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(71) Applicant: **ASSEMBLY BIOSCIENCES, INC.** [US/US]; 331 Oyster Point Boulevard, 4th Floor, South San Francisco, CA 94080 (US).

(72) Inventors: **HAYDAR, Simon, Nicolas**; 331 Oyster Point Boulevard, 4th Floor, South San Francisco, CA 94080 (US). **HECKRODT, Thilo**; 331 Oyster Point Boulevard, 4th Floor, South San Francisco, CA 94080 (US). **WALKER, Michael**; 331 Oyster Point Boulevard, 4th Floor, South San Francisco, CA 94080 (US). **ZHONG, Min**; 331 Oyster Point Boulevard, 4th Floor, South San Francisco, CA 94080 (US).

(74) Agent: **FIX, Amy, H.** et al.; Barnes & Thornburg LLP, 4208 Six Forks Road, Suite 1010, Raleigh, NC 27609 (US).

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(54) Title: PYRAZOLE CARBOXAMIDE COMPOUNDS FOR TREATMENT OF HBV

(57) Abstract: The present disclosure provides, in part, pyrazole carboxamide compounds, and pharmaceutical compositions thereof, useful for disruption of HBV core protein assembly, and methods of treating Hepatitis B (HBV) infection.

PYRAZOLE CARBOXAMIDE COMPOUNDS FOR TREATMENT OF HBV

BACKGROUND

Hepatitis B (HBV) causes viral hepatitis that can further lead to chronic liver disease *and i*ncrease the risk of liver cirrhosis and liver cancer (hepatocellular carcinoma). Worldwide, about 2 billion people have been infected with HBV, around 360 million people are chronically infected, and every year HBV infection causes more than one half million deaths. HBV can be spread by body fluids: from mother to child, by sex, and via blood products. Children born to HBV-positive mothers may also be infected, unless vaccinated at birth.

The hepatitis virus particle is composed of a lipid envelope studded with surface protein (HBsAg) that surrounds the viral core. The core is composed of a protein shell, or capsid, built of 120 core protein (Cp) dimers, which in turn contains the relaxed circular DNA (rcDNA) viral genome as well as viral and host proteins. In an infected cell, the genome is found as a covalently closed circular DNA (cccDNA) in the host cell nucleus. The cccDNA is the template for viral RNAs and thus viral proteins. In the cytoplasm, Cp assembles around a complex of full-length viral RNA (the so-called pregenomic RNA or pgRNA and viral polymerase (P). After assembly, P reverse transcribes the pgRNA to rcDNA within the confines of the capsid to generate the DNA-filled viral core.

At present, chronic HBV is primarily treated with nucleos(t)ide analogs (e.g., entecavir) that suppress the virus while the patient remains on treatment, but do not eliminate the infection, even after many years of treatment. Once a patient starts taking nucleos(t)ide analogs, most must continue taking them or risk the possibility of a life-threatening immune response due to viral rebound. Further, nucleotide therapy may lead to the emergence of antiviral drug resistance.

The only FDA approved alternative to nucleos(t)ide analogs is treatment with interferon α or pegylated interferon α. Unfortunately, the adverse event incidence and profile of interferon α can result in poor tolerability, and many patients are unable to complete therapy. Moreover, only a small percentage of patients are considered appropriate for

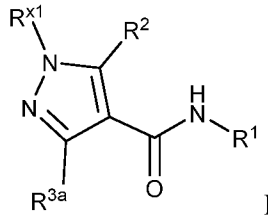
interferon therapy, as only a small subset of patients is likely to have a sustained clinical response to a course of interferon therapy. As a result, interferon-based therapies are used in only a small percentage of all diagnosed patients who elect treatment.

Thus, current HBV treatments can range from palliative to watchful waiting. Nucleotide analogs suppress virus production, treating the symptom, but leave the infection intact. Interferon α has severe side effects and less tolerability among patients and is successful as a finite treatment strategy in only a small minority of patients. There is a clear on-going need for more effective treatments for HBV infections.

SUMMARY

The present disclosure provides, in part, pyrazole carboxamide compounds and pharmaceutical compositions thereof, useful for disruption of HBV core protein assembly, and methods of treating HBV infections.

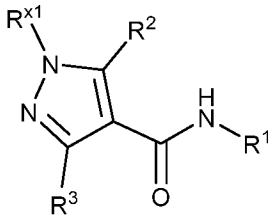
In one aspect, the disclosure provides a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, where the variables are described in the detailed description.

In another aspect, the disclosure provides a compound of Formula II:



Formula II

or a pharmaceutically acceptable salt thereof, where the variables are described in the detailed description.

In another aspect, the disclosure provides pharmaceutical compositions comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, the disclosure provides a method of treating an HBV infection in a subject in need thereof, comprising: administering to the subject a therapeutically effective amount of compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

In another aspect, the disclosure provides a method of treating an HBV infection in a subject in need thereof, comprising: administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF DRAWINGS

FIGURE 1 shows the ORTEP plot for compound CP-AIA-227-2.

FIGURE 2 shows the relative stereochemistry scheme of compound CP-AIA-227-2.

DETAILED DESCRIPTION

The features and other details of the disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

I. Definitions

The term “alkenyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 carbon atoms, referred to

herein as C_{2-6}alkenyl. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc….

The term "alkoxy" as used herein refers to a straight or branched alkyl group attached to oxygen (i.e., alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 1-4 carbon atoms, referred to herein as C_{1-6}alkoxy and C_{1-4}alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, and isopropoxy, etc.

The term "alkoxyalkyl" as used herein refers to an alkyl group substituted with an alkoxy group. Examples include, but are not limited to, $CH_3CH_2OCH_2$-, $CH_3OCH_2CH_2$- and CH_3OCH_2-, etc.

The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6 or 1-4 carbon atoms, referred to herein as C_{1-6} alkyl and C_{1-4} alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl, etc.

The term "alkylene" as used herein refers to a biradical alkyl group.

The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond. Exemplary alkynyl groups include, but are not limited to, straight or branched groups of 2-6 carbon atoms, referred to herein as C_{2-6}alkynyl. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and methylpropynyl, etc.

The term "carbonyl" as used herein refers to the biradical -C(O)-.

The term "cyano" as used herein refers to the radical -CN.

The term "cycloalkyl" as used herein refers to a saturated monocyclic hydrocarbon group of, for example, 3-6 carbons, referred to herein as C_{3-6} monocycloalkyl, or bicyclic hydrocarbon ring structure of, for example, 8-12 carbons, referred to herein as C_{8-}

$_{12}$bicycloalkyl. For bicyclic cycloalkyl groups, the two rings may be attached through the same or different carbons. Exemplary monocyclic cycloalkyl groups include, but are not limited to, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl and cyclopropyl. Exemplary bicyclic cycloalkyl groups include, but are not limited to, spiro[2.5]octanyl, spiro[3.5]nonanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, octahydropentalenyl, bicyclo[4.2.0]octanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, and bicyclo[2.2.2]octanyl.

The term "cycloalkenyl" as used herein refers to a partially unsaturated monocyclic hydrocarbon group of, for example, 4-6 carbons, referred to herein as C_{4-6}monocycloalkenyl, or bicyclic hydrocarbon ring structure of, for example, 8-12 carbons, referred to herein as C_{8-12}bicycloalkenyl. For bicyclic cycloalkenyl groups: 1) either one or both rings may contain one or more double bonds and 2) the two rings may be attached through the same or different ring carbons. Exemplary monocyclic cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. Exemplary bicyclic cycloalkenyl groups include, but are not limited to, spiro[2.5]oct-5-enyl, spiro[2.5]oct-4-enyl, spiro[3.5]non-5-enyl, spiro[3.5]non-6-enyl, bicyclo[4.1.0]hept-3-enyl, bicyclo[4.1.0]hept-2-enyl, and bicyclo[2.2.2]oct-2-enyl.

The term "carbocyclyl" as used herein refers to a bicyclic ring system formed by fusing a phenyl ring to a C_{3-6}monocycloalkyl or C_{4-6}monocycloalkenyl ring. Examples of carbocyclyls include, but are not limited to, 2,3-dihydro-1H-indenyl, 1,2,3,4-tetrahydronaphthalenyl and 1H-indenyl.

The terms "halo" or "halogen" as used herein refer to F, Cl, Br or I.

The term "haloalkyl" as used herein refers to an alkyl group substituted with one or more halogen atoms. For example, haloC_{1-6}alkyl refers to a straight or branched alkyl group of 1-6 carbon atoms substituted with one or more halogen atoms. Examples include, but are not limited to, CH_2F-, $CHCl_2$-, -CHF_2, CF_3-, CF_3CH_2-, CH_3CF_2, CF_3CCl_2- and CF_3CF_2-.

The term "haloalkoxy" as used herein refers to an alkoxy group substituted with one or more halogen atoms. Examples include, but are not limited to, CCl_3O-, CF_3O-, CHF_2O-CF_3CH_2O-, and CF_3CF_2O-.

The terms "heteroaryl" as used herein refers to a 5-6 membered monocyclic or 8-12 membered bicyclic aromatic ring system containing one to four independently selected heteroatoms, such as nitrogen, oxygen and sulfur. Where possible, the heteroaryl ring may be linked to the adjacent radical though carbon or nitrogen. Examples of 5-6 membered monocyclic heteroaryl groups include, but are not limited to, furanyl, thiophenyl (also referred to as thienyl), pyrrolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1,2,4-triazolyl, pyridinyl (also referred to as pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl and tetrazolyl. Examples of 8-12 membered bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, isobenzofuranyl, benzo[*b*]thiophenyl, benzo[*c*]thiophenyl, indolyl, isoindolyl, benzo[*d*]isoxazolyl, benzo[*c*]isoxazolyl, benzo[*d*]oxazolyl, benzo[*d*]isothiazolyl, benzo[*c*]isothiazolyl, benzo[*d*]thiazolyl, indazolyl, benzo[*d*]imidazolyl, benzo[*d*]imidazolyl, and benzo[*d*][1,2,3]triazolyl.

The term "heterocycloalkyl" refers to a saturated 3-6 membered monocyclic or 8-12 membered bicyclic ring system, referred to herein as C_{3-6}monoheterocycloalkyl and C_{8-12}biheterocycloalkyl, containing one to four independently selected heteroatoms, such as nitrogen, oxygen, and sulfur (including its oxidation states: S(O) and SO_2). Where possible, heterocycloalkyl rings may be linked to the adjacent radical through carbon or nitrogen. Examples of C_{3-6}monoheterocycloalkyl groups include, but are not limited to, aziridinyl, oxiranyl, thiiranyl 1,1-dioxide, oxetanyl, azetidinyl, thietanyl 1,1-dioxide, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydro-2H-pyranyl, morpholinyl, thiomorpholinyl, and piperazinyl. Examples of C_{8-12}biheterocycloalkyl groups include, but are not limited to, 1,4-dioxaspiro[4.5]decanyl and 1,5-dioxaspiro[5.5]undecanyl.

The term "heterocycloalkenyl" refers to a partially unsaturated 3-6 membered monocyclic or 8-12 membered bicyclic ring system, referred to herein as C_{3-6}monoheterocycloalkenyl and C_{8-12}biheterocycloalkenyl, containing one to four independently selected heteroatoms, such as nitrogen, oxygen, and sulfur (including its oxidation states: S(O) or $S(O)_2$). Where possible, heterocycloalkenyl rings may be linked to

the adjacent radical through carbon or nitrogen. For bicyclic heterocycloalkenyl groups: 1) either one or both rings may contain one or more double bonds and 2) the two rings may be attached through the same or different ring atoms. Examples of C_{3-6}monoheterocycloalkenyl groups include, but are not limited to, 2,3-dihydro-1H-pyrrolyl, 2,5-dihydro-1H-pyrrolyl, 4,5-dihydro-1H-pyrazolyl, 2,3-dihydro-1H-pyrazolyl, 4,5-dihydro-1H-imidazolyl, 2,3-dihydro-1H-imidazolyl, 2,3-dihydrothiophenyl, 2,5-dihydrothiophenyl, 4,5-dihydrothiazolyl, 2,3-dihydrothiazolyl, 4,5-dihydroisothiazolyl, 2,3-dihydroisothiazolyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, 4,5-dihydrooxazolyl, 2,3-dihydrooxazolyl, 4,5-dihydroisoxazolyl, 2,3-dihydroisoxazolyl, 3,4-dihydropyridinyl, 2,3-dihydropyridinyl, 2,3,4,5-tetrahydropyridinyl, 1,6-dihydropyridazinyl, 4,5-dihydropyridazinyl, 3,4,5,6-tetrahydropyridazinyl, 4,5-dihydropyrimidinyl, 1,2,5,6-tetrahydropyrimidinyl, 1,2-dihydropyrimidinyl, 1,2-dihydropyrazinyl, 2,3-dihydropyrazinyl, 1,2,3,6-tetrahydropyrazinyl, 4H-1,4-oxazinyl, 3,4-dihydro-2H-1,4-oxazinyl, 4H-1,4-thiazinyl, and 3,4-dihydro-2H-1,4-thiazinyl. Examples of C_{8-12}biheterocycloalkenyl groups include, but are not limited to, 6,7-dihydroindolyl, 4,5-dihydroindolyl, 7,8-dihydroimidazo[1,2-a]pyridinyl, 5,6-dihydroimidazo[1,2-a]pyridinyl, 4,5-dihydrobenzo[d]imidazolyl, 6,7-dihydro-1H-indazolyl, 4,5-dihydro-1H-indazolyl, 4,5-dihydropyrazolo[1,5-a]pyridinyl, and 6,7-dihydropyrazolo[1,5-a]pyridinyl.

The term “heterocyclyl” as used herein refers to a bicyclic ring system formed by either (1) fusing a phenyl ring to a 3-6 membered monocyclic heterocycloalkyl or 4-7 membered monocyclic heterocycloalkenyl ring, or (2) fusing a 5-6 membered monocyclic heteroaryl ring to a C_{3-6} cycloalkyl, C_{4-7} cycloalkenyl, 3-6 membered monocyclic heterocycloalkyl or 4-6 membered monocyclic heterocycloalkenyl ring. Where possible, the rings may be linked to the adjacent radical though carbon or nitrogen. Examples of heterocyclyls include, but are not limited to isochromanyl, 2H-quinolinyl, 6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine, 5,6,8,9-tetrahydro-[1,2,4]triazolo[4,3-d][1,4]oxazepane, 6,7-dihydro-5H,9H-[1,2,4]triazolo[3,4-c][1,4]oxazepane, 5,6,8,9-tetrahydro-7l2-[1,2,4]triazolo[4,3-d][1,4]diazepine, 8,9-dihydro-5H-[1,2,4]triazolo[4,3-a]azepine, 6,9-dihydro-5H-[1,2,4]triazolo[4,3-a]azepine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine,

5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazine, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine, and 5H,9H-[1,2,4]triazolo[3,4-c][1,4]oxazepine.

The terms "hydroxy" and "hydroxyl" as used herein refers to the radical -OH.

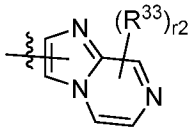
The term "hydroxyalkyl" as used herein refers to an alkyl group substituted with one or more hydroxy groups. Examples include, but are not limited to, $HOCH_2$-, $HOCH_2CH_2$-, $CH_3CH(OH)CH_2$- and $HOCH_2CH(OH)CH_2$-.

The term "hydroxyalkoxy" as used herein refers to an alkoxy group substituted with one or more hydroxy groups. Examples include but are not limited to $HOCH_2O$-, $HOCH_2CH_2O$-, $CH_3CH(OH)CH_2O$- and $HOCH_2CH(OH)CH_2O$-.

The term "$R^aR^bNC_{1-6}$ alkyl-," as used herein refers to an alkyl group substituted with a R^aR^bN- group, as defined herein. Examples include but are not limited to NH_2CH_2-, $NH(CH_3)CH_2$-, $N(CH_3)_2CH_2CH_2$- and $CH_3CH(NH_2)CH_2$-.

The term "$R^aR^bNC_{1-6}$alkoxy," as used herein refers to an alkoxy group substituted with a R^aR^bN- groups, as defined herein. Examples include but are not limited to NH_2CH_2-, $NH(CH_3)CH_2O$-, $N(CH_3)_2CH_2CH_2O$- and $CH_3CH(NH_2)CH_2O$-.

The term "oxo" as used herein refers to the radical =O.

As used herein, when a bicyclic ring is shown with a floating point of attachment and/or floating substituents, for example as in 

, it signifies that the bicyclic ring can be attached via a carbon atom on either ring, and that the substituents (e.g., the R^{33} group(s)) can be independently attached to either or both rings.

The terms "Individual," "patient," or "subject" are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds or pharmaceutical compositions of the disclosure can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.,* domestic animals (*e.g.,* dogs, cats, and the like), farm animals (*e.g.,* cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.,* rats, mice, guinea pigs,

dogs, primates, and the like). The mammal treated in the methods of the disclosure is desirably a mammal in which treatment of HBV infection is desired.

The term "modulation" includes antagonism (*e.g.,* inhibition), agonism, partial antagonism and/or partial agonism.

The term "Pharmaceutically acceptable" include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, fillers, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

The term "pharmaceutical composition" as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable excipients.

The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e.,

1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

The term "therapeutically effective amount" or "effective amount" as used herein refers to the amount of the subject compound that will elicit the biological or medical response of a tissue, system or animal, (e.g., mammal or human) that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds or pharmaceutical compositions of the disclosure are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect.

The term "treating" includes any effect, e.g., lessening, reducing, modulating, or eliminating, via disruption of HBV core protein assembly, that results in the improvement of the disease. "Disruption" includes inhibition of HBV viral assembly and infection.

The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term "stereoisomers" when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols "(+)," "(-)," "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present disclosure encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a carbon-carbon double bond. The symbol ⎓ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the "*Z*" or "*E*" configuration wherein the terms "*Z*" and "*E*" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "*E*" and "*Z*" isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond.

Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and therefore, exist as geometric isomers resulting from the arrangement of substituents around the ring. The arrangement of substituents around a carbocyclic or heterocyclic ring are designated as being in the *"Z"* or *"E"* configuration wherein the terms *"Z"* and *"E"* are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting carbocyclic or heterocyclic rings encompass both *"Z"* and *"E"* isomers. Substituents around a carbocyclic or heterocyclic ring may also be referred to as "cis" or "trans", where the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

Individual enantiomers and diastereomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers

on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well-known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantiomeric and diastereoselective transformations and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the disclosure embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

The disclosure also embraces isotopically labeled compounds of the disclosure which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. For example, a compound of the disclosure may have one or more H atom replaced with deuterium.

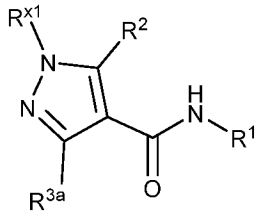
Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*,

increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the disclosure can generally be prepared by following procedures analogous to those disclosed in the examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

The term "prodrug" refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (such as by esterase, amidase, phosphatase, oxidative and or reductive metabolism) in various locations (such as in the intestinal lumen or upon transit of the intestine, blood or liver). Prodrugs are well known in the art (for example, see Rautio, Kumpulainen, *et al.,* Nature Reviews Drug Discovery 2008, 7, 255).

II. 5-Membered Heteroaryl Carboxamide Compounds

In one aspect, the present disclosure provides a compound of Formula I



Formula I

, or a pharmaceutically acceptable salt thereof, wherein:

L is C_{1-4}alkylene or haloC_{1-4}alkylene;

L^1 is a bond, C_{1-6}alkylene, O, NR^c, C(O), C(O)O, C(O)NR^c, $S(O)_t$ or $S(O)_tNR^c$;

X^3 is NR^4 or CR^4R^8;

X^4 is O or S;

X^5 is O, S or NR^0;

R^a, R^b and R^c are independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^d is hydrogen, OH, C_{1-6} alkyl or C_{1-6} alkoxy;

R^{x1} is hydrogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, haloC_{1-4} alkyl, or C_{3-6} monocycloalkyl; or R^{x1} and R^2 together form a -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -

CH_2CH_2O-, -CH_2OCH_2-, -$CH_2CH_2CH_2O$- -$CH_2CH_2OCH_2$-, -CH_2CH_2-NH- -CH_2NHCH_2-, -$CH_2CH_2CH_2NH$- or -$CH_2CH_2NHCH_2$- group;

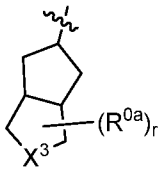
R^{0a} is independently selected for each occurrence from the group consisting of halogen, OH, CN, NO_2, R^aR^bN-, C_{1-4}alkyl and haloC_{1-5}alkyl;

R^{4a} and R^{6b} are independently hydrogen or C_{1-4} alkyl;

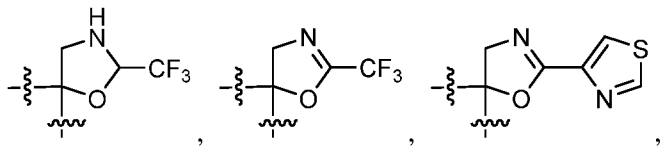
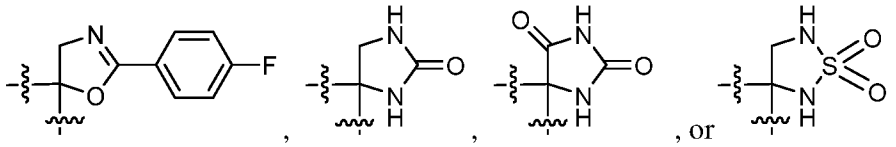
R^0, R^6 and R^{11} are independently selected for each occurrence from the group consisting of halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkyl-, HOC(O)C_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkylNR^c-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl-, haloC_{1-6}alkoxyC_{1-6}alkyl-, $R^aR^bNC(O)$-, C_{1-6}alkylC(O)-, C_{1-6}alkoxyC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkyl$S(O)_q$-, C_{1-6}alkyl$S(O)_tNR^c$-, C_{1-6}alkyl$S(O)_tC_{1-6}$alkyl-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkyl-, C_{3-6}cycloalkyl$S(O)_tC_{1-6}$alkyl-, C_{1-6}alkylC(O)C_{1-6}alkyl-, and C_{1-6}alkylC(O)OC_{1-6}alkyl-;

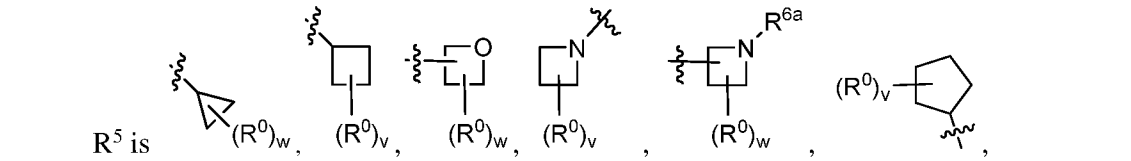
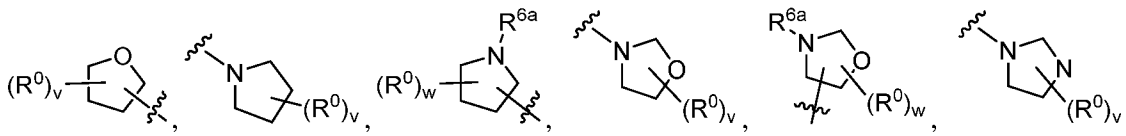
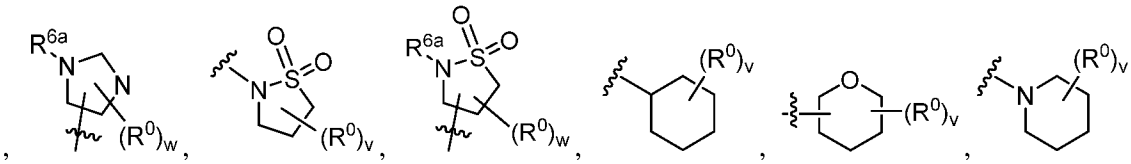
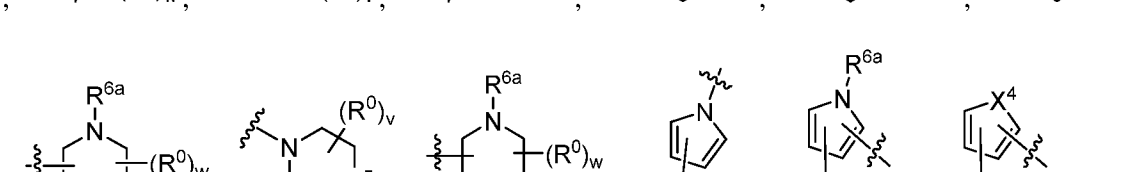
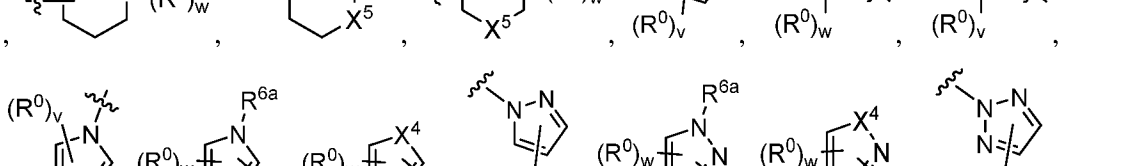
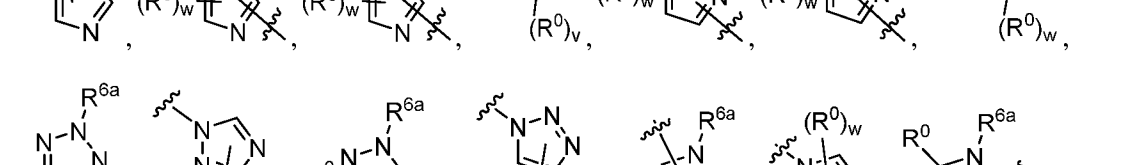
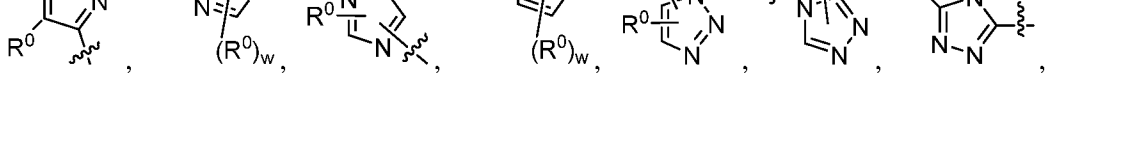
R^1 is a phenyl or 5-6 membered monocyclic heteroaryl, wherein the phenyl or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

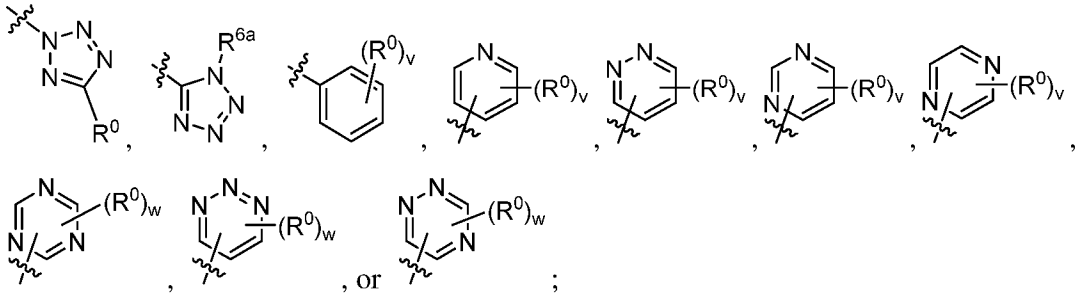
R^2 and R^8 are independently selected from the group consisting of hydrogen, halo, CN, OH, R^aR^bN, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}monocycloalkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy;

R^{3a} is 

;

R^4 is R^5-L^1- or R^9; or R^4 and R^8 together with the carbon atom to which they are attached form a  ,  , or group;

R^5 is  ,  ,  ,  ,  ,  ,  , ,  ,



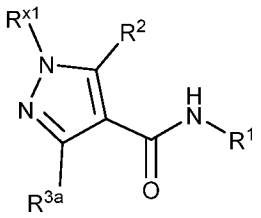
R^9 is $R^{14}S(O)_q$-L- , $R^{14}S(O)_qNH$-L-, or $R^{14}C(O)NH$-L-;

R^{14} is R^aR^bN-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or R^5-L^1-;

q, r, t, and w are independently selected for each occurrence from 0, 1 and 2; and

v is independently selected for each occurrence from 0, 1, 2 and 3.

In another aspect, the present disclosure provides a compound of Formula Ia



Formula Ia

, or a pharmaceutically acceptable salt thereof, wherein:

L is C_{1-4}alkylene or haloC_{1-4}alkylene;

L^1 is a bond, C_{1-6}alkylene, O, NR^c, C(O), C(O)O, $C(O)NR^c$, $S(O)_t$ or $S(O)_tNR^c$;

X^3 is NR^4 or CR^4R^8;

X^4 is O or S;

X^5 is O, S or NR^0;

R^a, R^b and R^c are independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^d is hydrogen, OH, C_{1-6} alkyl or C_{1-6} alkoxy;

R^{x1} is hydrogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, haloC_{1-4} alkyl, or C_{3-6} monocycloalkyl; or R^{x1} and R^2 together form a -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -

CH_2CH_2O-, -CH_2OCH_2-, -$CH_2CH_2CH_2O$- -$CH_2CH_2OCH_2$-, -CH_2CH_2-NH- -CH_2NHCH_2-, -$CH_2CH_2CH_2NH$- or -$CH_2CH_2NHCH_2$- group;

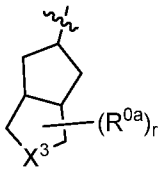
R^{0a} is independently selected for each occurrence from the group consisting of halogen, OH, CN, NO_2, R^aR^bN-, C_{1-4}alkyl and haloC_{1-5}alkyl;

R^{4a} and R^{6b} are independently hydrogen or C_{1-4} alkyl;

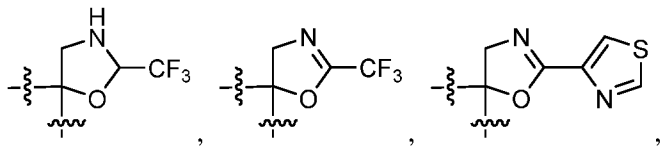
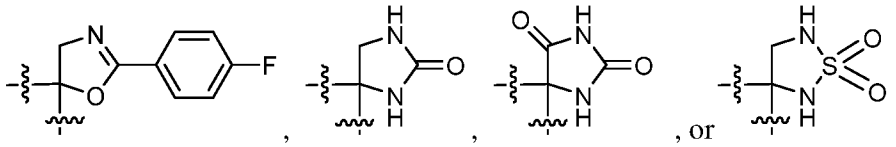
R^0, R^6 and R^{11} are independently selected for each occurrence from the group consisting of halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkyl-, HOC(O)C_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkylNR^c-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl-, haloC_{1-6}alkoxyC_{1-6}alkyl-, $R^aR^bNC(O)$-, C_{1-6}alkylC(O)-, C_{1-6}alkoxyC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkyl$S(O)_q$-, C_{1-6}alkyl$S(O)_tNR^c$-, C_{1-6}alkyl$S(O)_tC_{1-6}$alkyl-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkyl-, C_{3-6}cycloalkyl$S(O)_tC_{1-6}$alkyl-, C_{1-6}alkylC(O)C_{1-6}alkyl-, and C_{1-6}alkylC(O)OC_{1-6}alkyl-;

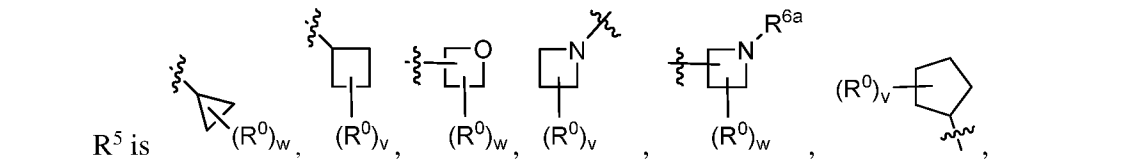
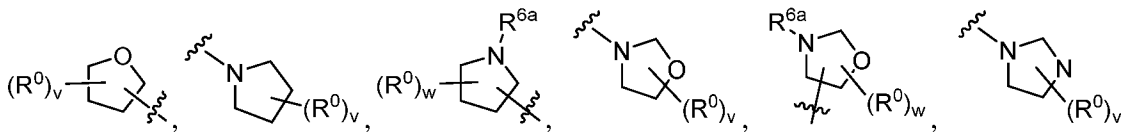
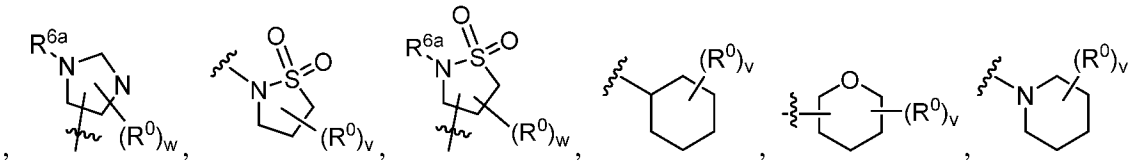
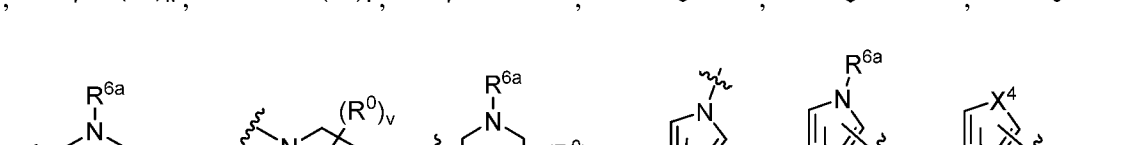
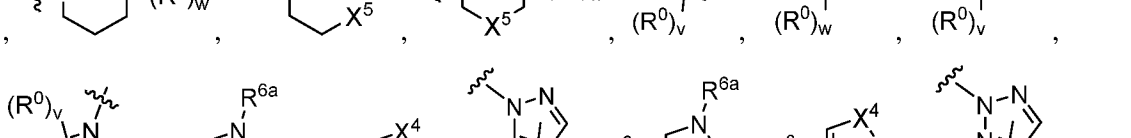
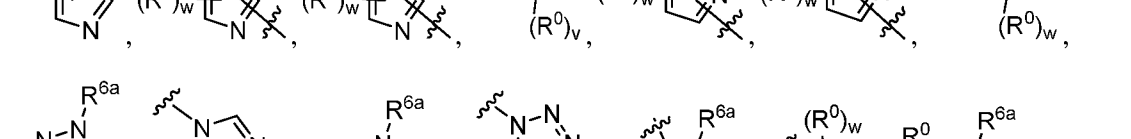
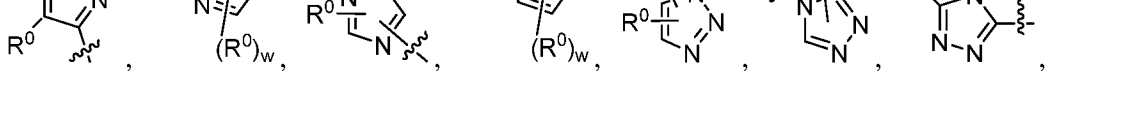
R^1 is a phenyl or 5-6 membered monocyclic heteroaryl, wherein the phenyl or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

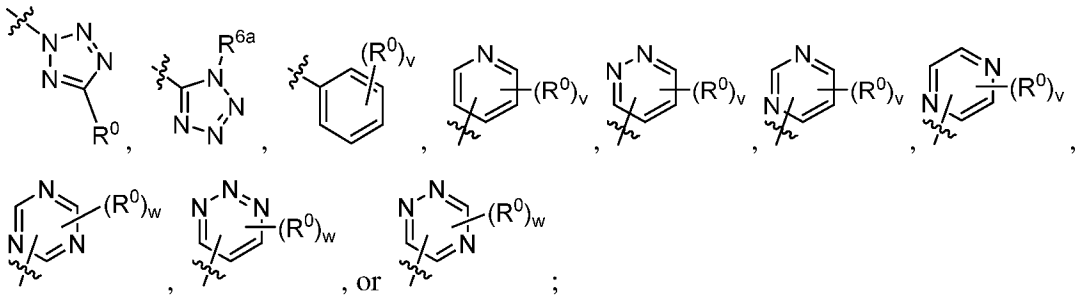
R^2 and R^8 are independently selected from the group consisting of hydrogen, halo, CN, OH, R^aR^bN, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}monocycloalkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy;

R^{3a} is 

;

R^4 is R^5-L^1-, R^6, or R^9; or R^4 and R^8 together with the carbon atom to which they are attached form a  ,  , or group;

R^5 is  ,  ,  ,  ,  ,  ,  , ,  ,



R^9 is $R^{14}S(O)_q$-L- , $R^{14}S(O)_qNH$-L-, or $R^{14}C(O)NH$-L-;

R^{14} is R^aR^bN-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or R^5-L^1-;

q, r, t, and w are independently selected for each occurrence from 0, 1 and 2; and

v is independently selected for each occurrence from 0, 1, 2 and 3.

The following embodiments further describe a compound of Formula I or Formula Ia, or a pharmaceutically acceptable salt thereof. It will be appreciated that all chemically allowable combinations of the embodiments described herein are envisioned as further embodiments of the invention.

In certain embodiments, R^{x1} is hydrogen of methyl.

In certain embodiments, R^{x1} is methyl.

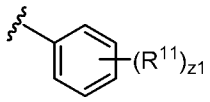
In certain embodiments, L^1 is a bond.

In certain embodiments, L^1 is a C_{1-6}alkylene.

In certain embodiments, X^3 is NR^4.

In certain embodiments, X^3 is CR^4R^8.

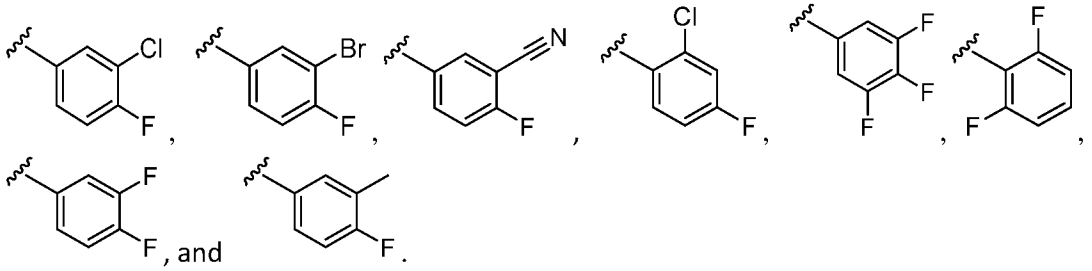
In certain embodiments, r is 0.

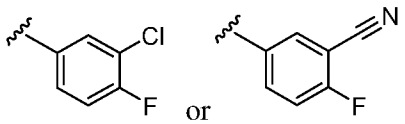
In certain embodiments, R^1 is  ; R^{11} is independently selected for each occurrence from the group consisting of halogen, CN, C_{1-6}alkyl and haloC_{1-6}alkyl; and z1 is 0, 1, 2 or 3.

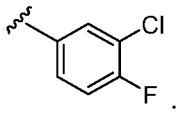
In certain embodiments, R^{11} is independently selected for each occurrence from the group consisting of halogen and CN.

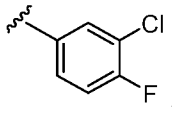
In certain embodiments, R^{11} is independently selected for each occurrence from the group consisting of F, Cl, Br and I.

In certain embodiments, R^1 is selected from the group consisting of:

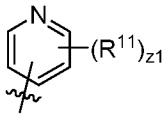


In certain embodiments, R^1 is  .

In certain embodiments, R^1 is  .

In certain embodiments, R^{x1} is hydrogen or methyl and R^1 is  .

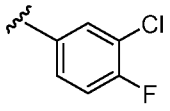
In certain embodiments, R^1 is a 5-6 membered monocyclic heteroaryl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6}alkyl, and haloC_{1-6}alkyl.

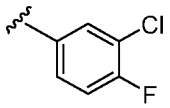
In certain embodiments, R^1 is  ; R^{11} is independently selected for each occurrence from the group consisting of halogen, CN, C_{1-6}alkyl and haloC_{1-6}alkyl; and z1 is 0, 1, 2 or 3.

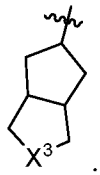
In certain embodiments, R^2 is R^aR^bN.

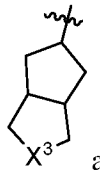
In certain embodiments, R^2 is R^aR^bN, and R^a and R^b are independently selected the group consisting of hydrogen and C_{1-6}alkyl.

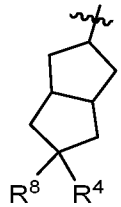
In certain embodiments, R^2 is NH_2.

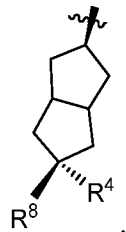
In certain embodiments, R^{x1} is hydrogen or methyl, R^1 is  , and R^2 is NH_2.

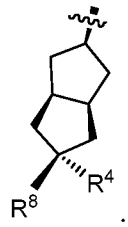
In certain embodiments, R^{x1} is hydrogen or methyl, R^1 is  , R^2 is NH_2; and r is 0.

In certain embodiments, R^{3a} is  .

In certain embodiments, R^{3a} is  and X3 is NR^4.

In certain embodiments, R^{3a} is  .

In certain embodiments, R^{3a} is  .

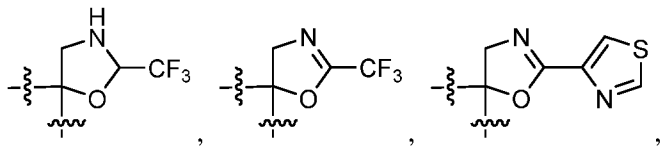
In certain embodiments, R^{3a} is  .

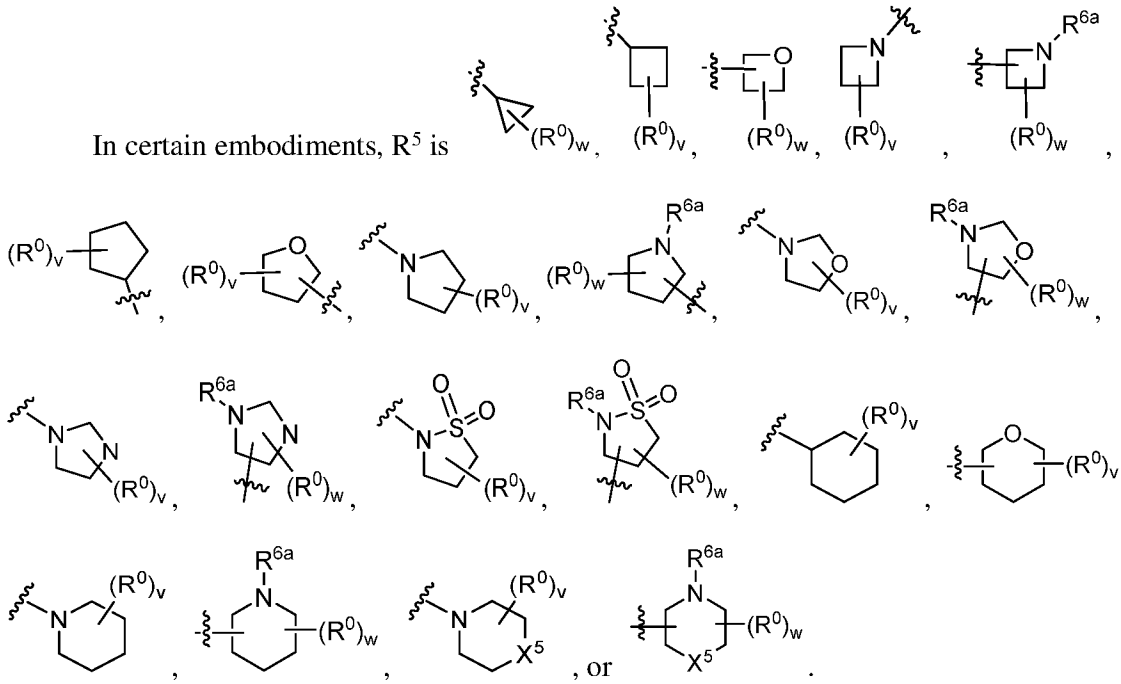
In certain embodiments, R^4 is R^5-L^1-.

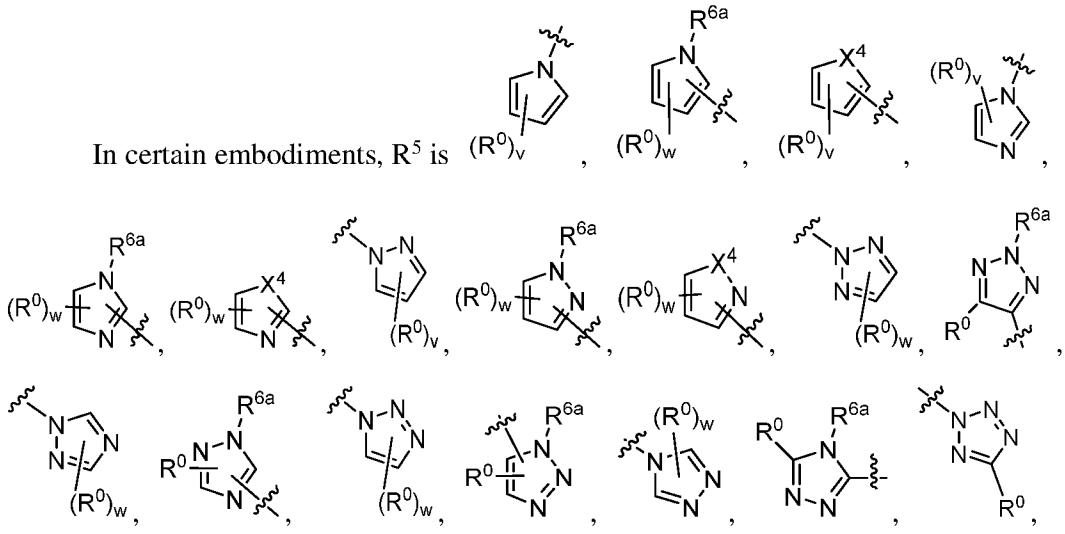
In certain embodiments, R^4 is R^5.

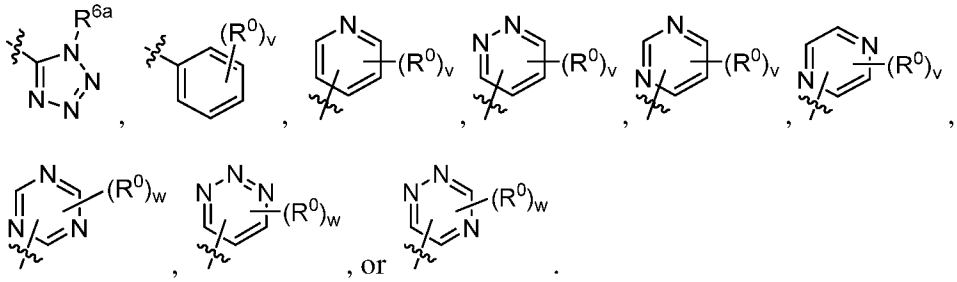
In certain embodiments, R^4 is R^6.

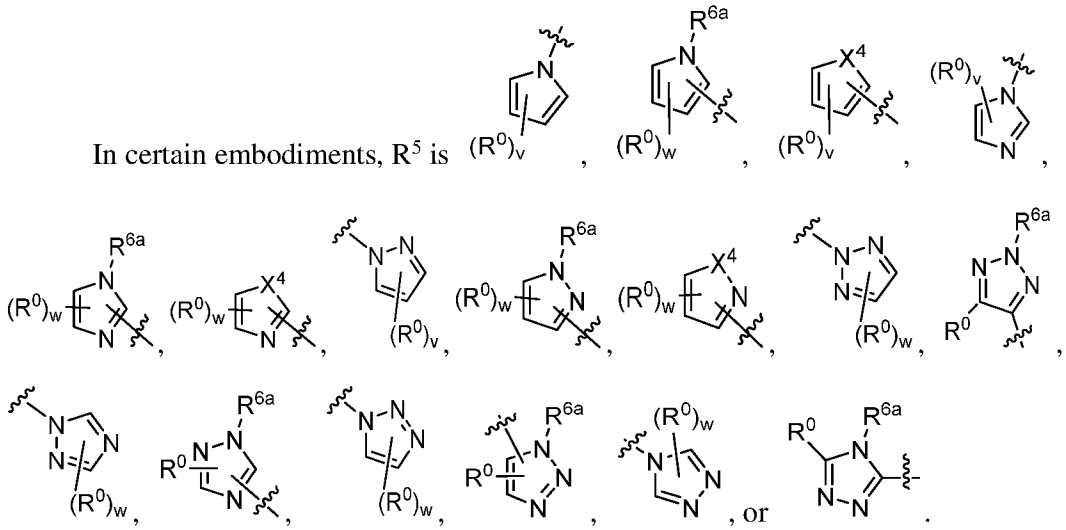
In certain embodiments, R^4 is R^9.

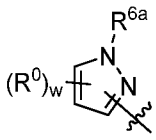
In certain embodiments, or R^4 and R^8 together with the carbon atom to which they are attached form a  group;

In certain embodiments, R^5 is 

In certain embodiments, R^5 is 



In certain embodiments, R^5 is 

In certain embodiments, R^5 is  .

In certain embodiments, R^8 is hydrogen, OH or C_{1-6}alkoxy.

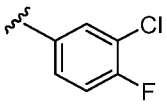
In certain embodiments, and R^8 is hydrogen.

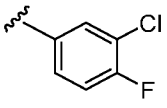
In certain embodiments, and R^8 is OH.

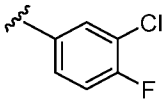
In certain embodiments, R^{14} is R^aR^bN-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, or C_{1-6}haloalkoxy.

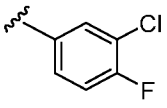
In certain embodiments, R^{14} is R^5-L^1-.

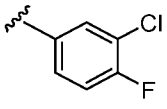
In certain embodiments, R^{14} is R^5.

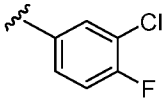
In certain embodiments, R^{x1} is hydrogen or methyl; R^1 is  ; R^2 is NH_2; X^3 is CR^4R^8; and R^8 is hydrogen, OH or $C_{1\text{-}6}$alkoxy.

In certain embodiments, R^{x1} is hydrogen or methyl, R^1 is  , R^2 is NH_2, X^3 is CR^4R^8, and R^8 is OH.

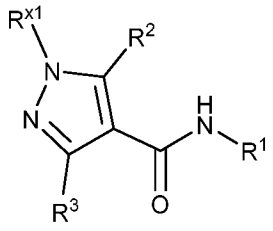
In certain embodiments, R^{x1} is hydrogen or methyl; R^1 is  ; R^2 is NH_2; X^3 is CR^4R^8; R^8 is hydrogen, OH or $C_{1\text{-}6}$alkoxy; and r is 0.

In certain embodiments, R^{x1} is hydrogen or methyl, R^1 is  , R^2 is NH_2, X^3 is CR^4R^8, R^8 is OH, and r is 0.

In certain embodiments, R^{x1} is hydrogen or methyl; R^1 is  ; R^2 is NH_2; and X^3 is NR^4.

In certain embodiments, R^{x1} is hydrogen or methyl; R^1 is  ; R^2 is NH_2; X^3 is NR^4; and r is 0.

In another aspect, the present disclosure provides a compound of Formula II



Formula II

, or a pharmaceutically acceptable salt thereof, wherein:

L is C_{1-4}alkylene or haloC_{1-4}alkylene;

L^1 is a bond, C_{1-6}alkylene, O, NR^c, C(O), C(O)O, C(O)NR^c, $S(O)_t$ or $S(O)_tNR^c$;

X^3 is O, NR^4, CR^4R^8, C(O) or $S(O)_t$;

X^4 is O or S;

X^5 is O, S or NR^0;

R^{x1} is hydrogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, haloC_{1-4} alkyl, or C_{3-6} monocycloalkyl; or R^{x1} and R^2 together form a $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2O-$, $-CH_2OCH_2-$, $-CH_2CH_2CH_2O-$ $-CH_2CH_2OCH_2-$, $-CH_2CH_2-NH-$ $-CH_2NHCH_2-$, $-CH_2CH_2CH_2NH-$ or $-CH_2CH_2NHCH_2-$ group;

R^a, R^b and R^c are independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^d is hydrogen, OH, C_{1-6} alkyl or C_{1-6} alkoxy;

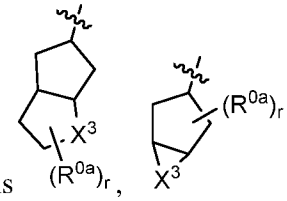
R^{0a} is independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, R^aR^bN-, C_{1-4}alkyl and haloC_{1-4}alkyl;

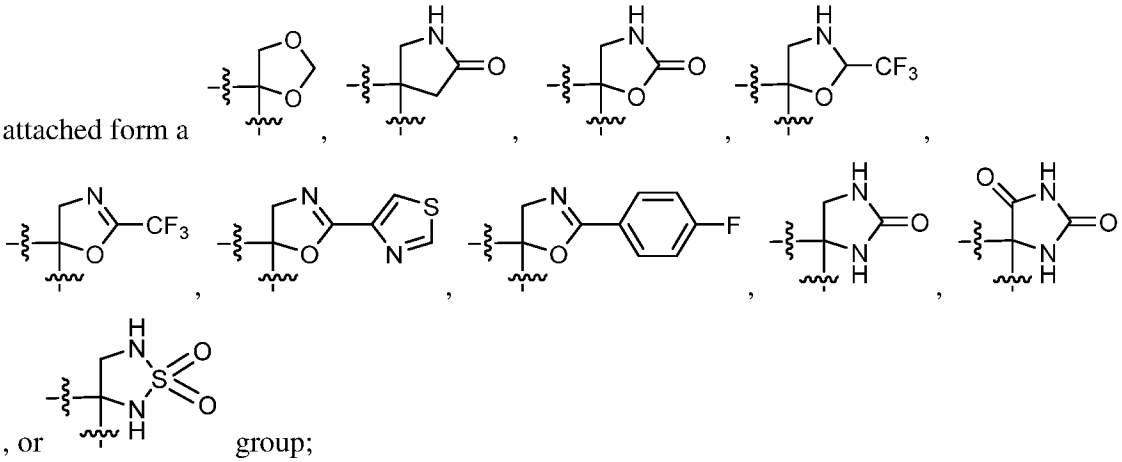
R^{4a} and R^{6a} are independently hydrogen or C_{1-4} alkyl;

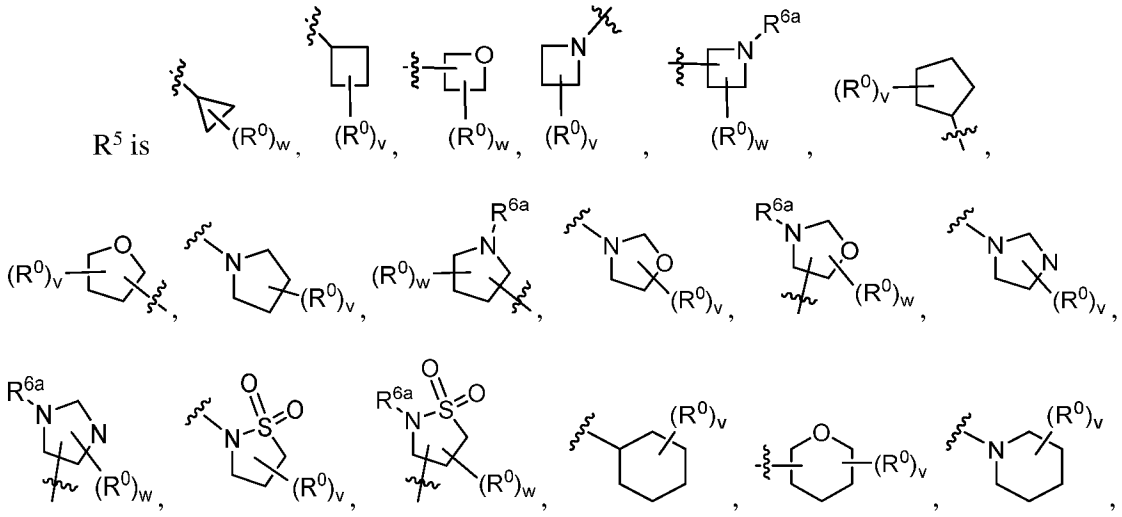
R^0, R^6 and R^{11} are independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, $R^dN=$, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t-$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkyl-, HOC(O)C_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkylNR^c-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl-, haloC_{1-6}alkoxyC_{1-6}alkyl-, $R^aR^bNC(O)-$, C_{1-6}alkylC(O)-, C_{1-6}alkoxyC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkyl$S(O)_q-$, C_{1-6}alkyl$S(O)_tNR^c-$, C_{1-6}alkyl$S(O)_tC_{1-6}$alkyl-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkyl-, C_{3-6}cycloalkyl$S(O)_tC_{1-6}$alkyl-, C_{1-6}alkylC(O)C_{1-6}alkyl-, and C_{1-6}alkylC(O)OC_{1-6}alkyl-;

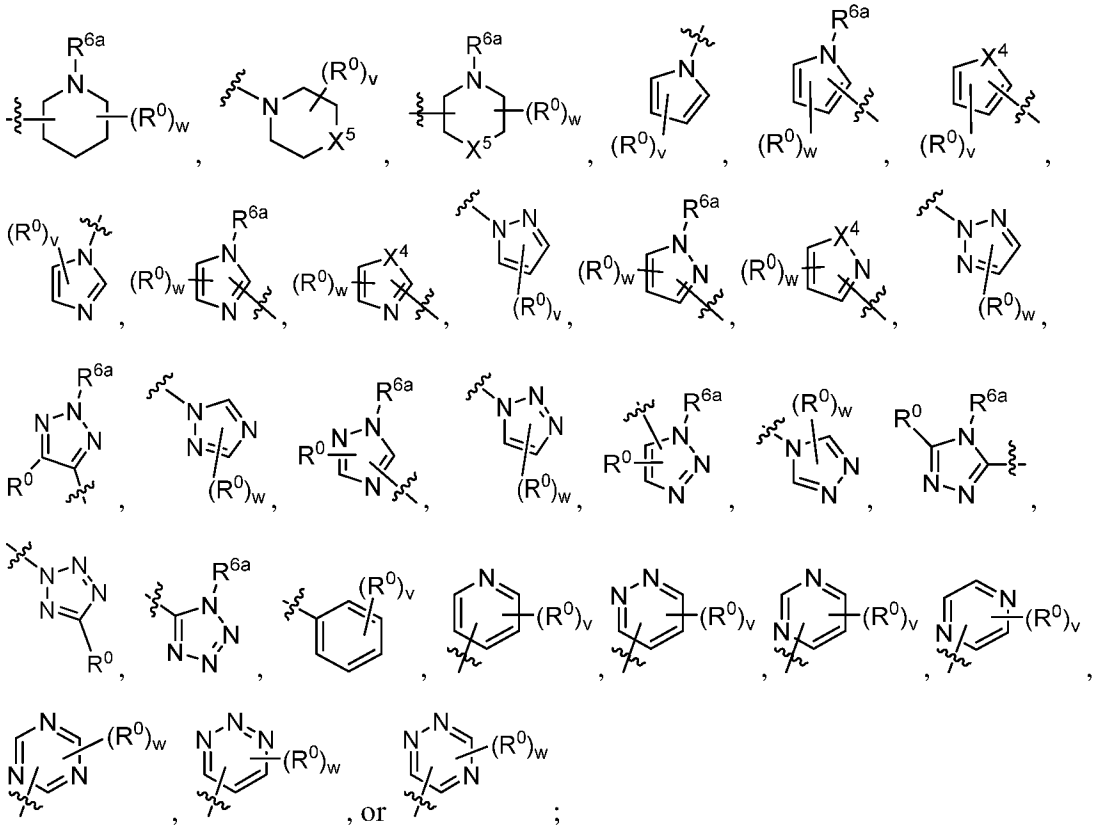
R^1 is a phenyl or 5-6 membered monocyclic heteroaryl, wherein the phenyl or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

R^2 and R^8 are independently selected from the group consisting of hydrogen, halo, CN, OH, R^aR^bN, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}monocycloalkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy;

R^3 is  ;

R^4 is R^5-L^1- or R^9; or R^4 and R^8 together with the carbon atom to which they are attached form a  , or group;

R^5 is  ;



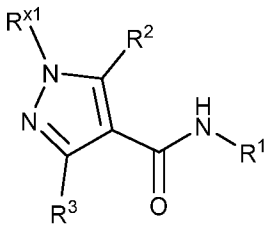
R^9 is R^{14}S(O)$_q$-L- , R^{14}S(O)$_q$NH-L-, or R^{14}C(O)NH-L-;

R^{14} is R^{a}R^{b}N-, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, C$_{1-6}$haloalkyl, C$_{1-6}$alkoxy, C$_{1-6}$haloalkyl, C$_{1-6}$haloalkoxy, or R^5-L^1-;

q, r, t, and w are independently selected for each occurrence from 0, 1 and 2; and

v is independently selected for each occurrence from 0, 1, 2 and 3.

In another aspect, the present disclosure provides a compound of Formula IIa



Formula IIa

, or a pharmaceutically acceptable salt thereof, wherein:

L is C$_{1-4}$alkylene or haloC$_{1-4}$alkylene;

L^1 is a bond, C_{1-6}alkylene, O, NR^c, C(O), C(O)O, $C(O)NR^c$, $S(O)_t$ or $S(O)_tNR^c$;

X^3 is O, NR^4, CR^4R^8, C(O) or $S(O)_t$;

X^4 is O or S;

X^5 is O, S or NR^0;

R^{x1} is hydrogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, haloC_{1-4} alkyl, or C_{3-6} monocycloalkyl; or R^{x1} and R^2 together form a $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2O-$, $-CH_2OCH_2-$, $-CH_2CH_2CH_2O-$ $-CH_2CH_2OCH_2-$, $-CH_2CH_2-NH-$ $-CH_2NHCH_2-$, $-CH_2CH_2CH_2NH-$ or $-CH_2CH_2NHCH_2-$ group;

R^a, R^b and R^c are independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^d is hydrogen, OH, C_{1-6} alkyl or C_{1-6} alkoxy;

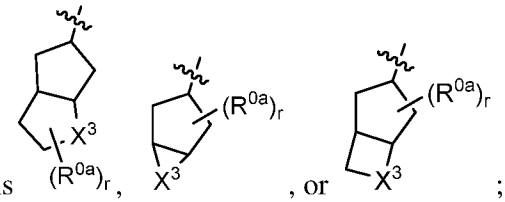
R^{0a} is independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, R^aR^bN-, C_{1-4}alkyl and haloC_{1-4}alkyl;

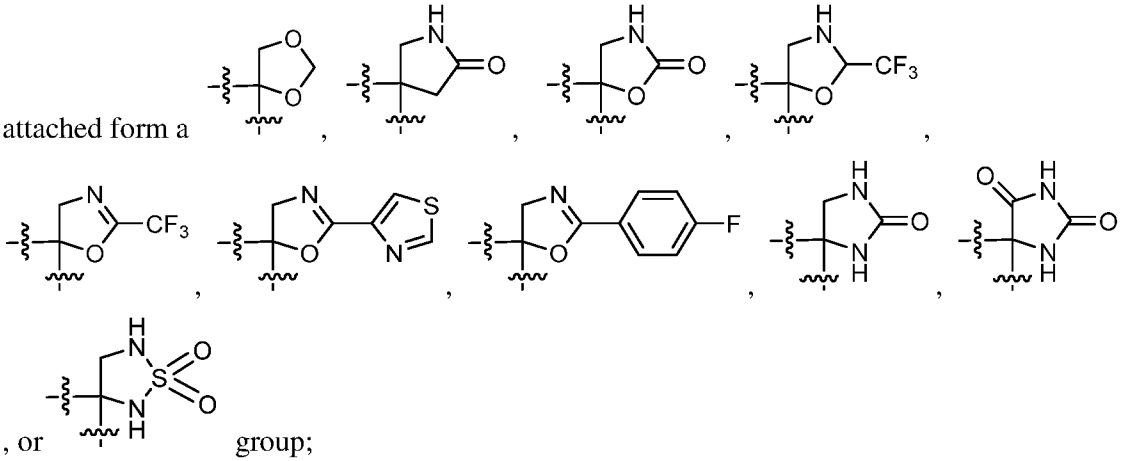
R^{4a} and R^{6a} are independently hydrogen or C_{1-4} alkyl;

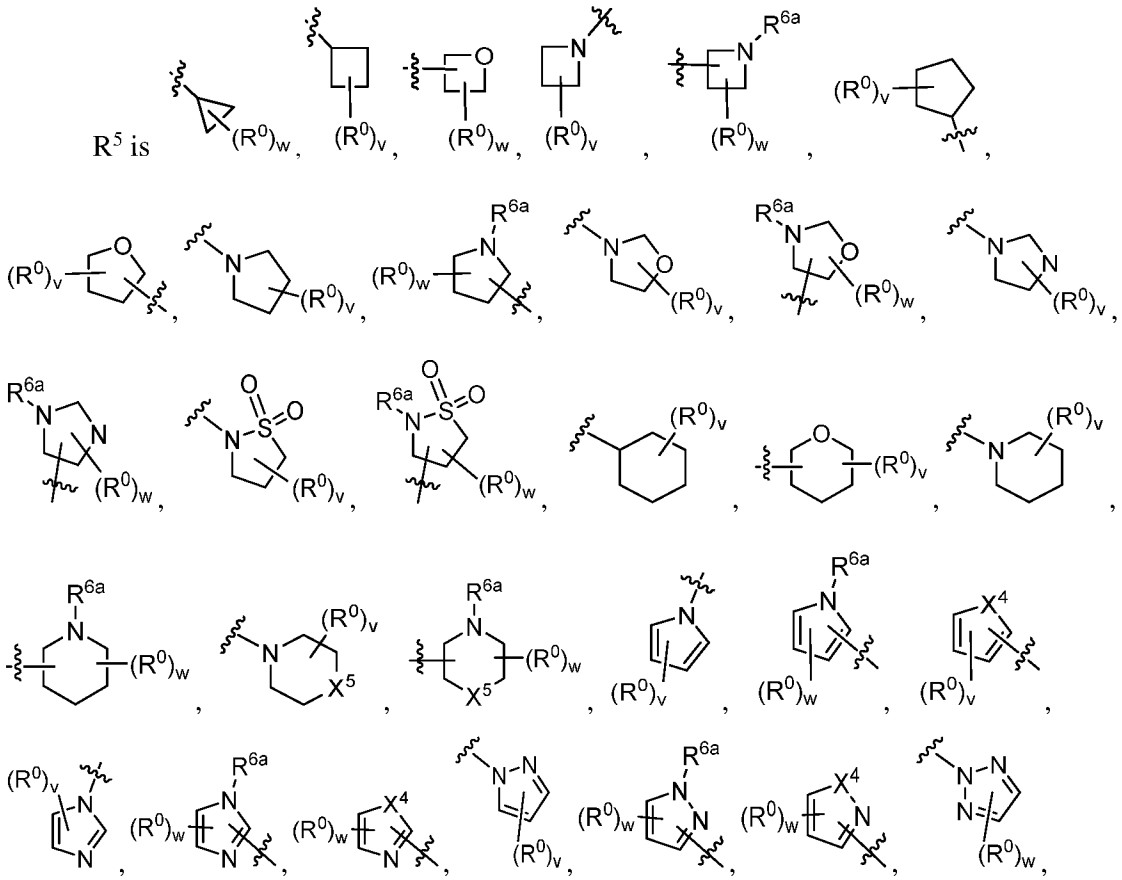
R^0, R^6 and R^{11} are independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, $R^dN=$, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t-$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkyl-, HOC(O)C_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkylNR^c-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl-, haloC_{1-6}alkoxyC_{1-6}alkyl-, $R^aR^bNC(O)-$, C_{1-6}alkylC(O)-, C_{1-6}alkoxyC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkyl$S(O)_q-$, C_{1-6}alkyl$S(O)_tNR^c-$, C_{1-6}alkyl$S(O)_tC_{1-6}$alkyl-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkyl-, C_{3-6}cycloalkyl$S(O)_tC_{1-6}$alkyl-, C_{1-6}alkylC(O)C_{1-6}alkyl-, and C_{1-6}alkylC(O)OC_{1-6}alkyl-;

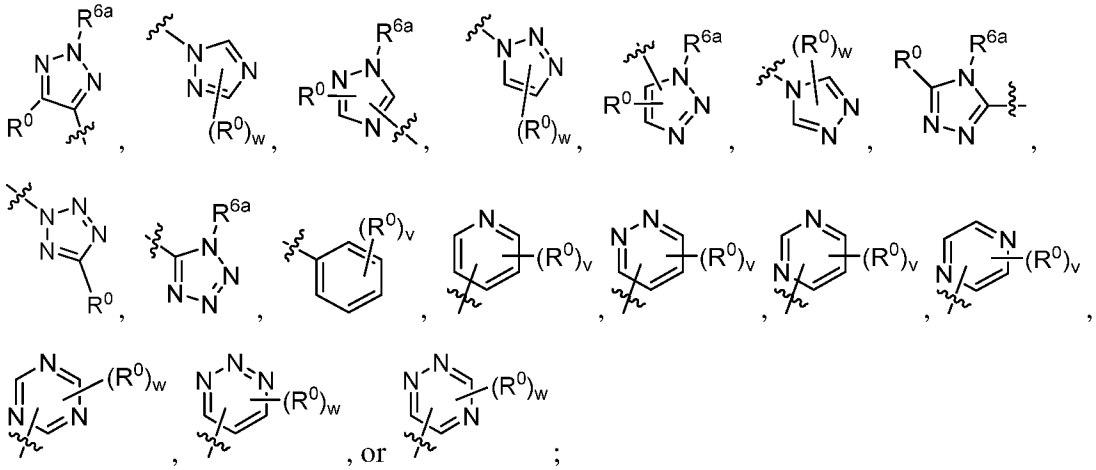
R^1 is a phenyl or 5-6 membered monocyclic heteroaryl, wherein the phenyl or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

R^2 and R^8 are independently selected from the group consisting of hydrogen, halo, CN, OH, R^aR^bN, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}monocycloalkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy;

R^3 is  ;

R^4 is R^5-L^1-, R^6, or R^9; or R^4 and R^8 together with the carbon atom to which they are attached form a  group;

R^5 is 



R^9 is $R^{14}S(O)_q$-L- , $R^{14}S(O)_qNH$-L-, or $R^{14}C(O)NH$-L-;

R^{14} is R^aR^bN-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or R^5-L^1-;

q, r, t, and w are independently selected for each occurrence from 0, 1 and 2; and

v is independently selected for each occurrence from 0, 1, 2 and 3.

The following embodiments further describe a compound of Formula II of IIa, or a pharmaceutically acceptable salt thereof. It will be appreciated that all chemically allowable combinations of the embodiments described herein are envisioned as further embodiments of the invention.

In certain embodiments, R^{x1} is hydrogen of methyl.

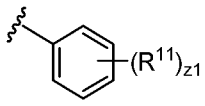
In certain embodiments, R^{x1} is methyl.

In certain embodiments, L^1 is a bond.

In certain embodiments, L^1 is a C_{1-6}alkylene.

In certain embodiments, X^3 is CR^4R^8.

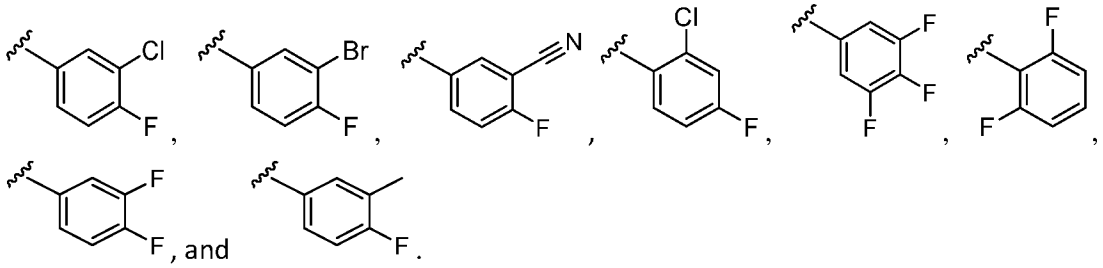
In certain embodiments, r is 0.

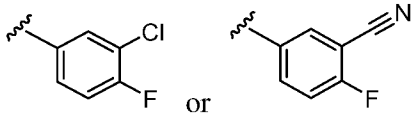
In certain embodiments, R^1 is  ; R^{11} is independently selected for each occurrence from the group consisting of halogen, CN, C_{1-6}alkyl and haloC_{1-6}alkyl; and z1 is 0, 1, 2 or 3.

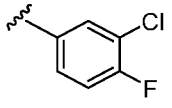
In certain embodiments, R^{11} is independently selected for each occurrence from the group consisting of halogen and CN.

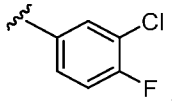
In certain embodiments, R^{11} is independently selected for each occurrence from the group consisting of F, Cl, Br and I.

In certain embodiments, R^1 is selected from the group consisting of:

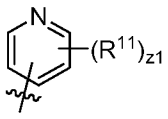


In certain embodiments, R^1 is  .

In certain embodiments, R^1 is  .

In certain embodiments, R^{x1} is hydrogen or methyl and R^1 is  .

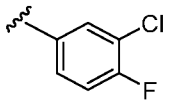
In certain embodiments, R^1 is a 5-6 membered monocyclic heteroaryl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6}alkyl, and haloC_{1-6}alkyl.

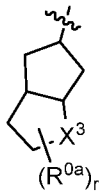
In certain embodiments, R^1 is  ; R^{11} is independently selected for each occurrence from the group consisting of halogen, CN, C_{1-6}alkyl and haloC_{1-6}alkyl; and z1 is 0, 1, 2 or 3.

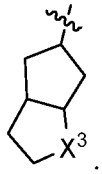
In certain embodiments, R^2 is R^aR^bN;

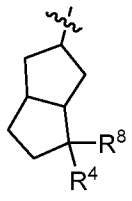
In certain embodiments, R^2 is R^aR^bN, and R^a and R^b are independently selected the group consisting of hydrogen and C_{1-6}alkyl.

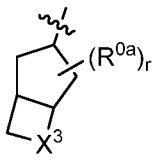
In certain embodiments, R^2 is NH_2.

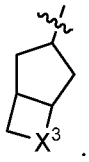
In certain embodiments, R^{x1} is hydrogen or methyl, R^1 is  , and R^2 is NH_2.

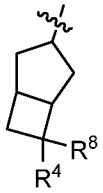
In certain embodiments, R^3 is  .

In certain embodiments, R^3 is  .

In certain embodiments, R^3 is  .

In certain embodiments, R^3 is  .

In certain embodiments, R^3 is  .

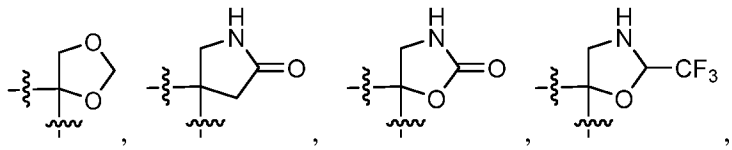
In certain embodiments, R^3 is  .

In certain embodiments, R^4 is R^5-L^1-.

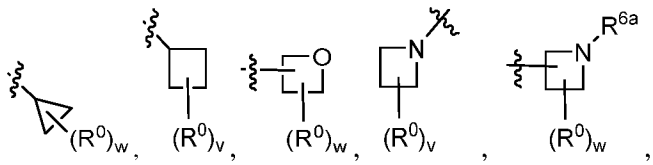
In certain embodiments, and R^4 is R^5.

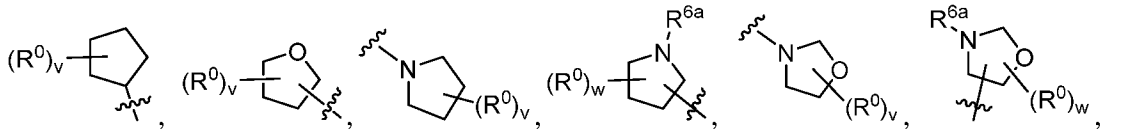
In certain embodiments, R^4 is R^6.

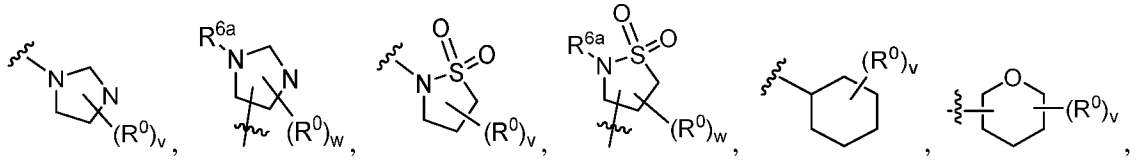
In certain embodiments, R^4 is R^9.

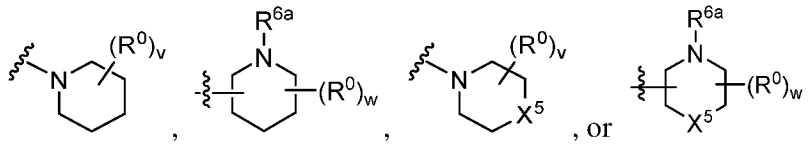
In certain embodiments, R^4 and R^8 together with the carbon atom to which they are attached form a  group;

.

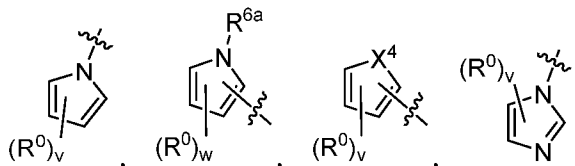
In certain embodiments, R^5 is 

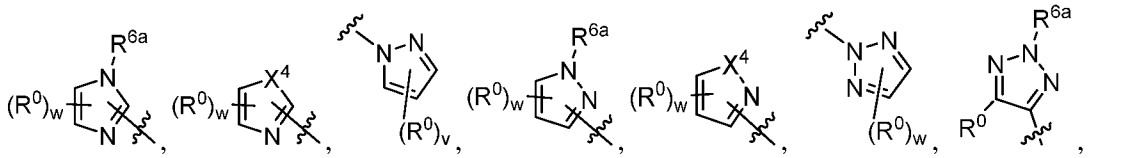


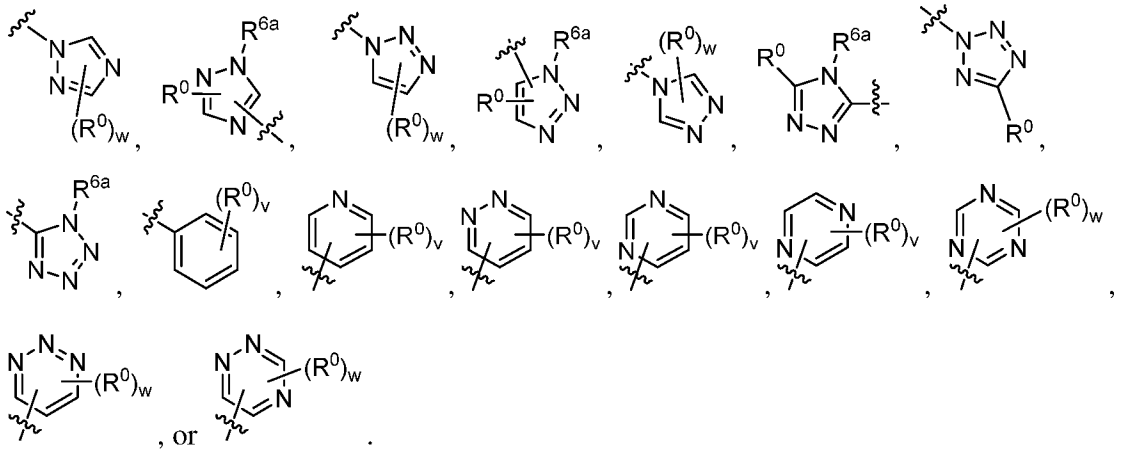


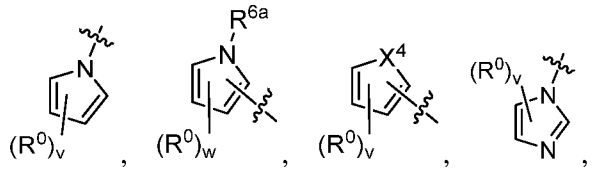


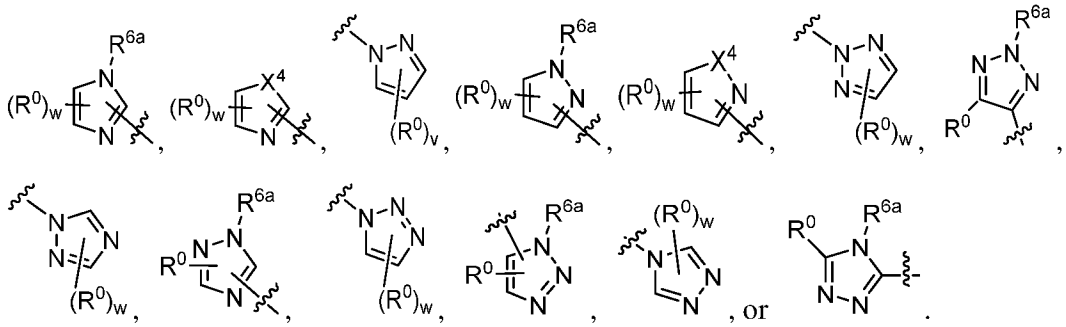
.

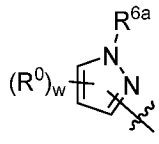
In certain embodiments, R^5 is 





In certain embodiments, R^5 is 



In certain embodiments, R^5 is  .

In certain embodiments, R^6 is C_{1-6}alkylS(O)$_t$$C_{1-6}$alkyl- or C_{1-6}alkylS(O)$_t$N$R^a$$C_{1-6}$alkyl-.

In certain embodiments, R^8 is hydrogen, OH or C_{1-6}alkoxy.

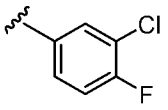
In certain embodiments, R^8 is hydrogen.

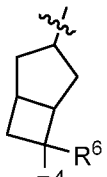
In certain embodiments, R^8 is OH.

In certain embodiments, R^{14} is R^aR^bN-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, or C_{1-6}haloalkoxy.

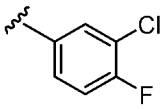
In certain embodiments, R^{14} is R^5-L^1-.

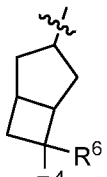
In certain embodiments, R^{14} is R^5.

In certain embodiments, R^{x1} is hydrogen or methyl; R^1 is 

; R^2 is NH_2; R^3 is 

; R^6 is C_{1-6}alkylS(O)$_t$$C_{1-6}$alkyl- or C_{1-6}alkylS(O)$_t$N$R^a$$C_{1-6}$alkyl-; R^8 is hydrogen, OH or C_{1-6}alkoxy.

In certain embodiments, R^{x1} is hydrogen or methyl; R^1 is 

; R^2 is NH_2; R^3 is 

; R^6 is C_{1-6}alkylS(O)$_t$$C_{1-6}$alkyl- or C_{1-6}alkylS(O)$_t$N$R^a$$C_{1-6}$alkyl-; and R^8 is OH.

IV. Pharmaceutical Compositions and Kits

In another aspect, the disclosure provides pharmaceutical compositions comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In particular, the present disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal, parenteral (e.g., subcutaneous, intramuscular,

intradermal, or intravenous), rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

In another aspect, the disclosure provides a pharmaceutical composition comprises a compound of Table 1 or 2, or a pharmaceutically acceptable salt and/or stereoisomer thereof.

Exemplary pharmaceutical compositions of this disclosure may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more compounds of the disclosure, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, *e.g.,* conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.,* water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the disclosure, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose,

mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut,

corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Compositions and compounds of the present disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in

the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

In another aspect, the disclosure provides enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of

about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal collophorium, and several commercially available enteric dispersion systems (e. g. , Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present disclosure.

Advantageously, the disclosure also provides kits for use by e.g., a consumer in need of HBV infection treatment. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form tomediate, reduce or prevent HBV infection. The instructions would direct the consumer or medical personnel to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of

relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, *e.g.,* in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.,* as follows "First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . ." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

IV. Methods

In a further aspect, a method for treating a hepatitis B infection in a patient in need thereof is provided, comprising administering to a subject or patient an effective amount of a disclosed compound, and/or administering a first disclosed compound and optionally, an additional, different disclosed compound(s). In another embodiment, a method for treating a hepatitis B infection in a patient in need thereof is provided, comprising administering to a subject or patient a therapeutically effective amount of a disclosed pharmaceutical composition or a pharmaceutical composition comprising a disclosed compound, or two or more disclosed compounds, and a pharmaceutically acceptable excipient.

For use in accordance with this aspect, the appropriate dosage is expected to vary depending on, for example, a particular compound employed, the mode of administration, and the nature and severity of the infection to be treated as well as the specific infection to be treated and is within the purview of the treating physician. Usually, an indicated administration dose may be in the range between about 0.1 to about 1000 μg/kg body weight. In some cases, the administration dose of the compound may be less than 400 μg/kg body weight. In other cases, the administration dose may be less than 200 μg/kg body weight. In yet other cases, the administration dose may be in the range between about 0.1 to about 100 μg/kg body weight. The dose may be conveniently administered once daily, or in divided doses up to, for example, four times a day or in sustained release form.

A compound of the present disclosure may be administered by any conventional route, in particular: enterally, topically, orally, nasally, e.g., in the form of tablets or capsules, via suppositories, or parenterally, e.g., in the form of injectable solutions or suspensions, for intravenous, intra-muscular, sub-cutaneous, or intra-peritoneal injection. Suitable formulations and pharmaceutical compositions will include those formulated in a conventional manner using one or more physiologically acceptable carriers or excipients, and any of those known and commercially available and currently employed in the clinical setting. Thus, the compounds may be formulated for oral, buccal, topical, parenteral, rectal or transdermal administration or in a form suitable for administration by inhalation or insufflation (either orally or nasally).

For oral administration, pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., 44ecarbonate44ed maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycollate); or wetting agents (e.g., sodium lauryl sulphate). Tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution

with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). Preparations may also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

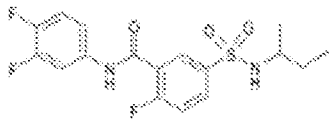
Preparations for oral administration may also be suitably formulated to give controlled-release or sustained release of the active compound(s) over an extended period. For buccal administration the compositions may take the form of tablets or lozenges formulated in a conventional manner known to the skilled artisan.

A disclosed compound may also be formulated for parenteral administration by injection e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain additives such as suspending, stabilizing and/or dispersing agents. Alternatively, the compound may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. Compounds may also be formulated for rectal administration as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

Also contemplated herein are methods and compositions that include a second active agent or administering a second active agent. For example, in addition to being infected with HBV, a subject or patient can further have HBV infection-related co-morbidities, i.e., diseases and other adverse health conditions associated with, exacerbated by, or precipitated by being infected with HBV. Contemplated herein are disclosed compounds in combination with at least one other agent that has previously been shown to treat these HBV-infection-related conditions.

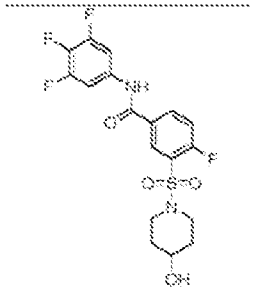
In some cases, a disclosed compound may be administered as part of a combination therapy in conjunction with one or more antivirals. Example antivirals include nucleoside

analogs, interferon α, and other assembly effectors, for instance heteroaryldihydropyrimidines (HAPs) such as methyl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(46ecarbon-2-yl)-1,4-dihydropyrimidine-5-carboxylate (HAP-1). For example, provided herein is a method of treating a patient suffering from hepatitis B infection comprising administering to the patient a first amount of a disclosed compound and a second amount of an antiviral, or other anti HBV agent, for example a second amount of a second compound selected from the group consisting of: a HBV capsid assembly promoter (for example, GLS4, BAY 41-4109, AT-130, DVR-23 (e.g., as depicted below),



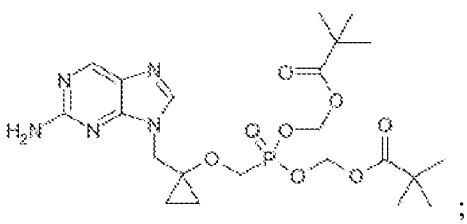
DVR-23 ;

NVR 3-778, NVR1221 (by code); and N890 (as depicted below):



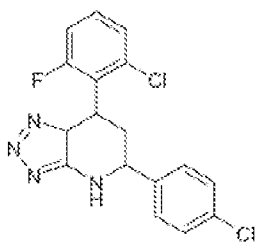
;

other capsid inhibitors such as those disclosed in the following patent applications hereby incorporated by reference: WO2014037480, WO2014184328, WO2013006394, WO2014089296, WO2014106019, WO2013102655, WO2014184350, WO2014184365, WO2014161888, WO2014131847, WO2014033176, WO2014033167, and WO2014033170; Nucleos(t)ide analogs interfering with viral polymerase, such as entecavir (Baraclude), Lamivudine, (Epivir-HBV), Telbivudine (Tyzeka, Sebivo), Adefovir dipivoxil (Hepsera), Tenofovir (Viread), Tenofovir alafenamide fumarate (TAF), prodrugs of tenofavir (e.g. AGX-1009), L-FMAU (Clevudine), LB80380 (Besifovir) and:

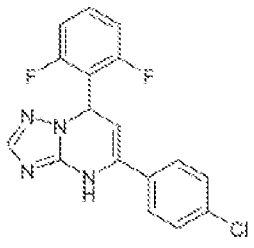


;

viral entry inhibitors such as Myrcludex B and related lipopeptide derivatives; HbsAg secretion inhibitors such as REP 9AC' and related nucleic acid-based amphipathic polymers, HBF-0529 (PBHBV-001), PBHBV-2-15 as depicted below:

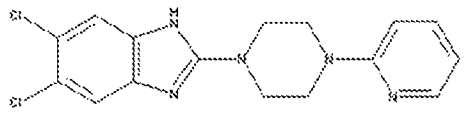


22: HBF-0529

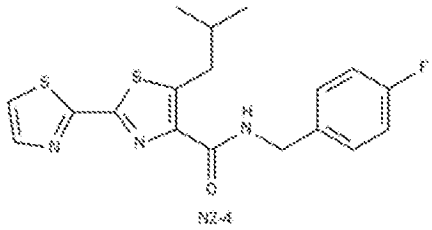


23: PBHBV-2-15 ;

and BM601 as depicted below:

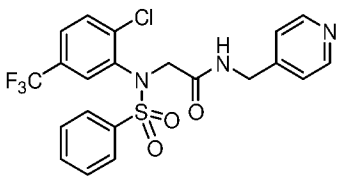
 ;

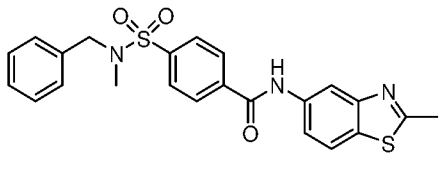
disruptors of nucleocapsid formation or integrity such as NZ-4/W28F:



NZ-4 ;

cccDNA formation inhibitors such as BSBI-25, CCC-0346, CCC-0975 (as depicted below):



 .

HBc directed transbodies such as those described in Wang Y., et al, Transbody against hepatitis B virus core protein inhibits hepatitis B virus replication in vitro, Int. Immunopharmacol (2014), located at //dx.doi.org/10.1016/j.intimp.2015.01.028; antiviral core protein mutant (such as Cp183-V124W and related mutations as described in WO/2013/010069, WO2014/074906, each incorporated by reference); inhibitors of HBx-interactions such as RNAi, antisense and nucleic acid based polymers targeting HBV RNA;, e.g., RNAi (for example ALN-HBV, ARC-520, TKM-HBV, ddRNAi), antisense (ISIS-

HBV), or nucleic acid based polymer: (REP 2139-Ca); immunostimulants such as Interferon alpha 2a (Roferon), Intron A (interferon alpha 2b), Pegasys (peginterferon alpha 2a), Pegylated IFN 2b, IFN lambda 1a and PEG IFN lambda 1a, Wellferon, Roferon, Infergen, lymphotoxin beta agonists such as CBE11 and BS1); Non-Interferon Immune enhancers such as Thymosin alpha-1 (Zadaxin) and Interleukin-7 (CYT107); TLR-7/9 agonists such as GS-9620, CYT003, Resiquimod; Cyclophilin inhibitors such as NVP018; OCB-030; SCY-635; Alisporivir; NIM811 and related cyclosporine analogs; vaccines such as GS-4774, TG1050, Core antigen vaccine; SMAC mimetics such as birinapant and other IAP-antagonists; Epigenetic modulators such as KMT inhibitors (EZH1/2, G9a, SETD7, Suv39 inhibitors), PRMT inhibitors, HDAC inhibitors, SIRT agonists, HAT inhibitors, WD antagonists (e.g., OICR-9429), PARP inhibitors, APE inhibitors, DNMT inhibitors, LSD1 inhibitors, JMJD HDM inhibitors, and Bromodomain antagonists; kinase inhibitors such as TKB1 antagonists, PLK1 inhibitors, SRPK inhibitors, CDK2 inhibitors, ATM & ATR kinase inhibitors; STING Agonists; Ribavirin; N-acetyl cysteine ; NOV-205 (BAM205); Nitazoxanide (Alinia), Tizoxanide; SB 9200 Small Molecule Nucleic Acid Hybrid (SMNH); DV-601; Arbidol; FXR agonists (such as GW 4064 and Fexaramin); antibodies, therapeutic proteins, gene therapy, and biologics directed against viral components or interacting host proteins.

In some embodiments, the disclosure provides a method of treating a hepatitis B infection in a patient in need thereof, comprising administering a first compound selected from any one of the disclosed compounds, and one or more other HBV agents each selected from the group consisting of HBV capsid assembly promoters, HBF viral polymerase interfering nucleosides, viral entry inhibitors, HbsAg secretion inhibitors, disruptors of nucleocapsid formation, cccDNA formation inhibitors, antiviral core protein mutant, HBc directed transbodies, RNAi targeting HBV RNA, immunostimulants, TLR-7/9 agonists, cyclophilin inhibitors, HBV vaccines, SMAC mimetics, epigenetic modulators, kinase inhibitors, and STING agonists. In some embodiments, the disclosure provides a method of treating a hepatitis B infection in a patient in need thereof, comprising administering an amount of a disclosed compound, and administering another HBV capsid assembly promoter.

In some embodiments, the first and second amounts together comprise a pharmaceutically effective amount. The first amount, the second amount, or both may be the same, more, or less than effective amounts of each compound administered as monotherapies. Therapeutically effective amounts of a disclosed compound and antiviral may be co-administered to the subject, i.e., administered to the subject simultaneously or separately, in any given order and by the same or different routes of administration. In some instances, it may be advantageous to initiate administration of a disclosed compound first, for example one or more days or weeks prior to initiation of administration of the antiviral. Moreover, additional drugs may be given in conjunction with the above combination therapy.

In another embodiment, a disclosed compound may be conjugated (e.g., covalently bound directly or through molecular linker to a free carbon, nitrogen (e.g., an amino group), or oxygen (e.g., an active ester) of a disclosed compound), with a detection moiety, for e.g., a fluorophore moiety (such a moiety may for example re-emit a certain light frequency upon binding to a virus and/or upon photon excitation). Contemplated fluorophores include AlexaFluor® 488 (Invitrogen) and BODIPY FL (Invitrogen), as well as fluorescein, rhodamine, cyanine, indocarbocyanine, anthraquinones, fluorescent proteins, aminocoumarin, methoxycoumarin, hydroxycoumarin, Cy2, Cy3, and the like. Such disclosed compounds conjugated to a detection moiety may be used in e.g. a method for detecting HBV or biological pathways of HBV infection, e.g., *in vitro* or *in vivo*; and/or methods of assessing new compounds for biological activity.

V. Examples

The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be

compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

At least some of the compounds identified as "intermediates" herein are contemplated as compounds of the disclosure.

Abbreviations:

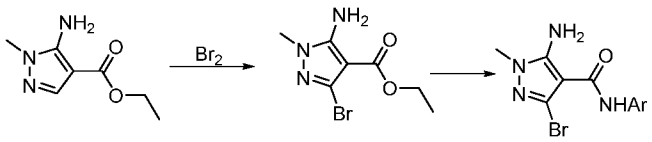
AcOH	Acetic acid
Boc_2O	Di-tert-butyl dicarbonate
nBuLi	n-Butyllithium
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIEA	Diisopropyl ethylamine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
EtOAc	Ethyl acetate
Et_3N	Triethylamine
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
h, hr	Hour(s)
HPLC	High performance liquid chromatography
LCMS	Liquid chromatography–mass spectrometry
MeOH	Methanol
MeCN	Acetonitrile
NBS	N-Bromosuccinimide
NMO	N-Methylmorpholine-N-Oxide

PE	Petroleum ether
iPrOH	Isopropanol

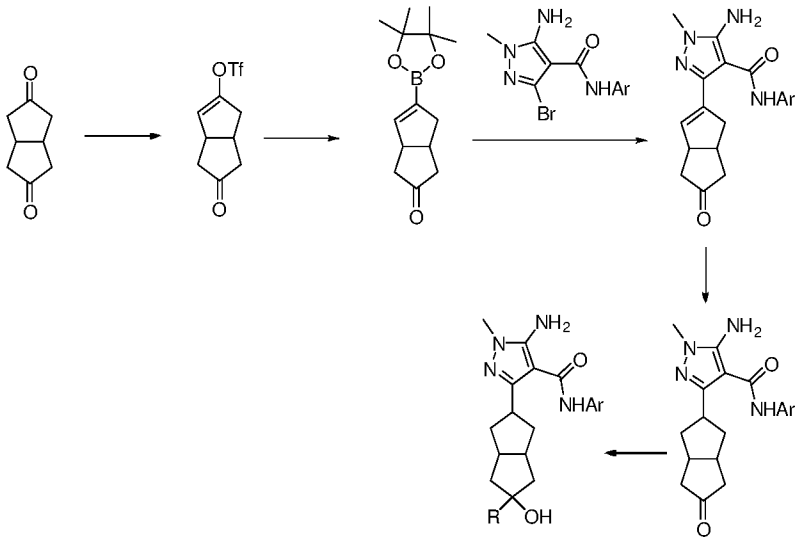
rt	Room temperature
SFC	Supercritical Fluid Chromatography
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography

XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

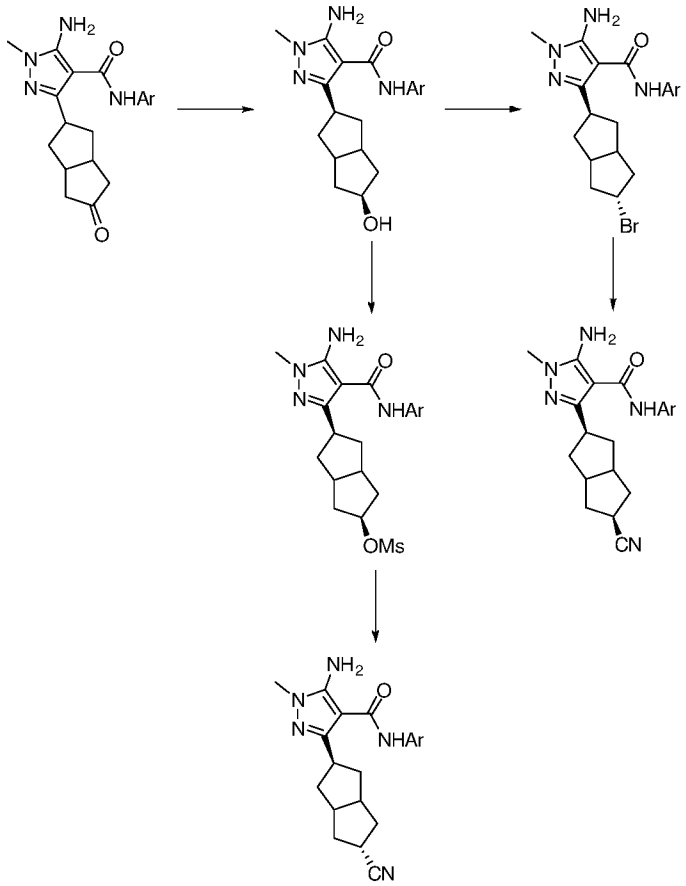
Scheme A



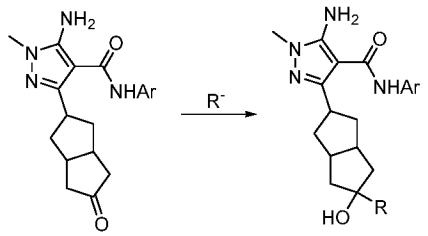
Scheme B



Scheme C



Scheme D



General procedure for amidation:

Method A (amide coupling using EDC·HCl): To a stirred solution of corresponding acid compound (1 eq.) in 1,4-dioxane (5.84 mL/mmol) were added EDC·HCl (1.1 eq.), HOBt (1.1 eq.) and corresponding amine (1 eq.) at 0 °C and stirred for 5 min. To this solution, DIPEA (3 eq.) was added and the reaction resulting reaction mixture was stirred at 90 °C for overnight. After completion, the reaction mixture was diluted with ice water and extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ solution, water, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound which was purified by silica gel column chromatography/prep. HPLC to afford the desired compound.

Method B (amide coupling using HATU): To a stirred solution of acid compound (1.1-1.2 eq.) in DMF/DCM (1.01 mL/mmol) at 0 °C, DIPEA (2-3 eq.) and HATU (1.5-2.5 eq.) were added and stirred for 5 min. To this solution, corresponding amine (1 eq.) was added. The resulting reaction mixture was stirred at room temperature for 12-16 hr. After completion, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a crude compound. The crude compound was purified by either prep-HPLC or combiflash column chromatography to afford the desired compound.

Method C ($AlMe_3$ mediated amidation): To a stirred solution of corresponding anilines (1.1 eq.) in DCM/Toluene(3 mL/mmol) at 0 °C under Argon atmosphere, $AlMe_3$ (2M in toluene, 2.5 eq.) was added and the reaction mixture was stirred at 0 °C for 10 min and continued stirring at room temperature for 1h. To this solution, corresponding ester

compound (1 eq.) was added at 0 °C under Argon atmosphere and resulting reaction mixture was refluxed at 100 °C for 16 hr. After completion, the reaction mixture was cooled to 0 °C; quenched with aqueous 1N HCl solution slowly and extracted with ethyl acetate. The combined organic layers were collected, dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude compound was purified by washing with methanol to afford the desired compound.

Method D (amide coupling using acid chloride/derivatives): To a stirred solution of amine compound (1 eq.) in DCM (1.01 mL/mmol) was added TEA (1.5-3 eq.) at 0 °C and stirred for 5 min. To this solution, corresponding acid chloride/carbamic chloride/chloroformate (1.1-1.5 eq.) was added slowly at 0 °C and the reaction mixture was allowed to stir at room temperature till completion. After completion, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate/DCM. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a crude compound. The crude compound was purified by either prep-HPLC or combiflash column chromatography to afford the desired compound.

General procedure for nucleophilic addition of keto compound :

Method A (at lower temperature): To a stirred solution of keto compound (1 eq.) in dry THF (0.2 mL/mmol) in an inert atmosphere was added a metallic reagent (e.g., Grignard reagent RMgX, RLi, R_2Zn, or R_3Al etc.) (10 eq.) slowly *via* glass syringe at -78 °C and stirred the reaction mixture for 4 hr at same temperature & then at room temperature for 2h. After completion, the reaction mixture was diluted with sat. aq. solution of ammonium chloride and extracted with ethyl acetate/DCM. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated on rota vapor to afford a crude compound. The crude compound was purified by either by combiflash column chromatography or prep-HPLC to afford the desired compound.

General method for Suzuki coupling:

Method A: To a mixture of halo compound (1 eq.) and corresponding boronic acid/boronate ester (1.2-1.5 eq.) in 1, 4-dioxane:water (4:1) (2.17 mL/mmol), Na_2CO_3 (2-3 eq.) was added and purged with Argon for 15 min. To this solution, $Pd(dppf)Cl_2$ (0.1 eq.) was added and purged with Argon for another 10 min. The resulting reaction mixture was stirred at 100 °C for 12-16 h. After completion of the reaction, the reaction mixture was filtered through Celite®545 and evaporated to dryness. The residue was taken in ethyl acetate, washed with water, followed by brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The crude product was purified by either combiflash column chromatography or prep-HPLC to afford the desired compound.

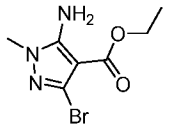
General procedure for hydrogenation:

Method A: To a stirred solution of olefinic compound (1 eq.) in EtOAc (2.67 mL/mmol) under nitrogen atomsphere, 10% Pd/C (20% by *w/w* of olefinic compound) was added. The reaction mixture was stirred under hydrogen atmosphere (100 *psi*) at 40-50 °C for 4-7 hr. After completion, the reaction mixture was filtered through a pad of Celite®545 and washed with EtOAc/methanol. The filtrate was concentrated under reduced pressure to compound which was purified by silica gel column chromatography or prep-HPLC to give the desired compound.

General procedure for Keto-reduction:

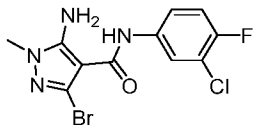
Method A: To a stirred solution of keto compound (1 eq.) in EtOH/MeOH (5 vol) (4.7 mL/mmol), at 0 °C under Argon atmosphere, $NaBH_4$ (1-2 eq.) was added and stirred at room temperature for 2-6 hr. After completion, the reaction mixture was concentrated *in vacuo*, the residue obtained was diluted with water and extracted using ethyl acetate. The combined organic layers were collected, dried over anhydrous sodium sulphate, filtered, concentrated *in vacuo* and purified by silica gel column chromatography/prep. HPLC to give the desired compound. Note: THF was also (1 vol) added as a co-solvent for substrates which are having poor solubility in alcoholic solvents.

Intermediate 1



Ethyl 5-amino-3-bromo-1-methyl-1H-pyrazole-4-carboxylate. To a yellow solution of ethyl 5-amino-1-methyl-pyrazole-4-carboxylate (0.206 g, 1.22 mmol, 1 eq) in EtOH (5 mL) was added a solution of sodium acetate (929.89 mg, 11.34 mmol, 9.28 eq) in H_2O (8 mL), followed by dropwise addition of Br_2 (1.12 g, 7.04 mmol, 362.82 uL, 5.78 eq). The orange suspension was stirred at 15 °C for 3 hr. The reaction mixture was poured into H_2O (15 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined and washed with saturated aqueous sodium thiosulfate solution (2 x 5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The solid was triturated with a solution of methyl t-butyl ether: petroleum ether (1:10) (10 mL) for 5 min. Ethyl 5-amino-3-bromo-1-methyl-pyrazole-4-carboxylate was obtained as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14 (br s, 2 H), 4.32 (q, J = 7.13 Hz, 2 H), 3.61 (s, 3 H), 1.38 (t, J = 7.15 Hz, 3 H) ppm.

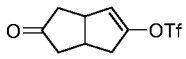
Intermediate 2



5-Amino-3-bromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide. To a colorless solution of 3-chloro-4-fluoro-aniline (281.65 mg, 1.93 mmol, 2 eq) in toluene (6 mL) was added Me_3Al (2 M in toluene) (2 M, 1.45 mL, 3 eq) at 0 °C. The light brown solution was allowed to warm to 15 °C and stirred for 0.5 hr. To the solution was added ethyl 5-amino-3-bromo-1-methyl-pyrazole-4-carboxylate (0.24 g, 967.44 umol, 1 eq). The brown solution was stirred at 80 °C for 16 hr. Dark brown suspension was observed. The mixture

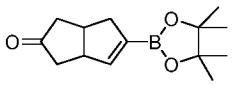
was cooled to 0 °C and quenched with 1 N HCl (2 mL). A brown suspension was observed. The mixture was filtered. The filtrate was diluted with water (10 mL), extracted with EtOAc (15 mL x 3). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under vacuum to give a residue as a yellow solid. The residue was triturated with methyl t-butyl ether (3 mL) for 5 min. 5-amino-3-bromo-N-(3-chloro-4-fluoro-phenyl)-1-methyl-pyrazole-4-carboxamide was obtained as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1 H), 7.80 (dd, *J* = 6.54, 2.63 Hz, 1 H), 7.29 - 7.41 (m, 1 H), 7.12 (t, *J* = 8.74 Hz, 1 H), 5.53 (br s, 2 H), 3.64 (s, 3 H), 1.57 (s, 3 H) ppm.

Intermediate 3



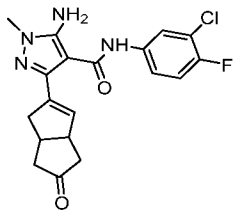
5-Oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl trifluoromethanesulfonate. To a solution of 1,3,3a,4,6,6a-hexahydropentalene-2,5-dione (40.0g, 289.5 mmol) and pyridine (24.0 g, 304.0 mmol) in DCM (600 ml) was added Tf_2O (89.8 g, 318.5 mmol) dropwise at room temperature. The mixture was stirred at room temperature for 3 h. Brine (300 mL) was added and the aqueous layer extracted with DCM (200 mL x 3). The organic layer was separated, dried over Na_2SO_4 and concentrated to give the crude product which was purified by silica gel column chromatography using 8:1 petroleum ether/ethyl acetate to afford 5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl trifluoromethanesulfonate as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.63 (q, *J* = 1.92 Hz, 1 H), 3.57 - 3.50 (m, 1 H), 3.14 - 3.00 (m, 2 H), 2.67 - 2.58 (m, 1 H), 2.56 -2.40 (m, 2 H), 2.34 - 2.26 (m, 1 H), 2.17 (ddd, *J* = 19.14, 7.34, 1.63 Hz, 1 H) ppm.

Intermediate 4



5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydropentalen-2(1H)-one. A mixture of 5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl trifluoromethanesulfonate (110.0 g, 407.0 mmol), 4,4,5,5-tetramethyl-2-(4, 4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (108.5 g, 427.4 mmol), $Pd(dppf)Cl_2$ (8.9 g, 12.2 mmol) and potassium acetate (119.7 g, 1221.0 mmol) in dioxane (1000 ml) was stirred at 80 °C under an N_2 atmosphere for 2 h. The reaction mixture was filtered through a pad of Celite® and the filter cake washed with EtOAc (250 mL x 3). The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using 8:1 petroleum ether/ethyl acetate to afford 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydropentalen-2(1H)-one as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.37 (q, J = 2.08 Hz, 1 H), 3.54 - 3.41 (m, 1 H), 3.05 - 2.93 (m, 1 H), 2.79 (ddt, J = 16.48, 7.58, 2.64, 2.64 Hz, 1 H), 2.55 - 2.24 (m, 4 H), 2.07 - 1.95 (m, 1 H), 1.28 (s, 13 H) ppm.

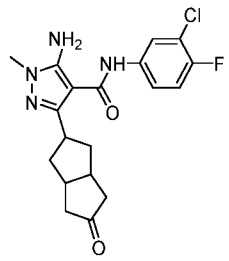
Intermediate 5



5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-1H-pyrazole-4-carboxamide. A mixture of 5-amino-3-bromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide (68.6 g, 197.5 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydropentalen-2(1H)-one (70.0 g, 282.1 mmol), $Pd(dppf)Cl_2$ (10.1 g, 13.8 mmol) and Na_2CO_3 (41.9 g, 395.0 mmol) in dioxane (1200 mL) and H_2O (150 mL) was stirred at 80 °C overnight under N_2. The mixture

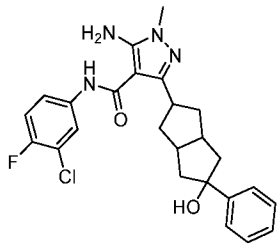
was a brown suspension. The solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography using 1:2 petroleum ether/ethyl acetate to afford 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-1H-pyrazole-4-carboxamide as a yellow solid. MS (*m/z*): calcd.: 388.1, Found: 389.0 [M+1]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19 (dd, *J*=19.20, 5.26 Hz, 1 H), 2.33 (br d, *J*=18.83 Hz, 1 H), 2.55 - 2.79 (m, 3 H), 3.15 - 3.28 (m, 2 H), 3.63 (s, 3 H), 3.66 (s, 1 H), 3.68 - 3.77 (m, 1 H), 5.24 - 5.45 (m, 2 H), 6.05 (d, *J*=1.71 Hz, 1 H), 6.95 - 7.20 (m, 2 H), 7.47 - 7.58 (m, 1 H), 7.68 - 7.86 (m, 2 H) ppm.

Intermediate 6

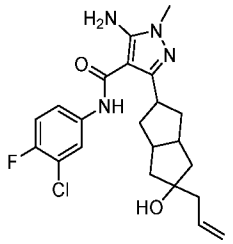


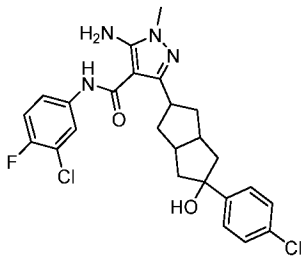
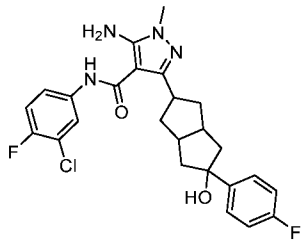
5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide. To a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydropentalen-2(1H)-one (5.0 g, 12.9 mmol) in EtOAc (500 ml) was added Pd/C (2.5 g, 10% w/w Pd). The mixture was stirred at 40 °C for 2 h under H_2. The mixture was filtered, and solvent removed under *vacuum* to give the target compound as a white solid. The crude product was used directly without any further purification. MS (*m/z*): Calcd.: 390.1, Found: 391.0 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 - 2.01 (m, 2 H), 2.07 - 2.29 (m, 2 H), 2.41 - 2.67 (m, 4 H), 2.83 - 3.06 (m, 2 H), 3.32 - 3.50 (m, 1 H), 3.54 - 3.61 (m, 3 H), 5.15 - 5.32 (m, 2 H), 7.12 (t, *J*=8.74 Hz, 1 H), 7.27 - 7.35 (m, 2 H), 7.65 - 7.83 (m, 1 H) ppm.

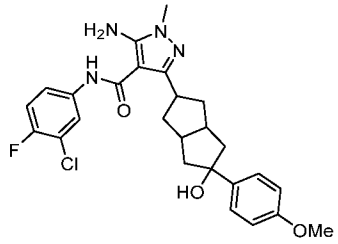
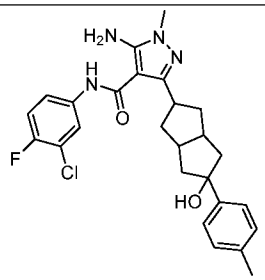
Example 1

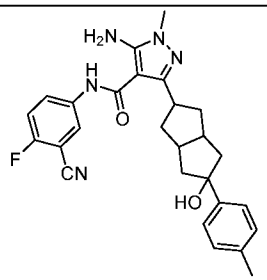
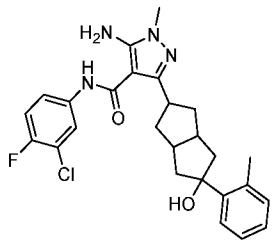
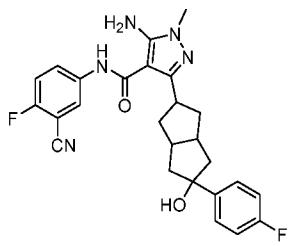


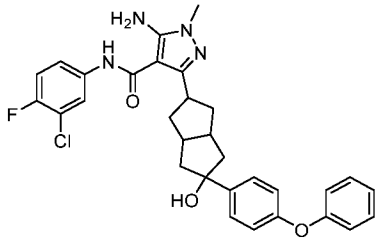
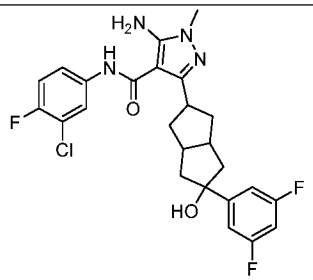
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-phenyl-octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. 2M PhMgBr in THF (6.4 mL, 12.8 mmol) was added to a stirred solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (0.5 g, 1.28 mmol) in THF (10 mL) at -40 °C, and the mixture stirred at room temperature for 3h. After completion, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude compound was purified by trituration with DCM and filtered to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-phenyl-octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. MS (*m/z*): Calcd. for $C_{25}H_{26}ClFN_4O_2$: 468.17, Found; 491.15 [M + Na]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.92 (dd, *J* = 7.0, 2.4 Hz, 1H), 7.56 - 7.48 (m, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 8.8 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.20 - 7.14 (m, 1H), 5.98 (s, 2H), 4.75 (s, 1H), 3.50 (s, 3H), 3.46 - 3.38 (m, 1H, merged), 2.68 - 2.58 (m, 2H), 2.20 - 2.02 (m, 4H), 2.00 - 1.88 (m, 2H), 1.86 - 1.76 (m, 2H) ppm.

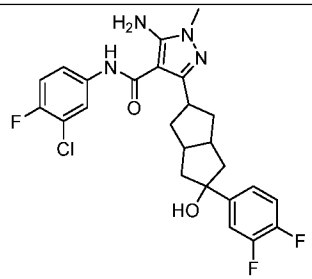
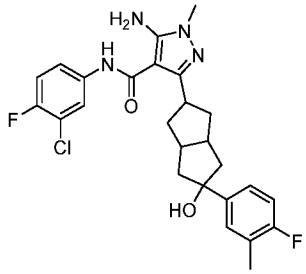
Example 2	

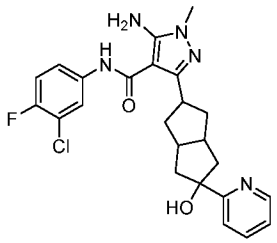
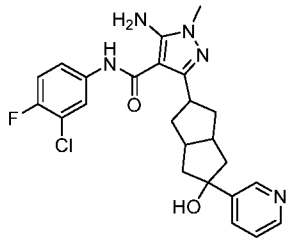
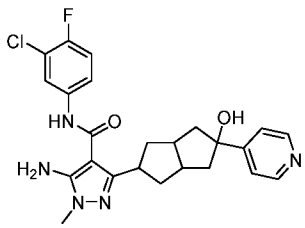
	3-(5-Allyl-5-hydroxyoctahydropentalen-2-yl)-5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide. MS (*m/z*): Calcd. for $C_{22}H_{26}ClFN_4O_2$: 432.17, Found: 433.16 [M+1]+; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.90 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.54 - 7.46 (m, 1H), 7.34 (t, *J* = 9.2 Hz, 1H), 5.96 (s, 2H), 5.92 - 5.80 (m, 1H), 5.00 (s, 1H), 4.98 - 4.96 (m, 1H), 4.24 (s, 1H), 3.48 (s, 3H), 3.48 - 3.38 (m, 1H), 2.48 - 2.32 (m, 2H), 2.20 - 2.10 (m, 4H), 1.76 - 1.58 (m, 4H), 1.42 - 1.36 (m, 2H) ppm.
Example 3	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(4-chlorophenyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{25}H_{25}Cl_2FN_4O_2$: 502.13, Found: 501.15 [M - 1]$^-$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.91 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.54 - 7.49 (m, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.37 - 7.31 (m, 3H), 5.98 (m, 2H), 4.87 (s, 1H), 3.49 (s, 3H), 3.45 - 3.30 (m, 1H), 2.67 - 2.60 (m, 2H), 2.15 - 1.78 (m, 8H) ppm.
Example 4	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(4-fluorophenyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{25}H_{25}ClF_2N_4O_2$: 486.16, Found: 486.90 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.91 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.54 - 7.51 (m, 1H), 7.50 - 7.42 (m, 2H), 7.34 (t, *J* = 9.6 Hz, 1H), 5.98 (m,

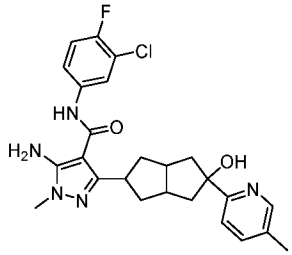
	2H), 7.08 (d, *J* = 8.8 Hz, 2H), 4.82 (s, 1H), 3.49 (s, 3H), 3.43 - 3.36 (m, 1H), 2.67 - 2.58 (m, 2H), 2.16 - 1.91 (m, 6H), 1.82 - 1.78 (m, 2H) ppm.
Example 5	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(4-methoxyphenyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{26}H_{28}ClFN_4O_3$: 498.18, Found: 481.00 [M-18]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.91 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.52 - 7.50 (m, 1H), 7.37 - 7.32 (m, 3H), 6.81 (d, *J* = 8.8 Hz, 1H), 5.98 (s, 3H), 4.66 (s, 1H), 3.71 (s, 3H), 3.49 (s, 3H), 3.48 - 3.35 (m, 1H), 2.58 - 2.56 (m, 2H), 2.14 - 1.75 (m, 8H) ppm.
Example 6	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(p-tolyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide**. MS (*m/z*): Calcd. for $C_{26}H_{28}ClFN_4O_2$: 482.19, Found: 465.10 [M - 18]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.90 (s, 1H), 7.92 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.67 - 7.29 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 5.98 (s, 2H), 4.68 (s, 1H), 3.50 (s, 3H), 3.45 - 3.37 (s, 1H), 2.59 - 2.53 (m, 2H), 2.25 (s, 3H), 2.15 - 1.76 (m, 8H) ppm.

Example 7	 **5-Amino-N-(3-cyano-4-fluorophenyl)-3-(5-hydroxy-5-(p-tolyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{27}H_{28}FN_5O_2$: 473.22, Found: 456.03 [M-18]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.04 (s, 1H), 8.12 (dd, *J* = 6.0, 3.3 Hz, 1H), 7.92 - 7.88 (m, 1H), 7.47 (t, *J* = 9.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 2H), 4.69 (s, 1H), 3.50 (s, 3H), 3.45 - 3.40 (m, 1H), 2.60 - 2.59 (m, 2H), 2.25 (s, 3H), 2.18 - 1.2.05 (m, 4H), 1.97 - 1.88 (m, 2H), 1.80 - 1.76 (m, 2H) ppm.
Example 8	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(o-tolyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{26}H_{28}ClFN_4O_2$: 482.19, Found: 465.10 [M-18]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91(s, 1H), 7.93 - 7.90 (m, 1H), 7.52 - 7.49 (m, 1H), 7.36 - 7.27 (m, 2H), 7.10 - 7.07 (m, 3H), 5.99 (s, 2H), 4.75 (s, 1H), 3.50 (s, 3H), 3.47 - 3.40 (m, 1H), 2.50 - 2.47 (s, 3H, merged), 2.46 - 2.40 (m, 2H), 2.30 - 2.25 (m, 2H), 2.17 - 2.14 (m, 2H), 1.91 - 1.75 (m, 4H) ppm.
Example 9	

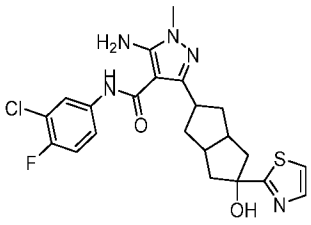
	5-Amino-N-(3-cyano-4-fluorophenyl)-3-(5-(4-fluorophenyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. MS (*m/z*): Calcd. for $C_{26}H_{25}F_2N_5O_2$: 477.20, Found: 460.45 [M-18]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.04 (s, 1H), 8.12-8.10 (m, 1H), 7.90 - 7.85 (m, 1H), 7.47 - 7.40 (m, 3H), 7.07 (t, *J* = 8.8 Hz, 2H), 6.01 (s, 2H), 4.82 (s, 1H), 3.49 (s, 3H), 3.48 - 3.35 (m, 1H, merged), 2.65 - 2.55 (m, 2H), 2.15 - 2.02 (m, 4H), 1.93 - 1.89 (m, 2H), 1.82 - 1.75 (m, 2H) ppm.
Example 10	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(4-phenoxyphenyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{31}H_{30}ClFN_4O_3$: 560.20, Found: 543.05 [M-18]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.94 - 7.90 (m, 1H), 7.53 - 7.50 (m, 1H), 7.45 - 7.32 (m, 5H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.98 - 6.90 (m, 4H), 5.99 (s, 2H), 4.79 (s, 1H), 3.50 (s, 3H), 3.48 - 3.32 (m, 1H), 2.60 - 2.55 (m, 2H), 2.15 - 2.04 (m, 4H), 1.95 - 1.91 (m, 2H), 1.83 - 1.79 (m, 2H) ppm.
Example 11	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(3,5-difluorophenyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{25}H_{24}ClF_3N_4O_2$: 504.15, Found: 505.45 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.94-7.90 (m, 1H), 7.54-7.50 (m, 1H), 7.35 (t, *J* = 8.8 Hz, 1H), 7.10 - 7.08 (m, 2H), 7.04 - 6.99 (m, 1H),

	5.96 (s, 2H), 5.03 (s, 1H), 3.50 (s, 3H), 3.42 - 3.36 (m, 1H), 2.70 - 2.64 (m, 2H), 2.15 - 2.04 (m, 4H), 1.99 - 1.90 (m, 2H), 1.81 - 1.76 (m, 2H) ppm.
Example 12	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(3,4-difluorophenyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{25}H_{24}ClF_3N_4O_2$: 504.15, Found: 487.15 [M-18]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.94 - 7.90 (m, 1H), 7.53 - 7.50 (m, 1H), 7.45 - 7.25 (m, 4H), 5.98 (s, 2H), 4.96 (s, 1H), 3.50 (s, 3H), 3.45 - 3.35 (m, 1H), 2.65 - 2.60 (m, 2H), 2.14 - 2.02 (m, 4H), 1.97 - 1.92 (m, 2H), 1.82 - 1.75 (m, 2H) ppm.
Example 13	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(4-fluoro-3-methylphenyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{26}H_{27}ClF_2N_4O_2$: 500.18, Found: 483.25 [M-18]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.93 - 7.89 (m, 1H), 7.52 - 7.48 (m, 1H), 7.36 - 7.25 (m, 3H), 7.00 (t, J = 8.8 Hz, 1H), 5.98 (s, 2H), 4.77 (s, 1H), 3.49 (s, 3H), 3.42-3.39 (m, 1H), 2.65 - 2.60 (m, 2H), 2.20 (s, 3H), 2.13 - 2.04 (m, 4H), 1.95 - 1.88 (m, 2H), 1.79 - 1.75 (m, 2H) ppm.

Example 14	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(pyridin-2-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS (*m/z*): Calcd. for $C_{24}H_{25}ClFN_5O_2$: 469.17, Found: 470 [M+1]+; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.47-8.44 (m, 1H), 7.93 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.76 - 7.70 (m, 1H), 7.65 - 7.62 (m, 1H), 7.54 - 7.50 (m, 1H), 7.35 (t, *J* = 8.8 Hz, 1H), 7.20 - 7.17 (m, 1H), 5.99 (s, 2H), 5.02 (s, 1H), 3.51 (s, 3H), 3.43 - 3.38 (m, 1H), 2.70 - 2.65 (m, 2H), 2.34 - 2.29 (m, 2H), 2.17 - 2.13 (m, 2H), 2.00 - 1.94 (m, 2H), 1.73 - 1.69 (m, 2H) ppm.
Example 15	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(pyridin-3-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS (*m/z*): Calcd. for $C_{24}H_{25}ClFN_5O_2$: 469.17, Found: 470.15 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.64 (s, 1H), 8.39-8.38 (m, 1H),7.93 - 7.91 (m, 1H), 7.80 - 7.78 (m, 1H), 7.52 - 7.51 (m, 1H), 7.37 - 7.28 (m, 2H), 5.98 (s, 2H), 4.98 (s, 1H), 3.50 (s, 3H), 2.46 - 2.42 (m, 1H), 2.63 (br.s, 2H), 2.15 - 2.07 (m, 4H), 1.95 - 1.93 (m, 2H), 1.86 - 1.83 (m, 2H) ppm.
Example 16	

	5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(pyridin-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide MS (*m/z*): Calcd.: 469.17, Found: 470.10 $[M + 1]^+$.
Example 17	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(5-methylpyridin-2-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.29 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.99 (s, 2H), 4.96 (s, 1H), 3.50 (s, 3H), 3.43 - 3.31 (m, 1H), 2.66 - 2.65 (m, 2H), 2.31 - 2.25 (m, 5H), 2.14 - 2.07 (m, 2H), 1.95 - 1.92 (m, 2H), 1.69 - 1.66 (m, 2H) ppm

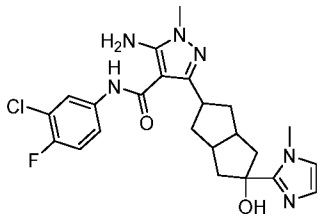
Example 18



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(thiazol-2-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of thiazole (87 mg, 1.0 mmol) in THF (2 mL) was added n-BuLi (0.4 mL, 2.5 M, 1.0 mmol) at -78 °C under N_2 and the mixture stirred at -78 °C for 1 h. To this was added 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (50 mg, 0.13 mmol) in one portion. The resulting mixture was kept -78 °C and stirred for 1 h. The reaction was quenched with sat. aqueous NH_4Cl and extracted with ethyl

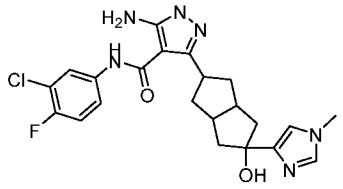
acetate. The organic layer was dried and concentrated. The crude residue was purified by prep-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(thiazol-2-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. TLC 100% ethyl acetate (R_f: 0.3). MS calcd.: 475.1; MS Found: 476.2 $[M + 1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6-): δ 8.93 (s, 1H), 7.94-7.92 (m, 1H), 7.67 (d, J = 3.2 Hz, 1H), 7.55-7.50 (m, 2H), 7.35 (t, J = 9.2 Hz, 1H), 6.00 (s, 2H), 5.86 (s, 1H), 3.50 (s, 3H), 3.45-3.38 (m, 1H), 2.70-2.69 (m, 2H), 2.28-2.23 (m, 2H), 2.19-2.15 (m, 2H), 1.90-1.83 (m, 4H) ppm.

Example 19



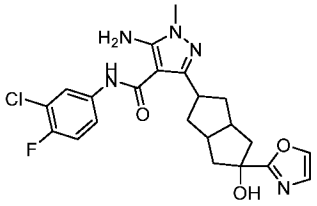
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-methyl-1H-imidazol-2-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of 1-methyl-1H-imidazole (410 mg, 5.0 mmol) in THF (5 mL) was added *n*-BuLi (2.5M in hexanes, 2.0 mL) at – 20 °C and stirred 0.5 h. To this was added 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (200 mg, 0.5 mmol) in THF (1 mL) and stirring continued for another 3 hr at – 20 °C. The reaction was quenched with sat. aqueous NH_4Cl (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by reversed column chromatography to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-methyl-1H-imidazol-2-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a yellow solid. MS calcd.: 472.2. Found 473.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.90 (s, 1H), 7.93 (dd, J = 7.2 Hz, 2.8 Hz, 1H), 7.53 - 7.49 (m, 1H), 7.35 (t, J = 8.8 Hz, 1H), 7.00 (s, 1H), 6.66 (s, 1H), 6.01 (s, 2H), 5.19 (s, 1H), 3.73 (s, 3H), 3.50 (s, 3H), 3.47 - 3.40 (m, 1H), 2.51-2.50 (m, 2H), 2.43 - 2.38 (m, 2H), 2.18 - 2.13 (m, 2H), 1.81 - 1.70 (m, 4H) ppm.

Example 20



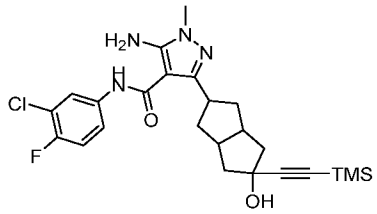
3-Amino-N-(3-chloro-4-fluorophenyl)-5-(5-hydroxy-5-(1-methyl-1H-imidazol-4-yl)octahydropentalen-2-yl)-2λ^2-pyrazole-4-carboxamide. To a solution of 4-iodo-1-methyl-1H-imidazole (166 mg, 0.8 mmol) in DCM (2 mL) was added EtMgBr (1.0 M, 0.8 mL, 0.8 mmol) at room temperature under nitrogen atmosphere. After stirring 1 h, a suspension of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (39 mg, 0.1 mmol) in THF (1 mL) was added. The reaction was stirred for 2 h at room temperature, quenched with sat. aqueous NH_4Cl and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the crude compound which was purified by prep-HPLC to afford 3-amino-N-(3-chloro-4-fluorophenyl)-5-(5-hydroxy-5-(1-methyl-1H-imidazol-4-yl)octahydropentalen-2-yl)-2λ^2-pyrazole-4-carboxamide as a white solid. TLC; 50% ethyl acetate/petroleum ether (R_f: 0.3). MS calcd.: 472.2, MS Found: 473.2 $[M + 1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.90 (brs, 1H), 7.92 (dd, J = 2.4 Hz, 6.4 Hz, 1H), 7.52-7.46 (m, 1H), 7.40 (s, 1H), 7.34 (t, J = 9.0 Hz, 1H), 6.85 (d, J = 1.6 Hz, 1H), 5.99 (s, 2H), 4.49 (s, 1H), 3.57 (6H, s), 3.49 (s, 1H), 2.50 (t, J = 1.8 Hz, 2H), 2.21-2.10 (m, 4H), 1.83-1.78 (m, 2H), 1.62-1.57 (m, 2H) ppm.

Example 21



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(oxazol-2-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. A solution of oxazole (142 mg, 2.0 mmol) and BH_3-THF (2.0 mL, 1.0 M, 2.0 mmol) was stirred for 30 min. The mixture was cooled to -78 °C , and n-BuLi (0.8 mL, 2.5 M, 2.0 mmol) added. The reaction was stirred at -78 °C for 1 h. Following this 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (100 mg, 0.26 mmol) was added in one portion. The resulting mixture was kept -78 °C and stirred for 1 h. The reaction was quenched with sat. aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was dried and concentrated. The residue was purified by prep-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(oxazol-2-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. TLC: 100% ethyl acetate (R_f: 0.4). MS calcd.: 459.1. Found: 460.2 $[M + 1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.01 (s, 1H), 7.94-7.91 (m, 1H), 7.54-7.50 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 7.11 (s, 1H), 6.00 (s, 2H), 5.51 (s, 1H), 3.50 (s, 3H), 3.46-3.40 (m, 1H), 2.51-2.50 (m, 2H), 2.35-2.30 (m, 2H), 2.19-2.15 (m, 2H), 1.83-1.72 (m, 4H) ppm.

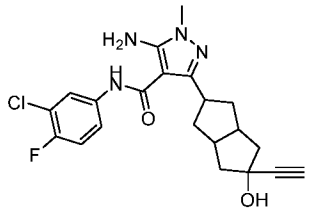
Intermediate 7



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-((trimethylsilyl)ethynyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide

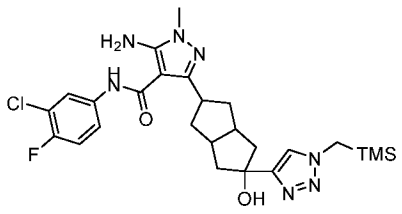
A solution of ethynyltrimethylsilane (2.0 g, 20.4 mmol) in THF (20 mL) was added n-BuLi (8.2 mL, 2.5 M, 20.5 mmol) at 0 °C under N_2, the mixture was stirred at 0 °C for 1 h. 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (1.0 g, 2.56 mmol) was then added in one portion. The resulting mixture was kept at 0 °C and stirred for 1 h. The reaction was quenched with NH_4Cl solution and extracted with ethyl acetate. The organic layer was dried and concentrated. The residue was purified through silica gel column chromatography (petroleum ether/ethyl acetate=1:50) to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-((trimethylsilyl)ethynyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. TLC; 100% ethyl acetate (R_f: 0.4). MS calcd.: 488.2. Found: 489.3 $[M + 1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H), 7.79 (dd, J = 7.2, 2.4 Hz, 1H), 7.41-7.37 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 5.87 (s, 2H), 5.16 (s, 1H), 3.37 (s, 3H), 3.30-3.26 (m, 1H), 2.43-2.38 (m, 2H), 2.01-1.98 (m, 2H), 1.89-1.84 (m, 2H), 1.59-1.94 (m, 4H), 0.00 (s, 9H) ppm.

Example 22



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-ethynyl-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-((trimethylsilyl)ethynyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (400 mg, 0.82 mmol) in MeOH (5 ml) was added K_2CO_3 (170 mg, 1.23 mmol). The mixture was stirred at room temperature for 2 h. Water (50 ml) was added and the solution extracted with ethyl acetate. The organic layer was dried and concentrated. The crude was purified through prep-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-ethynyl-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. TLC: 100% ethyl acetate (R_f: 0.2). MS; calcd; 416.1. Found; 417.3 $[M + 1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.35 (t, J = 8.8 Hz, 1H), 5.98 (s, 2H), 5.29 (s, 1H), 3.49 (s, 3H), 3.46-3.37 (m, 1H), 3.23 (s, 1H), 2.55-2.50 (m, 2H), 2.15-2.08 (m, 2H), 2.02-1.97 (m, 2H), 1.70-1.62 (m, 4H) ppm.

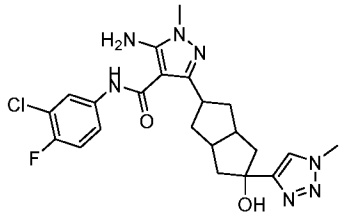
Intermediate 8



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-((trimethylsilyl)methyl)-1H-1,2,3-triazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-ethynyl-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (150 mg, 0.36 mmol) and (azidomethyl)trimethylsilane (56 mg, 0.43 mmol) in THF (2 ml) and H_2O(2 ml) was added $CuSO_4$ -$5H_2O$ (15 mg, 0.058 mmol) and Na ascorbate (15 mg, 0.076 mmol). The mixture was stirred at room temperature for 6 h. Water (20 ml) was added and the solution extracted with ethyl acetate. The organic layer was dried and concentrated. The crude product was purified by silica gel column chromatography using DCM/MeOH=20:1 to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-((trimethylsilyl)methyl)-1H-1,2,3-

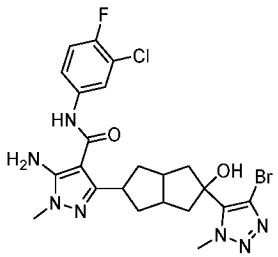
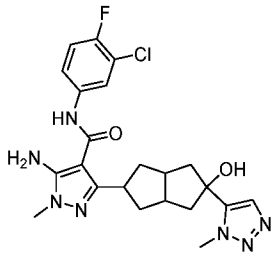
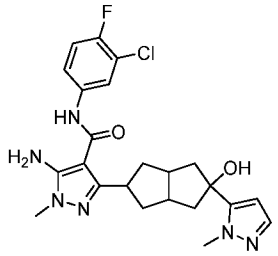
triazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. TLC: 5% MeOH/DCM (R_f: 0.5). MS Calcd.: 545.2. Found: 546.3 $[M+1]^+$.

Example 23



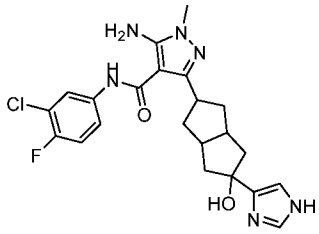
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-methyl-1H-1,2,3-triazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-((trimethylsilyl)methyl)-1H-1,2,3-triazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (180 mg, 0.33 mmol) in THF(3 ml) was added Bu_4NF (0.5 mL, 1.0 M, 0.5 mmol). The mixture was stirred at room temperature overnight. Water(50 ml) was added and extracted with ethyl acetate. The organic layer was dried and concentrated. The crude product was purified by prep-HPLC to afford **5-**amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-methyl-1H-1,2,3-triazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (30 mg, 19%) as a white solid. TLC: 5% MeOH/DCM (R_f: 0.3). MS Calcd.: 473.2. Found: 474.2 [M + 1]. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz, 1H), 7.81 (s, 1H), 7.53-7.49 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.00 (s, 2H), 4.99 (s, 1H), 3.98 (s, 3H), 3.50 (s, 3H), 3.43-3.40 (m, 1H), 2.54-2.50 (m, 2H), 2.26-2.21 (m, 2H), 2.18-2.13 (m, 2H), 1.84-1.72 (m, 4H) ppm.

Example	Structure and analysis

Example 24	 **5-Amino-3-(5-(4-bromo-1-methyl-1H-1,2,3-triazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide** ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.94 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.50-7.53 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 5.48 (s, 1H), 4.15 (s, 3H), 3.49 (s, 3H), 3.38-3.44 (m, 1H), 2.63-2.67 (m, 2H), 2.29-2.35 (m, 2H), 2.05-2.18 (m, 4H), 1.85-1.93 (m, 2H) ppm
Example 25	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-methyl-1H-1,2,3-triazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** ^{1}H-NMR (400 MHz, CD_3OD): 7.80 (dd, J = 6.8, 2.4 Hz, 1H), 7.57 (s, 1H), 7.39-7.42(m, 1H), 7.18 (t, J = 8.8 Hz, 1H), 4.17 (s, 3H), 3.58 (s, 3H), 3.43-3.47 (m, 1H), 2.66-2.67 (m, 2H), 2.32-2.37 (m, 2H), 2.01-2.05 (m, 2H), 1.85-1.93 (m, 2H) ppm
Example 26	

	5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.93 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 6.08 (d, J = 2 Hz, 1H), 5.99 (s, 2H), 5.17 (s, 1H), 3.90 (s, 3H), 3.50 (s, 3H), 3.46-3.40 (m, 1H), 2.51-2.49 (m, 2H), 2.20-2.16 (m, 4H), 1.90-1.85 (m, 2H), 1.81-1.73 (m, 2H) ppm

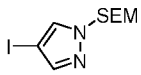
Example 27



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1H-imidazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide To a solution of 4-bromo-1H-imidazole (200.0 mg, 1.4 mmol) in THF (15 mL) was added n-Butyllithium (1.4 mL, 3.4 mmol, 2.5M) dropwise at -78°C. The resulting solution was allowed to warm to room temperature and stirred for 1 hour. The reaction was then cooled to -78°C and a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (200.0 mg, 0.5 mmol) in anhydrous tetrahydrofuran (4 mL) added over 5 min. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride solution (1 mL). The solvent was removed and the residue diluted with water, extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated to give the crude product which was purified by column chromatography (0-10% methanol in DCM) and basic *prep*-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1H-imidazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. TLC: 10%

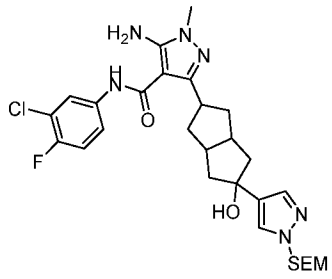
MeOH/DCM (R_f: 0.2). MS Calcd.: 458.2. Found: 441.0 [M - 18 + 1]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (dd, J = 6.8, 2.8 Hz, 1H), 7.59 (s, 1H), 7.42-7.38 (m, 1H), 7.18 (t, J = 8.8 Hz, 1H), 6.95 (s, 1H), 3.56 (s, 3H), 3.45-3.39 (m, 1H), 2.63-2.62 (m, 2H), 2.42-2.37 (m, 2H), 1.90-1.82 (m, 4H) ppm.

Intermediate 9



4-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole. A mixture of 4-iodo-1H-pyrazole (3.0 g, 15.5 mmol) and NaH (744.0 mg, 60%) in THF (30 mL) was stirred at 0°C for 30 min. SEMCl (2.84 g, 17.1 mmol) was then added dropwise over 5 min and the reaction mixture stirred for 2 hours. The mixture was quenched with saturated aqueous ammonium chloride solution (1 mL). The solvent was removed and the residue diluted with water, extracted with ethyl acetate (3 x 40 mL), dried over Na_2SO_4, filtered and concentrated to give the crude product which was purified by column chromatography using 0-25% petroleum ether in ethyl acetate to afford 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (4.5 g, 90.0%) as a colorless oil. TLC: 25% PE/EA (R_f: 0.6). MS Calcd.: 324.0. MS Found: 325.1 $[M + 1]^+$.

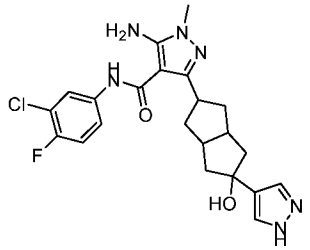
Intermediate 10



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-((2-(trimethylsilyl)-ethoxy)methyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. A mixture of 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (2.1 g,

6.4 mmol) and iPrMgCl (2.5 mL, 2M in THF) in THF (20 mL) was stirred at room temperature for 1 hour, then a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (500.0 mg, 1.3 mmol) in THF (4 mL) was added dropwise over 5 min. The reaction mixture was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride solution (1 mL). The solvent was removed and the residue diluted with water, extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by column chromatography using 0-15% methanol in DCM to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a brown solid. TLC: 10% MeOH/DCM (R_f: 0.3). MS Calcd.: 588.2. Found: 589.3 $[M + 1]^+$.

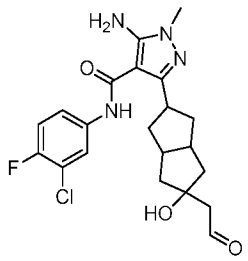
Example 28



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide A mixture of afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (100.0 mg, 0.17 mmol) and TFA (1 mL) in DCM (5 mL) was stirred at room temperature for 1 hour. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (1 mL) and the solvent removed. The mixture was diluted with water, basified by Sat. $NaHCO_3$ (aq.) (pH > 7) then extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated to give the crude product which was purified by column chromatography using 0-20% methanol in DCM and basic *prep*-HPLC to afford 5-amino-N-(3-chloro-4-

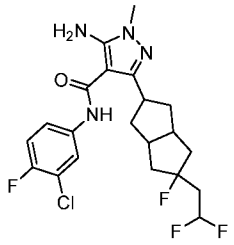
fluorophenyl)-3-(5-hydroxy-5-(1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. TLC: 15% MeOH/DCM (R_f: 0.3). MS Calcd.: 458.2. MS Found: 441.0 [M - 18]. ^{1}H NMR (400 MHz, DMSO-d_6,): δ 12.68 (brs, 1H), 9.00 (s, 1H), 7.92 (dd, J = 7.2, 2.8 Hz, 1H), 7.65 (brs, 2H), 7.55-7.51 (m, 1H), 7.36 (t, J = 8.8 Hz, 1H), 6.95 (s, 2H), 5.76 (s, 1H), 3.46 (s, 3H), 3.45-3.40 (m, 1H), 3.33-3.23 (m, 2H), 2.74-2.69 (m, 2H), 2.33-2.17 (m, 2H), 1.47-1.35 (m, 4H) ppm.

Intermediate 11



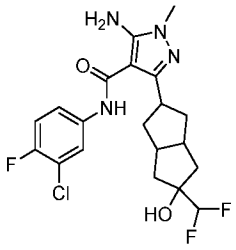
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(2-oxoethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. OsO_4 (15 mg, 0.0578 mmol) in *t*BuOH (5 mL) and $NaIO_4$ (0.74 g, 3.47 mmol) were added to a stirred solution of 3-(5-allyl-5-hydroxyoctahydropentalen-2-yl)-5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide (0.5 g, 1.15 mmol) in 10 mL 1:1 ether/H_2O and the reaction stirred at room temperature for 2 hr. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 0.3 g of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(2-oxoethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide which used for the next step without further purification.

Example 29



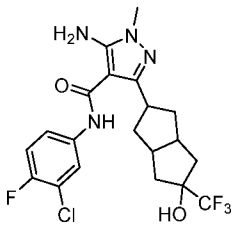
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(2,2-difluoroethyl)-5-fluorooctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. DAST (0.148g, 0.92 mmol) was added to a stirred solution of *5*-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(2-oxoethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (0.2 g, 0.46 mmol) in DCM (3 mL) at 0 °C and the mixture stirred at room temperature for 6 h. After completion, the reaction mixture was diluted with saturated $NaHCO_3$ and extracted with DCM. The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude compound was purified by prep. HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-(2,2-difluoroethyl)-5-fluorooctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as an off white solid. MS calcd for $C_{21}H_{23}ClF_4N_4O$; 485.15. Found; 495.50 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.91 (dd, J = 6.6, 2.0 Hz, 1H), 7.54-7.48 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 6.35-5.94 (m, 3H), 3.68-3.55 (m, 1H), 3.48 (s, 3H), 2.72-2.60 (m, 2H), 2.50-2.30 (m, 2H, merged), 2.22-2.04 (m, 4H), 1.66-1.44 (m, 4H) ppm.

Example 30



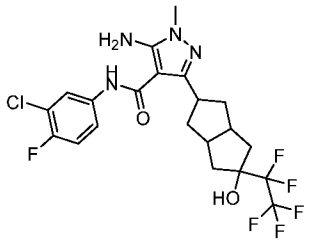
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(difluoromethyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. CsF (0.015 g, 0.10 mmol), 18-Crown-6 (0.026 g, 0.10 mmol) and (difluoromethyl)-trimethylsilane (0.31 mL, 2.56 mmol) were added to a stirred suspension of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (0.2 g, 0.51 mmol) in DME (2 mL) at 0 °C, and stirring continued at room temperature for 24 h. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude compound was purified by prep. HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-(difluoromethyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as an off-white solid. MS calcd for $C_{20}H_{22}ClF_3N_4O_2$; 442.14. Found; 443.05 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.91 (dd, J = 7.0, 2.4 Hz, 1H), 7.54-7.48 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.97 (s, 2H), 5.73 (t, J = 56.4 Hz, 1H), 5.02 (s, 1H), 3.49 (s, 3H), 3.49-3.35 (m, 1H), 2.60-2.54 (m, 2H, merged), 2.20-2.10 (m, 2H), 1.92-1.70 (m, 4H), 1.56-1.48 (m, 2H) ppm.

Example 31



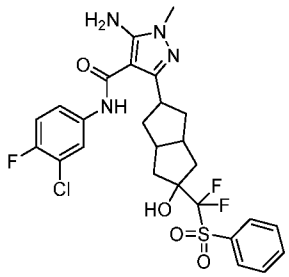
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(trifluoromethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. TBAF (10.24 mL THF solution, 1mol/L, 10.24 mmol), and trimethyl(trifluoromethyl)silane (13 mL, >20 eq) were added slowly to a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (2 g, 5.12 mmol) in THF (50 mL), at 0°C. The mixture was stirred at room temperature for 15 mins, then at 60 °C overnight. Additional trimethyl- (trifluoromethyl)silane (3 mL) was added slowly at room temperature and the mixture stirred at 60°C for another 3 h. The solution was quenched with H_2O, extracted with ethyl acetate. The organic layer was concentrated and the residue was purified by silica gel column chromatography (10%~20% CH_3OH/DCM), reversed phase column chromatography and then silica column chromatography (60%~80% ethyl acetate/petroleum ether) to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(trifluoromethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. MS calcd for $C_{20}H_{21}ClF_4N_4O_2$; 460.13. Found: 461.1 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.92 (dd, J = 2.4 Hz, 4.4 Hz, 1H), 7.52 - 7.51 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.99 (s, 2H), 5.70 (s, 1H), 3.49 (s, 3H), 3.41 - 3.37 (m, 1H), 2.65 - 2.63 (m, 2H), 2.16 - 2.13 (m, 2H), 2.01 - 1.95 (m, 2H), 1.82 - 1.80 (m, 2H), 1.70 - 1.67 (m, 2H) ppm.

Example 32



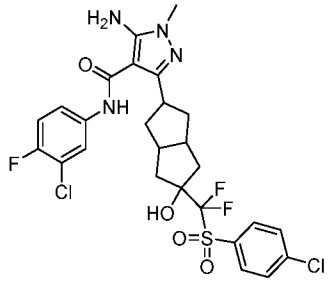
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(perfluoroethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide To solution of 1,1,1,2,2-pentafluoro-2-iodoethane (2.36 g, 5.4 eq, 9.59 mmol) in dry THF (40 mL) was added LiMe solution (1.6 M, 6 mL, 5.4 eq, 9.59 mmol) dropwise at -78 °C. The reaction was stirred for 1 h at -78 °C in an Ar atmosphere. Following this, a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-((2s,3aR,6aS)-5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (700 mg, 1.0 eq, 1.79 mmol) in dry THF (5 mL) was added dropwise at -78 °C. The reaction was stirred for 2 h at -78 °C. The mixture was quenched with NH_4Cl solution (40 mL) and extracted with EtOAc (20 mL x 3). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by reserve-phase column chromatography to afford a white solid (60 mg, 6.6% yield). MS Calcd.: 510.1, MS Found: 511.1 $[M + 1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz, 1H), 7.55 - 7.49 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 5.73 (s, 1H), 3.49 (s, 3H), 3.43 - 3.34 (m, 1H), 2.72 - 2.60 (m, 2H), 2.20 - 2.09 (m, 2H), 2.04 - 1.94 (m, 2H), 1.91 - 1.80 (m, 2H), 1.76 (d, J =13.6 Hz, 2H) ppm.

Example 33

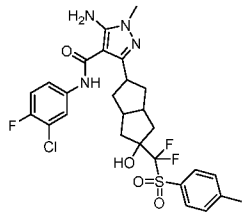
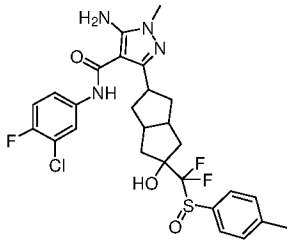


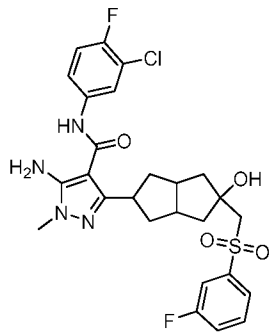
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(difluoro(phenylsulfonyl)methyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. LiHMDS (2.3 mL, 2.3 mmol, 1M in THF) was added to a stirred solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (0.2 g, 0.51 mmol), ((difluoromethyl)-sulfonyl)benzene (0.29 g, 1.53 mmol) in THF (5 mL) at -78°C, and stirring continued for 1.5 h. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. After completion, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude compound was purified by prep. HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-(difluoro(phenylsulfonyl)methyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. MS calcd for $C_{26}H_{26}ClF_3N_4O_4S$; 582.13. Found; 583.10 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.98-7.80 (m, 4H), 7.71 (t, J = 7.2 Hz, 2H), 7.55-7.48 (m, 1H), 7.38-7.30 (m, 1H), 5.97 (s, 2H), 5.66 (s, 1H), 3.48 (s, 3H), 3.38-3.26 (m, 1H, merged), 2.71-2.54 (m, 2H), 2.19-2.00 (m, 4H), 1.92-1.74 (m, 4H) ppm.

Example 34

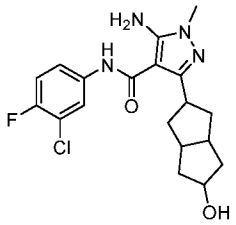


5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(((4-chlorophenyl)sulfonyl)difluoromethyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a stirred solution of compound 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (300mg, 0.76 mmol) and 1-chloro-4-(difluoromethyl)sulfonyl)benzene (366mg, 1.61 mmol) in THF (5 mL) at -78 °C, was added LiHMDS (2.5M in THF) (0.7 mL,1.76 mmol) and the reaction mixture stirred at room temperature for16 h. After completion, the mixture was diluted with ice cold water and extracted with ethyl acetate. The combined organic layers were collected, dried over anhydrous sodium sulphate, filtered,concentrated *in vacuo* and purified by prep. HPLC to give 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-(((4-chlorophenyl)sulfonyl)difluoromethyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid . MS calc for $C_{26}H_{25}Cl_2F_3N_4O_4S$; 616.09. Found; 617.03 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.96-7.90 (m, 3H), 7.77 (d, J = 8.0 Hz, 2H), 7.52-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.97 (m, 2H), 5.67 (s, 1H), 3.48 (s, 3H), 3.34-3.30 (m, 1H, merged), 2.63-2.62 (m, 2H), 2.13-2.03 (m, 4H), 1.87-1.73 (m, 4H) ppm.

Example	Structure and analysis
Example 35	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(difluoro(tosyl)methyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd for $C_{27}H_{28}ClF_3N_4O_4S$; 596.15. Found; 596.95 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.92-7.90 (m, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 3H), 7.36-7.32 (m, 1H), 5.97 (s, 2H), 5.61 (s, 1H), 3.57-3.50 (m, 1H), 3.49 (s, 3H), 3.11-2.97 (m, 4H), 2.62-2.50 (m, 1H), 2.45-2.35 (m, 1H), 2.24-2.04 (m, 5H), 1.95-1.85 (m, 2H) ppm.
Example 36	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(difluoro(p-tolylsulfinyl)methyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd for $C_{27}H_{28}ClF_3N_4O_3S$; 580.15. Found; 581.05 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.55-7.50 (m, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 9.2 Hz, 1H), 5.99 (s, 3H), 3.50 (s, 3H), 3.42-3.32 (m, 1H), 2.68-2.52 (m, 2H), 2.40 (s, 3H), 2.20-1.62 (m, 8H) ppm.

Example 37	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(((3-fluorophenyl)sulfonyl)methyl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.92 (s, 1H), 7.90 (dd, J = 6.8, 2.4 Hz, 1H), 7.73-7.65 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.94 (d, J = 6.4 Hz, 2H), 4.46 (s, 1H), 3.56 (s, 2H), 3.47 (s, 3H), 3.42-3.32 (m, 1H), 2.50-2.49 (m, 2H), 2.09-2.07 (m, 2H), 1.96-1.91 (m, 2H), 1.66-1.57 (m, 4H) ppm.

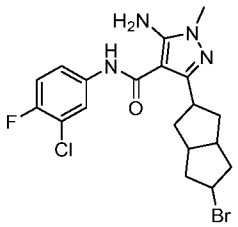
Intermediate 12



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. $NaBH_4$ (0.98 g, 25.70 mmol) was added to a stirred solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (5 g, 12.85 mmol) in MeOH (50 mL) at 0 °C under an Ar atmosphere and the reaction stirred at 0 °C for 2 h. After completion, the reaction mixture was quenched with water and concentrated *in vacuo*. The residue was diluted with water and extracted with 10% MeOH/DCM. The combined organic layers were collected, dried over anhydrous sodium sulphate, filtered, concentrated *in vacuo* and purified by silica gel column

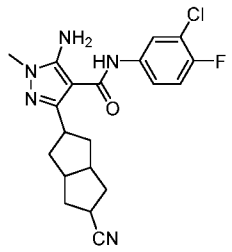
chromatography to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. TLC; 70% EtOAc/ hexanes (R_f: 0.1). LCMS calcd for $C_{19}H_{22}ClFN_4O_2$; 392.14. Found; 393.5. $[M + 1]^+$.^{1}H NMR (400 MHz, DMSO-d_6,): δ 8.94 (s, 1H), 7.92-7.90 (m, 1H), 7.53-7.50 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 4.46-4.44 (m, 1H), 4.10-4.04 (m, 1H), 3.50 (s, 3H), 3.46-3.38 (m, 1H), 2.40-2.35 (m, 2H), 2.17-2.13 (m, 2H), 1.93-1.86 (m, 2H), 1.63-1.54 (m, 2H), 1.31-1.26 (m, 2H) ppm.

Intermediate 13



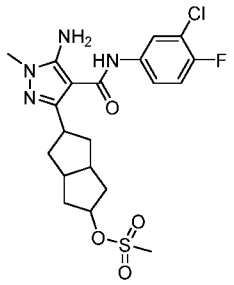
5-Amino-3-(5-bromooctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide. Triphenylphosphine (1.99 g, 7.63 mmol) was added to a stirred solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (2 g, 5.08 mmol) in DCM (30 mL) at 0 °C under an Argon atmosphere and stirring continued for 10 min. CBr_4 (2.86 g, 8.63 mmol) was added portion-wise to this solution,. The reaction mixture was stirred at room temperature for 16 h. After completion, the mixture was diluted with water and extracted with DCM. The combined organic layers were collected, dried over anhydrous sodium sulphate, filtered, concentrated *in vacuo* and purified by silica gel column chromatography to afford 5-amino-3-(5-bromooctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide. TLC; EtOAc (R_f: 0.2). LCMS Calculated for $C_{19}H_{21}BrClFN_4O$: 454.06; Found; 455.3 $[M + 1]^+$.

Intermediate 14



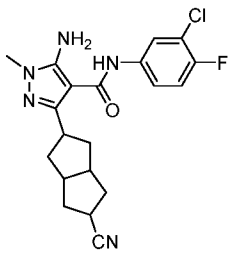
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-cyanooctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide, Isomer I. NaCN (0.719 g, 14.5 mmol) was added to a stirred solution of 5-amino-3-(5-bromooctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide (4.4 g, 9.69 mmol) in DMSO (50 mL). The reaction mixture was stirred at 60 °C for 4 h. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were collected, dried over anhydrous sodium sulphate, filtered, concentrated *in vacuo* and purified by silica gel column chromatography to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-cyanooctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide, Isomer I as an off white solid. TLC; 100% EtOAc (R_f: 0.3). MS calcd for $C_{20}H_{21}ClFN_5O$; 401.4. Found; 402.50 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 7.91-7.89 (m, 1H), 7.59-7.49 (m, 1H), 7.35 (t, J = 8.8 Hz, 1H), 5.97 (s, 2H), 3.56-3.49 (m, 4H), 3.00-2.95 (m, 1H), 2.50-2.48 (m, 2H, merged), 2.20-2.15 (m, 4H), 1.60-1.50 (m, 4H) ppm.

Intermediate 15



5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl methanesulfonate. DMAP (0.03 g, 0.254 mmol) and TEA (1.04 mL, 7.62 mmol) were added to a stirred solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (1 g, 2.54 mmol) in DCM (10 mL) at 0 °C and stirring continued for 10 min. To this solution was added MsCl (0.41 mL, 5.08 mmol). The mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were collected, dried over anhydrous sodium sulphate, filtered, concentrated *in vacuo* and purified by silica gel column chromatography to afford 5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl methanesulfonate. TLC; 5% MeOH/DCM (R_f: 0.5). LCMS calcd for $C_{20}H_{24}ClFN_4O_4S$; 470.12. Found; 471.20 $[M + 1]^+$.

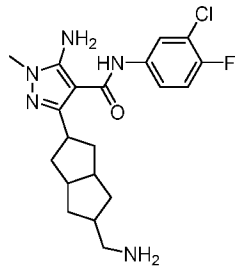
Intermediate 16



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-cyanooctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II. NaCN (0.125 g, 2.35 mmol) was added to a

stirred solution of 5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl methanesulfonate (0.6 g, 1.27 mmol) in DMSO (6 mL). The reaction mixture was stirred at 70 °C for 4 h. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were collected, dried over sodium sulphate, filtered, concentrated *in vacuo* and purified by silica gel column chromatography to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-cyanooctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide, Isomer II. MS calcd for $C_{20}H_{21}ClFN_5O$; 401.14. Found; 402.50 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 7.90 (dd, J = 6.8, 2.0 Hz, 1H), 7.53-7.49 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 3.48 (s, 3H), 3.33-3.27 (m, 1H, merged), 2.94-2.88 (m, 1H), 2.60-2.57 (m, 2H), 2.16-2.12 (m, 2H), 1.86-1.73 (m, 4H), 1.30-1.22 (m, 2H) ppm.

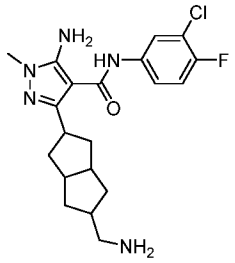
Intermediate 17



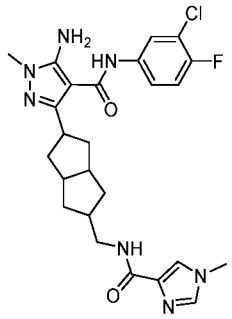
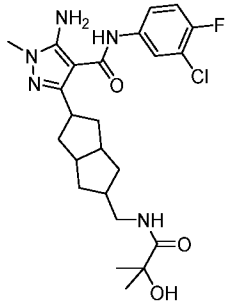
5-Amino-3-(5-(aminomethyl)octahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide Isomer I. A solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-cyanooctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide, Isomer I (130.0 mg, 0.3 mmol) in BH_3-THF (1.0 M, 15 mL, 15 mmol) was stirred at 70 °C for 2 h. The reaction was quenched with MeOH. The solvent was removed *in vacuo.* The residue was purified by reversed phase chromatography to provide 5-amino-3-(5-(aminomethyl)octahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide Isomer I as a white solid. MS calcd; 405.2. Found; 406.3 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.92 (dd, J = 6.8, 2.8 Hz, 1H), 7.54-7.50 (m, 1H), 7.35 (t, J = 8.8 Hz, 1H), 5.97 (s, 2H), 3.59-3.49 (m, 5H), 2.43-2.33 (m, 3H), 2.16-2.12 (m, 2H),

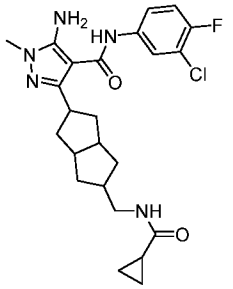
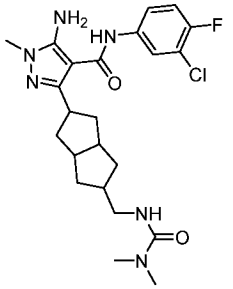
1.96-1.94 (m, 3H), 1.45-1.37 (m, 2H), 0.93-0.86 (m, 2H) ppm. ^{1}H NMR (400 MHz, CD_3OD): δ 7.82 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.45-7.41 (m, 1H), 7.21 (t, *J* = 8.8 Hz, 1H), 3.61-3.54 (m, 4H), 2.72 (d, *J* = 6.0 Hz, 2H), 2.64-2.61 (m, 2H), 2.34-2.27 (m, 2H), 2.14-2.11 (m, 3H), 1.59-1.51 (m, 2H), 1.08-1.00 (m, 2H) ppm.

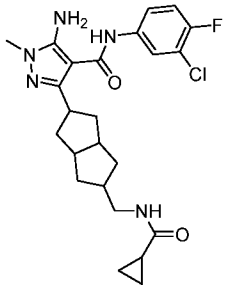
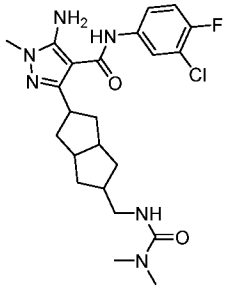
Intermediate 18

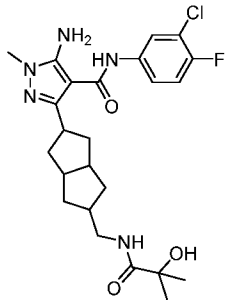
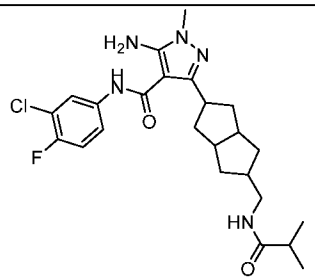


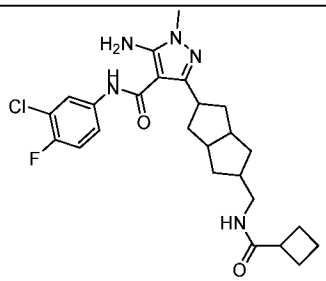
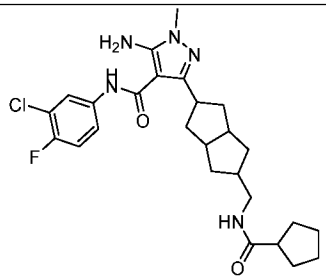
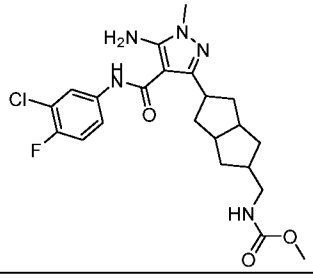
5-Amino-3-(5-(aminomethyl)octahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II. A solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-cyanooctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II (100 mg, 0.249mmol) in BH_3-THF (1.0 M, 10 mL, 10 mmol) was stirred at 70 °C for 2 h. The reaction was quenched with MeOH. The solvent was removed *in vacuo.* The residue was purified by reversed phase chromatography to provide 5-amino-3-(5-(aminomethyl)octahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II as a white solid. MS calcd; 405.2. Found: 406.3 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.92 (dd, *J* = 6.8,2.4 Hz, 1H), 7.54-7.50 (m, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 5.97 (s, 2H), 3.49 (s, 3H), 3.32-3.24 (m, 2H), 2.48-2.42 (m, 3H), 2.17-2.11 (m, 2H), 1.96-1.88 (m, 1H), 1.74-1.65 (m, 2H), 1.49 (dd, *J* = 12.4, 6.0 Hz, 2H), 1.31-1.13 (m, 4H) ppm. ^{1}H NMR (400 MHz, CD_3OD): 7.82 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.45-7.41 (m, 1H), 7.21 (t, *J* = 8.8 Hz, 1H), 3.57 (s, 3H), 3.30-3.26 (m, 1H),2.67-2.60 (m, 4H), 2.33-2.27 (m, 2H), 2.18-2.11 (m, 1H), 1.66 (dd, *J* = 12.4, 6.0 Hz, 2H), 1.45-1.26 (m, 4H) ppm.

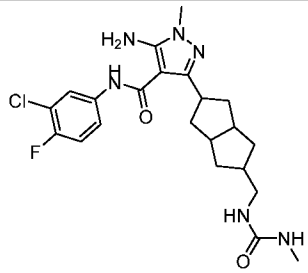
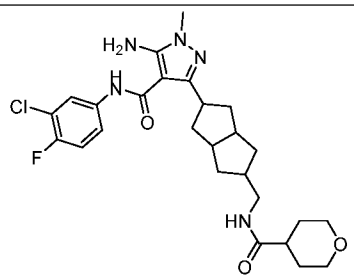
Example	Structure and analysis
Example 38	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((1-methyl-1H-imidazole-4-carboxamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide** MS calcd for $C_{25}H_{29}ClFN_7O_2$; 513.21. Found: 514.25 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.74 (t, J = 6.4 Hz, 1H), 7.62 (s, 1H), 7.56 (s, 1H), 7.52-7.50 (m, 1H), 7.33 (t, J = 9.6 Hz, 1H), 5.95 (s, 2H), 3.66 (s, 3H), 3.57-3.53 (m, 1H), 3.49 (s, 3H), 3.19 (t, J = 6.4 Hz, 2H), 2.43-1.89 (m, 7H), 1.42-1.26 (m, 2H), 0.97-0.95 (m, 2H) ppm.
Example 39	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-((2-hydroxy-2-methylpropanamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer I.** MS calcd for $C_{24}H_{31}ClFN_5O_3$; 492.21. Found 493.25 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.89 (dd, J = 6.8, 2.0 Hz, 1H), 7.54-7.49 (m, 2H), 7.34 (t, J = 8.8 Hz, 1H), 5.96 (s, 2H), 5.29 (s, 1H), 3.55-3.52 (m, 1H), 3.49 (s, 3H), 3.04 (t, J = 6.4 Hz, 2H), 2.42-2.40 (m, 2H), 2.15-2.06 (m, 3H), 1.91-1.87 (m, 2H), 1.45-1.37 (m, 2H), 1.27-1.21 (m, 6H), 0.93-0.85 (m, 2H) ppm.

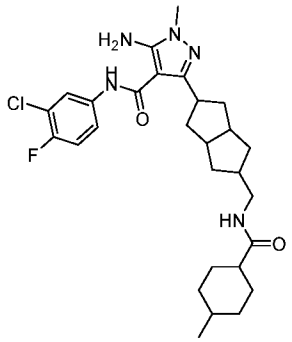
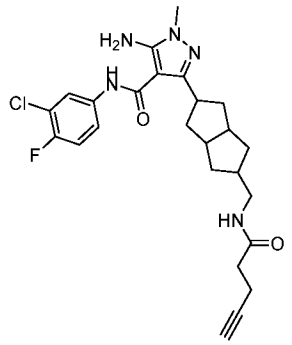
Example 40	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(cyclopropanecarboxamidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer I.** MS calcd for $C_{24}H_{29}ClFN_5O_2$; 473.20. Found; 474.10 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.97 (t, J = 6.0 Hz, 1H), 7.90 (dd, J = 6.8, 2.4 Hz, 1H), 7.53-7.44 (m, 1H), 7.34 (t, J = 9.6 Hz, 1H), 5.96 (s, 2H), 3.57-3.52 (m, 1H), 3.49 (s, 3H), 3.03 (t, J = 6.0 Hz, 2H), 2.45-2.40 (m, 2H), 2.15-1.90 (m, 5H), 1.54-1.37 (m, 3H), 0.96-0.88 (m, 2H), 0.62-0.58 (m, 4H) ppm.
Example 41	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-((3,3-dimethylureido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** Isomer I. MS calcd for $C_{23}H_{30}ClFN_6O_2$; 476.21. Found; 477.5 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 6.15 (t, J = 5.6 Hz, 1H), 5.95 (s, 2H), 3.56-3.52 (m, 1H), 3.49 (s, 3H), 2.97 (t, J = 5.6 Hz, 2H), 2.74 (s, 6H), 2.41-2.40 (m, 2H), 2.15-1.88 (m, 5H), 1.45-1.37 (m, 2H), 0.95-0.86 (m, 2H) ppm.

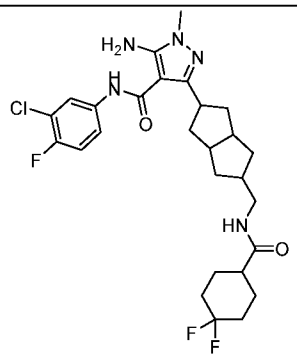
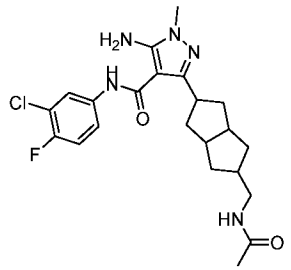
Example 42	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(cyclopropanecarboxamidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II.** MS calcd for $C_{24}H_{29}ClFN_5O_2$; 473.20. Found; 474.10 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.93 (s, 1H), 7.98 (t, J = 5.2 Hz, 1H), 7.89 (dd, J = 6.8 , 2.4 Hz, 1H), 7.52-7.48 (m, 1H), 7.33 (t, J = 8.8 Hz, 1H), 5.95 (s, 2H), 3.48 (s, 3H), 3.28-3.23 (m, 1H, merged), 3.03-3.00 (m, 2H), 2.48-2.44 (m, 2H, merged), 2.14-2.00 (m, 3H), 1.55-1.43 (m, 3H), 1.29-1.15 (m, 4H), 0.64-0.56 (m, 4H) ppm.
Example 43	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-((3,3-dimethylureido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II** MS calcd for $C_{23}H_{30}ClFN_6O_2$; 476.21. Found; 477.15 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.93 (s, 1H), 7.90-7.88 (m, 1H), 7.52-7.47 (m, 1H), 7.33 (t, J = 9.2 Hz, 1H), 6.17 (t, J = 5.6 Hz, 1H), 5.94 (s, 2H), 3.48 (s, 3H), 3.28-3.24 (m, 1H, merged), 2.97-2.93 (m, 2H), 2.74 (s, 6H), 2.50-2.40 (m, 1H, merged), 2.13-2.08 (m, 4H), 1.44-1.39 (m, 2H), 1.28-1.17 (m, 4H) ppm.

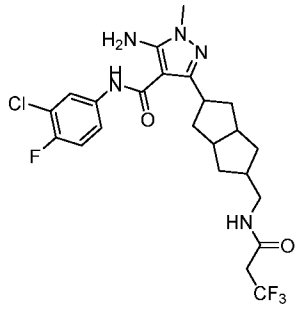
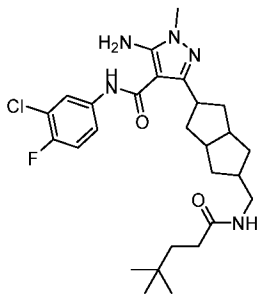
Example 44	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-((2-hydroxy-2-methylpropanamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II** MS calcd for $C_{24}H_{31}ClFN_5O_3$; 491.21. Found; 492.14 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.92-7.89 (m, 1H), 7.60-7.57 (m, 1H), 7.52-7.49 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 5.96 (s, 2H), 5.29 (s, 1H), 3.49 (s, 3H), 3.31-3.26 (m, 1H, merged), 3.05-3.02 (m, 2H), 2.50-2.40 (m, 2H, merged), 2.15-2.05 (m, 3H), 1.44-1.39 (m, 2H), 1.28-1.17 (m, 10H).
Example 45	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(isobutyramidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd for $C_{24}H_{31}ClFN_5O_2$; 475.22. Found; 476.05 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.64 (t, J = 5.6 Hz, 1H), 7.53-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.95 (s, 2H), 3.56-3.52 (m, 1H), 3.49 (s, 3H), 3.00 (t, J = 5.6 Hz, 2H), 2.45-2.29 (m, 3H), 2.15-1.87 (m, 5H), 1.45-1.37 (m, 2H), 0.97-0.88 (m, 8H) ppm.

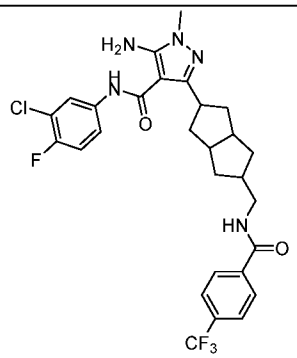
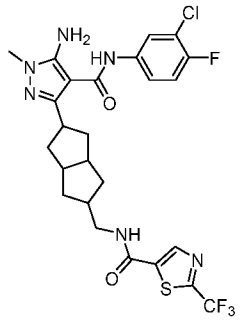
Example 46	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(cyclobutanecarboxamidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{25}H_{31}ClFN_5O_2$; 487.22. Found; 488.05 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (d, J = 5.2 Hz, 1H), 7.57-7.50 (m, 2H), 7.34 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 3.56-3.53 (m, 1H), 3.49 (s, 3H), 3.01-2.92 (m, 3H), 2.41-2.39 (m, 2H), 2.11-1.71 (m, 11H), 1.45-1.37 (m, 2H), 0.94-0.86 (m, 2H) ppm.
Example 47	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(cyclopentanecarboxamidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{26}H_{33}ClFN_5O_2$; 501.23. Found; 502.15 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.66 (t, J = 6.0 Hz, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 3.55-3.53 (m, 1H), 3.49 (s, 3H), 3.01 (t, J = 6.0 Hz, 2H), 2.41-2.39 (m, 2H), 2.14-1.87 (m, 5H), 1.71-1.37 (m, 11H), 0.95-0.87 (m, 2H) ppm.
Example 48	

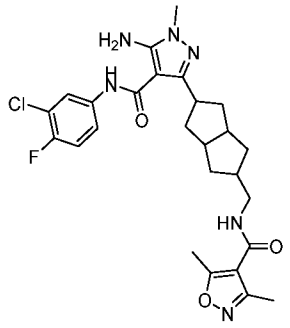
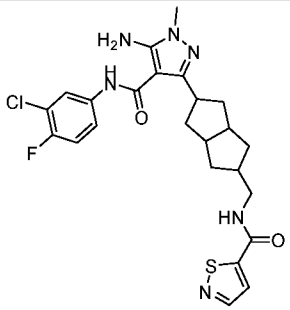
	Methyl ((5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)carbamate. MS calcd for $C_{22}H_{27}ClFN_5O_3$; 463.18. Found; 464.05 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.53-7.50 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 7.08 (t, J = 6.0 Hz, 1H), 5.95 (s, 2H), 3.55-3.46 (m, 7H), 2.95 (t, J = 6.0 Hz, 2H), 2.42-2.41 (m, 2H), 2.16-1.88 (m, 5H), 1.45-1.36 (m, 2H), 0.95-0.87 (m, 2H) ppm.
Example 49	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((3-methylureido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{22}H_{28}ClFN_6O_2$; 462.19. Found; 463.20 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.91 (d, J = 5.6 Hz, 1H), 7.52-7.50 (m, 1H), 7.35 (t, J = 8.4 Hz, 1H), 5.97 (s, 2H), 5.82-5.80 (m, 1H), 5.61-5.60 (m, 1H), 3.56-3.52 (m, 1H), 3.50 (s, 3H), 2.98-2.97 (m, 2H), 2.50-2.43 (m, 4H, merged), 2.15-1.90 (m, 5H), 1.44-0.90 (m, 5H) ppm.
Example 50	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((tetrahydro-2H-pyran-4-carboxamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{26}H_{33}ClFN_5O_3$; 517.23. Found; 518.5 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.71 (t, J = 6.0 Hz, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.95 (s, 2H), 3.85-3.82 (m, 2H), 3.57-3.53 (m, 1H), 3.49 (s, 3H), 3.29-

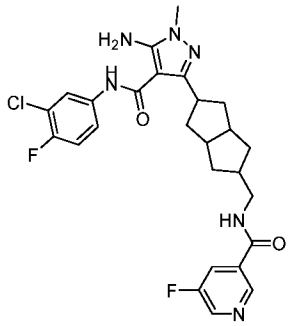
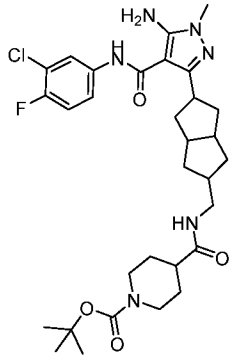
	3.23 (m, 2H), 3.01 (t, *J* = 6.0 Hz, 2H), 2.40-2.32 (m, 3H), 2.14-1.87 (m, 5H), 1.57-1.37 (m, 6H), 0.95-0.88 (m, 2H) ppm.
Example 51	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((4-methylcyclohexane-1-carboxamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{28}H_{37}ClFN_5O_2$; 529.26. Found; 530.40 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.59-7.55 (m, 1H), 7.53-7.49 (m, 1H), 7.33 (t, *J* = 9.2 Hz, 1H), 5.96 (s, 2H), 3.55-3.52 (m, 1H), 3.49 (s, 3H), 3.02-2.98 (m, 2H), 2.41-1.28 (m, 18H), 0.98-0.83 (m, 6H) ppm.
Example 52	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(pent-4-ynamidomethyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{25}H_{29}ClFN_5O_2$; 485.20. Found; 487.5 $[M + 2]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (d, *J* = 6.8 Hz, 1H), 7.84-7.82 (m, 1H), 7.52-7.50 (m, 1H), 7.33 (t, *J* = 9.2 Hz, 1H), 5.95 (s, 2H), 3.56-3.52 (m, 1H), 3.49 (s, 3H), 3.03 (t, *J* =6.0 Hz, 2H), 2.74 (s, 1H), 2.41-1.89 (m, 11H), 1.45-1.38 (m, 2H), 0.97-0.89 (m, 2H) ppm

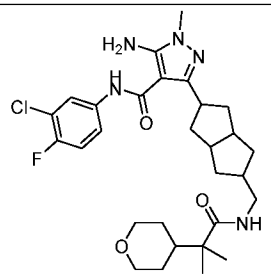
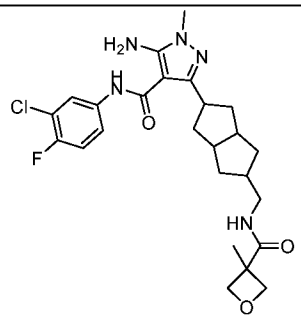
Example 53	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-((4,4-difluorocyclohexane-1-carboxamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{27}H_{33}ClF_3N_5O_2$; 551.23. Found; 552.2 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.90-7.89 (m, 1H), 7.79-7.77 (m, 1H), 7.52-7.49 (m, 1H), 7.33 (t, J = 9.6 Hz, 1H), 5.95 (s, 2H), 3.55-3.51 (m, 1H), 3.48 (s, 3H), 3.01 (t, J = 5.6 Hz, 2H), 2.41-1.57 (m, 16H), 1.45-1.40 (m, 2H), 0.95-0.91 (m, 2H) ppm.
Example 54	 **3-(5-(Acetamidomethyl)octahydropentalen-2-yl)-5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{22}H_{27}ClFN_5O_2$; 447.18. Found; 448.05 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.89 (dd, J = 7.2, 2.4 Hz, 1H), 7.78-7.74 (m, 1H), 7.52-7.51 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 3.57-3.54 (m, 1H), 3.49 (s, 3H), 3.00 (t, J = 6.0 Hz, 2H), 2.42-2.41 (m, 2H), 2.14-1.89 (m, 5H), 1.77 (s, 3H), 1.45-1.37 (m, 2H), 0.95-0.87 (m, 2H) ppm.

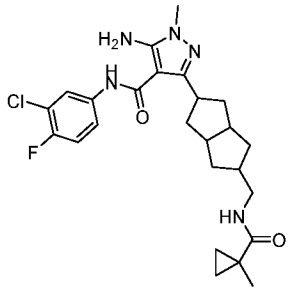
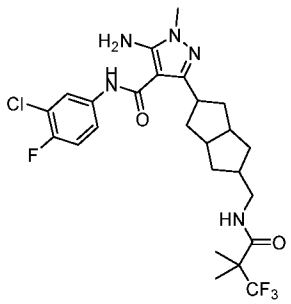
Example 55	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((3,3,3-trifluoropropanamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{23}H_{26}ClF_4N_5O_2$; 515.17. Found; 516.10 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.19-8.18 (m, 1H), 7.92-7.89 (m, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 3.55-3.50 (m, 1H), 3.49 (s, 3H), 3.27-3.16 (m, 2H), 3.07 (t, J = 6.0 Hz, 2H), 2.43-2.42 (m, 2H), 2.14-1.90 (m, 5H), 1.45-1.40 (m, 2H), 0.94-0.92 (m, 2H) ppm.
Example 56	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-((4,4-dimethylpentanamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{27}H_{37}ClFN_5O_2$; 517.26. Found; 518.25 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (d, J = 4.8 Hz, 1H), 7.73-7.72 (m, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.95 (s, 2H), 3.56-3.52 (m, 1H), 3.49 (s, 3H), 3.00 (t, J = 5.6 Hz, 2H), 2.42-2.11 (m, 2H), 2.14-1.88 (m, 7H), 1.40-1.36 (m, 4H), 0.92-0.84 (m, 11H) ppm.

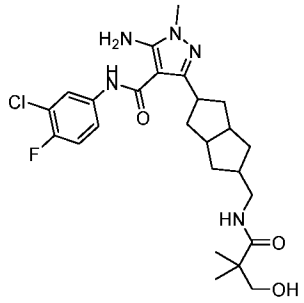
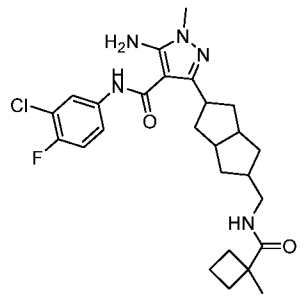
Example 57	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((4-(trifluoromethyl)benzamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{28}H_{28}ClF_4N_5O_2$; 577.19. Found; 578.10 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.68-8.66 (m, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.52-7.50 (m, 1H), 7.33 (t, J = 8.8 Hz, 1H), 5.96 (s, 2H), 3.55-3.52 (m, 1H), 3.48 (s, 3H), 3.26 (t, J = 6.0 Hz, 2H), 2.48-1.95 (m, 7H), 1.45-1.43 (m, 2H), 1.01-1.00 (m, 2H) ppm.
Example 58	 **N-((5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)-2-(trifluoromethyl)thiazole-5-carboxamide.** MS calcd for $C_{25}H_{25}ClF_4N_6O_2S$; 584.14. Found; 585.20 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 9.10-8.93 (m, 2H), 8.62 (s, 1H), 7.90 (d, J = 7.2 Hz, 1H), 7.55-7.48 (m, 1H), 7.33 (t, J = 8.8 Hz, 1H), 5.96 (s, 2H), 3.61-3.50 (m, 1H), 3.48 (s, 3H), 3.32-3.24 (m, 2H, merged), 2.50-2.40 (m, 1H), 2.24-2.08 (m, 4H), 2.04-1.92 (m, 2H), 1.50-1.38 (m, 2H), 1.08-0.54 (m, 2H) ppm

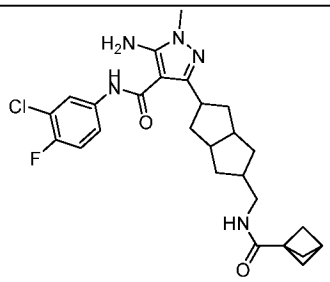
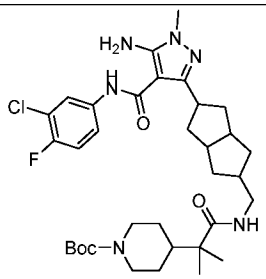
Example 59	 **N-((5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)-3,5-dimethylisoxazole-4-carboxamide**. MS calcd for $C_{26}H_{30}ClFN_6O_3$; 528.21. Found; 529.15 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.98-7.96 (m, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 3.55-3.52 (m, 1H), 3.48 (s, 3H), 3.19 (t, J = 6.0 Hz, 2H), 2.48-2.44 (m, 5H), 2.25 (s, 3H), 2.16-2.13 (m, 2H), 1.97-1.94 (m, 3H), 1.45-1.43 (m, 2H), 1.01-0.98 (m, 2H) ppm.
Example 60	 **N-((5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)isothiazole-5-carboxamide.** MS calcd for $C_{24}H_{26}ClFN_6O_2S$; 516.15. Found; 517.16 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.85-8.84 (m, 1H), 8.64-8.63 (m, 1H), 7.91-7.89 (m, 2H), 7.52-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 3.57-3.54 (m, 1H), 3.49 (s, 3H), 3.25-3.24 (m, 2H), 2.45-2.44 (m, 2H), 2.19-2.12 (m, 3H), 1.98-1.95 (m, 2H), 1.47-1.42 (m, 2H), 1.00-0.99 (m, 2H) ppm.

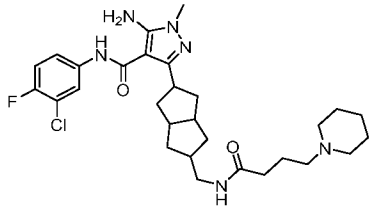
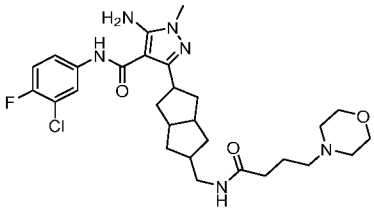
Example 61	 **N-((5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)-5-fluoronicotinamide**. MS calcd for $C_{26}H_{27}ClFN_6O_2$; 528.19. Found; 529.25 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.85 (s, 1H), 8.72-8.69 (m, 2H), 8.06-8.03 (m, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.52-7.48 (m, 1H), 7.35 (t, J = 8.6 Hz, 1H), 5.95 (s, 2H), 3.58-3.52 (m, 1H), 3.48 (s, 3H), 3.41-3.39 (m, 2H, merged), 2.49-2.51 (m, 2H, merged), 2.22-2.12 (m, 3H), 1.99-1.96 (m, 2H), 1.48-1.40 (m, 2H), 1.05-0.96 (m, 2H) ppm.
Example 62	 **tert-Butyl 4-(((5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)carbamoyl)piperidine-1-carboxylate.** MS calcd for $C_{31}H_{42}ClFN_6O_4$; 616.29. Found; 617.20 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.90 (dd, J = 6.8, 2.0 Hz, 1H), 7.75 (t, J = 8.8 Hz, 1H), 7.54-7.48 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 3.98-3.86 (m, 2H), 3.60-3.52 (m, 1H), 3.49 (s, 3H), 3.01 (t, J = 5.6 Hz, 2H), 2.74-2.60 (m, 2H), 2.46-2.38 (m, 2H), 2.30-2.20 (m, 1H), 2.18-1.98 (m, 3H), 1.92-

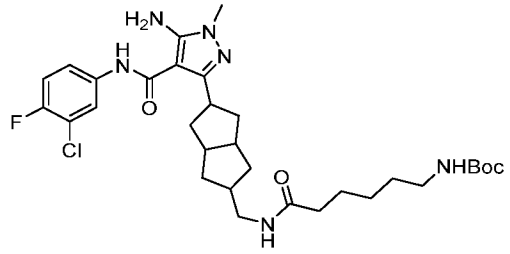
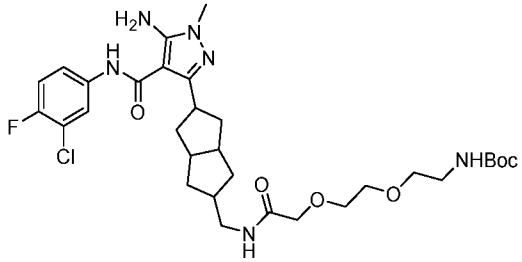
	1.80 (m, 2H), 1.64-1.54 (m, 2H), 1.48-1.30 (m, 13H), 0.98-0.86 (m, 2H) ppm.
Example 63	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((2-methyl-2-(tetrahydro-2H-pyran-4-yl)propanamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{29}H_{39}ClFN_5O_3$; 559.3. Found; 560.1 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.52-7.49 (m, 1H), 7.38-7.29 (m, 2H), 5.96 (s, 2H), 3.84 (d, J = 8.0 Hz, 2H), 3.57-3.53 (m, 1H), 3.48 (s, 3H), 3.20 (t, J = 11.2 Hz, 2H), 3.02 (t, J = 5.6 Hz, 2H), 2.40-2.10 (m, 5H), 1.88-1.74 (m, 3H), 1.41-1.20 (m, 7H), 0.97-0.91 (m, 7H) ppm.
Example 64	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((3-methyloxetane-3-carboxamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{25}H_{31}ClFN_5O_3$; 503.21. Found; 504.1 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.89 (dd, J = 6.8, 2.0 Hz, 1H), 7.77 (t, J = 6.0 Hz, 1H), 7.52-7.49 (m, 1H), 7.33 (t, J = 9.2 Hz, 1H), 5.95 (s, 2H), 4.66 (d, J = 5.6 Hz, 2H), 4.20 (d, J = 6.0 Hz, 2H), 3.55-3.53 (m, 1H), 3.48 (s, 3H), 3.06 (t, J = 6.0 Hz, 2H), 2.42-2.11 (m, 2H), 2.15-1.88 (m, 5H), 1.45-1.40 (m, 5H), 0.97-0.92 (m, 2H) ppm.

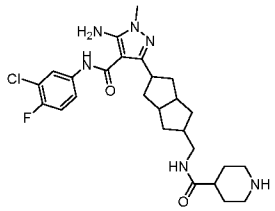
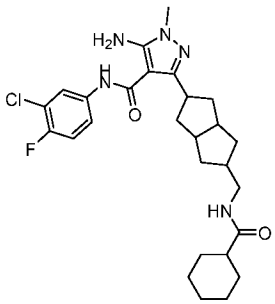
Example 65	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((1-methylcyclopropane-1-carboxamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{25}H_{31}ClFN_5O_2$; 487.22. Found; 488.0 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.53-7.52 (m, 1H), 7.41 (t, J = 6.0 Hz, 1H), 7.34 (t, J = 8.8 Hz, 1H), 6.0 (br.s, 2H), 3.55-3.53 (m, 1H), 3.49 (s, 3H), 3.03 (t, J = 6.0 Hz, 2H), 2.41-2.40 (m, 2H), 2.13-2.11 (m, 3H), 1.91-1.87 (m, 2H), 1.42-1.40 (m, 2H), 1.22-1.19 (m, 3H), 0.92-0.89 (m, 4H), 0.45-0.44 (m, 2H) ppm.
Example 66	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((3,3,3-trifluoro-2,2-dimethylpropanamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{25}H_{30}ClF_4N_5O_2$; 543.20. Found; 544.1 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.92-7.86 (m, 2H), 7.53-7.50 (m, 1H), 7.34 (t, J = 9.6 Hz, 1H), 6.00 (br.s, 2H), 3.55-3.53 (m, 1H), 3.49 (s, 3H), 3.07 (t, J = 5.6 Hz, 2H), 2.42-2.40 (m, 2H), 2.15-2.07 (m, 3H), 1.89-1.86 (m, 2H), 1.45-1.40 (m, 2H), 1.31 (s, 6H), 0.93-0.91 (m, 2H) ppm.

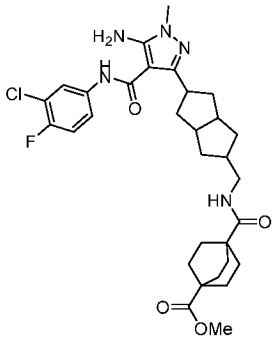
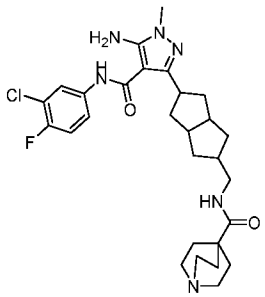
Example 67	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-((3-hydroxy-2,2-dimethylpropanamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{25}H_{33}ClFN_5O_3$; 505.23. Found; 506.1 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.41-7.31 (m, 2H), 5.95 (s, 2H), 4.85 (t, *J* = 5.2 Hz, 1H), 3.57-3.53 (m, 1H), 3.49 (s, 3H), 3.34-3.20 (m, 2H, merged), 3.03 (t, *J* = 5.6 Hz, 2H), 2.41-2.40 (m, 2H), 2.15-2.05 (m, 3H), 1.91-1.87 (m, 2H), 1.45-1.37 (m, 2H), 0.99 (s, 6H), 0.95-0.87 (m, 2H) ppm.
Example 68	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((1-methylcyclobutane-1-carboxamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide**. MS calcd for $C_{26}H_{33}ClFN_5O_2$; 501.23. Found; 502.15 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.52-7.50 (m, 1H), 7.36 (t, *J* = 6.0 Hz, 1H), 7.34 (t, *J* = 9.2 Hz, 1H), 5.96 (s, 2H), 3.55-3.53 (m, 1H), 3.49 (s, 3H), 3.01 (t, *J* = 6.0 Hz, 2H), 2.41-1.40 (m, 15H), 1.27 (s, 3H), 0.92-0.91 (m, 2H) ppm.

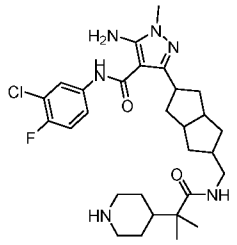
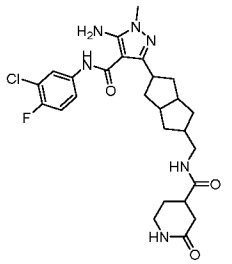
Example 69	 **5-Amino-3-(5-((bicyclo[1.1.1]pentane-1-carboxamido)methyl)octahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{26}H_{31}ClFN_5O_2$; 499.22. Found; 500.15 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.61 (t, J = 6.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.33 (t, J = 9.2 Hz, 1H), 5.95 (s, 2H), 3.57-3.53 (m, 1H), 3.48 (s, 3H), 2.98 (t, J = 6.4 Hz, 2H), 2.45-2.36 (m, 2H), 2.14-2.03 (m, 3H), 1.91-1.86 (m, 8H), 1.44-1.19 (m, 3H), 0.93-0.85 (m, 2H) ppm.
Example 70	 **tert-Butyl 4-(1-(((5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)amino)-2-methyl-1-oxopropan-2-yl)piperidine-1-carboxylate.** MS calcd for $C_{34}H_{48}ClFN_6O_4$; 658.34. Found; 659.26 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.93 (s, 1H), 7.89 (dd, J = 7.2, 2.8 Hz, 1H), 7.53-7.49 (m, 1H), 7.37-7.31 (m, 2H), 5.95 (s, 2H), 3.96 (d, J = 9.2 Hz, 2H), 3.57-3.53 (m, 1H), 3.49 (s, 3H), 3.02 (t, J = 6.0 Hz, 2H), 2.41-2.40 (m, 2H), 2.14-2.07 (m, 3H), 1.88-1.85 (m, 2H), 1.67-1.61 (m, 1H), 1.45-1.36 (m, 14H), 1.02-0.87 (m, 11H) ppm.

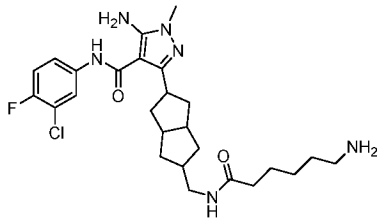
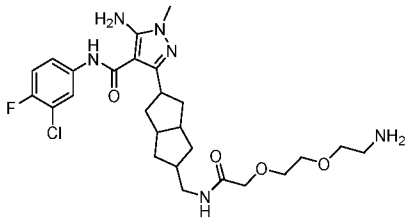
Example 71	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((4-(piperidin-1-yl)butanamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide**. MS calcd for $C_{29}H_{40}ClFN_6O_2$; 558.29. Found; 559.55 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.92-7.89 (m, 1H), 7.73-7.70 (m, 1H), 7.52-7.49 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 5.96 (s, 2H), 3.60-3.52 (m, 1H), 3.49 (s, 3H), 3.03-2.99 (m, 2H), 2.45-2.38 (m, 2H), 2.33-2.27 (m, 4H), 2.20-2.11 (m, 4H), 2.06-2.02 (m, 3H), 1.92-1.88 (m, 2H), 1.64-1.58 (m, 2H), 1.48-1.35 (m, 8H), 0.96-0.91 (m, 2H) ppm.
Example 72	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((4-morpholinobutanamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide**. MS calcd for $C_{28}H_{38}ClFN_6O_3$; 560.27. Found; 561.1 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.94 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.73-7.70 (m, 1H), 7.52-7.49 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 5.96 (s, 2H), 3.55-3.52 (m, 4H), 3.49 (s, 3H), 3.35-3.30 (m, 1H, merged), 3.03-2.99 (m, 2H), 2.45-2.40 (m, 2H), 2.30-2.25 (m, 4H), 2.22-2.17 (m, 2H), 2.14-2.11 (m, 2H), 2.07-2.01 (m, 3H), 1.91-1.88 (m, 2H), 1.63-1.59 (m, 2H), 1.45-1.40 (m, 2H), 0.93-0.90 (m, 2H) ppm.

Example 73	 **tert-Butyl (6-(((5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)amino)-6-oxohexyl)carbamate.** MS calcd for $C_{31}H_{44}ClFN_6O_4$; 618.3. Found: 619.2 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.91-7.89 (m, 1H), 7.72-7.68 (m, 1H), 7.55-7.50 (m, 1H), 7.34 (t, J = 9.6 Hz, 1H), 6.75-6.70 (m, 1H), 5.96 (s, 2H), 3.55-3.47 (m, 4H), 3.32-3.28 (m, 2H), 2.90-2.84 (m, 2H), 2.45-2.40 (m, 2H), 2.15-2.10 (m, 2H), 2.05-1.96 (m, 3H), 1.95-1.90 (m, 2H), 1.50-1.30 (m, 14H), 1.20-1.15 (m, 3H), 0.95-0.89 (m, 2H) ppm.
Example 74	 **tert-Butyl (2-(2-(2-(((5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)amino)-2-oxoethoxy)ethoxy)ethyl)carbamate.** MS calcd for $C_{31}H_{44}ClFN_6O_6$; 650.30. Found; 651.5 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.62-7.58 (m, 1H), 7.52-7.49 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 6.80-6.70 (m, 1H), 5.96 (s, 2H), 3.84 (s, 2H), 3.60-3.49 (m, 8H), 3.39 (t, J = 5.6 Hz, 2H), 3.12-3.04 (m, 4H), 2.45-2.40 (m, 2H), 2.15-2.10 (m, 3H), 1.94-1.88 (m, 2H), 1.45-1.34 (m, 11H), 0.96-.092 (m, 2H) ppm.

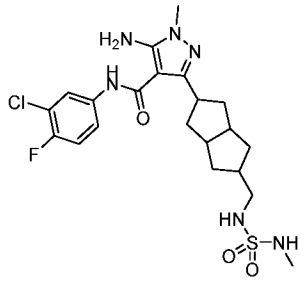
Example 75	 **N-((5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)piperidine-4-carboxamide** MS calcd for $C_{26}H_{34}ClFN_6O_2$; 516.24. Found; 517.15 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.36 (s, 1H), 7.90 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.75 (t, *J* = 5.2 Hz, 1H), 7.56-7.48 (m, 1H), 7.34 (t, *J* = 9.2 Hz, 1H), 5.96 (s, 2H), 3.58-3.50 (m, 1H), 3.49 (s, 3H), 3.10-3.06 (m, 2H), 3.04-2.98 (m, 2H), 2.68-2.54 (m, 2H), 2.46-2.34 (m, 2H), 2.32-2.18 (m, 1H), 2.16-1.98 (m, 3H), 1.96-1.84 (m, 2H), 1.72-1.50 (m, 4H), 1.46-1.36 (m, 2H), 0.97-0.86 (m, 2H) ppm.
Example 76	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(cyclohexanecarboxamidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd for $C_{27}H_{35}ClFN_5O_2$; 515.25. Found; 516.65 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.94 (s, 1H), 7.93-7.88 (m, 1H), 7.60 (t, J = 5.6 Hz, 1H), 7.55-7.46 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 5.95 (s, 2H), 3.57-3.52 (m, 1H), 3.49 (s, 3H), 2.99 (t, J = 5.6 Hz, 2H), 2.43-2.35 (m, 2H), 2.18-1.98 (m, 4H), 1.94-1.82 (m, 2H), 1.72-1.56 (m, 4H), 1.49-1.08 (m, 8H), 0.98-0.85 (m, 2H) ppm.

Example 77	 **Methyl 4-(((5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)carbamoyl)bicyclo[2.2.2]octane-1-carboxylate.** MS calcd for $C_{31}H_{39}ClFN_5O_4$; 599.27. Found; 600.30 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.94 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.55-7.46 (m, 1H), 7.33 (t, J = 8.8 Hz, 1H), 5.95 (s, 2H), 3.56 (s, 3H), 3.54-3.52 (m, 1H), 3.48 (s, 3H), 2.99 (t, J = 6.4 Hz, 2H), 2.45-2.34 (m, 2H), 2.18-2.02 (m, 3H), 1.92-1.80 (m, 2H), 1.64-1.58 (m, 12H), 1.48-1.34 (m, 2H), 0.96-0.84 (m, 2H) ppm; NH proton not observed.
Example 78	 **N-((5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)quinuclidine-4-carboxamide.** MS calcd for $C_{28}H_{36}ClFN_6O_2$; 542.26. Found; 543.20 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.95 (s, 1H), 8.25 (s, 1H), 7.90-7.88 (m, 1H), 7.51-7.50 (m, 1H), 7.37-7.31 (m, 2H), 5.96 (s, 2H), 3.49 (s, 3H), 3.04-3.01 (m, 3H), 2.86-2.82 (m, 6H), 2.45-2.35 (m, 2H), 2.25-2.05 (m, 3H), 1.87-1.84 (m, 2H), 1.63-1.60 (m, 6H), 1.45-1.35 (m 2H), 0.95-0.85 (m, 2H) ppm.

Example 79	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-((2-methyl-2-(piperidin-4-yl)propanamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide** MS calcd for $C_{29}H_{40}ClFN_6O_2$; 558.29. Found; 559.25 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.94 (s, 1H), 7.91-7.89 (m, 1H), 7.52-7.50 (m, 1H), 7.36-7.31 (m, 2H), 5.95 (s, 2H), 3.55-3.51 (m, 1H), 3.48 (s, 3H), 3.03-3.00 (m, 2H), 2.93-2.91 (m, 2H), 2.42-2.30 (m, 4H), 2.15-2.05 (m, 3H), 1.87-1.85 (m, 2H), 1.60-1.50 (m, 1H), 1.41-1.34 (m, 4H), 1.30-1.20 (m, 1H), 1.10-1.00 (m, 2H), 1.00-0.88 (m, 7H) ppm. NH protons not observed.
Example 80	 **N-((5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalen-2-yl)methyl)-2-oxopiperidine-4-carboxamide** MS calcd for $C_{26}H_{32}ClFN_6O_3$; 530.22. Found; 532.05 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.94 (s, 1H), 7.91-7.89 (m, 1H), 7.85-7.82 (m, 1H), 7.52-7.49 (m, 1H), 7.42 (s, 1H), 7.36-7.31 (m, 1H), 5.95 (s, 2H), 3.57-3.50 (m, 1H), 3.49 (s, 3H), 3.11-2.97 (m, 4H), 2.62-2.50 (m, 2H, merged), 2.45-2.35 (m, 1H), 2.24-2.04 (m, 5H), 1.95-1.85 (m, 2H), 1.85-1.75 (m, 1H), 1.65-1.55 (m, 1H), 1.45-1.38 (m, 2H), 0.95-0.90 (m, 2H) ppm.

Example 81	 **5-Amino-3-(5-((6-aminohexanamido)methyl)octahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd for $C_{26}H_{36}ClFN_6O_2$; 518.26. Found; 519.35 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.97 (s, 1H), 8.43 (s, 1H), 7.91-7.89 (m, 1H), 7.55-7.72 (m, 1H), 7.53-7.49 (m, 1H), 7.36-7.32 (m, 1H), 5.96 (s, 2H), 3.60-3.50 (m, 1H), 3.49 (s, 3H), 3.03-3.00 (m, 3H), 2.69-2.65 (m, 2H), 2.45-2.35 (m, 2H), 2.28-2.10 (m, 2H), 2.10-1.95 (m, 3H), 1.95-1.85 (m, 2H), 1.50-1.37 (m, 6H), 1.30-1.20 (m, 2H), 1.00-0.85 (m, 2H) ppm.
Example 82	 **5-Amino-3-(5-((2-(2-(2-aminoethoxy)ethoxy)acetamido)methyl)octahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{26}H_{36}ClFN_6O_4$; 550.25. Found; 551.00 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 9.02 (s, 1H), 7.91-7.89 (m, 1H), 7.88-7.78 (m, 3H), 7.72-7.68 (m, 1H), 7.51-7.50 (m, 1H), 7.37-7.33 (m, 1H), 3.88 (s, 2H), 3.80-3.5 (m, 7H, merged), 3.50 (s, 3H), 3.11-3.08 (m, 2H), 2.97-2.96 (m, 2H), 2.50-2.40 (m, 3H), 2.20-2.00 (m, 3H), 1.95-1.85 (m, 2H), 1.45-1.35 (m, 2H), 1.00-0.90 (m, 2H) ppm.

Example 83

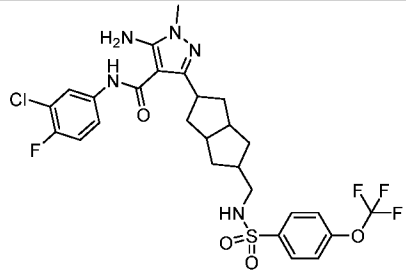
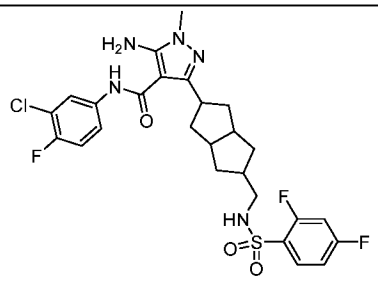


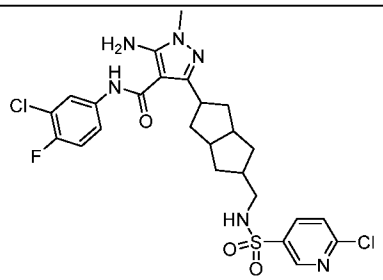
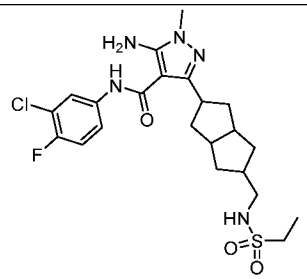
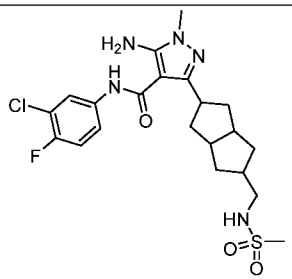
5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((N-methylsulfamoyl)amino)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.

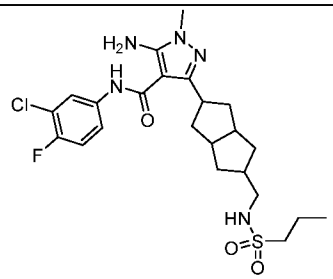
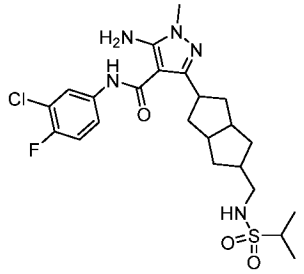
To a stirred solution of compound 5-amino-3-(5-(aminomethyl)octahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II (0.06 g, 0.148 mmol) in DCM (3 mL) at 0°C, triethyl amine (0.022 g, 0.22 mmol) was added methylsulfamoyl chloride (0.022 g, 0.177 mmol) and stirring continued for 1 h. After completion, the reaction mixture was diluted with ice cold water and extracted with DCM. The combined organic layer was dried over dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude compound was purified by Prep. HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((N-methylsulfamoyl)amino)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide as off white solid .

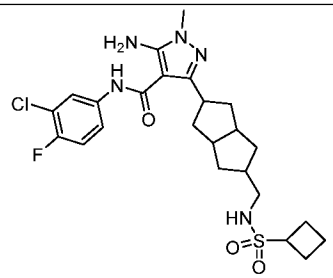
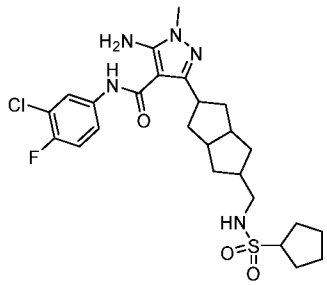
General procedure for Sulphonamidation:

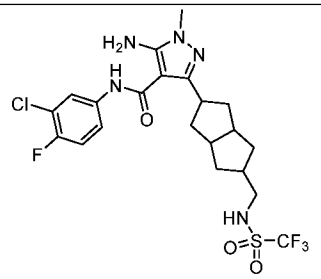
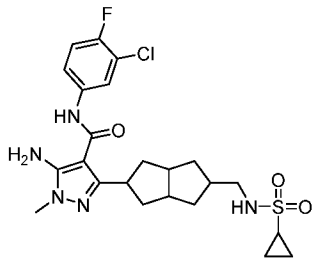
To a stirred solution of 5-amino-3-(5-(aminomethyl)octahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II (0.24 mmol, 1 eq.) in DCM/ DMF (2.5 mL) at 0 °C was added sulfonyl chloride (0.029 mmol) and TEA (0.038 mmol) and the reaction mixture stirred at room temperature for 15 min. After completion, the reaction mixture was diluted with water and extracted with DCM. The combined organic layers were collected, dried over anhydrous sodium sulphate, filtered, concentrated *in vacuo* and purified by prep. HPLC to afford the desired compound.

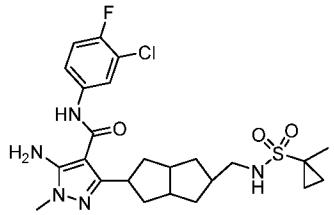
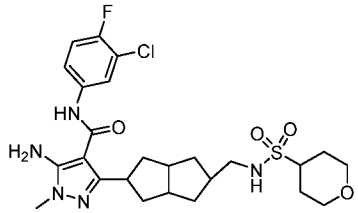
Example	Structure and analysis
Example 84	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((4-(trifluoromethoxy)phenyl)sulfonamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide** MS calcd for $C_{27}H_{28}ClF_4N_5O_4S$; 629.15. Found; 630.10 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.94-7.88 (m, 3H), 7.75-7.68 (m, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.53-7.48 (m, 1H), 7.33 (t, J = 8.8 Hz, 1H), 5.95 (s, 2H), 3.58-3.50 (m, 1H), 3.47 (s, 3H), 2.74 (t, J = 6.4 Hz, 2H), 2.42-2.30 (m, 2H), 2.16-2.04 (m, 2H), 2.03-1.92 (m, 1H), 1.88-1.82 (m, 2H), 1.42-1.32 (m, 2H), 0.92-0.80 (m, 2H) ppm.
Example 85	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(((2,4-difluorophenyl)sulfonamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd for $C_{26}H_{27}ClF_3N_5O_3S$; 581.15. Found; 582.20 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.93(s, 1H), 7.97-7.95 (m, 1H), 7.91-7.88 (m, 1H), 7.86-7.80 (m, 1H), 7.55-7.48 (m, 2H), 7.34 (t, J = 9.6 Hz, 1H), 7.28-7.24 (m, 1H), 5.96 (s, 2H), 3.55-3.48 (m, 4H), 2.84-2.80 (m, 2H), 2.45-2.30 (m, 2H), 2.11-2.07 (m, 2H), 2.00-1.97 (m, 1H), 1.88-1.85 (m, 2H), 1.41-1.33 (m, 2H), 0.90-0.81 (m, 2H) ppm.

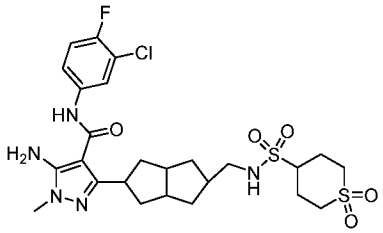
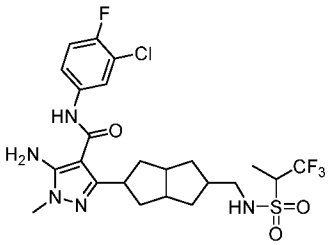
Example 86	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(((6-chloropyridine)-3-sulfonamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd for $C_{25}H_{27}Cl_2FN_6O_3S$; 580.12. Found; 580.8 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.76-8.74 (m, 1H), 8.20-8.15 (m, 1H), 7.91-7.89 (m, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.53-7.48 (m, 1H), 7.34 (t, J = 9.6 Hz, 1H), 5.96 (s, 2H), 3.57-3.52 (m, 1H), 3.48 (s, 3H), 2.82-2.75 (m, 2H), 2.49-2.30 (m, 2H), 2.12-2.08 (m, 2H), 2.00-1.96 (m, 1H), 1.89-1.85 (m, 2H), 1.44-1.34 (m, 2H), 0.95-0.83 (m, 2H) ppm.
Example 87	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(ethylsulfonamidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd; 497.17. Found; 498.25 $[M + 1]^+$.
Example 88	

	5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(methylsulfonamidomethyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide MS clalcd for $C_{21}H_{27}ClFN_5O_3S$; 483.15. Found; 484.00 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.90-7.87 (m, 1H), 7.51-7.49 (m, 1H), 7.33 (t, J = 9.2 Hz, 1H), 6.90 (t, J = 5.6 Hz, 1H), 5.95 (s, 2H), 3.56-3.50 (m, 1H), 3.48 (s, 3H), 2.90-2.87 (m, 2H), 2.84 (s, 3H), 2.45-2.40 (m, 2H), 2.15-1.90 (m, 5H), 1.45-1.37 (m, 2H), 1.00-0.88 (m, 2H) ppm.
Example 89	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(propylsulfonamidomethyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide.** MS calcd for $C_{23}H_{31}ClFN_5O_3S$; 511.18. Found; 512.15 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.93 (s, 1H), 7.88 (dd, J = 6.8, 2.4 Hz, 1H), 7.52-7.47 (m, 1H), 7.32 (t, J = 8.8 Hz, 1H), 6.93 (t, J = 5.6 Hz, 1H), 5.94 (s, 2H), 3.58-3.51 (m, 1H), 3.47 (s, 3H), 2.92-2.85 (m, 4H), 2.45-2.35 (m, 2H), 2.15-1.90 (m, 5H), 1.67-1.57 (m, 2H), 1.45-1.36 (m, 2H), 0.96-0.89 (m, 5H) ppm.
Example 90	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((1-methylethyl)sulfonamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide**. MS calcd for $C_{23}H_{31}ClFN_5O_3S$; 511.18.

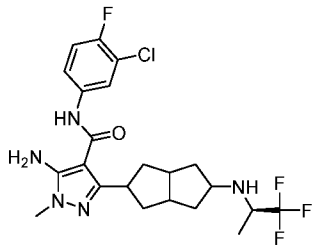
	Found; 512 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.91-7.89 (m, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 6.95-6.93 (m, 1H), 6.00-5.95 (m, 2H), 3.60-3.30 (m, 4H), 3.15-3.10 (m, 1H), 2.92-2.89 (m, 2H), 2.48-2.40 (m, 2H), 2.15-1.92 (m, 5H), 1.46-1.38 (m, 2H), 1.19 (d, J = 6.8 Hz, 6H), 1.00-0.95 (m, 2H) ppm.
Example 91	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(cyclobutanesulfonamidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{24}H_{31}ClFN_5O_3S$; 523.18. Found; 524.10 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.91-7.89 (m, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 6.95-6.92 (m, 1H), 5.96 (s, 2H), 3.90-3.78 (m, 1H), 3.60-3.49 (m, 1H), 3.49 (s, 3H), 2.92-2.89 (m, 2H), 2.48-2.40 (m, 2H), 2.35-1.80 (m, 11H), 1.46-1.38 (m, 2H), 1.05-0.95 (m, 2H) ppm.
Example 92	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(cyclopentanesulfonamidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd for $C_{25}H_{33}ClFN_5O_3S$; 537.20. Found: 538.1 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.93 (s, 1H), 7.89 (dd, J = 6.8 , 2.0 Hz, 1H), 7.51-7.48 (m, 1H), 7.33 (t, J = 9.2 Hz, 1H), 6.92 (t, J = 5.6 Hz, 1H), 5.94 (s, 2H), 3.55-3.42 (m, 4H),

	2.92-2.88 (m, 2H), 2.45-2.40 (m, 2H), 2.13-1.92 (m, 5H), 1.84-1.79 (m, 4H), 1.20-1.12 (m, 1H), 1.62-1.37 (m, 6H), 0.97-0.0.83 (m, 2H) ppm.
Example 93	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((trifluoromethyl)sulfonamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide** MS calcd for $C_{21}H_{24}ClF_4N_5O_3S$; 537.12. Found; 538.30 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.93-7.88 (m, 1H), 7.54-7.48 (m, 1H), 7.34 (t, J = 9.6 Hz, 1H), 5.96 (s, 2H), 3.61-3.48 (m, 1H), 3.49 (s, 3H), 3.13-3.04 (m, 2H), 2.48-2.39 (m, 2H), 2.20-2.02 (m, 3H), 2.00-1.89 (m, 2H), 1.49-1.37 (m, 2H), 1.04-0.94 (m, 2H) ppm; NH proton not observed.
Example 94	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(cyclopropanesulfonamidomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd for $C_{23}H_{29}ClFN_5O_3S$; 509.17. Found; 510.10 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.91 (dd, J = 6.4, 2.4 Hz, 1H), 7.54-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 7.00-6.97 (m, 1H), 5.97 (s, 2H), 3.56-3.52 (m, 1H), 3.49 (s, 3H), 2.96-2.93 (m, 2H), 2.43 (br.s, 2H), 2.14-2.04 (m, 3H), 1.97-1.94 (m, 2H), 1.46-1.38 (m, 2H), 0.99-0.86 (m, 7H) ppm.

Example 95	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((1-methylcyclopropane)-1-sulfonamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide** MS calcd for $C_{24}H_{31}ClFN_5O_3S$; 523.18. Found; 524.15 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.90 (dd, J = 6.4, 2.4 Hz, 1H),7.52-7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 7.08 (t, J = 6.0 Hz, 1H), 5.96 (s, 2H), 3.54-3.52 (m, 1H), 3.49 (s, 3H), 2.92 (t, J = 6.0 Hz, 2H), 2.50-2.43 (m, 2H), 2.14-1.94 (m, 5H), 1.46-1.41 (m, 2H), 1.38 (s, 3H), 1.10-1.08 (m, 2H), 0.96-0.94 (m, 2H), 0.76-0.74 (m, 2H) ppm.
Example 96	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((tetrahydro-2H-pyran)-4-sulfonamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide** MS calcd for $C_{25}H_{33}ClFN_5O_4S$; 553.19. Found; 554.00 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.89 (d, J = 4.8 Hz, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 7.05 (m, 1H), 5.96 (s, 2H), 3.91 (d, J = 7.6 Hz, 2H), 3.56-3.52 (m, 3H), 3.27-3.16 (m, 2H), 2.92 (m, 2H), 2.49-2.43 (m, 4H), 2.14-1.94 (m, 5H), 1.84-1.81(m, 2H), 1.61-1.41 (m, 4H), 0.95-0.94 (m, 2H) ppm

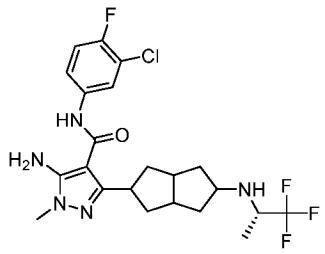
Example 97	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-(((1,1-dioxidotetrahydro-2H-thiopyran)-4-sulfonamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd for $C_{25}H_{33}ClFN_5O_5S_2$; 601.16. Found; 602.05 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.89 (d, J = 6.8 Hz, 1H), 7.50 (m, 1H), 7.36-7.32 (m, 2H), 5.96 (s, 2H), 3.64 (m, 1H), 3.48 (s, 3H), 3.32-3.14 (m, 4H), 2.92 (m, 2H), 2.50-2.33 (m, 5H), 2.15-1.96 (m, 7H), 1.43-1.41 (m, 2H), 0.96-0.94 (m, 2H) ppm.
Example 98	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((2,2,2-trifluoro-1-methylethyl)sulfonamido)methyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide** MS calcd for $C_{25}H_{33}ClFN_5O_5S_2$; 601.16. Found; 602.05 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.91 (dd, J = 6.4, 2.4 Hz, 1H), 7.77-7.74 (m, 1H), 7.52-7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 4.35-4.31 (m, 1H), 3.56-3.52 (m, 1H), 3.48 (s, 3H), 2.97-2.94 (m, 2H), 2.50 (m, 2H, merged), 2.48-2.43 (m, 2H), 2.15-2.07 (m, 2H), 1.97-1.94 (m, 2H), 1.42-1.40 (m, 4H), 0.96-0.94 (m, 2H) ppm.

Example 99



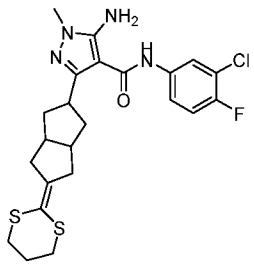
5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((R)-1,1,1-trifluoropropan-2-yl)amino)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide. To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (100 mg, 0.26 mmol) and (R)-1,1,1-trifluoropropan-2-amine hydrochloride (114 mg, 0.77 mmol) in DCE (2 mL) was added acetic acid (0.1 mL) and the mixture was stirred at 40 °C for 5 h. $Na(OAc)_3BH$ (108 mg, 0.52 mmol) was added at r.t., and the reaction mixture stirred at 40 °C for 16 h. The reaction was quenched with 10 mL of water and extracted with ethyl acetate (10 mL x 3). The organic layers were concentrated and purified by Prep-TLC (petroleum ether/ethyl acetate=1/1) to provide the crude product. The crude product was purified by Prep-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((R)-1,1,1-trifluoropropan-2-yl)amino)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide. MS Calcd.: 487.2, MS Found: 488.2 $[M + 1]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, J = 2.8, 6.4 Hz, 1H), 7.32-7.27 (m, 2H), 7.10 (t, J = 8.8 Hz, 1H), 5.25 (brs, 2H), 3.58 (s, 3H), 3.40-3.28 (m, 2H), 3.25-3.14 (m, 2H), 2.60-2.48 (m, 2 H), 2.40-2.30 (m, 2H), 2.28-2.14 (m, 2H), 1.86-1.75 (m, 2H), 1.26-1.19 (m, 5H) ppm.

Example 100



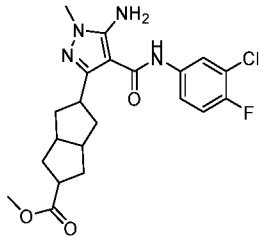
5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((S)-1,1,1-trifluoropropan-2-yl)amino)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide. To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (100 mg, 0.26 mmol), (S)-1,1,1-trifluoropropan-2-amine (114 mg, 0.77 mmol) in DCE (2 mL) was added acetic acid (0.1 mL) and the mixture was stirred at 40 °C for 5 h. $Na(OAc)_3BH$ (108 mg, 0.52 mmol) was added and then the reaction mixture was stirred at 40 °C for 16 h. The reaction was quenched with 10 mL of water and extracted with ethyl acetate (10 mL x 3). The organic layers were concentrated and purified by Prep-TLC (petroleum ether/ethyl acetate =1/1) to the crude product. The crude product was purified by Prep-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((S)-1,1,1-trifluoropropan-2-yl)amino)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide. MS Calcd.: 487.2, Found: 488.2 $[M + 1]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, J = 2.8, 6.4 Hz, 1H), 7.35-7.27 (m, 2H), 7.10 (t, J = 8.8 Hz, 1H), 5.26 (brs, 2H), 3.57 (s, 3H), 3.40-3.28 (m, 1H), 3.25-3.14 (m, 2H), 2.62-2.46 (m, 2 H), 2.42-2.29 (m, 2H), 2.28-2.15 (m, 2H), 1.86-1.74 (m, 2H), 1.30-1.11 (m, 5H) ppm.

Intermediate 19



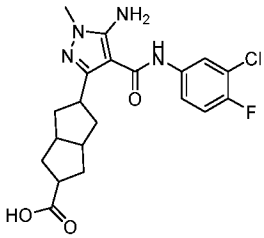
3-(5-(1,3-Dithian-2-ylidene)octahydropentalen-2-yl)-5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide. A solution of (1,3-dithian-2-yl)trimethylsilane (7.4 g, 38.5 mmol) in THF (70 mL) was cooled at -78°C under a nitrogen atmosphere to which was added *n*-BuLi (15.4mL, 38.5 mmol). The reaction was stirred at -78°C for 1 hour. 5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (2.0 g, 5.1 mmol) was added in one portion. The reaction was stirred at -78°C for 3 hours then quenched with sat. NH_4Cl. The mixture was extracted with ethyl acetate.The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the crude product which was purified by silica gel column (eluted with petroleum ether/ethyl acetate = 1/2) to afford 3-(5-(1,3-dithian-2-ylidene)octahydropentalen-2-yl)-5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide (1.1 g, 43%) as white solid. TLC: 67% petroleum ether/ethyl acetate (Rf: 0.3). MS Calcd.: 492.1. Found: 493.3 $[M + 1]^+$.

Intermediate 20



Methyl 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalene-2-carboxylate. To a solution of 3-(5-(1,3-dithian-2-ylidene)octahydropentalen-2-yl)-5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide (1.1 g, 2.2 mmol) in MeOH (25 mL) was added successively, HCl (6N, 1.1 mL, 6.7 mmol), $HgCl_2$ (1.4 g, 5.0 mmol) and trifluoroacetate (637 mg, 5.6 mmol). The reaction was stirred at room temperature for 4 hours. The milky mixture was filtered through Celite® and the filter cake washed with methanol. The solvent was removed and the residue purified by silica gel column chromatography (eluted with petroleum ether/ethyl acetate = 1/3) to afford methyl 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalene-2-carboxylate as a white solid. TLC: 67% petroleum ether/ ethyl acetate (Rf: 0.2). MS Calcd.: 434.2. Found: 435.3 $[M + 1]^+$.

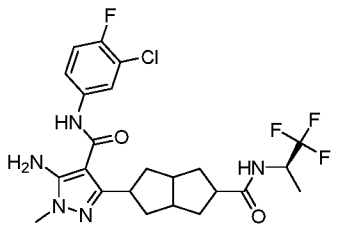
Intermediate 21



5-(5-Amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydro pentalene-2-carboxylic acid. Methyl 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydropentalene-2-carboxylate (130

mg, 0.3 mmol) was dissolved in methanol (10 mL) and water (5 mL), then $LiOH.H_2O$ (50 mg, 1.2 mmol) was added in one portion. The reaction was stirred at room temperature for 4 hours. After the starting material was consumed, the reaction was acidified with dilute HCl and extracted with ethyl acetate. The organic layer was wash with brine, dried over Na_2SO_4, filtered and concentrated to afford crude 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydro pentalene-2-carboxylic acid as a white solid. TLC: 10% MeOH/ CH_2Cl_2 (Rf: 0.4). MS Calcd.: 420.1; MS Found: 421.2 $[M + 1]^+$.

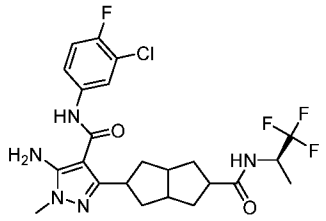
Example 101



5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((R)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide Isomer I. To a solution of compound 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydro pentalene-2-carboxylic acid (50 mg, 0.1 mmol) and (R)-1,1,1-trifluoropropan-2-amine hydrochloride (23 mg, 0.15 mmol) in DMF (2 mL) was added HATU (136 mg, 0.36 mmol) and Et_3N (36 mg, 0.36 mmol). The reaction was stirred at room temperature for 2 h. After the starting material was consumed, the reaction was diluted with ethyl acetate, washed with H_2O, then brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by pre-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((R)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide as a mixture of isomers. Chiral-separation to afforded 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((R)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide Isomer I and 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((R)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-

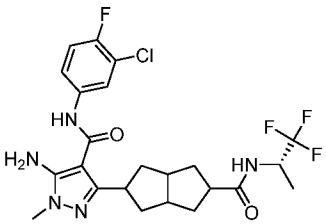
carboxamide Isomer II. TLC: 67% ethyl acetate / petroleum ether (R_f: 0.3). MS Calcd.: 515.2; MS Found: 516.3 $[M + 1]^+$; ^1H NMR (400 MHz, CD_3OD): δ 7.80 (dd, J = 6.8, 2.4 Hz, 1H), 7.43-7.39 (m, 1H), 7.19 (t, J = 8.8 Hz, 1H), 4.66-4.58 (m, 1H), 3.56 (s, 3H), 3.31-3.25 (m, 1H), 2.83-2.75 (m, 1H), 2.72-2.67 (m, 2H), 2.33-2.26 (m, 2H), 1.87-1.78 (m, 2H), 1.70-1.63 (m, 2H), 1.43-1.35 (m, 2H), 1.29 (d, J = 7.2 Hz, 3H) ppm.

Example 102



5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((R)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide Isomer II. ^1H NMR (400 MHz, CD_3OD): δ 7.79 (dd, J = 6.4, 2.4 Hz, 1H), 7.43-7.39 (m, 1H), 7.19 (t, J = 9.2 Hz, 1H), 4.64-4.57 (m, 1H), 3.63-3.58 (m, 1H), 3.56 (s, 3H), 2.82-2.77 (m, 1H), 2.62-2.58 (m, 2H), 2.32-2.26 (m, 2H), 2.14-2.03 (m, 2H), 1.64-1.54 (m, 4H), 1.28 (d, J = 7.2 Hz, 3H) ppm.

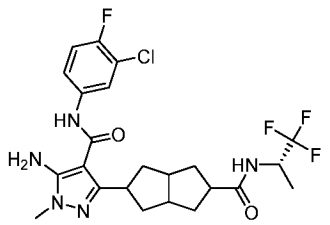
Example 103



5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((S)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide Isomer I. To a solution of 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)octahydro pentalene-2-carboxylic acid (80 mg, 0.19 mmol) and (S)-1,1,1-trifluoropropan-

2-amine hydrochloride (37 mg, 0.25 mmol) in DMF (2 mL) was added HATU (217 mg, 0.57 mmol) and Et_3N (58 mg, 0.57 mmol). The reaction was stirred at room temperature for 2 h. After the starting material was consumed, the reaction was diluted with ethyl acetate, washed with H_2O, then brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by pre-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((S)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide as a mixture of diastereomers Isomer I and Isomer II. Chiral-separation to afforded 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((S)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide as a mixture of diastereomers Isomer I and 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((S)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide as a mixture of diastereomers Isomer II. TLC: 67% ethyl acetate / petroleum ether (Rf: 0.3). MS Calcd.: 515.2. Found: 516.3 $[M + 1]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.80 (dd, J = 6.8, 2.8 Hz, 1H), 7.43-7.39 (m, 1H), 7.19 (t, J = 8.8 Hz, 1H), 4.64-4.60 (m, 1H), 3.56 (s, 3H), 3.31-3.26 (m, 1H), 2.81-2.77 (m, 1H), 2.72-2.67 (m, 2H), 2.33-2.26 (m, 2H), 1.85-1.77 (m, 2H), 1.70-1.63 (m, 2H), 1.43-1.35 (m, 2H), 1.29 (d, J = 7.2 Hz, 3H) ppm.

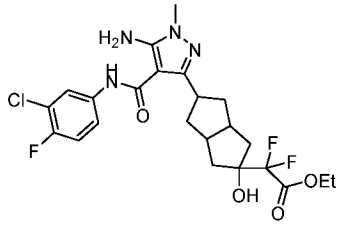
Example 104



5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-(((S)-1,1,1-trifluoropropan-2-yl)carbamoyl)octahydropentalen-2-yl)-1H-pyrazole-4-carboxamide Isomer II. ^1H NMR (400 MHz, CD_3OD): δ 7.79 (dd, J = 6.8, 2.8 Hz, 1H), 7.43-7.39 (m, 1H), 7.19 (t, J = 9.2 Hz, 1H), 4.64-4.57 (m, 1H), 3.63-3.58 (m, 1H), 3.56 (s, 3H), 2.82-2.77 (m, 1H), 2.61-2.59

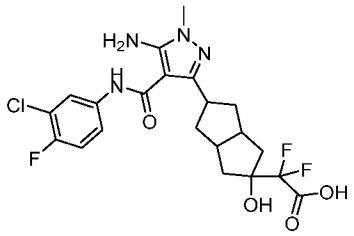
(m, 2H), 2.32-2.26 (m, 2H), 2.14-2.03 (m, 2H), 1.64-1.54 (m, 4H), 1.28 (d, *J* = 7.2 Hz, 3H) ppm.

Example 105



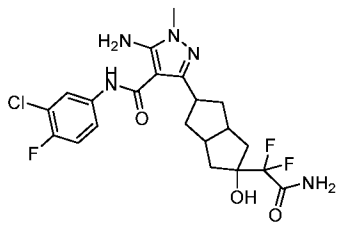
Ethyl 2-(5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-hydroxyoctahydropentalen-2-yl)-2,2-difluoroacetate. To a mixture of Zn powder (12 eq, 18.46 mmol) in dry THF (40 mL) was added ethyl 2-bromo-2,2-difluoroacetate (11 eq, 16.92 mmol) at 60 °C, the mixture was stirred for 0.5 h at 60 °C in an Ar atmosphere. The mixture was cooled to 45 °C, a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (600 mg, 1 eq, 1.54 mmol) in dry THF (5 mL) was added. The mixture was cooled to room temperature, and Et_2AlCl (1.0 M, 1.1 eq, 1.69 mmol) was added. The reaction mixture was stirred for 6 h at room temperature. The mixture was quenched with sat. aq. NH_4Cl (40 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by reserved column chromatography to afford ethyl 2-(5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-hydroxyoctahydropentalen-2-yl)-2,2-difluoroacetate as a white solid. MS Calcd; 514.1. Found: 515.2 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.93 (s, 1H), 7.92 (dd, *J* = 7.0, 2.6 Hz, 1H), 7.55-7.47 (m, 1H), 7.35 (t, *J* = 9.0 Hz, 1H), 5.98 (s, 2H), 5.47 (s, 1H), 4.26 (q, *J* = 7.2 Hz, 1H), 3.48 (s, 3H), 3.42-3.30 (m, 1H), 2.65-2.55 (m, 2H), 2.17-2.07 (m, 2H), 2.06-1.96 (m, 2H), 1.85-1.73 (m, 2H), 1.67 (d, *J* =14.0 Hz, 2H), 1.25 (t, *J* =7.2 Hz, 3H) ppm.

Example 106



2-(5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-hydroxyoctahydropentalen-2-yl)-2,2-difluoroacetic acid. To a solution of ethyl 2-(5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-hydroxyoctahydropentalen-2-yl)-2,2-difluoroacetate (130 mg, 1 eq, 0.25 mmol) in MeOH (5 mL) was added LiOH (10 eq, 2.53 mmol). The reaction was stirred for 1 h at room temperature. The reaction mixture was adjusted to pH 3 with 1N HCl and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by reserved column chromatography to afford 2-(5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-hydroxyoctahydropentalen-2-yl)-2,2-difluoroacetic acid a a white solid. MS Calcd.: 486.1. Found: 487.1 $[M + 1]^+$.^{1}H NMR (400 MHz, CD_3OD): δ 7.81 (dd, J = 6.6, 2.6 Hz, 1H), 7.44-7.37 (m, 1H), 7.19 (t, J = 9.0 Hz, 1H), 3.59 (s, 3H), 3.44-3.32 (m, 1H), 2.80-2.66 (m, 2H), 2.36-2.16 (m, 4H), 1.96-1.83 (m, 2H), 1.76 (d, J =14.0 Hz, 2H) ppm.

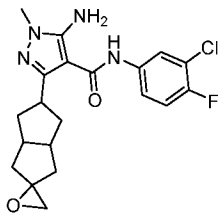
Example 107



5-Amino-3-(5-(2-amino-1,1-difluoro-2-oxoethyl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of ethyl 2-(5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-

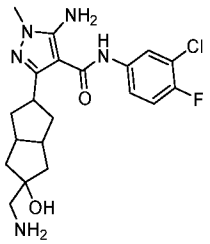
hydroxyoctahydropentalen-2-yl)-2,2-difluoroacetate (100 mg, 1 eq, 0.19 mmol) in MeOH (2 mL) was added NH_4OH (2 mL) and the reaction mixture stirred for 2 h at 70 °C in a sealed tube. The reaction mixture was concentrated *in vacuo*. The residue was purified by reserved column chromatography to afford a white solid 5-amino-3-(5-(2-amino-1,1-difluoro-2-oxoethyl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide. MS Calcd.: 485.1. Found: 486.3 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO): δ 8.93 (s, 1H), 7.92 (dd, J = 7.0, 2.6 Hz, 1H), 7.79 (brs, 1H), 7.74 (brs, 1H), 7.54-7.48 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 5.19 (s, 1H), 3.48 (s, 3H), 3.42-3.34 (m, 1H), 2.62-2.52 (m, 2H), 2.17-2.00 (m, 4H), 1.86-1.72 (m, 2H), 1.62 (d, J =13.6 Hz, 2H) ppm.

Intermediate 22



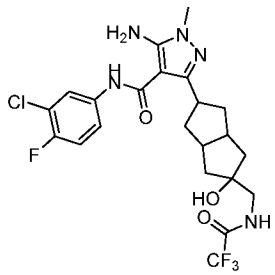
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(hexahydro-1'H-spiro[oxirane-2,2'-pentalene]-5'-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of potassium 2-methylpropan-2-olate (230 mg, 2.05 mmol) in THF (30 mL) was added trimethylsulfoxonium iodide (450 mg, 2.05 mmol). The mixture was stirred at RT for 1h under N_2. 5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxooctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide (200mg, 0.53mmol) was then added to the mixture and stirring continued at 60°C for 5 h under an N_2 atmosphere. The solvent was removed under vacuum and the product purified by silica gel column chromatography using 1:1 ethyl acetate/petroleum ether to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(hexahydro-1'H-spiro[oxirane-2,2'-pentalene]-5'-yl)-1-methyl-1H-pyrazole-4-carboxamide. (200 mg, 96.6%) as yellow solid. MS Calcd.: 404.1; MS Found: 405.2 $[M+1]^+$.

Intermediate 23



5-Amino-3-(5-(aminomethyl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(hexahydro-1'H-spiro[oxirane-2,2'-pentalen]-5'-yl)-1-methyl-1H-pyrazole-4-carboxamide (200 mg, 0.495 mmol) in THF (5 mL) was added NH_4OH (5 mL). The mixture was stirred at room temperature overnight. The solvent was removed and the product purified by silica gel column chromatography using ethyl acetate to afford 5-amino-3-(5-(aminomethyl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. MS Calcd.: 421.1; MS Found: 422.3 $[M + 1]^+$.

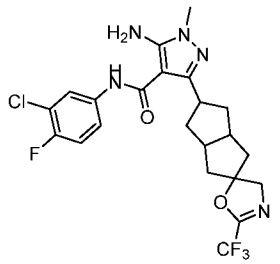
Intermediate 24



5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-((2,2,2-trifluoroacetamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of 5-amino-3-(5-(aminomethyl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide (150 mg, 0.38 mmol), Et_3N (76 mg, 0.76 mmol) in THF (2 mL) and DCM (2 mL), at 0 °C was added trifluoroacetic

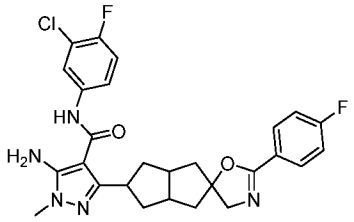
anhydride (88 mg, 0.42 mmol) and the reaction stirred at r.t for 2 h. The reaction was quenched with 30 mL of water and extracted with ethyl acetate (30 mL x 2). The organic layers were concentrated. The residue was purified by Prep-TLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-((2,2,2-trifluoroacetamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. MS Calcd.: 517.2. MS Found: 518.2 $[M + 1]^+$.

Example 108



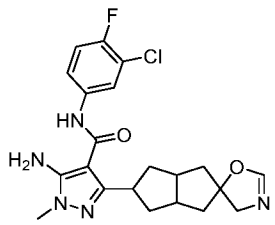
5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(trifluoromethyl)-3',3a',4',5',6',6a'-hexahydro-1'H,4H-spiro[oxazole-5,2'-pentalen]-5'-yl)-1H-pyrazole-4-carboxamide. To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-((2,2,2-trifluoroacetamido)methyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (60 mg, 0.12 mmol) in THF (1 mL) was added P_2O_5 (50 mg, 0.35 mmol). The reaction mixture was irradiated with microwave radiation for 1 h at 90 °C. The reaction was poured into 30 mL of aq. $NaHCO_3$ and extracted with ethyl acetate (30 mL x 2). The organic layers were concentrated, and the residue was purified by Prep-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(trifluoromethyl)-3',3a',4',5',6',6a'-hexahydro-1'H,4H-spiro[oxazole-5,2'-pentalen]-5'-yl)-1H-pyrazole-4-carboxamide. MS Calcd.: 499.1. Found: 500.2 $[M + 1]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, J = 2.4, 6.4 Hz, 1H), 7.32-7.27 (m, 2H), 7.12 (t, J = 8.8 Hz, 1H), 6.34 (brs, 1H), 5.55 (s, 1H), 5.25 (s, 2H), 4.00 (s, 2H), 3.58 (s, 3 H), 3.35-3.25 (m, 1H), 3.15-3.05 (m, 1H), 2.90-2.80 (m, 1H), 2.64-2.55 (m, 1H), 2.45-2.33 (m, 2H), 2.18-2.11 (m, 1H), 1.73-1.64 (m, 2H) ppm.

Example 109



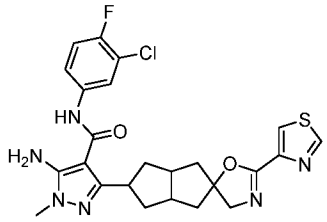
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(2-(4-fluorophenyl)-3',3a',4',5',6',6a'-hexahydro-1'H,4H-spiro[oxazole-5,2'-pentalen]-5'-yl)-1-methyl-1H-pyrazole-4-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ 9.01 (s, 1H), 7.98-7.91 (m, 3H), 7.55-7.51 (m, 1H), 7.38-7.27 (m, 3H), 6.01 (s, 2H), 3.83 (s, 2H), 3.60 (s, 3H), 3.45-3.39 (m, 1H), 2.67 (s, 2H), 2.22-2.16 (m, 2H), 1.95-1.84 (m, 6H) ppm.

Example 110



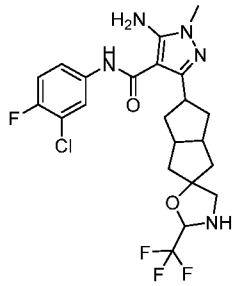
5-Amino-N-(3-chloro-4-fluorophenyl)-3-(3',3a',4',5',6',6a'-hexahydro-1'H,4H-spiro[oxazole-5,2'-pentalen]-5'-yl)-1-methyl-1H-pyrazole-4-carboxamide. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.93-7.90 (dd, J = 7.2, 2.4 Hz, 1H), 7.53-7.51 (m, 1H), 7.35 (t, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.41 (s, 1H), 3.70 (d, J = 4.8, 2H), 3.42 (s, 3H), 3.39-3.30 (m, 1H), 3.10-3.08 (m, 1H), 2.67-2.63 (m, 1H), 2.45-2.38 (m, 1H), 2.22-2.14 (m, 2H), 1.99-1.95 (m, 1H), 1.39-1.31 (m, 2H) ppm.

Example 111



5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(thiazol-4-yl)-3',3a',4',5',6',6a'-hexahydro-1'H,4H-spiro[oxazole-5,2'-pentalen]-5'-yl)-1H-pyrazole-4-carboxamide. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.92-7.90 (m, 1H), 7.53-7.49 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.96 (s, 2H), 5.37 (s, 1H), 3.88-3.87 (m, 2H), 3.48 (s, 3H), 3.40-3.37 (m, 1H), 3.10-3.08 (m, 1H), 2.68-2.66 (m, 1H), 2.49-2.44 (m, 1H), 2.22-2.14 (m, 2H), 2.02-1.98 (d, J = 16 Hz, 1H), 1.37-1.33 (m, 2H) ppm.

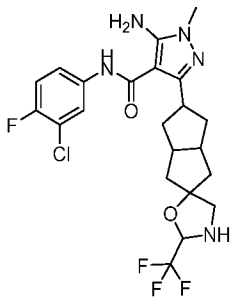
Example 112



5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(trifluoromethyl)hexahydro-1'H-spiro[oxazolidine-5,2'-pentalen]-5'-yl)-1H-pyrazole-4-carboxamide Isomer I. To a solution of 5-amino-3-(5-(aminomethyl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide (150 mg, 0.36 mmol) in toluene (2 mL) was added 1-ethoxy-2,2,2-trifluoroethanal (71 mg (81% purity), 0.39 mmol) and PPTS (9 mg, 0.036 mmol). The reaction solution was stirred at 90°C for 1 hour. After the starting material was consumed, the volatiles were removed in *vacuo*, and the product purified by pre-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-

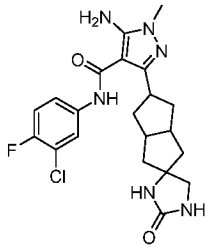
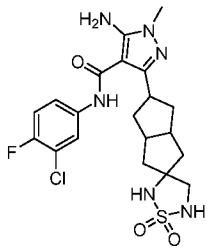
(trifluoromethyl)hexahydro-1'H-spiro[oxazolidine-5,2'-pentalen]-5'-yl)-1H-pyrazole-4-carboxamide as a mixture of Isomer I and Isomer II. Chiral-separation afforded 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(trifluoromethyl)hexahydro-1'H-spiro[oxazolidine-5,2'-pentalen]-5'-yl)-1H-pyrazole-4-carboxamide Isomer I and 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(trifluoromethyl)hexahydro-1'H-spiro[oxazolidine-5,2'-pentalen]-5'-yl)-1H-pyrazole-4-carboxamide Isomer II. TLC: 9% MeOH / DCM (R_f: 0.3). MS Calcd.: 501.2. MS Found: 502.2 $[M + 1]^+$. ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (dd, J = 6.4, 2.4 Hz, 1H), 7.43-7.39 (m, 1H), 7.19 (t, J = 9.2 Hz, 1H), 4.92-4.88 (m, 1H), 3.56 (s, 3H), 3.44-3.40 (m, 1H), 2.93 (dd, J = 116, 11.6 Hz, 2H), 2.55-2.53 (m, 2H), 2.33-2.28 (m, 2H), 1.93-1.61 (m, 6H) ppm.

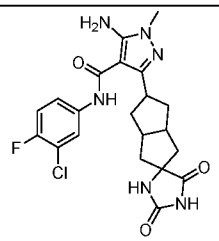
Example 113



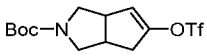
5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(trifluoromethyl)hexahydro-1'H-spiro[oxazolidine-5,2'-pentalen]-5'-yl)-1H-pyrazole-4-carboxamide Isomer II. ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (dd, J = 6.8, 2.4 Hz, 1H), 7.43-7.39 (m, 1H), 7.19 (t, J = 8.8 Hz, 1H), 4.92-4.88 (m, 1H), 3.56 (s, 3H), 3.44-3.40 (m, 1H), 2.94 (dd, J = 116, 11.6 Hz, 2H), 2.55-2.54 (m, 2H), 2.33-2.28 (m, 2H), 1.94-1.61 (m, 6H) ppm.

Example	Structure and analysis

Example 114	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-oxohexahydro-1'H-spiro[imidazolidine-4,2'-pentalen]-5'-yl)-1H-pyrazole-4-carboxamide** MS calcd. for $C_{21}H_{24}ClFN_6O_2$: 446.2; Found: 447.2 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.54-7.48 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 6.61 (s, 1H), 6.01 (s, 1H), 5.94 (s, 2H), 3.54-3.50 (m, 1H), 3.48 (s, 3H), 3.21 (s, 2H), 2.64-2.56 (m, 2H), 2.20-2.12 (m, 2H), 1.90-1.81 (m, 2H), 1.48-1.34 (m, 4H).
Example 115	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(1',1'-dioxidohexahydro-1H-spiro[pentalene-2,3'-[1,2,5]-thiadiazolidin]-5-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd. for $C_{20}H_{24}ClFN_6O_3S$: 482.1; Found; 483.0 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.96-7.88 (m, 2H), 7.56-7.48 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 6.86 (t, J = 6.4 Hz, 1H), 6.80-5.20 (m, 2H), 3.62-3.32 (m, 4H, merged), 3.21 (s, 2H), 2.60-2.52 (m, 2H, merged), 2.20-2.08 (m, 4H), 1.48-1.36 (m, 4H) ppm.

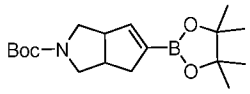
Example 116	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(2,5-dioxohexahydro-1'H-spiro[imidazolidine-4,2'-pentalen]-5'-yl)-1-methyl-1H-pyrazole-4-carboxamide** MS calcd. for $C_{21}H_{22}ClFN_6O_3$: 460.1; Found; 461.2 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 9.00 (s, 1H), 8.36 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.55-7.49 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 5.96 (s, 2H), 3.68-3.58 (m, 1H), 3.50 (s, 3H), 2.73-2.62 (m, 2H), 2.22-2.12 (m, 2H), 1.91-1.82 (m, 2H), 1.77-1.68 (m, 2H), 1.56-1.44 (m, 2H) ppm.

Intermediate 25



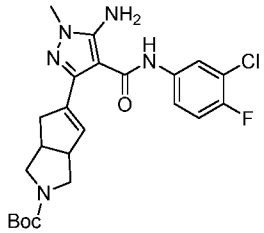
tert-Butyl 5-(trifluoromethylsulfonyloxy)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate. LiHMDS (60 mL, 60 mmol, 1.0 M in THF) was added slowly to a solution of tert-butyl 5-oxohexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (4.5 g, 20 mmol) in anhydrous THF (50 mL) at -78 °C for 30 min. 1,1,1-Trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (14.3 g, 40 mmol) in THF (30 mL) was added slowly and the mixture stirred for 2 h. The reaction mixture was warmed to room temperature and quenched with NH_4Cl (aq.). The solution was extracted with ethyl acetate (50 mL x 3). The combined organic layers were dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using 5 - 10% ethyl acetate / petroleum ether (*v/v*) to afford compound tert-butyl 5-(trifluoromethylsulfonyloxy)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (4.5 g, 63%) as a pale-yellow solid. TLC: 30% ethyl acetate / petroleum ether (R_f: 0.3).

Intermediate 26



tert-Butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate. A solution of tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (4.5 g, 12.6 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)-1,3,2-dioxaborolane (4.2 g, 16.4 mmol), $Pd(dppf)Cl_2$ (182.9 mg, 0.25 mmol) and potassium phosphate (3.5 g, 16.4 mmol) in dioxane (80 mL) was stirred at 80 °C for 16 h under N_2 atmosphere. The reaction was then filtered through a pad of Celite and the cake washed with ethyl acetate (20 mL x 2). The filtrate was concentrated in vacuum and the crude product, tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate was used in the next step without further purification.

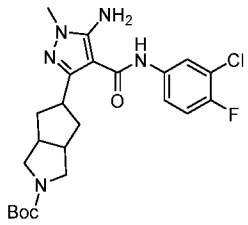
Intermediate 27



tert-Butyl 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate. To a solution of crude tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (12.6 mmol) in dioxane/H_2O (80 mL/16 mL) was added potassium phosphate (3.5 g, 16.4 mmol), $Pd(dppf)Cl_2$ ((182.9 mg, 0.25 mmol) and ethyl 5-amino-3-bromo-1-methyl-pyrazole-4-carboxylate (4.4 g, 12.6 mmol). The

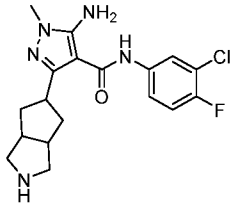
reaction was stirred at 80°C for 4 h under N_2 atmosphere. The mixture was quenched with H_2O and extracted with ethyl acetate (50mL x 2). The organic layer was concentrated *in vacuo* and the residue purified by silica gel column chromatography to afford tert-butyl 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (3.2 g, 53.4 % for two steps). MS Calcd.: 475.2; Found: 420.2 [M^+-55].

Intermediate 28

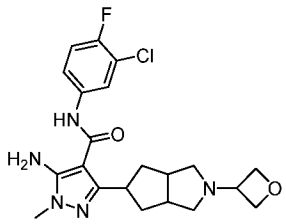


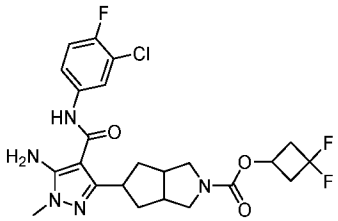
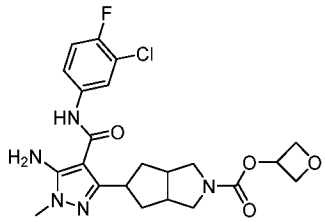
tert-Butyl 5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate. To a solution of tert-butyl 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)-3,3a,6,6atetrahydrocyclopenta [c]pyrrole-2(1H)-carboxylate (3.1 g, 6.5 mmol) in THF (90 mL) was added 10% Pd/C (1 g, containing 67% H_2O). The reaction was stirred at 15 °C for 15 min under a H_2 atmosphere (1 atm.) then filtered. The filtrate was concentrated, and the residue purified by silica gel column chromatography to give tert-butyl 5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate as a white solid. TLC; 50% ethyl acetate / petroleum ether (R_f: 0.3). MS Calcd.: 477.2; Found: 422.3 [M^+ - 55]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.54-7.50 (m, 1H), 7.34 (t, J = 9.6 Hz, 1H), 5.98 (s, 2H), 3.59-3.52 (m, 1H), 3.49 (s, 3H), 3.32 (s, 2H), 3.14-3.10 (m, 2H), 2.61-2.57 (m, 2H), 2.21-2.14 (m, 2H), 1.56-1.48 (m, 2H), 1.38 (s, 9H) ppm.

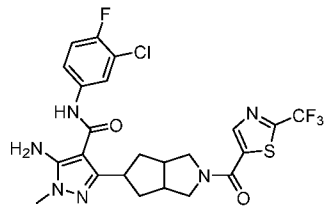
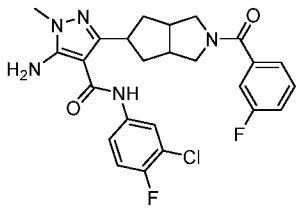
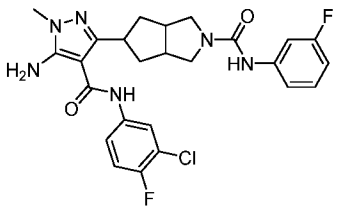
Intermediate 29

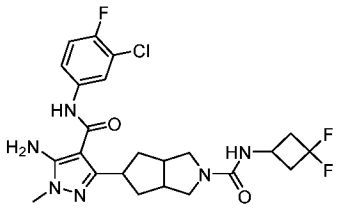
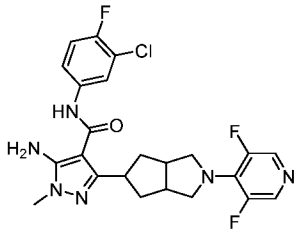


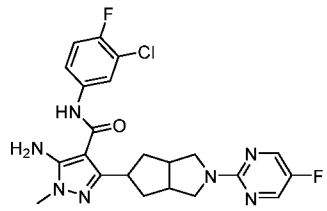
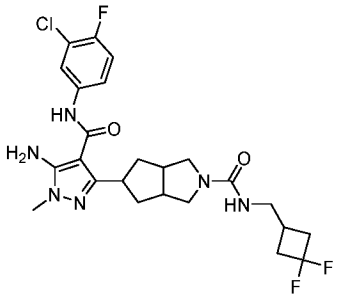
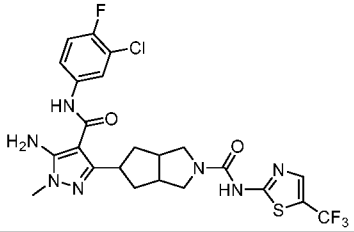
5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(octahydrocyclopenta[c]pyrrol-5-yl)-1H-pyrazole-4-carboxamide. A solution of tert-butyl 5-(5-amino-4-(3-chloro-4-fluorophenylcarbamoyl)-1-methyl-1H-pyrazol-3-yl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (3 g, 6.3 mmol) in 2 M HCl/dioxane (30 mL) was stirred at room temperature for 1 h. The reaction was concentrated and diluted with DCM. The DCM solution was adjusted to pH 8 ~ 9 with $NaHCO_3$ and extracted with DCM (30 mL x 3). The organic layer was dried and concentrated. The residue was purified by reversed column chromatography to afford 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(octahydrocyclopenta[c]pyrrol-5-yl)-1H-pyrazole-4-carboxamide (2.1 g, 84%) as a white solid. TLC: 10% MeOH / DCM (R_f: 0.4); MS Calcd.: 377.2; Found: 378.2 $[M^+ + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 7.91 (dd, J = 6.8, 2.8 Hz, 1H), 7.53-7.51 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.97 (s, 2H), 3.55-3.53 (m, 1H), 3.49 (s, 3H), 3.44-3.41 (m, 3H), 3.22-3.14 (m, 1H), 2.57 (s, 3H), 2.19-2.13 (m, 2H), 1.52-1.50 (m, 1H), 1.34-1.32 (m, 1H) ppm.

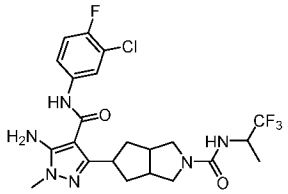
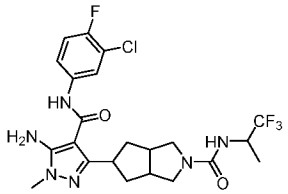
Example	Structure and analysis
Example 117	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(oxetan-3-yl)octahydrocyclopenta[c]pyrrol-5-yl)-1H-pyrazole-4-carboxamide.**

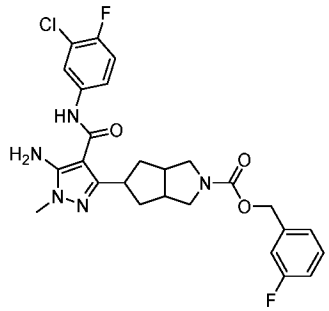
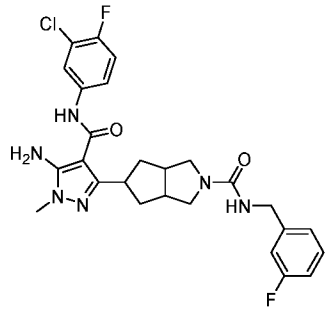
	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz, 1H), 7.54-7.50 (m, 1H), 7.37 (t, J = 9.2 Hz, 1H), 5.98 (d, J = 6.4 Hz, 2H), 3.62-3.53 (m, 1H), 3.49 (s, 3H), 3.40-3.31 (m, 2H), 3.23-3.20 (m, 2H), 3.05-2.95 (m, 2H), 2.63-2.50 (m, 4H), 2.23-2.07 (m, 2H), 1.57-1.50 (m, 2H) ppm.
Example 118	 **3,3-Difluorocyclobutyl 5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (s, 1H), 7.92 (dd, J = 7.2, 2.4 Hz, 1H), 7.55-7.51 (m, 1H), 7.37 (t, J = 9.2 Hz, 1H), 5.99 (s, 2H), 4.81-4.75 (m, 1H), 4.55 (t, J = 6.4 Hz, 2H), 4.41 (t, J = 6 Hz, 2H), 3.50 (s, 3H), 3.45-3.42 (m, 1H), 3.37 (m, 1H), 2.50-2.49 (m, 4H), 2.18-2.13 (m, 2H), 2.03-2.00 (m, 2H), 1.50-1.48 (m, 2H) ppm.
Example 119	 **Oxetan-3-yl 5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate.** ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.00 (s, 1H), 7.92 (dd, J = 6.8, 2.8 Hz, 1H), 7.54-7.52 (m, 1H), 7.37 (t, J = 9.2 Hz, 1H), 5.99 (s, 2H), 5.29-5.25 (m, 1H), 4.75-4.72 (m, 2H), 4.50-4.46 (m, 2H), 3.61-3.54 (m, 1H), 3.42-3.33 (m, 5H), 3.31-3.14 (m, 2H), 2.70-2.66 (m, 2H), 2.21-2.18 (m, 2H), 1.58-1.5- (m, 2H) ppm

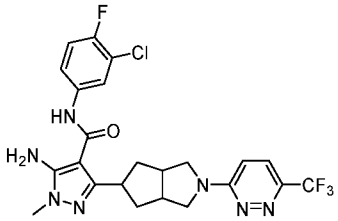
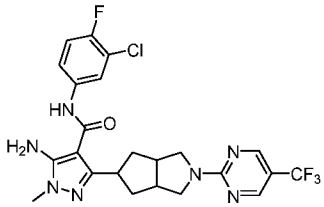
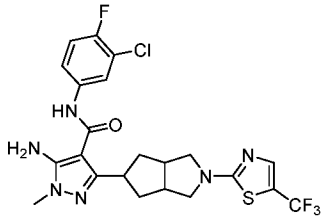
Example 120	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(2-(trifluoromethyl)thiazole-5-carbonyl)octahydrocyclopenta[c]pyrrol-5-yl)-1H-pyrazole-4-carboxamide.** ^{1}H NMR (400 MHz, MeOD): δ 8.39 (d, J = 1.2 Hz, 1H), 7.80 (dd, J = 2.8, 6.8 Hz, 1H), 7.46-7.40 (m, 1H), 7.19 (t, J = 9 Hz, 1H), 3.95-4.02 (m, 1H), 3.78-3.60 (m, 4H), 3.55 (s, 3H), 2.96-2.78 (m, 2H), 2.41-2.36 (m, 2H), 1.82-1.75 (m, 2H) ppm.
Example 121	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(2-(3-fluorobenzoyl)octahydrocyclopenta[c]pyrrol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 7.92-7.89 (m, 1H), 7.55-7.50 (s, 1H), 7.49-7.45(m, 1H), 7.37-7.27 (m, 3H), 6.00 (s, 2H), 3.60-3.55 (m, 4H), 3.51 (s, 3H), 3.23-3.21 (m, 1H), 2.67 (s, 2H), 2.26-2.11 (m, 2H), 1.64-1.45 (m, 2H) ppm.
Example 122	 **5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-N-(3-fluorophenyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxamide.**

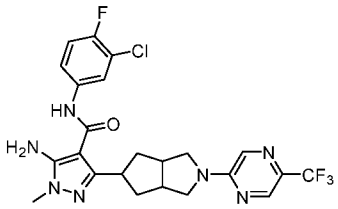
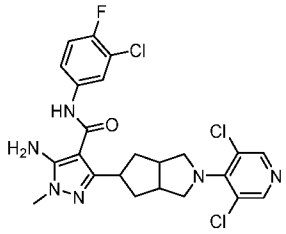
	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 1H), 8.34 (s, 1H), 7.93-7.91 (m, 1H), 7.56-7.47 (m, 2H), 7.38-7.33 (m, 1H), 7.29-7.20 (m, 2H), 6.73-6.69 (m, 1H), 5.99 (s, 2H), 3.59 (t, *J* =7.6 Hz, 1H), 3.49 (m, 2H), 3.36-3.32 (m, 2H), 2.69-2.67 (m, 2H), 2.26-2.20 (m, 2H), 1.63-1.56 (m, 2H) ppm.
Example 123	 **5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-N-(3,3-difluorocyclobutyl)hexahydrocyclopenta[c]-pyrrole-2(1H)-carboxamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 7.91 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.55-7.51 (m, 1H),7.35 (t, *J* = 9.2 Hz, 1H), 6.50 (d, *J* = 6.8 Hz, 1H), 6.00 (s, 2H), 3.97-3.94 (m, 1H), 3.59-3.54 (m, 1H), 3.49 (s, 3H), 3.32-3.26 (m, 2H), 3.17-3.14 (m, 2H),2.81-2.73 (m, 2H), 2.66-2.56 (m, 4H), 2.22-2.16 (m, 2H),1.56-1.48 (m, 2H) ppm.
Example 124	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(2-(3,5-difluoropyridin-4-yl)octahydrocyclopenta[c]pyrrol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide.** ^{1}H NMR (400 MHz, CD_3OD): δ 7.97 (q, *J* = 1.6 Hz, 2H), 7.82 (dd, *J* = 2.4, 6.8 Hz, 1H), 7.45-7.41 (m, 1H), 7.21(t, *J* = 8.8 Hz, 1H), 3.74-3.64 (m, 4H), 3.58-3.54 (m, 4H), 2.80-2.78 (m, 2H), 2.42-2.35 (m, 2H), 1.75-1.67 (m, 2H) ppm.

Example 125	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(2-(5-fluoropyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00(s, 1H), 8.41 (s, 2H), 7.90-7.93 (m, 1H), 7.52-7.56 (m, 1H), 7.35(t, *J*=8.8Hz, 1H), 5.99 (S, 2H), 3.52-3.63 (m, 3H), 3.40-3.44(m, 5H), 2.76-2.78 (m, 2H), 2.24-2.50 (m, 2H), 1.57-1.64 (m, 2H) ppm
Example 126	 **5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-N-((3,3-difluorocyclobutyl)methyl)-hexahydrocyclopenta[c]pyrrole-2(1H)-carboxamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.55-7.51 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.30 (t, J = 5.6 Hz, 1H), 6.00 (s, 2H), 3.56-3.53 (m, 1H), 3.49 (s, 3H), 3.29-3.25 (m, 2H), 3.16-3.09 (m, 4H), 2.62-2.61 (m, 2H), 2.58-2.54 (m, 2H), 2.33-2.15 (m, 5H),1.55-1.48 (m, 2H) ppm.
Example 127	

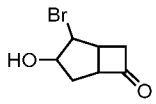
	5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-N-(5-(trifluoromethyl)thiazol-2-yl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 9.01 (s, 1H), 7.97 (d, J = 1.6 Hz, 1H), 7.92 (dd, J = 6.8, 2.4 Hz, 1H), 7.56-7.52 (m, 1H),7.35 (t, J = 8.8 Hz, 1H), 6.00 (s, 2H), 3.63-3.60 (m, 1H), 3.58-3.48 (m, 5H), 3.42-3.39 (m, 2H), 2.73-2.71 (m, 2H), 2.26-2.19 (m, 2H), 1.61-1.23 (m, 2H) ppm.
Example 128	 **5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-N-(1,1,1-trifluoropropan-2-yl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxamide Isomer I.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (s, 1H), 7.91 (dd, J = 7.2, 2.4 Hz, 1H), 7.54-7.52 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 6.00 (s, 2H), 4.53-4.42 (m, 1H), 3.58-3.50 (m, 1H), 3.49 (s, 3H), 3.37-3.36 (m, 1H), 3.28-3.15 (m, 3H), 2.64-2.63 (m, 2H), 2.21-2.18 (m, 2H), 1.55-1.52 (m, 2H), 1.24 (d, J = 7.2 Hz, 3H) ppm.
Example 129	 **5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-N-(1,1,1-trifluoropropan-2-yl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (s, 1H), 7.91 (dd, J = 7.2, 2.4 Hz, 1H), 7.54-7.52 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 6.00 (s, 2H), 4.52-4.44 (m, 1H), 3.60-3.53 (m, 1H), 3.49 (s, 3H),

	3.37-3.36 (m, 1H), 3.28-3.15 (m, 3H), 2.66-2.64 (m, 2H), 2.21-2.18 (m, 2H), 1.55-1.52 (m, 2H), 1.24 (d, J = 7.2 Hz, 3H) ppm.
Example 130	 **3-fluorobenzyl 5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate.** ^{1}H NMR Data (400 MHz, CD_3OD): δ 7.79 (dd, J = 2.8 Hz, 6.8 Hz, 1H), 7.44 - 7.40 (m, 1H), 7.37 - 7.32 (m, 1H), 7.16 (t, J = 9.2 Hz, 2H), 7.09 (d, J = 9.6 Hz, 1H), 7.79 (td, J = 2.4 Hz, 8.4 Hz, 1H), 5.10 (s, 2H), 3.61 - 3.47 (m, 6H), 3.39 (t, J = 12.4 Hz, 2H), 2.76 (s, 2H), 2.37 - 2.30 (m, 2H), 1.70 – 1.62 (m, 2H) ppm.
Example 131	 **5-(5-Amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-N-(3-fluorobenzyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxamide.** ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (dd, J = 2.8 Hz, 6.8 Hz, 1H), 7.45 - 7.41 (m, 1H), 7.32 - 7.26 (m, 1H), 7.19 (t, J = 8.8 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 10.0 Hz, 1H), 6.93 (td, J = 2.4 Hz, 8.4 Hz, 1H), 4.34 (s, 2H), 3.66 - 3.57 (m, 1H), 3.55 (s, 3H), 3.51 - 3.47 (m, 2H), 3.36

	- 3.33 (m, 2H), 2.83 - 2.77 (m, 2H), 2.39 - 2.32 (m, 2H), 1.74 - 1.67 (m, 2H) ppm.
Example 132	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(6-(trifluoromethyl)pyridazin-3-yl)octahydrocyclopenta[c]pyrrol-5-yl)-1H-pyrazole-4-carboxamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.03 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.76 (d, J = 9.6 Hz, 1H), 7.57-7.53 (m, 1H), 7.36 (t, J = 9.2 Hz, 1H), 7.03 (d, J = 9.6 Hz, 1H), 5.99 (s, J = 6.4 Hz, 2H), 3.70-3.63 (m, 3H), 3.50-3.45 (m, 5H), 2.87-2.85 (m, 2H), 2.32-2.25 (m, 2H), 1.71-1.64 (m, 2H) ppm.
Example 133	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(5-(trifluoromethyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-yl)-1H-pyrazole-4-carboxamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 1H), 8.67-8.66 (d, J = 0.8 Hz, 2H), 7.93-7.91 (dd, J = 6.8, 2.8 Hz, 1H), 7.56-7.52 (m, 1H), 7.38-7.33 (m, 1H), 5.99 (s, 2H), 3.70-3.65 (m, 3H), 3.54-3.50 (m, 2H), 3.45 (s, 3H), 2.82-2.78 (m, 2H), 2.30-2.23 (m, 2H), 1.68-1.60 (m, 2H) ppm
Example 134	

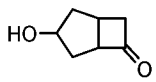
	5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(5-(trifluoromethyl)thiazol-2-yl)octahydrocyclopenta[c]pyrrol-5-yl)-1H-pyrazole-4-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.02 (s, 1H), 7.91 (dd, J = 7.2, 2.8 Hz, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.56-7.52 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.99 (s, 2H), 3.67-3.54 (m, 3H), 3.45 (s, 3H), 3.34-3.31 (m, 2H), 2.89-2.85 (m, 2H), 2.30-2.23 (m, 2H), 1.68-1.61 (m, 2H) ppm
Example 135	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(2-(5-(trifluoromethyl)pyrazin-2-yl)octahydrocyclopenta[c]pyrrol-5-yl)-1H-pyrazole-4-carboxamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.02 (s, 1H), 8.45 (s, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 7.91 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.57-7.53 (m, 1H), 7.38-7.33 (m, 1H), 5.99 (s, 2H), 3.68-3.62 (m, 3H), 3.50-3.45 (m, 5H), 2.84 (s, 2H), 2.29-2.24 (m, 2H), 1.68-1.65 (m, 2H) ppm.
Example 136	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(2-(3,5-dichloropyridin-4-yl)octahydrocyclopenta[c]pyrrol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 8.36 (s, 2H), 7.91 (dd, J = 2.4, 6.8 Hz, 1H), 7.56-7.52 (m, 1H), 7.36 (t, J = 9.2 Hz, 1H), 5.99 (s, 2H), 3.58-3.54 (m, 2H), 3.49 (s, 3H), 3.39-3.37 (m, 2H), 2.72-2.67 (m, 2H), 2.25-2.19 (m, 2H), 1.71-1.63 (m, 2H) ppm.

Intermediate 30



2-Bromo-3-hydroxybicyclo[3.2.0]heptan-6-one. To a solution of 3-hydroxybicyclo[3.2.0]heptan-6-one (11.0 g, 101 mmol) in acetone (100mL) and water (30 mL) was added NBS (23.0 g, 130 mmol) in portions. The reaction mixture was stirred at room temperature for 20 h, and the aqueous sodium metabisulfite (80 mL; 10% *w/w*) was added to the solution until the initial yellow color had faded. The acetone was removed under reduced pressure. The residue (white precipitate in water) was re-dissolved in EtOAc (500 mL) and washed twice with water (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and the residue was purified by crystallization in EtOAc (50 mL) and PE (100 mL) to give 2-bromo-3-hydroxybicyclo[3.2.0]heptan-6-one as white crystals. ^1H NMR (400 MHz, $CDCl_3$): δ 4.64 (d, J = 4.0 Hz, 1H), 4.32 (s, 1H), 3.78-3.83 (m, 1H), 3.19-3.34 (m, 3H), 2.65 (brs, 1H), 2.48-2.55 (m, 1H), 2.26 (d, J = 14.8 Hz, 1H) ppm.

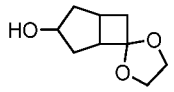
Intermediate 31



3-Hydroxybicyclo[3.2.0]heptan-6-one. To a solution of 2-bromo-3-hydroxybicyclo[3.2.0]heptan-6-one (11.0 g, 54 mmol) in dry toluene (100 mL) was added under nitrogen *n*-tributyltinhydride (23.0 g, 81 mmol) and AIBN (30 mg, 0.2 mmol). The reaction mixture was heated to 80°C for 1 h, allowed to cool to room temperature and concentrated under reduced pressure providing a yellow liquid. The tin residues were removed by partitioning between acetonitrile (200 mL) and hexane (150 mL) and extracting

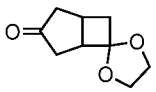
the acetonitrile layer with hexane (4 *x* 150 mL). The combined hexane layers were evaporated under reduced pressure and the crude product was purified by chromatography on silica gel with PE/EtOAc (2:1, *v/v*) to give 3-hydroxybicyclo[3.2.0]heptan-6-one as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 4.54 (brs,1H), 3.58-3.64 (m, 1H), 3.17-3.25 (m, 1H), 3.01-3.07 (m, 1H), 2.89-2.93 (m, 1H), 2.13-2.28 (m, 2H), 1.83-1.98 (m, 3H) ppm.

Intermediate 32



Spiro[bicyclo[3.2.0]heptane-6,2'-[1,3]dioxolan]-3-ol. To a solution of 3-hydroxybicyclo[3.2.0]heptan-6-one (6.5 g, 51 mmol) in toluene (150 mL) was added ethanediol (5 mL) and TsOH (30 mg). The mixture was then refluxed and stirred overnight. After cooling to room temperature, the mixture was quenched with saturated sodium bicarbonate solution (50 ml). The toluene phase was separated and concentrated to a residue. The residue was purified by chromatography on silica gel with PE/EtOAc (3:1, *v/v*) to give spiro[bicyclo[3.2.0]heptane-6,2'-[1,3]dioxolan]-3-ol as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38-4.40 (m, 1H), 3.87-3.95 (m, 4H), 3.55 (d, *J* = 8.0 Hz, 1H), 2.98-3.03 (m, 1H), 2.56-2.66 (m, 2H), 2.32-2.37 (m, 1H), 2.01-2.05 (m, 1H), 1.82-1.83 (m, 2H) ppm.

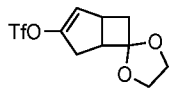
Intermediate 33



Spiro[bicyclo[3.2.0]heptane-6,2'-[1,3]dioxolan]-3-one. To a solution of spiro[bicyclo[3.2.0]heptane-6,2'-[1,3]dioxolan]-3-ol (2.0 g, 11 mmol) in DCM (100 mL) was added PCC (9.5 g, 44 mmol) and NaOAc (1.8 g, 22 mmol). The mixture was then refluxed and stirred overnight. The solvent was evaporated, and the residue was purified by chromatography on silica gel with PE/EtOAc (5:1, *v/v*) to give spiro[bicyclo[3.2.0]heptane-

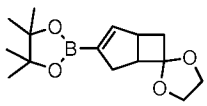
6,2'-[1,3]dioxolan]-3-one (2.1 g, 67%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79-3.94 (m, 4H), 3.17-3.22(m, 1H), 2.68-2.79 (m, 2H), 2.43-2.54 (m, 2H), 2.17-2.35 (m, 2H), 2.02-2.08 (m, 1H) ppm.

Intermediate 34



Spiro[bicyclo[3.2.0]hept[2]ene-6,2'-[1,3]dioxolane]-3-yltrifluoro methanesulfonate. To a solution of spiro[bicyclo[3.2.0]heptane-6,2'-[1,3]dioxolan]-3-one (2.0 g, 12 mmol) in THF (100 mL) was added LiHMDS (15 mmol, 1 M, 15 mL) at -78°C. The reaction mixture was stirred at -78°C for 1h and then a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methane sulfonamide (5.4 g, 15 mmol) in THF (25 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. The solvent was evaporated, and the residue was purified by column chromatography in silica gel using PE/EA = 5/1 (*v/v*) to afford spiro[bicyclo[3.2.0]hept[2]ene-6,2'-[1,3]dioxolane]-3-yltrifluoro methanesulfonate (2.7g, 75%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66-5.69 (m, 1H), 3.80-3.97 (m, 4H), 3.47-3.50 (m, 1H), 2.59-2.87 (m, 3H), 2.23-2.43 (m, 2H) ppm.

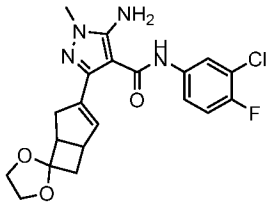
Intermediate 35



4,4,5,5-Tetramethyl-2-(spiro[bicyclo[3.2.0]hept[2]ene-6,2'-[1,3]dioxolane]-3-yl)-1,3,2-dioxaborolane. A mixture of spiro[bicyclo[3.2.0]hept[2]ene-6,2'-[1,3]dioxolane]-3-yltrifluoro methanesulfonate (2.7 g, 9 mmol) ,4,4,5,5-tetramethyl-2-(4, 4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.5 g, 10 mmol), $Pd(dppf)Cl_2$ (292 mg, 0.4 mmol) and potassium acetate (2.0 g, 20 mmol) in dioxane (50 mL) was stirred at 80 °C under

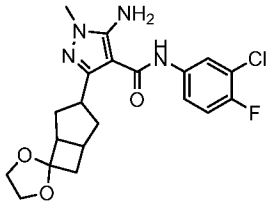
N_2 atmosphere for 4 h. The reaction was filtered through a pad of celite, the cake was washed with EtOAc (10 mL x 3). The filtrate was concentrated in vacuum and the residue was purified through silica gel column chromatography using PE/EA = 5/1 (*v/v*) to afford compound 4,4,5,5-tetramethyl-2-(spiro[bicyclo[3.2.0]hept[2]ene-6,2'-[1,3]dioxolane]-3-yl)-1,3,2-dioxaborolane as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40-6.46 (m, 1H), 3.83-3.96 (m, 4H), 3.55-3.57 (m, 1H), 2.35-2.69 (m, 4H), 2.05-2.13 (m, 1H), 1.24-1.30 (m, 12H) ppm.

Intermediate 36



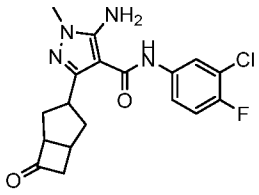
5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(spiro[bicyclo[3.2.0] hept[2]ene-6,2'-[1,3]dioxolane]-3-yl)-1H-pyrazole-4-carboxamide. A mixture of 4,4,5,5-tetramethyl-2-(spiro[bicyclo[3.2.0]hept[2]ene-6,2'-[1,3]dioxolane]-3-yl)-1,3,2-dioxaborolane (2.2 g, 7.9 mmol), 5-amino-3-bromo-N-(3-chloro-4-fluoro-phenyl)-1-methyl-pyrazole-4-carboxamide (2.7 g, 7.9 mmol), K_3PO_4 (3.1 g, 14.5 mmol) and $Pd(dppf)Cl_2$ (530 mg, 0.7 mmol) in dioxane (60 mL) and H_2O (3 mL) were stirred at 100 °C overnight under N_2 atmosphere. The solvent was removed in vacuum and the residue was purified by silica gel column chromatography using PE/EA = 3/1 (*v/v*) to afford compound 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(spiro[bicyclo[3.2.0] hept[2]ene-6,2'-[1,3]dioxolane]-3-yl)-1H-pyrazole-4-carboxamide (1.7 g, 51% yield) as a yellow solid. TLC**:** 50% PE/EA (*v/v*) (R_f: 0.4), MS calcd.: 418.2; Found: 419.2 $[M + 1]^+$.

Intermediate 37



5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(spiro[bicyclo[3.2.0] heptane-6,2'-[1,3]dioxolane]-3-yl)-1H-pyrazole-4-carboxamide. A mixture of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(spiro[bicyclo[3.2.0] hept[2]ene-6,2'-[1,3]dioxolane]-3-yl)-1H-pyrazole-4-carboxamide (850 mg, 2.0 mmol) and Pt/C (100 mg) in methanol (100 mL) was stirred under H_2 at room temperature for two days. The mixture was filtered with a pad of celite, the filtrate was concentrated to afford compound 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(spiro[bicyclo[3.2.0] heptane-6,2'-[1,3]dioxolane]-3-yl)-1H-pyrazole-4-carboxamide as a yellow solid which was directly used for next step without further purification. TLC**:** 50% PE/EA (*v/v*) (R_f: 0.4), MS calcd.: 420.8; Found: 421.2 $[M + 1]^+$.

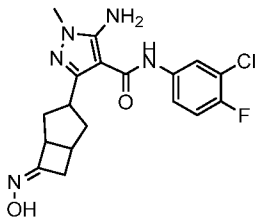
Example 137



5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(6-oxobicyclo[3.2.0] heptan-3-yl)-1H-pyrazole-4-carboxamide. To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(spiro[bicyclo[3.2.0] heptane-6,2'-[1,3]dioxolane]-3-yl)-1H-pyrazole-4-carboxamide (850 mg, 2.0 mmol) in acetone (20 mL) was added water (1.0 mL) and TsOH (172 mg, 1.0 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with saturated sodium bicarbonate solution (5 mL) and concentrated

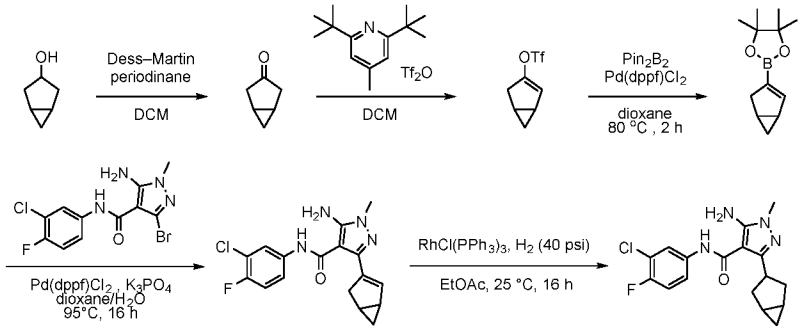
under reduced pressure to a residue. The residue was purified through silica gel column chromatography using PE/EA = 1/1 (*v/v*) to afford compound 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(6-oxobicyclo[3.2.0] heptan-3-yl)-1H-pyrazole-4-carboxamide as a white solid. MS calcd.: 376.8; Found: 377.2 $[M+1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 7.89 (dd, *J* = 2.8, 6.8 Hz, 1H), 7.51-7.55 (m, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 6.00 (s, 2H), 3.77-3.81 (m, 1H), 3.61-3.67 (m, 1H), 3.47 (s, 3H), 3.05-3.12 (m, 1H), 2.78-2.83 (m, 1H), 2.58-2.65(m, 1H), 2.30-2.37 (m, 1H), 2.02-2.11 (m, 2H), 1.77-1.84 (m, 1H) ppm.

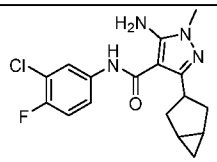
Example 138



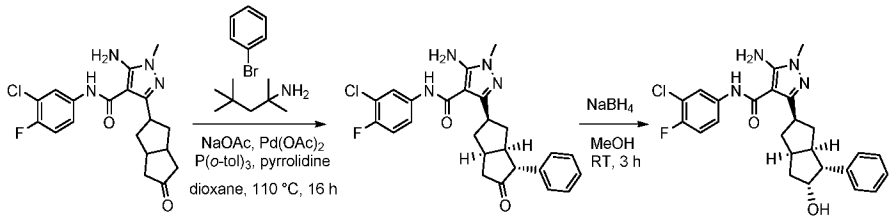
(E)-5-Amino-N-(3-chloro-4-fluorophenyl)-3-(6-(hydroxyimino) bicyclo[3.2.0]heptan-3-yl)-1-methyl-1H-pyrazole-4-carboxamide. A mixture of 5-amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(6-oxobicyclo[3.2.0] heptan-3-yl)-1H-pyrazole-4-carboxamide (350 mg, 0.9 mmol), $NH_2OH.HCl$ (67 mg, 1.0 mmol), $NaHCO_3$ (168 mg, 2.0 mmol) in methanol (25 mL) was stirred at 50 °C overnight. The solvent was evaporated, and the residue was purified by chromatography on silica gel using DCM/MeOH = 10/1 (*v/v*) to afford compound (E)-5-amino-N-(3-chloro-4-fluorophenyl)-3-(6-(hydroxyimino) bicyclo[3.2.0]heptan-3-yl)-1-methyl-1H-pyrazole-4-carboxamide as a white solid. MS calcd.: 391.8; Found: 392.2 $[M+1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.05 (brs, 1H), 9.00 (s, 1H), 7.89-7.91 (m, 1H), 7.50-7.54 (m, 1H), 7.35 (t, *J* = 5.2 Hz, 1H), 5.98 (s, 2H), 3.56-3.65 (m, 1H), 3.32-3.44 (m, 4H), 2.79-2.90 (m, 1H), 2.66-2.70 (m, 1H), 2.41-2.48 (m, 1H), 2.15-2.33(m, 2H), 1.89-2.00 (m, 1H), 1.66-1.73 (m, 1H) ppm.

Scheme 1

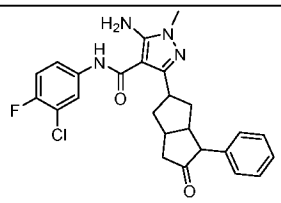
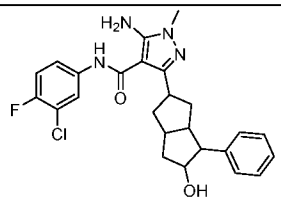
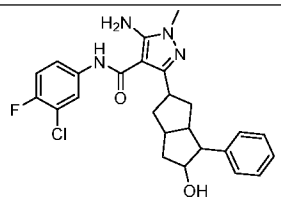


Example	Structure and analysis
Example 139	 **5-Amino-3-(bicyclo[3.1.0]hexan-3-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide.** MS calcd. for $C_{17}H_{18}ClFN_4O$: 348.1; Found: 349.2 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.80-8.76 (m, 1H), 7.92 (d, *J*=6.69 Hz, 1H), 7.54 (ddd, *J*=9.02, 4.31, 2.57 Hz, 1H), 7.35 (t, *J*=9.11 Hz, 1H), 6.00 (s, 2 H), 3.96-3.88 (m, 1H), 3.48 (s, 3H), 2.22-2.13 (m, 2H), 2.08-1.99 (m, 2H), 1.28-1.21 (m, 2H), 0.32 (td, *J*=8.01, 4.28 Hz, 1H), 0.24 (q, *J*=4.03 Hz, 1H) ppm.

Scheme 2

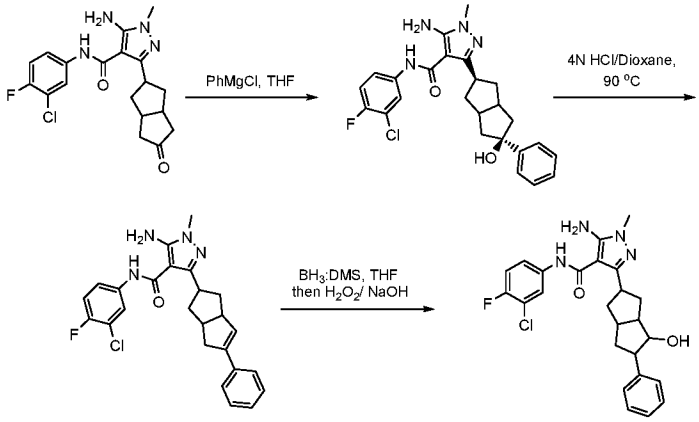


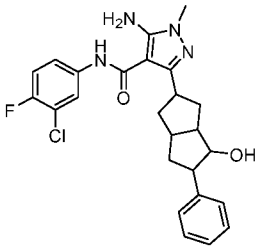
Example	Structure and analysis

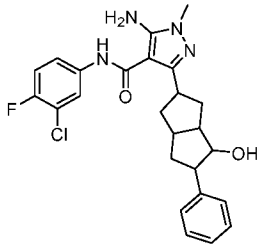
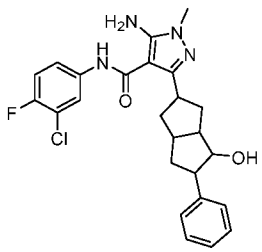
Example 140	 **5-Amino-N-(3-chloro-4-fluorophenyl)-1-methyl-3-(5-oxo-4-phenyloctahydropentalen-2-yl)-1H-pyrazole-4-carboxamide** MS calcd. for $C_{25}H_{24}ClFN_4O_2$: 466.2; Found: 467.0 $[M + 1]^+$. 1H NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 1H), 7.90 (dd, J = 7.2, 2.4 Hz 1H), 7.55-7.51 (m, 1H), 7.36-7.21 (m, 4H), 7.14-7.12 (m, 2H), 5.99 (s, 2H), 3.75-3.70 (m, 1H), 3.52 (s, 3H), 3.36-3.31 (m, 1H), 2.77 (br.s, 2H), 2.62-2.58 (m, 1H), 2.34-2.55 (m, 3H), 2.86 -1.70 (m, 2H) ppm.
Example 141	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-4-phenyloctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer I.** MS calcd. for $C_{25}H_{26}ClFN_4O_2$: 468.2; Found: 469.1 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.88 (dd, J = 6.8, 2.4 Hz 1H), 7.51-7.47 (m, 1H), 7.34-7.22 (m, 5H), 7.17-7.13 (m, 1H), 5.96 (s, 2H), 4.67 (d, J = 6.4 Hz, 1H), 4.05 (m, 1H), 3.51 (s, 3H), 3.49-3.44 (m, 1H), 2.56-2.53 (m, 1H), 2.50-2.38 (m, 2H), 2.24-2.18 (m, 2H), 2.11-2.04 (m, 1H), 1.64-1.52 (m, 2H), 1.39-1.32 (m, 1H) ppm.
Example 142	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-4-phenyloctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II.**

	MS calcd. for $C_{25}H_{27}FN_4O_2$: 434.2; Found: 435.3 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H), 7.56-7.53 (m, 1H), 7.26-7.18 (m, 4H), 7.15-7.05 (m, 3H), 6.92 (s, 1H), 5.89 (br.s, 2H), 4.03-4.02 (m, 1H), 3.49 (s, 3H), 2.54-2.48 (br.s, 2H, merged), 2.42-2.38 (m, 2H), 2.22-2.21 (m, 2H), 2.07-2.05 (m, 2H), 1.60-1.53 (m, 2H), 1.35-1.33 (m, 1H) ppm.

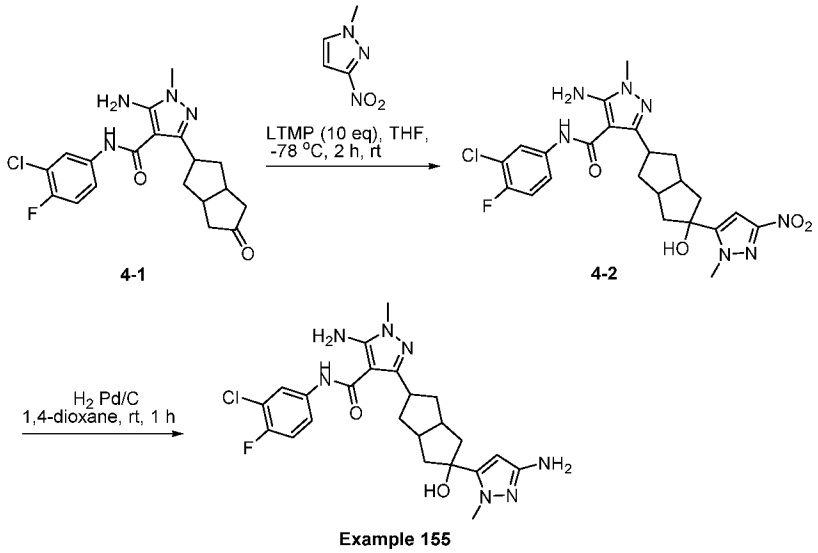
Scheme 3



Example	Structure and analysis
Example 143	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(4-hydroxy-5-phenyloctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer I** MS calcd. for $C_{25}H_{26}ClFN_4O_2$: 468.2; Found: 469.1 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz 1H), 7.55-7.51 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 7.27-7.21 (m, 4H), 7.17-7.13 (m, 1H), 5.99 (s, 2H), 4.66 (d, J = 4 Hz, 1H), 3.72-3.54 (m, 2H), 3.52 (s, 3H),

	3.32-2.61 (m, 1H), 2.58-2.49 (m, 1H), 2.35-2.08 (m, 4H), 1.74-1.67 (m, 1H), 1.58-1.45 (m, 2H) ppm.
Example 144	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(4-hydroxy-5-phenyloctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer II** MS calcd. for $C_{25}H_{26}ClFN_4O_2$: 468.2; Found: 469.2 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz 1H), 7.54-7.52 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 7.27-7.21 (m, 4H), 7.17-7.13 (m, 1H), 6.00 (s, 2H), 4.66 (d, J = 4 Hz, 1H), 3.71-3.61 (m, 2H), 3.52 (s, 3H), 2.92-2.88 (m, 1H), 2.58-2.54 (m, 1H), 2.35-2.31 (m, 1H), 2.25-2.07 (m, 3H), 1.74-1.66 (m, 1H), 1.61-1.48 (m, 2H) ppm.
Example 145	 **5-Amino-N-(3-chloro-4-fluorophenyl)-3-(4-hydroxy-5-phenyloctahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide Isomer III** MS calcd. for $C_{25}H_{26}ClFN_4O_2$: 468.2; Found: 469.1 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz 1H),7.55-7.51 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 7.27-7.22 (m, 4H), 7.17-7.13 (m, 1H), 6.00 (s, 2H), 4.66 (br.s, 1H), 3.71-3.59 (m, 2H), 3.52 (s, 3H), 2.95-2.88 (m, 1H), 2.58-2.54 (m, 1H), 2.35-2.31 (m, 1H), 2.26-2.07 (m, 3H), 1.74-1.69 (m, 1H), 1.61-1.45 (m, 2H) ppm.

Scheme 4

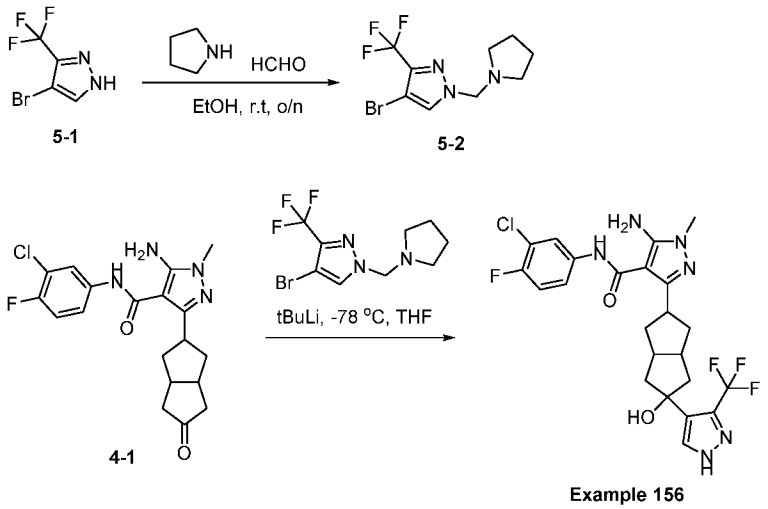


Step 1. Synthesis of 5-amino-N-(3-chloro-4-fluorophenyl)-3-((2s,3aR,5r,6aS)-5-hydroxy-5-(1-methyl-3-nitro-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide: To a solution of 1-methyl-3-nitro-1H-pyrazole (0.488 g, 3.8 mmol) in dry THF (8 mL), LTMP (2.0 mL, 3.8 mmol) was added in one portion at -78 °C under Ar. After the mixture was stirred at -78 °C for 0.5 h, Compd. **4-1** (0.15 g, 0.38 mmol) in THF (1 mL) was added and stirred at rt for 2 h. The solution was quenched by NH_4Cl aq. and extracted with EA (20 mL x 2), washed with brine (20 mL) then concentrated and purified by *prep*-HPLC to afford Compd. **4-2** (148 mg, 74%) as a white solid. **TLC:** 10% MeOH/DCM (R_f: 0.4); **MS** Calcd.: 517.2; Found: 518.2 $[M+1]^+$. ^1H NMR (400 Hz, DMSO-d_6): δ 8.93 (s, 1H), 7.93-7.90 (dd, J = 6.8 Hz, 2.8 Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 6.93 (s, 1H), 5.98 (s, 2H), 5.53 (s, 1H), 4.03 (s, 3H), 3.50 (s, 3H), 3.44-3.22 (m, 1H), 2.51-2.49 (m, 2H), 2.27-219 (m, 4H), 2.07-1.89 (m, 2H),1.89-1.76 (m, 2H) ppm.

Step 2. Synthesis of 5-amino-3-((2s,3aR,5r,6aS)-5-(3-amino-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-pyrazole-4-carboxamide (**Example 155**): To a solution of Compd. **4-2** (148 mg, 0.28 mmol) in 1,4-

dioxane (5 mL) was added Pd/C (70 mg). The flask was then evacuated and backfilled with H_2. The solution was stirred at rt for 1 h. Then the mixture was filtered and concentrated. And the residue was purified by *prep*-HPLC to afford Example 155 (36 mg, 25%) as a white solid, TLC: 65% EA/PE (*v/v*) (R_f: 0.3); MS Calcd.: 487.2; Found: 488.19 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.93-7.91 (m, 1H), 7.52-7.49 (m, 1H), 7.34 (t, J = 9.0 Hz, 1H), 5.99 (s, 2H), 5.24 (s, 1H), 5.03 (s, 1H), 4.33 (s, 2H), 3.62 (s, 3H), 3.49 (s, 3H), 3.46-3.40 (m, 1H), 2.50-2.49 (m, 2H), 2.15-2.06 (m, 4H), 1.81-1.71 (m, 4H) ppm.

Scheme 5

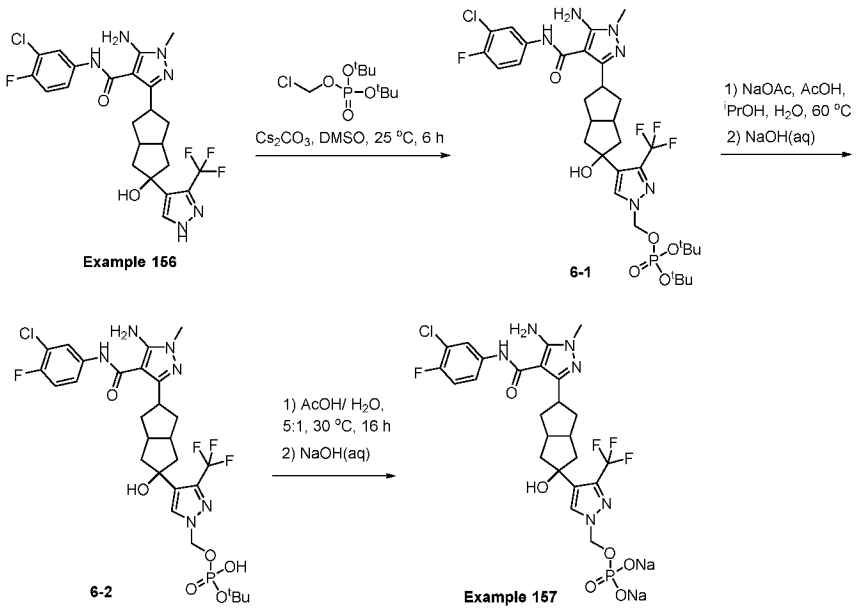


Step 1. Synthesis of 4-bromo-1-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)-1H-pyrazole (**5-2**): To a solution of Compd. **5-1** (15.0 g, 70.0 mmol) in EtOH (200 mL) was added pyrrolidine (4.98 g, 70.0 mmol), the reaction was stirred at room temperature and HCHO (11.4 mL, 140.0 mmol, 37% in H_2O) was added. The reaction mixture was stirred at room temperature overnight. After concentration in vacuo, the residue was to give crude Compd. **5-2** (20.5 g, 98% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 1H), 5.04 (s, 2H), 2.69 (m, 4H), 1.77 (m, 4H) ppm.

Step 2. Synthesis of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (**Example 156**): To a solution of Compd. **5-2** (5.96 g, 20.0 mmol) in Ether (30 mL)

was added t-BuLi (15.4 mL, 20.0 mmol, 1.3 M) dropwise (about 1 min) at -78 °C. The reaction mixture was stirred at -78 °C for 5 min, then Compd. **4-1** (391 mg, 1.0 mmol) was added. The mixture was stirred at -78 °C for 2 h, sat. aq. NH_4Cl solution was added, concentrated, and purified by flash (MeOH in DCM, 0~15%) to give the crude product. The crude was purified by prep-HPLC to give Example 156 (156 mg, 30% yield) as a white solid. MS Calcd.: 526.2; Found: 528.0 [M + 2] $^+$. ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (dd, J = 6.8, 2.4 Hz, 1H), 7.71 (s, 1H), 7.43 – 7.36 (m, 1H), 7.18 (t, J = 9.2 Hz, 1H), 3.55 (s, 3H), 3.47 – 3.38 (m, 1H), 2.69 – 2.57 (m, 2H), 2.39 – 2.25 (m, 4H), 1.97 – 1.83 (m, 4H) ppm.

Scheme 6



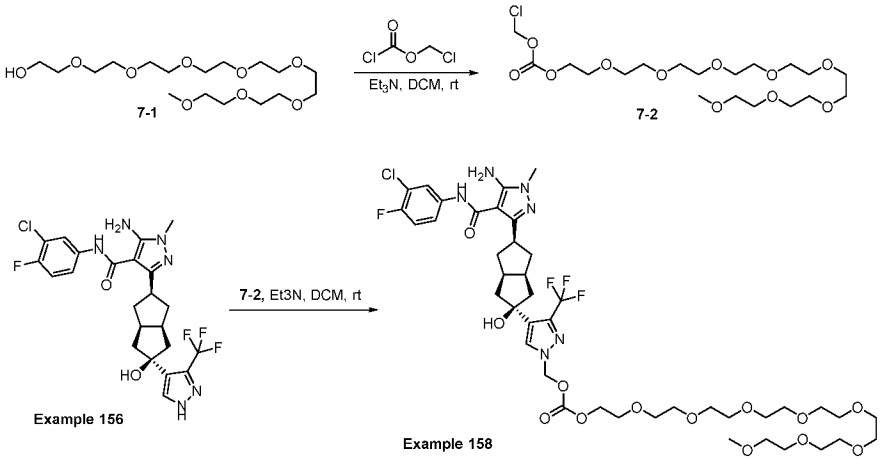
Step 1. Synthesis of (4-(5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl di-tert-butyl phosphate (**6-1**): To a solution of **Example 156** (80 mg, 0.15 mmol) in DMSO (1.5 mL) was added di-tert-butyl (chloromethyl) phosphate (58 mg, 0.225 mmol) and Cs_2CO_3 (54 mg, 0.165 mmol), the reaction was stirred at 25 °C for 6 h. The mixture was purified by prep-HPLC to give Compd. **6-1** (75 mg, 67% yield) as a white solid. MS Calcd.: 748.3; Found: 730.8 [M - H_2O]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 7.97 (s, 1H), 7.90 (dd, J = 6.8, 2.4 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 5.92 – 5.75 (m, 2H), 4.97 (s, 1H),

3.50 (s, 3H), 3.44 – 3.37 (m, 1H), 2.57 – 2.47 (m, 2H), 2.20 – 2.01 (m, 4H), 1.87 – 1.71 (m, 4H), 1.37 (s, 18H) ppm.

Step 2. Synthesis of (4-(5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl tert-butyl hydrogen phosphate (**6-2**): To a solution of Compd. **6-1** (115 mg, 0.154 mmol) in ^{i}PrOH (4 mL) was added NaOAc (101 mg, 1.23 mmol) in H_2O (2 mL) and AcOH (230 mg, 3.85 mmol). The reaction mixture was stirred at 60 °C for 4 h, then the mixture was cooled to 0 °C, and the resulting mixture was adjusted to pH 8 ~ 9 with 2M aq. NaOH. The residue was concentrated and purified by prep-HPLC to give Compd. **6-2** (70 mg, 66% yield) as a white solid. MS Calcd.: 692.2; Found: 694.0 $[M + 2]^+$. ^{1}H NMR (400 MHz, CD_3OD): δ 7.92 (s, 1H), 7.80 (dd, J = 6.8, 2.4 Hz, 1H), 7.45 – 7.35 (m, 1H), 7.19 (t, J = 9.2 Hz, 1H), 5.71 (d, J = 10.8 Hz, 2H), 3.55 (s, 3H), 3.49 – 3.40 (m, 1H), 2.70 – 2.58 (m, 2H), 2.37 – 2.25 (m, 4H), 1.97 – 1.79 (m, 4H), 1.35 (s, 9H) ppm.

Step 3. Synthesis of sodium sodium (4-(5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl phosphate (**Example 157**): To a solution of Compd. 6-2 (70 mg, 0.10 mmol) in AcOH/H_2O (1.2 mL, v/v, 5:1), the reaction mixture was stirred at 30 °C for 10 h, then added ice water (2 mL). The resulting mixture was adjusted to pH 8 ~ 9 with 6 N aq. NaOH solution. The residue was concentrated and purified by prep-HPLC to give **Example 157** (20 mg, 29% yield) as a white solid. MS Calcd.: 680.1; Found: 636.8 $[M - 2Na + 2]^+$. ^{1}H NMR (400 MHz, CD_3OD): δ 7.97 (s, 1H), 7.82 (dd, J = 6.8, 2.4 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.19 (t, J = 9.2 Hz, 1H), 5.72 (d, J = 9.6 Hz, 2H), 3.55 (s, 3H), 3.50 – 3.42 (m, 1H), 2.69 – 2.58 (m, 2H), 2.39 – 2.25 (m, 4H), 1.95 – 1.80 (m, 4H) ppm.

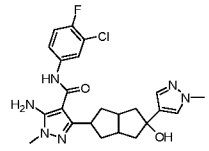
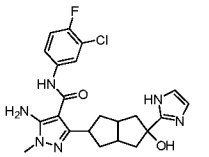
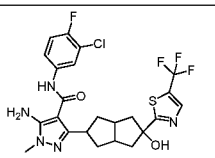
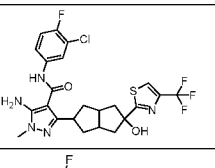
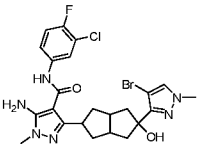
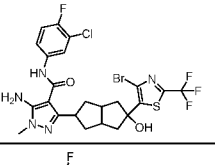
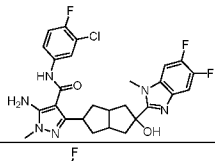
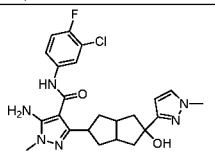
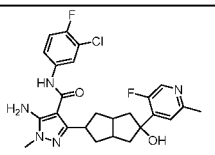
Scheme 7

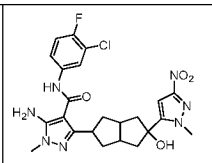
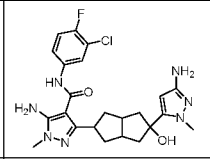
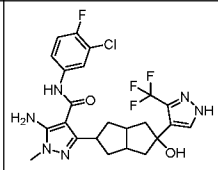
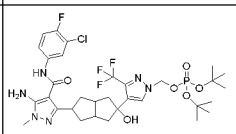
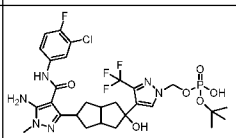
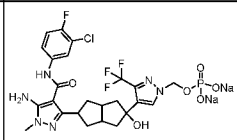
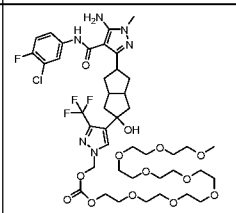
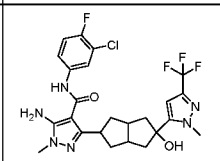
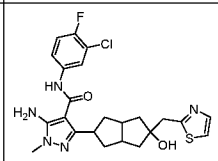
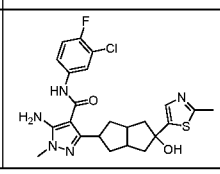


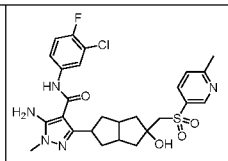
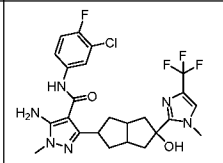
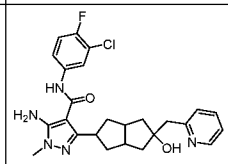
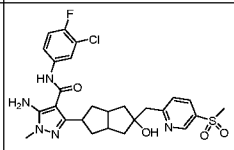
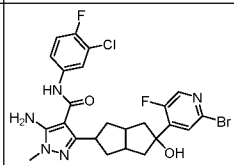
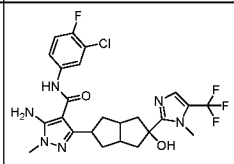
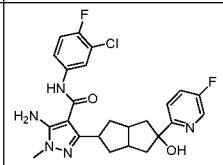
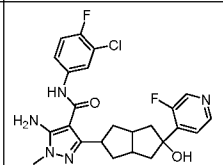
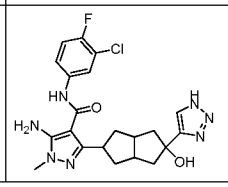
Step 1. Synthesis of chloromethyl (2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl) carbonate (**7-2**): To a solution of Compd. **7-1** (768 mg, 2 mmol) and Et_3N (404 mg, 4 mmol) in DCM (15 mL), chloromethyl carbonochloridate (384 mg, 3 mmol) was added. The solution was stirred at rt for overnight. The mixture was quenched by water (20 ml) and extracted with DCM (15 mL x 3). The organic solvent was concentrated in *vacuum* and the residue was purified by chromatography (20 g silica gel), eluted with EA in PE from 10-55% (*v/v*) to afford Compd. **7-2** (280 mg, 29%) as a colorless liquid. TLC: 50% EA/PE (R_f: 0.25).

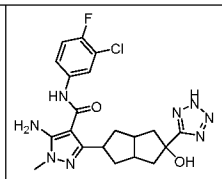
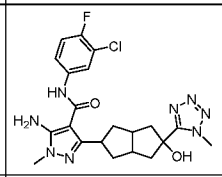
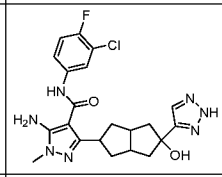
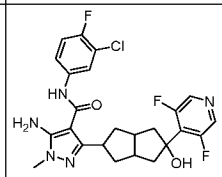
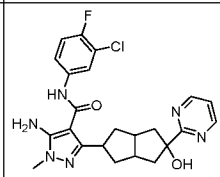
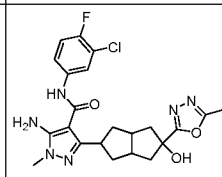
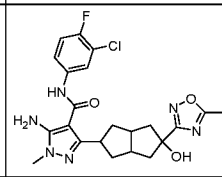
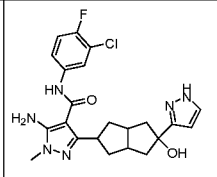
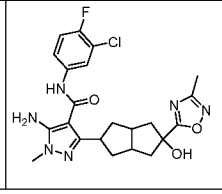
Step 2. Synthesis of (4-((2r,3aR,5s,6aS)-5-(5-amino-4-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl (2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl) carbonate (**Example 158**): To a solution of **Example 156** (105 mg, 0.2 mmol) and Et_3N (40.4 mg, 0.4 mmol) in DCM (5 mL), **Compd. 7-2** (143 mg, 0.3 mmol) was added. The solution was stirred at rt overnight. The mixture was quenched by water (10 ml) and extracted with DCM (10 mL x 3). The organic solvent was concentrated in *vacuum* and the residue was purified by *prep*-HPLC to afford **Example 158** (20 mg, 10%) as a yellow oil. TLC: 10% MeOH/DCM (*v/v*) (R_f: 0.35); MS Calcd.: 966.3; Found: 966.8 $[M + 1]^+$.

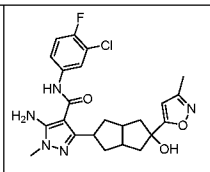
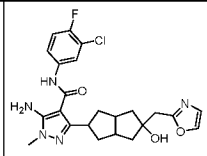
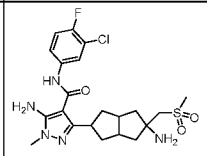
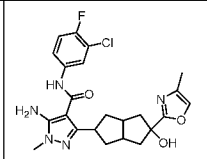
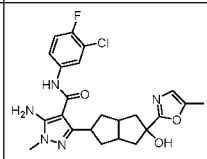
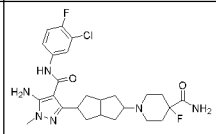
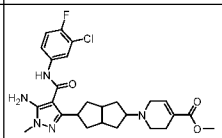
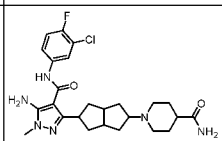
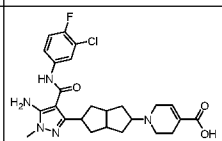
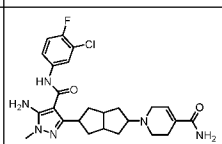
The following examples were readily synthesized by following similar synthetic routes described above with the corresponding starting materials:

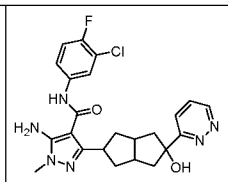
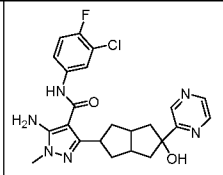
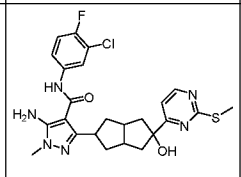
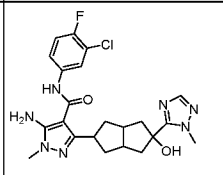
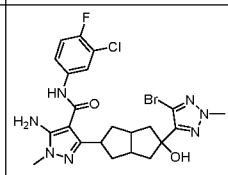
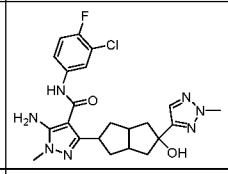
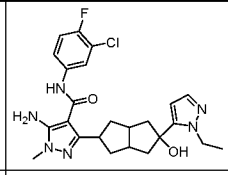
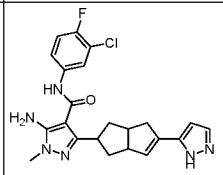
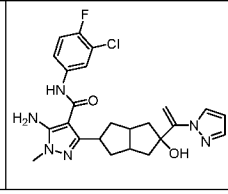
Compd.	STRUCTURE	MS [M + 1]$^+$	^{1}H NMR
Example 146		473.3	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.92 (s, 1H), 7.92 (dd, J_1 = 3.6 Hz, J_2 = 6.8 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.35 (t, J = 8.8 Hz, 1H), 7.29 (s, 1H), 5.99 (s, 2H), 4.68 (s, 1H), 3.75 (m, 3H), 3.41 (s, 1H), 3.35 (m, 1H), 2.50 (m, 2H), 2.14 – 2.12 (m, 2H), 2.04 – 2.00 (m, 2H), 1.78 – 1.70 (m, 4H) ppm.
Example 147		459.3	^{1}H NMR (DMSO-d6, 400 MHz): δ 11.70 (s, 1H), 8.90 (s, 1H), 7.93 (dd, J_1 = 2.8 Hz, J_2 = 4.4 Hz, 1H), 7.51 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.85 (s, 2H), 6.00 (m, 2H), 5.11 (s, 1H), 3.50 (s, 3H), 3.41 (m, 1H), 2.56 – 2.51 (m, 2H), 2.30 – 2.25 (m, 2H), 2.17 – 2.11 (m, 2H), 1.85 – 1.65 (m, 4H) ppm.
Example 148		544.2	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.95 (s, 1H), 8.30 (d, J = 1.2 Hz, 1H), 7.93 (dd, J_1 = 2.4 Hz, J_2 = 6.4 Hz, 1H), 7.53 (m, 1H), 7.35 (t, J = 5.2 Hz, 1H), 6.33 (s, 1H), 6.00 (s, 2H), 3.50 (s, 3H), 3.42 (m, 1H), 2.80 – 2. 60 (m, 2H), 2.33 – 2.16 (m, 4H), 1.92 – 1.81 (m, 4H) ppm.
Example 149		544.2	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.94 (s, 1H), 8.33 (d, J = 0.8 Hz, 1H), 7.93 (dd, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 1H), 7.53 (m, 1H), 7.35 (t, J = 8.8 Hz, 1H), 6.17 (s, 1H), 6.00 (s, 2H), 3.50 (s, 3H), 3.43 (m, 1H), 2.80 – 2.73 (m, 2H), 2.27 – 2.16 (m, 4H), 1.91 – 1.86 (m, 4H) ppm.
Example 150		533.2 [M-H_2O+1]$^+$	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.89 (s, 1H), 7.92 (dd, J_1 = 2.8 Hz, J_2 = 6.8 Hz, 1H), 7.80 (s, 1H), 7.51 (m, 1H), 7.37 (t, J = 9.2 Hz, 1H), 5.99 (br s, 2H), 4.78 (s, 1H), 3.75 (s, 3H), 3.50 (s, 3H), 3.40 (m, 1H), 2.42 – 2.36 (m, 4H), 2.15 – 2.12 (m, 2H), 1.78 – 1.72 (m, 4H) ppm
Example 151		622.0	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.96 (s, 1H), 7.93 (dd, J_1 = 2.8 Hz, J_2 = 6.8 Hz, 1H), 7.52 (m, 1H), 7.35 (t, J = 5.2 Hz, 1H), 6.35 (s, 1H), 5.99 (s, 2H), 3.50 9S, 3H), 3.40 (m, 1H), 2.80 – 2.70 (m, 2H), 2.54 – 2.50 (m, 2H), 2.20 – 2.10 (m, 2H), 1.94 – 1.89 (m, 4H) ppm.
Example 152		559.3	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.96 (s, 1H), 7.92 (dd, J_1 = 1.6 Hz, J_2 = 5.2 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.53 – 7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 6.00 (br s, 2H), 5.61 (s, 1H), 3.91 (s, 3H), 3.51 (s, 3H), 3.47 (m, 1H), 2.55 – 2.46 (m, 4H), 2.20 – 2.17 (m, 2H), 1.93 – 1.90 (m, 2H), 1.82 – 1.77 (m, 2H) ppm
Example 153		455.3 [M-H_2O+1]$^+$	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.90 (s, 1H), 7.92 (dd, J_1 = 2.4 Hz, J_2 = 5.6 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.35 (t, J = 9.2 Hz, 1H), 6.14 (d, 1H), 5.99 (s, 1H), 4.71 (s, 1H), 3.75 (s, 3H), 3.50 (s, 3H), 3.36 (m, 1H), 2.51 – 2.48 (m, 2H), 2.22 – 2.10 (m, 4H), 1.82 – 1.78 (m, 2H), 1.72 – 1.68 (m, 2H) ppm
Example 154		502.1	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.94 (s, 1H), 8.24 (d, J = 3.2 Hz, 1H), 7.93 (dd, J_1 = 2.8 Hz, J_2 = 6.8 Hz, 1H), 7.52 (m, 1H), 7.37 – 7.35 (m, 2H), 5.99 (br s, 2H), 5.15 (s, 1H), 3.50 (s, 3H), 3.40 (m, 1H), 2.69 – 2.64 (m, 2H), 2.44 (s, 3H), 2.25 – 2.13 (m, 2H), 2.00 – 1.92 (m, 2H), 1.84 – 1.80 (m, 2H) ppm

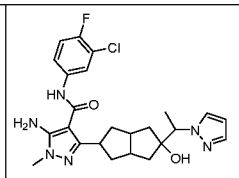
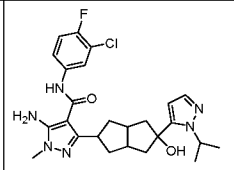
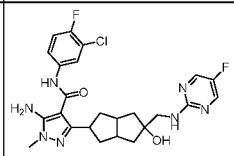
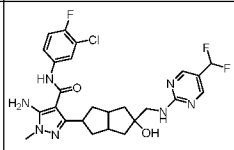
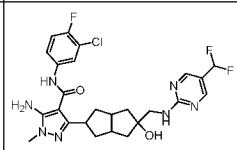
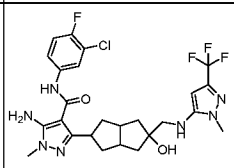
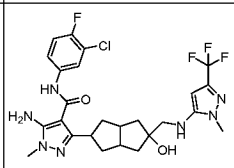
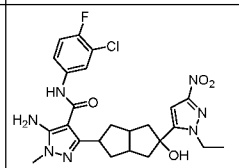
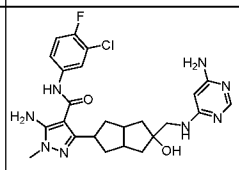
Compd. 4-2		518.9	^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.93 (s, 1H), 7.93-7.90 (dd, *J* = 6.8 Hz, 2.8 Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, *J* = 9.2 Hz, 1H), 6.93 (s, 1H), 5.98 (s, 2H), 5.53 (s, 1H), 4.03 (s, 3H), 3.50 (s, 3H), 3.44-3.22 (m, 1H), 2.51-2.49 (m, 2H), 2.27-219 (m, 4H), 2.07-1.89 (m, 2H),1.89-1.76 (m, 2H) ppm
Example 155		488.9	^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.91 (s, 1H), 7.93-7.91 (m, 1H), 7.52-7.49 (m, 1H), 7.34 (t, *J* = 9.0 Hz, 1H), 5.99 (s, 2H), 5.24 (s, 1H), 5.03 (s, 1H), 4.33 (s, 2H), 3.62 (s, 3H), 3.49 (s, 3H), 3.46-3.40 (m, 1H), 2.50-2.49 (m, 2H), 2.15-2.06 (m, 4H), 1.81-1.71 (m, 4H) ppm
Example 156		526.9	^{1}H NMR (400 MHz, MeOD-d4) δ 7.80 (dd, J = 6.8, 2.4 Hz, 1H), 7.71 (s, 1H), 7.43 – 7.36 (m, 1H), 7.18 (t, J = 9.2 Hz, 1H), 3.55 (s, 3H), 3.47 – 3.38 (m, 1H), 2.69 – 2.57 (m, 2H), 2.39 – 2.25 (m, 4H), 1.97 – 1.83 (m, 4H) ppm
Compd. 6-1		730.8 [M+H-18]$^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 8.98 (s, 1H), 7.97 (s, 1H), 7.90 (dd, J = 6.8, 2.4 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 5.92 – 5.75 (m, 2H), 4.97 (s, 1H), 3.50 (s, 3H), 3.44 – 3.37 (m, 1H), 2.57 – 2.47 (m, 2H), 2.20 – 2.01 (m, 4H), 1.87 – 1.71 (m, 4H), 1.37 (s, 18H) ppm
Cpmpd. 6-2		691.2 [M-H]$^-$	^{1}H NMR (400 MHz, MeOD-d4) δ 7.92 (s, 1H), 7.80 (dd, J = 6.8, 2.4 Hz, 1H), 7.45 – 7.35 (m, 1H), 7.19 (t, J = 9.2 Hz, 1H), 5.71 (d, J = 10.8 Hz, 2H), 3.55 (s, 3H), 3.49 – 3.40 (m, 1H), 2.70 – 2.58 (m, 2H), 2.37 – 2.25 (m, 4H), 1.97 – 1.79 (m, 4H), 1.35 (s, 9H) ppm
Example 157		635.2 [M-H]$^-$	^{1}H NMR (400 MHz, MeOD-d4) δ 7.97 (s, 1H), 7.82 (dd, J = 6.8, 2.4 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.19 (t, J = 9.2 Hz, 1H), 5.72 (d, J = 9.6 Hz, 2H), 3.55 (s, 3H), 3.50 – 3.42 (m, 1H), 2.69 – 2.58 (m, 2H), 2.39 – 2.25 (m, 4H), 1.95 – 1.80 (m, 4H) ppm
Example 158		967.3	^{1}H NMR (DMSO-*d6*, 400 MHz): δ 8.94 (s, 1H), 8.00 (s, 1H), 7.92 (dd, *J* = 2.4, 2.4Hz, 1H), 7.52-7.49 (m, 1H), 7.34 (t, *J* = 8.8Hz, 1H), 6.07 (s, 2H), 5.98 (s, 2H), 4.95 (s, 1H), 4.25-4.22 (m, 2H), 3.62-3.60 (m, 2H), 3.54-3.49 (m, 32H), 3.22 (s, 3H), 2.50-2.49 (m, 2H), 2.15-2.03 (m, 4H), 1.85-1.79 (m, 4H) ppm
Example 159		541.2	^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.92 (brs, 1H), 7.92 (dd, J = 7.0, 2.6 Hz, 1H), 7.54-7.49 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.59 (s, 1H), 6.00 (brs, 2H), 5.39 (s, 1H), 3.99 (s, 3H), 3.50 (s, 3H), 3.48-3.39 (m, 1H), 2.58-2.52 (m, 2H), 2.26-2.12 (m, 4H), 1.90 (dd, J =12.8, 2.8 Hz, 2H), 1.84-1.72 (m, 2H) ppm
Example 160		490.2	^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.92 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.67 (d, J = 3.2 Hz, 1H), 7.54 (d, J = 3.6 Hz, 1H), 7.53-7.48 (m, 1H), 7.35 (dd, J = 9.2, 9.2 Hz, 1H), 5.98 (s, 2H), 4.78 (s, 1H), 3.49 (s, 3H), 3.47-3.38 (m, 1H), 3.10 (s, 2H), 2.46-2.39 (m, 2H), 2.19-2.06 (m, 2H), 1.84-1.74 (m, 2H), 1.67-1.55 (m, 2H), 1.48-1.35 (m, 2H).
Example 161		490.3	^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.92 (s, 1H), 7.92 (dd, J = 7.0, 2.6 Hz, 1H), 7.56-7.47 (m, 1H), 7.39 (s, 1H), 7.35 (dd, J = 9.2, 9.2 Hz, 1H), 5.99 (s, 2H), 5.41 (s, 1H), 3.49 (s, 3H), 3.46-3.36 (m, 1H), 2.57 (s, 5H), 2.18-2.05 (m, 4H), 1.90-1.73 (m, 4H) ppm

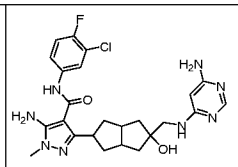
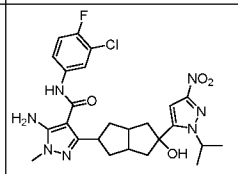
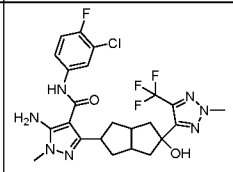
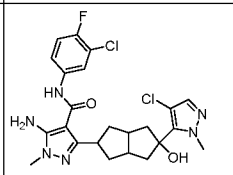
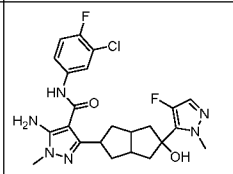
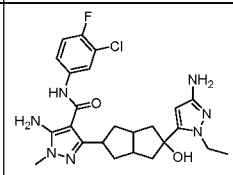
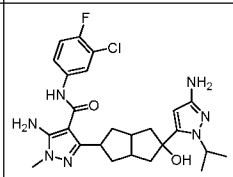
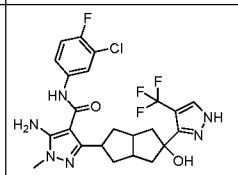
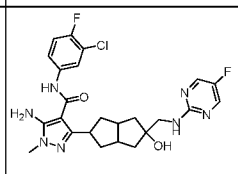
Example 162		562.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (s, 1H), 8.83 (d, J = 2.0 Hz, 1H), 8.10 (dd, J = 8.4, 2.4 Hz, 1H), 7.91-7.89 (m, 1H), 7.50-7.47 (m, 2H), 7.34 (t, J = 9.2 Hz, 1H), 5.95 (s, 2H), 4.41 (s, 1H), 3.55 (s, 2H), 3.47 (s, 3H), 3.33-3.32 (m, 1H), 2.56 (s, 3H), 2.52-2.50 (m, 2H), 2.09-2.06 (m, 2H), 1.93-1.92 (m, 2H), 1.65-1.57 (m, 4H) ppm
Example 163		541.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.89 (s, 1H), 7.92 (dd, J = 7.2, 2.4 Hz, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.53-7.49 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.00 (s, 2H), 5.40 (s, 1H), 3.79 (s, 3H), 3.50 (s, 3H), 3.48 – 3.40 (m, 1H), 2.58 - 2.53 (m, 2H), 2.41 - 2.36 (m, 2H), 2.19 – 2.13 (m, 2H), 1.88 – 1.69 (m, 4H) ppm
Example 164		484.2	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (brs, 1H), 8.46 (d, J = 4.0 Hz, 1H), 7.91 (dd, J = 7.0, 2.6 Hz, 1H), 7.71-7.66 (m, 1H), 7.54-7.48 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.24-7.19 (m, 1H), 5.97 (brs, 2H), 4.85 (s, 1H), 3.48 (s, 3H), 3.47-3.36 (m, 1H), 2.86 (s, 2H), 2.47-2.38 (m, 2H), 2.16-2.08 (m, 2H), 1.82-1.75 (m, 2H), 1.66-1.56 (m, 2H), 1.37 (dd, J = 12.8, 4.8 Hz, 2H) ppm
Exmaple 165		562.0	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.94 (d, *J*=2 Hz, 1H), 8.93 (s, 1H), 8.20-8.18 (dd, *J*=8.4, 2.4 Hz, 1H), 7.92-7.90 (dd, *J* = 6.8 ,2.8 Hz, 1H), 7.56 (d, *J*=8.0 Hz,1H), 7.50 (t, *J*=2.4 Hz, 1H), 7.35 (t, *J* = 9.2 Hz ,1H), 5.96 (s, 2H), 4.66 (s,1H), 3.47 (s, 3H), 3.45-3.37 (m,1H), 3.29(s, 3H), 2.98 (s, 2H), 2.51-2.49 (m,2H), 2.14-2.07 (m, 2H), 1.85-1.80 (m,2H),1.65-1.57 (m, 2H), 1.41-1.37 (dd, *J*=12.8, 4.4Hz, 2H) ppm
Example 166		567.8 $[M+2]^+$	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.94 (s, 1H), 8.32 (d, *J*=2.8 Hz, 1H), 7.93-9-7.91(dd, *J* = 6.8, 2.4 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.54-7.50 (m, 1H), 7.32 (t, *J* = 9.2 Hz, 1H), 5.99 (s, 2H), 5.36 (s,1H), 3.50 (s, 3H), 3.47-3.36 (m, 1H), 2.72-2.66 (m, 2H), 2.25-2.13 (m, 4H), 1.99-1.91 (m, 2H), 1.82 (d, *J*=13.2 Hz, 1H) ppm
Example 167		541.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.91 (s, 1H), 7.92 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.53 - 7.49 (m, 1H), 7.39 – 7.29 (m, 2H), 6.00 (s, 2H), 5.55 (s, 1H), 3.84 (s, 3H), 3.50 (s, 3H), 3.50 - 3.42 (m, 1H), 2.50 – 2.40 (m, 4H), 2.20 - 2.12 (m, 2H), 1.87 - 1.81 (m, 2H), 1.79 - 1.69 (m, 2H) ppm
Example 168		488.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.91 (s, 1H), 8.32-8.31 (m, 1H), 7.91 (dd, J = 7.2, 2.8 Hz, 1H), 7.66-7.61 (m, 1H), 7.52-7.49 (m, 1H), 7.40-7.36 (m, 1H), 7.34 (t, J = 8.8 Hz, 1H), 5.99 (s, 2H), 5.18 (s, 1H), 3.50 (s, 3H), 3.43-3.42 (m, 1H), 2.51-2.43 (m, 4H), 2.16-2.14 (m, 2H), 1.85-1.82 (m, 4H) ppm
Example 169		488.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (s, 1H), 8.41-8.36 (m, 2H), 7.92 (dd, J = 7.2, 2.4 Hz, 1H), 7.55-7.51 (m, 3H), 7.35 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 5.23 (s, 1H), 3.50 (s, 3H), 3.42-3.37 (m, 1H), 2.71-2.69 (m, 2H), 2.23-2.14 (m, 4H), 1.98-1.97 (m, 2H), 1.85-1.82 (m, 2H) ppm
Example 170		460.2	^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.89 (s, 1H), 7.91-7.89 (dd, J = 6.8, 2.8 Hz, 1H), 7.64 (s, 1H), 7.51-7.47 (m, 1H), 7.35-7.30 (t, J = 9.2 Hz, 1H), 5.97 (s, 2H), 5.04 (s, 1H), 3.48 (s, 3H), 3.41-3.38 (m, 1H), 2.49-2.47 (m, 2H), 2.16-2.05 (m, 4H), 1.82-1.74 (m, 4H) ppm

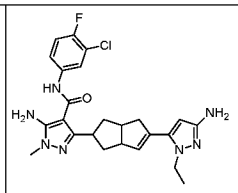
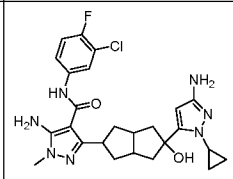
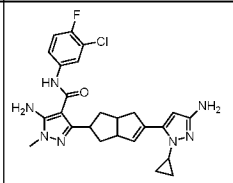
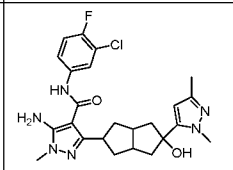
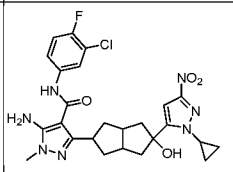
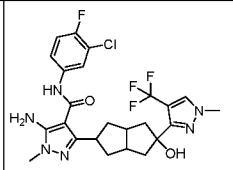
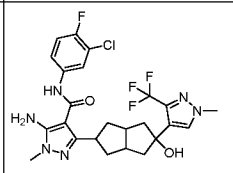
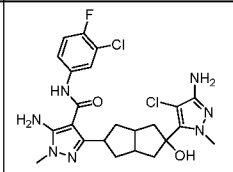
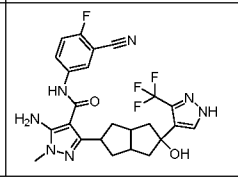
Example 171		461.2	^{1}H NMR (CD_3OD, 400 MHz): δ 7.81 (dd, J = 6.8, 2.4 Hz, 1H), 7.44-7.38 (m, 1H), 7.19 (t, J = 8.8 Hz, 1H), 3.56 (s, 3H), 3.47-3.40 (m, 1H), 2.80-2.70 (m, 2H), 2.50-2.30 (m, 4H), 2.06-1.80 (m, 4H) ppm
Example 172		475.3	^{1}H NMR (CD_3OD, 400 MHz): δ 7.81 (dd, J = 6.8, 2.4 Hz, 1H), 7.44-7.38 (m, 1H), 7.19 (t, J = 8.8 Hz, 1H), 4.20 (s, 3H), 3.56 (s, 3H), 3.50-3.40 (m, 1H), 2.80-2.70 (m, 2H), 2.45-2.53 (m, 2H), 2.33-2.40 (m, 2H),2.09-1.95 (m, 2H), 1.90-1.80 (m, 2H) ppm
Example 173		460.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.63 (s, 1H), 8.91 (s, 1H), 7.93 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.77 (s, 1H), 7.58 – 7.45 (m, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 6.00 (s, 2H), 5.43 (s, 1H), 3.50 (s, 3H), 3.47 – 3.39 (m, 1H), 2.70 – 2.54 (m, 2H), 2.36 – 2.10 (m, 4H), 1.91 – 1.69 (m, 4H) ppm
Example 174		506.2	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.94 (s, 1H), 8.41 (d, J = 1.2, 2H), 7.93 (dd, J = 6.8, 2.4 Hz, 1H), 7.52-7.51 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 5.41 (s, 1H), 3.49(s, 3H), 2.67-2.60 (m, 2H), 2.33-2.26 (m, 3H), 2.17-2.14 (m, 4H), 1.94-1.91 (m, 2H) ppm
Example 175		471.9	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (s, 1H), 8.79 (d, *J* = 4.8 Hz, 2H), 7.94-7.91 (m, 1H), 7.53-7.49 (m,1H), 7.38-7.32 (m, 2H), 5.98 (s, 2H), 5.05 (s, 1H), 3.51 (s, 3H), 3.46-3.35 (m, 1H), 2.67-2.62 (m, 2H), 2.65-2.38 (m, 2H), 2.18-2.12 (m, 2H), 1.92-1.84 (m, 2H), 1.74 (d,*J* = 12.4 Hz, 2H) ppm
Example 176		475.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz, 1H), 7.51-7.49 (m, 1H), 7.34 (t, *J* = 9.2 Hz, 1H), 5.99 (s, 2H), 5.76 (s, 1H), 3.49 (s, 3H), 3.43-3.38 (m, 1H), 2.54-2.50 (m, 2H), 2.47 (s, 3H), 2.32-2.27 (m, 2H), 2.17-2.15 (m, 2H), 1.87-1.82 (m, 2H), 1.75-1.73 (m, 2H) ppm
Example 177		475.2	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (s, 1H), 7.92 (dd, *J* = 7.2, 2.8 Hz, 1H), 7.53-7.49 (m, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 5.99 (s, 2H), 5.45 (s, 1H), 3.50 (s, 3H), 3.45-3.40 (m, 1H), 3.33-3.23 (m, 2H), 2.55 (s, 3H), 2.54-2.51 (m, 1H), 2.27-2.22 (m, 2H), 2.18-2.12 (m, 2H), 1.82-1.74 (m, 4H) ppm
Example 178		459.1	^{1}H NMR (CD3OD, 400 MHz): δ 8.19 (d, *J* = 2.8 Hz, 1H), 7.91 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.56-7.52 (m, , 1H), 7.24 (t, *J* = 9.2 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 3.80 (s, 3H), 3.65 – 3.54 (m, 1H), 2.97 – 2.85 (m, 2H), 2.51 – 2.40 (m, 2H), 2.29-2.24 (m, 2H), 2.14-2.11 (m, , 2H), 2.06 – 1.93 (m, 2H) ppm
Example 179		475.2	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (s, 1H), 7.92 (dd, *J* = 7.2, 2.8 Hz, 1H), 7.54-7.49 (m, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 6.00-5.98 (m, 2H), 5.88 (s, 1H), 3.50 (s, 3H), 3.45-3.40 (m, 1H), 2.62-2.61 (m, 2H), 2.31 (s, 3H), 2.29-2.15 (m, 4H), 1.92-1.89 (m, 2H), 1.81-1.79 (m, 2H) ppm

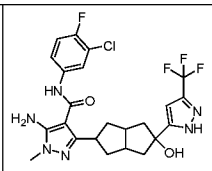
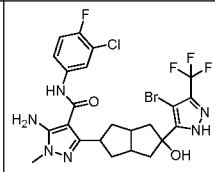
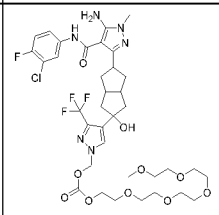
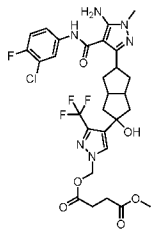
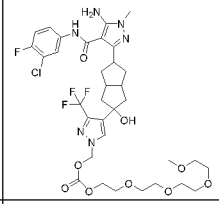
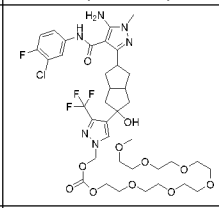
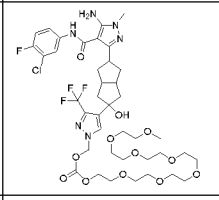
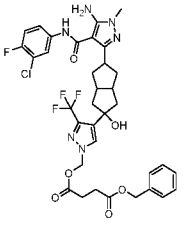
Example 180		474.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.93 (s, 1H), 7.94-7.91 (dd, J = 7.2, 2.8 Hz, 1H), 7.54-7.50 (m, 1H), 7.37-7.33 (t, J = 9.2 Hz, 1H), 6.15 (s, 1H), 6.00 (s, 2H), 5.45 (s, 1H), 3.50 (s, 3H), 3.46-3.39 (m, 3H), 2.58 (s, 2H), 2.18-1.85 (m, 7H), 1.81-1.78 (d, J = 11.6 Hz, 4H) ppm
Example 181		474.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (s, 1H), 7.97 (d, J = 1.2 Hz, 1H), 7.91 (dd, J = 7.0, 2.6 Hz, 1H), 7.53-7.48 (m, 1H), 7.35 (t, J = 9.0 Hz, 1H), 7.09 (d, J = 0.4 Hz, 1H) 5.97 (s, 2H), 4.58 (s, 1H), 3.48 (s, 3H), 3.44-3.56 (m, 1H), 2.87 (s, 2H), 2.46-2.41 (m, 2H), 2.17-2.07 (m, 2H), 1.92-1.82 (m, 2H), 1.72-1.60 (m, 2H), 1.48 (dd, J =13.0, 3.8 Hz, 2H) ppm
Example 182		484.1	^{1}H NMR (CD3OD, 400 MHz): δ 7.78 (dd, J = 6.8, 2.8 Hz, 1H), 7.44-7.40 (m, 1H), 7.19 (t, J = 8.8 Hz, 1H), 3.56-3.45 (4H, m), 3.35 (s, 2H), 3.01 (s, 3H), 2.68-2.60 (m, 2H), 2.37-2.29 (m, 4H), 1.66-1.45 (m, 4H) ppm
Example 183		474.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.90 (s, 1H), 7.92 (dd, J = 7.2, 2.8 Hz, 1H), 7.68 (s, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 6.00 (s, 2H), 4.42 (s, 1H), 3.49 (s, 3H), 3.41-3.39 (m, 1H), 2.50-2.48 (m, 2H), 2.31-2.26 (m, 2H), 2.16-2.13 (m, 2H), 2.04 (s, 3H), 1.78-1.73 (m, 4H) ppm
Example 184		474.3	^{1}H NMR (CD_3OD, 400 MHz): δ 7.81 (dd, J = 7.2, 2.4 Hz, 1H), 7.41-7.38 (m, 1H), 7.18 (t, J = 8.8 Hz, 1H), 3.55 (s, 3H), 3.43-3.39 (m, 1H), 2.66-2.64 (m, 2H), 2.49-2.44 (m, 2H), 2.33-2.30 (m, 5H), 1.93-1.83 (m, 4H) ppm
Example 185		521.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.97 (s, 1H), 7.92-7.89 (dd, J = 6.8, 2.8 Hz, 1H), 7.54-7.50 (m, 2H), 7.37-7.32 (t, J = 9.2 Hz, 2H), 5.97 (s, 2H), 3.50 (s, 4H), 2.81 (s, 2H), 2.59 (s, 1H), 2.38 (s, 2H), 2.19-2.13 (m, 3H), 2.11-2.01 (m, 4H), 1.96-1.88 (m, 1H), 1.72-1.66 (t, J = 12.4 Hz, 2H), 1.49-1.45 (m, 2H), 1.15-1.13 (m, 2H) ppm
Example 186		516.3	^{1}H NMR (CD3OD, 400 MHz): δ 7.80 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.19 (t, *J* = 9.2 Hz, 1H), 6.91 – 6.85 (m, 1H), 3.73 (s, 3H), 3.55 (s, 3H), 3.54 – 3.46 (m, 1H), 3.29 – 3.21 (m, 4H), 2.86 – 2.77 (m, 1H), 2.75 – 2.68 (m, 2H), 2.60 – 2.51 (m, 2H), 2.41 (s, 2H), 2.38 – 2.23 (m, 4H), 1.63 – 1.54 (m, 2H) ppm
Example 187		503.3	^{1}H NMR (CD3OD, 400 MHz): δ 7.79 (dd, J = 6.8, 2.8 Hz, 1H), 7.44 – 7.38 (m, 1H), 7.19 (t, J = 9.0 Hz, 1H), 4.62 (s, 2H), 3.55 (S, 3H), 3.55 – 3.47 (m, 1H), 3.11 (d, J = 12.8 Hz, 2H), 2.77 – 2.62 (m, 1H), 2.58 – 2.44 (m, 2H), 2.36 – 2.28 (m, 2H), 2.27 – 2.18 (m, 3H), 2.17 – 2.07 (m, 2H), 1.86 – 1.68 (m, 4H), 1.63 – 1.52 (m, 2H) ppm
Example 188		502.3	^{1}H NMR (CD3OD, 400 MHz): δ 7.79 (dd, J = 6.8, 2.8 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.19 (t, J = 9.2 Hz, 1H), 6.54 (s, 1H), 3.78 (s, 2H), 3.63 – 3.50 (m, 5H), 3.30 – 3.27 (m, 2H), 2.68 – 2.56 (m, 4H), 2.51 – 2.42 (m, 2H), 2.41 – 2.32 (m, 2H), 1.70 – 1.60 (m, 2H), 1.56 – 1.46 (m, 2H) ppm
Example 189		501.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.97 (s, 1H), 7.91 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 7.26 (s, 1H), 6.88 (s, 1H), 6.47 (s, 1H), 5.97 (s, 2H), 3.59 – 3.51 (m, 1H), 3.49 (s, 3H), 3.02 (d, *J* = 2.4 Hz, 2H), 2.67 – 2.57 (m, 1H), 2.46 – 2.29 (m, 3H), 2.24 – 2.13 (m, 4H), 2.12 – 2.04 (m, 2H), 2.03 – 1.93 (m, 1H), 1.51 – 1.41 (m, 2H), 1.19 – 1.09 (m, 2H) ppm

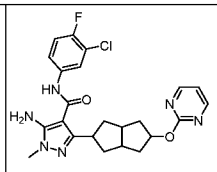
Example 190		471.3	^{1}H NMR (CD_3OD, 400 MHz): δ9.03-9.01 (m, 1H), 7.99-7.96 (m, 1H), 7.82 (dd, J = 6.8, 2.8 Hz, 1H), 7.70-7.67 (m, 1H), 7.44-7.40 (m, 1H), 7.19 (t, J = 9.2 Hz, 1H), 3.56 (s, 3H), 3.46-3.44 (m, 1H), 2.85-2.84 (m, 2H), 2.57-2.52 (m, 2H), 2.36-2.31 (m, 2H), 2.04-1.93 (m, 4H) ppm
Example 191		471.9	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (s, 1H), 8.88 (s, 1H), 8.87-8.52 (m, 1H), 8.87 (d, *J* = 2.8 Hz, 1H), 7.94-7.91 (dd, *J* = 6.8 Hz, 2.8 Hz,1H), 7.54-7.50 (m, 1H), 7.35 (t, *J* = 9.0 Hz, 1H), 5.99 (s, 2H), 5.28 (s, 1H), 3.51 (s, 3H), 3.49-3.38 (m, 1H), 2.68 (d, *J* = 5.6 Hz, 2H), 2.32-2.24 (m, 2H), 2.19-2.13 (m, 2H),1.98-1.90 (m, 2H), 1.77 (t, *J* = 11.0 Hz, 2H) ppm
Example 192		518.0	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.94 (s, 1H), 8.57 (t, *J* = 2.0 Hz, 1H), 7.92 (d, *J* = 4 Hz, 1H), 7.52 (t, *J* = 4.6 Hz,1H), 7.38-7.33 (m, 2H), 5.99 (s, 2H), 5.25 (s, 1H), 3.50 (s, 3H), 3.43-3.40 (m, 1H), 3.33-3.26 (m, 3H), 2.75 (d, *J* = 4.4 Hz, 2H), 2.26-2.23 (m, 2H), 2.21-2.15 (m, 2H), 1.96-1.91 (m, 2H), 1.72 (d, *J* = 13.2 Hz, 2H) ppm
Example 193		474.3	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (brs, 1H), 7.92 (dd, J = 7.0, 2.6 Hz, 1H), 7.71 (s, 1H), 7.55-7.48 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.00 (s, 2H), 5.54 (s, 1H), 3.93 (s, 3H), 3.50 (s, 3H), 3.49-3.39 (m, 1H), 2.60-2.53 (m, 2H), 2.40-2.30 (m, 2H), 2.21-2.11 (m, 2H), 1.86 (dd, J = 13.2, 3.2 Hz, 2H), 1.82-1.71 (m, 2H) ppm
Example 194		552.2	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.91 (brs, 1H), 7.92 (dd, J = 6.8, 2.8 Hz, 1H), 7.54-7.47 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.00 (brs, 2H), 5.12 (s, 1H),4.07 (s, 3H), 3.50 (s, 3H), 3.47-3.37 (m, 1H), 2.48-2.41 (m, 2H), 2.37-2.28 (m, 2H), 2.20-2.10 (m, 2H) 1.88-1.69 (m, 4H) ppm
Example 195		474.2	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.91 (brs, 1H), 7.92 (dd, J = 6.8, 2.8 Hz, 1H), 7.57 (s, 1H), 7.54-7.47 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.00 (brs, 2H), 5.08 (s, 1H),4.06 (s, 3H), 3.50 (s, 3H), 3.46-3.39 (m, 1H), 2.46-2.40 (m, 2H),2.21-2.09 (m, 4H), 1.85-1.69 (m, 4H) ppm
Example 196		486.9	^{1}H NMR (DMSO-d_6, 400 MHz): δ8.92 (s, 1H), 7.92 (dd, J = 6.8, 2.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 7.25 (s, 1H), 6.03 (s, 1H), 5.99 (s, 2H), 5.19 (s, 1H), 4.30-4.24 (m, 2H), 3.50 (s, 3H), 3.44-3.39 (m, 1H), 3.33-3.30 (m, 2H), 2.18-2.13 (m, 4H), 1.90-1.86 (m, 2H), 1.82-1.77 (m, 2H), 1.32 (t, J = 7.6 Hz, 3H) ppm
Example 197		440.2	^{1}H NMR (CD3OD, 400 MHz): δ 7.91-7.89 (dd, J = 7.2, 2.4 Hz, 1H), 7.62 (s, 1H), 7.54-7.50 (m, 1H), 7.33 (s, 1H), 7.24 (t, J = 8.8 Hz, 1H), 6.03 (d, J = 1.6 Hz, 1H), 3.77 (s, 1H), 3.44-3.42 (m, 2H), 3.01-2.83 (m, 2H), 2.64-2.60 (m, 1H), 2.42-2.26 (m, 2H), 2.16 (s, 3H), 1.75-1.63 (m, 2H) ppm
Example 198		484.8	^{1}H NMR (DMSO-d_6, 400 MHz):δ 8.93 (s, 1H), 8.11 (d, *J* = 1.2 Hz, 1H), 7.91 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.58 (d, J =0.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, *J* = 9.2 Hz, 1H), 6.35 (t, *J* = 2.0 Hz, 1H), 5.98 (d, *J* = 3.2 Hz, 2H), 5.41 (s, 1H), 5.34 (s, 1H), 5.15 (s, 1H), 3.50 (s, 3H), 3.47-3.38 (m, 1H), 2.50-2.52 (m, 2H), 2.15-2.08 (m, 4H), 1.79-1.65 (m, 4H) ppm

Example 199		486.9	^{1}H NMR (CD3OD, 400 MHz): δ 7.79 (dd, *J* = 6.4, 2.4 Hz, 1H),7.68 (d, *J* =1.2 Hz, 1H), 7.44-7.38 (m, 2H), 7.18 (t, *J* = 9.2 Hz, 1H), 6.27 (t, *J* = 2.0 Hz, 1H), 4.30 (dd, *J* =14.0, 7.2 Hz, 1H),3.54 (s, 3H), 3.41-3.33 (m, 1H), 2.65-2.62 (m, 2H), 2.31-2.18 (m, 2H), 1.97-1.91 (m, 1H), 1.85-1.76 (m, 2H), 1.71-1.65 (m, 2H), 1.49 (d, *J* = 3.6 Hz, 3H), 1.23-1.19 (m, 1H) ppm
Example 200		501.2	^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.93 (s, 1H), 7.93-7.91 (m, 1H), 7.53-7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 7.26 (d, J = 1.6 Hz, 1H), 6.00-5.99 (m, 3H), 5.22 (s, 1H), 5.09-5.06 (m, 1H), 3.50 (s, 3H), 3.44-3.40 (m, 1H), 2.51-2.50 (m, 2H), 2.18-2.14 (m, 4H), 1.91-1.87 (m, 2H), 1.83-1.75 (m, 2H), 1.35-1.33 (m, 6H) ppm
Example 201		518.9	^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.92 (s, 1H), 8.32 (s, 2H), 7.91 (dd, *J* = 6.8 Hz, 1.6 Hz, 1H), 7.53-7.49 (m, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 6.80 (t, J = 6.0 Hz, 1H), 5.98 (s, 2H), 4.56 (s, 1H), 3.49 (s, 3H), 3.42-3.38 (m, 1H), 2.51-2.44 (m, 4H), 2.15-2.10 (m, 2H), 1.84-1.79 (m, 2H), 1.68-1.60 (m, 2H), 1.42-1.38 (m, 2H) ppm
Example 202A		550.0	Isomer A: ^{1}H NMR (CD3OD-d$_4$, 400 MHz): δ 8.30 (s, 1H), 7.69 (dd, J = 6.8, 2.4 Hz, 1H), 7.32-7.29 (m, 1H), 7.06 (t, J = 9.2 Hz, 1H), 6.74 (s, 1H), 6.61 (s, 1H),6.47(s, 1H),4.51 (s, 2H), 3.49 (s, 2H), 3.47 (s, 1H),3.45 (s, 3H), 3.21-3.20 (m, 2H), 2.74-2.69 (m, 2H),2.23-2.19 (m, 2H),1.87-1.82 (m,2H),1.46-1.38 (m,4H) ppm
Example 202B		550.0	Isomer B: ^{1}H NMR (CD3OD-d$_4$, 400 MHz): δ 8.30 (s, 1H), 7.70 (dd, J = 6.8, 2.4 Hz, 1H), 7.33-7.29 (m, 1H), 7.06 (t, J = 9.2 Hz, 1H), 6.74 (s, 1H), 6.60 (s, 1H), 6.46 (s, 1H),4.51 (s, 2H), 3.45 (s, 2H), 3.43 (s, 3H), 3.38-3.32 (m, 1H), 3.21-3.20 (m, 2H), 2.55-2.50 (m, 2H),2.24-2.18 (m, 2H),1.93-1.88 (m,2H),1.65-1.57 (m,2H),1.49-1.44 (m,2H) ppm
Example 203A		570.2	Isomer A: ^{1}H NMR (DMSO-d6, 400 MHz): δ 8.94 (s, 1H), 7.92 – 7.90 (m, 1H), 7.53 – 7.49 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 5.75 (s, 1H), 5.48 (t, J = 6.0 Hz, 1H), 4.50 (s, 1H), 3.60 (s, 3H), 3.49 (s, 3H), 3.46 – 3.37 (m, 1H), 2.98 (d, J = 6.0 Hz, 2H), 2.47 – 2.42 (m, 2H), 2.17 – 2.12 (m, 2H), 1.89 – 1.84 (m, 2H), 1.73 – 1.65 (m, 2H), 1.45 (dd, J = 12.8, 4.0 Hz, 2H) ppm
Example 203B		570.0	Isomer B: ^{1}H NMR (DMSO-d6, 400 MHz): δ 8.95 (s, 1H), 7.92 – 7.90 (m, 1H), 7.54 – 7.50 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.98 (s, 2H), 5.73 (s, 1H), 5.53 (t, J = 6.0 Hz, 1H), 4.35 (s, 1H), 3.60 (s, 3H), 3.57 – 3.51 (m, 1H), 3.48 (s, 3H), 3.06 (d, J = 6.0 Hz, 2H), 2.71 – 2.61 (m, 2H), 2.20 – 2.09 (m, 2H), 1.84 – 1.79 (m, 2H), 1.44 – 1.34 (m, 4H) ppm
Example 20		532.1	^{1}H-NMR (DMSO-d$_6$, 400 MHz): δ 8.93 (s, 1H), 7.93-7.90 (m, 1H), 7.53-7.49 (m, 1 H), 7.34 (t, *J* = 9.2 Hz, 1H), 6.90 (s, 1H), 5.98 (s, 2H), 5.58 (s, 1 H), 4.44-4.38 (m, 2H), 3.49 (s, 3H), 3.47-3.43 (m, 1H), 2.55-2.49 (m, 2H), 2.25-2.14 (m, 4H), 1.94-1.90 (m, 2H), 1.83-1.75 (m, 2H), 1.41-1.37 (t, *J* = 7.0 Hz, 3H) ppm
Example 205A		515.0	Isomer A: ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.93 (s, 1H), 7.89 (dd, J = 6.8, 2.4 Hz, 1H), 7.82 (s, 1H), 7.53-7.49 (m, 1H),7.32 (t, J = 9.2 Hz, 1H), 6.35 (s, 1H), 6.01(s, 2H),5.97 (s, 2H), 5.40(s, 1H), 4.52 (s, 1H),3.57-3.51 (m, 1H), 3.48 (s, 3H), 3.21(s,2H), 2.64(s,2H), 2.11(t,J = 11.6 Hz, 2H), 1.78-1.73 (m, 2H),1.38-1.29 (m, 4H) ppm

Example 205B		515.0	Isomer B: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (s, 1H), 7.90 (dd, J = 6.8, 2.4 Hz, 1H), 7.82 (s, 1H), 7.53-7.49 (m, 1H),7.32 (t, J = 9.2 Hz, 1H), 6.41 (s, 1H),6.02(s, 2H),5.98 (s, 2H), 5.43(s, 1H), 4.82 (s, 1H), 3.49 (s, 3H),3.46-3.39 (m, 1H),3.18(s,2H),2.43(s,2H),2.16-2.11(m,2H), 1.84-1.78 (m, 2H),1.66-1.58 (m, 2H),1.40-1.36 (m, 2H) ppm
Example 206		546.2	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (s, 1H), 7.93-7.90 (m, 1H), 7.53-7.49 (m, 1H), 7.35 (t, J = 9.0 Hz, 1H), 6.87 (s, 1H), 5.99 (s, 2H), 5.62 (s, 1H), 5.24-5.22 (m, 1H), 3.49 (s, 3H), 3.44-3.31 (m, 1H), 2.55-2.49 (m, 2H), 2.24-2.16 (m, 4 H), 1.92 (d, J = 11.2 Hz, 2H), 1.81-1.78 (m, 2H), 1.40 (d, J = 6.8 Hz, 6H) ppm
Example 207		541.9	^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.93 (s, 1H), 7.93 – 7.91 (m, 1H), 7.54 – 7.50 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 6.00 (s, 2H), 5.29 (s, 1H), 4.17 (s, 3H), 3.50 (s, 3H), 3.46 – 3.38 (m, 1H), 2.62 – 2.53 (m, 2H), 2.25 – 2.12 (m, 4H), 1.88 – 1.75 (m, 4H) ppm
Example 208		507.1	^{1}H NMR (MeOD-d4, 400 MHz) δ 7.71 (dd, J = 6.8, 2.8 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.19 (s, 1H), 7.10 (t, J = 9.2 Hz, 1H), 3.92 (s, 3H), 3.46 (s, 3H), 3.39 – 3.29 (m, 1H), 2.72 – 2.60 (m, 2H), 2.46 (dd, J = 13.6, 8.8 Hz, 2H), 2.27 – 2.18 (m, 2H), 2.02 (d, J = 12.8 Hz, 2H), 1.95 – 1.83 (m, 2H) ppm
Example 209		491.0	^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.71 (dd, J = 6.8, 2.8 Hz, 1H), 7.38 – 7.27 (m, 1H), 7.16 – 7.05 (m, 2H), 3.84 (s, 3H), 3.46 (s, 3H), 3.40 – 3.30 (m, 1H), 2.65 – 2.53 (m, 2H), 2.38 – 2.27 (m, 2H), 2.27 – 2.17 (m, 2H), 1.98 – 1.88 (m, 2H), 1.88 – 1.76 (m, 2H) ppm
Example 210		502.9	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.91 (s, 1H), 7.93-7.91 (m, 1H), 7.53-7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.97 (s, 2H), 5.20 (s, 1H), 5.04 (s, 1H), 4.36 (s, 2H), 4.03-3.98 (m, 2H), 3.49 (s, 3H), 3.44-3.38 (m, 1H), 2.51-2.49 (m, 2H), 2.16-2.05 (m, 4H), 1.82-1.76 (m, 4H), 1.23 (t, J = 7.0 Hz, 3H) ppm
Example 211		517.0	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (s, 1H), 7.93-7.91 (m, 1H), 7.53-7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.97 (s,2H), 5.17 (s, 1H), 5.06 (s, 1H), 4.85-4.79 (m, 1H), 4.41-4.34 (m, 2H), 3.49 (s, 3H), 3.46-3.30 (m, 1H), 2.51-2.49 (m, 2H), 2.15-2.03 (m, 4H), 1.83-1.74 (m, 4H), 1.25 (d, J = 6.4 Hz, 6H) ppm
Example 212		527.1	^{1}H NMR (MeOH-d_4, 400 MHz): δ 7.88-7.62 (m, 2H), 7.33-7.29 (m, 1H), 7.09 (t, J = 8.8 Hz, 1H), 3.46 (s, 3H), 3.36-3.27 (m, 1H), 2.63-2.61 (m, 2H), 2.44-2.17 (m, 4H), 1.85-1.84 (m, 4H) ppm
Example 213		518.9	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (s, 1H), 8.32 (d, J = 0.8 Hz, 2H), 7.91 (dd, J1 = 6.8 Hz, 2.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 6.90 (t, J = 6.0 Hz, 1H), 5.97 (s, 2H), 4.37 (s, 1H), 3.56-3.51 (m, 1H), 3.48 (s, 3H), 3.36-3.31 (m, 2H), 2.68-2.63 (m, 2H), 2.16-2.11 (m, 2H), 1.78-1.73 (m, 2H), 1.40-1.32 (m, 4H) ppm

Example 214		484.9	^{1}H NMR (DMSO-d_6, 400 MHz): δ: 9.01 (s, 1H), 7.93-7.91 (m, 1H), 7.55-7.51 (m, 1H), 7.35 (t, *J* = 9.0 Hz,1H), 5.96 (s, 2H), 5.78 (s, 1H), 5.35 (s, 1H), 4.45 (s, 2H), 3.94-3.89 (m, 2H), 3.46-3.42 (m, 4H), 2.79-2.66 (m, 2H), 2.39-2.27 (m, 3H), 2.23-2.19 (m, 1H), 1.50-1.40 (m, 2H), 1.23-1.61 (m, 3H) ppm
Example 215		514.9	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (s, 1H), 7.93-7.91 (dd, *J* = 2.8 Hz, 6.8 Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, *J* = 9.2 Hz, 1H), 5.99 (s, 2H), 5.26 (s, 1H), 5.09 (s, 1H), 4.37 (s, 2H), 3.94-3.90 (m, 1H), 3.49 (s, 3H), 3.46-3.39 (m, 1H), 2.51-2.49 (m, 2H), 2.20-2.07 (m, 4H), 1.91-1.82 (m, 2H), 1.79-1.74 (m, 2H), 1.01-0.97 (m, 2H), 0.77-0.72 (m, 2H) ppm
Example 216		496.9	^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.02 (s, 1H), 7.93-7.93 (dd, *J* = 7.2 Hz, 2.8 Hz, 1H), 7.55-7.51 (m, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 6.16 (s, 1H), 5.97 (s, 2H), 5.36 (s, 1H), 4.48 (s, 2H), 3.49 (s, 4H), 3.47-3.36 (m, 1H), 2.83-2.66 (m, 2H), 2.51-2.49 (m, 1H), 2.33-2.25 (m, 2H), 2.24-2.19 (m, 1H), 2.15-2.13 (m, 2H), 0.93-0.89 (m, 4H) ppm
Example 217		487.2	^{1}H NMR (CD_3OD, 400 MHz): δ 7.71 (dd , *J* = 6.4, 2.4 Hz, 1H), 7.32-7.29 (m, 1H), 7.09 (t, *J* = 9.2 Hz, 1H), 5.87 (s, 1H), 3.79 (s, 3H), 3.47 (s, 3H), 3.40-3.33 (m, 1H), 2.52 (s, 2H), 2.29-2.20 (m, 4H), 2.05 (s, 3H), 1.86-1.81 (m, 2H), 1.78-1.69 (m, 2H) ppm
Example 218		544.9	^{1}H NMR (DMSO-$d_6$400 MHz): δ 8.93 (s, 1H), 7.93-7.90 (m, 1H), 7.53-7.49 (m, 1H), 7.34 (t, *J* = 9.2 Hz, 1H), 6.95 (s, 1H), 5.99 (s, 2H), 5.62 (s, 1H), 4.40-4.36 (m, 1H), 3.49 (s, 3H), 3.46-3.41 (m, 1H), 2.53-2.50 (m, 2H), 2.34-2.29 (m, 2H), 2.19-2.16 (m, 2H), 2.00 (d, *J* = 11.2 Hz, 2H), 1.84-1.76 (m, 2H),1.24-1.20 (m, 2H), 1.09-1.04 (m, 2H) ppm
Example 219		540.8	^{1}H NMR (MeOH-d_4, 400 MHz): δ 7.80 (s, 1H), 7.71 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.62 (s, 1H), 7.33-7.29 (m, 1H), 7.09 (t, *J* = 9.2 Hz, 1H), 3.74 (s, 3H), 3.46 (s, 3H), 3.35-3.32 (m, 1H), 2.58-2.56 (m, 2H), 2.39-2.34 (m, 2H), 2.22-2.18 (m, 2H), 1.82-1.76 (m, 4H) ppm
Example 220		541.0	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.93 – 7.91 (m, 1H), 7.78 (s, 1H), 7.52 – 7.50 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.99 (s, 2H), 4.81 (s, 1H), 3.83 (s, 3H), 3.50 (s, 3H), 3.45 – 3.39 (m, 1H), 2.54 – 2.46 (m, 2H),2.20 – 2.04 (m, 4H), 1.83 – 1.75 (m, 4H) ppm
Example 221		523.4 $[M + 2]^+$	^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (s, 1H), 7.93-7.91 (m, 1H), 7.53-7.49 (m, 1H), 7.35 (t, *J = 9.0 Hz, 1H*), 5.97 (s, 2H), 5.19 (s, 1H), 4.55 (d, *J* = 9.0 Hz, 2H), 3.71 (s, 3H), 3.49 (s, 3H), 3.34-3.37 (m, 1H), 2.59-2.50 (m, 2H), 2.34-2.28 (m, 2H), 2.17-2.12 (m, 2H), 1.96 (d, *J* = 12.8 Hz, 2H), 1.92-1.84 (m, 2H) ppm
Example 222		518.0	^{1}H NMR (400 MHz, MeOD-d4): δ 8.03 (dd, J = 2.8, 5.6 Hz, 1H), 7.82-7.78 (m, 1H), 7.72 (s, 1H), 7.31 (t, J = 8.8 Hz, 1H), 3.55 (s, 3H), 3.48-3.39 (m, 1H), 2.65-2.61 (m, 2H), 2.34-2.28 (m, 4H), 1.96-1.84 (m, 4H) ppm

Example 223		527.0	^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.37 (s, 1H), 8.92 (s, 1H), 7.93 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.53-7.49 (m, 1H), 7.35 (t, *J* = 9.2, 1H), 6.50 (s, 1H), 6.00 (s, 2H), 5.32 (s, 1H), 3.49 (s, 3H), 3.42-3.34 (m, 1H), 2.57-2.52 (m, 2H), 2.16-2.10 (m, 4H), 1.86-1.78 (m, 4H) ppm
Example 224		606.8 [M + 2]$^+$	^{1}H NMR (DMSO-d6, 400 MHz): δ 13.65 (s, 1H), 8.94 (s, 1H), 7.93 (dd, J = 7.2, 2.8 Hz, 1H), 7.54-7.50 (m, 1H), 7.35 (t, J = 8.8, 1H), 5.99 (s, 2H), 5.46 (s, 1H), 3.49 (s, 3H), 3.45-3.39 (m, 1H), 2.67-2.66 (m, 2H), 2.34-2.29 (m, 2H), 2.16-2.13 (m, 2H), 1.95 -1.89 (m, 4H) ppm
Example 225		791.2	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.94 (s, 1H), 8.00 (s, 1H), 7.91 (dd, J = 6.8, 2.8Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, J = 9.2, 1H), 6.06 (s, 2H), 5.97 (s, 2H), 4.95 (s, 1H), 4.24-4.22 (m, 2H), 3.62-3.60 (m, 2H), 3.52-3.51 (m, 13H), 3.50-3.47 (m, 3H), 3.22 (s, 3H), 2.51-2.50 (m, 2H), 2.15-2.03 (m, 4H), 1.85-1.79 (m, 4H) ppm
Example 226		671.2	^{1}H NMR (DMSO-*d6* , 400 MHz): δ 8.95 (s, 1H), 7.97 (s, 1H), 7.92 (dd, *J* = 2.4, 2.8Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, *J* = 8.8Hz, 1H), 6.03 (s, 2H), 5.98 (s, 2H), 4.94 (s, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 3.49-3.33 (m, 1H), 2.67-2.53 (m, 6H), 2.15-2.03 (m, 4H), 1.85-1.79 (m, 4H) ppm
Example 227		835.3	^{1}H NMR (DMSO-d6, 400 MHz): δ 8.95 (s, 1H), 8.00 (s, 1H), 7.92 (dd, J = 6.4, 2.0Hz, 1H), 7.52-7.50 (m, 1H), 7.34 (t, J = 9.6, 1H), 6.07 (s, 2H), 5.98 (s, 2H), 4.96 (s, 1H), 4.23-4.22 (m, 2H), 3.62-3.61 (m, 2H), 3.57-3.39 (m, 20H), 3.22 (s, 3H), 2.67-2.50 (m, 2H), 2.08-2.03 (m, 4H), 1.85-1.75 (m, 4H) ppm
Example 228		879.3	^{1}H NMR (DMSO-*d6* , 400 MHz): δ 8.93 (s, 1H), 8.00 (s, 1H), 7.92 (dd, *J* = 2.4, 2.0Hz, 1H), 7.53-7.49 (m, 1H), 7.34 (t, *J* = 8.8Hz, 1H), 6.07 (s, 2H), 5.97 (s, 2H), 4.94 (s, 1H), 4.24-4.22 (m, 2H), 3.62-3.60 (m, 2H), 3.54-3.49 (m, 21H), 3.42-3.38 (m, 3H), 3.22 (s, 3H), 2.50-2.49 (m, 2H), 2.15-2.03 (m, 4H), 1.85-1.75 (m, 4H) ppm
Example 229		923.3	^{1}H NMR (DMSO-*d6* , 400 MHz): δ 8.94 (s, 1H), 8.00 (s, 1H), 7.92 (dd, *J* = 2.4, 2.4Hz, 1H), 7.52-7.49 (m, 1H), 7.34 (t, *J* = 8.8Hz, 1H), 6.07 (s, 2H), 5.98 (s, 2H), 4.95 (s, 1H), 4.24-4.22 (m, 2H), 3.62-3.60 (m, 2H), 3.52-3.49 (m, 25H), 3.44-3.37 (m, 3H), 3.22 (s, 3H), 2.50-2.49 (m, 2H), 2.15-2.03 (m, 4H), 1.85-1.75 (m, 4H) ppm
Example 230		747.2	^{1}H NMR (DMSO-*d6* , 400 MHz): δ 8.95 (s, 1H), 7.96 (s, 1H), 7.92 (dd, *J* = 2.8, 2.8Hz, 1H), 7.53-7.49 (m, 1H), 7.38-7.31 (m, 6H), 6.03 (s, 2H), 5.98 (s, 2H), 5.07 (s, 2H), 4.94 (s, 1H), 3.49 (s, 3H), 3.42-3.36 (m, 1H), 2.67-2.64 (m, 4H), 2.51-2.49 (m, 2H), 2.16-2.02 (m, 4H), 1.88-1.77 (m, 4H) ppm

Example 231		471.2	^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.51 (d, *J* = 4.7 Hz, 2H), 7.74 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.53 (d, *J* = 3.1 Hz, 1H), 7.32 (ddd, *J* = 9.0, 4.1, 2.6 Hz, 1H), 7.12 (q, *J* = 8.4 Hz, 1H), 6.92 (t, *J* = 4.7 Hz, 1H), 5.44 (p, *J* = 5.8 Hz, 1H), 5.25 (s, 1H), 3.62 (s, 3H), 3.21 (dq, *J* = 11.7, 5.9 Hz, 1H), 3.08 (s, 1H), 2.66 (d, *J* = 27.3 Hz, 2H), 2.42 (dd, *J* = 12.3, 6.5 Hz, 2H), 2.33 (ddd, *J* = 13.5, 7.6, 5.5 Hz, 2H), 2.12 – 1.94 (m, 2H), 1.87 (dt, *J* = 13.8, 5.1 Hz, 2H) ppm

VI. Biological Data

Assay Measuring Activity of Test Compounds on Viral Production from HepAD38 Cells

HepAD38 cells grown in a T-150 flask (Corning, cat#: 430825) with Growth Medium (DMEM/F12 (1:1) (Hyclone, cat#: SH30023.02), 1X Pen/Strep (Invitrogen, cat#: 15140-122), 10% FBS (Tissue Culture Biologics, cat#: 101), 250 µg/mL G418 (Alfa Aesar, cat#: J62671), 1µg/mL Tetracycline (Teknova, cat#: T3320)) were detached with 0.25% trypsin-EDTA (Invitrogen, cat#: 25200-056). Tetracycline-free treatment medium (15 mL DMEM/F12 (1:1), 1x Pen/step, with 2% FBS, Tet-system approved (Clontech, cat#: 631106) were then added to mix, transferred into a 50 ml conical tube (Falcon, cat#: 21008-918,) and spun at 1300 rpm for 5 min. Pelleted cells were then re-suspended/washed with 50 mL of 1X DPBS (Invitrogen, cat#: 14190-136) 2 times and 50 mL treatment medium twice. HepAD38 cells were then re-suspended with 10 mL of treatment medium, syringed and counted. Wells of 96-well clear bottom TC plate (Corning, cat#: 3904,) were seeded at 50,000 cells/well in 180 µL of treatment medium, and 20 µL of either 10% DMSO (Sigma, cat#: D4540) as controls or a 10X solution of test compounds in 10% DMSO in treatment media was added for a final compound concentration starting at 10 µM, and plates were incubated in 5% CO_2 incubator at 37°C for 5 days.

Subsequently viral load production was assayed by quantitative PCR (qPCR) of the HBV core sequence. PCR reaction mixture containing forward primers HBV-f 5'-CTGTGCCTTGGGTGGCTTT-3' (IDT DNA), Reverse primers HBV-r 5'-AAGGAAAGAAGTCAGAAGGCAAAA-3' (IDT DNA), Fluorescent TaqMan™ Probes HBV-probe 5′-FAM/AGCTCCAAA/ZEN/TTCTTTATAAGGGTCGATGTC/3IABkFQ -3′ (IDT DNA), 10 µL/well of PerfeCTa® qPCR ToughMix® (Quanta Biosciences, Cat#: 95114-05K), and 6 µL/well of DEPC water (Alfa Aesar, cat#: J62087) was prepared. Four µL of

supernatant was added to 16 µL of the reaction mixture in a qPCR plate (Applied Biosytems, Cat#: 4309849), sealed with a film (Applied Biosystems, Cat#: 4311971), centrifuged for a few seconds, and subsequently run on an Applied Biosystems VIIA7. The PCR mixture was incubated at 45°C for 5 min, then 95 °C for 10 min, followed by 40 cycles of 10 seconds at 95 °C and 20 seconds at 60°C. Viral load was quantified against known HBV DNA standards by using ViiA™ 7 Software. Viral load in the supernatant from wells with treated cells were compared against viral load in supernatant from DMSO control wells (≥ 3 per plate). Cell viability assay was performed with CellTiter-Glo Luminescent Cell Viability Assay (Promega, cat#: G7573) with modification. Mixed appropriate amount of CellTiter-Glo (CTG) 1X DPBS in a 1:1 ratio, added 100 uL of the mixture to each well followed completely removal of all supernatant in each well without touching cell surface. Incubated the plate at room temperature for 10 min on an orbital shaker, and then read the plate with a plate reader (TECAN M1000 or Envision). EC_{50} or CC_{50} values were calculated through curve-fitting of the four-parameter nonlinear-logistic-regression model (GraphPad Prism or Dotmatics). CC_{50} values were all >10 µM.

Table 1 gives the viral load lowering EC_{50} values for exemplified compounds of the invention grouped in the following ranges: **A** indicates $EC_{50} \leq 0.010$ µM; **B** indicates EC_{50} of > 0.010 and ≤ 0.050 µM; **C** indicates EC_{50} of > 0.050 and ≤ 0.500 µM; and **D** indicates > 0.500 µM

Table 1. Viral load lowering for exemplified compounds of the invention

Example #	**Activity**
Example 1	A
Example 2	A
Example 3	B
Example 4	B
Example 5	A
Example 6	A
Example 7	A
Example 8	A
Example 9	A
Example 10	A

Example 11	B
Example 12	B
Example 13	B
Example 14	A
Example 15	A
Example 16	A
Example 17	A
Example 18	A
Example 19	A
Example 20	A
Example 21	A
Example 22	A
Example 23	A
Example 24	A
Example 25	A
Example 26	A
Example 27	B
Example 28	B
Example 29	B
Example 30	B
Example 31	B
Example 32	B
Example 33	B
Example 34	B
Example 35	B
Example 36	B
Example 37	A
Example 38	A
Example 39	A
Example 40	A
Example 41	A
Example 42	A
Example 43	A
Example 44	A
Example 45	A
Example 46	A
Example 47	A
Example 48	A
Example 49	A
Example 50	A
Example 51	B
Example 52	A
Example 53	A

Example 54	A
Example 55	A
Example 56	A
Example 57	B
Example 58	B
Example 59	A
Example 60	A
Example 61	A
Example 62	A
Example 63	B
Example 64	A
Example 65	A
Example 66	B
Example 67	A
Example 68	A
Example 69	A
Example 70	B
Example 71	B
Example 72	A
Example 73	B
Example 74	A
Example 75	B
Example 76	B
Example 77	C
Example 78	C
Example 79	C
Example 80	C
Example 81	C
Example 82	C
Example 83	A
Example 84	C
Example 85	A
Example 86	A
Example 87	A
Example 88	A
Example 89	A
Example 90	A
Example 91	B
Example 92	B
Example 93	B
Example 94	A
Example 95	A
Example 96	A

Example 97	B
Example 98	B
Example 99	B
Example 100	B
Example 101	B
Example 102	B
Example 103	B
Example 104	B
Example 105	C
Example 106	C
Example 107	A
Example 108	B
Example 109	B
Example 110	B
Example 111	A
Example 112	A
Example 113	B
Example 114	C
Example 116	C
Example 117	C
Example 118	C
Example 119	B
Example 120	C
Example 121	B
Example 122	B
Example 123	C
Example 124	B
Example 125	B
Example 126	C
Example 127	C
Example 128	C
Example 129	C
Example 130	B
Example 131	B
Example 132	B
Example 133	C
Example 134	C
Example 135	C
Example 136	C
Example 146	A
Example 147	B
Example 148	B

Example 149	B
Example 150	A
Example 151	C
Example 152	B
Example 153	A
Example 154	A
Compd. 4-2	A
Example 155	A
Example 156	A
Compd. 6-1	B
Cpmpd. 6-2	B
Example 157	A
Example 158	A
Example 159	B
Example 160	A
Example 161	A
Example 162	A
Example 163	B
Example 164	B
Exmaple 165	A
Example 166	B
Example 167	B
Example 168	A
Example 169	A
Example 170	A
Example 171	D
Example 172	B
Example 173	B
Example 174	A
Example 175	A
Example 176	B
Example 177	A
Example 178	A
Example 179	A
Example 180	A
Example 181	A
Example 182	D
Example 183	A

Example 184	A
Example 185	B
Example 186	C
Example 187	C
Example 188	D
Example 189	B
Example 190	A
Example 191	A
Example 192	B
Example 193	A
Example 194	A
Example 195	A
Example 196	A
Example 197	A
Example 198	A
Example 199	A
Example 200	A
Example 201	A
Example 202A	B
Example 202B	C
Example 203A	A
Example 203B	B
Example 20	A
Example 205A	A
Example 205B	C
Example 206	A
Example 207	A
Example 208	A
Example 209	A
Example 210	A
Example 211	A
Example 212	A
Example 213	B
Example 214	A
Example 215	A
Example 216	B
Example 217	A
Example 218	A

Example 219	A
Example 220	A
Example 221	A
Example 222	A
Example 223	A
Example 224	B
Example 225	A
Example 226	A
Example 227	A
Example 228	A
Example 229	A
Example 230	A
Example 231	B

Table 2 gives the viral load lowering EC_{50} values for exemplified compounds of the invention grouped in the following ranges: **A** indicates EC_{50} < 0.1 μM; **B** indicates EC_{50} of ≥ 0.1 to <1.0 μM; **C** indicates EC_{50} of ≥1.0 to <10 μM.

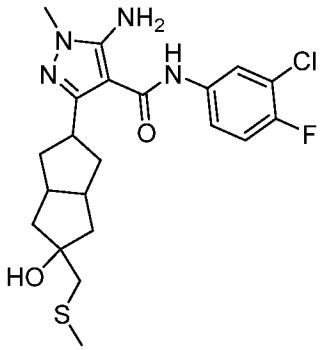
Table 2. Viral load lowering for exemplified compounds of the invention

	VL HepAD38 EC_{50} range
Example 137	A
Example 138	A
Example 139	A
Example 140	A
Example 141	A
Example 142	A
Example 143	A
Example 144	A

Example 145	A

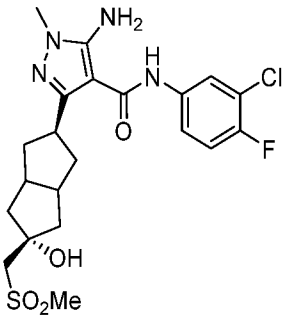
Stereochemistry of Example

AIA-225

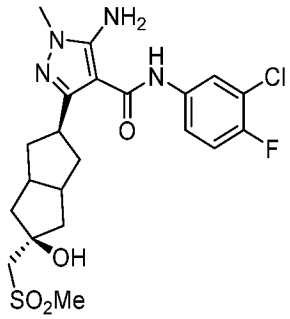


5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(methylthiomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(hexahydro-1'H-spiro[oxirane-2,2'-pentalene]-5'-yl)-1-methyl-1H-pyrazole-4-carboxamide (200 mg, 0.495 mmol) in THF/H_2O (6 mL/2 mL) was added NaSMe (138.6 mg, 1.98 mmol). The mixture was stirred at rt overnight. The solvent was removed and the crude product purified by silica gel column chromatography using 3:1 petroleum ether/ethyl acetate to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(methylthiomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (100 mg, 44.7%) as a yellow solid. MS (m/z): Calcd.: 452.1, Found: 452.2 $[M+1]^+$.

AIA-227-1, AIA-227-2



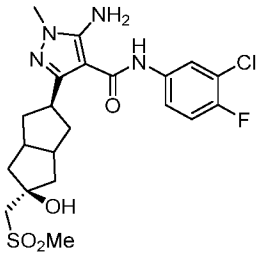
CP-AIA-227-1



CP-AIA-227-2

5-Amino-N-(3-chloro-4-fluorophenyl)-3-((2r,5r)-5-hydroxy-5-(methylsulfonylmethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (AIA-227-1) and 5-Amino-N-(3-chloro-4-fluorophenyl)-3-((2s,5s)-5-hydroxy-5-(methylsulfonylmethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (AIA-227-2). To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(methylthiomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (100 mg, 0.22 mmol) in DCM (5 mL) was added m-CPBA (114.8 mg, 0.66 mmol). The mixture was stirred at rt overnight. The solvent was removed, and the crude material purified by silica gel column chromatography using 3:1 (*v/v*) DCM/MeOH to afford AIA-227 (40 mg, 37.3%) as a white solid. MS (*m/z*): Calcd.: 484.1, Found: 484.3 $[M+1]^+$. AIA-227 was separated by SFC to give AIA-227-1 (4 mg) as a white solid and AIA-227-2 (4 mg) as a white solid. AIA-227-1: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.54-7.50 (m, 1H), 7.35 (t, J = 9.2 Hz, 1H), 5.97 (s, 2H), 4.79 (s, 1H), 3.59-3.53 (m, 1H), 3.49 (s, 3H), 3.35 (s, 2H), 2.97 (s, 3H), 2.67-2.60 (m, 2H), 2.18-2.12 (m, 2H), 2.07-2.02 (m, 2H), 1.45-1.36 (m, 4H) ppm. AIA-227-2: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.91 (dd, J = 2.8, 2.4 Hz, 1H), 7.53 - 7.49 (m, 1H), 7.34 (t, J = 9.2 Hz, 1H), 5.97 (s, 2H), 4.87 (s, 1H), 3.49 (s, 3H), 3.43 - 3.35 (m, 1H), 3.25 (s, 2H), 2.97 (s, 3H), 2.49 (s, 2H), 2.15 - 2.09 (m, 2H), 2.02 - 1.97 (m, 2H), 1.73 - 1.60 (m, 4H) ppm.

AIA-227-2



Alternative synthesis of 5-amino-N-(3-chloro-4-fluorophenyl)-3-((2s,5s)-5-hydroxy-5-(methylsulfonylmethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of dimethylsulfone (77.0 g, 818.7 mmol) in THF (800 mL) was added n-BuLi (327.5 mL, 818.7 mmol, 2.5M) dropwise at -78 °C. The resulting solution was allowed to warm to -20 °C and stirred for 1 hr. The reaction was cooled to -78 °C, and a solution of AIA-002 (40.0 g, 102.3 mmol) in anhydrous tetrahydrofuran (1200 mL) was added over 2 hr. The mixture was warmed to rt and stirred for an additional 4 hr. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (200 mL). The solvent was removed, followed by dilution with water, extraction with ethyl acetate (3 x 200 mL), drying over Na_2SO_4, filtration, and concentration to give the crude product. The crude product was purified by column chromatography using 0-5% (*v/v*) methanol in DCM and basic prep-HPLC to afford 5-amino-N-(3-chloro-4-fluorophenyl)-3-((2s,5s)-5-hydroxy-5-(methylsulfonylmethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide (26.0 g, 52.4%) as a white solid. MS (*m/z*): Calcd.: 484.1, Found: 485.2 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.92 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.35 (t, *J* = 8.8 Hz, 1H), 5.98 (s, 2H), 4.88 (s, 1H), 3.49 (s, 3H), 3.42 - 3.37 (m, 1H), 3.25 (s, 2H), 2.97 (s, 3H), 2.15 - 2.10 (m, 2H), 2.03 - 1.97 (m, 2H), 1.73 - 1.60 (m, 4H) ppm.

A crystal with size of 0.08 x 0.10 x 0.20mm of compound AIA-227-2 was obtained from EtOH after 20 days of volatilization and was used for X-ray diffraction data collection. The data were collected on a Bruker SMART CCD area-detector diffractometer at room temperature using CuKα radiation by ω/φ scan mode. 10846 reflections were collected, of which 3754 reflections were unique (Rint = 0.0507).

The crystal belongs to monoclinic crystal system, with a space group $P2_1/c$. The unit cell parameters were as follows: a= 6.6143(3)，b=14.0381(8)，c=23.6870(14)Å，$\alpha=\gamma$=90.0°，β=97.702(3) °， V= 2179.5(2)Å^3， Z=4.

The structure was solved by direct methods and all of the non-H atoms were refined against F^2 by full-matrix least-squares methods using the SHELXTL program. All H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms. Multi-scans absorption correction method was used, and the maximum and minimum transmission parameters were 0.7531 and 0.6017, respectively. The final R, wR_2, GOF are 0.0457, 0.1293 and 1.024, respectively.

There is one $C_{21}H_{26}FClN_4O_4S$ molecule in the asymmetric unit and hydrogen bonds can be found between them, which play an important role for the stable packing of the crystal structure.

The ORTEP plot for compound AIA-227-2 is present in Fig. 1. The relative stereochemistry scheme of compound AIA-227-2 is shown in Fig. 2. The depictions of stereochemistry in the chemical structures of related examples are based on this assignment.

INCORPORATION BY REFERENCE

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

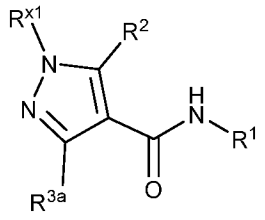
EQUIVALENTS

While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure.

CLAIMS:

1. A compound of Formula I



Formula I

, or a pharmaceutically acceptable salt thereof, wherein:

L is C_{1-4}alkylene or haloC_{1-4}alkylene;

L^1 is a bond, C_{1-6}alkylene, O, NR^c, C(O), C(O)O, C(O)NR^c, $S(O)_t$ or $S(O)_tNR^c$;

X^3 is NR^4 or CR^4R^8;

X^4 is O or S;

X^5 is O, S or NR^0;

R^a, R^b and R^c are independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^d is hydrogen, OH, C_{1-6} alkyl or C_{1-6} alkoxy;

R^{x1} is hydrogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, haloC_{1-4} alkyl, or C_{3-6} monocycloalkyl; or R^{x1} and R^2 together form a $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2O-$, $-CH_2OCH_2-$, $-CH_2CH_2CH_2O-$ $-CH_2CH_2OCH_2-$, $-CH_2CH_2-NH-$ $-CH_2NHCH_2-$, $-CH_2CH_2CH_2NH-$ or $-CH_2CH_2NHCH_2-$ group;

R^{0a} is independently selected for each occurrence from the group consisting of halogen, OH, CN, NO_2, R^aR^bN-, C_{1-4}alkyl and haloC_{1-4}alkyl;

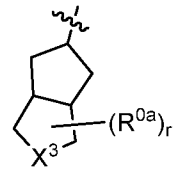
R^{4a} and R^{6b} are independently hydrogen or C_{1-4} alkyl;

R^0, R^6 and R^{11} are independently selected for each occurrence from the group consisting of halogen, OH, CN, NO_2, oxo, $R^dN=$, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t-$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkyl-, HOC(O)C_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkylNR^c-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl-, haloC_{1-6}alkoxyC_{1-6}alkyl-, $R^aR^bNC(O)-$, C_{1-6}alkylC(O)-, C_{1-6}alkoxyC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkyl$S(O)_q-$, C_{1-6}alkyl$S(O)_tNR^c-$, C_{1-6}alkyl$S(O)_tC_{1-6}$alkyl-

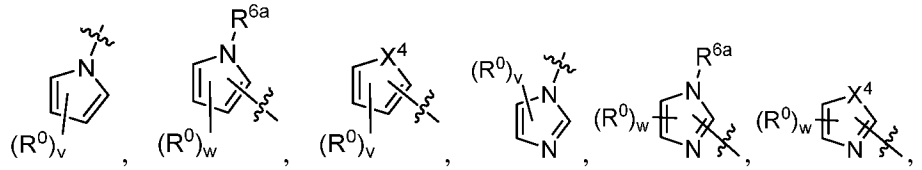
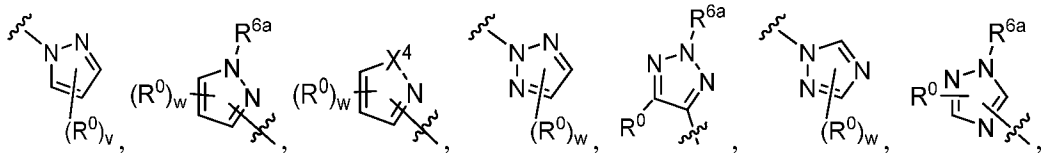
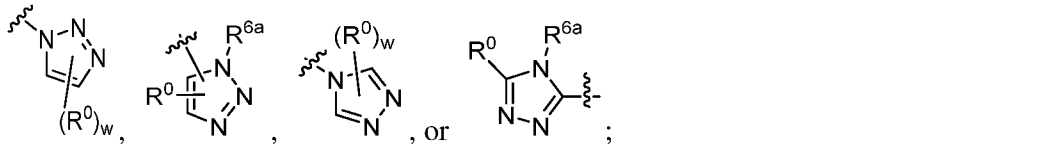
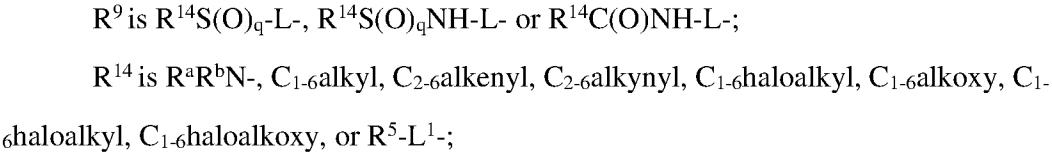
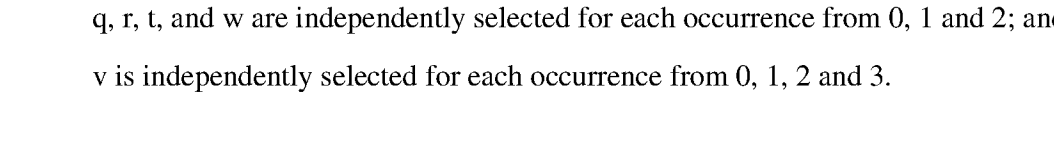
, C_{1-6}alkylS(O)$_t$NR^{a}C$_{1-6}$alkyl-, C_{3-6}cycloalkylS(O)$_t$C$_{1-6}$alkyl-, C_{1-6}alkylC(O)C$_{1-6}$alkyl-, and C_{1-6}alkylC(O)OC$_{1-6}$alkyl-;

R^1 is a phenyl or 5-6 membered monocyclic heteroaryl, wherein the phenyl or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

R^2 and R^8 are independently selected from the group consisting of hydrogen, halo, CN, OH, R^{a}R^{b}N, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}monocycloalkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy;

R^{3a} is  ;

R^4 is R^5-L^1- or R^9;

R^5 is  ,  ,  ,  , or  ;

R^9 is R^{14}S(O)$_q$-L-, R^{14}S(O)$_q$NH-L- or R^{14}C(O)NH-L-;

R^{14} is R^{a}R^{b}N-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or R^5-L^1-;

q, r, t, and w are independently selected for each occurrence from 0, 1 and 2; and

v is independently selected for each occurrence from 0, 1, 2 and 3.

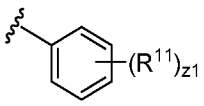
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{x1} is hydrogen or methyl.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{x1} is methyl.

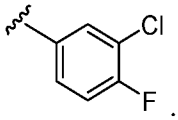
4. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein r is 0.

5. The compound according to any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^2 is R^aR^bN.

6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^2 is NH_2.

7. The compound according to any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, wherein: R^1 is  ; R^{11} is independently selected for each occurrence from the group consisting of halogen, CN, C_{1-6} alkyl and haloC_{1-6} alkyl; and z1 is 0, 1, 2 or 3.

8. The compound of Claim 7, or a pharmaceutically acceptable salt thereof, wherein for each occurrence R^{11} is independently selected from the group consisting of CN, F, Cl, Br and I.

9. The compound of Claim 8, or a pharmaceutically acceptable salt thereof, wherein R^1 is  .

10. The compound according to any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein X^3 is CR^4R^8.

11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein R^4 is R^9.

12. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein R^4 is R^5-L^1-.

13. The compound of 12, or a pharmaceutically acceptable salt thereof, wherein L^1 is a bond.

14. The compound according to any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen, OH or C_{1-6} alkoxy.

15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein R^8 is OH.

16. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen.

17. A pharmaceutical composition comprising the compound according to any one of claims 1-16, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

18. A method of treating Hepatitis B (HBV) infection in a subject in need thereof, the method comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-16, or a pharmaceutically acceptable salt thereof.

19. A method of treating Hepatitis B (HBV) infection in a subject in need thereof, the method comprising: administering to the subject a therapeutically effective amount of pharmaceutical composition of claim 17.

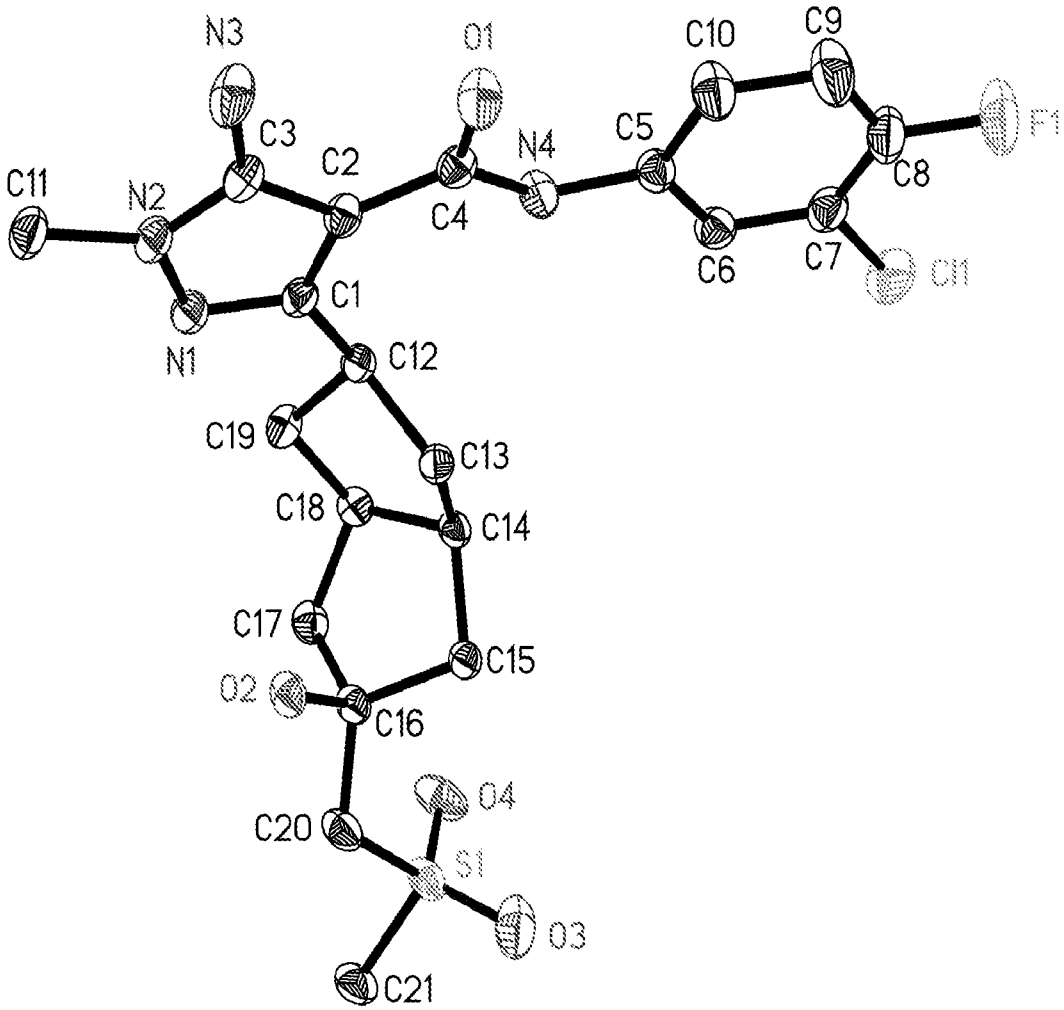

N3
O1
C10
C9
C3
C2
N4
C5
F1
C11
N2
C4
C8
C6
C7
Cl1
C1
N1
C12
C19
C13
C18
C14
C17
C15
O2
C16
O4
C20
S1
O3
C21

Fig. 1

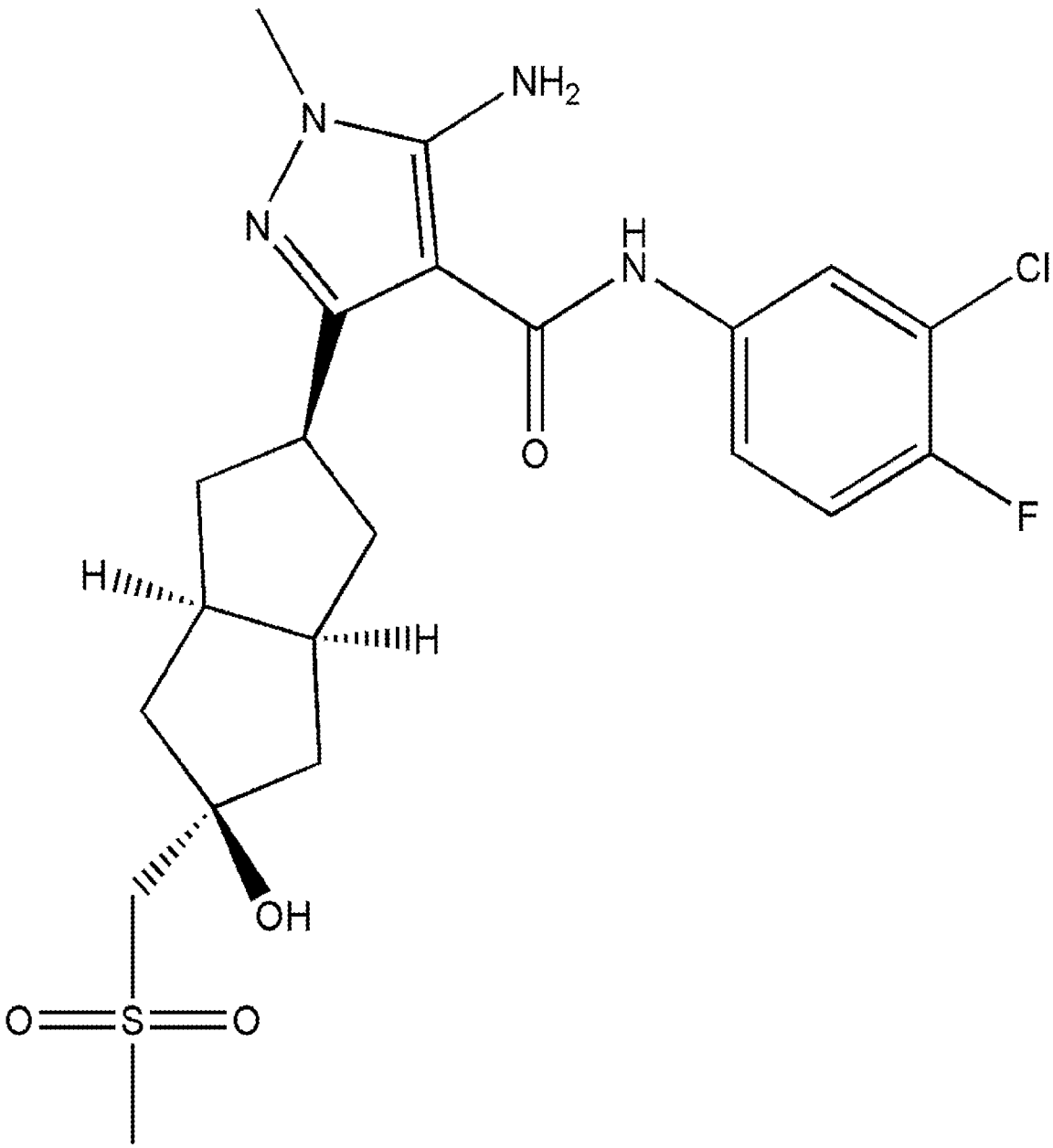


Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/028305

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P31/12 C07D231/38 C07D401/08 C07D417/08 C07D403/08
C07D413/08 C07D405/12 C07D413/12 C07D417/12 C07D409/12
C07D413/04 C07D417/14 C07D403/04 C07D417/04 C07D405/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/184365 A1 (JANSSEN R & D IRELAND [IE]) 20 November 2014 (2014-11-20) cited in the application compounds of examples; claims 1,10,11; table 1	1-19
A	WO 2015/011281 A1 (JANSSEN R & D IRELAND [IE]) 29 January 2015 (2015-01-29) compounds of examples; claims 1,10,11	1-19

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2021	30/07/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Guspanová, Jana

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/028305

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THOMAS LAHLALI ET AL: "Novel Potent Capsid Assembly Modulators Regulate Multiple Steps of the Hepatitis B Virus Life Cycle", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 62, no. 10, 16 July 2018 (2018-07-16) , pages 1-15, XP055584508, US ISSN: 0066-4804, DOI: 10.1128/AAC.00835-18 the whole document -----	1-19
X,P	WO 2020/086533 A1 (ASSEMBLY BIOSCIENCES INC [US]) 30 April 2020 (2020-04-30) compounds AIA-028, 048, 029, 030, 074, 075, 031, 042, 087, 086, 225, 258, 262, 227, 250, 259, 310, 024, 085, 049, 119, 121, 118, 129, intermediates 106, 108, 142; claims 1, 14-16, 18, 19, 25-27; table 17 -----	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/028305

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/028305

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014184365 A1	20-11-2014	AU 2014267235 A1	12-11-2015
		BR 112015028538 A2	25-07-2017
		CA 2909742 A1	20-11-2014
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		EA 201592198 A1	31-03-2016
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		IL 242141 A	26-09-2019
		JP 6441315 B2	19-12-2018
		JP 2016518437 A	23-06-2016
		LT 2997019 T	26-11-2018
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		PT 2997019 T	21-11-2018
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WO 2015011281 A1	29-01-2015	AU 2014294997 A1	21-01-2016
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		NO 3024819 T3	21-07-2018
		PH 12016500027 A1	21-03-2016
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		PT 3024819 T	25-05-2018
		SG 10201805033X A	30-07-2018
		SG 11201600522U A	26-02-2016
		SI 3024819 T1	29-06-2018
		TR 201807090 T4	21-06-2018
		UA 118680 C2	25-02-2019
		US 2016176817 A1	23-06-2016

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/028305

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