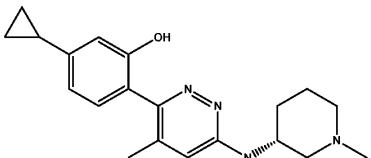
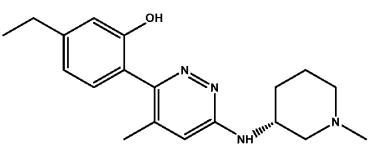
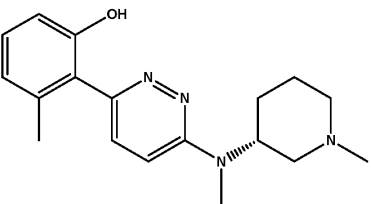
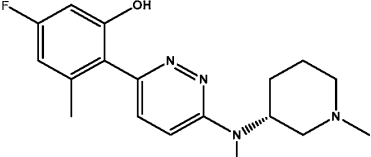
properties of functional groups attached at R¹ position have a significant effect on whether compounds will display favorable properties in humans. Without wishing to be bound by theory, functional groups at the R¹ position that present a small steric dimension paired with electron withdrawing properties impart potent IL-1 β activity and low hERG inhibition. Accordingly, compounds 2, 21, 22, and 51 (and similar analogs thereof) show surprisingly favorable data for application in humans.

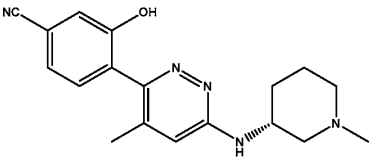
A comparison of IL-1 β , IL-6, and hERG activity is assessed for select compounds in Table 11.

For Table 11 – The activity ranges are as stated above for IL-1 β , IL-6, and hERG (see, Tables 3, 4, and 5, respectively).

Table 11

Cpd No.	Cpd Structure	IL-1 β Activity (nM)	IL-6 Activity (μ M)	hERG Activity (μ M)
A		++++	+	++++++
B		++++++	+	+++++
C		++++++	+	+++

Cpd No.	Cpd Structure	IL-1 β Activity (nM)	IL-6 Activity (μ M)	hERG Activity (μ M)
D		++++++	+	++++
2		+++++	++	+
3		++++++	++	++++
15		++++++	*	++++
21		++++	++	+
22		++++	+	+

Cpd No.	Cpd Structure	IL-1 β Activity (nM)	IL-6 Activity (μ M)	hERG Activity (μ M)
51		++++++	++	+

The characterization data of the compounds A, B, C, and D are summarized below in Table 12.

Table 12

Cpd No.	Characterization
A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 14.56 (br s, 1H), 8.14 (s, 1H), 8.08 (d, <i>J</i> = 8.8 Hz, 1H), 7.18-7.27 (m, 2H), 6.32 (br d, <i>J</i> = 7.6 Hz, 1H), 4.18-4.30 (m, 1H), 2.88-2.98 (m, 1H), 2.50-2.70 (m, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 1.83-1.98 (m, 3H), 1.66-1.75 (m, 1H), 1.50-1.63(m, 1H), 1.37-1.49 (m, 1H). LCMS[M+H] ⁺ = 367.1
B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 14.56 (brs, 1H), 8.14 (s, 1H), 8.08 (d, <i>J</i> = 8.8 Hz, 1H), 7.18-7.27 (m, 2H), 6.32 (br d, <i>J</i> = 7.6 Hz, 1H), 4.18-4.30 (m, 1H), 2.88-2.98 (m, 1H), 2.50-2.70 (m, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 1.83-1.98 (m, 3H), 1.66-1.75 (m, 1H), 1.50-1.63(m, 1H), 1.37-1.49 (m, 1H). LCMS[M+H] ⁺ = 383.0
C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.20 (brs, 1H), 7.27 (d, <i>J</i> = 9.2 Hz, 3H), 6.83-6.87 (m, 2H), 6.61-6.70 (m, 2H), 3.99-4.05 (m, 1H), 2.88-2.92 (m, 1H), 2.56-2.58 (m, 1H) (overlap with DMSO- <i>d</i> ₆ single), 2.21 (s, 3H), 1.91-2.08 (m, 5H), 1.79-1.90 (m, 1H), 1.65-1.75 (m, 1H), 1.45-1.57 (m, 1H), 1.21-1.37 (m, 1H). LCMS[M+H] ⁺ = 313.3

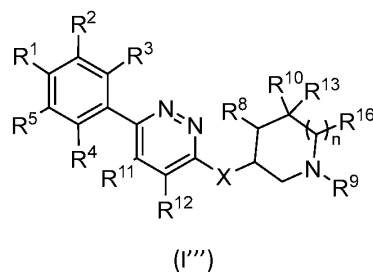
Cpd No.	Characterization
D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.22 (s, 1H), 7.05 (d, <i>J</i> = 7.6 Hz, 1H), 6.73 (s, 1H), 6.69 (d, <i>J</i> = 9.6 Hz, 2H), 6.62 (d, <i>J</i> = 8.0 Hz, 1H), 4.05-4.10 (m, 1H), 2.91-3.11 (m, 1H), 2.65-2.7 (m, 1H), 2.25-2.32 (m, 6H), 2.14-2.22 (m, 1H), 2.00-2.10 (m, 4H), 1.82-1.90 (m, 1H), 1.71-1.80 (m, 1H), 1.53-1.65 (m, 1H), 1.27-1.40 (m, 1H). LCMS[M+H] ⁺ = 333.1

The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, including U.S. Provisional Application No. 63/341,975, filed on May 13, 2022, are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary, to employ concepts of the various patents, applications and publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

1. A compound having structure (I'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

X is CR_aR_b, NR_a or O;

R_a and R_b are each, independently, H or C₁₋₆ alkyl;

R¹ is H, F or CN;

R² and R⁵ are each, independently, H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OC₁₋₆ alkyl or OC₁₋₆ haloalkyl;

one of R³ or R⁴ is OH and the other is H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OC₁₋₆ alkyl or OC₁₋₆ haloalkyl;

R⁸ is H or halo;

R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

R^{9'} is OH, halo or C₃₋₅ cycloalkyl;

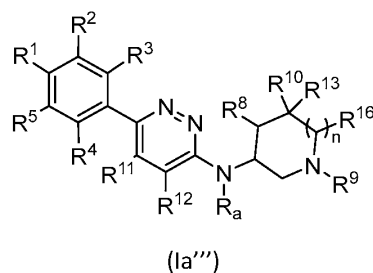
R¹⁰ and R¹³ are each, independently, H or halo;

R¹¹ and R¹² are each, independently, is H, halo, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl or OC₁₋₆ alkyl;

R¹⁶ is H or CO₂H; and

n is 0, 1 or 2.

2. The compound of claim 1, having structure (Ia'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C_{1-6} alkyl;

R^1 is H, F or CN;

R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

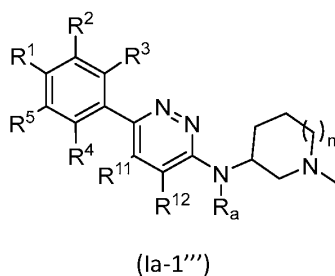
R^{10} and R^{13} are each, independently, H or halo;

R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

R^{16} is H or CO_2H ; and

n is 0, 1 or 2.

3. The compound of claim 1 or 2, having structure (Ia-1'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C_{1-6} alkyl;

R^1 is H, F or CN;

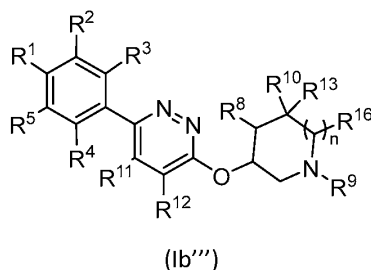
R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H or C_{1-6} alkyl;

R^{11} and R^{12} are each, independently, H, F or C_{1-6} alkyl; and

n is 0, 1 or 2.

4. The compound of claim 1, having structure (Ib'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^1 is H, F or CN;

R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

R^8 is H or halo;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more R^9 ;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

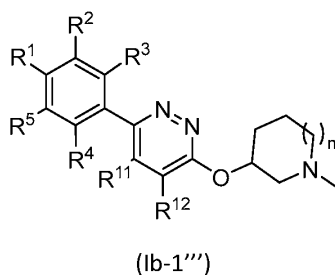
R^{10} and R^{13} are each, independently, H or halo;

R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

R^{16} is H or CO_2H ; and

n is 0, 1 or 2.

5. The compound of claim 1 or 4, having structure (Ib-1'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^1 is H, F or CN;

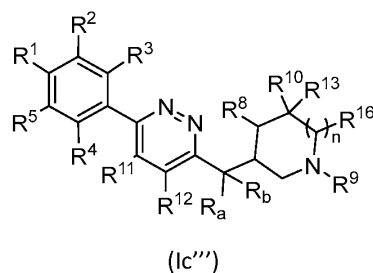
R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H or C_{1-6} alkyl;

R^{11} and R^{12} are each, independently, H or C_{1-6} alkyl; and

n is 0, 1 or 2.

6. The compound of claim 1, having structure (Ic''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a and R_b are each, independently, H or C₁₋₆ alkyl;

R^1 is H, F or CN;

R² and R³ are each, independently, H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OC₁₋₆ alkyl or OC₁₋₆ haloalkyl;

one of R³ or R⁴ is OH and the other is H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OC₁₋₆ alkyl or OC₁₋₆ haloalkyl;

R⁸ is H or halo;

R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

R^{9'} is OH, halo or C₃₋₅ cycloalkyl;

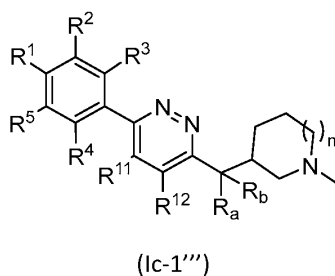
R¹⁰ and R¹³ are each, independently, H or halo;

R¹¹ and R¹² are each, independently, is H, halo, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl or OC₁₋₆ alkyl;

R¹⁶ is H or CO₂H; and

n is 0, 1 or 2.

7. The compound of claim 1 or 6, having structure (Ic-1'''):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a and R_b are each, independently, H or C_{1-6} alkyl;

R^1 is H, F or CN;

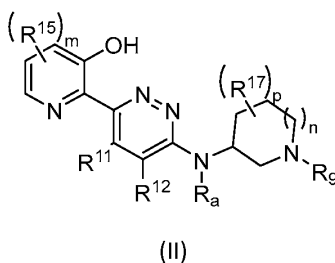
R^2 and R^5 are each, independently, H or C_{1-6} alkyl;

one of R^3 or R^4 is OH and the other is H or C_{1-6} alkyl;

R^{11} and R^{12} are each, independently, H or C_{1-6} alkyl; and

n is 0, 1 or 2.

8. A compound having structure (II):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C_{1-6} alkyl;

each R^{15} is, independently, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl, OC_{1-6} haloalkyl or C_{3-5} cycloalkyl;

R^9 is H, C_{3-5} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

each R^{17} is, independently, halo or CO_2H ;

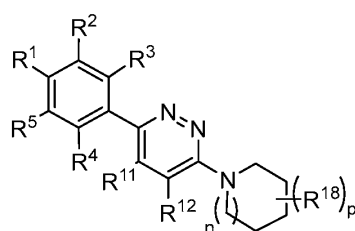
R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, or OC_{1-6} alkyl; and

n is 0- 2;

m is 0- 3; and

p is 0-9.

9. A compound having structure (III):



(III)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^1 is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl, OC_{1-6} haloalkyl or C_{3-5} cycloalkyl;

R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

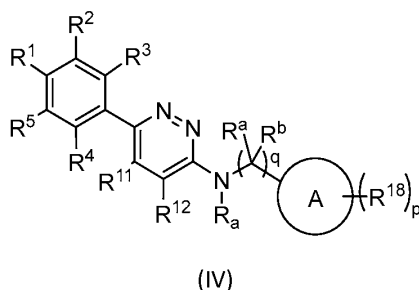
each R^{18} is halo, CO_2H , aminyl, C_{3-5} cycloalkyl, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl;

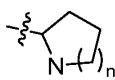
n is 1 or 2; and

p is 1-9.

10. A compound having structure (IV):



or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:



ring A is C₃₋₈ cycloalkyl, R⁹ or a saturated heterocyclic ring wherein the heteroatoms consist of 1-2 oxygen atoms;

each R_a and R_b are each, independently, H or C₁₋₆ alkyl;

R¹ is H, halo, OH, CN, C₁₋₆ alkyl, OC₁₋₆ alkyl, OC₁₋₆ haloalkyl or C₃₋₅ cycloalkyl;

R² and R⁵ are each, independently, H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OC₁₋₆ alkyl or OC₁₋₆ haloalkyl;

one of R³ or R⁴ is OH and the other is H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OC₁₋₆ alkyl or OC₁₋₆ haloalkyl;

R⁹ is H, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more R^{9'};

R¹¹ and R¹² are each, independently, is H, halo, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl or OC₁₋₆ alkyl;

each R¹⁸ is halo, CO₂H, aminyl, C₃₋₅ cycloalkyl, or C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one or more R^{9'};

R^{9'} is OH, halo or C₃₋₅ cycloalkyl;

n is 0, 1 or 2;

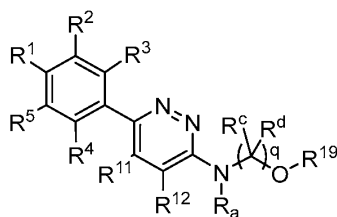
p is 0-9; and

q is 1-3.



provided that when R^1 is H and A is R^9 then R^9 is not unsubstituted ethyl.

11. A compound having structure (V):



(V)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R_a is H or C_{1-6} alkyl;

each R_c and R_d are each, independently, H or C_{1-6} alkyl, or R_c and R_d join together to form oxo;

R^1 is H, halo, OH, CN, C_{1-6} alkyl, OC_{1-6} haloalkyl or C_{3-5} cycloalkyl;

R^2 and R^5 are each, independently, H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

one of R^3 or R^4 is OH and the other is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl or OC_{1-6} haloalkyl;

R^{11} and R^{12} are each, independently, is H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl or OC_{1-6} alkyl;

R^{19} is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with one or more $R^{9'}$;

$R^{9'}$ is OH, halo or C_{3-5} cycloalkyl; and

q is 1-3.

12. The compound of claim 1, wherein X is NR_a .

13. The compound of claim 1 or 12, wherein X is O.
14. The compound of any one of claims 1, 12, or 13, wherein X is CR_aR_b.
15. The compound of any one of claims 1-14, wherein one of R¹¹ and R¹² is H.
16. The compound of any one of claims 1-15, wherein R¹¹ is C₁₋₆ alkyl and R¹² is H.
17. The compound of any one of claims 1-15, wherein R¹¹ is H and R¹² is C₁₋₆ alkyl.
18. The compound of any one of claims 1-14, wherein both R¹¹ and R¹² are H.
19. The compound of any one of claims 1-14, wherein both R¹¹ and R¹² are not H.
20. The compound of any one of claims 1-7 or 9-19, wherein R¹ is H.
21. The compound of any one of claims 1-7 or 9-19, wherein R¹ is F.
22. The compound of any one of claims 1-7 or 9-19, wherein R¹ is CN.
23. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R² and R⁵ are each, independently, H, C₁₋₆ alkyl, F, Cl, CF₃, or CN.
24. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R² is OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl, and R⁵ is H.
25. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R² is H and R⁵ is OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl.
26. The compound of any one of claims 1-7 or 9-22, wherein R² is H.
27. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R² is OH.

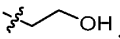
28. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R^2 is CF_3 .
29. The compound of any one of claims 1-7 or 9-22, wherein R^2 is C_{1-6} alkyl.
30. The compound of claim 29, wherein R^2 is methyl.
31. The compound of claim 29, wherein R^2 is ethyl.
32. The compound of claim 29, wherein R^2 is isopropyl.
33. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R^2 is CN.
34. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R^2 is F.
35. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R^2 is Cl.
36. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R^2 is Br.
37. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R^2 is OCF_3 .
38. The compound of any one of claims 1-2, 4, 6, or 9-22, wherein R^2 is OC_{1-6} alkyl.
39. The compound of claim 38, wherein R^2 is OCH_3 .
40. The compound of any one of claims 1-7, 9-22 or 26-39, wherein R^5 is H.
41. The compound of any one of claims 1-7, 9-22 or 26-39, wherein R^5 is OH.
42. The compound of any one of claims 1-7, 9-22 or 26-39, wherein R^5 is CF_3 .
43. The compound of any one of claims 1-7 or 9-22, wherein R^5 is C_{1-6} alkyl.

44. The compound of claim 43, wherein R⁵ is methyl.
45. The compound of claim 43, wherein R⁵ is ethyl.
46. The compound of claim 43, wherein R⁵ is isopropyl.
47. The compound of any one of claims 1-7, 9-22 or 26-39, or 14-39, wherein R⁵ is CN.
48. The compound of any one of claims 1-7, 9-22 or 26-39, wherein R⁵ is F.
49. The compound of any one of claims 1-7, 9-22 or 26-39, wherein R⁵ is Cl.
50. The compound of any one of claims 1-7, 9-22 or 26-39, wherein R⁵ is Br.
51. The compound of any one of claims 1-7, 9-22 or 26-39, wherein R⁵ is OCF₃.
52. The compound of any one of claims 1-7, 9-22 or 26-39, wherein R⁵ is OC₁₋₆ alkyl.
53. The compound of claim 52, wherein R⁵ is OCH₃.
54. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R³ is OH and R⁴ is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl.
55. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R⁴ is OH and R³ is H, OH, CF₃, C₁₋₆ alkyl, CN, halo, OCF₃ or OC₁₋₆ alkyl.
56. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R³ is OH and R⁴ is H or C₁₋₆ alkyl.
57. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R⁴ is OH and R³ is H or C₁₋₆ alkyl.

58. The compound of any one of claims 1-7 or 9-53, wherein R^3 is OH.
59. The compound of any one of claims 1-7 or 9-53, wherein R^3 is H.
60. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^3 is CF_3 .
61. The compound of any one of claims 1-7 or 9-53, wherein R^3 is C_{1-6} alkyl.
62. The compound of claim 61, wherein R^3 is methyl.
63. The compound of claim 61, wherein R^3 is ethyl.
64. The compound of claim 61, wherein R^3 is isopropyl.
65. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^3 is CN.
66. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^3 is F.
67. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^3 is Cl.
68. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^3 is Br.
69. The compound of any one of claims 1-7 or 9-53, wherein R^3 is OCF_3 .
70. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^3 is OC_{1-6} alkyl.
71. The compound of claim 70, wherein R^3 is OCH_3 .
72. The compound of any one of claims 1-7, 9-53 or 59-71, wherein R^4 is OH.
73. The compound of any one of claims 1-7 or 9-53, wherein R^4 is H.

74. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^4 is CF_3 .
75. The compound of any one of claims 1-7 or 9-53, wherein R^4 is C_{1-6} alkyl.
76. The compound of claim 75, wherein R^4 is methyl.
77. The compound of claim 75, wherein R^4 is ethyl.
78. The compound of claim 75, wherein R^4 is isopropyl.
79. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^4 is CN.
80. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^4 is F.
81. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^4 is Cl.
82. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^4 is Br.
83. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^4 is OCF_3 .
84. The compound of any one of claims 1, 2, 4, 6, or 9-53, wherein R^4 is OC_{1-6} alkyl.
85. The compound of claim 84, wherein R^4 is OCH_3 .
86. The compound of any one of claims 1, 2, 4, 6, or 12-85, wherein R^8 is H.
87. The compound of any one of claims 1, 2, 4, 6, or 12-85, wherein R^8 is F.
88. The compound of any one of claims 1, 2, 4, 6, or 12-85, wherein R^8 is Cl.
89. The compound of any one of claims 1, 2, 4, 6, or 12-85, wherein R^8 is Br.

90. The compound of any one of claims 1, 2, 4, 6, 8, or 12-89, wherein R^9 is H.
91. The compound of any one of claims 1, 2, 4, 6, 8, or 12-89, wherein R^9 is not H.
92. The compound of any one of claims 1, 2, 4, 6, 8, or 12-89, wherein R^9 is C_{1-6} alkyl.
93. The compound of claim 92, wherein R^9 is methyl.
94. The compound of claim 92, wherein R^9 is ethyl.
95. The compound of claim 92, wherein R^9 is isopropyl.
96. The compound of any one of claims 1, 2, 4, 6, 8, or 12-89, wherein R^9 is C_{1-6} alkyl optionally substituted with one or more F.
97. The compound of claim 96, wherein R^9 is $-CH_2CH_2F$.
98. The compound of claim 96, wherein R^9 is $-CH_2CHF_2$.
99. The compound of claim 96, wherein R^9 is $-CH_2CF_3$.
100. The compound of any one of claims 1, 2, 4, 6, 8, or 12-89, wherein R^9 is C_{3-5} cycloalkyl.
101. The compound of claim 100, wherein R^9 is cyclopropyl.
102. The compound of any one of claims 1, 2, 4, 6, 8, or 12-89, wherein R^9 is C_{1-6} alkyl optionally substituted with one or more C_{3-5} cycloalkyl.
103. The compound of claim 102, wherein R^9 is .

104. The compound of any one of claims 1, 2, 4, 6, 8, or 12-89, wherein R⁹ is C₁₋₆ alkyl optionally substituted with one or more OH.
105. The compound of claim 104, wherein R⁹ is .
106. The compound of any one of claims 1, 2, 4, 6, or 12-105, wherein R¹⁰ and R¹³ are both H.
107. The compound of any one of claims 1, 2, 4, 6, or 12-105, wherein R¹⁰ and R¹³ are both halo.
108. The compound of any one of claims 1, 2, 4, 6, or 12-105, wherein R¹⁰ is H and R¹³ is halo.
109. The compound of any one of claims 1, 2, 4, 6, or 12-105, wherein R¹⁰ is F.
110. The compound of any one of claims 1, 2, 4, 6, or 12-105, wherein R¹⁰ is Cl.
111. The compound of any one of claims 1, 2, 4, 6, or 12-105, wherein R¹⁰ is Br.
112. The compound of any one of claims 1, 2, 4, 6, 12-105 or 109-111, wherein R¹³ is F.
113. The compound of any one of claims 1, 2, 4, 6, 12-105 or 109-111, wherein R¹³ is Cl.
114. The compound of any one of claims 1, 2, 4, 6, 12-105 or 109-111, wherein R¹³ is Br.
115. The compound of any one of claims 8, 15-19, 90-105, wherein R¹⁵ is H.
116. The compound of any one of claims 8, 15-19 or 90-105, wherein R¹⁵ is halo.
117. The compound of claim 116, wherein R¹⁵ is F.

118. The compound of any one of claims 8, 15-19 or 90-105, wherein R^{15} is CN.
119. The compound of any one of claims 8, 15-19 or 90-105, wherein R^{15} is C_{1-6} haloalkyl.
120. The compound of claim 119, wherein R^{15} is CF_3 .
121. The compound of any one of claims 1, 2, 4, 6 or 12-114, wherein R^{16} is H.
122. The compound of any one of claims 1, 2, 4, 6 or 12-114, wherein R^{16} is CO_2H .
123. The compound of any one of claims 8, 15-19, 90-105 or 115-120, wherein R^{17} is halo.
124. The compound of claim 123, wherein R^{17} is F.
125. The compound of any one of claims 8, 15-19, 90-105 or 115-120, wherein R^{17} is CO_2H .
126. The compound of any one of claims 9, 10 or 15-85, wherein R^{18} is aminyl.
127. The compound of claim 126, wherein R^{18} is $NH(CH_3)_2$.
128. The compound of any one of claims 9, 10 or 15-85, wherein R^{18} is halo.
129. The compound of claim 128, wherein R^{18} is F.
130. The compound of any one of claims 11 or 15-85, wherein R^{19} is methyl.
131. The compound of any one of claims 1-8 or 10-130, wherein R_a is H.
132. The compound of any one of claims 1-8 or 10-130, wherein R_a is C_{1-6} alkyl.
133. The compound of claim 132, wherein R_a is methyl.

134. The compound of any one of claims 1, 6, 7, 10, 14, 15-114 or 124-133, wherein Rb is H.
135. The compound of any one of claims 1, 6, 7, 10, 14, 15-114 or 124-133, wherein Rb is C₁₋₆ alkyl.
136. The compound of claim 135, wherein Rb is methyl.
137. The compound of any one of claims 11, 15-85 or 128-133, wherein Rc is H.
138. The compound of any one of claims 11, 15-85 or 128-133, wherein Rc is C₁₋₆ alkyl.
139. The compound of claim 138, wherein Rc is methyl.
140. The compound of any one of claims 11, 15-85, 130-133 or 137-139, wherein Rd is H.
141. The compound of any one of claims 11, 15-85, 130-133 or 137-139, wherein Rd is C₁₋₆ alkyl.
142. The compound of claim 141, wherein Rd is methyl.
143. The compound of any one of claims 11, 15-85 or 130-133, wherein Rc and Rd join together to form oxo.
144. The compound of any one of claims 1-8 or 10-143, wherein n is 0.
145. The compound of any one of claims 1-143, wherein n is 1.
146. The compound of any one of claims 1-143, wherein n is 2.
147. The compound of claim 8, wherein m is 1.

148. The compound of claim 8, wherein p is 0.

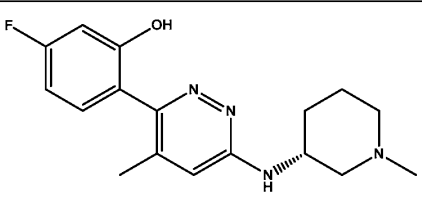
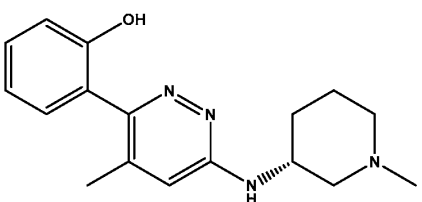
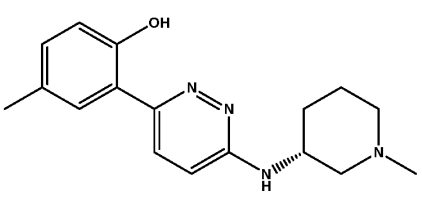
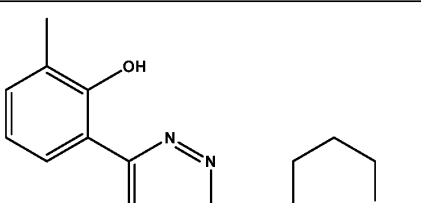
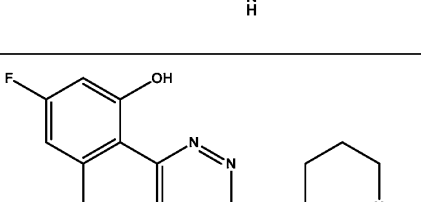
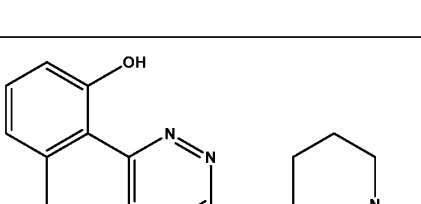
149. The compound of claim 9 or 10, wherein p is 1.

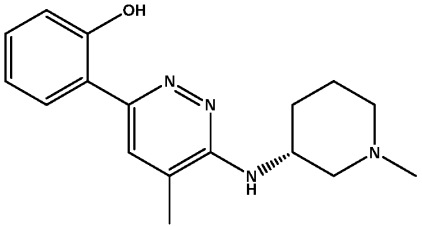
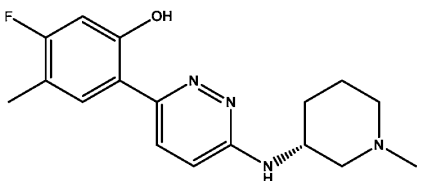
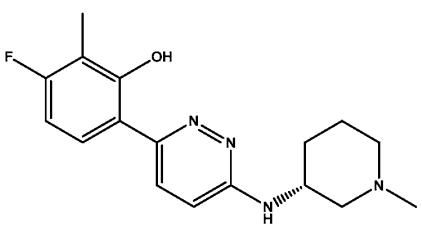
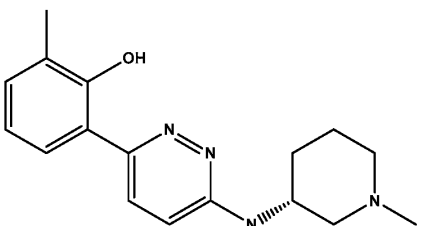
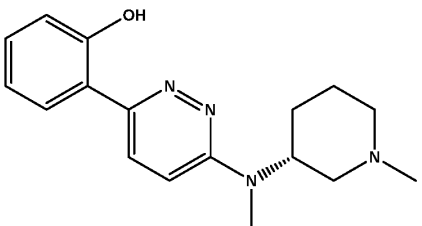
150. The compound of claim 10, wherein p is 2.

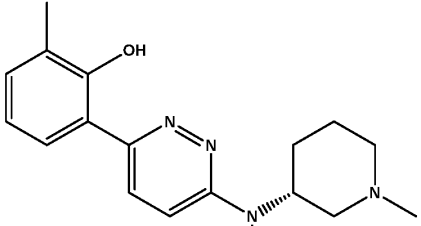
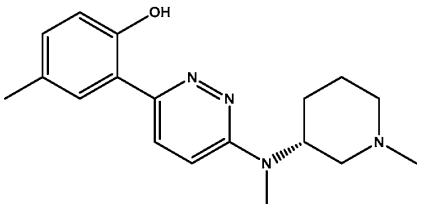
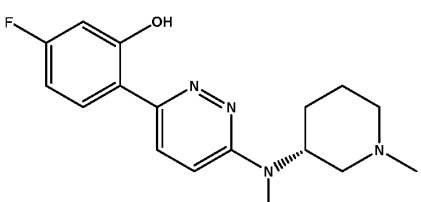
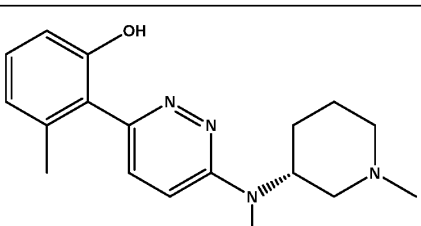
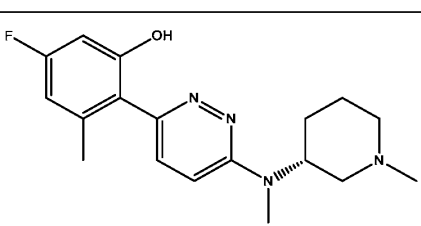
151. The compound of claim 10, wherein q is 1.

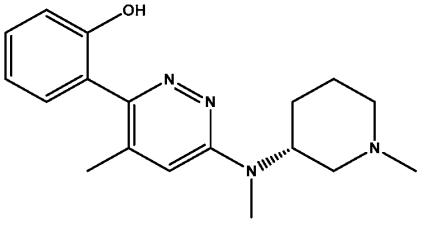
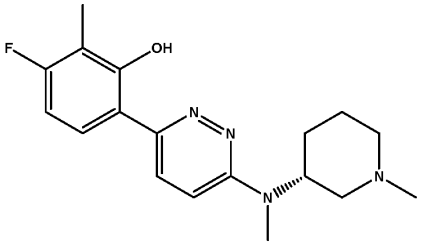
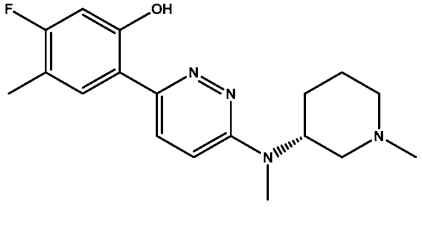
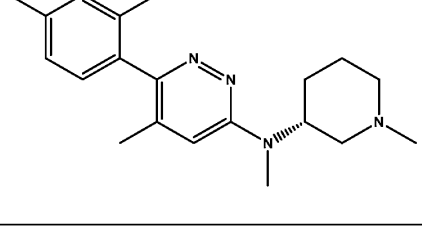
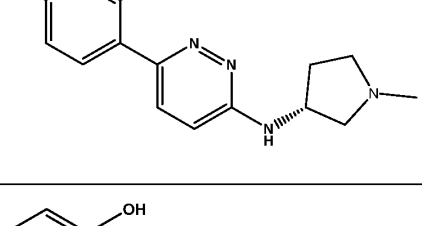
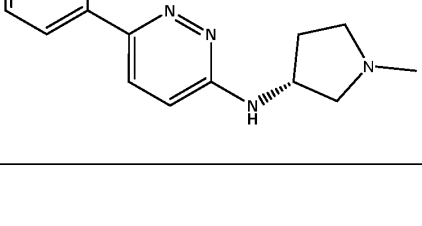
152. The compound of claim 11, wherein q is 2.

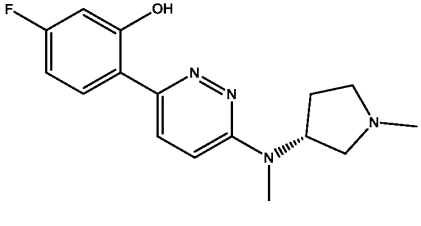
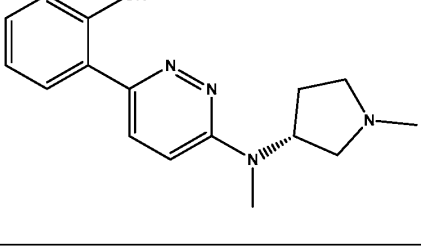
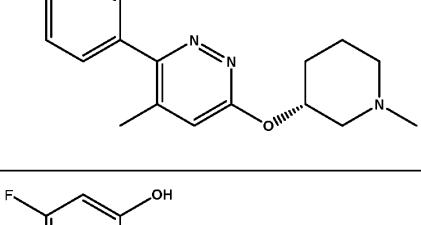
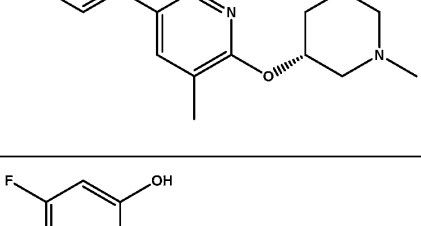
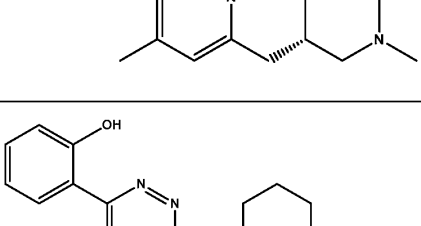
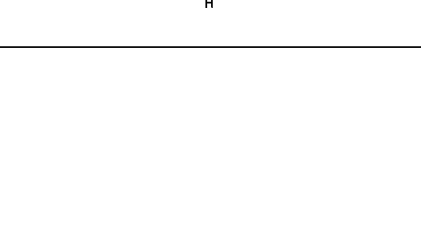
153. The compound of claim 1, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound has the following structure:

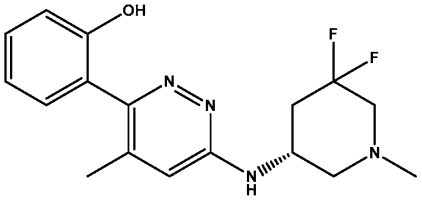
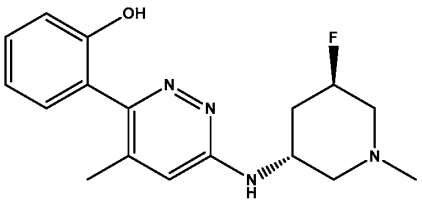
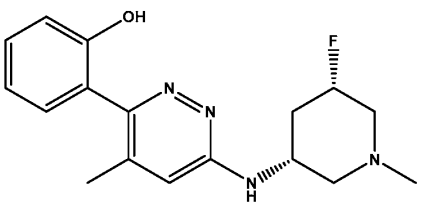
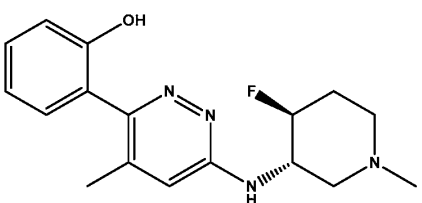
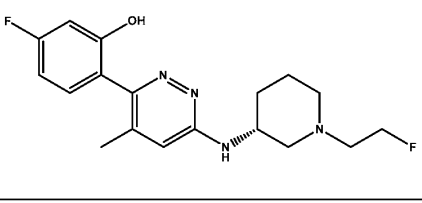
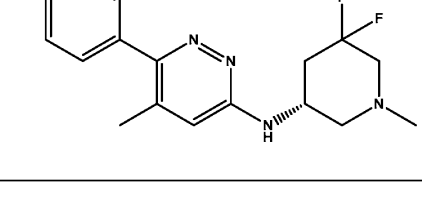
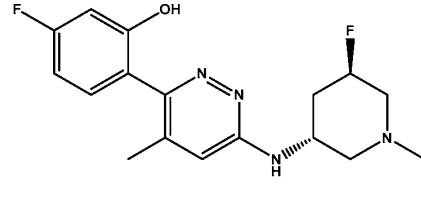
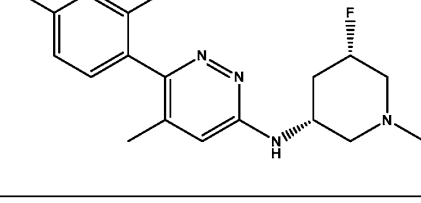
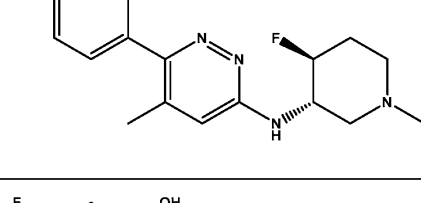
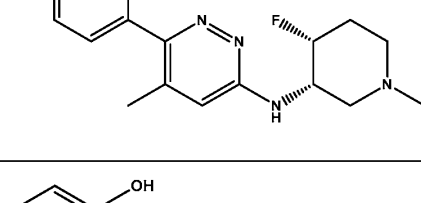
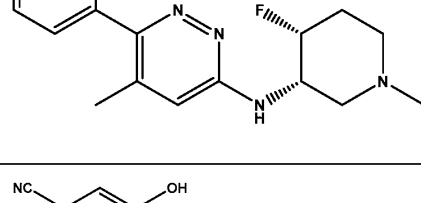
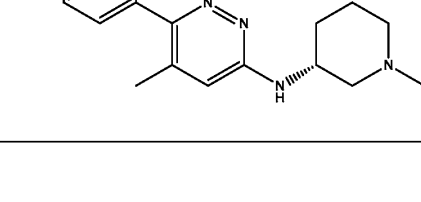
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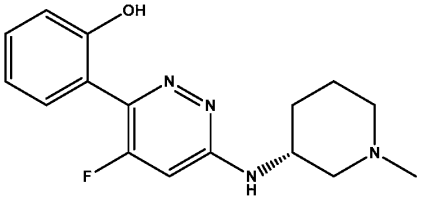
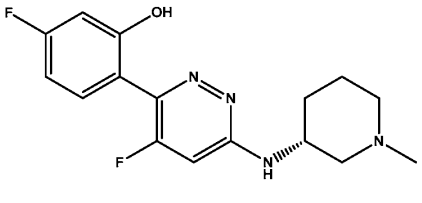
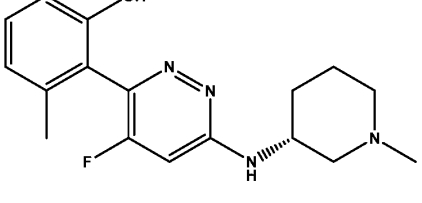
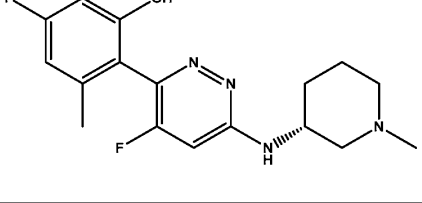
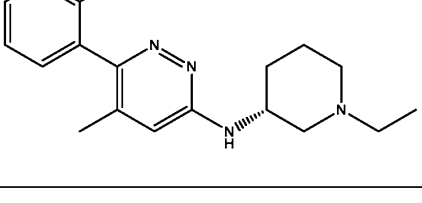
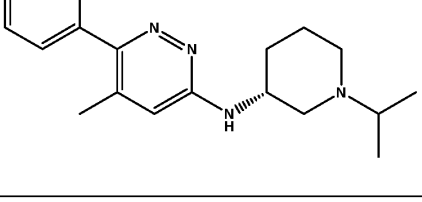
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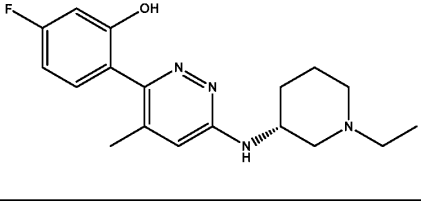
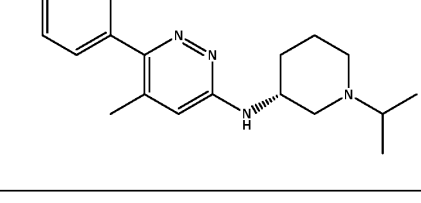
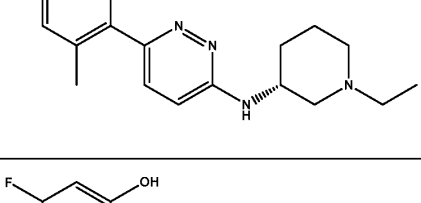
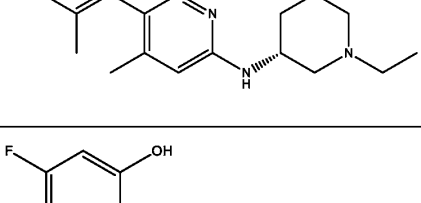
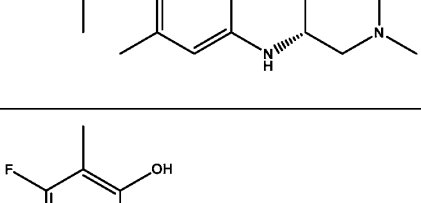
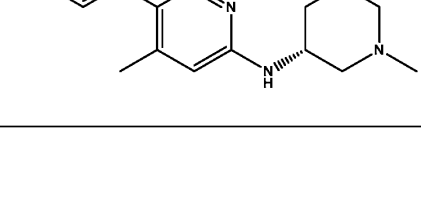
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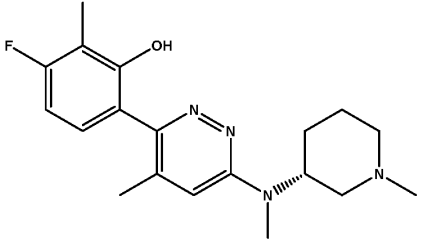
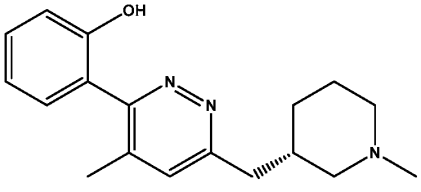
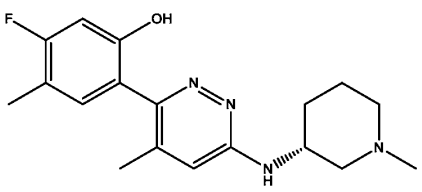
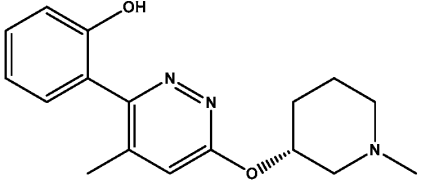
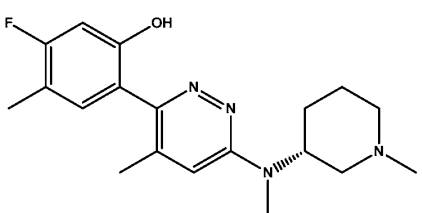
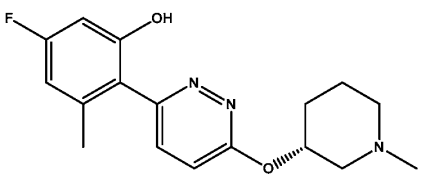
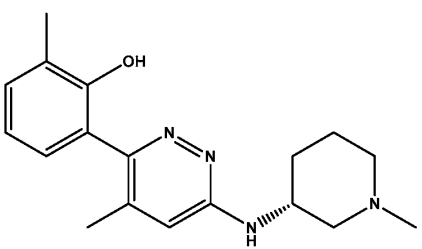
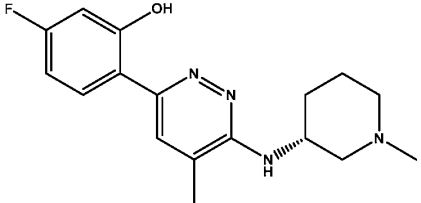
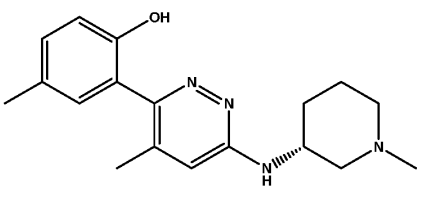
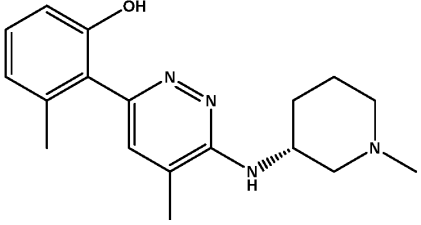
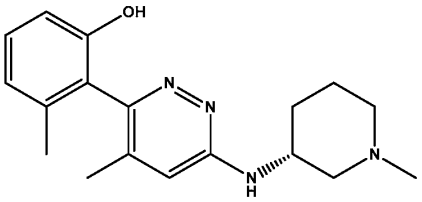
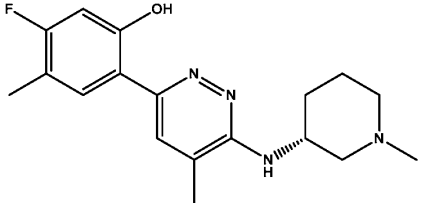
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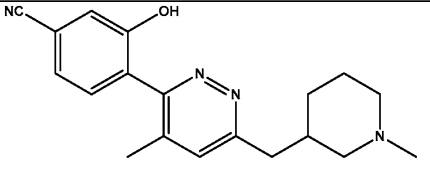
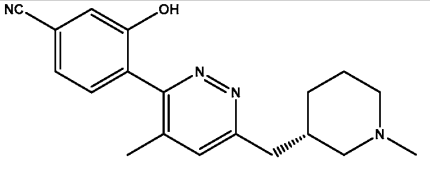
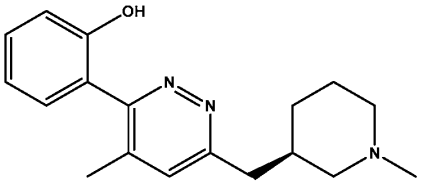
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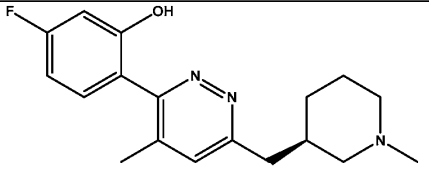
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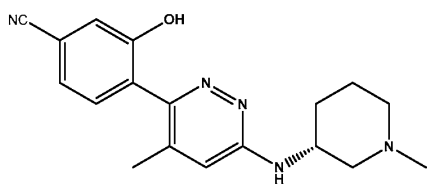
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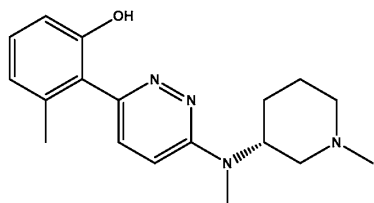
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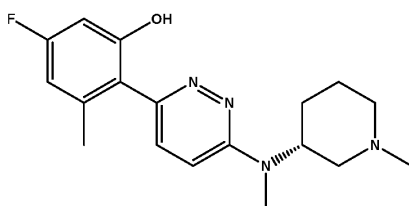
154. The compound of claim 153, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound has the following structure:



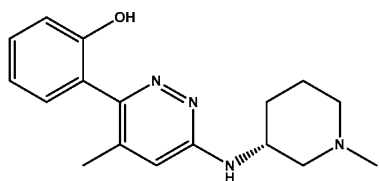
155. The compound of claim 153, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound has the following structure:



156. The compound of claim 153, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound has the following structure:



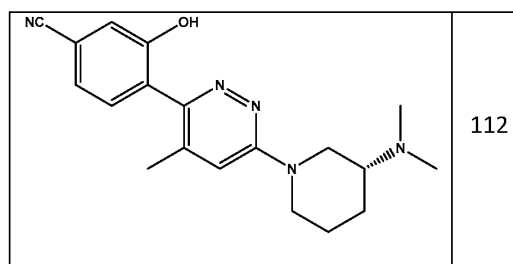
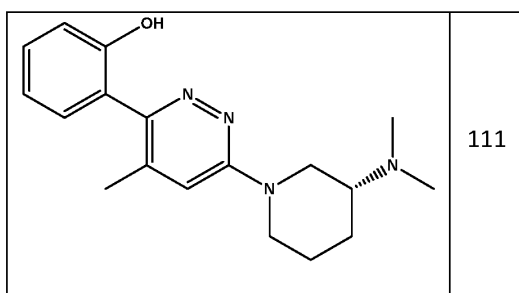
157. The compound of claim 153, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound has the following structure:



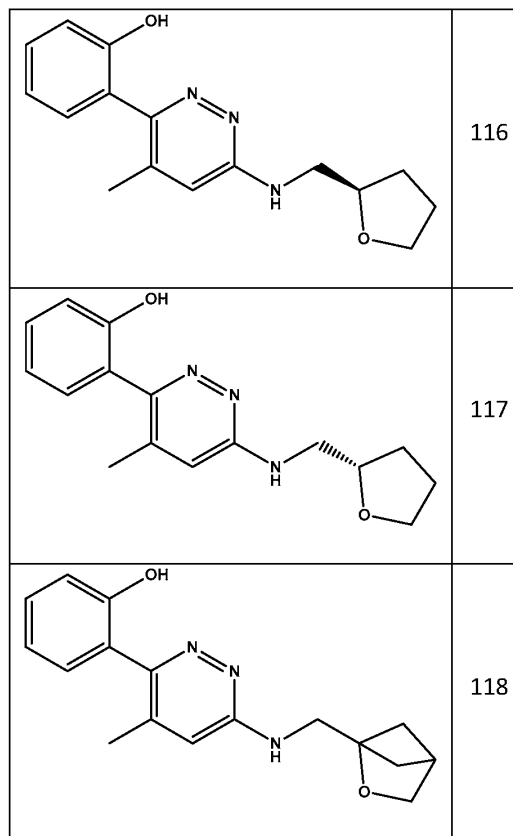
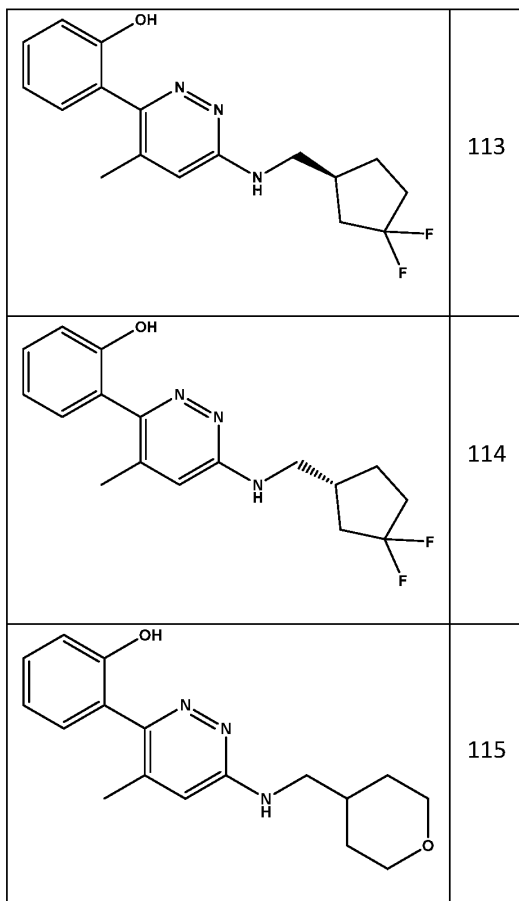
158. The compound of claim 8, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound has the following structure:

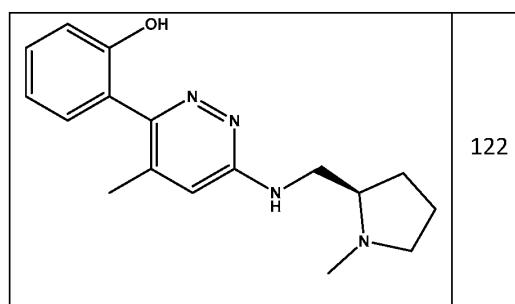
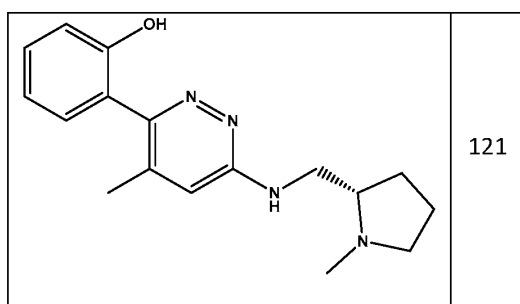
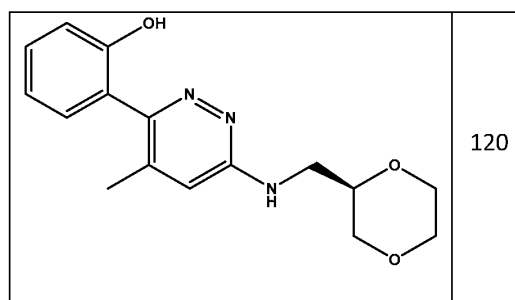
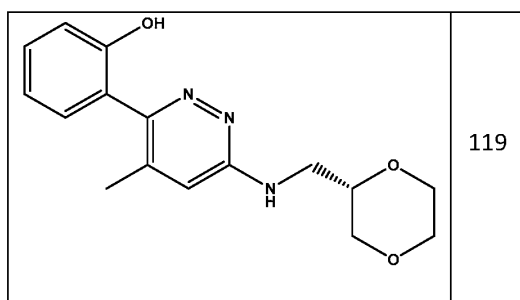
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159. The compound of claim 9, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound has the following structure:

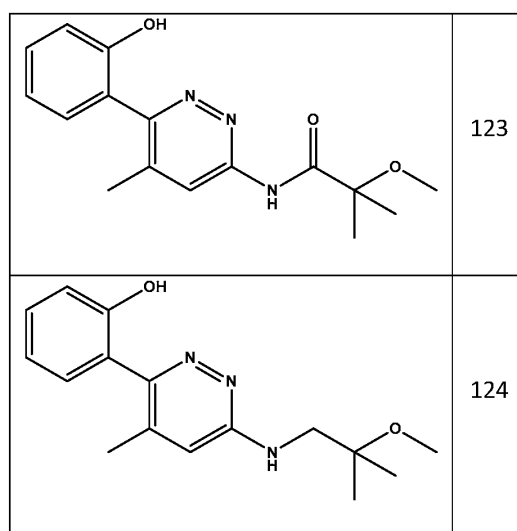


160. The compound of claim 10, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound has the following structure:





161. The compound of claim 11, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound has the following structure:



162. A pharmaceutical composition comprising the compound of any one of claims 1-161, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, and at least one pharmaceutically acceptable excipient.

163. A method of modulating NLRP3 inflammasome activity by contacting NLRP3 inflammasome with an effective amount of the pharmaceutical composition of claim 162.

164. The method of claim 163, wherein the pharmaceutical composition is selective for modulating NLRP3 inflammasome activity over hERG activity.

165. The method of claim 164, where in the selectivity for NLRP3 inflammasome activity is $\geq 1,000$ -fold over hERG activity.

166. A method of treating NLRP3 inflammasome dependent condition by administering to a subject in need thereof an effective amount of the pharmaceutical composition of claim 162.

167. The method of claim 166, wherein the NLRP3 inflammasome dependent condition is neuroinflammation-related disorders or neurodegenerative diseases.