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

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

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

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(54) Title: 5-MEMBERED HETEROARYL CARBOXAMIDE COMPOUNDS FOR TREATMENT OF HBV

(57) Abstract: The present disclosure provides, in part, 5-membered heteroaryl carboxamide compounds, and pharmaceutical compositions thereof, useful for disruption of HBV core protein assembly, and methods of treating Hepatitis B (HBV) infection.

5-MEMBERED HETEROARYL CARBOXAMIDE COMPOUNDS FOR TREATMENT OF HBV

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 62/257,776, filed October 20, 2021, the contents of which are hereby incorporated by reference.

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

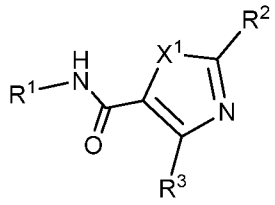
interferon therapy, as only a small subset of patients is likely to have a sustained clinical response to a course of interferon therapy. As a result, interferon-based therapies are used in only a small percentage of all diagnosed patients who elect treatment.

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, 5-membed heteroaryl 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 pharmaceutical compositions comprising a compound of Formula I, 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 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 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, and 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 $C_{2\text{-}6}$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 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, halo$C_{1\text{-}6}$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 term "heteroaryl" as used herein refers to a 5-6 membered monocyclic 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.

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

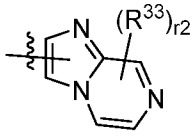
The term "hydroxyalkyl" as used herein refers to an alkyl group substituted with one or more hydroxy groups. Examples include, but are not limited to, $HOCH_2$-, $HOCH_2CH_2$-, $CH_3CH(OH)CH_2$- and $HOCH_2CH(OH)CH_2$-.

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 "$R^aR^bNC_{1\text{-}6}$ 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 "$R^aR^bNC_{1\text{-}6}$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.

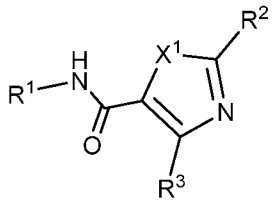
Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and

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^1 is a bond, C_{1-4}alkylene, C_{1-4}alkenylene, C_{1-4}alkynylene, haloC_{1-4}alkylene, hydroxyC_{1-4}alkylene, NR^cC_{1-4}alkyl, OC_{1-4}alkyl, O, NR^c, C(O), C(O)O, C(O)NR^c, $S(O)_t$, $S(O)_tNR^c$, $S(O)_tC_{1-4}$alkyl, and $S(O)_t$haloC_{1-4}alkyl;

L^3 is C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, wherein the C_{1-6}alkylene, C_{2-6}alkenylene, C_{2-6}alkynylene is optionally substituted with 1-10 substituents independently selected from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, R^aR^bN-C_{1-6}alkoxy, and haloC_{1-6}alkylNR^c-;

X^1 is NR^{x1}, O or S;

X^4 is O or S;

X^5 is O, S or NR^{6a};

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

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;

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;

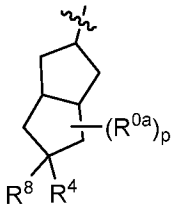
R^{6a} is hydrogen, C_{1-4} alkyl, haloC_{1-4} alkyl or C_{3-4}cycloalkyl;

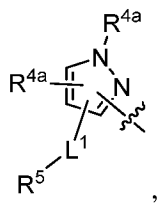
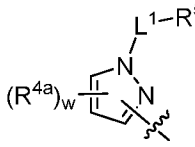
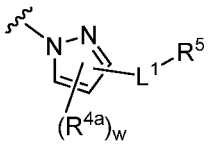
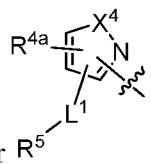
R^{6b} is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl is optionally substituted with 1-10 substituents independently selected from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, R^aR^bN-C_{1-6}alkoxy, and haloC_{1-6}alkylNR^c-;

R^0, R^{4a}, 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-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, R^{6b}, $R^{6b}C(O)$-, $R^{6b}C(O)O$-, $R^{6b}C(O)NR^c$-, $R^{6b}S(O)_tNR^c$-, $R^{6b}S(O)_t$-, $R^{6b}O$-, $R^{6b}NR^c$-, $R^{6b}C(O)$-L^3-, and $R^{6b}C(O)O$-L^3-, $R^{6b}C(O)NR^c$-L^3-, $R^{6b}S(O)_tNR^c$-L^3-, $R^{6b}S(O)_q$-L^3-, $R^{6b}O$-L^3-, and $R^{6b}NR^c$-L^3-;

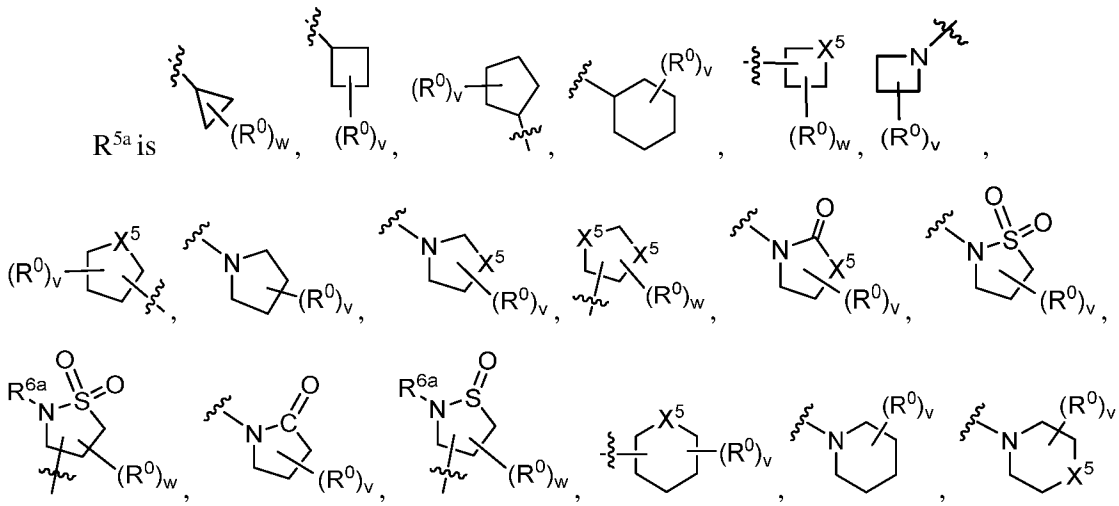
R^1 is a phenyl or 5-6 membered monocyclic heteroaryl, wherein the phenyl or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

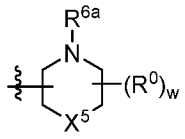
R^2 and R^8 are independently selected from the group consisting of hydrogen, halo, CN, OH, R^aR^bN, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}monocycloalkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy;

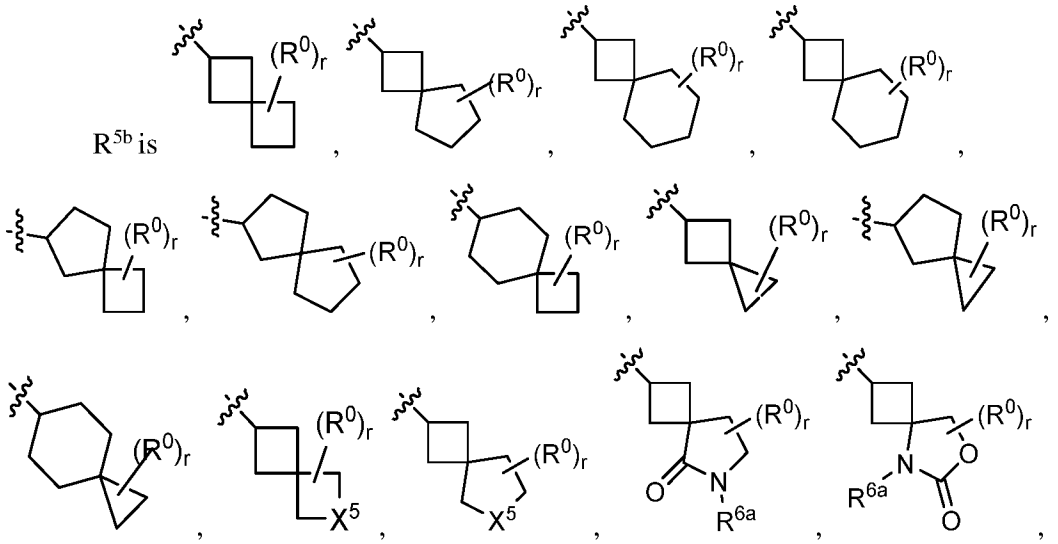
R^3 is 

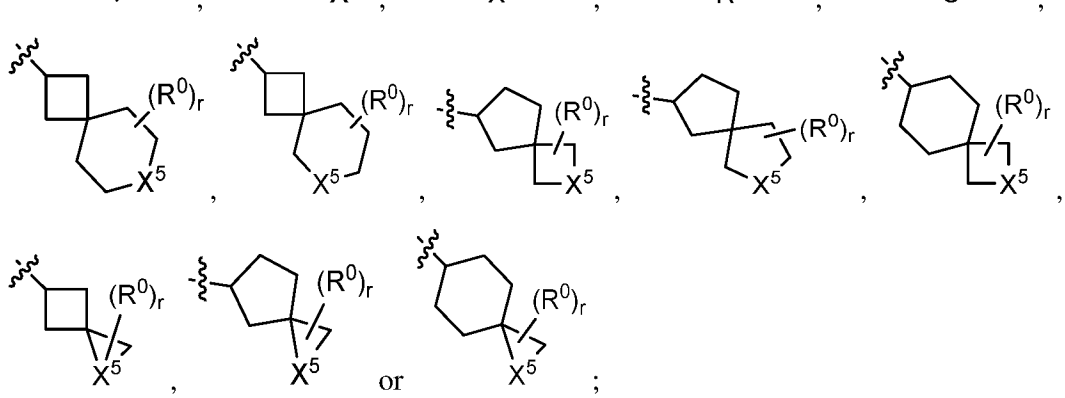
R^4 is  ,  ,  or  ;

R^5 is R^{5a}, R^{5b}, R^{5c}, R^{5d} or R^6;

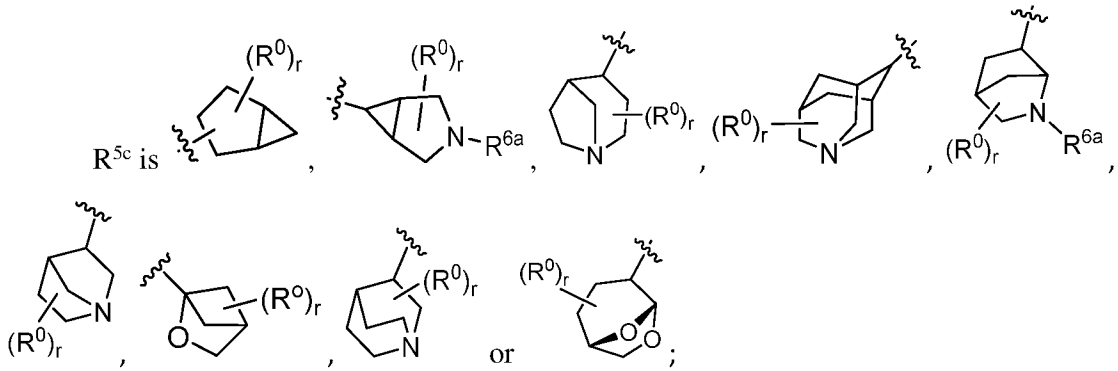
R^{5a} is 

or  ;

R^{5b} is 

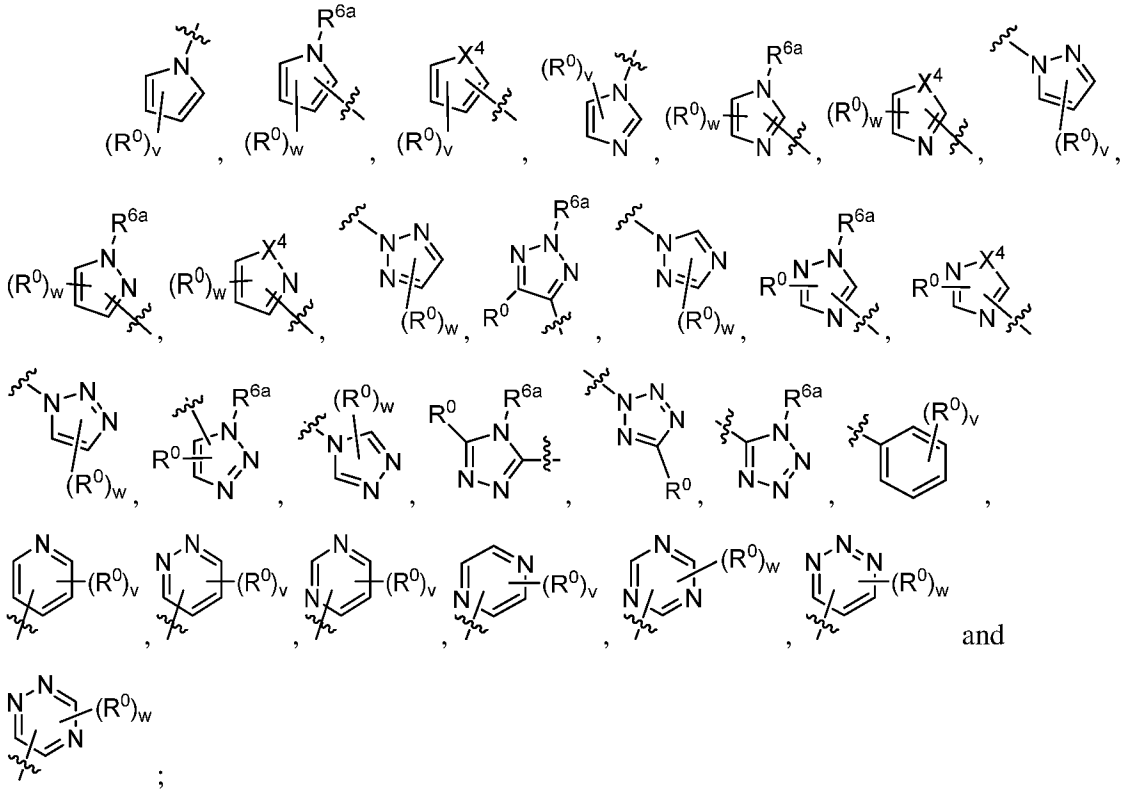


or ;

R^{5c} is 

or ;

R^{5d} is selected from the group consisting of:



;

p is independently selected for each occurrence from the group consisting of 0, 1, 2 and 3;

r is independently selected for each occurrence from the group consisting of 0, 1 and 2;

t is independently selected for each occurrence from the group consisting of 0, 1 and 2;

v is independently selected for each occurrence from the group consisting of 0, 1, 2 and 3; and

w is independently selected for each occurrence from the group consisting of 0, 1 and 2.

The following embodiments further describe a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In certain embodiments, X^1 is S.

In certain embodiments, X^1 is NR^{x1}.

In certain embodiments, X^1 is NR^{x1} and R^{x1} is hydrogen of methyl.

In certain embodiments, X^1 is NR^{x1} and R^{x1} is methyl.

In certain embodiments, L^1 is a bond.

In certain embodiments, L^1 is C_{1-4}alkylene.

In certain embodiments, p is 0.

In certain embodiments, R^0 is selected from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, 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-, C_{1-6}alkylC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkylC(O)NR^c-, C_{1-6}alkyl$S(O)_t$-, C_{1-6}alkyl$S(O)_tNR^c$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkyleneNR^c-, C_{1-6}alkoxyC_{1-6}alkylene-, haloC_{1-6}alkoxyC_{1-6}alkylene-, C_{1-6}alkoxyC(O)-, C_{1-6}alkyl$S(O)_tC_{1-6}$alkylene-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkylene-, C_{1-6}alkylC(O)C_{1-6}alkylene-, C_{1-6}alkylC(O)OC_{1-6}alkylene- and R^9, wherein:

R^9 is $R^{12}S(O)_t$-C_{1-6}alkylene-, $R^{12}S(O)_tNH$-C_{1-6}alkylene-, $R^{12}C(O)NH$-C_{1-6}alkylene-, $R^{12}S(O)_t$-haloC_{1-6}alkylene-, $R^{12}S(O)_tNH$-haloC_{1-6}alkylene-, or $R^{12}C(O)NH$-haloC_{1-6}alkylene-; and

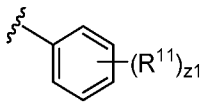
R^{12} is R^aR^bN-, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, or C_{1-6}haloalkoxy.

In certain embodiments, R^0 is selected from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, 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-, C_{1-6}alkylC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkylC(O)NR^c-, C_{1-6}alkyl$S(O)_t$-, C_{1-6}alkyl$S(O)_tNR^c$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkyleneNR^c-, C_{1-6}alkoxyC_{1-6}alkylene-, haloC_{1-6}alkoxyC_{1-6}alkylene-, C_{1-6}alkoxyC(O)-, C_{1-6}alkyl$S(O)_tC_{1-6}$alkylene-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkylene-, C_{1-6}alkylC(O)C_{1-6}alkylene-, and C_{1-6}alkylC(O)OC_{1-6}alkylene-.

In certain embodiments, R^0 is R^9; wherein:

R^9 is $R^{12}S(O)_t$-C_{1-6}alkylene-, $R^{12}S(O)_tNH$-C_{1-6}alkylene-, $R^{12}C(O)NH$-C_{1-6}alkylene-, $R^{12}S(O)_t$-haloC_{1-6}alkylene-, $R^{12}S(O)_tNH$-haloC_{1-6}alkylene-, or $R^{12}C(O)NH$-haloC_{1-6}alkylene-; and

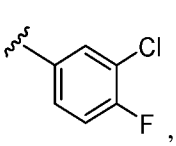
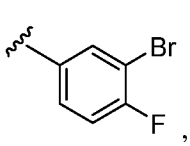
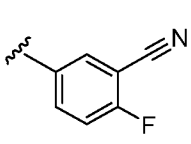
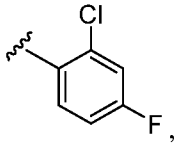
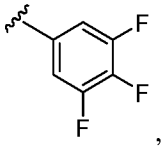
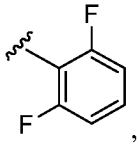
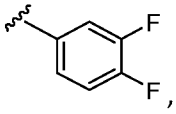
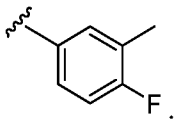
R^{12} is R^aR^bN-, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, or C_{1-6}haloalkoxy.

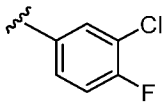
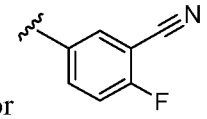
In certain embodiments, R^1 is  ; R^{11} is independently selected for each occurrence from the group consisting of halogen, CN, C_{1-6}alkyl and haloC_{1-6}alkyl; and z1 is 0, 1, 2 or 3.

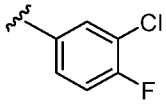
In certain embodiments, R^{11} is independently selected for each occurrence from the group consisting of halogen and CN.

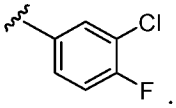
In certain embodiments, R^{11} is independently selected for each occurrence from the group consisting of F, Cl, Br and I.

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

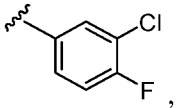









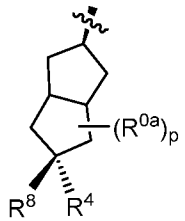
In certain embodiments, R^1 is  or  .

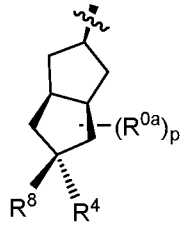
In certain embodiments, R^1 is  .

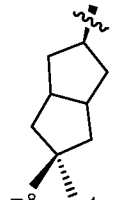
In certain embodiments, X^1 is NR^{x1}, R^{x1} is hydrogen or methyl, and R^1 is  .

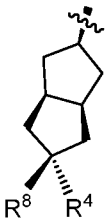
In certain embodiments, R^2 is hydrogen.

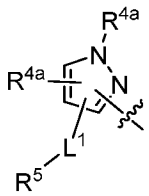
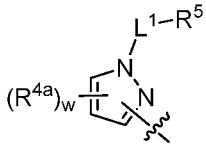
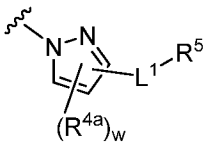
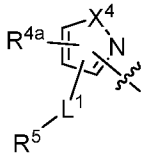
In certain embodiments, X^1 is NR^{x1}, R^{x1} is hydrogen or methyl, R^1 is  , and R^2 is hydrogen.

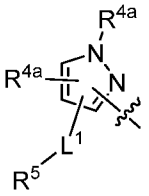
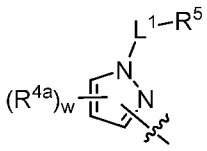
In certain embodiments, R^3 is  .

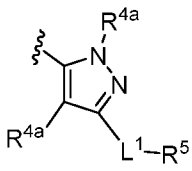
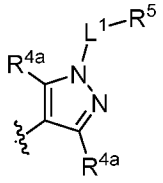
In certain embodiments, R^3 is  .

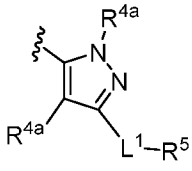
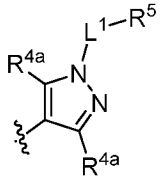
In certain embodiments, R^3 is  .

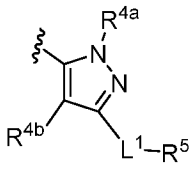
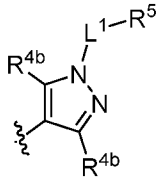
In certain embodiments, R^3 is  .

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

In certain embodiments, R^4 is  or  .

In certain embodiments, R^4 is  or  .

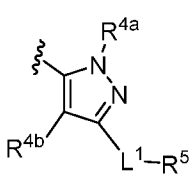
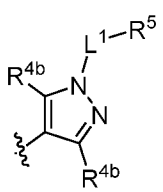
In certain embodiments, R^4 is  or  .

In certain embodiments, R^4 is  or  , wherein:

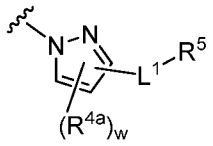
R^{4b} is selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl-, $R^aR^bNC_{1-6}$alkyl-, HOC(O)C_{1-6}alkyl-, C_{1-6}alkylC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkylC(O)NR^c-, C_{1-6}alkylS$(O)_{qt}$-, C_{1-6}alkylS$(O)_tNR^c$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkyleneNR^c-, C_{1-6}alkoxyC_{1-6}alkylene-, haloC_{1-6}alkoxyC_{1-6}alkylene-, C_{1-6}alkoxyC(O)-, C_{1-6}alkylS$(O)_tC_{1-6}$alkylene-, C_{1-6}alkylS$(O)_tNR^aC_{1-6}$alkylene-, C_{1-6}alkylC(O)C_{1-6}alkylene-, C_{1-6}alkylC(O)OC_{1-6}alkylene- and R^9, wherein:

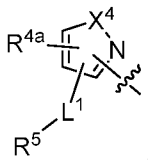
R^9 is $R^{12}S(O)_t$-C_{1-6}alkylene-, $R^{12}S(O)_tNH$-C_{1-6}alkylene-, $R^{12}C(O)NH$-C_{1-6}alkylene-, $R^{12}S(O)_t$-haloC_{1-6}alkylene-, $R^{12}S(O)_tNH$-haloC_{1-6}alkylene-, or $R^{12}C(O)NH$-haloC_{1-6}alkylene-; and

R^{12} is R^aR^bN-, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, or C_{1-6}haloalkoxy.

In certain embodiments, R^4 is  or  , wherein:

R^{4b} is 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-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, 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-, C_{1-6}alkylC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkylC(O)NR^c-, C_{1-6}alkyl$S(O)_t$-, C_{1-6}alkyl$S(O)_tNR^c$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkyleneNR^c-, C_{1-6}alkoxyC_{1-6}alkylene-, haloC_{1-6}alkoxyC_{1-6}alkylene-, C_{1-6}alkoxyC(O)-, C_{1-6}alkyl$S(O)_tC_{1-6}$alkylene-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkylene-, C_{1-6}alkylC(O)C_{1-6}alkylene-, and C_{1-6}alkylC(O)OC_{1-6}alkylene-.

In certain embodiments, R^4 is  .

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

In certain embodiments, R^5 is R^{5a}, R^{5b}, R^{5d} or R^6.

In certain embodiments, R^5 is R^{5a}, R^{5d} or R^6.

In certain embodiments, R^5 is R^{5a} or R^{5d}.

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

In certain embodiments, R^4 is R^{5a}.

In certain embodiments, R^4 is R^{5d}.

In certain embodiments, L^1 is a bond, C_{1-4}alkylene, C_{1-4}alkenylene, C_{1-4}alkynylene, haloC_{1-4}alkylene or hydroxyC_{1-4}alkylene.

In certain embodiments, L^1 is a bond.

In certain embodiments, R^6 is selected from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, 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-, C_{1-6}alkylC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkylC(O)NR^c-, C_{1-6}alkyl$S(O)_t$-, C_{1-6}alkyl$S(O)_tNR^c$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkyleneNR^c-, C_{1-6}alkoxyC_{1-6}alkylene-, haloC_{1-6}alkoxyC_{1-6}alkylene-, C_{1-6}alkoxyC(O)-, C_{1-6}alkyl$S(O)_tC_{1-6}$alkylene-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkylene-, C_{1-6}alkylC(O)C_{1-6}alkylene-, C_{1-6}alkylC(O)OC_{1-6}alkylene- and R^9, wherein:

R^9 is $R^{12}S(O)_t$-C_{1-6}alkylene-, $R^{12}S(O)_tNH$-C_{1-6}alkylene-, $R^{12}C(O)NH$-C_{1-6}alkylene-, $R^{12}S(O)_t$-haloC_{1-6}alkylene-, $R^{12}S(O)_tNH$-haloC_{1-6}alkylene-, or $R^{12}C(O)NH$-haloC_{1-6}alkylene-; and

R^{12} is R^aR^bN-, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, or C_{1-6}haloalkoxy.

In certain embodiments, R^6 is selected from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, 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-, C_{1-6}alkylC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkylC(O)NR^c-, C_{1-6}alkyl$S(O)_t$-, C_{1-6}alkyl$S(O)_tNR^c$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkyleneNR^c-, C_{1-6}alkoxyC_{1-6}alkylene-, haloC_{1-6}alkoxyC_{1-6}alkylene-, C_{1-6}alkoxyC(O)-, C_{1-6}alkyl$S(O)_tC_{1-6}$alkylene-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkylene-, C_{1-6}alkylC(O)C_{1-6}alkylene-, and C_{1-6}alkylC(O)OC_{1-6}alkylene-.

In certain embodiments, R^6 is R^9, wherein:

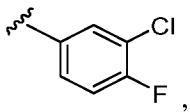
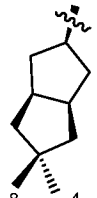
R^9 is $R^{12}S(O)_t$-C_{1-6}alkylene-, $R^{12}S(O)_tNH$-C_{1-6}alkylene-, $R^{12}C(O)NH$-C_{1-6}alkylene-, $R^{12}S(O)_t$-haloC_{1-6}alkylene-, $R^{12}S(O)_tNH$-haloC_{1-6}alkylene-, or $R^{12}C(O)NH$-haloC_{1-6}alkylene-; and

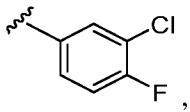
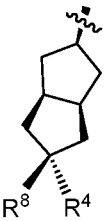
R^{12} is R^aR^bN-, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, or C_{1-6}haloalkoxy.

In certain embodiments, R^8 is hydrogen, halogen, methyl, methoxy or OH.

In certain embodiments, R^8 is hydrogen or OH.

In certain embodiments, R^8 is OH.

In certain embodiments, X^1 is NR^{x1}; R^{x1} is hydrogen or methyl; R^1 is  , R^2 is H; R^3 is  ; and R^8 is hydrogen, OH or C_{1-6}alkoxy.

In certain embodiments, X^1 is NR^{x1}; R^{x1} is hydrogen or methyl; R^1 is  , R^2 is H; R^3 is  ; and R^8 is OH.

It will be appreciated that all chemically allowable combinations of the aforementioned embodiments are also contemplated as embodiments of the invention.

III. Pharmaceutical Compositions and Kits

In another aspect, the disclosure provides pharmaceutical compositions comprising a compound of Formula I, 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 according to any combination of the Examples described herein, 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, the 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., pregelatinised 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.

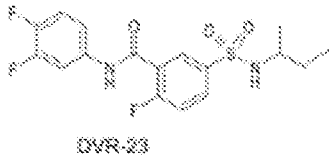
Preparations for oral administration may also be suitably formulated to give controlled-release or sustained release of the active compound(s) over an extended period. For buccal administration the compositions may take the form of tablets or lozenges formulated in a conventional manner known to the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

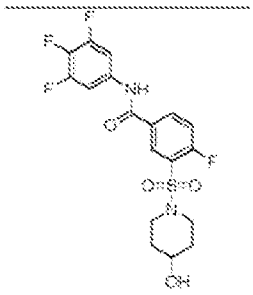
In some cases, a disclosed compound may be administered as part of a combination therapy in conjunction with one or more antivirals. Example antivirals include nucleoside analogs, interferon α, and other assembly effectors, for instance heteroaryldihydropyrimidines (HAPs) such as methyl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(pyridin-2-yl)-1,4-dihydropyrimidine-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: an HBV capsid assembly promoter (for example, GLS4, BAY 41-4109, AT-130, DVR-23 (e.g., as depicted below),



DVR-23 ;

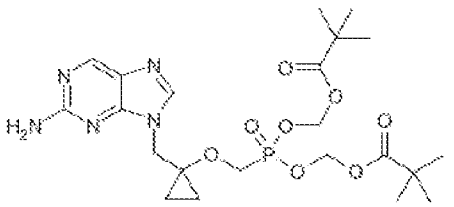
NVR 3-778, NVR1221 (by code); and N890 (as depicted below):



;

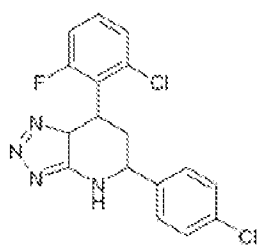
other capsid inhibitors such as those disclosed in the following patent applications hereby incorporated by reference: WO2014037480, WO2014184328, WO2013006394, WO2014089296, WO2014106019, WO2013102655, WO2014184350, WO2014184365, WO2014161888, WO2014131847, WO2014033176, WO2014033167, and WO2014033170;

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:

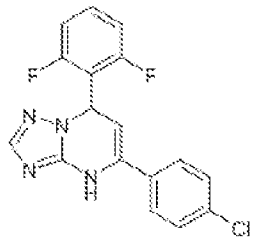


;

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:



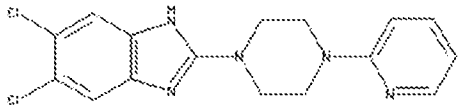
22: HBF-0529



23: PBHBV-2-15

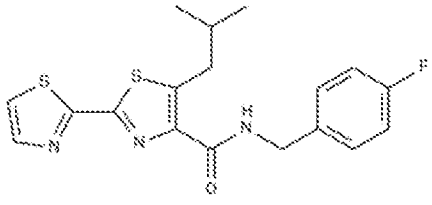
;

and BM601 as depicted below:



;

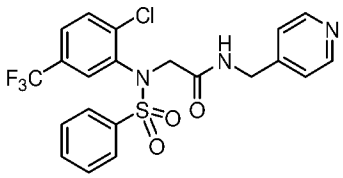
disruptors of nucleocapsid formation or integrity such as NZ-4/W28F:

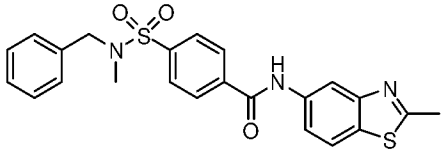


NZ-4

;

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.

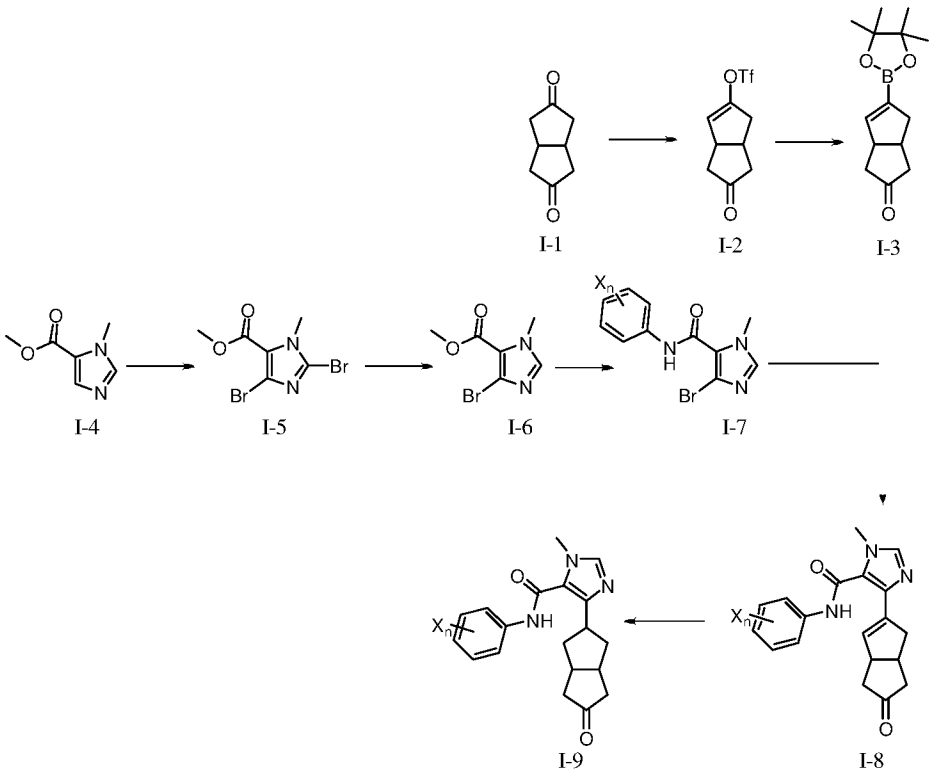
At least some of the compounds identified as "intermediates" herein are contemplated as compounds of the disclosure.

Abbreviations:

AcOH	Acetic acid
ACN	Acetonitrile
Boc_2O	Di-tert-butyl dicarbonate
nBuLi	n-Butyllithium
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIEA	Diisopropyl ethylamine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide

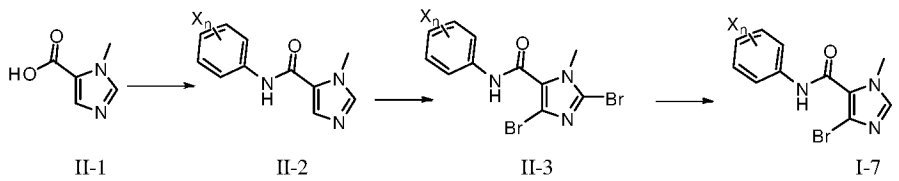
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
EA, EtOAc	Ethyl acetate
Et_3N	Triethylamine
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
h, hr	Hour(s)
HPLC	High performance liquid chromatography
LCMS	Liquid chromatography–mass spectrometry
MeOH	Methanol
NMO	N-Methylmorpholine-N-Oxide
NBS	N-Bromosuccinimide
PE	Petroleum ether
iPrOH	Isopropanol
rt, r.t.	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 I



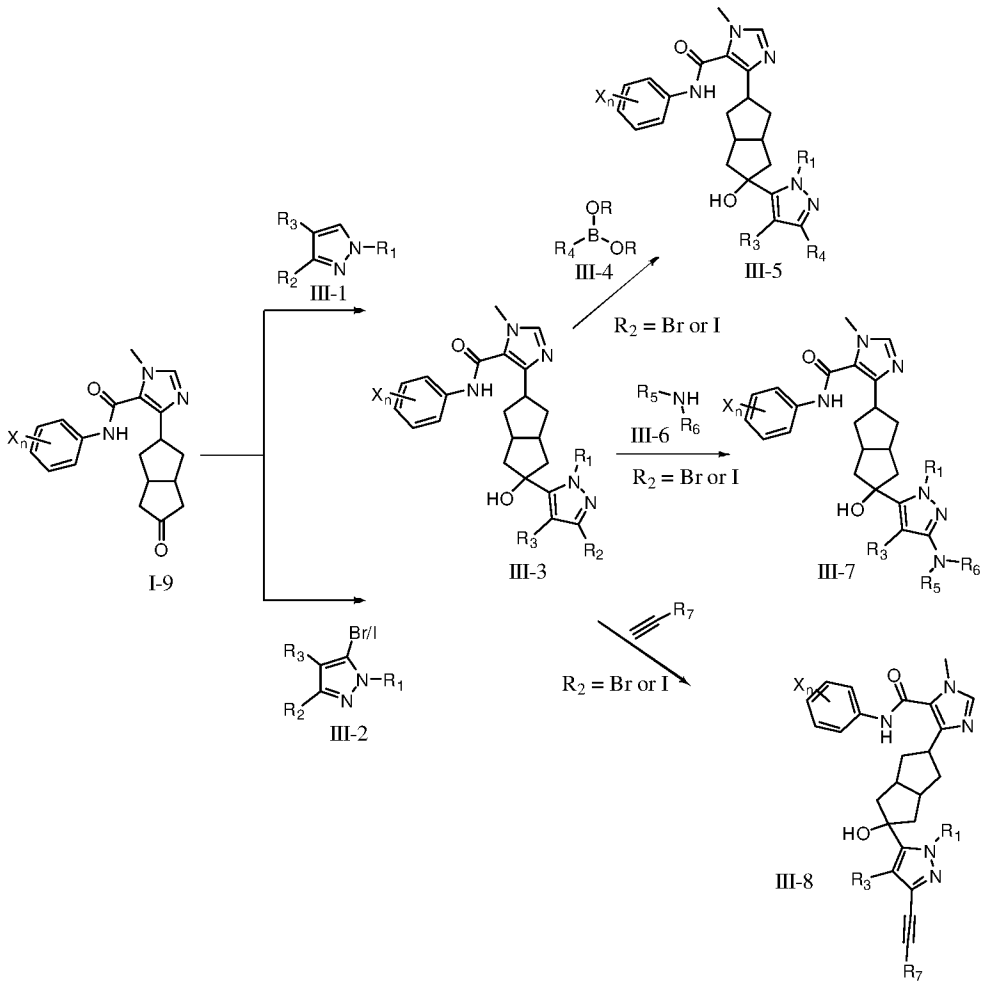
The synthesis of the common intermediate I-9 is illustrated in Scheme I. The bicyclic octadien, I-1) can be converted to the corresponding boranae ester I-3 in two steps. Likewise, The the imidazole bromide intermediate can be synthesized starting from imidazole ester I-4in three steps. The two compounds, I-3 and I-7 can be coupled together via a palladium catalyzed coupling reaction to prived I-8. Reductionof the double bound can be carried out using standard Pd or Pt catalyzed hydrogenation reaction conditions.

Scheme II



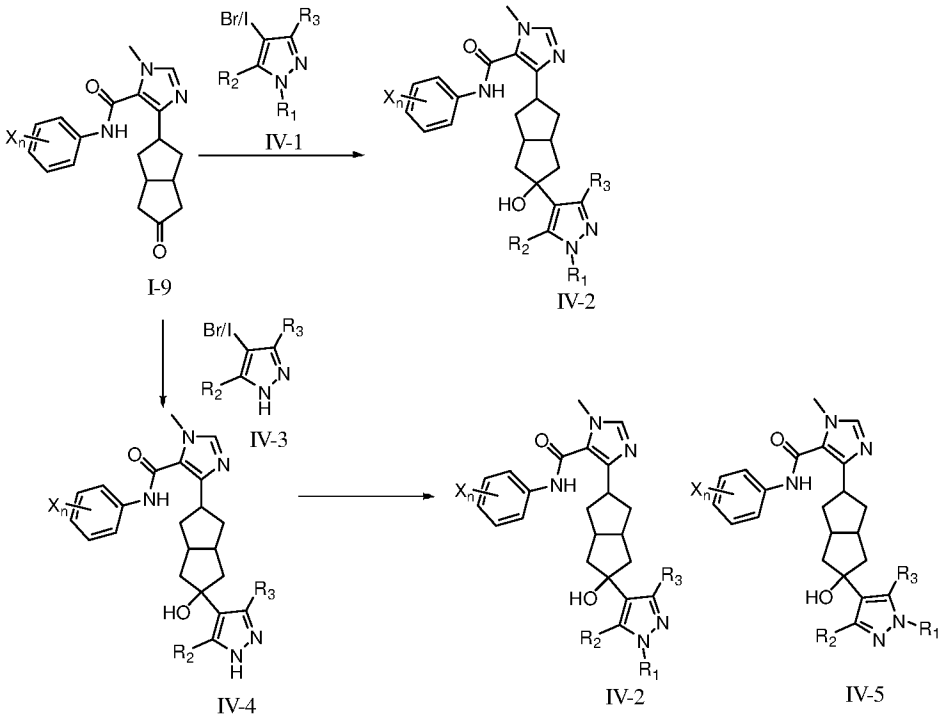
An alternative synthesis of intermedaite I-7 is shown in Scheme II. The method starts with imidazole carboxylic acid II which is sequentially converted to amide II-2, bis-bromated follwoed by selective debromination to removethe bromineat C-2.

Scheme III



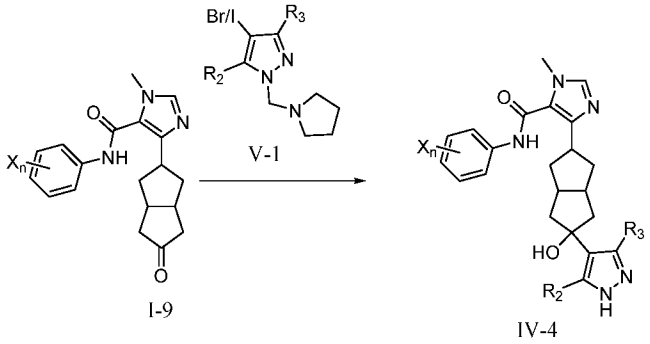
Compounds having general structure III-3 can be synthesized according to the methods shown in Scheme III. In the first procedure intermediate III-1 can be treated with LDA, BuLi then reacted with I-9 to yield III-3. In the second, C5-halogenated (Br or I) pyrazole III-2 undergoes metal halogen exchange with Mg, a Grignard reagent, Li or BuLi and the resulting anion reacted with I-9 to form III-3. For R_2 is Br or I,than III-3 can be treated with boronic acid or ester, III-4 under Suzuki reaction conditions yield III-5. Likewise, compounds III-7 and III-8 can obtained by treating III-3 (R_2 = Br or I)with an amine or alkyne under Buchwald or Sonogashira reaction conditions.

Scheme IV



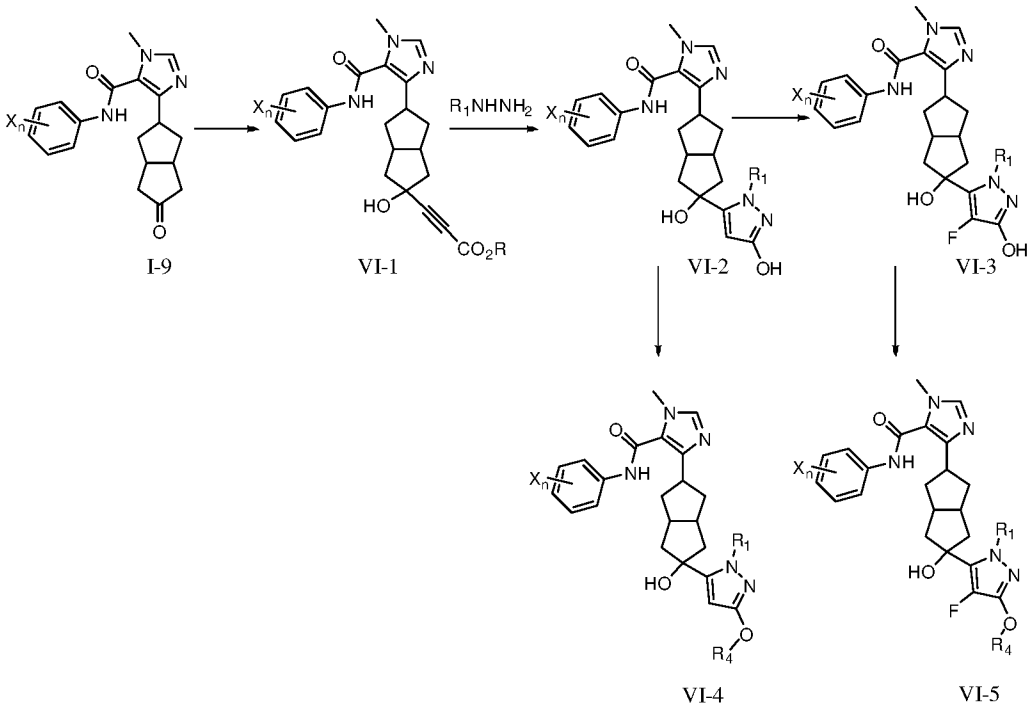
Scheme IV illustrates the synthesis of compounds of the general structures IV-2 and IV-5. C4 halogenated intermediate IV-1 or IV-3 can be treated with Mg, Grignard reagent, Li or BuLi to genrate the coresponding metallated hetereocycles, whch upon addtion of I-9 form either IV-2 and IV-4, respectively. IV-4 can be further derivatized with and appropriate alkylating agent for form IV-2 and IV-5.

SchemeV



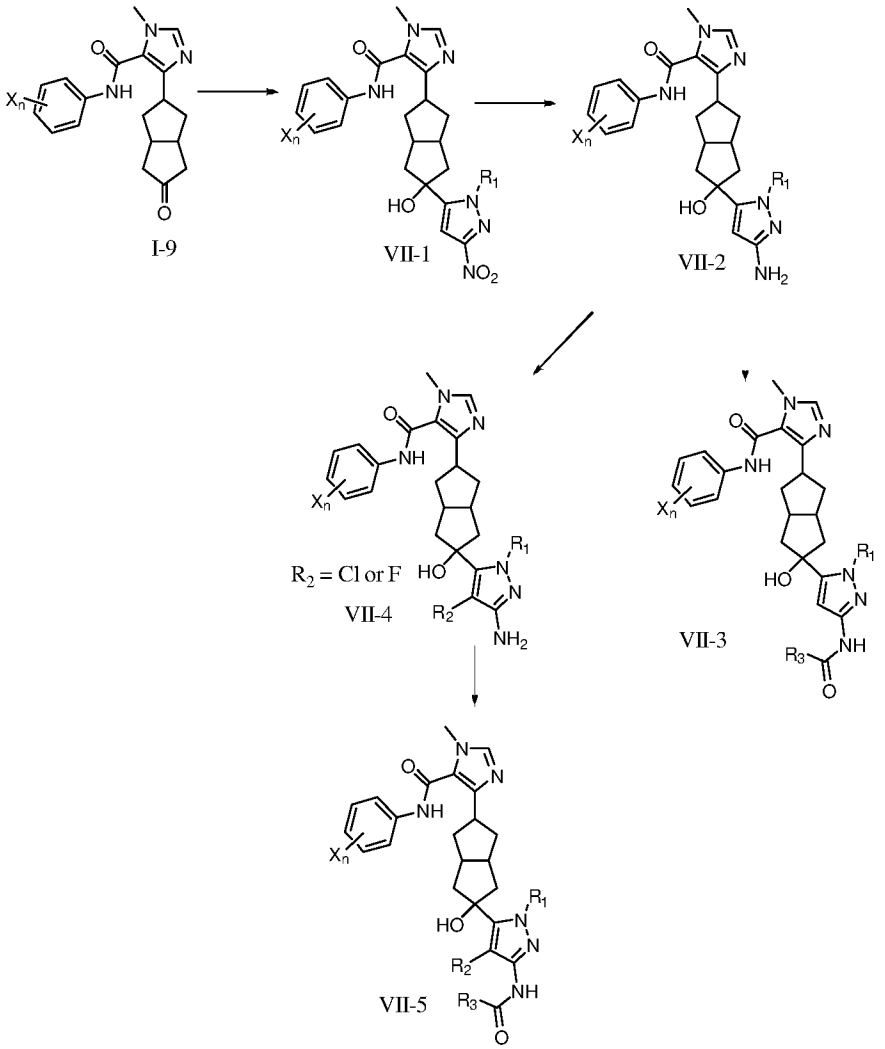
An alternative synthesis of IV-4 is shown in Scheme V, the nitrogen atom of the pyrazole is protected as it's corresponding pyrrolidine aminal.

SchemeVI



In Scheme VI an ester of propionic acid can be reacted with I-9 under basic conditions to form VI-1. The alkyne undergoes a reaction with an appropriately substituted hydrazine to form VI-2. This compound can be fluorinated under standard conditions to yield VI. Both VI-2 and VI-3 are further derivatized via alkylation of the pyrazole OH forming VI-4 and VI-5, respectively.

Scheme VII



Coumpounds of general structure VII-3 and VII-5 can be synthesized according to the method shown in Scheme VII. I-9 can be reactied with an appropriately substituted 3-nitro pyrazole to form VII-1 which can be reduced to yield VII-2. Amidation of VII-2 provide VII-3. Halogentation of VII-2 yields VII-4, which can likewise be amidated obtain VII-5.

Following LCMS method have been used for the analysis of some of the final compounds

Method A: X-Bridge BEH C-18 (3 x 50 mm x 2.5µm); Mobile phase: A; 0.025% formic acid in H_2O; B; CH_3CN; injection volume:2 µL; Flow rate:1.2 mL/min, column temperature: 50 °C; Gradient program: 2% B to 98% B in 2.2 min, hold until 3 min, at 3.2 min B conc. is 2 % until 4 min.

Method B: X-select CSH 18 (3 x 50 mm x 2.5µm); Mobile phase: A; 0.025% formic acid in H_2O; B; CH_3CN; Injection voloume:2 uL; Flow rate:1.2 mL/min, column temperature: 50 °C; Gradient program: 0% B to 98% B in 2 min, hold until 3 min, at 3.2 min B conc. is 0 % until 4 min.

Method C: X-select CSH 18 (3 x 50mm x 2.5µm); Mobile phase: A; 0.05% formic acid in H_2O:CH_3CN (95:5); B; 0.05% formic acid in CH_3CN; Injection volume: 2 µL; Flow rate: 1.2 mL/min, column temperature: 50 °C; Gradient program: 0% B to 98% B in 2 min, hold till 3 min, at 3.2 min B conc. is 0 % until 4 min.

Method D: X-select CSH C18 (3 x 50 mm x 2.5µm); Mobile phase: A; 2mM in Ammonium Bicarbonate; B; CH_3CN; Injection voloume:2 µL; Flow rate:1.2 mL/min, column temperature: 50 °C; Gradient program: 0% B to 98% B in 2 min, hold until 3 min, at 3.2 min B conc. is 0 % until 4 min.

Method E: X-select CSH 18 (3 x 50 mm x 2.5µm); Mobile phase: A; 0.05% formic acid in H_2O; B; CH_3CN; Injection volume: 2 µL; Flow rate:1.5 mL/min, column temperature: 50 °C; Gradient program: 0% B to 100% B in 1.5 min, hold until 2.2 min, at 2.6 min B conc. is 0 % until 3 min.

Synthetic procedures

Details useful for the methods described in Schemes I-VII and for the procedures that follow are listed below.

Procedure for *O*-Alkylation

Method 1 (Using alkyl halide)

To a stirred solution of Het-Ar-OH compound (1 eq.) and corresponding alkyl halide compound (2 eq.) in acetonitrile/DMF (4 mL/mmol) was added K_2CO_3 or Cs_2CO_3 (2 eq.) and KI (0.5 eq.). The reaction mixture was stirred at 60 °C-80 °C for 2h-16 h. The reaction progress was monitored by TLC. After completion, reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were collected, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to obtain crude product which was purified by silica gel column chromatography or prep-HPLC to afford the desired compound.

Method 2 (Using epoxide)

To a stirred solution of Het-Ar-OH compound (1 eq.) and corresponding epoxide compound (1.5/2 eq.) in DMF/ACN (6 mL/mmol) was added Cs_2CO_3 (2.5 eq.). The reaction mixture was stirred at room temperature/ 60 °C for 4-12 h. The reaction progress was monitored by TLC. After completion, reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were collected, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to obtain crude product which was purified by silica gel column chromatography or prep-HPLC to afford the desired compound.

Method for Suzuki coupling

Method 3

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. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through Celite 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.

Method 4

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), K_3PO_4 (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 10 h-16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through Celite 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.

Method 5

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), K_3PO_4 (2-3 eq.) was added and purged with Argon for 15 min. To this solution, S-Phos (0.2 eq.) and $Pd(dppf)Cl_2$ (0.1 eq.) was added and purged with Argon for another 10 min. The resulting reaction mixture was stirred at 100 °C for 10 h-16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through Celite 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.

Procedure for Sonogashira coupling

Method 6

To a mixture of halo compound (1 eq.) and corresponding alkyne compound (3 eq.) in dry THF (3 mL/mmol), CuI (0.2 eq.) and triethylamine (3 eq.) were added and purged with Argon for 15 min. To this solution, $Pd(PPh_3)_2Cl_2$ (0.1 eq.) was added and purged with Argon for another 10 min. The resulting reaction mixture was stirred at room temperature for 12h-16h. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was filtered through Celite 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.

Method 7

To a mixture of halo compound (1 eq.) in DMA: H_2O (3:1), CuI (0.15 eq.), triethylamine (5 eq.) and K_2CO_3 (1.5 eq.) were added and purged with Argon for 15 min. To this solution, $Pd(PPh_3)_4$ (0.1 eq.) and corresponding alkyne compound (10 eq.) was added and purged with Argon for another 10 min. The resulting reaction mixture was stirred in microwave at 120 °C for 4h. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was filtered through Celite and evaporated to dryness. The crude product was purified by either CombiFlash column chromatography or prep-HPLC to afford the desired compound.

Procedure for Copper-Catalyzed N-Arylation

Method 8

To a mixture of halo compound (1 eq.) and corresponding amine (2.5 eq.) in DMSO (2 mL), K_2CO_3 (2.5 eq.) and L-proline (0.4 eq.) were added and purged with Argon for 10 min. To this solution, CuI (0.2 eq.) was added and purged with Argon for another 10 min. The resulting reaction mixture was stirred at 100°C for 16h. The progress of the reaction was monitored by TLC. 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. The crude product was purified by CombiFlash column chromatography or prep-HPLC to afford the desired compound.

Procedure for reduction

Method 9

To a stirred solution nitro compound (1 eq.) in MeOH (20 mL/ mmol) at 0°C, 10% Pd/C and $NaBH_4$ (2.5 eq.) were added. The reaction mixture was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was filtered through a pad of Celite and washed with methanol. The filtrate was concentrated under reduced pressure. The crude product was purified by either silica gel column chromatography or prep-HPLC to afford the desired compound.

Procedure for amidation reaction

Method 10

To a stirred solution of acid compound (1.1-1.2 eq.) in DMF/dichloromethane (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 12-16h. The progress of the reaction was monitored by TLC. 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 product. The crude product

was purified by either prep-HPLC or Combiflash column chromatography to afford the desired compound.

Method 11

To a stirred solution of acid compound (1.1-1.2 eq.) in DMF/Acetonitrile (1.01 mL/mmol) at 0 °C, Pyridine (5-10 eq.) and HATU (1.5-2.5 eq.) were added and stirred for 5 min. To this solution, corresponding amine (1-1.1.5 eq.) was added. The resulting reaction mixture was stirred at 80 °C for 12-16h. The progress of the reaction was monitored by TLC. 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 product. The crude product was purified by either prep-HPLC or Combiflash column chromatography to afford the desired compound.

Method 12 (amide coupling using acid chloride/derivatives)

To a stirred solution of amine compound (1 eq.) in dichloromethane/DMF (1.01 mL/mmol) was added triethylamine/DIPEA (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. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate/dichloromethane. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a crude product. The crude product was purified by either prep-HPLC or Combiflash column chromatography to afford the desired compound.

Method 13

To a stirred solution of ester compound (1 eq.) in methanol (1 mL/mmol), $MeNH_2$ (2M in THF) was added. The reaction mixture was stirred at 70°C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture concentrated under reduced pressure to afford a crude product. The crude product was purified by silica gel column chromatography to afford the desired compound.

Procedure for *N*-acylation, *N*-Sulfonylation, *N*-Sulfamoylation and *N*-Carbamoylation.

Method 14

To a stirred solution of Amine compound (1 eq.) in DMF (10 vol.) was added triethylamine or pyridine (5 eq.) followed by dropwise addition of corresponding acid chloride/ sulfonylchloride/ sulfamoyl chloride / carbamoylchloride (2.5 eq) at 0 °C. The reaction mixture was stirred at room temperature for 5-6 h. The progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was quenched with ice cold water and extracted with dichloromethane. The organic layer was concentrated under reduced pressure. The crude product was purified by either silica gel column chromatography or prep-HPLC to afford the desired compound.

Procedure for *N*-alkylation

Method 15

To a stirred solution of amine compound (1 eq.) in THF (10 vol.) was added DIPEA (5 eq.) corresponding alkyl *O*-Triflate (2 eq) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. The progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was quenched with ice cold water and extracted with dichloromethane. The organic layer was concentrated under reduced pressure. The crude product was purified by either silica gel column chromatography or prep-HPLC to afford the desired compound.

Procedure for Grignard Reaction

Method 16

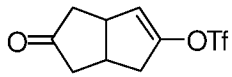
To a stirred solution of keto compound (1 eq.) in dry THF (0.2 mL/mmol) in an inert atmosphere was added Grignard reagent (5 eq.) slowly *via* glass syringe at 0°C and stirred the reaction mixture at room temperature for 3h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with sat. aq. solution of ammonium chloride and extracted with ethyl acetate/dichloromethane. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a crude product. The crude product was purified by either by Combiflash column chromatography or prep-HPLC to afford the desired compound.

Procedure for Reductive amination

Method 17

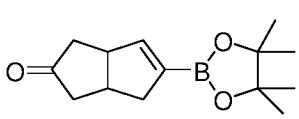
To a stirred solution of aldehyde/keto compound (2 eq) in MeOH (0.1 mL/mmol) at 0 °C, AcOH (5 eq) was added and stirred at RT for 30 min. To this solution, amine (1 eq) and sodium cyano borohydride (5 eq) were added. The resulting reaction mixture was stirred at RT for overnight. The reaction progress was monitored by TLC. After completion reaction was diluted with sat. $NaHCO_3$ solution and extracted with 10% MeOH/dichloromethane. The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated *in vacuo* to obtain crude product. The crude product was purified by column chromatography to afford desired compound.

Intermediate 1



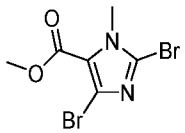
5-Oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl trifluoromethanesulfonate. To a solution of 1,3,3a,4,6,6a-hexahydropentalene-2,5-dione (40.0g, 289.5 mmol) and pyridine (24.0 g, 304.0 mmol) in dichloromethane (600 ml) was added Tf_2O (89.8 g, 318.5 mmol) dropwise at room temperature. The mixture was stirred at room temperature for 3 h. Brine (300 mL) was added, and the aqueous layer extracted with dichloromethane (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 (*v/v*) petroleum ether/ethyl acetate to afford 5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl trifluoromethanesulfonate as a yellow oil. ^1H 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 2



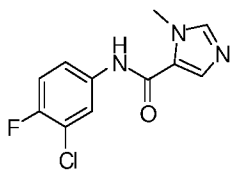
5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydropentalen-2(1H)-one. A mixture of 5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl trifluoromethanesulfonate (110.0 g, 407.0 mmol), 4,4,5,5-tetramethyl-2-(4, 4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (108.5 g, 427.4 mmol), $Pd(dppf)Cl_2$ (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®545 and the filter cake was washed with EtOAc (250 mL x 3). The filtrate was concentrated under vacuo 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 3



Methyl 2,4-dibromo-1-methyl-1H-imidazole-5-carboxylate. To a solution of methyl 1-methyl-1H-imidazole-5-carboxylate (16.6 g, 118.5 mmol) in $CHCl_3$ (200 mL) was added NBS (78.3 g, 414.8 mmol) and AIBN (1.95 g, 11.9 mmol). The reaction mixture was stirred at 60 °C for 24 h. The mixture was concentrated and purified by column chromatography (R_f=0.4, petroleum ether: ethyl acetate=5:1) to give methyl 2,4-dibromo-1-methyl-1H-imidazole-5-carboxylate (22.2 g, 63% yield) as a yellow solid.

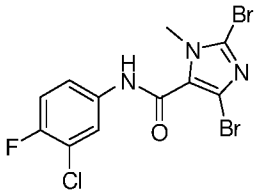
Intermediate 4



N-(3-Chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of 1-methyl-1H-imidazole-5-carboxylic acid (10 g, 83 mmol), 3-chloro-4-fluoroaniline (18 g, 124 mmol) and Et_3N (16 g, 160 mmol) in DMF (100 mL) was added

HATU (63 g, 160 mmol) at room temperature. The reaction mixture was stirred at 25 °C overnight then poured into water (200 mL). Yellow solids were formed from the solution which was filtered and dried to provide N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide as a pale white solid. TLC; (50% ethyl acetate/petroleum ether) (Rf: 0.3). MS calcd. for $C_{11}H_9ClFN_3O$: 253.0; Found: 254.1 $[M+1]^+$.

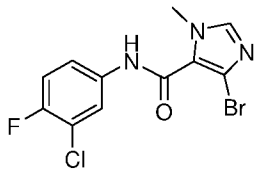
Intermediate 5



2,4-Dibromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide (4 g, 15 mmol) in $CHCl_3$ (100 mL) was added NBS (10 g, 60 mmol) and AIBN (0.25 g, 1.5 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 18 h. The mixture was evaporated under *vacuo* to give a yellow residue. The residue was purified by silica gel chromatography to give 2,4-dibromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide as yellow solid. TLC; 40% ethyl acetate / petroleum ether (*Rf*: 0.3). MS calcd. for $C_{11}H_7Br_2ClFN_3O$: 408.9; Found; 411.2 $[M+2]^+$.

Alternative synthesis of 2,4-Dibromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of 2,4-dibromo-1-methyl-1H-imidazole-5-carboxylic acid (9.94 g, 35.0 mmol) in DMF (50 mL) was added HATU (13.3 g, 35.0 mmol) and DIPEA (9.69 g, 175 mmol) at 0 °C, the reaction mixture was stirred at 0 °C for 1 h. Then 3-chloro-4-fluoroaniline (6.1 g, 42.0 mmol) was added and the reaction mixture stirred at room temperature overnight. The mixture was added dropwise to water (600 mL), and the resulting precipitate filtered to provide 2,4-dibromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide (12.5 g, 87% yield) as a yellow solid.

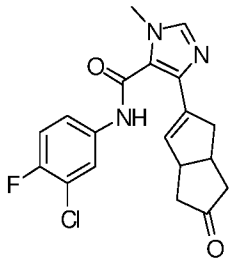
Intermediate 6



4-Bromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of 2,4-dibromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide (1.1 g, 2.0 mmol) in THF (50 mL) was added CH_3MgI (2 mL, 4.0 mmol) slowly at room temperature. The reaction mixture was stirred at 50 °C for 4 h then poured into water (50 ml) and extracted with ethyl acetate (20 mL x 3). The organic layer was dried and concentrated. The residue was purified by silica gel chromatography to give 4-bromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide as a yellow solid. TLC; 50% ethyl acetate/petroleum ether (Rf: 0.3). MS calcd. for $C_{11}H_8BrClFN_3O$: 331.0; Found: 332.1 $[M + 1]^+$.

Alternative procedure for the synthesis of 4-bromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. The titled compound was synthesized following the general procedure described above for amidation (Method C) to afford 4-bromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide as a brown solid. TLC; 30% EtOAc/ hexanes (R_f: 0.45); ^1H NMR (DMSO-d_6, 400 MHz): δ 10.41 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.85 (s, 1H), 7.63-7.60 (m, 1H), 7.43 (t, J = 9.6 Hz, 1H), 3.75 (s, 3H); MS calcd. for $C_{11}H_8BrClFN_3O$: 331.0; Found: 332.1 $[M + 1]^+$.

Intermediate 7

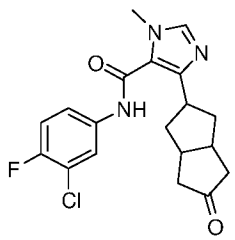


N-(3-Chloro-4-fluorophenyl)-1-methyl-4-(5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-1H-imidazole-5-carboxamide. A mixture of 4-bromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide (600 mg, 1.8 mmol), 5-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydropentalen-2(1H)-one (448 mg, 1.8 mmol), $Pd(dppf)Cl_2$ (62 mg, 0.077 mmol) and K_3PO_4 (814 mg, 3.6 mmol) in dioxane (20 mL) and water (4 mL) was stirred at 100 °C for 4 h under N_2. EtOAc (20 mL) was then added to the mixture. The mixture was filtered, and the filtrate washed with H_2O (35 mL x 3). The organic layer was separated, dried over Na_2SO_4, and evaporated *in vacuo* to give a yellow residue. The residue was purified by silica gel column chromatography using 20 - 50% petroleum ether/ethyl acetate to give N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-1H-imidazole-5-carboxamide as a brown solid. TLC; 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{19}H_{17}ClFN_3O_2$: 373.13. Found; 374.1 $[M+1]^+$.

Alternative synthesis of N-(3-Chloro-4-fluorophenyl)-1-methyl-4-(5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-1H-imidazole-5-carboxamide. To a solution of 4-bromo-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide (13.3 g, 40.0 mmol) in 1,4-dioxane/H_2O (v/v = 7/1 (v/v), 120 mL) were added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,6,6a-tetrahydropentalen-2(1H)-one (12.2 g, 48.0 mmol), $Pd(dppf)Cl_2$ (2.9 g, 4.0 mmol) and Na_2CO_3 (10.6 g, 100.0 mmol), respectively, and the mixture was stirred at 100 °C overnight. The reaction mixture was cooled to room temperature, filtered through a pad of Celite. The solid was washed with ethyl acetate and the filtrate was concentrated to give the crude product, which was purified by column chromatography on silica gel with 5% of methanol in dichloromethane (120 g silica gel column, 60 mL/min) to afford N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-1H-imidazole-5-carboxamide (12.8 g, 85.6%) as a brown solid. TLC: 7% methanol/dichloromethane (R_f: 0.5); MS calcd. for $C_{19}H_{17}ClFN_3O_2$: 373.1; Found: 374.3 $[M+1]^+$.

Example 1



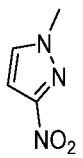
N-(3-Chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide. To a solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxo-

1,3a,4,5,6,6a-hexahydropentalen-2-yl)-1H-imidazole-5-carboxamide (300 mg, 0.8 mmol) in THF (20 ml) was added Pd/C (30 mg, 10% Pd). The mixture was stirred at 30 °C for 5 h under H_2. The mixture was filtered, and the filtrate was evaporated *in vacuo* to give a yellow residue. The residue was purified by silica gel chromatography to give N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide a brown solid, as a single diastereomer. TLC; 50% ethyl acetate / petroleum ether (R_f: 0.3). MS calcd. for $C_{19}H_{19}ClFN_3O_2$: 375.2; Found; 376.2 $[M + 1]^+$.

Alternative synthesis of N-(3-Chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide

To a solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-1H-imidazole-5-carboxamide (12.8 g, 34.2 mmol) in THF (200 mL) was added Pd/C (6.4 g, 10%) under H_2 and the mixture stirred at room temperature for 4 hours. The mixture was filtered through a pad of Celite and washed with methanol. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel with 5% of methanol in dichloromethane (80 g silica gel column, 50 mL/min) to afford N-(3-Chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide, a gray solid, as a single diastereomer. TLC: 7% methanol/dichloromethane (R_f: 0.5); MS calcd. for $C_{19}H_{19}ClFN_3O_2$: 375.2; MS Found: 376.3 $[M + 1]^+$.

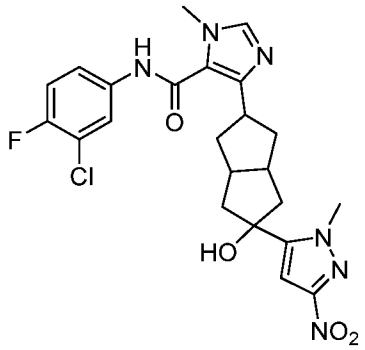
Intermediate 8



1-Methyl-3-nitro-1H-pyrazole. NaOtBu (19.11 g, 199.1 mmol) was added to a stirred solution of 3-nitro-1H-pyrazole (15 g, 132.7 mmol) in DMF (150 mL) at 0 °C, and the reaction was stirred for 20 minutes. To this solution was added MeI (9.91 mL 159.24 mmol) dropwise. The resulting reaction mixture was stirred at RT for 16 h. After completion, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to

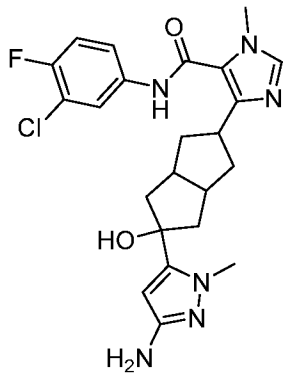
afford the title compound as an off-white solid. TLC: 20% EtOAc/hexane (R_f: 0.2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (s, 1H), 7.03 (d, J = 2.0 Hz, 1H), 3.97 (s, 3H).

Intermediate 9



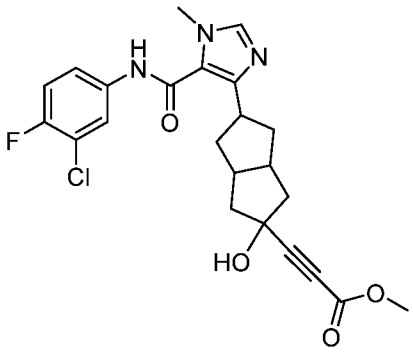
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-nitro-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Under an inert atmosphere, LDA (2M in THF, 60 mL, 120 mmol) was added dropwise to a stirred solution of 1-methyl-3-nitro-1H-pyrazole (10.16 g, 80 mmol) in dry THF (100 mL) at -78 °C, and the stirring continued for 2 h. To this was added a solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (3 g, 8 mmol) in THF at -78 °C. The mixture was stirred at -78°C for 1 h. The reaction was then quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the title compound as an off-white solid. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{23}H_{24}ClFN_6O_4$: 502.15; Found: 503.3 $[M+1]^+$.

Intermediate 10



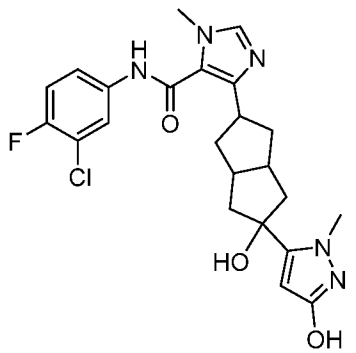
4-(5-(3-Amino-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. Under a nitrogen atmosphere 10% Pd/C (0.5 g) and $NaBH_4$ (1.06 g, 27.88 mmol) were added to a stirred solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-nitro-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (2 g, 3.98 mmol) in MeOH (20 mL). The reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was filtered through a pad of Celite and washed with methanol. The filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the title compound as an off-white solid. TLC: 10% MeOH/dichloromethane (R_f: 0.1). MS calcd for $C_{23}H_{26}ClFN_6O_2$; 472.18. Found; 471.20 $[M-1]^-$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H), 7.95 (d, J = 4.4 Hz, 1H), 7.76 (s, 1H), 7.58-7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 6.62-5.57 (br.s, 2H), 5.39 (s, 1H), 5.17 (s, 1H), 3.69 (s, 6H), 3.32-3.31 (m, 1H, merged), 2.50-2.32(m, 2H, merged), 2.29-2.11 (m, 4H), 1.85-1.83 (m, 4H).

Intermediate 11



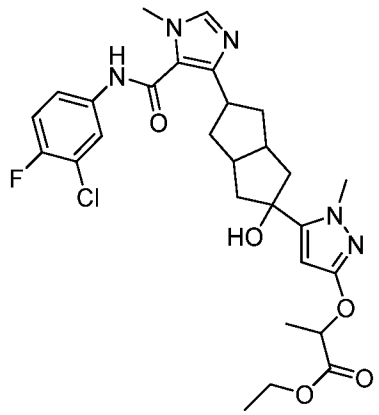
Methyl 3-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)propiolate. In an inert atmosphere *n*-BuLi (1.19 g, 18.6 mmol) was added to a stirred solution of methyl propionate (1.56 g, 18.6 mmol) in dry THF (40 mL) at -78 °C and the reaction mixture was stirred for 30 minutes. A solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (1 g, 2.66 mmol) in THF was added at -78 °C. The mixture was stirred at -78 °C for 2h. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the title compound as an off-white solid. TLC: 5% MeOH/dichloromethane (R_f: 0.3). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.95 (d, J = 6.4 Hz, 1H), 7.74-7.68 (m, 1H), 7.59-7.55 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.79 (s, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 3.28-3.23 (m, 1H), 2.58-2.54 (m, 2H), 2.09-2.06 (m, 4H), 1.80-1.76 (m, 4H). MS calcd. for $C_{23}H_{23}ClFN_3O_4$: 459.14; Found: 460 $[M+1]^+$.

Intermediate 12



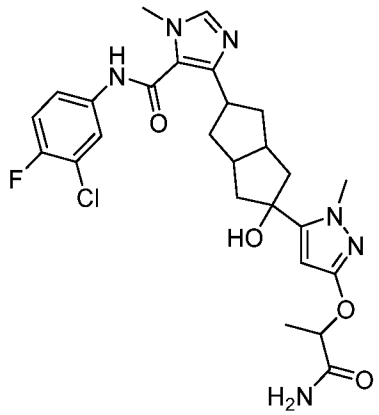
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Triethylamine (2 g, 19.82 mmol) and methyl 3-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)propiolate (1.3 g, 2.83 mmol) were added to a stirred solution of methyl hydrazine sulphate (2.85 g, 19.82 mmol) in EtOH (20 mL). The reaction mixture was stirred at 50 °C for 24 h. The mixture was concentrated under reduced pressure. The residue was diluted with 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 the title compound as a white solid. TLC: 8% MeOH/dichloromethane (R_f: 0.2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.18 (s, 1H), 9.27 (s, 1H), 7.95 (d, J = 4.4 Hz, 1H), 7.64 (s, 1H), 7.61-7.55 (m, 1H), 7.39 (t, J = 8.8 Hz, 1H), 5.28 (s, 1H), 5.13 (s, 1H), 3.66 (s, 6H), 3.38-3.18 (m, 1H, merged), 2.60-2.38 (m, 2H, merged), 2.20-2.01 (m, 4H), 1.91-1.75 (m, 4H). MS calcd. for $C_{23}H_{25}ClFN_5O_3$; 473.16; Found: 473.90 $[M+1]^+$.

Intermediate 13



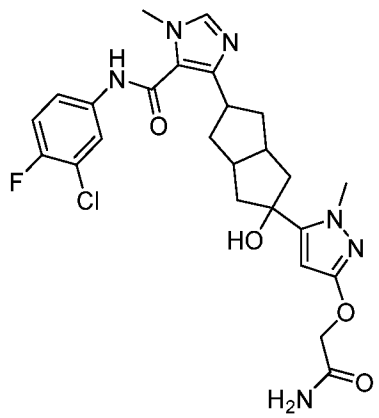
Ethyl 2-((5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)oxy)propanoate. The title compound was synthesized from **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** and ethyl 2-bromopropanoate according to method 1. TLC: 10% MeOH/dichloromethane (R_f: 0.5). MS calcd. for $C_{28}H_{33}ClFN_5O_5$; 573.22; Found: 572.35 $[M-1]^-$.

Example 2



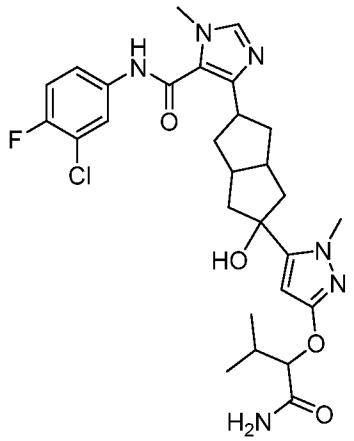
4-(5-(3-((1-Amino-1-oxopropan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. A mixture of ethyl 2-((5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)oxy)propanoate (70 mg, 0.122 mmol) and methanolic ammonia (3 mL) was heated at 70°C for 12 h. The mixture was concentrated under reduced pressure. The crude product was purified by CombiFlash column chromatography followed by prep. HPLC to afford the title compound as an off-white solid. MS calcd. for $C_{26}H_{30}ClFN_6O_4$; 544.20. Found; 545.15 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.98-7.94 (m, 1H), 7.65 (s, 1H), 7.56-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 7.26 (s, 1H), 7.10 (s, 1H), 5.53 (s, 1H), 5.25 (s, 1H), 4.67 (q, J = 6.8 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.25-3.20 (m, 1H), 2.50-2.44 (m, 2H), 2.15-2.06 (m, 4H), 1.88-1.80 (m, 4H), 1.34 (d, J = 6.4 Hz, 3H) ppm.

Example 3



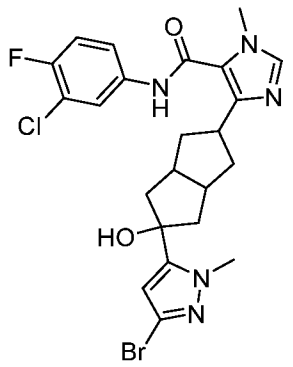
4-(5-(3-(2-Amino-2-oxoethoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. Methanolic ammonia (2 mL) was added to a stirred solution of ethyl 2-((5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)oxy)acetate (70 mg, 0.125 mmol) in THF (1 mL). The reaction mixture was stirred at 70°C for 10 h. The mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the title compound as an off-white solid. MS calcd. for $C_{25}H_{28}ClFN_6O_4$; 530.18. Found; 531.15 531.15 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.96 (d, J = 4.8 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 7.30-7.22 (m, 2H), 5.56 (s, 1H), 5.26 (s, 1H), 4.38 (s, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 3.27-3.21 (m, 1H), 2.50-2.42 (m, 2H), 2.19-2.06 (m, 4H), 1.90-1.80 (m, 4H) ppm.

Example 4



4-(5-(3-((1-Amino-3-methyl-1-oxobutan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. The title compound was synthesized from N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide and 2-bromo-3-methylbutanamideaccording to Method 1. TLC: 7% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{28}H_{34}ClFN_6O_4$; 572.23. Found; 555.20 $[M-18+1]^+$; ^1H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.65 (s. 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 7.19 (s, 1H), 7.11 (s, 1H), 5.55 (s, 1H), 5.25 (s, 1H), 4.36 (d, J = 4.8 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.28-3.22 (m, 1H), 2.48-2.44 (m, 3H, merged), 2.18-2.06 (m, 4H), 1.90-1.80 (m, 4H), 0.96-0.90 (m, 6H) ppm.

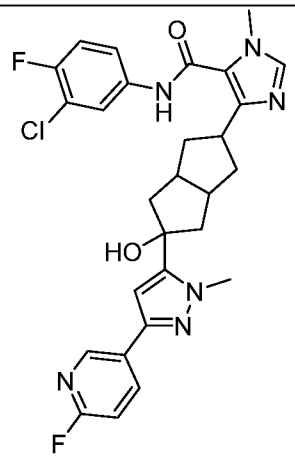
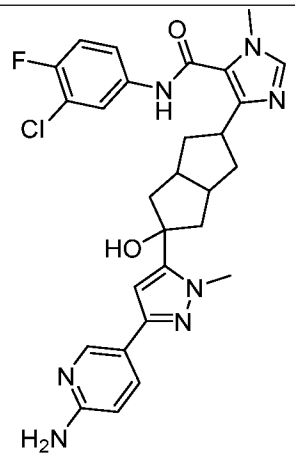
Intermediate 14

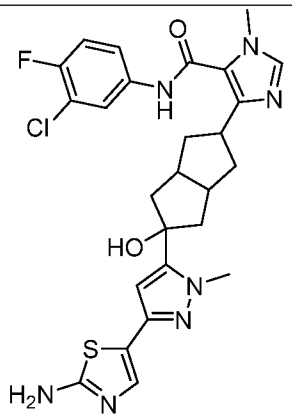
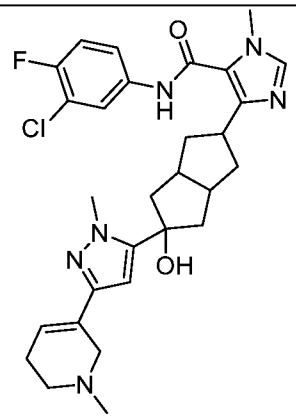


4-(5-(3-Bromo-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. In an inert atmosphere *n*-BuLi (2 M in THF, 7.8 mL, 15.96 mmol) was added dropwise to a stirred solution of 3,5-dibromo-1-methyl-1*H*-pyrazole (3.8 g, 15.96 mmol) in dry THF (50 mL) at -78 °C and the mixture stirred for 35 minutes. To this was added a solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (1 g, 2.65 mmol) in THF slowly at -78°C. The mixture was allowed to regain room temperature and stirred for 16 h. The reaction mixture was diluted with sat. aq. ammonium chloride and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the title compound. TLC: 5% MeOH/dichloromethane (R_f: 0.3). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.58-7.55 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 6.23 (s, 1H), 5.37 (s, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 3.29-3.23 (m, 1H), 2.50-2.46 (m, 2H, merged), 2.22-2.07 (m, 4H), 1.87-1.83 (m, 4H) ppm. MS calcd. for $C_{23}H_{24}BrClFN_5O_2$; 535.08; Found: 536.10 $[M+1]^+$.

Tables 1-5 show structures and analytical data for representative Examples of the invention. While the structures of the Examples shown throughout this specification are drawn without stereochemistry, unless otherwise specified they represent single isomer with stereochemistry consistent with the crystal structure shown below for reference compound AIA-227.

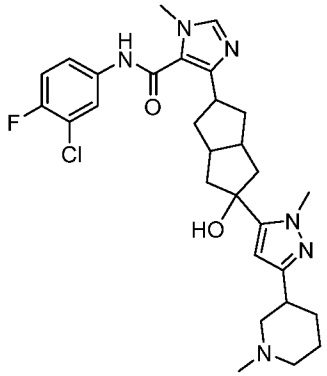
Table 1. Examples 5-8 were synthesized from 4-(5-(3-bromo-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide and the corresponding boronic acid according to Method 3, Method 4 or Method 5.

Example	Structure, ^{1}H NMR, and MS
5	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(6-fluoropyridin-3-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{28}H_{27}ClF_2N_6O_2$; 552.19. Found; 553.10 $[M+1]^+$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 8.59 (s, 1H), 8.29 (t, J = 7.6 Hz, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.65 (s, 1H), 7.61-7.52 (m, 1H), 7.39 (t, J = 8.8 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 6.71 (s, 1H), 5.36 (s, 1H), 3.96 (s, 3H), 3.67 (s, 3H), 3.41-3.20 (m, 1H, merged), 2.36-2.24 (m, 3H), 2.19-2.08 (m, 2H), 1.96-1.79 (m, 5H) ppm.
6	

	4-(5-(3-(6-Aminopyridin-3-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide MS calcd. for $C_{28}H_{29}ClFN_7O_2$; 549.21. Found; 550.00 $[M+1]^+$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 8.29 (s, 1H), 7.96 (d, J = 5.2 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.66 (s, 1H), 7.8-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 6.44-6.40 (m, 2H), 5.92 (s, 2H), 5.26 (s, 1H), 3.90 (s, 3H), 3.68 (s, 3H), 3.20-3.22 (m, 1H), 2.55-2.40 (m, 2H, merged), 2.30-2.23 (m, 2H), 2.14-2.08 (m, 2H), 1.92-1.80 (m, 4H) ppm.
7	 **4-(5-(3-(2-aminothiazol-5-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-Chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{26}H_{27}ClFN_7O_2S$; 555.16. Found; 556.10 $[M+1]^+$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.96 (d, J = 6.4 Hz, 1H), 7.66 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 7.19 (s, 1H), 6.93 (s, 2H), 6.33 (s, 1H), 5.29 (s,1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.29-3.24 (m, 1H), 2.55-2.45 (m, 2H, merged), 2.26-2.21 (m, 2H), 2.15-2.08 (m, 2H), 1.90-1.85 (m, 4H) ppm.
8	

	N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide MS calcd. for $C_{29}H_{34}ClFN_6O_2$; 552.24. Found; 553 $[M+1]^+$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.79 (s, 1H), 8.74 (s, 1H), 7.96 (d, J = 4.8 Hz, 1H), 7.62-7.55 (m, 1H), 7.44 (t, J = 8.8 Hz, 1H), 6.40 (s, 1H), 6.33 (s, 1H), 5.58-5.12 (m, 1H), 4.29-4.18 (m, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.53-3.44 (m, 2H), 3.39-3.26 (m, 1H), 3.19-3.03 (m, 1H), 2.91 (s, 3H), 2.60-2.38 (m, 4H, merged), 2.31-2.18 (m, 4H), 1.96-1.70 (m, 4H) ppm.

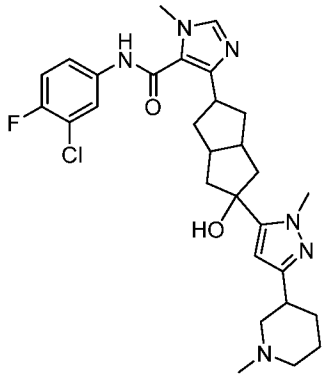
Example 9



N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(1-methylpiperidin-3-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I. 20% $Pd(OH)_2$ (20 mg) was added to a stirred solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide(55 mg, 0.099 mmol) in EtOAc (30 mL) in an autoclave, under nitrogen atmosphere. The reaction mixture was stirred at 40°C under a hydrogen atmosphere (100 psi) for 8 h. The reaction mixture was then filtered through a pad of Celite and washed with methanol. The filtrate was concentrated under reduced pressure to the crude product was purified by prep-HPLC to afford the title compound (8 mg, 14.4%) as a mixture of enantiomers. TLC: 5% MeOH/dichloromethane (R_f: 0.4). The reaction was repeated on 150 mg scale to afford 80 mg of racemic compound which was purified for chiral prep HPLC purification to afford the pure enantiomers (Isomer I and Isomer II). N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(1-methylpiperidin-3-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer

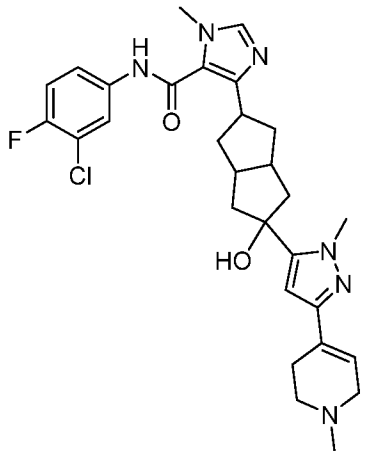
I and Isomer II. Isomer I MS calcd. for $C_{29}H_{36}ClFN_6O_2$; 554.26. Found; 553.60 $[M-1]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.65 (s, 1H), 7.60-7.52 (m, 1H), 7.40 (t, J = 9.6 Hz, 1H), 5.90 (s, 1H), 5.17 (s, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.30-3.20 (m, 2H), 2.87-2.82 (m, 1H), 2.72-2.60 (m, 2H), 2.45-2.40 (m, 3H), 2.10-2.05 (m, 7H), 1.90-1.72 (m, 6H), 1.65-1.50 (m, 2H) ppm.

Example 10



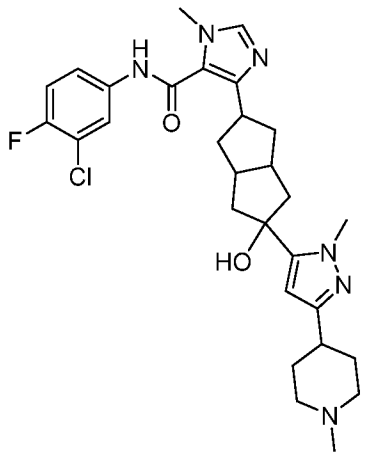
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(1-methylpiperidin-3-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II. MS calcd. for $C_{29}H_{36}ClFN_6O_2$; 554.26. Found; 555.70 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.96 (d, J = 4.4 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.91 (s, 1H), 5.18 (s, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 2.92-2.88 (m, 1H), 2.80-2.74 (m, 1H), 2.70-2.64 (m, 1H), 2.49-2.42 (m, 2H), 2.20-2.06 (m, 8H), 1.94-1.80 (m, 8H), 1.64-1.50 (m, 2H) ppm.

Intermediate 15



N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. The above title was synthesized from 4-(5-(3-bromo-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide and (1-methyl-1,2,3,6-tetrahydropyridin-4-yl)boronic acid according to Method 4.

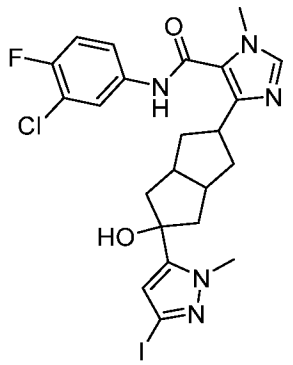
Example 11



N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(1-methylpiperidin-4-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. In an autoclave, 10% Pd/C (20 mg) was added to a stirred solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-

pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (50 mg, 0.090 mmol) in EtOAc (10 mL) under nitrogen atmosphere. The reaction mixture was stirred in at 40°C under hydrogen atmosphere (100 psi) for 16 h. The reaction mixture was then filtered through a pad of Celite and washed with methanol. The filtrate was concentrated under reduced pressure. The crude product was purified by prep-HPLC to afford the title compound as an off-white solid. MS calcd. for $C_{29}H_{36}ClFN_6O$; 554.26. Found; 555.70 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.98-7.94 (m, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.90 (s, 1H), 5.16 (s, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.35-3.20 (m, 2H, merged), 2.88-2.82 (m, 2H), 2.45-2.36 (m, 2H), 2.23 (s, 3H), 2.20-2.15 (m, 2H), 2.08-2.00 (m, 4H), 1.90-1.78 (m, 6H), 1.62-1.54 (m, 2H) ppm.

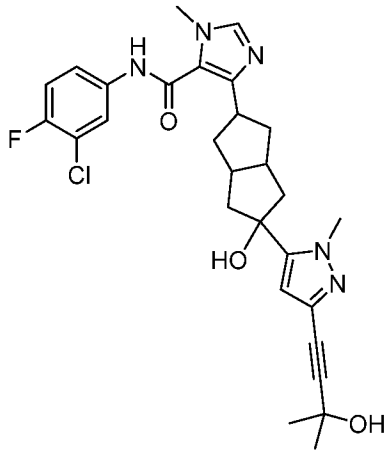
Intermediate 16



N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-iodo-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. LDA (2.8 g, 2.66 mmol) was added slowly to a stirred solution of 3-iodo-1-methyl-1*H*-pyrazole (5.5 g, 2.66 mmol) in dry THF (30 mL) at -78 °C and the mixture stirred for 1 h. To this solution was added N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (1 g, 2.66 mmol) at -78 °C. The resulting reaction mixture was stirred at RT for 2 h. The reaction was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using 1-2% MeOH in dichloromethane to afford the title compound as a white solid. TLC: 10% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{23}H_{24}ClFIN_5O_2$; 583.06; Found; 584.05 $[M+1]^+$; ^1H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (d, J = 4.8 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.0 Hz, 1H),

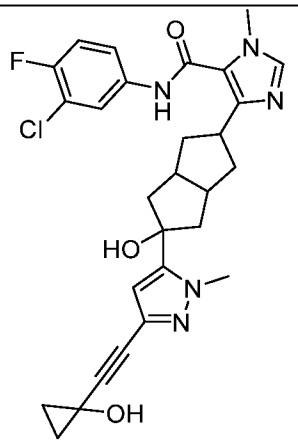
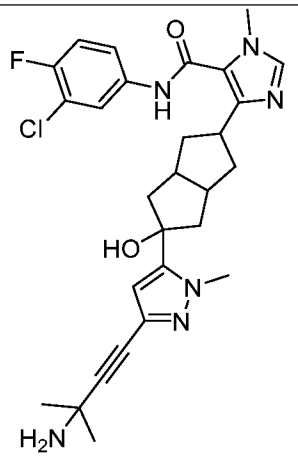
6.29 (s, 1H), 5.33 (s, 1H), 3.90 (s, 3H), 3.67 (s, 3H), 3.26-3.23 (m, 1H), 2.49-2.45 (m, 2H), 2.21-2.14 (m, 2H), 2.10-2.07 (m, 2H), 1.87-1.83 (m, 4H) ppm.

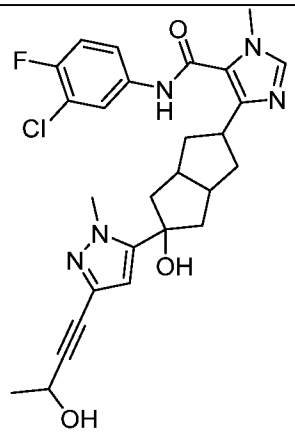
Example 12

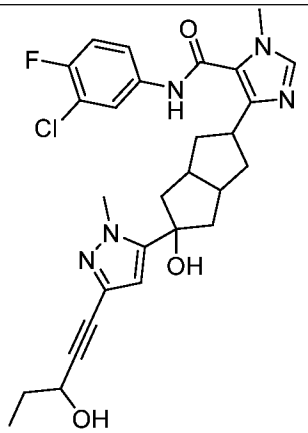
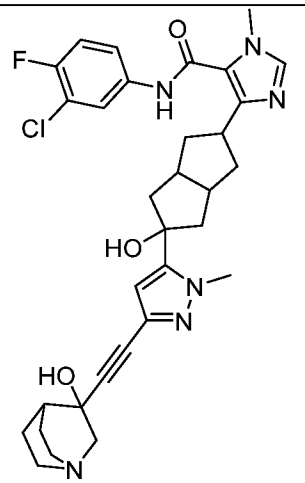


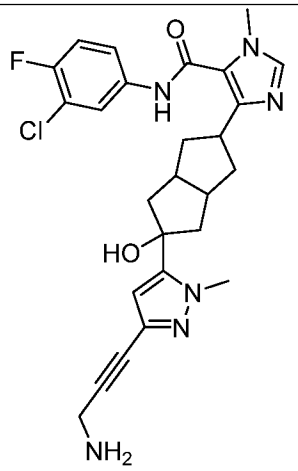
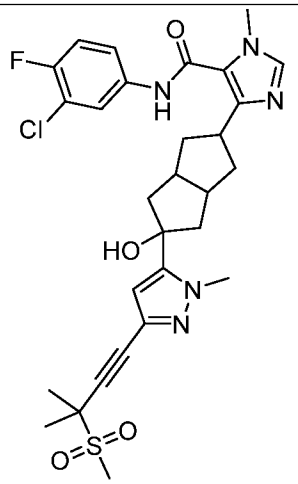
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. The title compound was synthesized from N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-iodo-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide and 2-methylbut-3-yn-2-ol according to Method 6. TLC**:** 10% MeOH in dichloromethane (*Rf*: 0.5). MS calcd. for $C_{28}H_{31}ClFN_5O_3$; 539.21. Found; 522.15 $[M-18+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.70-7.64 (m, 1H), 7.60-7.52 (m, 1H), 7.40 (t, *J* = 9.6 Hz, 1H), 6.20 (s, 1H), 5.40 (s, 1H), 5.33 (s, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.28-3.20 (m, 1H), 2.48-2.40 (m, 2H), 2.24-2.16 (m, 2H), 2.12-2.02 (m, 2H), 1.90-1.76 (m, 4H), 1.41 (s, 6H) ppm.

Table 2. Examples 13-19 were synthesized from 4-(5-(3-bromo-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide and the corresponding boronic acid according to Method 6

Example	Structure ^{1}H NMR and MS
13	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1-hydroxycyclopropyl)ethynyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{28}H_{29}ClFN_5O_3$: 537.19. Found; 538.10 $[M+1]^+$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.96 (d, J = 6.0 Hz, 1H), 7.65 (s, 1H), 7.60-7.52 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 6.24-6.20 (m, 2H), 5.32 (s, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.30-3.20 (m, 1H), 2.50-2.40 (m, 2H), 2.22-2.00 (m, 4H), 1.90-1.80 (m, 4H), 0.95-0.85 (m, 4H) ppm.
14	

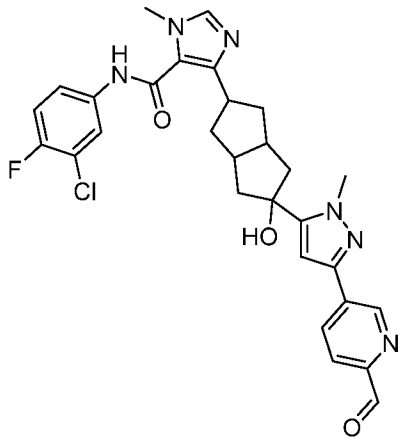
	4-(5-(3-(3-Amino-3-methylbut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide MS calcd. for $C_{28}H_{32}ClFN_6O_2$: 538.23. Found: 540.15 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.95 (d, J = 4.8 Hz, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6. 20 (s, 1H), 5.34 (s, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.50-3.20 (m, 3H, merged), 2.45-2.20 (m, 2H), 2.22-2.19 (m, 2H), 2.10-2.07 (m, 2H), 1.90-1.83 (m, 4H), 1.42 (s, 6H) ppm.
15	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxybut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** MS calcd. for $C_{27}H_{29}ClFN_5O_3$: 525.19. Found: 526.6 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.97-7.93 (m, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6.22 (s, 1H), 5.40 (d, J = 5.2 Hz, 1H), 5.33 (s, 1H), 4.53 (p, J = 6.4 Hz, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.26-3.20 (m, 1H), 2.46-2.40 (m, 2H), 2.22-2.14 (m, 2H), 2.10-2.04 (m, 2H), 1.90-1.82 (m, 4H), 1.33 (d, J = 6.8 Hz, 3H) ppm.

16	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxypent-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{28}H_{31}ClFN_5O_3$: 539.21. Found: 540.15 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.65 (s, 1H), 7.60-7.52 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6.22 (s, 1H), 5.37 (d, J = 5.2 Hz, 1H), 5.32 (s, 1H), 4.33-4.28 (m, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 3.26-3.20 (m, 1H), 2.45-2.40 (m, 2H), 2.22-2.17 (m, 2H), 2.10 -2.08 (m, 2H), 1.90-1.82 (m, 4H), 1.65-1.58 (m, 2H), 0.93 (t, J= 7.2 H, 3H) ppm.
17	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((3-hydroxyquinuclidin-3-yl)ethynyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{32}H_{36}ClFN_6O_3$: 606.25. Found: 304.5 $[M/2+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.94 (d, J = 6.0 Hz, 1H), 7.65 (s, 1H), 7.60-7.52 (m, 1H), 7.39 (t, J = 9.2 Hz, 1H), 6.22 (s, 1H), 5.85 (s, 1H),

	5.32 (s, 1H), 3.88 (s, 3H), 3.66 (s, 3H), 3.20-3.10 (m, 1H), 2.98-2.92 (m, 2H), 2.88-2.80 (m, 4H), 2.45-2.40 (m, 2H), 2.22-2.16 (m, 2H), 2.10-1.90 (m, 4H), 1.86-1.80 (m, 5H), 1.70-1.40 (m, 2H) ppm.
18	 **4-(5-(3-(3-Aminoprop-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for C26H28ClFN6O2: 510.19. Found: 511.05 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6.21 (s, 1H), 5.33 (br.s, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.50-3.20 (m, 3H, merged), 2.45-2.40 (m, 2H), 2.22-2.16 (m, 2H), 2.10-2.06 (m, 2H), 1.88-1.82 (m, 4H) ppm. NH_2 proton not observed.
19	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide**

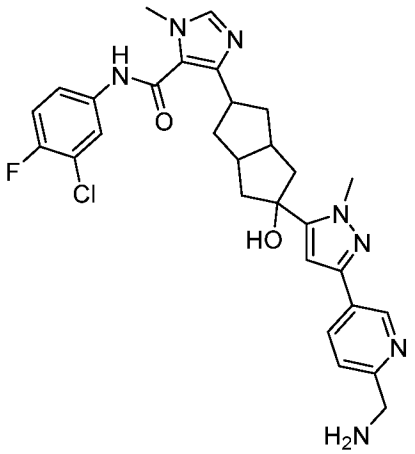
	MS calcd. for $C_{29}H_{33}ClFN_5O_4S$; 601.19. Found: 602.3 $[M+1]^+$ ^1H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.97-7.93 (m, 1H), 7.66 (s, 1H), 7.58-7.55 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 6.34 (s, 1H), 5.36 (s, 1H), 3.91 (s, 3H), 3.67 (s, 3H), 3.29-3.23 (m, 1H), 3.11 (s, 3H), 2.50-2.43 (m, 2H), 2.25-2.15 (m, 2H), 2.10-2.07 (m, 2H), 1.87-1.83 (m, 4H), 1.60 (s, 6H) ppm.

Intermediate 17



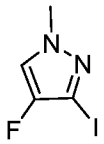
N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(6-formylpyridin-3-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. The above titled compound was synthesized from 4-(5-(3-bromo-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide and (6-formylpyridin-3-yl)boronic acid according to Method 4.TLC: 10% MeOH in dichloromethane (R_f: 0.2). MS calcd. for $C_{29}H_{28}ClFN_6O_3$: 562.19. Found; 563 $[M+1]^+$.

Example 20



4-(5-(3-(6-(Aminomethyl)pyridin-3-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. Ammonium acetate (54.8 mg, 0.71 mmol) was added to a stirred solution of N-(3-chloro-4-fluorophenyl)-4-(5-(3-(6-formylpyridin-3-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (40 mg, 0.071 mmol) in MeOH (2 mL) at 0 °C and the mixture stirred at RT for 1 h. Sodium cyano borohydride (6.7 mg, 0.106 mmol) was then added and stirring continued at RT for 16 h. The reaction mixture was then concentrated under reduced pressure. The crude product was purified by prep. HPLC to afford the title compound as an off-white solid. TLC: 20% MeOH in dichloromethane (R_f: 0.1). MS calcd. for $C_{29}H_{31}ClFN_7O_2$: 563.22. Found: 564.03 $[M+1]^+$. ^1H NMR (400 MHz, CD_3OD): δ 9.02 (s, 1H), 8.38-8.30 (m, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 4.4 Hz, 1H), 7.56-7.52 (m, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 8.8 Hz, 1H), 6.69 (s, 1H), 4.29 (s, 2H), 4.08 (s, 3H), 3.89 (s, 3H), 3.50-3.35 (m, 1H), 2.70-2.65 (m, 2H), 2.49-2.35 (m, 4H), 2.11-1.90 (m, 4H) ppm. NH_2 proton not observed.

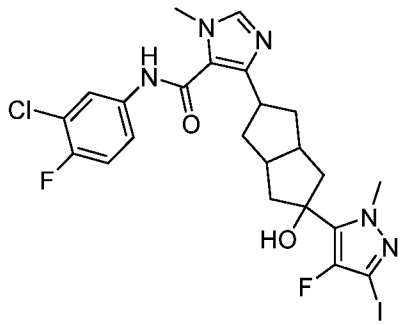
Intermediate 18



4-Fluoro-3-iodo-1-methyl-1*H*-pyrazole. N-Iodosuccinimide (20.4 g, 90.69 mmol) was added to a stirred solution of 4-fluoro-1-1*H*-pyrazole (7.8 g, 90.69 mmol) in $CHCl_3$ (120

mL). The reaction mixture was stirred at RT for 16 h. The reaction mixture was filtered, and the filtrate diluted with saturated sodium thiosulphate solution and extracted with chloroform. The organic layer was collected; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by CombiFlash column chromatography to afford 4-fluoro-3-iodo-1*H*-pyrazole as a white solid. TLC: 50% EtOAc/hexane (R_f: 0.4); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.18 (s, 1H), 7.83 (s, 1H). To a stirred solution of 4-fluoro-3-iodo-1*H*-pyrazole (6g, 28.3) in dry THF (60 mL at 0 °C) was added NaH (1.36 g, 33.9 mmol) in portions and the reaction mixture stirred at 0 °C for 5 min. MeI (8.81 mL, 141 mmol) was then added dropwise. The reaction mixture was stirred at RT for 2h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the title compound as an off-white solid. TLC: 20% EtOAc/Hexane (R*f*: 0.6). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (d, J = 8 Hz, 1H), 3.79 (s, 3H) ppm.

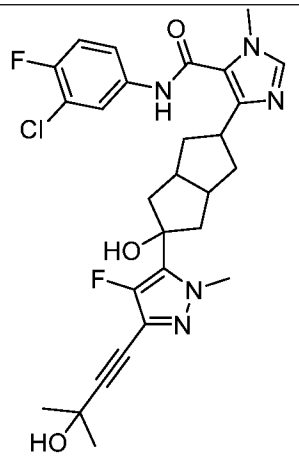
Intermediate 19

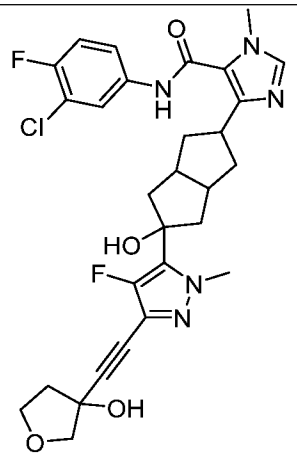
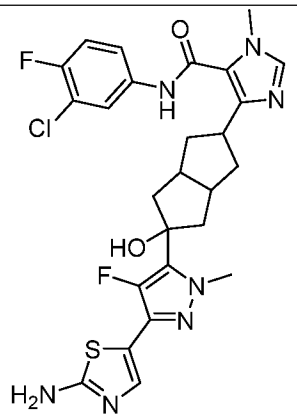


N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-iodo-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. LDA (5.33 mL, 10.66 mmol) was added dropwise to a stirred solution of 4-fluoro-3-iodo-1-methyl-1*H*-pyrazole (2.42 g, 10.66 mmol) in dry THF (30 mL) at -78°C and the reaction mixture stirred for 2 h. To this, a solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (0.4 g, 1.06 mmol) in THF was added at -78°C. The reaction mixture was allowed to warm to room temperature and stirred for 3h. The reaction was then quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica

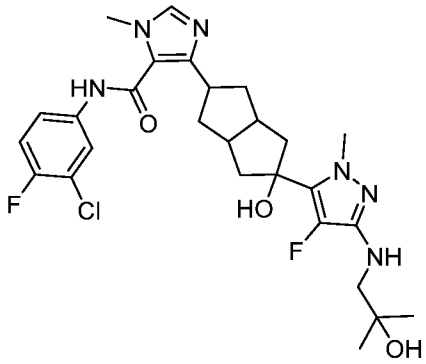
gel column chromatography to afford the title compound as an off-white solid. TLC: 5% MeOH/ dichloromethane (R_f: 0.3). ^{1}H NMR (400 MHz, DMSO-d_6): δ10.20 (s, 1H), 7.98-7.94 (m, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.44 (s, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 3.28-3.18 (m, 1H), 2.55-2.40 (m, 2H, merged), 2.24-2.18 (m, 2H), 2.10-2.06 (m, 2H), 1.98-1.90 (m, 4H) ppm. MS calcd. for $C_{23}H_{23}ClF_2IN_5O_2$: 601.06; Found: 602.10 $[M+1]^+$.

Table 3. Examples 21-23 were synthesized from N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-iodo-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide and the corresponding boronic acid according to Method 6

Example	Structure, ^{1}H NMR and MS
21	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(3-hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{28}H_{30}ClF_2N_5O_3$: 557.20. Found; 558.20 $[M+1]^+$ ^{1}H NMR (400 MHz, DMSO- d_6): δ 10.21 (s, 1H), 8.00-7.92 (m, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 5.51 (s, 1H), 5.45 (s, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 3.28-3.20 (m, 1H), 2.56-2.44 (m, 2H, merged),2.26-2.18 (m, 2H), 2.14-2.00 (m, 2H), 1.98-1.92 (m, 4H), 1.43 (s, 6H) ppm.

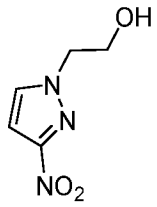
22	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-((3-hydroxytetrahydrofuran-3-yl)ethynyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{29}H_{30}ClF_2N_5O_4$: 585.20. Found: 586.30 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.30 (br.s, 1H), 7.96 (dd, *J* = 7.2, 2.8 Hz, 1H), 7.60-7.55 (m, 1H), 7.41 (t, *J* = 8.8 Hz, 1H), 5.98-5.82 (br.s, 1H), 5.54 (s, 1H), 3.90-3.84 (m, 6H), 3.81-3.66 (m, 4H), 3.34-3.30 (m,1H), 2.60-2.54 (m, 2H), 2.30-2.12 (m, 6H), 2.00-1.82 (m, 4H) ppm.
23	 **4-(5-(3-(2-Aminothiazol-5-yl)-4-fluoro-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{26}H_{26}ClF_2N_7O_2S$: 573.15. Found: 288.00 $[M/2+1]^+$ ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.21 (s, 1H), 7.96 (d, *J* = 6.4 Hz, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, *J* = 8.8 Hz, 1H), 7.12-7.08 (m, 3H), 5.41 (s, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.10-2.90 (m, 1H), 2.58-2.44 (m, 2H, merged), 2.34-2.24 (m, 2H), 2.15-2.08 (m, 2H), 2.00-1.90 (m, 4H) ppm.

Example 24



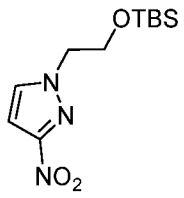
N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-((2-hydroxy-2-methylpropyl)amino)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. K_2CO_3 (99 mg, 0.415 mmol) and L-proline (7.6 mg, 0.066 mmol) were added to a mixture of N-(3-chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-iodo-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (100 mg, 0.166 mmol) and 1-amino-2-methylpropan-2-ol (29.6 mg, 0.33 mmol) in DMSO (3 mL) which was then purged with Argon for 10 min. To this solution, CuI (6.3 mg, 0.033 mmol) was added, and purging continued for another 10 min. The resulting reaction mixture was stirred at 90 °C for 16 h. The mixture was diluted with water and extracted with 10% MeOH/dichloromethane. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by prep. HPLC to afford the title compound. TLC: 10% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{27}H_{33}ClF_2N_6O_3$: 562.23. Found: 563.20 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (d, J = 6.8 Hz, 1H), 7.64 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.25 (s, 1H), 4.53 (t, J = 6.4 Hz, 1H), 4.45 (s, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 3.26-3.22 (m, 1H), 2.94 (d, J = 6.0 Hz, 2H),2.55-2.40 (m, 2H, merged), 2.25-2.20 (m, 2H), 2.12-2.06 (m, 2H), 1.98-1.85 (m, 4H), 1.10 (s, 6H) ppm.

Intermediate 20



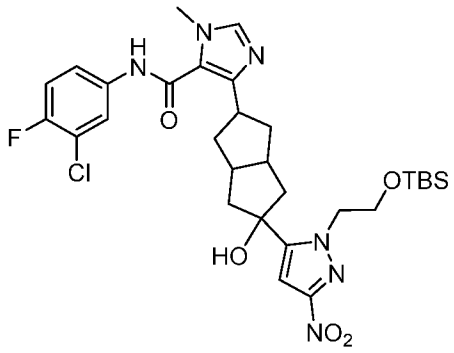
2-(3-Nitro-1*H*-pyrazol-1-yl)ethan-1-ol. To a stirred solution of compound 3-nitro-1H-pyrazole (5 g, 44.247 mmol) in THF (50 mL) was added, K_2CO_3 (12.22 g, 88.50 mmol) followed by 2-bromoethan-1-ol (8.22 g, 66.371 mmol) dropwise. The resulting reaction mixture was stirred at 70 °C for 16 h. After completion, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by column chromatography (100-200 mesh, using a gradient method of 80-90% EtOAc in hexane) to afford the title compound as an off white solid. TLC: 60% EtOAc/hexane (R_f: 0.2).

Intermediate 21



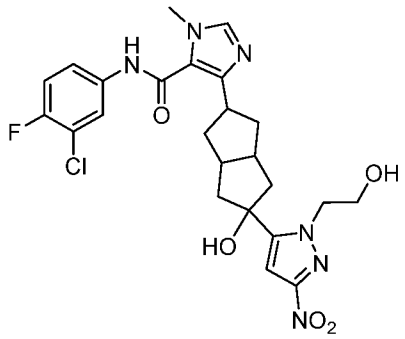
1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-3-nitro-1*H*-pyrazole. To a stirred solution of compound 2-(3-nitro-1*H*-pyrazol-1-yl)ethan-1-ol (2 g, 12.740 mmol) in dichloromethane (20 mL) was added imidazole (1.30 g, 19.108 mmol) followed by TBDMS-Cl (2.30 g 15.286 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 2 h. After completion the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by column chromatography (100-200 mesh, using a gradient method of 40-50% EtOAc in hexane) to afford the title compound as an off white solid. TLC: 50% EtOAc/hexane (R_f: 0.5).

Intermediate 22



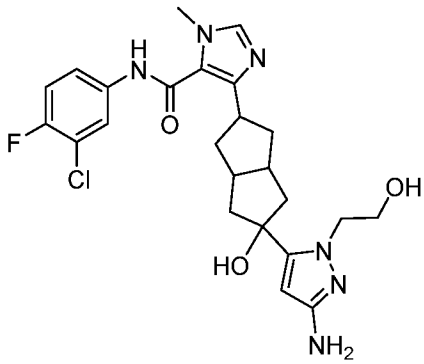
4-(5-(1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-3-nitro-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a stirred solution of compound 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-nitro-1*H*-pyrazole (23.12 g, 85.33 mmol) in dry THF (50 mL) at -78 °C in an inert atmosphere, LDA (2M in THF, 53.33 mL, 106.66 mmol) was added dropwise and the reaction mixture stirred at -78 °C for 2 h. To this, a solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (4.0 g, 10.66 mmol) in THF was added at -78 °C and the resulting reaction mixture was stirred at -78 °C for 2 h. After completion, the reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine; dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by Combiflash® column chromatography (using a gradient method of 1-2% MeOH in DCM) to afford the title compound as a pale yellow solid. TLC: 10% MeOH/DCM (R_f: 0.3). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 8.01 - 7.91 (m, 1H), 7.70 - 7.62 (m, 1H), 7.61 - 7.52 (m, 1H), 7.45 - 7.34 (m, 1H), 6.95 - 6.88 (m, 1H), 5.73 - 5.66 (m, 1H), 4.55 - 4.44 (m, 2H), 4.11 - 4.00 (m, 2H), 3.68 (s, 3H), 2.45 - 2.37 (m, 2H), 2.17 - 2.05 (m, 2H), 1.89 - 1.68 (m, 3H), 1.65 - 1.53 (m, 1H), 1.34 - 1.09 (m, 2H), 0.97 - 0.64 (m, 16H); MS calcd. for $C_{30}H_{40}ClFN_6O_5Si$: 646.25, Found: 647.55 $[M+1]^+$.

Intermediate 23



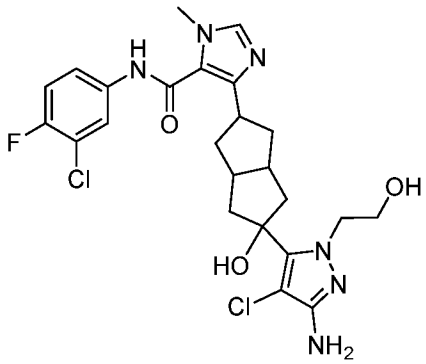
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-hydroxyethyl)-3-nitro-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide To a stirred solution of 4-(5-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-nitro-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide (0.55 g, 0.892 mmol) in THF (15 mL) under nitrogen atmosphere, was added TBAF (0.7 g, 2.678 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was quenched with aq. $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by column chromatography on silica gel (100-200 mesh, using a gradient method of 1-2% MeOH in dichloromethane) to afford the title compound as an off white solid. TLC: 10% MeOH/dichloromethane (R_f: 0.4).

Example 25



4-(5-(3-Amino-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a stirred solution of 4-(5-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-nitro-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide (0.55g, 0.892 mmol) in THF (15 mL) under nitrogen atmosphere, was added TBAF (0.7g, 2.678 mmol) and the mixture was stirred at RT for 2h. The reaction mixture was then quenched with aq. $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a thick oil. The crude product was purified by silica gel column chromatography to afford alcohol compound (0.247g, 56%) as an off-white solid. TLC: 10% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{24}H_{28}ClFN_6O_3$: 502.19. Found: 501.20 [M-1]$^-$. 10% Pd/C (15mg) and $NaBH_4$ (35mg, 0.92 mmol) were added to a stirred solution of the alcohol (0.1 g, 0.187 mmol) in MeOH (10 mL) under nitrogen atmosphere. The reaction mixture was stirred at RT for 5h. The reaction mixture was then filtered through a pad of Celite and washed with methanol. The filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography followed by prep-HPLC to afford the title compound as an off-white solid. TLC: 10% MeOH/dichloromethane (R_f: 0.1).

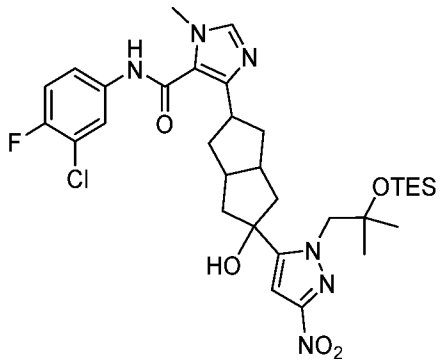
Example 26



4-(5-(3-Amino-4-chloro-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. N-Chlorosuccinimide (10 mg, 0.075 mmol) was added to a stirred solution of

4-(5-(3-amino-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide **SL-AIA-1222** (25 mg, 0.0498 mmol) in DMF (1.5 mL). The reaction mixture was stirred at RT for 2 h. The reaction was quenched with ice cold water and extracted with 5% MeOH/dichloromethane. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by CombiFlash column chromatography followed by prep. HPLC to afford the title compound as a white solid. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{24}H_{27}Cl_2FN_6O_3$: 536.15. Found: 519.10 $[M-18+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.96 (d, J = 5.6 Hz, 1H), 7.64 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.29 (s, 1H), 4.95-4.90 (m, 1H), 4.62 (s, 2H), 4.18 (t, J = 6.4 Hz, 2H), 3.70-3.60 (m, 5H), 3.30-3.15 (m, 1H), 2.60-2.55 (m, 2H), 2.42-2.30 (m, 2H), 2.08-1.90 (m, 6H) ppm.

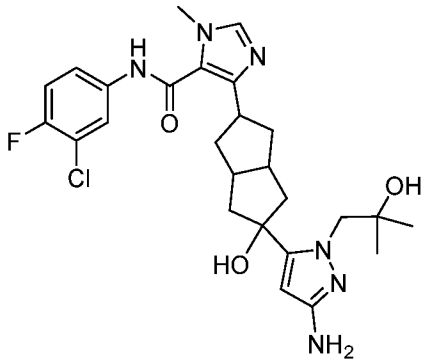
Intermediate 24



N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-methyl-2-((triethylsilyl)oxy)propyl)-3-nitro-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. LDA (1.99 g, 18.66 mmol) was added slowly to a stirred solution of 1-(2-methyl-2-((triethylsilyl)oxy)propyl)-3-nitro-1H-pyrazole (5.58 g, 1.866 mmol) in dry THF (40 mL) at -78°C in an inert atmosphere, and the reaction mixture stirred for 2 h. To this, a solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (0.7 g, 1.86 mmol) in THF was added at -78°C. The resulting reaction mixture was stirred at -78°C for 2 h. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to

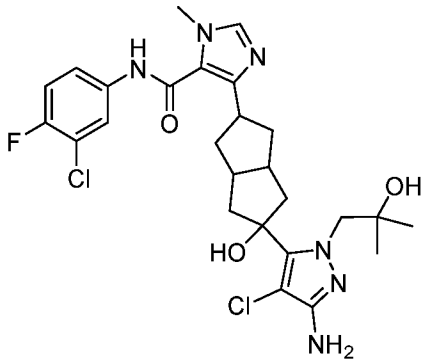
afford the title compound. TLC: 10% MeOH/dichloromethane (R_f: 0.3). MS Calculated for $C_{32}H_{44}ClFN_6O_5Si$: 674.28; Found: 675.05 $[M+1]^+$.

Example 27



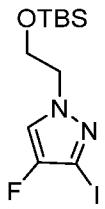
4-(5-(3-Amino-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. 10% Pd/C (70 mg) and $NaBH_4$ (96 mg, 2.59 mmol) were added to a stirred solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-methyl-2-((triethylsilyl)oxy)propyl)-3-nitro-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (0.7 g, 1.04 mmol) in MeOH (20 mL) under nitrogen atmosphere. The mixture was stirred at RT for 6 h. The reaction mixture was then filtered through a pad of Celite and washed with methanol. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the title compound. TLC: 10% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{26}H_{32}ClFN_6O_3$: 530.22; Found: 529.45 $[M-1]^-$.

Example 28



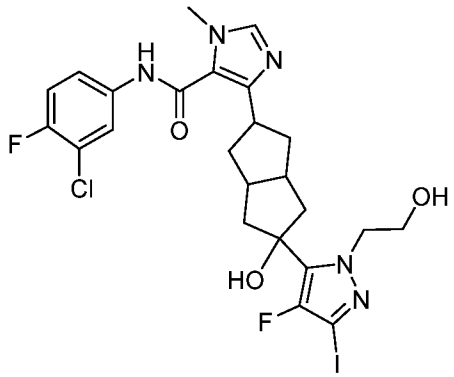
4-(5-(3-Amino-4-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. N-Chlorosuccinimide (45.34 mg, 0.339 mmol) was added to a stirred solution of 4-(5-(3-amino-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide (0.15 g, 0.283 mmol) in ACN (10 mL). The reaction mixture was stirred at RT for 12 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with 10% MeOH/dichloromethane. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by prep. HPLC to afford the title compound as a white solid. TLC: 10% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{26}H_{31}Cl_2FN_6O_3$: 564.18. Found: 565.20 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (dd, J = 6.4 Hz, 2.0 Hz, 1H), 7.64 (s, 1H), 7.60-7.55 (m, 1H), 7.41 (t, J = 9.6 Hz, 1H), 5.70 (s, 1H), 5.60 (s, 1H), 4.73 (s, 2H), 4.15 (s, 2H), 3.67 (s, 3H), 3.24-3.15 (m, 1H), 2.65-2.55 (m, 2H), 2.45-2.36 (m, 2H), 2.10-1.95 (m, 4H), 1.90-1.82 (m, 2H), 1.07 (s, 6H) ppm.

Intermediate 25



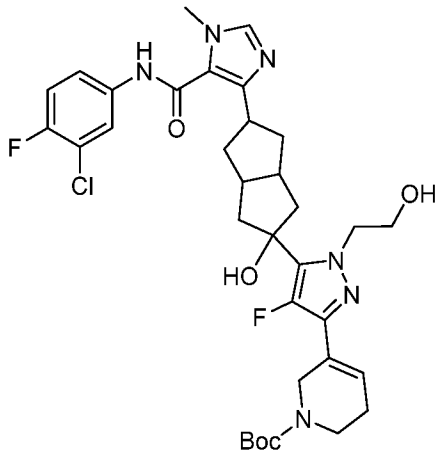
1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-4-fluoro-3-iodo-1*H*-pyrazole The title compound has been synthesized from 4-fluoro-3-iodo-1H-pyrazoleand (2-bromoethoxy)(tert-butyl)dimethylsilane according Method 1. TLC: 30% EtOAc/hexane (R_f: 0.4); ^1H NMR (400 MHz, DMSO-d_6): δ 7.81 (d, J = 4.8 Hz, 1H), 4.11 (t, J = 4.8 Hz, 2H), 3.86 (t, J = 4.8 Hz, 2H), 0.78 (s, 9H), 0.08 (s, 6H) ppm.

Example 29



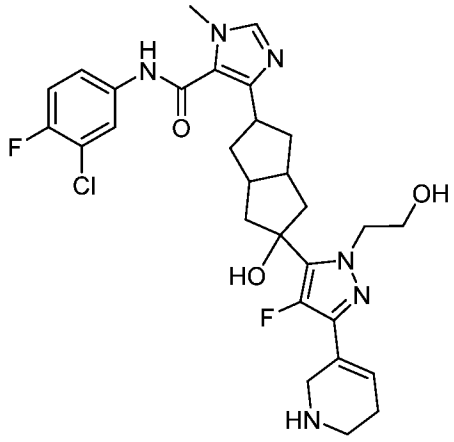
N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-1-(2-hydroxyethyl)-3-iodo-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. LDA (2M in THF, 13.3 mL, 26.6 mmol) was added dropwise to a stirred solution of 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-fluoro-3-iodo-1*H*-pyrazole (7.89g, 21.32 mmol) in dry THF (150 mL) at -78 °C in an inert atmosphere and the reaction mixture was stirred for 2 h. To this, a solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (1 g, 2.66 mmol) in THF was added at -78 °C. The resulting reaction mixture was stirred at RT for 16 h. The reaction was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was collected; washed with brine; dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the title compound as an off-white solid. TLC: 5% MeOH/dichloromethane (R_f: 0.4). MS Calculated for $C_{24}H_{25}ClF_2IN_5O_3$: 631.07; Found: 631.90 $[M+1]^+$.

Example 30



tert-Butyl 5-(5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-4-fluoro-1-(2-hydroxyethyl)-1H-pyrazol-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate. The title compound was synthesized from N-(3-chloro-4-fluorophenyl)-4-(5-(4-fluoro-1-(2-hydroxyethyl)-3-iodo-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide and *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate according to Method 4. TLC: 5% MeOH in dichloromethane (R_f: 0.5); MS calcd. for $C_{34}H_{41}ClF_2N_6O_5$: 686.28; Found: 669.20 $[M-18+1]^+$.

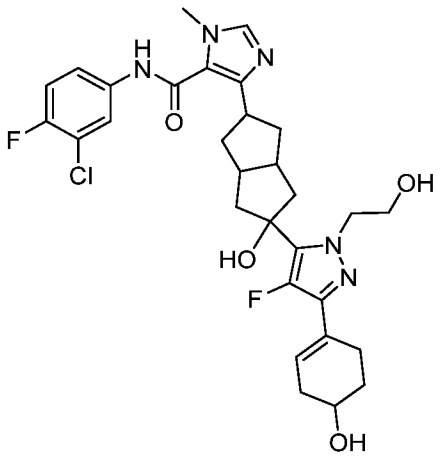
Example 31



N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-1-(2-hydroxyethyl)-3-(1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. $SnCl_4$ (11.3 mg, 0.047 mmol) was added to a stirred solution

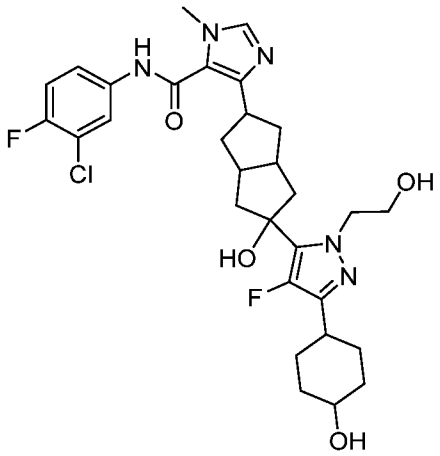
of tert-butyl 5-(5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-4-fluoro-1-(2-hydroxyethyl)-1H-pyrazol-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (30 mg, 0.043 mmol) in ACN (5 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min. The reaction mixture was diluted with sat. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by prep. HPLC to afford the title compound as an off-white solid; TLC: 10% MeOH in dichloromethane (R_f: 0.1). LC MS calcd. for $C_{29}H_{33}ClF_2N_6O_3$: 586.23. Found: 587.15 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.96 (d, J = 5.2 Hz, 1H), 7.64 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.6 Hz, 1H), 6.25 (s, 1H), 5.43 (s, 1H), 4.92-4.88 (m, 1H), 4.24-4.22 (m, 2H), 3.75-3.60 (m, 7H), 3.50-3.20 (m, 1H, merged), 2.94-2.92 (m, 2H), .60-2.40 (m, 2H, merged), 2.35-2.20 (m, 4H), 2.15-2.08 (m, 2H), 1.98-1.92 (m, 4H) ppm. NH proton is not observed.

Example32



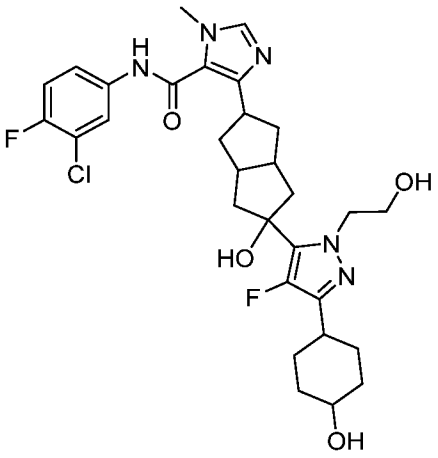
N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(4-hydroxycyclohex-1-en-1-yl)-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. The title compound was synthesized from N-(3-chloro-4-fluorophenyl)-4-(5-(4-fluoro-1-(2-hydroxyethyl)-3-iodo-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide and dimethyl cyclohex-1-en-1-ylboronate according to Method 4. MS calcd for $C_{30}H_{34}ClF_2N_5O_4$: 601.23. Found: 602.10 $[M+1]^+$.

Example 33



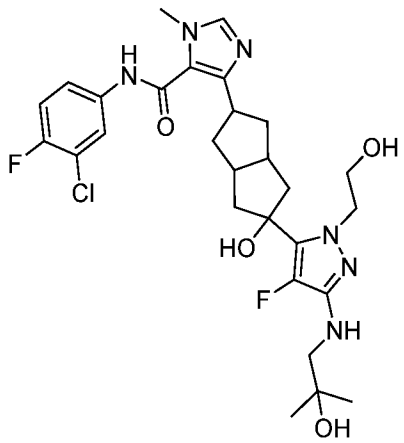
N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(4-hydroxycyclohexyl)-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I. In an autoclave, 10% Pd/C (30 mg) was added to a stirred solution of N-(3-chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(4-hydroxycyclohex-1-en-1-yl)-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (100mg, 0.16 mmol) in EtOAc (10 mL) under nitrogen atmosphere. The reaction mixture was stirred in at 45°C under hydrogen atmosphere (100 *psi*) for 36 h. The reaction mixture was filtered through a pad of Celite and washed with methanol. The filtrate was concentrated under reduced pressure. The crude product was purified by prep-HPLC to afford the compound N-(3-chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(4-hydroxycyclohexyl)-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I and Isomer II. Isomer I; MS calcd. for $C_{30}H_{36}ClF_2N_5O_4$: 603.24. Found: 586.20 $[M-18+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.97 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.64 (s, 1H), 7.58-7.55 (m, 1H), 7.41 (t, J = 8.8 Hz, 1H), 5.35 (s, 1H), 4.88 (t, J = 5.2 Hz, 1H), 4.53 (d, J = 4.4 Hz, 1H), 4.19 (t, J = 6.4 Hz, 2H), 3.72-3.67 (m, 5H), 3.39-3.21 (m, 3H), 2.55-2.40 (m, 2H, merged), 2.24-2.20 (m, 2H), 2.10-2.06 (m, 2H), 1.94-1.80 (m, 8H), 1.48-1.44 (m, 2H), 1.24-1.18 (m, 2H) ppm.

Example 34



N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(4-hydroxycyclohexyl)-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.97 (dd, J = 6.4 Hz, 2.4 Hz, 1H), 7.64 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 8.8 Hz, 1H), 5.35 (s, 1H), 4.90-4.85 (m,1H), 4.29 (d, J = 3.2 Hz, 1H), 4.20 (t, J = 6.0 Hz, 2H), 3.80-3.76 (m, 1H), 3.74-3.69 (m, 2H), 3.68 (s, 3H), 3.28-3.20 (m, 2H), 2.60-2.45 (m, 2H, merged), 2.30-2.25(m, 2H), 2.12-2.06 (m, 2H), 1.98-1.86 (m, 6H), 1.70-1.62 (m, 2H), 1.52-1.46 (m, 4H) ppm.

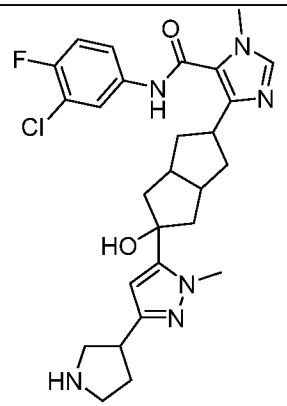
Example 35

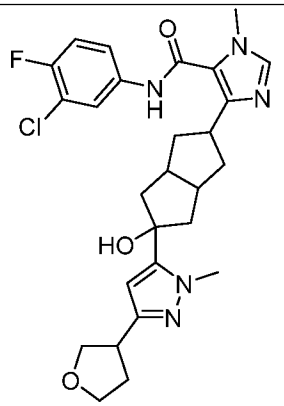
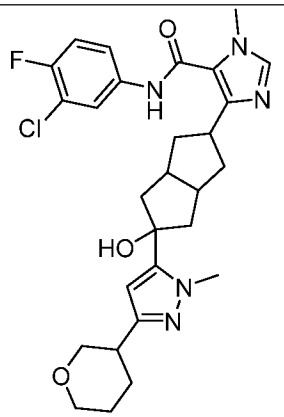


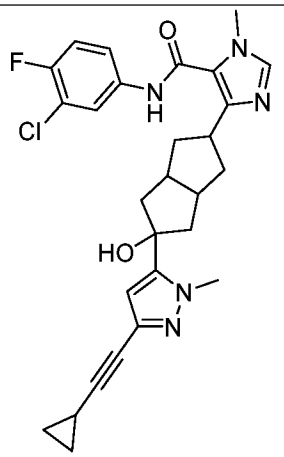
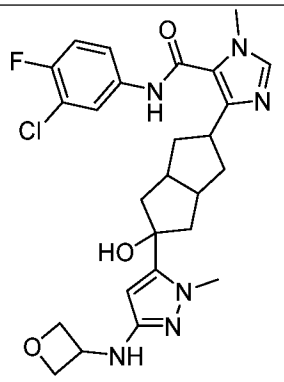
N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-((2-hydroxy-2-methylpropyl)amino)-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. K_2CO_3 (32.7 mg, 0.237 mmol) and L-proline (3.63 mg, 0.031 mmol) were added to a mixture of N-(3-

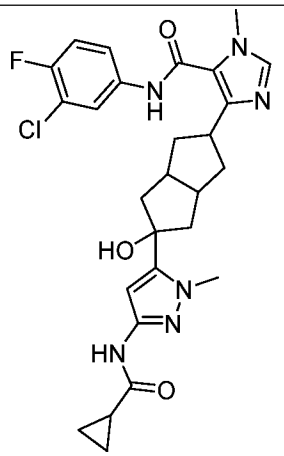
chloro-4-fluorophenyl)-4-(5-(4-fluoro-1-(2-hydroxyethyl)-3-iodo-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (50 mg, 0.079 mmol) and 1-amino-2-methylpropan-2-ol (14.1 mg, 0.158 mmol) in DMSO (2 mL) and the solution purged with Argon for 10 min. To this solution was added CuI (3 mg, 0.016 mmol) and purging with Argon continued for another 10 min. The resulting reaction mixture was stirred at 100°C for 16h. The reaction mixture was then 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. The crude product was purified by CombiFlash column chromatography to afford the title compound. TLC:5% MeOH/dichloromethane (R_f: 0.3). MS calcd for $C_{28}H_{35}ClF_2N_6O_4$: 592.24; Found: 593.05 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.96 (d, J = 6.8 Hz, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.31 (s, 1H), 4.84-4.80 (m, 1H), 4.61 (t, J = 4.8 Hz, 1H), 4.46 (s, 1H), 4.05 (t, J = 6.4 Hz, 2H), 3.70-3.62 (m, 5H), 3.25-3.22 (m, 1H), 2.96 (d, J = 6.4 Hz, 2H), 2.60-2.50(m, 2H, merged), 2.28-2.22 (m, 2H), 2.10-2.06 (m, 2H), 2.00-1.88 (m, 4H), 1.10 (s, 6H) ppm.

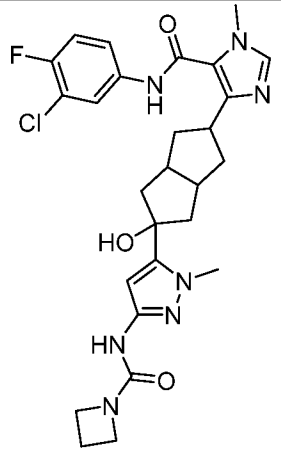
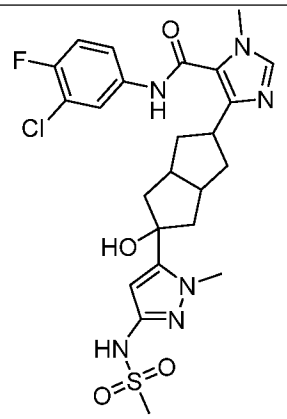
Table 4. Examples 36 were synthesized according to the methods described elsewhere in this case.

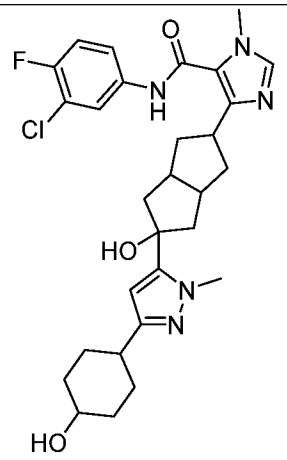
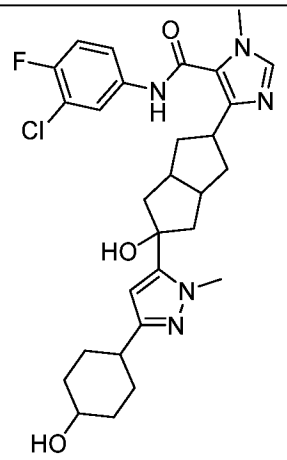
Example	Structure, ^{1}H NMR, and MS
36	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(pyrrolidin-3-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.94 (d, J = 6.8 Hz, 1H), 7.65 (s, 1H), 7.58-7.56 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6.01 (s, 1H), 5.23 (br.s,

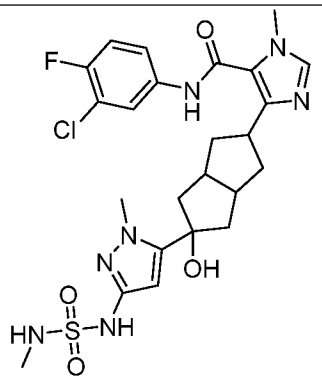
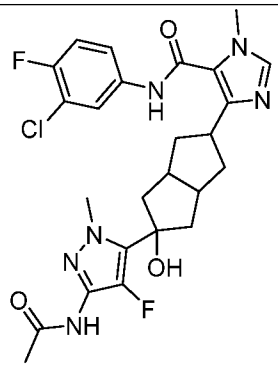
	1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.42-3.92 (m, 6H), 2.50-2.48 (m, 2H, merged), 2.20-2.08 (m, 5H), 1.87-1.83 (m, 5H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{27}H_{32}ClFN_6O_2$: 526.23; Found: 527.10 $[M+1]^+$.
37	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(tetrahydrofuran-3-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (dd, J = 7.2 and 2.8 Hz, 1H), 7.66 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.95 (s, 1H), 5.18 (s, 1H), 3.92 (t, J = 7.2 Hz, 1H), 3.82 (s, 3H), 3.83-3.78 (m, 1H), 3.72 (q, J = 7.6 Hz, 1H), 3.67 (s, 3H), 3.53 (t, J = 7.2 Hz, 1H), 3.24 (t, J = 7.2 Hz, 2H), 2.49-2.39 (m, 2H), 2.25-2.02 (m, 5H), 2.00-1.78 (m, 5H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{27}H_{31}ClFN_5O_3$: 527.21; Found: 528.20 $[M+1]^+$.
38	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers**

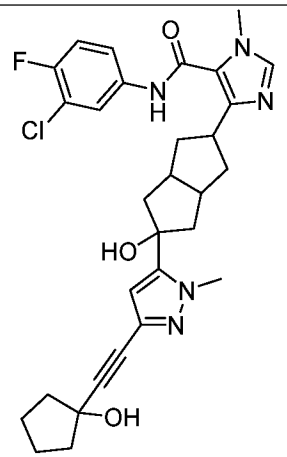
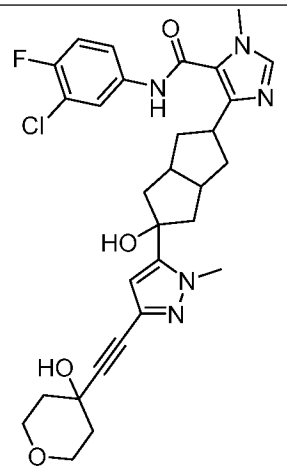
	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.98-7.95 (m, 1H), 7.65 (s, 1H), 7.61-7.55 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.94 (s, 1H), 5.18 (s, 1H), 3.90-3.76 (m, 5H), 3.67 (s, 3H), 3.30-3.18 (m, 3H), 2.72-2.62 (m, 1H), 2.48-2.39 (m, 2H), 2.22-2.04 (m, 4H), 1.98-1.79 (m, 5H), 1.58 (s, 3H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{28}H_{33}ClFN_5O_3$: 541.23; Found: 542.05 $[M+1]^+$.
39	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(cyclopropylethynyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (d, J = 6.0 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6.17 (s, 1H), 5.30 (s, 1H), 3.86 (s, 3H), 3.67 (s, 3H), 3.28-3.20 (m, 1H), 2.45-2.40 (m, 2H), 2.20-2.14 (m, 2H), 2.09-2.06 (m, 2H), 1.85-1.81 (m, 4H), 1.49-1.43 (m, 1H), 0.85-0.82 (m, 2H), 0.67-0.64 (m, 2H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{28}H_{29}ClFN_5O_2$: 521.20; Found: 522.6 $[M+1]^+$.
40	

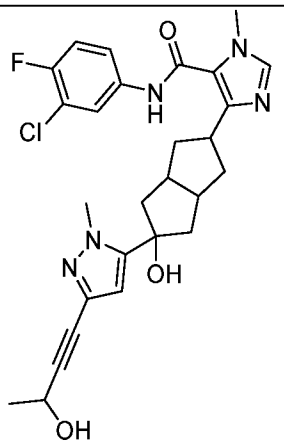
	N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(oxetan-3-ylamino)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.98-7.94 (m, 1H), 7.64 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.69 (d, J =8.0 Hz, 1H), 5.28 (s, 1H), 5.11 (s, 1H), 4.69 (t, J = 6.4 Hz, 2H), 4.50-4.40 (m, 1H), 4.34 (t, J = 6.0 Hz, 2H), 3.66 (d, J = 5.2 Hz, 6H), 3.28-3.18 (m, 1H), 2.48-2.39 (m, 2H), 2.19-2.02 (m, 4H), 1.90-1.78 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{26}H_{30}ClFN_6O_3$: 528.21; Found: 527.10 [M-1]$^-$.
41	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(cyclopropanecarboxamido)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 10.19 (s, 1H), 7.96 (dd, J = 6.8 and 2.0 Hz, 1H), 7.65 (s, 1H), 7.60-7.53 (m, 1H), 7.39 (t, J = 8.8 Hz, 1H), 6.30 (s, 1H), 5.25 (s, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.28-3.18 (m, 1H), 2.48-2.39 (m, 2H), 2.22-2.04 (m, 4H), 1.91-1.72 (m, 5H), 0.76-0.68 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{27}H_{30}ClFN_6O_3$: 540.21; Found: 539.05 [M-1]$^-$.

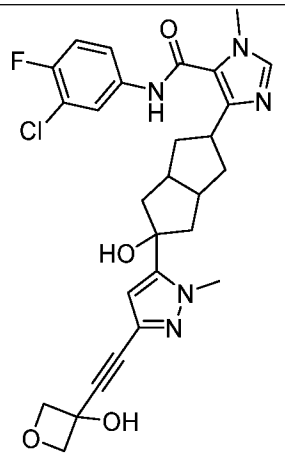
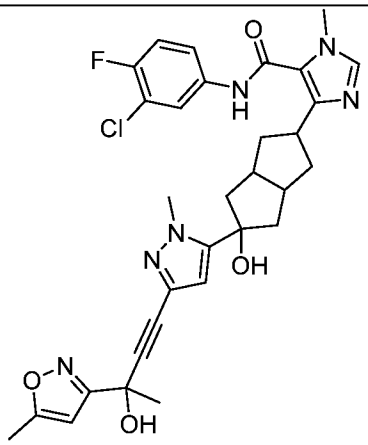
42	 **4-(5-(3-(Azetidine-1-carboxamido)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.18 (s, 1H), 8.71 (s, 1H), 7.97-7.91 (m, 1H), 7.63 (s, 1H), 7.58-7.51 (m, 1H), 7.38 (t, J = 9.2 Hz, 1H), 6.14 (s, 1H), 5.21 (s, 1H), 3.84 (t, J = 7.6 Hz, 4H), 3.74 (s, 3H), 3.65 (s, 3H), 3.28-3.14 (m, 1H), 2.46-2.36 (m, 2H), 2.20-2.02 (m, 6H), 1.89-1.76 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{27}H_{31}ClFN_7O_3$: 555.21; Found: 554.10 $[M-1]^-$.
43	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(methylsulfonamido)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 9.64 (s, 1H), 8.00-7.92 (m, 1H), 7.65 (s, 1H), 7.61-7.54 (m, 1H), 7.44-7.36 (m, 1H), 5.82 (s, 1H), 5.29 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.39-3.21 (m, 1H, merged), 2.99 (s, 3H), 2.57-2.41 (2H, merged), 2.22-2.04 (m, 4H), 1.92-1.80 (m, 4H) ppm. TLC: 5%

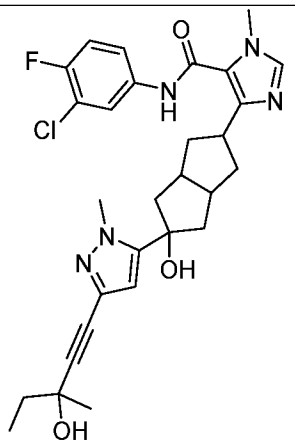
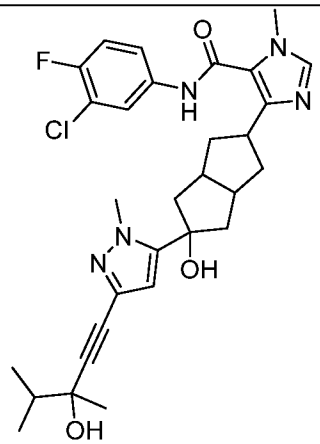
	MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{24}H_{28}ClFN_6O_4S$: 550.16; Found: 550.90 $[M+1]^+$.
44	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(4-hydroxycyclohexyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.98-7.95 (m, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.87 (s, 1H), 5.16 (s, 1H), 4.26 (d, J = 3.2 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 1H), 3.67 (s, 3H), 3.28-3.18 (m, 1H), 2.54-2.40 (m, 3H), 2.22-2.03 (m, 4H), 1.91-1.71 (m, 6H), 1.65-1.41 (m, 6H). TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{29}H_{35}ClFN_5O_3$: 555.24; Found: 554.15 $[M-1]^-$.
45	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(4-hydroxycyclohexyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II**

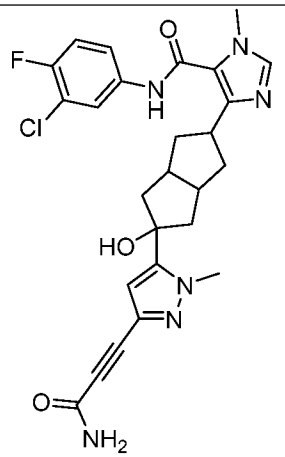
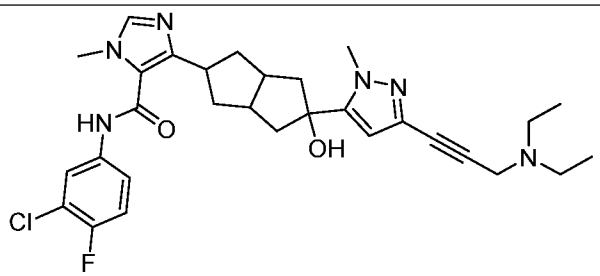
	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.98-7.95 (m, 1H), 7.64 (s, 1H), 7.60-7.55 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.86 (s, 1H), 5.15 (s, 1H), 4.49 (d, J = 4.4 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.28-3.17 (m, 2H), 2.58-2.28 (m, 4H), 2.21-2.02 (m, 4H), 1.91-1.78 (m, 7H), 1.41-1.12 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{29}H_{35}ClFN_5O_3$: 555.24; Found: 554.15 $[M-1]^-$.
46	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-((N-methylsulfamoyl)amino)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 9.53 (s, 1H), 7.96 (d, J = 5.2 Hz, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.6 Hz, 1H), 6.92-6.88 (m, 1H), 5.84 (s, 1H), 5.26 (s, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 3.30-3.20 (m, 1H), 2.48-2.45 (m, 5H), 2.10-2.06 (m, 4H), 1.90-1.85 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{24}H_{29}ClFN_7O_4S$: 565.17; Found: 566.6 $[M+1]^+$.
47	 **4-(5-(3-Acetamido-4-fluoro-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-Chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide**

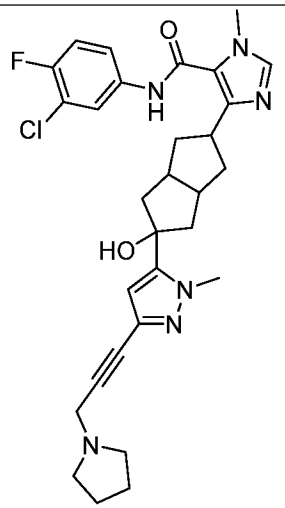
	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.25 (br.s, 1H), 9.63 (s, 1H), 7.98-7.94 (m, 1H), 7.80-7.60 (m, 1H), 7.59-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 5.41 (s, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.27-3.22 (m, 1H), 2.60-2.50 (m, 2H, merged), 2.26-2.21 (m, 2H), 2.12-2.10 (m, 2H), 1.96-1.90 (m, 7H). TLC: 10% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{25}H_{27}ClF_2N_6O_3$: 532.18; Found: 533.05 $[M+1]^+$.
48	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1-hydroxycyclopentyl)ethynyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.96 (d, J = 6.4 Hz, 1H), 7.67-7.65 (m, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 6.21 (s, 1H), 5.33 (s, 1H), 5.26 (s, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 3.27-3.22 (m, 1H), 2.49-2.43 (m, 2H), 2.33-2.18 (m, 2H), 2.10-2.07 (m, 2H), 1.90-1.79 (m, 8H), 1.72-1.63 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{30}H_{33}ClFN_5O_3$: 565.23; Found: 548.05 $[M-18+1]^+$.
49	

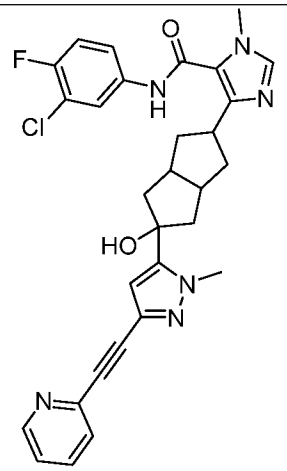
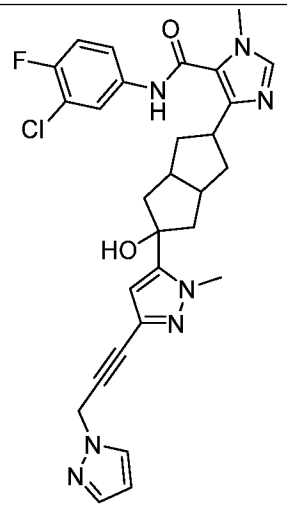
	N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((4-hydroxytetrahydro-2H-pyran-4-yl)ethynyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6.25 (s, 1H), 5.68 (s, 1H), 5.33 (s, 1H), 3.88 (s, 3H), 3.77-3.74 (m, 2H), 3.67 (s, 3H), 3.51 (t, J = 8.8 Hz, 2H), 3.26-3.22 (m, 1H), 2.50-2.43 (m, 2H), 2.22-2.18 (m, 2H), 2.10-2.07 (m, 2H), 1.90-1.78 (m, 6H), 1.69-1.62 (m, 2H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{30}H_{33}ClFN_5O_4$: 581.22; Found: 564.15 [M-18+1]$^+$.
50	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxybut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.97-7.95 (m, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.22 (s, 1H), 5.40 (d, J = 4.4 Hz, 1H), 5.33 (s, 1H), 4.54-4.50 (m, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.25-3.22 (m, 1H), 2.50-2.43 (m, 2H), 2.22-2.16 (m, 2H), 2.10-2.07 (m, 2H), 1.87-1.82 (m, 4H), 1.33 (d, J = 6.4 Hz, 3H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{27}H_{29}ClFN_5O_3$: 525.19; Found: 508.15[M-18+1]$^+$.

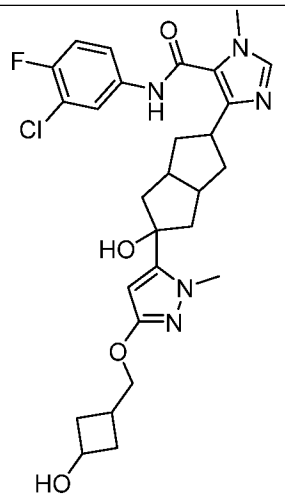
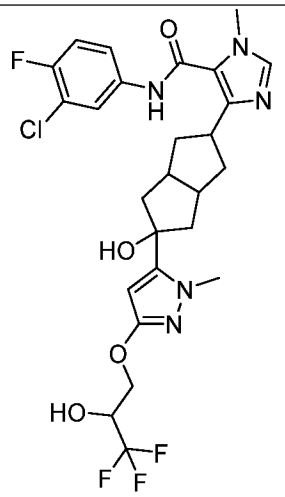
51	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((3-hydroxyoxetan-3-yl)ethynyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.97-7.93 (m, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.58 (s, 1H), 6.31 (s, 1H), 5.36 (s, 1H), 4.68 (d, J = 5.6 Hz, 2H), 4.56 (d, J = 6.4 Hz, 2H), 3.91 (s, 3H), 3.67 (s, 3H), 3.30-3.20 (m, 1H), 2.49-2.40 (m, 2H), 2.25-2.15 (m, 2H), 2.10-2.05 (m, 2H), 1.90-1.83 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{28}H_{29}ClFN_5O_4$: 553.19; Found: 536.15 $[M-18+1]^+$.
52	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxy-3-(5-methylisoxazol-3-yl)but-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.97-7.94 (m, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6.45 (s, 1H), 6.29 (s, 1H), 6.25

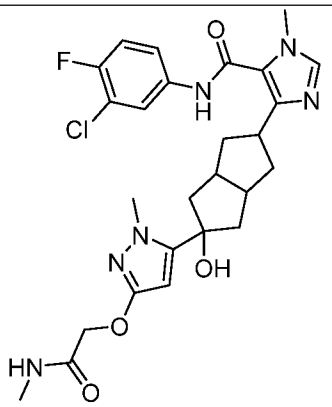
	(s, 1H), 5.35 (s, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 3.30-3.20 (m, 1H, merged), 2.49-2.42 (m, 2H), 2.39 (s, 3H), 2.25-2.15 (m, 2H), 2.10-2.06 (m, 2H), 1.90-1.82 (m, 4H), 1.74 (s, 3H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{31}H_{32}ClFN_6O_4$: 606.22; Found: 589.15 $[M-18+1]^+$.
53	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxy-3-methylpent-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (d, J = 4.8 Hz, 1H), 7.65 (s, 1H), 7.58-7.56 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 6.20 (s, 1H), 5.32 (s, 1H), 5.28 (s, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 3.26-3.20 (m, 1H), 2.45-2.40 (m, 2H), 2.23-2.16 (m, 2H), 2.10-2.07 (m, 2H), 1.90-1.82 (m, 4H), 1.64-1.55 (m, 2H), 1.37 (s, 3H), 0.95 (t, J = 8.0 Hz, 3H) ppm. TLC: 10% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{29}H_{33}ClFN_5O_3$: 553.23; Found: 554.05 $[M+1]^+$.
54	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxy-3,4-dimethylpent-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers**

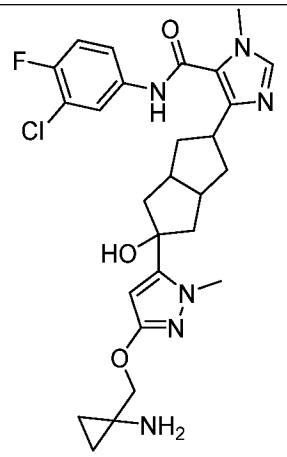
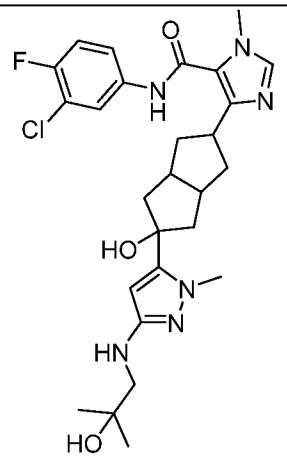
	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (d, J = 6.4 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6.19 (s, 1H), 5.31 (s, 1H), 5.20 (s, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 3.26-3.23 (m, 1H), 2.49-2.43 (m, 2H), 2.23-2.16 (m, 2H), 2.10-2.07 (m, 2H), 1.90-1.82 (m, 4H), 1.74-1.69 (m, 1H), 1.34 (s, 3H), 0.98-0.91 (m, 6H) ppm. TLC: 10% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{30}H_{35}ClFN_5O_3$: 567.24; Found: 550.10 $[M-18+1]^+$.
55	 **4-(5-(3-(3-Amino-3-oxoprop-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 8.10 (s, 1H), 7.95 (d, J = 5.6 Hz, 1H), 7.65 (s, 1H), 7.62-7.53 (m, 2H), 7.40 (t, J = 8.8 Hz, 1H), 6.45 (s, 1H), 5.40 (s, 1H), 3.94 (s, 3H), 3.67 (s, 3H), 3.30-3.23 (m, 1H), 2.45-2.44 (m, 2H), 2.25-2.18 (m, 2H), 2.12-2.07 (m, 2H), 1.90-1.85 (m, 4H). TLC: 10% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{26}H_{26}ClFN_6O_3$: 524.17; Found: 506.95 $[M-18+1]^+$.
56	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(3-(diethylamino)prop-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide**

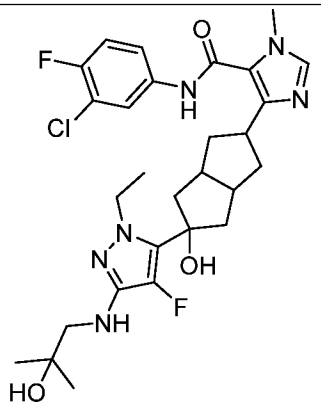
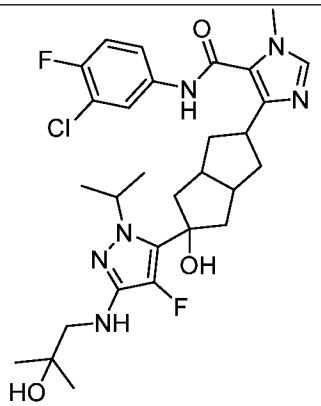
	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.95 (d, J = 4.8 Hz, 1H), 7.66 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.28 (s, 1H), 5.34 (s, 1H), 3.89 (s, 3H), 3.83-3.81 (m, 2H), 3.67 (s, 3H), 3.50-3.20 (m, 1H, merged), 2.75-2.70 (m, 4H), 2.49-2.43 (m, 2H), 2.23-2.16 (m, 2H), 2.10-2.07 (m, 2H), 1.88-179 (m, 4H), 1.07 (t, J = 7.2 Hz, 6H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{30}H_{36}ClFN_6O_2$: 566.26; Found: 284.60 $[M/2+1]^+$.
57	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (d, J = 6.4 Hz, 1H), 7.66 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 6.25 (s, 1H), 5.32 (s, 1H), 3.88 (s, 3H), 3.66 (s, 3H), 3.61 (s, 2H), 3.30-3.20 (m, 1H), 2.60-2.58 (m, 4H), 2.50-2.43 (m, 2H), 2.21-2.17 (m, 2H), 2.10-2.08 (m, 2H), 1.87-1.82 (m, 4H), 1.72-1.70 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{30}H_{34}ClFN_6O_2$: 564.24; Found: 565.20 $[M+1]^+$.

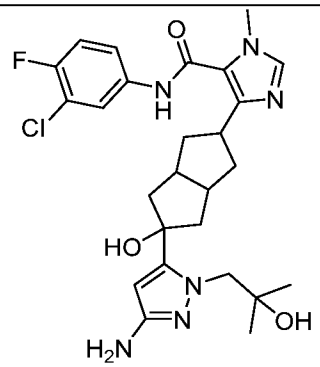
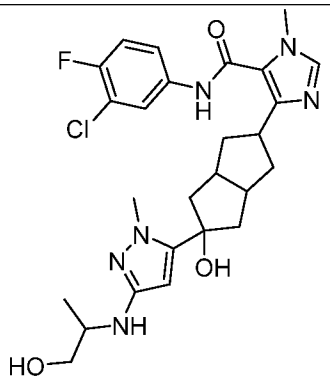
58	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(pyridin-2-ylethynyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H), 8.58-8.56 (m, 1H), 7.94 (d, J = 6.4 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.78-7.62 (m, 1H), 7.58-7.54 (m, 2H), 7.42-7.36 (m, 2H), 6.46 (s, 1H), 5.40 (s, 1H), 3.94 (s, 3H), 3.69 (s, 3H), 3.29-3.20 (m, 1H), 2.55-2.45 (m, 2H, merged), 2.26-2.10 (m, 4H), 1.90-1.81 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{30}H_{28}ClFN_6O_2$: 558.19; Found: 280.45 $[M/2+1]^+$.
59	 **4-(5-(3-(3-(1H-Pyrazol-1-yl)prop-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.95 (d, J = 6.4 Hz, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.48 (s, 1H), 7.40 (t, J = 8.8 Hz, 1H),

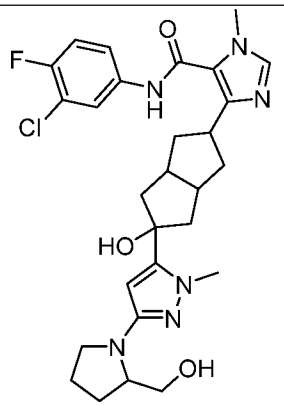
	6.30-6.27 (m, 2H), 5.35 (s, 1H), 5.24 (s, 2H), 3.89 (s, 3H), 3.67 (s, 3H), 3.32-3.22 (m, 1H), 2.49-2.43 (m, 2H), 2.22-2.15 (m, 2H), 2.10-2.07 (m, 2H), 1.90-1.82 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{29}H_{29}ClFN_7O_2$: 561.21; Found: 562.15 $[M+1]^+$.
60	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((3-hydroxycyclobutyl)methoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.98-7.94 (m, 1H), 7.68-7.65 (m, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.50 (s, 1H), 5.21 (s, 1H), 4.99-4.96 (m, 1H), 3.96-3.88 (m, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.26-3.22 (m, 1H), 2.46-2.40 (m, 2H), 2.33-2.02 (m, 7H), 1.85-1.78 (m, 4H), 1.58-1.54 (m, 2H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{28}H_{33}ClFN_5O_4$: 557.22; Found: 558.15 $[M+1]^+$.
61	

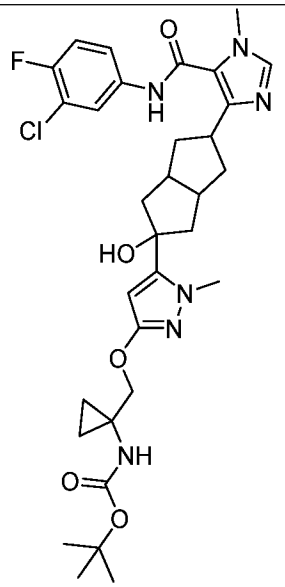
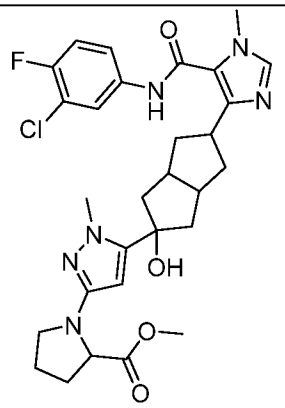
	N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(3,3,3-trifluoro-2-hydroxypropoxy)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.95 (d, J = 6.4 Hz, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 6.55 (d, J = 6.4 Hz, 1H), 5.56 (s, 1H), 5.25 (s, 1H), 4.35-4.30 (m, 1H), 4.20-4.15 (m, 1H), 4.09-4.03 (m, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.32-3.23 (m, 1H), 2.49-2.40 (m, 2H), 2.20-2.06 (m, 4H), 1.90-1.80 (m, 4H) ppm. TLC: 10% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{26}H_{28}ClF_4N_5O_4$: 585.18; Found: 584.25 $[M-1]^-$.
62	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(2-(methylamino)-2-oxoethoxy)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (d, J = 4.8 Hz, 1H), 7.84 (s, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.56 (s, 1H), 5.26 (s, 1H), 4.42 (s, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 3.28-3.21 (m, 1H), 2.60 (d, J = 4.4 Hz, 3H), 2.50-2.44 (m, 2H), 2.19-2.06 (m, 4H), 1.90-1.81 (m, 4H) ppm. TLC: 10% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{26}H_{30}ClFN_6O_4$: 544.20; Found: 545.25 $[M+1]^+$.

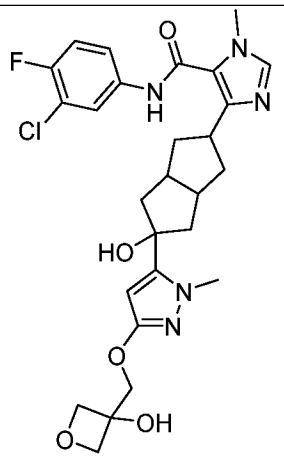
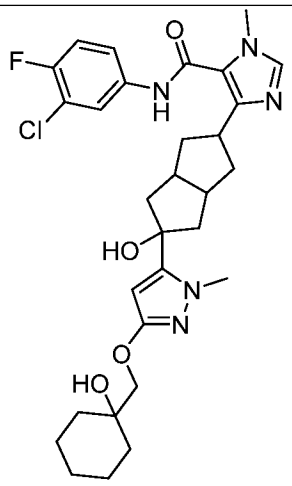
63	 **4-(5-(3-((1-Aminocyclopropyl)methoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.95 (d, J = 5.6 Hz, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.6 Hz, 1H), 5.53 (s, 1H), 5.40-5.10 (m, 1H), 3.90 (s, 2H), 3.72 (s, 3H), 3.67 (s, 3H), 3.26-3.24 (m, 1H), 2.49-2.43 (m, 2H), 2.20-2.06 (m, 4H), 1.85-1.80 (m, 4H), 0.60-0.57 (m, 4H) ppm. NH_2 proton was not found. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{27}H_{32}ClFN_6O_3$: 542.22; Found: 272.45 $[M/2+1]^+$.
64	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((2-hydroxy-2-methylpropyl)amino)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.94 (d, J = 4.8 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.33 (s, 1H), 5.12 (s, 1H), 4.63-4.60 (m, 1H), 4.47 (s, 1H), 3.67-3.63 (m, 6H), 3.30-3.20 (m, 1H), 2.88 (d,

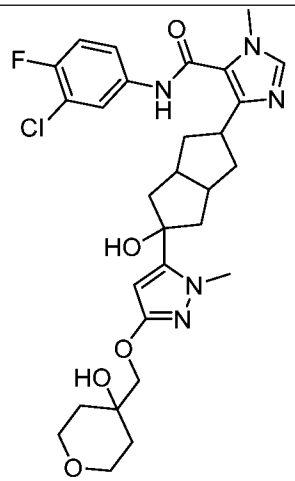
	J = 5.2 Hz, 2H), 2.48-2.42 (m, 2H), 2.15-2.07 (m, 4H), 1.82-1.75 (m, 4H), 1.08 (s, 6H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{27}H_{34}ClFN_6O_3$: 544.24; Found: 545.25 $[M+1]^+$.
65	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-ethyl-4-fluoro-3-((2-hydroxy-2-methylpropyl)amino)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.96 (d, *J* = 6.8 Hz, 1H), 7.64 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, *J* = 9.6 Hz, 1H), 5.29 (s, 1H), 4.57 (t, *J* = 5.6 Hz, 1H), 4.49 (s, 1H), 4.02 (q, *J* = 6.8 Hz, 2H), 3.67 (s, 3H), 3.15-3.19 (m, 1H), 2.97 (d, *J* = 6.4 Hz, 2H), 2.55-2.45 (m, 2H, merged), 2.25-2.20 (m, 2H), 2.10-2.06 (m, 2H), 1.98-1.86 (m, 4H), 1.22 (t, *J* = 6.4 Hz, 3H), 1.10 (s. 6H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{28}H_{35}ClF_2N_6O_3$: 576.24; Found: 577.20 $[M+1]^+$.
66	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-((2-hydroxy-2-methylpropyl)amino)-1-isopropyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide**

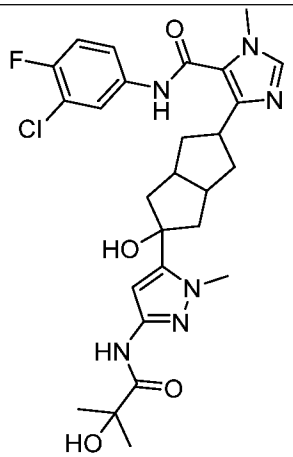
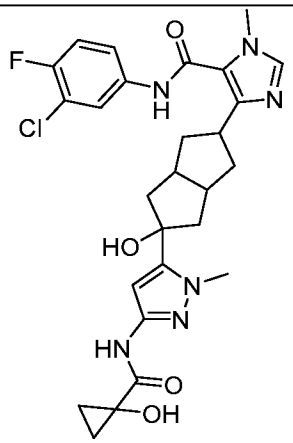
	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 (br. S, 1H), 7.98-7.94 (m, 1H), 7.60-7.54 (m, 1H), 7.42 (t, J = 9.2 Hz, 1H), 5.34 (s, 1H), 4.79 (t, J = 6.8 Hz, 1H), 4.60-4.56 (m, 1H), 3.72 (s, 3H), 3.40-3.20 (m, 1H, merged), 2.98 (s, 2H), 2.50-2.40 (m, 2H, merged), 2.25-2.12 (m, 4H), 1.92-1.87 (m, 4H), 1.25 (d, J = 6.4 Hz, 6H), 1.10 (s, 6H) ppm. OH proton was not found. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{29}H_{37}ClF_2N_6O_3$: 590.26; Found: 591.15 $[M+1]^+$.
67	 **4-(5-(3-Amino-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.96 (d, J = 6.4 Hz, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.79 (s, 1H), 5.28 (s, 1H), 5.26 (s, 1H), 4.62 (br. S, 2H), 3.97 (s, 2H), 3.67 (s, 3H), 3.25-3.20 (m, 1H), 2.45-2.40 (m, 2H), 2.16-2.05 (m, 4H), 1.90-1.80 (m, 4H), 1.05 (s, 6H) ppm. TLC: 10% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{26}H_{32}ClFN_6O_3$: 530.22; Found: 531.15 $[M+1]^+$.
68	

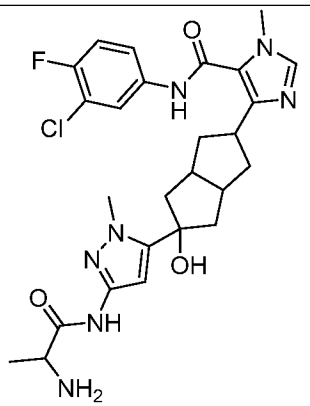
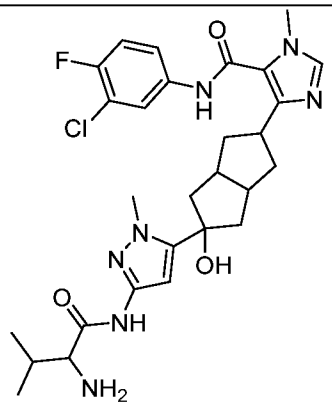
	N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1-hydroxypropan-2-yl)amino)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.64 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.29 (s, 1H), 5.09 (s, 1H), 4.56-4.50 (m, 2H), 3.68-3.65 (m, 6H), 3.25-3.16 (m, 4H), 2.45-2.38 (m, 2H), 2.17-2.05 (m, 4H), 1.90-1.78 (m, 4H), 1.03 (d, J = 6.4 Hz, 3H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{26}H_{32}ClFN_6O_3$: 530.22; Found: 531.15 $[M+1]^+$.
69	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-(hydroxymethyl)pyrrolidin-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (d, J = 6.8 Hz, 1H), 7.67 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.36 (s, 1H), 5.13 (s, 1H), 4.75-4.70 (m, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.51-3.44 (m, 2H), 3.27-3.22 (m, 2H), 3.16-3.12 (m, 1H), 2.96-2.93 (m, 1H), 2.49-2.46 (m, 2H), 2.21-2.15 (m, 2H), 2.10-2.08 (m, 2H), 1.90-1.74 (m, 8H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{28}H_{34}ClFN_6O_3$: 556.24; Found: 557.15 $[M+1]^+$.

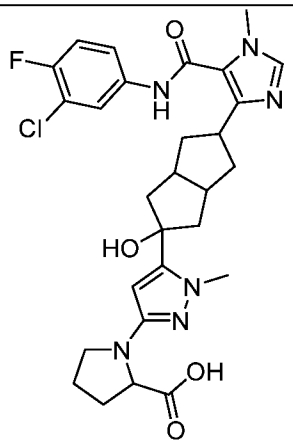
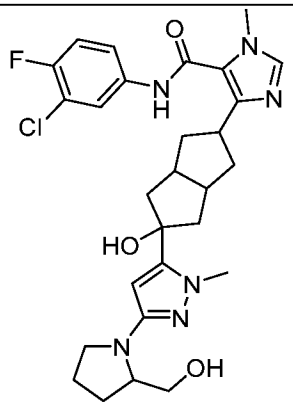
70	 **tert-Butyl (1-(((5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclopropyl)carbamate** ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.20 (s, 1H), 7.95 (d, *J* = 6.4 Hz, 1H), 7.70-7.60 (m, 1H), 7.60-7.54 (m, 1H), 7.40 (t, *J* = 6.4 Hz, 1H), 7.22-7.18 (m, 1H), 5.49 (s, 1H), 5.23 (s, 1H), 3.94 (s, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 3.25-3.21 (m, 1H), 2.45-2.43 (m, 2H), 2.20-2.08 (m, 4H), 1.85-1.78 (m, 4H), 1.34 (s, 9H), 0.73-0.64 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R$_f$: 0.4) MS calcd. for $C_{32}H_{40}ClFN_6O_5$: 642.27; Found: 643.15 $[M+1]^+$.
71	 **Methyl (5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)prolinate.** ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.21 (s, 1H), 7.96 (d, *J* = 6.8 Hz, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.40 (t, *J* = 8.8 Hz, 1H), 5.31 (s, 1H), 5.15 (s, 1H),

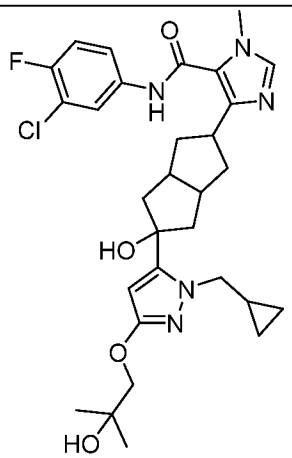
	4.08-4.05 (m, 1H), 3.68 (s, 6H), 3.58 (s, 3H), 3.50-3.31 (m, 1H), 3.26-3.12 (m, 2H), 2.45-2.38 (m, 2H), 2.20-2.05 (m, 5H), 1.95-1.78 (m, 7H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2) MS calcd. for $C_{29}H_{34}ClFN_6O_4$:584.23; Found: 585.10 $[M+1]^+$.
72	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((3-hydroxyoxetan-3-yl)methoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H), 7.95 (dd, J = 6.8, 2.4 Hz, 1H), 7.69-7.57 (m, 1H), 7.56-7.42 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.91 (s, 1H), 5.57 (s, 1H), 5.24 (s, 1H), 4.44 (2d, J = 6.4 Hz, 2x2H), 4.11 (s, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.30-3.28 (m, 1H, merged), 2.50-2.48 (m, 2H, merged), 2.21-2.15 (m, 4H), 1.85-1.81 (m, 4H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{27}H_{31}ClFN_5O_5$: 559.20; Found: 560.20 $[M+1]^+$.
73	

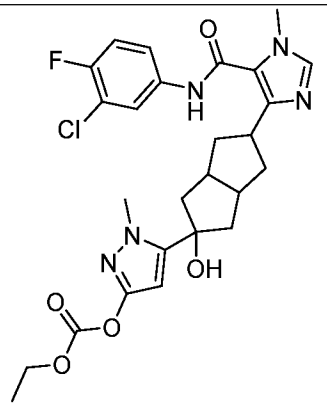
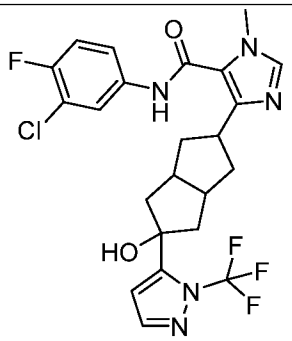
	N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1-hydroxycyclohexyl)methoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.97 (dd, J = 6.8, 2.4 Hz, 1H), 7.64 (s, 1H), 7.58-7.55 (m, 1H), 7.39 (t, J = 9.2 Hz, 1H), 5.50 (s, 1H), 5.20 (s, 1H), 4.25 (s, 1H), 3.75-3.66 (m, 8H), 3.30-3.28 (m, 1H, merged), 2.50-2.48 (m, 2H, merged), 2.19-2.06 (m, 4H), 1.85-1.79 (m, 4H), 1.57-1.06 (m, 10H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{30}H_{37}ClFN_5O_4$: 585.25; Found: 586.30 $[M+1]^+$.
74	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((4-hydroxytetrahydro-2H-pyran-4-yl)methoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.95 (dd, J = 6.8, 2.4 Hz, 1H), 7.64 (s, 1H), 7.58-7.55 (m, 1H), 7.39 (t, J = 9.2 Hz, 1H), 5.52 (s, 1H), 5.21 (s, 1H), 4.61 (s, 1H), 3.78 (s, 2H), 3.72 (s, 3H), 3.67 (s, 3H), 3.64-3.58 (m, 4H), 3.30-3.28 (m, 1H, merged), 2.50-2.48 (m, 2H, merged), 2.20-2.07 (m, 4H), 1.88-1.80 (m, 4H), 1.69-1.61 (m, 2H), 1.40-1.36 (m, 2H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{29}H_{35}ClFN_5O_5$: 587.23; Found: 586.50 $[M-1]^-$.

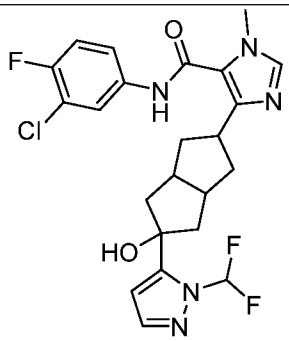
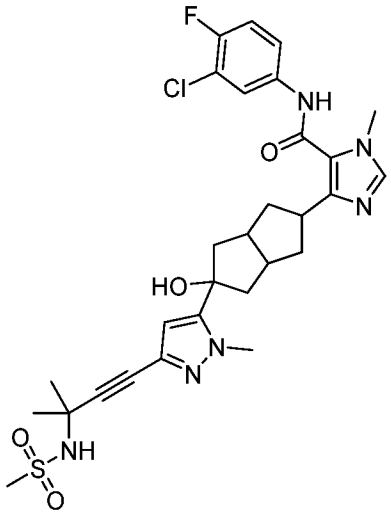
75	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-hydroxy-2-methylpropanamido)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 9.24 (s, 1H) 7.96 (dd, J = 6.4, 2.0 Hz, 1H), 7.63 (s, 1H), 7.58-7.51 (m, 1H), 7.37 (t, J = 9.2 Hz, 1H), 6.34 (s, 1H), 5.75 (br.s, 1H), 5.28 (br.s, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.30-3.20 (m, 1H, merged), 2.50-2.40 (m, 2H), 2.27-2.18 (m, 2H), 2.17-2.05 (m, 2H), 1.92-1.78 (m, 4H), 1.30 (s, 6H) ppm. TLC: 10% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{27}H_{32}ClFN_6O_4$: 558.22; Found: 559.20 $[M+1]^+$.
76	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(1-hydroxycyclopropane-1-carboxamido)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 9.33 (s, 1H) 7.96 (dd, J = 6.4, 2.0 Hz, 1H), 7.63 (s, 1H), 7.58-7.51 (m, 1H), 7.37 (t, J = 9.2 Hz, 1H), 6.33 (s, 1H), 5.33 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.34-3.24 (m, 1H, merged), 2.50-

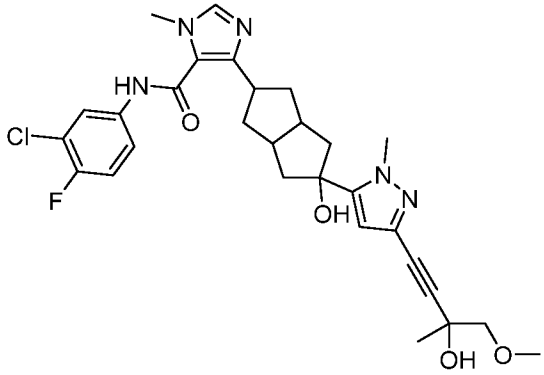
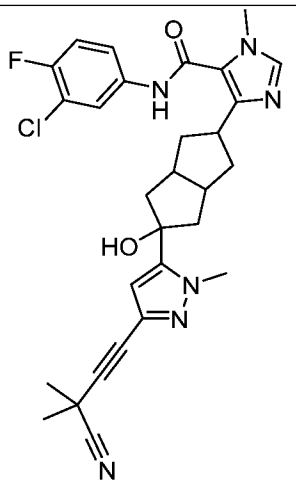
	2.40 (m, 2H, merged), 2.35-2.25 (m, 2H), 2.25-2.05 (m, 2H), 1.95-1.80 (m, 4H), 1.12-1.08 (m, 2H), 0.96-1.90 (m, 2H) ppm. 1-OH proton was not observed. TLC: 10% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{27}H_{30}ClFN_6O_4$: 556.20; Found: 555.40 $[M-1]^-$.
77	 **4-(5-(3-(2-Aminopropanamido)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 8.26 (s, 1H) 7.95 (dd, J = 6.4, 2.0 Hz, 1H), 8.26 (s, 1H), 7.58-7.54 (m, 1H), 7.39 (t, J = 9.2 Hz, 1H), 6.35 (s, 1H), 5.53 (br.s, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.52-3.42 (m, 3H), 3.30-3.20 (m, 1H), 2.50-2.45 (m, 2H, merged), 2.24-2.12 (m, 2H), 2.12-2.05 (m, 2H), 1.91-1.80 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H) ppm. TLC: 5% MeOH:NH_3 [9:1]/dichloromethane (R_f: 0.2). MS calcd. for $C_{26}H_{31}ClFN_7O_3$: 543.22; Found: 544.20 $[M+1]^+$.
78	 **4-(5-(3-(2-amino-3-methylbutanamido)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide.**

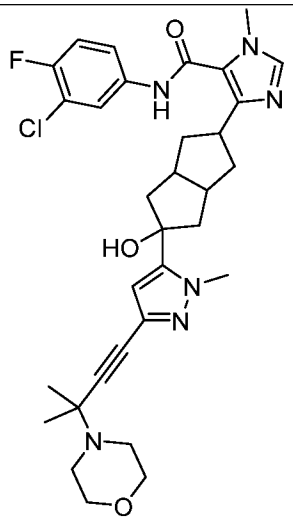
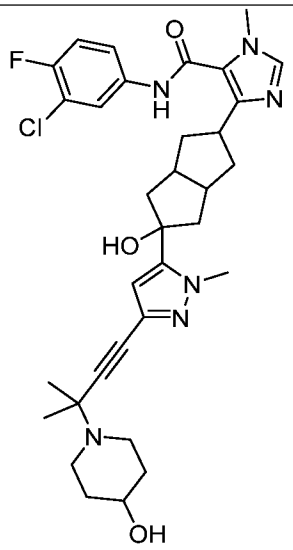
	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 8.25 (br.s, 1H) 7.97 (dd, J = 6.4, 2.0 Hz, 1H), 7.66 (s, 1H) 7.60-7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 6.38 (s, 1H), 5.51 (s, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.60-3.30 (m, 3H, merged), 3.14 (d, J = 5.16 Hz, 1H), 2.60-2.50 (m, 2H, merged), 2.28-2.18 (m, 2H), 2.17-2.08 (m, 2H), 1.95-1.82 (m, 5H), 0.90-0.80 (m, 6H) ppm. TLC: 10% MeOH:NH_3 [9:1]/dichloromethane (R_f: 0.2). MS calcd. for $C_{28}H_{35}ClFN_7O_3$: 571.25; Found: 572.30 $[M+1]^+$.
79	 **(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)proline. Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.98-7.94 (m, 1H), 7.65 (s, 1H) 7.58-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 5.30 (s, 1H), 5.10 (s, 1H), 3.95 (d, J = 6.8 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.45-3.20 (m, 3H, merged), 2.50-2.42 (m, 2H, merged), 2.42-2.10 (m, 5H), 1.95-1.78 (m, 7H) ppm. COOH proton was not observed. TLC: 10% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{28}H_{32}ClFN_6O_4$: 570.22; Found: 571.20 $[M-1]^-$.
80	

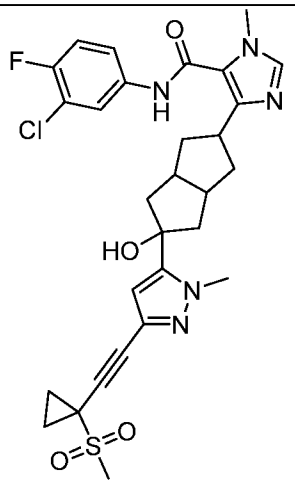
	N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-(hydroxymethyl)pyrrolidin-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Isomer II ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (dd, J = 7.2, 2.8 Hz, 1H), 7.65 (s, 1H), 7.58-7.55 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.36 (s, 1H), 5.13 (s, 1H), 4.71 (t, J = 4.8 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.52-3.48 (m, 2H), 3.30-3.15 (m, 3H), 2.95-2.93 (m, 1H), 2.50-2.48 (m, 2H, merged), 2.21-2.07 (m, 4H), 1.85-1.75 (m, 8H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.2). MS calcd. for $C_{28}H_{34}ClFN_6O_3$: 556.24; Found: 557.30 $[M+1]^+$.
81	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(cyclopropylmethyl)-3-(2-hydroxy-2-methylpropoxy)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.58-7.56 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.50 (s, 1H), 5.24 (s, 1H), 4.55 (s, 1H), 3.96-3.93 (m, 2H), 3.73 (s, 2H), 3.67 (s, 3H), 3.30-3.24 (m, 1H, merged), 2.50-2.48 (m, 2H, merged), 2.19-2.06 (m, 4H), 1.85-1.82 (m, 4H), 1.32-1.20 (m, 1H), 1.14 (s, 6H), 0.45-0.43 (m, 2H), 0.36-0.34 (m, 2H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{30}H_{37}ClFN_5O_4$: 587.25; Found: 586.70 $[M+1]^+$.

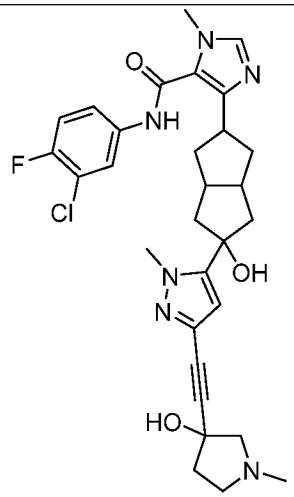
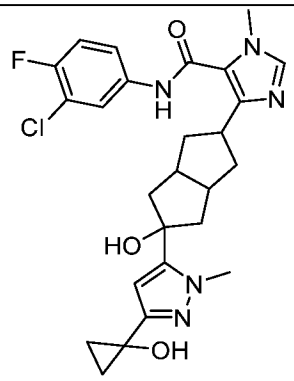
82	 **5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl ethyl carbonate** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.97-7.93 (m, 1H), 7.65 (s, 1H), 7.58-7.56 (m, 1H), 7.39 (t, J = 8.8 Hz, 1H), 5.95 (s, 1H), 5.38 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 3.30-3.28 (m, 1H, merged), 2.50-2.48 (m, 2H, merged), 2.18-2.07 (m, 4H), 1.88-1.84 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H) ppm. TLC: 5% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{26}H_{29}ClFN_5O_5$: 545.18; Found: 546.2 $[M+1]^+$.
83	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(trifluoromethyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.95 (d, J = 5.7 Hz, 1H), 7.72 (s, 1H), 7.66 (s, 1H), 7.57 (s, 1H), 7.40 (t, J = 9.0 Hz, 1H), 6.50 (s, 1H), 5.47 (s, 1H), 3.68 (s, 3H), 3.29 (s, 2H), 2.34 – 2.22 (m, 2H), 2.09 (d, J = 9.9 Hz, 3H), 1.89 (dd, J = 27.2, 12.1 Hz, 3H) ppm. MS calcd. for $C_{23}H_{22}ClF_4N_5O_2$: 511.14; Found: 510.0 $[M-H]^-$.

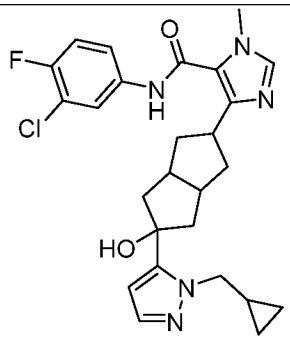
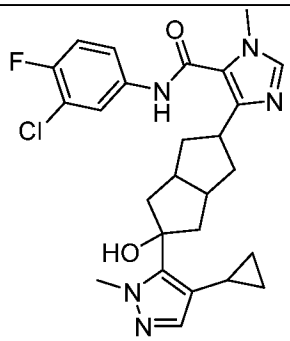
84	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(difluoromethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.91 (t, *J* = 57.8 Hz, 1H), 7.77 – 7.68 (m, 1H), 7.60 (s, 1H), 7.43 (s, 1H), 7.35 (dt, *J* = 9.0, 3.5 Hz, 1H), 7.16 (t, *J* = 8.7 Hz, 1H), 6.16 (s, 1H), 3.80 (s, 3H), 3.30 (td, *J* = 10.8, 5.5 Hz, 1H), 2.89 – 2.66 (m, 2H), 2.29 (dddd, *J* = 29.0, 21.8, 13.1, 6.4 Hz, 6H), 2.17 (dd, *J* = 13.7, 2.6 Hz, 2H), 2.05 (s, 1H) ppm. MS calcd. for $C_{23}H_{23}ClF_3N_5O_2$: 493.15; Found: 492.2 $[M-H]^-$.
85	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(3-methyl-3-(methylsulfonamido)but-1-yn-1-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.90 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.67 (s, 1H), 7.51 (ddd, *J* = 8.9, 4.1, 2.7 Hz, 1H), 7.25 (t, *J* = 9.0 Hz, 1H), 6.33 (s, 1H), 3.98 (s, 3H), 3.78 (s, 3H), 3.37 (dd, *J* = 12.1, 6.0 Hz, 1H), 3.13 (s, 3H), 2.58 (s, 2H), 2.39 (dd, *J* = 13.2, 7.1 Hz, 2H), 2.26 (dd, *J* = 14.5, 8.3 Hz, 2H), 2.03 – 1.79 (m,

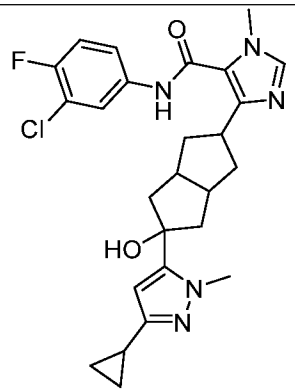
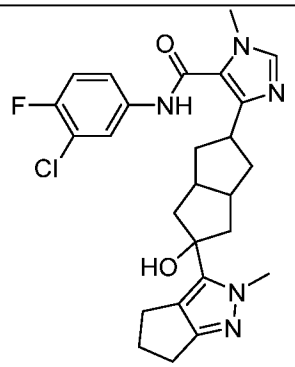
	4H), 1.64 (s, 6H) ppm. MS calcd. for $C_{29}H_{34}ClFN_6O_4S$: 616.2; Found: 615.0 $[M-H]^-$.
86	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxy-4-methoxy-3-methylbut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.90 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.67 (s, 1H), 7.57 – 7.47 (m, 1H), 7.29 – 7.17 (m, 1H), 6.30 (d, *J* = 0.9 Hz, 1H), 3.97 (d, *J* = 1.0 Hz, 3H), 3.78 (s, 3H), 3.53 – 3.34 (m, 6H), 2.57 (s, 2H), 2.39 (dd, *J* = 13.7, 7.0 Hz, 2H), 2.25 (dd, *J* = 15.2, 8.8 Hz, 2H), 2.18 – 1.71 (m, 4H), 1.49 (d, *J* = 1.0 Hz, 3H) ppm. MS calcd. for $C_{29}H_{33}ClFN_5O_4$: 569.22; Found: 568.2 $[M-H]^-$.
87	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(3-cyano-3-methylbut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.90 (dd, *J* = 6.8, 2.6 Hz, 1H), 7.69 (s, 1H), 7.51 (dt, *J* = 9.1, 3.3 Hz, 1H), 7.25 (t, *J* = 8.9 Hz, 1H), 6.36 (s, 1H), 3.99 (s, 3H), 3.78 (s, 3H), 3.37 (d, *J* = 10.9 Hz, 1H), 2.58 (s, 2H), 2.38 (dd, *J* = 13.0, 7.1

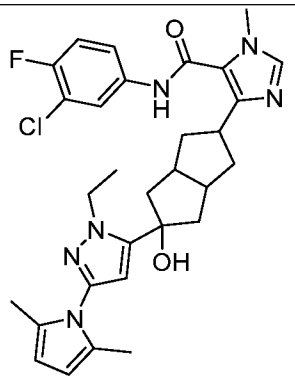
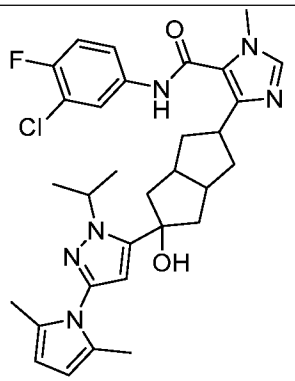
	Hz, 2H), 2.33 – 2.22 (m, 2H), 2.07 – 1.84 (m, 4H), 1.72 (s, 6H) ppm. MS calcd. for $C_{29}H_{30}ClFN_6O_2$: 548.21; Found: 547.2 [M-H]$^-$.
88	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(3-methyl-3-morpholinobut-1-yn-1-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.90 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.67 (s, 1H), 7.51 (ddd, *J* = 9.0, 4.2, 2.7 Hz, 1H), 7.25 (t, *J* = 9.0 Hz, 1H), 6.29 (s, 1H), 3.97 (s, 3H), 3.78 (s, 3H), 3.74 (t, *J* = 4.8 Hz, 4H), 3.38 (dd, *J* = 12.3, 6.2 Hz, 1H), 2.73 (t, *J* = 4.7 Hz, 4H), 2.58 (s, 2H), 2.40 (dd, *J* = 12.9, 7.9 Hz, 2H), 2.32 – 2.21 (m, 2H), 2.04 – 1.81 (m, 4H), 1.45 (s, 6H) ppm. MS calcd. for $C_{32}H_{38}ClFN_6O_3$: 608.27; Found: 607.2 [M-H]$^-$.
89	

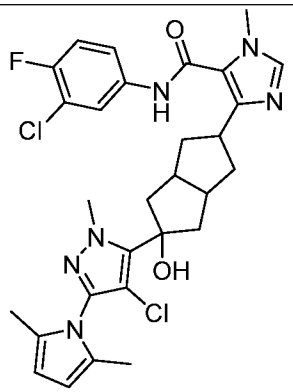
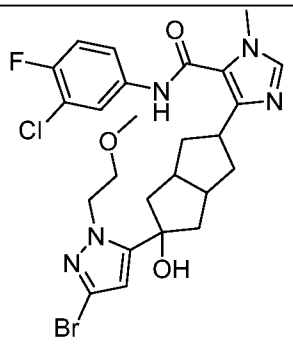
	N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-(4-hydroxypiperidin-1-yl)-3-methylbut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide ^{1}H NMR (400 MHz, MeOH-d4): δ 7.90 (d, *J* = 6.6 Hz, 1H), 7.67 (s, 1H), 7.50 (s, 1H), 7.25 (t, *J* = 8.9 Hz, 1H), 6.28 (s, 1H), 3.97 (s, 3H), 3.78 (s, 3H), 3.36 (d, *J* = 6.0 Hz, 1H), 3.07 (s, 2H), 2.58 (s, 2H), 2.47 (s, 2H), 2.40 (d, *J* = 13.4 Hz, 2H), 2.26 (s, 2H), 2.05 (s, 2H), 2.01 – 1.83 (m, 6H), 1.59 (d, *J* = 11.4 Hz, 2H), 1.48 (s, 6H) ppm. MS calcd. for $C_{33}H_{40}ClFN_6O_3$: 622.28; Found: 621.4 $[M-H]^-$.
90	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-((1-(methylsulfonyl)cyclopropyl)ethynyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.67 (s, 1H), 7.51 (ddd, *J* = 9.0, 4.2, 2.7 Hz, 1H), 7.25 (t, *J* = 9.0 Hz, 1H), 6.38 (d, *J* = 1.2 Hz, 1H), 3.99 (d, *J* = 1.2 Hz, 3H), 3.78 (s, 3H), 3.42 – 3.33 (m, 1H), 3.16 (s, 3H), 2.57 (s, 2H), 2.39 (dd, *J* = 13.3, 7.4 Hz, 2H), 2.31 – 2.20 (m, 2H), 2.06 – 1.81 (m, 4H), 1.77 – 1.66 (m, 2H), 1.56 – 1.45 (m, 2H) ppm. MS calcd. for $C_{29}H_{31}ClFN_5O_4S$: 599.18; Found: 598.0 $[M-H]^-$.

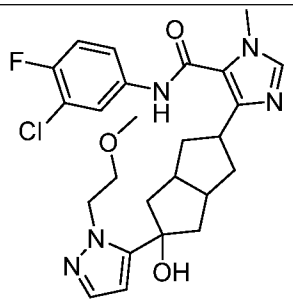
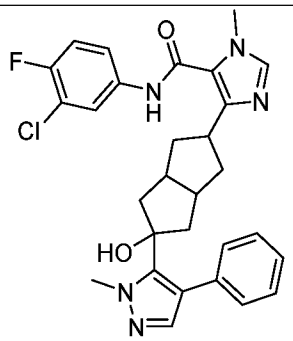
91	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((3-hydroxy-1-methylpyrrolidin-3-yl)ethynyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, *J* = 6.6, 2.7 Hz, 1H), 7.67 (s, 1H), 7.52 (ddd, *J* = 9.0, 4.2, 2.6 Hz, 1H), 7.25 (t, *J* = 8.9 Hz, 1H), 6.33 (s, 1H), 3.99 (s, 3H), 3.78 (s, 3H), 3.25 (s, 2H), 3.10 (s, 1H), 2.68 (d, *J* = 11.8 Hz, 3H), 2.57 (s, 2H), 2.42 (ddd, *J* = 30.5, 12.6, 6.1 Hz, 3H), 2.34 – 2.13 (m, 3H), 2.05 – 1.79 (m, 4H) ppm. MS calcd. for $C_{30}H_{34}ClFN_6O_3$: 580.24; Found: 579.2 [M-H].
92	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(1-hydroxycyclopropyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, *J* = 6.8, 2.6 Hz, 1H), 7.67 (s, 1H), 7.57 – 7.47 (m, 1H), 7.25 (t, *J* = 8.9 Hz, 1H), 6.19 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.40 – 3.33 (m, 1H), 2.58 (s, 2H), 2.42 (dd, *J* = 13.1, 7.1 Hz, 2H), 2.35 –

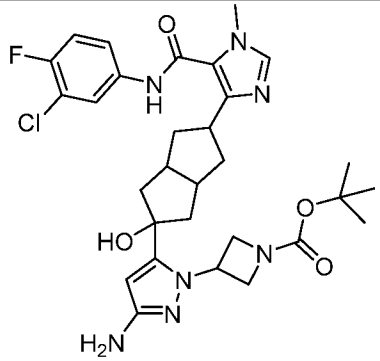
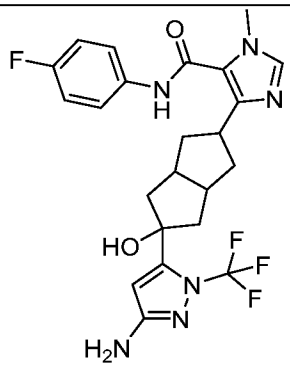
	2.17 (m, 2H), 2.03 – 1.77 (m, 4H), 1.21 – 0.85 (m, 4H) ppm. MS calcd. for $C_{26}H_{29}ClFN_5O_3$: 513.19; Found: 512.2 $[M-H]^-$.
93	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(cyclopropylmethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 7.96 (dd, J = 6.8, 2.5 Hz, 1H), 7.65 (s, 1H), 7.56 (s, 1H), 7.40 (t, J = 9.1 Hz, 1H), 7.25 (d, J = 1.8 Hz, 1H), 6.05 (d, J = 1.8 Hz, 1H), 5.26 (s, 1H), 4.11 (d, J = 7.0 Hz, 3H), 3.68 (s, 4H), 2.27 – 2.15 (m, 2H), 2.07 (s, 3H), 1.88 (d, J = 11.4 Hz, 4H), 1.31 (s, 1H), 0.45 (d, J = 8.1 Hz, 2H), 0.37 (d, J = 5.0 Hz, 2H) ppm. MS calcd. for $C_{26}H_{29}ClFN_5O_2$: 497.2; Found: 496.2 $[M-H]^-$.
94	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, Chloroform-d): δ 8.64 (s, 1H), 7.99 – 7.74 (m, 2H), 7.45 (s, 1H), 7.15 (t, J = 8.7 Hz, 1H), 7.08 (s, 1H), 4.01 (s, 3H), 3.89 (s, 3H), 3.33 (t, J = 9.3 Hz, 1H), 2.85 (s, 2H), 2.53 (dd, J = 13.9, 7.8 Hz, 2H), 2.45 – 2.27 (m, 7H), 1.63 (s, 1H), 0.81 (dd, J = 8.2, 1.9 Hz, 2H), 0.54 (d, J = 4.7 Hz, 2H) ppm. MS calcd. for $C_{26}H_{29}ClFN_5O_2$: 497.2; Found: 496.0 $[M-H]^-$.

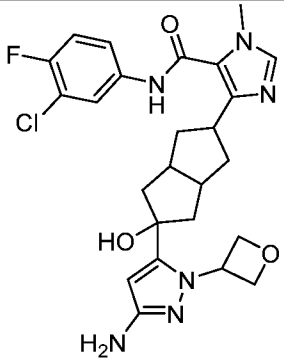
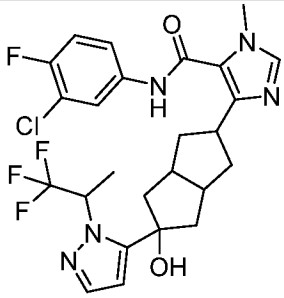
95	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (dd, J = 6.8, 2.5 Hz, 1H), 7.64 (s, 1H), 7.57 (d, J = 9.6 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.88 (d, J = 2.3 Hz, 1H), 4.75 (s, 1H), 3.94 (s, 2H), 3.67 (s, 3H), 3.30 – 3.17 (m, 2H), 2.40 (s, 2H), 2.07 (s, 2H), 1.87 – 1.61 (m, 5H), 1.35 (dd, J = 13.5, 5.1 Hz, 2H), 0.81 (dt, J = 6.2, 3.2 Hz, 2H), 0.57 (d, J = 5.1 Hz, 2H) ppm. MS calcd. for $C_{26}H_{29}ClFN_5O_2$: 497.2; Found: 496.2 [M-H]$^-$.
96	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(2-methyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.94 (dd, J = 6.9, 2.6 Hz, 1H), 7.62 (s, 1H), 7.55 (ddd, J = 9.0, 4.3, 2.6 Hz, 1H), 7.39 (t, J = 9.1 Hz, 1H), 5.05 (s, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.21 (s, 1H), 2.56 (t, J = 7.1 Hz, 2H), 2.52 (s, 2H), 2.45 (d, J = 7.4 Hz, 3H), 2.22 (d, J = 7.3 Hz, 2H), 2.13 (dd, J = 13.0, 7.9 Hz, 2H), 2.10 – 2.03 (m, 2H), 1.95 – 1.85 (m, 3H) ppm. MS calcd. for $C_{26}H_{29}ClFN_5O_2$: 497.2; Found: 496.0 [M-H]$^-$.

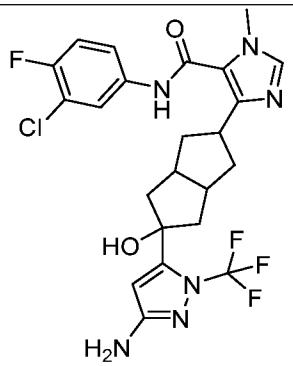
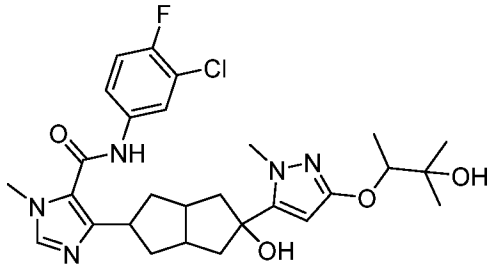
97	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.94 (dd, J = 6.8, 2.6 Hz, 1H), 7.64 (s, 1H), 7.55 (ddd, J = 9.0, 4.3, 2.6 Hz, 1H), 7.38 (t, J = 9.1 Hz, 1H), 6.08 (s, 1H), 5.70 (s, 2H), 5.43 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.66 (s, 3H), 3.28 – 3.21 (m, 1H), 2.50 (s, 2H), 2.23 (dd, J = 13.2, 7.6 Hz, 2H), 2.09 (dt, J = 13.6, 7.2 Hz, 2H), 2.01 (s, 6H), 1.95 – 1.81 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H) ppm. MS calcd. for $C_{30}H_{34}ClFN_6O_2$: 564.24; Found: 563.0 $[M-H]^-$.
98	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, Chloroform-d): δ 8.05 (d, J = 7.9 Hz, 2H), 7.84 – 7.71 (m, 2H), 7.57 (d, J = 15.2 Hz, 2H), 7.48 (t, J = 7.9 Hz, 2H), 7.36 (d, J = 7.0 Hz, 2H), 7.16 (t, J = 8.6 Hz, 1H), 3.86 (d, J = 2.0 Hz, 3H), 3.33 (s, 1H), 2.84 (s, 2H), 2.49 (dd, J = 13.4, 7.5 Hz, 2H), 2.31 (s, 4H), 2.13 (d, J = 13.3 Hz, 2H) ppm. MS calcd. for $C_{31}H_{36}ClFN_6O_2$: 578.26; Found: 519.2 $[M-H]^-$.

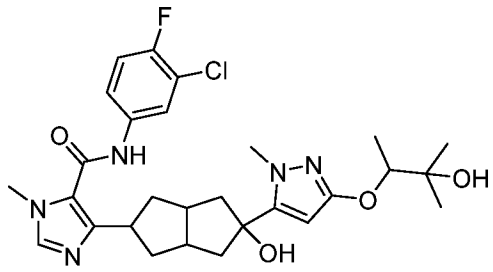
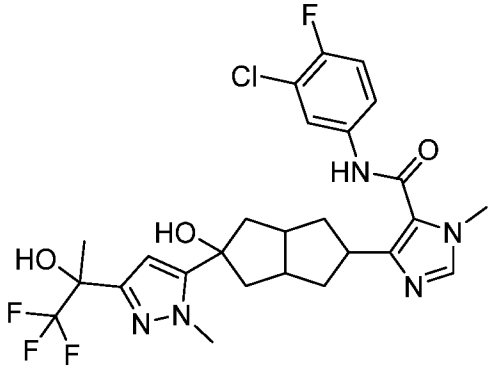
99	 **4-(5-(4-Chloro-3-(2,5-dimethyl-1H-pyrrol-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, Chloroform-*d*): δ 10.18 (s, 1H), 8.53 (s, 1H), 8.02 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 7.16 (t, *J* = 8.7 Hz, 1H), 5.87 (s, 2H), 4.06 (s, 3H), 4.01 (s, 3H), 3.45 (s, 1H), 2.90 (s, 2H), 2.60 (s, 2H), 2.49 (s, 2H), 2.34 (d, *J* = 14.3 Hz, 3H), 2.02 (s, 6H), 1.27 (s, 2H) ppm. MS calcd. for $C_{29}H_{31}Cl_2FN_6O_2$: 584.19; Found: 583.2 $[M-H]^-$.
100	 **4-(5-(3-Bromo-1-(2-methoxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.79 (dd, *J* = 6.5, 2.6 Hz, 1H), 7.58 (d, *J* = 24.1 Hz, 2H), 7.36 (dd, *J* = 8.8, 3.7 Hz, 1H), 7.16 (t, *J* = 8.7 Hz, 1H), 6.11 (s, 1H), 4.55 (t, *J* = 5.1 Hz, 2H), 3.86 (s, 3H), 3.76 (t, *J* = 5.1 Hz, 2H), 3.31 (s, 3H), 3.26 (dt, *J* = 11.9, 6.1 Hz, 1H), 2.70 (s, 2H), 2.25 (ddt, *J* = 36.7, 21.8, 9.7 Hz, 7H), 2.15 – 2.07 (m, 2H) ppm. MS calcd. for $C_{25}H_{28}BrClFN_5O_3$: 579.1; Found: 580.2 $[M-H]^-$.

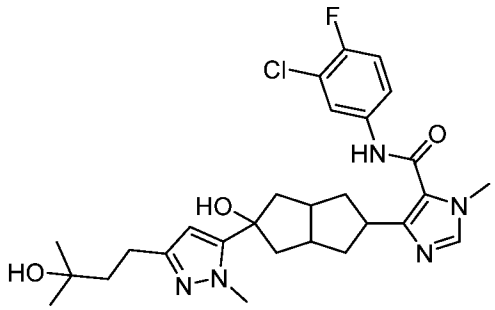
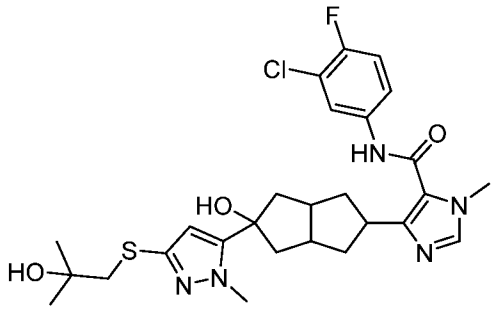
101	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-methoxyethyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.77 (dd, *J* = 6.5, 2.7 Hz, 1H), 7.53 – 7.37 (m, 3H), 7.33 (dt, *J* = 9.2, 3.3 Hz, 1H), 7.15 (t, *J* = 8.8 Hz, 1H), 6.11 (d, *J* = 2.0 Hz, 1H), 4.59 (t, *J* = 5.1 Hz, 2H), 3.84 (s, 3H), 3.79 (t, *J* = 5.1 Hz, 2H), 3.50 (d, *J* = 2.2 Hz, 1H), 3.29 (d, *J* = 2.1 Hz, 3H), 3.25 (t, *J* = 5.9 Hz, 1H), 2.68 (d, *J* = 7.3 Hz, 2H), 2.37 (dd, *J* = 13.8, 7.0 Hz, 2H), 2.31 – 2.15 (m, 4H), 2.11 (dd, *J* = 13.3, 4.0 Hz, 2H) ppm. MS calcd. for $C_{25}H_{29}ClFN_5O_3$: 501.19; Found: 500.2 $[M-H]^-$.
102	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-4-phenyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 – 7.89 (m, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.38 (t, *J* = 9.0 Hz, 1H), 7.31 (q, *J* = 6.9 Hz, 5H), 7.13 (s, 1H), 5.22 (s, 1H), 4.02 (s, 3H), 3.66 (d, *J* = 4.2 Hz, 3H), 3.10 (s, 1H), 2.33 (s, 2H), 1.93 (d, *J* = 16.8 Hz, 6H), 1.83 (s, 2H) ppm. MS calcd. for $C_{29}H_{29}ClFN_5O_2$: 533.2; Found: 532.2 $[M-H]^-$.

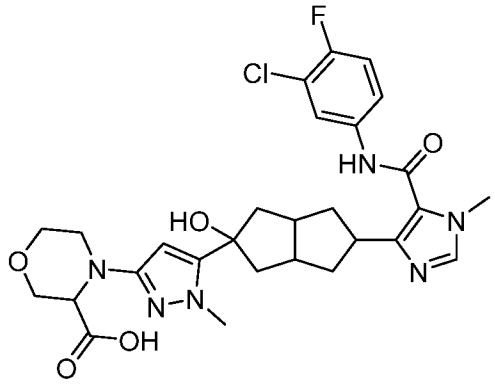
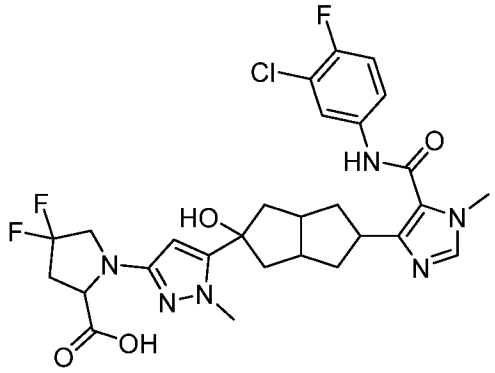
103	 **tert-Butyl 3-(3-amino-5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate** ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.94 (dd, J = 6.8, 2.5 Hz, 1H), 7.63 (s, 1H), 7.59 – 7.50 (m, 1H), 7.38 (t, J = 9.1 Hz, 1H), 5.43 (p, J = 6.7 Hz, 1H), 5.28 (s, 1H), 5.20 (s, 1H), 4.61 (d, J = 14.2 Hz, 2H), 4.08 (s, 4H), 3.66 (s, 3H), 3.21 (dt, J = 12.1, 5.9 Hz, 1H), 2.45 – 2.38 (m, 2H), 2.16 – 1.95 (m, 4H), 1.88 – 1.64 (m, 4H), 1.37 (s, 9H) ppm. MS calcd. for $C_{30}H_{37}ClFN_7O_4$: 613.26; Found: 612.2 $[M-H]^-$.
104	 **4-(5-(3-Amino-1-(trifluoromethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, Acetonitrile-d_3): δ 8.27 (s, 1H), 7.76 – 7.57 (m, 2H), 7.49 (s, 1H), 7.29 – 6.98 (m, 2H), 5.85 (s, 1H), 4.32 (s, 2H), 3.75 (s, 3H), 3.49 (s, 1H), 3.43 – 3.34 (m, 1H), 3.32 (s, 1H), 2.63 (s, 2H), 2.36 (dd, J = 13.8, 7.6 Hz, 2H), 2.02 (s, 1H) ppm. MS calcd. for $C_{23}H_{24}F_4N_6O_2$: 492.19; Found: 491.2 $[M-H]^-$.

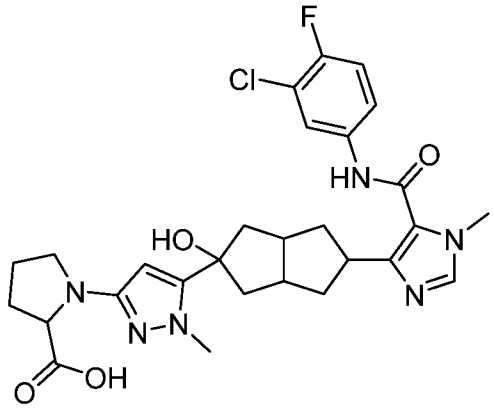
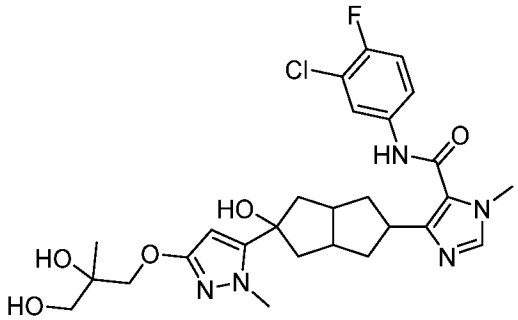
105	 **4-(5-(3-Amino-1-(oxetan-3-yl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, Acetonitrile-d_3): δ 8.34 (s, 1H), 7.89 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.54 (ddd, *J* = 9.0, 4.2, 2.6 Hz, 1H), 7.49 (s, 1H), 7.27 (t, *J* = 9.0 Hz, 1H), 5.91 (t, *J* = 7.2 Hz, 1H), 5.47 (s, 1H), 4.98 (t, *J* = 6.2 Hz, 2H), 4.85 (dd, *J* = 7.9, 5.9 Hz, 2H), 3.91 (s, 2H), 3.75 (s, 3H), 3.33 (dt, *J* = 11.8, 5.9 Hz, 2H), 2.22 (s, 2H), 1.94 – 1.88 (m, 2H) ppm. MS calcd. for $C_{25}H_{28}ClFN_6O_3$: 514.19; Found: 513.2 $[M-H]^-$.
106	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.90 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.67 (s, 1H), 7.52 (ddd, *J* = 9.0, 4.2, 2.6 Hz, 1H), 7.45 (d, *J* = 1.9 Hz, 1H), 7.25 (t, *J* = 9.0 Hz, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 5.81 (p, *J* = 7.1 Hz, 1H), 3.37 (dd, *J* = 12.0, 6.2 Hz, 1H), 3.31 (s, 3H), 2.67 (d, *J* = 2.4 Hz, 1H), 2.62 (dd, *J* = 16.4, 9.0 Hz, 2H), 2.40 (dd, *J* = 13.2, 7.9 Hz, 1H), 2.28 (ddd, *J* = 19.3, 14.0, 7.4 Hz, 3H), 2.04 – 1.83 (m, 4H), 1.66 (d, *J* = 6.9 Hz, 3H) ppm. MS calcd. for $C_{25}H_{26}ClF_4N_5O_2$: 539.17; Found: 538.2 $[M-H]^-$.

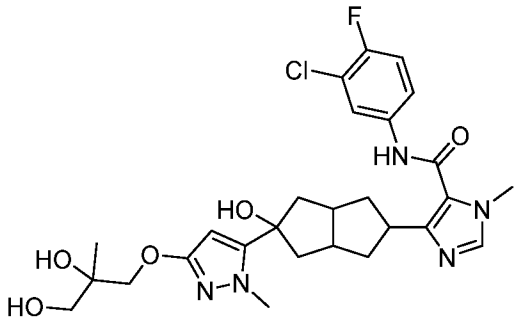
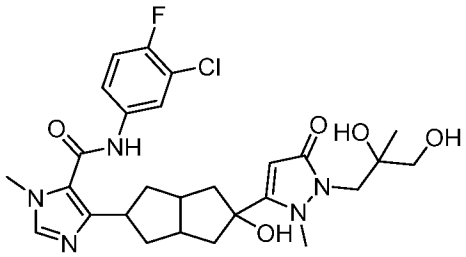
107	 **4-(5-(3-Amino-1-(trifluoromethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (dd, J = 6.9, 2.7 Hz, 1H), 7.64 (s, 1H), 7.41 (t, J = 9.1 Hz, 1H), 5.58 (s, 1H), 5.25 (s, 1H), 3.67 (s, 3H), 2.58 (s, 1H), 2.54 (s, 2H), 2.20 (s, 2H), 2.14 – 1.87 (m, 5H), 1.87 – 1.50 (m, 5H) ppm. MS calcd. for $C_{23}H_{23}ClF_4N_6O_2$: 526.15; Found: 525.0 $[M-H]^-$.
108	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((3-hydroxy-3-methylbutan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** 1H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.95 (dd, J = 2.4 Hz, 6.8 Hz, 1H), 7.64 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.47 (s, 1H), 5.20 (s, 1H), 4.36 (s, 1H), 4.25 (q, J = 6.4 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.25-3.20 (m, 1H), 2.50-2.48 (m, 2H merged), 2.18-2.07 (m, 4H), 1.88-1.80 (m, 4H), 1.14 (d, J = 6.4 Hz, 3H), 1.10 (s, 3H), 1.06 (s, 3H) ppm. TLC: 5% MeOH/DCM (R_f: 0.3). MS calcd. for $C_{28}H_{35}ClFN_5O_4$: 559.24; Found: 542.00 $[M-18+1]^+$.

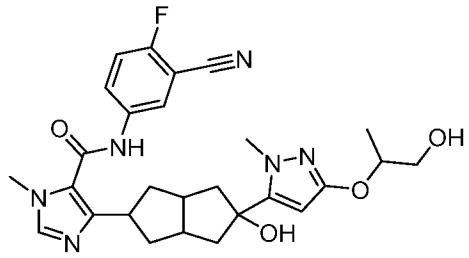
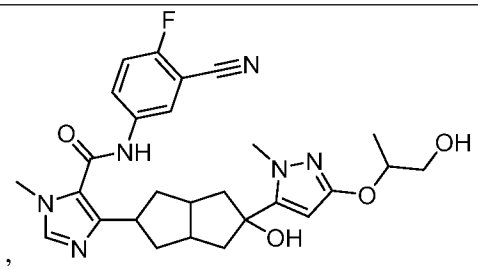
109	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((3-hydroxy-3-methylbutan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** 1H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (dd, J = 2.4 Hz, 6.8 Hz, 1H), 7.64 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 5.47 (s, 1H), 5.20 (s, 1H), 4.36 (s, 1H), 4.25 (q, J = 6.4 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.25-3.20 (m, 1H), 2.50-2.48 (m, 2H merged), 2.18-2.07 (m, 4H), 1.88-1.80 (m, 4H), 1.14 (d, J = 6.4 Hz, 3H), 1.10 (s, 3H), 1.06 (s, 3H) ppm. TLC: 5% MeOH/DCM (R_f: 0.3). MS calcd. for $C_{28}H_{35}ClFN_5O_4$: 559.24; Found: 542.00 $[M-18+1]^+$.
110	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.28 (br s, 1H), 8.13 (s, 1H), 7.96 (s, 1H), 7.73 (dt, J = 1.6, 4.4 Hz, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.41 - 7.41 (m, 1H), 6.26 - 6.25 (m, 1H), 6.19 - 6.18 (m, 1H), 5.30 - 5.29 (m, 1H), 3.91 - 3.90 (m, 3H), 3.71 - 3.70 (m, 3H), 3.23 (br s, 1H), 2.45 (br s, 1H), 2.23 - 2.20 (m, 4H), 1.91 - 1.90 (m, 4H), 1.59 - 1.58 (m, 3H) ppm. TLC: 5% MeOH/DCM (R_f: 0.3). MS calcd. for $C_{26}H_{28}ClF_4N_5O_3$: 569.18; Found: 568.30 $[M-1]^-$.

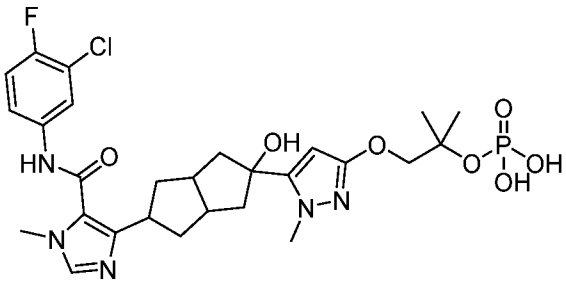
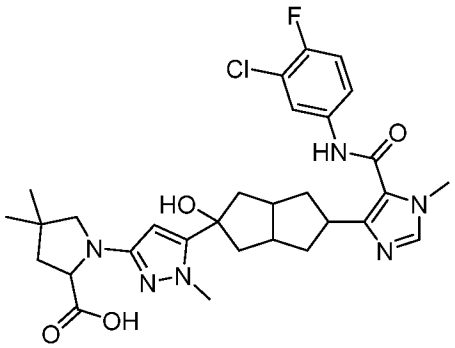
111	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxy-3-methylbutyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.96 (d, J = 2.8 Hz, 1H), 7.64 (s, 1H), 7.58-7.54 (m, 1H), 7.39 (t, J = 9.2 Hz, 1H), 5.85 (s, 1H), 5.15 (s, 1H), 4.15 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 2.52-2.49 (m, 3H, merged), 2.43-2.33 (m, 3H), 2.30-2.09 (m, 3H), 1.86-1.83 (m, 4H), 1.70-1.60 (m, 2H), 1.10 (s, 6H) ppm. TLC: 10% MeOH/DCM (R_f: 0.5). MS calcd. for $C_{28}H_{35}ClFN_5O_3$: 543.24; Found: 544.25 $[M+1]^+$.
112	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((2-hydroxy-2-methylpropyl)thio)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (dd, J = 6.8 Hz, 7.2 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.40 (t, J = 9.2 Hz, 1H), 6.07 (s, 1H), 5.27 (s, 1H), 4.60 (s, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.27-3.20 (m, 1H), 2.95 (s, 2H), 2.50-2.44 (m, 2H), 2.21-2.15 (m, 2H), 2.12-2.07 (m, 2H), 1.90-1.80 (m, 4H), 1.15 (s, 6H) ppm. TLC: 10% MeOH/DCM (R_f: 0.5). MS calcd. for $C_{27}H_{33}ClFN_5O_3S$: 561.20; Found: 562.20 $[M+1]^+$.

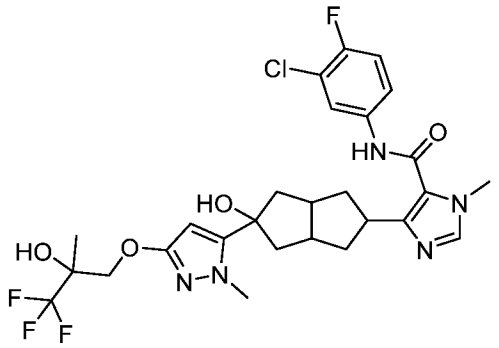
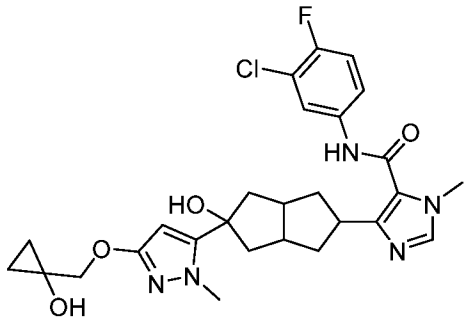
113	 **4-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)morpholine-3-carboxylic acid Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.39 (brs, 1H), 10.20 (s, 1H), 7.96 (d, J = 8 Hz, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.40 (t, J = 8 Hz, 1H), 5.51 (s, 1H), 5.18 (s, 1H), 4.10-4.07 (m, 2H), 3.85-3.69 (m, 1H), 3.67-3.53 (m, 6H), 3.39-3.35 (m, 2H), 3.31-3.18 (m, 3H), 2.51-2.45 (m, 2H), 2.22-2.12 (m, 4H), 1.87-1.79 (m, 4H) ppm. TLC: 10% MeOH/DCM (R_f: 0.2). MS calcd. for $C_{28}H_{32}ClFN_6O_5$: 586.21; Found: 586.10 $[M+1]^+$.
114	 **1-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)-4,4-difluoropyrrolidine-2-carboxylic acid Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.88 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 7.68 (s, 1H), 7.54-7.48 (m, 1H), 7.24 (t, J = 8 Hz, 1H), 5.51 (s, 1H), 4.33-4.30 (m, 1H), 4.00-3.94 (m, 1H), 3.88-3.85 (m, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 2.84-2.78 (m, 1H), 2.57-2.55 (m, 3H), 2.40-2.35 (m, 3H), 2.26-2.22 (m, 2H), 1.94-1.85 (m, 4H) ppm. TLC: 10% MeOH/DCM (R_f: 0.2). MS calcd. for $C_{28}H_{30}ClF_3N_6O_4$: 606.20,; Found: 605.80 $[M-1]^-$.

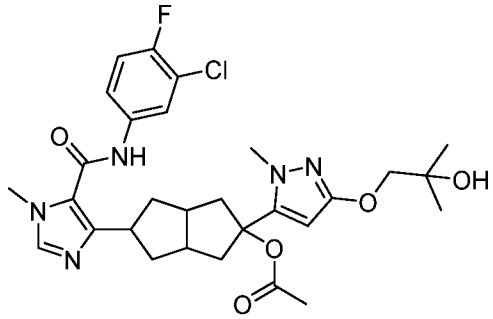
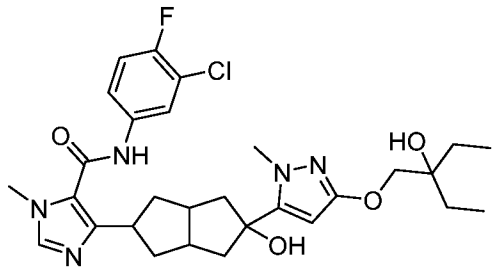
115	 **(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)proline Isomer II** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 7.97-7.95 (m, 1H), 7.59-7.55 (m, 1H), 7.45 (t, J = 9.2 Hz, 1H), 5.36 (s, 1H), 4.15-3.96 (m, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.35-3.31 (m, 2H), 3.17-3.15 (m, 1H), 2.50-2.49 (m, 2H merged), 2.24-2.15 (m, 5H), 1.91-1.84 (m, 7H) ppm. TLC: 10% MeOH:DCM (R_f: 0.2). MS calcd. for $C_{28}H_{32}ClFN_6O_4$: 570.22; Found: 571.10 $[M+1]^+$.
116	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(2,3-dihydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.96 (dd, J = 6.8 Hz, 6.4 Hz, 1H), 7.64 (s, 1H), 7.58-7.55 (m, 1H), 7.39 (t, J = 8.8 Hz, 1H), 5.50 (s, 1H), 5.21 (s, 1H), 4.57 (t, J = 6 Hz, 1H), 4.43 (s, 1H), 3.85 (d, J = 10 Hz, 1H), 3.86-3.84 (m, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.30-3.16 (m, 2H merged), 2.50-2.49 (m, 2H, merged), 2.19-2.07 (m, 4H), 1.88-1.86 (m, 4H), 1.06 (s, 3H) ppm. TLC: 5% MeOH/DCM (R_f: 0.5). MS calcd. for $C_{27}H_{33}ClFN_5O_5$: 561.22; Found: 562.20 $[M+1]^+$.

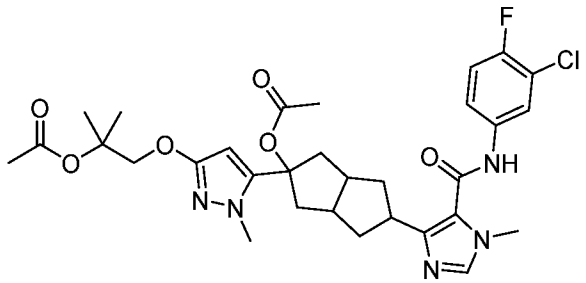
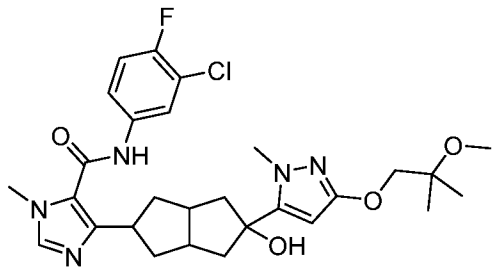
117	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(2,3-dihydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.97 (dd, J = 6.8 Hz, 6.2 Hz, 1H), 7.64 (s, 1H), 7.58-7.54 (m, 1H), 7.39 (t, J = 9.2 Hz, 1H), 5.50 (s, 1H), 5.21 (s, 1H), 4.57 (t, J = 5.6 Hz, 1H), 4.43 (s, 1H), 3.86-3.75 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.30-3.16 (m, 3H), 2.50-2.49 (m, 3H, merged), 2.19-2.07 (m, 4H), 2.09-1.84 (m, 4H), 1.83 (s, 3H) ppm. TLC: 5% MeOH/DCM (R_f: 0.5). MS calcd. for $C_{27}H_{33}ClFN_5O_5$: 561.22; Found: 562.20 $[M+1]^+$.
118	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(2,3-dihydroxy-2-methylpropyl)-2-methyl-5-oxo-2,5-dihydro-1H-pyrazol-3-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.96 (dd, J = 6.8 Hz, 6.4 Hz, 1H), 7.64 (s, 1H), 7.58-7.55 (m, 1H), 7.39 (t, J = 8.8 Hz, 1H), 5.50 (s, 1H), 5.21 (s, 1H), 4.57 (t, J = 6 Hz, 1H), 4.43 (s, 1H), 3.85 (d, J = 10 Hz, 1H), 3.77 (d, J = 9.6 Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.30-3.16 (m, 2H, merged), 2.50-2.49 (m, 3H, merged), 2.19-2.07 (m, 4H), 1.88-1.86 (m, 4H), 1.06 (s, 3H) ppm. TLC: 5% MeOH/DCM (R_f: 0.5). MS calcd. for $C_{27}H_{33}ClFN_5O_5$: 561.22; Found: 562.20 $[M+1]^+$.

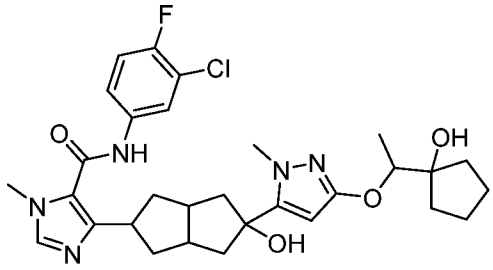
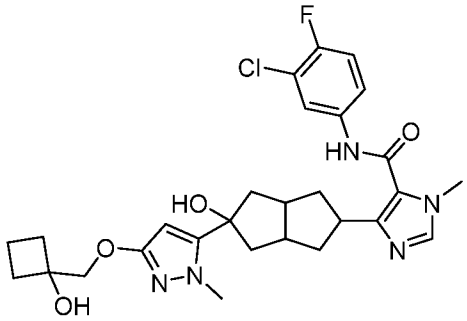
119	 **N-(3-cyano-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1-hydroxypropan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H), 8.16 (dd, J = 6.4, 2.4 Hz, 1H), 7.98-7.90 (m, 1H), 7.67 (s, 1H), 7.53 (t, J = 9.2 Hz, 1H), 5.48 (s, 1H), 5.21 (s, 1H), 4.72-4.70 (m, 1H), 4.53 (q, J = 6.4 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.48-3.40 (m, 1H), 3.38-3.26 (m, 1H), 2.51-2.50 (m, 3H, merged), 2.19-2.08 (m, 4H), 1.89-1.82 (m,, 4H), 1.18 (d, J = 6.0 Hz, 3H) ppm. MS calcd. for $C_{27}H_{31}FN_6O_4$: 522.24; Found: 521.45 [M-1]$^-$.
120	 , **N-(3-Cyano-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1-hydroxypropan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H), 8.16 (dd, J = 6.8, 2.4 Hz, 1H), 7.98-7.90 (m, 1H), 7.67 (s, 1H), 7.53 (t, J = 9.2 Hz, 1H), 5.48 (s, 1H), 5.21 (s, 1H), 4.72-4.70 (m, 1H), 4.53 (q, J = 6.4 Hz, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.48-3.40 (m, 1H), 3.38-3.26 (m, 1H), 2.51-2.50 (m, 2H, merged), 2.19-2.08 (m, 4H), 1.89-1.82 (m, 4H), 1.18 (d, J = 6.0 Hz, 3H) ppm. MS calcd. for $C_{27}H_{31}FN_6O_4$: 522.24; Found: 521.45 [M-1]$^-$.

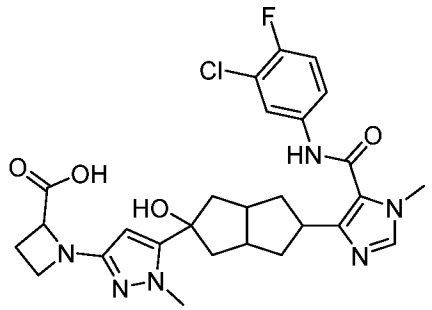
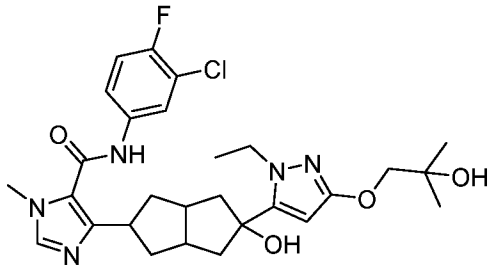
121	 **1-((5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)oxy)-2-methylpropan-2-yl dihydrogen phosphate** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.20 (s, 1H), 7.96 (dd, J = 2.5, 6.9 Hz, 1H), 7.65 (s, 1H), 7.58-7.55 (m, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.54 (s, 1H), 5.22 (br s, 1H), 3.97 (s, 2H), 3.74-3.72 (m, 4H), 3.67 (2s, 6H), 3.21 (d, J = 6.1 Hz, 1H), 2.49 - 2.46 (m, 1H), 2.17 (dd, J = 7.8, 12.7 Hz, 2H), 2.12 - 2.04 (m, 1H), 1.89 - 1.79 (m, 4H), 1.42 (s, 6H) ppm. TLC: 5% MeOH/DCM (R_f: 0.3). MS calcd. for $C_{26}H_{34}ClFN_5O_7P$: 625.19; Found: 626.25 $[M+H]^+$.
122	 **1-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)-4,4-dimethylpyrrolidine-2-carboxylic acid Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 - 10.17 (m, 1H), 7.96 (d, J = 4.6 Hz, 1H), 7.65 (s, 1H), 7.61 - 7.50 (m, 1H), 7.48 - 7.33 (m, 1H), 5.26 (s, 1H), 5.15 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.20 - 3.12 (m, 2H), 2.48 - 2.41 (m, 4H), 2.17 - 1.98 (m, 5H), 1.87 - 1.76 (m, 4H), 1.11 - 0.92 (m, 6H) ppm. TLC: 5% MeOH/DCM (R_f: 0.3). MS calcd. for $C_{30}H_{36}ClFN_6O_4$: 598.25; Found: 599.10 $[M+1]^+$.

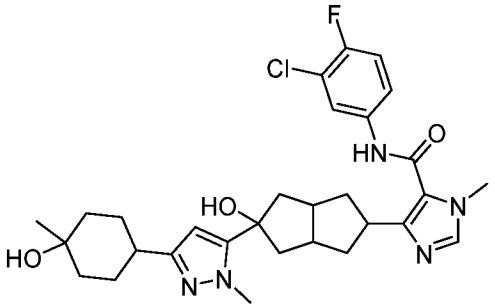
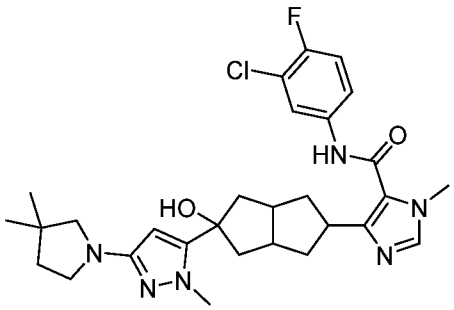
123	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(3,3,3-trifluoro-2-hydroxy-2-methylpropoxy)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamideMixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.97 - 7.93 (m, 1H), 7.65 (s, 1H), 7.59 - 7.55 (m, 1H), 7.40 (t, J = 9.1 Hz, 1H), 6.24 (s, 1H), 5.59 - 5.56 (m, 1H), 5.24 (s, 1H), 4.13 - 4.07 (m, 1H), 4.04 - 3.96 (m, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.26 (br s, 1H), 2.47 - 2.45 (m, 2H), 2.21 - 2.15 (m, 2H), 2.12 - 2.05 (m, 2H), 1.89 - 1.81 (m, 4H), 1.34 (s, 3H) ppm. TLC: 5% MeOH/DCM (R_f: 0.3). MS calcd. for $C_{27}H_{30}ClF_4N_5O_4$: 599.19; Found: 600.16 $[M+1]^+$.
124	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1-hydroxycyclopropyl)methoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.69 - 8.49 (m, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.59 - 7.56 (m, 1H), 7.49 - 7.41 (m, 1H), 5.53 (s, 1H), 5.34 - 5.29 (m, 1H), 3.96 (s, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 2.50-2.48 (m, 2H, merged), 2.23 - 2.15 (m, 4H), 1.89 - 1.76 (m, 4H), 0.65 - 0.54 (m, 4H) ppm. TLC: 5% MeOH/DCM (R_f: 0.3). MS calcd. for $C_{27}H_{31}ClFN_5O_4$: 543.20; Found: 544.25 $[M+1]^+$.

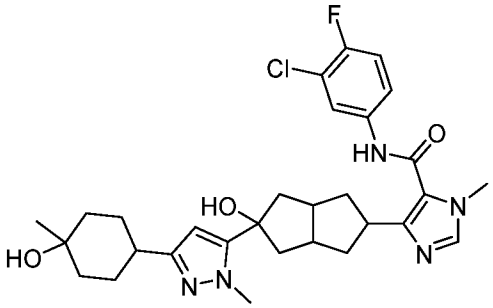
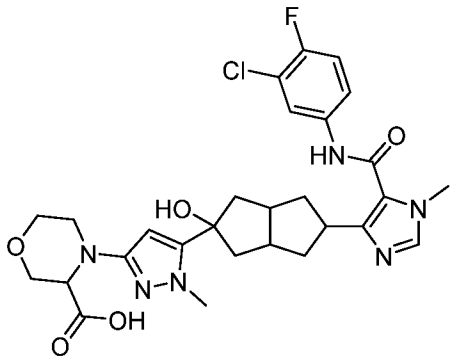
125	 **5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-(3-(2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl acetate** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (dd, J = 2.6, 6.8 Hz, 1H), 7.67 (s, 1H), 7.57 (ddd, J = 2.6, 4.4, 9.1 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.65 (s, 1H), 4.52 (s, 1H), 3.72 (s, 2H), 3.68 (s, 3H), 3.63 (s, 3H), 3.28 - 3.26 (m, 1H), 2.61 - 2.55 (m, 2H), 2.36 - 2.31 (m, 2H), 2.26 - 2.21 (m, 2H), 2.13 (d, J = 5.5 Hz, 1H), 2.10 (s, 4H), 1.84 - 1.76 (m, 2H), 1.13 (s, 6H) ppm. TLC: 5% MeOH/DCM (R_f: 0.3). MS calcd. for $C_{29}H_{35}ClFN_5O_5$: 587.23; Found: 586.25 $[M-1]^-$.
126	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(2-ethyl-2-hydroxybutoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.76 (br s, 1H), 7.96 (dd, J = 2.4, 6.8 Hz, 1H), 7.57 (dd, J = 4.4, 7.0 Hz, 1H), 7.49 - 7.43 (m, 1H), 5.53 (s, 1H), 5.37 - 5.37 (m, 1H), 5.43 - 5.21 (m, 1H), 3.85 - 3.84 (m, 2H), 3.77 - 3.75 (m, 3H), 3.71 - 3.70 (m, 3H), 3.35 - 3.30 (m, 1H), 2.25 (br s, 4H), 1.87 - 1.77 (m, 4H), 1.48 - 1.42 (m, 5H), 0.84 - 0.79 (m, 6H) ppm. TLC: 5% MeOH/DCM (R_f: 0.4). MS calcd. for: $C_{29}H_{37}ClFN_5O_4$: 573.25; Found: 574.00 $[M+1]^+$.

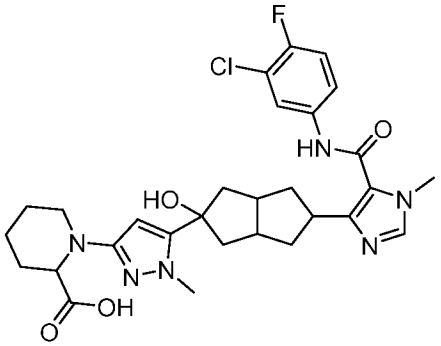
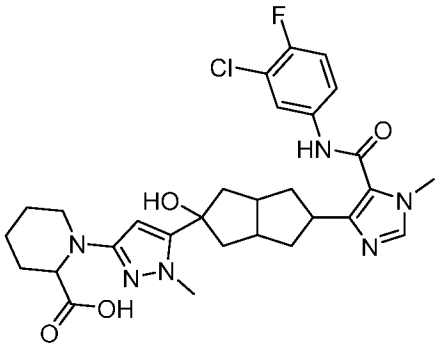
127	 **2-(3-(2-Acetoxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)-5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)octahydropentalen-2-yl acetate** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 - 10.08 (m, 1H), 8.18 - 8.15 (m, 1H), 8.24 - 8.07 (m, 1H), 8.41 - 7.82 (m, 1H), 7.80 - 7.34 (m, 3H), 5.80 - 5.67 (m, 1H), 4.20 - 4.09 (m, 2H), 3.82 - 3.67 (m, 3H), 3.67 - 3.61 (m, 3H), 3.39 - 3.35 (m, 1H), 2.57 - 2.53 (m, 1H), 2.32 (br s, 1H), 2.25 - 2.20 (m, 1H), 2.23 - 2.18 (m, 1H), 2.13 (br d, J = 6.5 Hz, 1H), 2.11 - 2.11 (m, 1H), 2.10 (s, 3H), 1.93 (s, 3H), 1.82 - 1.75 (m, 2H), 1.44 (s, 6H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{31}H_{37}ClFN_5O_6$: 629.24; Found: 628.25 $[M-1]^-$.
128	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-methoxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.95 (dd, J = 2.6, 6.8 Hz, 1H), 7.66 - 7.64 (m, 1H), 7.57 (dd, J = 2.6, 4.3, 9.1 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.54 (s, 1H), 5.22 (s, 1H), 3.85 (s, 2H), 3.17 (s, 1H), 3.13 (s, 3H), 3.12 (s, 3H), 2.19 - 2.07 (m, 4H), 1.87 - 1.80 (m, 4H), 1.15 - 1.13 (m, 9H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{28}H_{35}ClFN_5O_4$: 559.24 Found: 560.30 $[M+1]^+$.

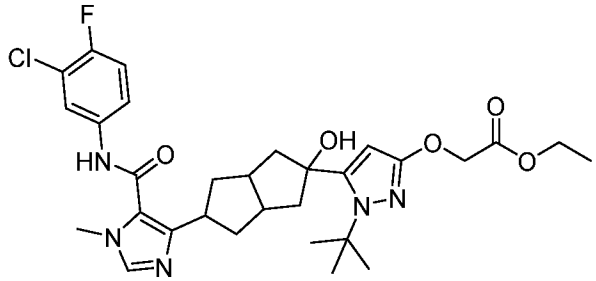
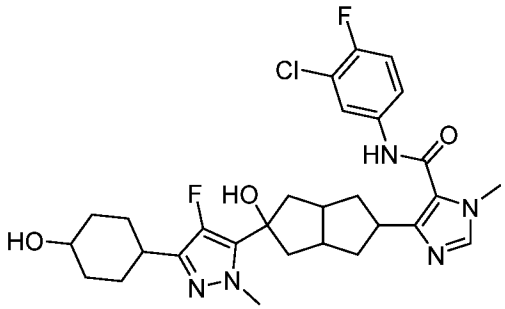
129	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(1-(1-hydroxycyclopentyl)ethoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.34 - 10.26 (m, 1H), 8.13 (s, 1H), 8.00 - 7.95 (m, 1H), 7.86 - 7.73 (m, 1H), 7.60 - 7.56 (m, 1H), 7.45 - 7.40 (m, 1H), 5.47 (s, 1H), 5.22 (br s, 1H), 4.39 (d, J = 6.1 Hz, 1H), 4.26 - 4.17 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.24 - 3.16 (m, 1H), 2.45 (br s, 2H), 2.16 (br dd, J = 7.2, 12.8 Hz, 2H), 1.89 - 1.82 (m, 2H), 1.71 - 1.41 (m, 11H), 1.19 (d, J = 6.2 Hz, 3H) ppm. TLC: 4% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{30}H_{37}ClFN_5O_4$: 585.25 Found: 585.95 $[M+1]^+$.
130	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1-hydroxycyclobutyl)methoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (d, J = 1.0 Hz, 1H), 7.66 (s, 1H), 7.60 - 7.53 (m, 1H), 7.41 (t, J = 9.1 Hz, 1H), 5.54 (s, 1H), 5.23 (s, 1H), 5.13 (s, 1H), 3.91 (s, 2H), 3.74 (s, 3H), 3.68 (s, 3H), 3.29 - 3.25 (m, 1H), 2.47 (d, J = 4.6 Hz, 2H), 2.23 - 2.17 (m, 2H), 2.13 - 2.04 (m, 4H), 1.97 - 1.92 (m, 2H), 1.84 (br dd, J = 4.4, 13.1 Hz, 4H), 1.70 - 1.61 (m, 1H), 1.53 - 1.46 (m, 1H) ppm. TLC: 3% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{28}H_{33}ClFN_5O_4$: 557.22; Found: 556.85 $[M-1]^-$.

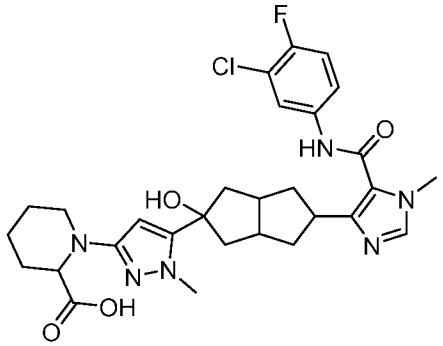
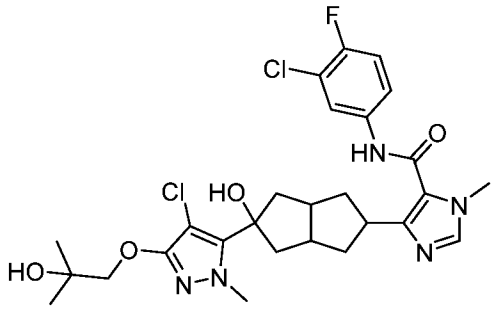
131	 **1-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)azetidine-2-carboxylic acid Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.86 (d, J = 1.0 Hz, 1H), 7.66 (s, 1H), 7.50 (t, J = 9.0 Hz, 1H), 7.23 (s, 1H), 5.55 - 5.45 (m, 1H), 3.79-3.77 (m, 7H), 3.28 - 3.05 (m, 3H), 2.63 - 2.45 (m, 3H), 2.40 - 2.30 (m, 2H), 2.28 - 2.20 (m, 2H), 1.98 - 1.77 (m, 5H) ppm. TLC: 10% MeOH/DCM (R_f: 0.2). MS calcd. for $C_{27}H_{30}ClFN_6O_4$: 556.20; Found: 557.05 $[M+1]^+$.
132	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-ethyl-3-(2-hydroxy-2-methylpropoxy)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (dd, J = 2.4, 6.8 Hz, 1H), 7.64 (s, 1H), 7.56 (td, J = 2.3, 4.4 Hz, 1H), 7.43 - 7.38 (m, 1H), 5.47 (s, 1H), 5.22 (s, 1H), 4.51 (s, 1H), 4.16 - 4.09 (m, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 3.24-3.22 (m, 2H), 2.18 - 2.14 (m, 2H), 2.11 - 2.07 (m, 2H), 1.89 - 1.82 (m, 4H), 1.30 - 1.26 (m, 3H), 1.13 (s, 6H) ppm. TLC: 5% MeOH/DCM (R_f: 0.5). MS calcd. for $C_{28}H_{35}ClFN_5O_4$: 559.24; Found: 560.25 $[M+1]^+$.

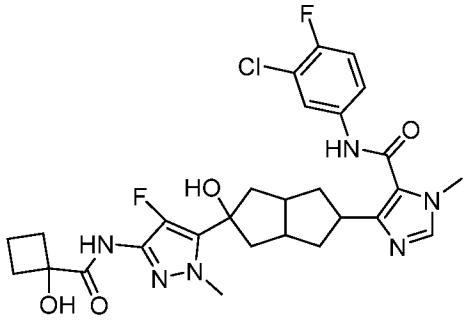
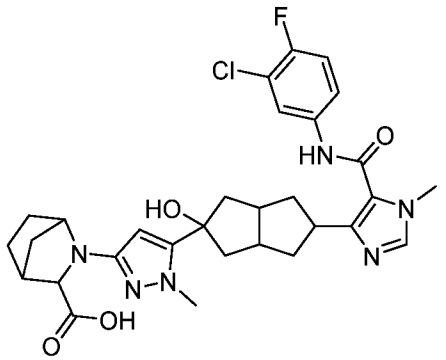
133	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(4-hydroxy-4-methylcyclohexyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.19 (s, 1H), 7.96 (dd, *J* = 2.6, 6.8 Hz, 1H), 7.64 (s, 1H), 7.58-7.55 (m, 1H), 7.40 (t, *J* = 9.1 Hz, 1H), 5.86 (s, 1H), 5.14 (s, 1H), 3.91 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.26 (d, *J* = 0.7 Hz, 1H), 2.46 - 2.41 (m, 4H), 2.22 - 2.14 (m, 2H), 2.12 - 2.04 (m, 2H), 1.91 - 1.80 (m, 4H), 1.74 - 1.65 (m, 2H), 1.57-1.55 (m, 4H), 1.38 - 1.27 (m, 2H), 1.10 (s, 3H) ppm. TLC: 5% MeOH/DCM (R$_f$: 0.6). MS calcd. for $C_{30}H_{37}ClFN_5O_3$: 569.26; Found: 568.40 [M-1]$^-$.
134	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(3,3-dimethylpyrrolidin-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 10.22 (s, 1H), 7.97 (dd, *J* = 2.6, 6.8 Hz, 1H), 7.66 (s, 1H), 7.58 (ddd, *J* = 2.1, 4.4, 6.8 Hz, 1H), 7.42 (t, *J* = 9.1 Hz, 1H), 5.31 (s, 1H), 5.12 (s, 1H), 3.73 - 3.68 (m, 6H), 3.28 (br s, 2H), 3.24 - 3.19 (m, 2H), 2.91 (s, 2H), 2.49 - 2.44 (m, 2H), 2.25 - 2.16 (m, 2H), 2.14 - 2.08 (m, 2H), 1.91 - 1.80 (m, 4H), 1.67 - 1.61 (m, 1H), 1.06 (s, 6H) ppm. TLC: 5% MeOH/DCM (R$_f$: 0.6). MS calcd. for $C_{29}H_{36}ClFN_6O_2$: 554.28; Found: 553.40 [M-1]$^-$.

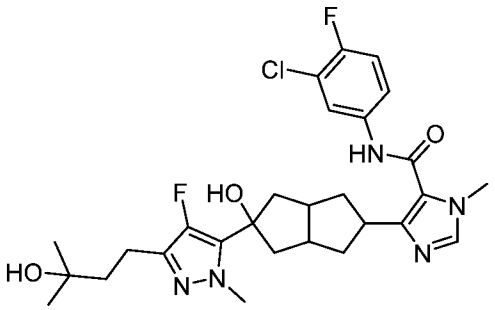
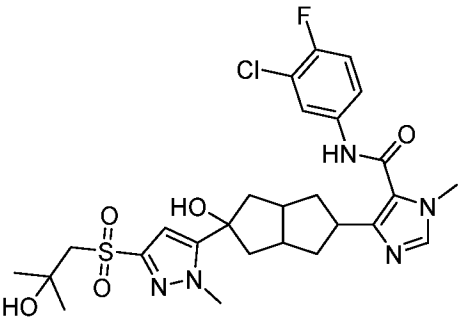
135	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(4-hydroxy-4-methylcyclohexyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.96 (dd, J = 2.6, 6.8 Hz, 1H), 7.64 (s, 1H), 7.57 (dd, J = 2.7, 4.3, 9.0 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.86 (s, 1H), 5.14 (s, 1H), 3.91 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.25 - 3.20 (m, 2H), 2.48 - 2.46 (m, 3H), 2.24 - 2.16 (m, 2H), 2.13 - 2.06 (m, 2H), 1.97 - 1.79 (m, 4H), 1.77 - 1.67 (m, 2H), 1.56 (br d, J = 10.6 Hz, 4H), 1.10 (s, 3H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{30}H_{37}ClFN_5O_3$: 569.26; Found: 568.35 $[M-1]^-$.
136	 **4-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)morpholine-3-carboxylic acid Isomer II** ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.41 (br s, 1H), 10.20 (s, 1H), 7.96 (d, J = 2.5 Hz, 1H), 7.65 (s, 1H), 7.58 (td, J = 2.3, 4.4 Hz, 1H), 7.44 - 7.40 (m, 1H), 5.51 (s, 1H), 5.18 (s, 1H), 4.14 - 4.06 (m, 3H), 3.87 - 3.82 (m, 1H), 3.69 (s, 6H), 3.50 (dt, J = 3.1, 11.3 Hz, 2H), 3.39 - 3.35 (m, 1H), 3.27 - 3.22 (m, 1H), 2.46 - 2.44 (m, 2H), 2.23 - 2.12 (m, 4H), 1.88 - 1.83 (m, 4H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{28}H_{32}ClFN_6O_5$: 586.21; Found: 590.21 $[M+4]^+$.

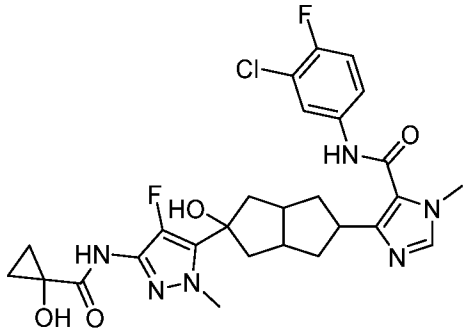
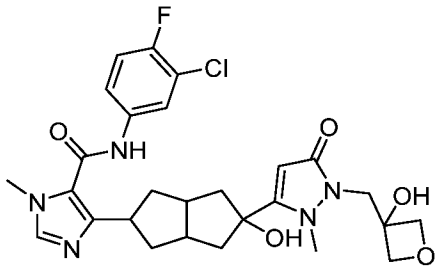
137	 **1-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)piperidine-2-carboxylic acid Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (t, J = 1.0 Hz, 1H), 7.64 (s, 1H), 7.60 - 7.55 (m, 1H), 7.43 - 7.37 (m, 1H), 5.47 (s, 1H), 5.15 (s, 1H), 4.29 - 4.23 (m, 1H), 3.70 - 3.63 (m, 6H), 3.37 (br s, 2H), 3.26 - 3.13 (m, 3H), 2.45 (br d, J = 2.0 Hz, 2H), 2.20 - 2.06 (m, 4H), 1.97 (br d, J = 12.8 Hz, 1H), 1.86 - 1.79 (m, 4H), 1.72 - 1.55 (m, 3H), 1.49 - 1.40 (m, 1H), 1.31 - 1.22 (m, 1H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{29}H_{34}ClFN_6O_4$: 584.23; Found: 585.30 $[M+1]^+$.
138	 **1-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)piperidine-2-carboxylic acid Isomer II** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (t, J = 1.0 Hz, 1H), 7.64 (s, 1H), 7.60 - 7.55 (m, 1H), 7.43 - 7.37 (m, 1H), 5.47 (s, 1H), 5.15 (s, 1H), 4.29 - 4.23 (m, 1H), 3.70 - 3.63 (m, 6H), 3.37 (br s, 2H), 3.26 - 3.13 (m, 3H), 2.45 (br d, J = 2.0 Hz, 2H), 2.20 - 2.06 (m, 4H), 1.97 (br d, J = 12.8 Hz, 1H), 1.86 - 1.79 (m, 4H), 1.72 - 1.55 (m, 3H), 1.49 - 1.40 (m, 1H), 1.31 - 1.22 (m, 1H) ppm. TLC: 5%

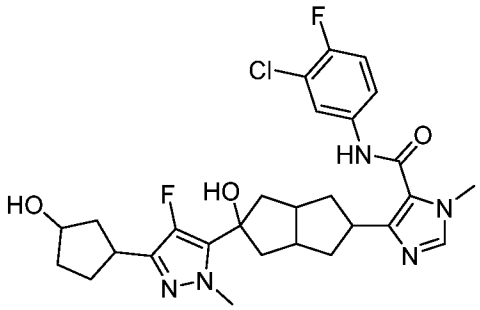
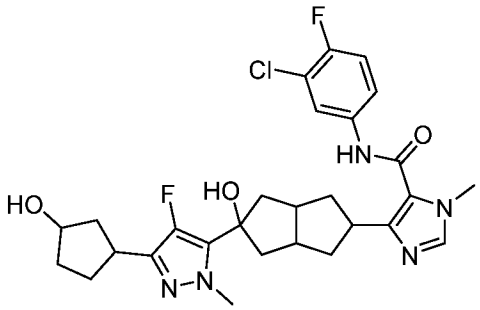
	MeOH/DCM (R_f: 0.6). MS calcd. for $C_{29}H_{34}ClFN_6O_4$: 584.23; Found: 585.30 $[M+1]^+$.
139	 **Ethyl 2-((1-(tert-butyl)-5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1H-pyrazol-3-yl)oxy)acetate** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (s, 1H), 7.88 (t, J = 1.0 Hz, 1H), 7.60 (s, 1H), 7.55 - 7.51 (m, 1H), 7.25 (t, J = 1.0 Hz, 1H), 4.14 - 4.10 (m, 2H), 3.76 (s, 3H), 3.48 (s, 3H), 3.26 (br d, J = 2.8 Hz, 2H), 2.87 (br d, J = 7.8 Hz, 2H), 2.35 - 2.30 (m, 4H), 2.02 - 1.95 (m, 2H), 1.81 (s, 2H), 1.27 - 1.23 (m, 3H), 1.06 (s, 9H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{30}H_{37}ClFN_5O_5$: 601.25; Found: 602.22 $[M+1]^+$.
140	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(4-hydroxycyclohexyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.96 (dd, J = 2.6, 6.8 Hz, 1H), 7.64 (s, 1H), 7.59 - 7.55 (m, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.28 (s, 1H), 4.54 - 4.49 (m, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.28 - 3.25 (m, 1H), 2.45 (br s, 2H), 2.22 (br dd, J = 6.6, 12.8 Hz, 2H), 2.12 - 2.05 (m, 2H), 1.95 - 1.83 (m, 6H), 1.53 - 1.37 (m, 3H), 1.27 - 1.15 (m, 3H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{29}H_{34}ClF_2N_5O_3$: 573.23; Found: 556.30 $[M-18+1]^+$.

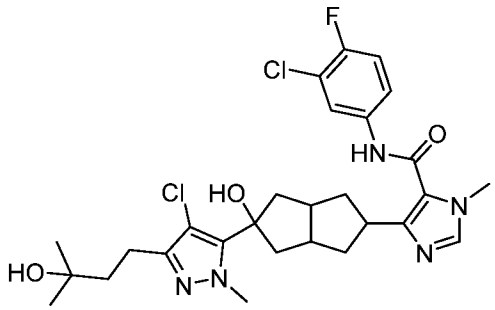
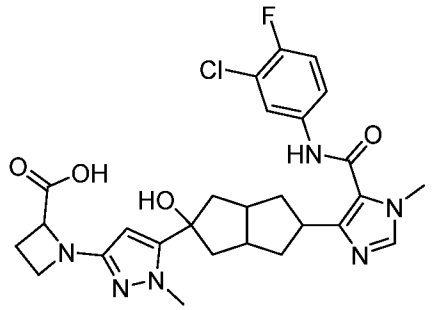
141	 **1-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)piperidine-2-carboxylic acid Isomer II** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.96 (t, J = 1.0 Hz, 1H), 7.64 (s, 1H), 7.57 (dd, J = 2.3, 4.4, 6.7 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.27 (s, 1H), 4.27 (d, J = 2.9 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.24 (br dd, J = 6.0, 12.1 Hz, 2H), 2.59 - 2.52 (m, 2H), 2.23 (br dd, J = 7.3, 13.1 Hz, 2H), 2.14 - 2.05 (m, 2H), 1.99 - 1.81 (m, 7H), 1.69 - 1.60 (m, 2H), 1.54 - 1.44 (m, 4H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{29}H_{34}ClF_2N_5O_3$: 573.23; Found: 572.30 $[M-1]^-$.
142	 **4-(5-(4-Chloro-3-(2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (t, J = 1.0 Hz, 1H), 7.64 (s, 1H), 7.57 (dt, J = 2.6, 4.5 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.35 (s, 1H), 4.55 (s, 1H), 4.04 (s, 1H), 3.83 - 3.78 (m, 4H), 3.67 (s, 3H), 3.23 (br d, J = 6.0 Hz, 1H), 2.56 (br s, 2H), 2.40 - 2.34 (m, 2H), 2.13 - 2.06 (m, 2H), 2.02 - 1.95 (m, 4H), 1.22 - 1.15 (m, 6H) ppm. TLC: 5% MeOH/DCM (R_f: 0.4). MS calcd. for $C_{27}H_{32}Cl_2FN_5O_4$: 578.40; Found: 579.18 $[M+1]^+$.

143	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(1-hydroxycyclobutane-1-carboxamido)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 - 10.53 (m, 1H), 9.14 (s, 1H), 7.99 (dd, J = 2.5, 6.8 Hz, 1H), 7.64 - 7.58 (m, 1H), 7.47 - 7.43 (m, 1H), 6.25 - 6.02 (m, 1H), 5.56 - 5.42 (m, 1H), 3.83 (s, 6H), 3.36 - 3.32 (m, 1H), 2.62 - 2.59 (m, 2H), 2.46 - 2.41 (m, 3H), 2.32 - 2.25 (m, 4H), 2.14 - 2.08 (m, 2H), 2.00 (br s, 2H), 1.89 (br d, J = 9.3 Hz, 2H), 1.83 - 1.74 (m, 2H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{28}H_{31}ClF_2N_6O_4$: 588.21; Found: 589.20 $[M+1]^+$.
144	 **2-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 8.20 (s, 1H), 7.90 (t, J = 1.0 Hz, 1H), 7.71 (s, 1H), 7.30 - 7.28 (m, 1H), 5.51 (s, 1H), 4.17 (s, 1H), 4.09 (br s, 1H), 3.84 - 3.81 (m, 6H), 2.89 (br s, 1H), 2.63 - 2.60 (m, 1H), 2.42 (br d, J = 4.2 Hz, 2H), 2.30 (br d, J = 4.2 Hz, 2H), 1.95 (br d, J = 5.5 Hz, 4H), 1.81 - 1.74 (m, 4H), 1.62 (br s, 2H), 1.55 (s, 2H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{30}H_{34}ClFN_6O_4$: 596.23; Found: 597.10 $[M+1]^+$.

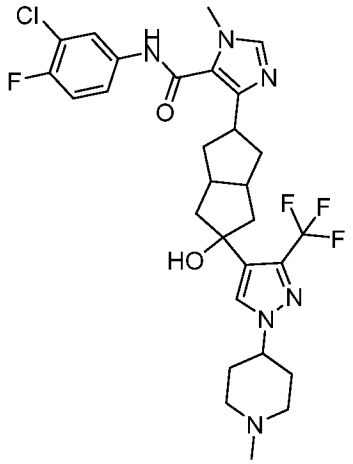
145	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(3-hydroxy-3-methylbutyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (dd, J = 2.6, 6.8 Hz, 1H), 7.64 (s, 1H), 7.57 (dd, J = 2.6, 4.3, 9.0 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.75 (s, 1H), 5.28 (s, 1H), 4.20 (s, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.26 - 3.22 (m, 1H), 2.46 - 2.40 (m, 4H), 2.26 - 2.19 (m, 2H), 2.14 - 2.04 (m, 2H), 1.98 - 1.88 (m, 4H), 1.66 - 1.58 (m, 2H), 1.10 (s, 6H) ppm. MS calcd. for $C_{28}H_{34}ClF_2N_5O_3$: 561.23; Found: 562.20 $[M+1]^+$.
146	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((2-hydroxy-2-methylpropyl)sulfonyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.95 (t, J = 1.0 Hz, 1H), 7.65 (s, 1H), 7.57 (dd, J = 2.6, 4.2, 9.2 Hz, 1H), 7.42 - 7.36 (m, 1H), 6.60 (s, 1H), 5.48 (s, 1H), 4.82 (s, 1H), 4.02 (s, 3H), 3.68 (s, 3H), 3.39 (s, 2H), 3.26 - 3.21 (m, 1H), 2.59 - 2.55 (m, 2H), 2.29 - 2.24 (m, 2H), 2.15 - 2.09 (m, 2H), 1.95 - 1.86 (m, 4H), 1.27 (s, 6H) ppm. MS calcd. for $C_{27}H_{33}ClFN_5O_5S$: 593.19; Found: 594.20 $[M+1]^+$.

147	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(1-hydroxycyclopropane-1-carboxamido)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 - 10.55 (m, 1H), 9.49 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.56 (br s, 1H), 7.46 (t, J = 1.0 Hz, 1H), 6.48 - 6.43 (m, 1H), 5.55 - 5.50 (m, 1H), 3.79 (s, 6H), 3.35 - 3.35 (m, 1H), 2.58 - 2.57 (m, 2H), 2.28 - 2.24 (m, 5H), 2.01 - 1.98 (m, 2H), 1.92 (br d, J = 2.3 Hz, 2H), 1.09 - 1.06 (m, 2H), 0.94 - 0.92 (m, 2H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{27}H_{29}ClF_2N_6O_4$: 574.19; Found: 575.15 $[M+1]^+$.
148	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxyoxetan-3-yl)methyl)-2-methyl-5-oxo-2,5-dihydro-1H-pyrazol-3-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.96 (t, J = 1.0 Hz, 1H), 7.65 (s, 1H), 7.57 (dd, J = 2.7, 4.3, 9.0 Hz, 1H), 7.44 - 7.38 (m, 1H), 6.49 (s, 1H), 5.46 (s, 1H), 5.19 - 5.13 (m, 1H), 4.51 (d, J = 6.6 Hz, 2H), 4.36 (d, J = 6.6 Hz, 2H), 4.07 (s, 2H), 3.67 (s, 3H), 3.55 (s, 3H), 3.25 - 3.20 (m, 1H), 2.19 - 2.04 (m, 6H), 1.87 - 1.79 (m, 4H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{27}H_{31}ClFN_5O_5$: 559.20; Found: 560.30 $[M+1]^+$.

149	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(3-hydroxycyclopentyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.96 (dd, J = 2.4, 6.8 Hz, 1H), 7.64 (s, 1H), 7.57 (dt, J = 2.6, 4.5 Hz, 1H), 7.41 (t, J = 1.0 Hz, 1H), 5.27 (s, 1H), 4.46 (d, J = 3.3 Hz, 1H), 4.25 - 4.20 (m, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.25 - 3.17 (m, 2H), 2.48 - 2.47 (m, 2H), 2.23 (br dd, J = 6.9, 12.4 Hz, 2H), 2.13 - 2.05 (m, 2H), 2.04 - 1.97 (m, 1H), 1.97 - 1.87 (m, 5H), 1.82 - 1.72 (m, 2H), 1.65 - 1.57 (m, 1H), 1.56 - 1.46 (m, 1H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{28}H_{32}ClF_2N_5O_3$: 559.22; Found: 542.20 $[M-18+1]^+$.
150	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(4-fluoro-3-(3-hydroxycyclopentyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.96 (t, J = 1.0 Hz, 1H), 7.64 (s, 1H), 7.57 (dd, J = 2.2, 4.4, 6.7 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.28 (br s, 1H), 4.60 - 4.46 (m, 1H), 4.18 - 4.08 (m, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.26 (br d, J = 6.0 Hz, 2H), 2.95 - 2.86 (m, 1H), 2.27 - 2.21 (m, 2H), 2.19 - 2.15 (m, 2H), 2.14 - 2.06 (m, 2H), 1.98 - 1.88 (m, 4H), 1.85 - 1.73 (m, 3H), 1.64 - 1.51 (m, 2H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{28}H_{32}ClF_2N_5O_3$: 559.22; Found: 560.20 $[M+1]^+$.

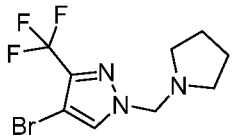
151	 **4-(5-(4-Chloro-3-(3-hydroxy-3-methylbutyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.16 (br s, 1H), 7.97 (t, J = 1.0 Hz, 1H), 7.64 (s, 1H), 7.59 - 7.54 (m, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.29 (s, 1H), 4.21 (s, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 3.26 - 3.21 (m, 2H), 2.39 (br dd, J = 5.7, 13.8 Hz, 2H), 2.14 - 2.06 (m, 2H), 2.00 (br d, J = 11.5 Hz, 4H), 1.64 - 1.57 (m, 2H), 1.12 - 1.08 (m, 6H) ppm. TLC: 10% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{28}H_{34}Cl_2FN_5O_3$: 577.40; Found: 577.40 $[M+1]^+$.
152	 **1-(5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)azetidine-2-carboxylic acid Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (t, J = 1.0 Hz, 1H), 7.66 (s, 1H), 7.53 - 7.46 (m, 1H), 7.24 (t, J = 1.0 Hz, 1H), 5.55 - 5.47 (m, 1H), 3.80 (s, 1H), 3.79 - 3.69 (m, 6H), 3.25 - 3.05 (m, 2H), 2.60 - 2.47 (m, 3H), 2.42 - 2.34 (m, 2H), 2.30 - 2.22 (m, 2H), 1.96 - 1.81 (m, 6H) ppm. TLC: 5% MeOH/DCM (R_f: 0.6). MS calcd. for $C_{27}H_{30}ClFN_6O_4$: 556.20; Found: 555.35 $[M-1]^-$.

Example 153



N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(1-methylpiperidin-4-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide 200 mg, 0.39 mmol), Cs_2CO_3 (140 mg, 0.43 mmol) in DMF (2 mL) was added 4-bromo-1-methylpiperidine (207 mg , 1.17 mmol). The mixture was stirred at 50°C for 16 hours. The reaction was diluted with water (50 mL), extracted with ethyl acetate (3 x 40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC (dichloromethane/MeOH, 15:1] to give the crude product which was purified by prep-HPLC to afford the title compound as a white solid. MS calcd. for $C_{29}H_{33}ClF_4N_6O_2$: 608.2; Found: 609.0 $[M + H]^+$; ^1H NMR (400 MHz, MeOH-d_4): δ 7.77 (dd, J = 6.8, 2.8 Hz, 1H), 7.63 (s, 1H), 7.55 (s, 1H), 7.44-7.38 (m, 1H), 7.14 (t, J = 8.8 Hz, 1H), 4.15-4.05 (m, 1H), 3.66 (s, 3H), 3.19-3.14 (m, 1H), 2.97-2.88 (m, 2H), 2.53-2.42 (m, 2H), 2.27 (s, 3H), 2.25-2.10 (m, 6H), 2.12-1.94 (m, 4H), 1.86-1.74 (m, 4H) ppm.

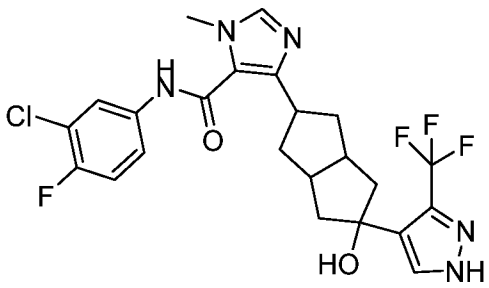
Intermediate 26



4-Bromo-1-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)-1H-pyrazole (R-1): To a solution of 4-bromo-3-(trifluoromethyl)-1H-pyrazole (65.0 g, 303.7 mmol) in EtOH (300 mL) was added pyrrolidine (21.6 g, 303.7 mmol) and HCHO (44.0 g, 542.7 mmol). The

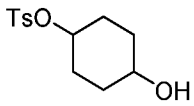
reaction was stirred overnight at room temperature. The solution was concentrated *in vacuo* to afford the title compound as a yellow solid. MS calcd. for $C_9H_{11}BrF_3N_3$: 297; Found: 298 $[M + 1]^+$.

Example 154



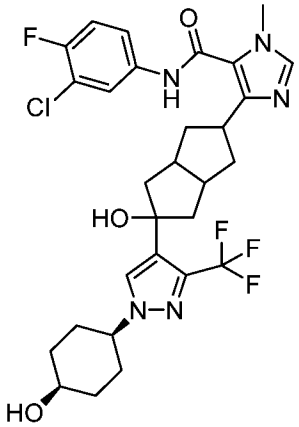
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of 4-bromo-1-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)-1H-pyrazole (6.0 g, 20.2 mmol) in dry ether (45 mL) was added t-BuLi (1.3 M, 15.5 mL, 20.2 mmol) dropwise. The reaction was stirred for 8 mins at -78 °C under an Ar atmosphere. A solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl)-1H-imidazole-5-carboxamide (600 mg, 1.60 mmol) in dry THF (5 mL) was dropwise added at -78 °C. The reaction was stirred for 2 h at -78 °C under an Ar atmosphere. The reaction was quenched with NH_4Cl solution (40 mL) and extracted with EtOAc (20 mLx3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by prep-TLC (DCM/MeOH, 15:1) and reverse phase column chromatography to afford the title compound as a white solid. MS calcd. for $C_{23}H_{22}ClF_4N_5O_2$: 511.1; Found: 511.9 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO): δ 13.25 (s, 1H), 10.23 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 9.0 Hz, 1H), 4.83 (s, 1H), 3.67 (s, 3H), 3.28-3.16 (m, 1H), 2.48-2.41 (m, 2H), 2.15-2.03 (m, 4H), 1.95-1.79 (m, 4H) ppm.

Intermediate 27



4-Hydroxycyclohexyl 4-methylbenzenesulfonate. A solution of cyclohexane-1,4-diol (2.0 g, 1.0 eq, 17.24 mmol) in dry dichloromethane (80 mL) was added triethylamine (8.7 g, 5.0 eq, 86.21 mmol), TsCl (6.6 g, 2.0 eq, 34.48 mmol) and DMAP (42 mg, 0.02 eq, 0.34 mmol). The reaction mixture was stirred for 2 d at room temperature. The mixture was then washed with $NaHCO_3$ solution (30 mLx2) and brine (30 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by reverse-phase column chromatography to afford 4-hydroxycyclohexyl 4-methylbenzenesulfonate as a light yellow solid.

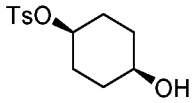
Example 155



N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1s,4s)-4-hydroxycyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (160 mg, 1.0 eq, 0.31 mmol) in DMF (7 mL) was added 4-hydroxycyclohexyl 4-methylbenzenesulfonate (423 mg, 5.0 eq, 1.57 mmol) and Cs_2CO_3 (112 mg, 1.1 eq, 0.34 mmol). The reaction mixture was stirred overnight at 100 °C in a sealed tube. Ethyl acetate (10 mL) and the organic solution washed with LiCl solution (5 mL x 2) and brine (5 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-TLC (dichloromethane/MeOH, 15:1 and ethyl acetate/MeOH, 10:1) to

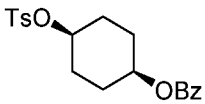
afford the title compound as a white solid. MS calcd. for $C_{29}H_{32}ClF_4N_5O_3$: 609.2; Found: 592.0 $[M-18+1]^+$; ^1H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.93 (dd, J = 6.8, 2.4 Hz, 1H), 7.77 (s, 1H), 7.62 (s, 1H), 7.57-7.51 (m, 1H), 7.38 (t, J = 9.0 Hz, 1H), 4.83 (s, 1H), 4.46 (d, J = 2.8 Hz, 1H), 4.17-4.06 (m, 1H), 3.79 (d, J = 2.0 Hz, 1H), 3.64 (s, 3H), 3.24-3.15 (m, 1H), 2.45-2.39 (m, 2H), 2.13-2.00 (m, 6H), 1.90-1.75 (m, 4H), 1.72-1.62 (m, 4H), 1.56-1.45 (m, 2H) ppm.

Intermediate 28



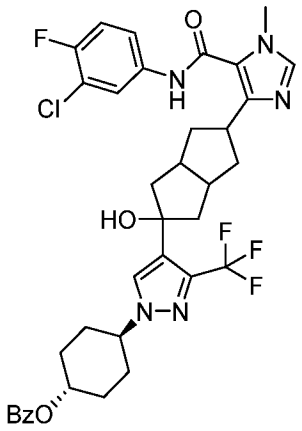
(1s,4s)-4-Hydroxycyclohexyl 4-methylbenzenesulfonate. To a solution of (1s,4s)-cyclohexane-1,4-diol (2.0 g, 1.0 eq, 17.24 mmol) in dry dichloromethane (80 mL) was added triethylamine (8.7 g, 5.0 eq, 86.21 mmol), TsCl (4.9 g, 1.5 eq, 25.86 mmol) and DMAP (42 mg, 0.02 eq, 0.34 mmol). The reaction mixture was stirred for 2 d at room temperature. The mixture was then washed with $NaHCO_3$ solution (30 mL x 2) and brine (30 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was used in the next step without further purification.

Intermediate 29



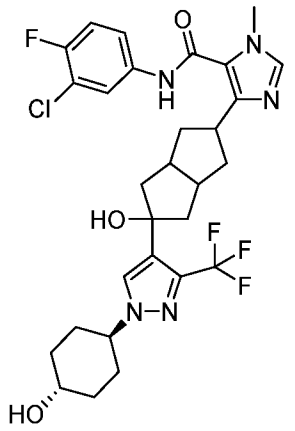
(1s,4s)-4-(Tosyloxy)cyclohexyl benzoate. To a solution of ((1s,4s)-4-hydroxycyclohexyl 4-methylbenzenesulfonate) (3.0 g, 1.0 eq, 11.11 mmol) in dry dichloromethane (50 mL) was added triethylamine (5.6 g, 5.0 eq, 55.56 mmol) and benzoyl chloride (3.1 g, 2.0 eq, 22.22 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was then washed with $NaHCO_3$ solution (30 mL x 2) and brine (30 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10/1-to-5/1) to afford the title compound as a white solid.

Intermediate 30



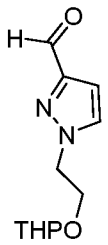
(1r,4r)-4-(4-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl benzoate. To a solution N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5- (800 mg, 1.0 eq, 1.57 mmol) in DMF (30 mL) was added (1s,4s)-4-(tosyloxy)cyclohexyl benzoate (1.2 g, 2.0 eq, 3.13 mmol) and Cs_2CO_3 (1.0 g, 2.0 eq, 3.13 mmol). The reaction mixture was stirred overnight at 100 °C in a sealed tube. To the mixture was added ethyl acetate (30 mL) and the solution washed with LiCl solution (10 mL x 2) and brine (10 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (dichloromethane/MeOH, 30:1 – 25:1) to afford the title compound as a light yellow solid.

Example 156



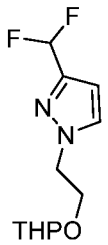
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1r,4r)-4-hydroxycyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of (1r,4r)-4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl benzoate (620 mg, 1.0 eq, 0.87 mmol) in MeOH (30 mL) was added LiOH-H_2O (365 mg, 10.0 eq, 8.70 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was adjusted to pH = 7 with 6N HCl solution and extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-TLC (dichloromethane/MeOH = 15/1 and ethyl acetate/MeOH = 10/1) to afford the title compound as a white solid. MS calcd. for $C_{29}H_{32}ClF_4N_5O_3$: 609.2; Found: 609.9 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO): δ 10.22 (s, 1H), 7.93 (dd, J = 6.8, 2.4 Hz, 1H), 7.79 (s, 1H), 7.62 (s, 1H), 7.57-7.51 (m, 1H), 7.38 (t, J = 9.0 Hz, 1H), 4.84 (s, 1H), 4.65 (d, J = 4.0 Hz, 1H), 4.16-4.05 (m, 1H), 3.64 (s, 3H), 3.50-3.39 (m, 1H), 3.25-3.13 (m, 1H), 2.45-2.38 (m, 2H), 2.11-1.99 (m, 4H), 1.95-1.67 (m, 10H), 1.34-1.19 (m, 2H) ppm.

Intermediate 31



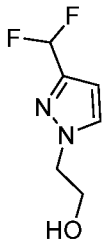
1-(2-(Tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole-3-carbaldehyde. To a solution of 1H-pyrazole-5-carbaldehyde (4500.0 mg, 46.88 mmol) in DMF (25 ml) was added 2-(2-bromoethoxy)tetrahydro-2H-pyran (9750.0 mg, 46.88 mmol) and NaH (1238.0 mg,51.57 mmol). The reaction was stirred for 16 hours at room temperature then quenched with H_2O (75 ml) and extracted with EtOAc (50 ml x 3). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, and concentrated to dryness. The residue was purified by column chromatography using 0-7% methanol in dichloromethane to afford the title compound as a yellow oil. TLC: 7% MeOH/dichloromethane (R_f: 0.4), MS calcd. for $C_{11}H_{16}N_2O_3$: 224.3; Found: 225.0 $[M+1]^+$.

Intermediate 32



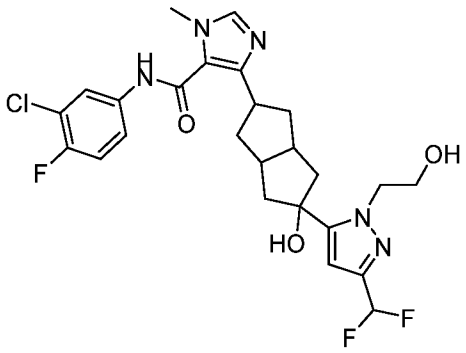
3-(Difluoromethyl)-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole. To a solution of 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole-3-carbaldehyde (8000.0 mg, 35.71 mmol) in dichloromethane(50 ml) was added DAST (11500.0 mg, 71.43 mmol). The reaction stirred for 16 hours in room temperature then quenched with H_2O (10 ml) in 0°C.The solvent was removed to give the crude product, which was purified by column chromatography using 0-30% ethyl acetate in petroleum ether to afford the title compound as a yellow oil. TLC: 30% ethyl acetate/petroleum ether (R_f: 0.4). MS calcd. for $C_{11}H_{16}F_2N_2O_2$: 246.3; Found: 247.0 $[M+1]^+$.

Intermediate 33



2-(3-(Difluoromethyl)-1H-pyrazol-1-yl)ethanol. To a solution of 3-(difluoromethyl)-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole (4000.0 mg, 16.26 mmol) in THF/H_2O (30 ml,v/v=2/1) was added HCl(aq.) until pH 3. The reaction stirred for 16 hours at room temperature. H_2O (50 mL) was added and the mixture extracted with ethyl acetate (30 ml x 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, and concentrated to dryness. The residue was purified by column chromatography using 0-20% methanol in dichloromethane to afford the title compound as a white solid. TLC: 20% MeOH/dichloromethane (R_f: 0.5), MS calcd. for $C_6H_8F_2N_2O$: 162.1; Found: 163.0 $[M+1]^+$.

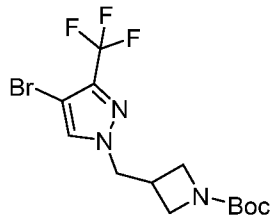
Example 157



N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of 2-(3-(difluoromethyl)-1H-pyrazol-1-yl)ethanol (1300.0 mg, 8.0 mmol) in THF (50 mL) was added s-BuLi (12 mL) in -78°C and the mixture stirred for 1 hour . To the reaction mixture was added N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (300 mg,0.8 mmol) and stirring continued for 1 hour. The reaction was quenched with NH_4Cl (aq.) and extracted with EtOAc

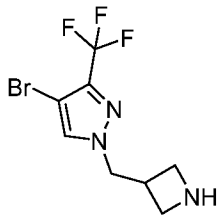
(30 ml x 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, and concentrated to dryness, The residue was purified by column chromatography using 0-10% methanol in dichloromethane and prep-HPLC to afford the title compound as a yellow solid. TLC: 10% CH_3OH/dichloromethane (R_f: 0.5), MS calcd. for $C_{25}H_{27}ClF_3N_5O_3$: 537.96; Found: 538.0 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.97 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.42 (t, J = 8.8 Hz, 1H), 7.02 (t, J = 54.8 Hz, 1H), 6.33 (s, 1H), 5.42 (s, 1H), 4.95 (t, J = 5.6 Hz, 1H), 4.37 (t, J = 6.4 Hz, 2H), 3.80-3.75 (m, 2H), 3.67 (s, 3H), 3.26-3.23 (m, 1H), 2.50-2.49 (m, 2H), 2.28-2.22 (m, 2H), 2.13-2.07 (m, 2H), 1.92-1.87 (m, 4H) ppm.

Intermediate 34



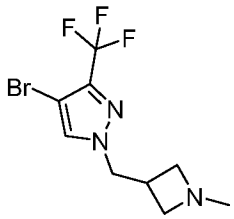
tert-Butyl 3-((4-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)azetidine-1-carboxylate. To a solution of 4-bromo-3-(trifluoromethyl)-1H-pyrazole (2.24 g, 10.5 mmol), Cs_2CO_3 (2.24 g, 21.0 mmol) in DMF (15 mL) was added tert-butyl 3-(iodomethyl)azetidine-1-carboxylate (3.74 g , 12.6 mmol). The mixture was stirred at room temperature for 16 hours. The reaction was then diluted with water (50 mL), 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 (0-30% ethyl acetate in petroleum ether) to afford the title compound as a white solid. TLC: 10% ethyl acetate/petroleum ether (R_f: 0.3) MS calcd. for $C_{13}H_{17}BrF_3N_3O_2$: 383.0; Found: 328.0 $[M - 56 + H]^{+\cdot}$

Intermediate 35



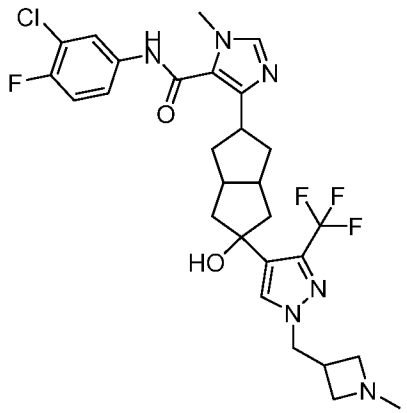
1-(Azetidin-3-ylmethyl)-4-bromo-3-(trifluoromethyl)-1H-pyrazole. To a mixture of tert-butyl 3-((4-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)azetidine-1-carboxylate (3.0 g, 9.09 mmol) in dichloromethane (10 mL) was added TFA (2 mL), and the reaction stirred at room temperature for 16 hours. The reaction mixture was adjusted to pH 8 using $NaHCO_3$ solution, then extracted with ethyl acetate (40 mL x 3), dried over Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by reversed column chromatography to give the title compound as a white solid. MS calcd. for $C_8H_9BrF_3N_3$: 283.0; Found: 284.1 $[M + 1]^+$.

Intermediate 36



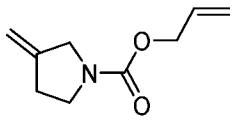
4-Bromo-1-((1-methylazetidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazole. A mixture of 1-(azetidin-3-ylmethyl)-4-bromo-3-(trifluoromethyl)-1H-pyrazole (1.4 g, 4.9 mmol) and HCHO (37 % in water, 3.97 g, 49.0 mmol) in MeOH (5 mL) was stirred at room temperature for 8 hours. $NaBH(OAc)_3$ (2.10 g, 9.9 mmol) was then added dropwise over 5 min and the reaction mixture stirred at room temperature for 2 hours. The reaction mixture was quenched with $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product, which was purified by reverse phase column chromatography to afford the title compound as a yellow oil. MS calcd. for $C_9H_{11}BrF_3N_3$: 297.0; Found: 298.0 $[M + 1]^+$.

Example 158



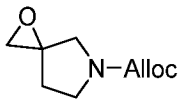
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1-methylazetidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of 4-bromo-1-((1-methylazetidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazole (505 mg, 1.7 mmol) in diethyl ether (2 mL) was added t-butyllithium (2.0 mL, 2.6 mmol, 1.3 M) dropwise at -78°C, the mixture was stirred for 2 min at -78 °C in an Ar atmosphere. A solution of N-(3-chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (65 mg, 0.17 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise at -78 °C. The reaction mixture was stirred for 1 h at -78 °C under an Ar atmosphere. The reaction was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (dichloromethane/MeOH=15/1) and reverse phase column chromatography to afford the title compound as a white solid. MS calcd. for $C_{28}H_{31}ClF_4N_6O_2$: 594.2; Found: 595.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOH-d_4): δ 7.86 (dd, J = 6.4, 2.4 Hz, 1H), 7.70 (brs, 1H),7.64 (s, 1H), 7.53-7.47 (m, 1H), 7.23 (t, J = 8.8 Hz, 1H), 4.27 (d, J = 7.2 Hz, 2H), 3.75 (s, 3H), 3.44-3.36 (m, 2H), 3.35-3.31 (m, 1H), 3.11-3.02 (m, 2H), 2.96-2.85 (m, 1H), 2.62-2.48 (m, 2H), 2.38-2.28 (m, 5H), 2.27-2.18 (m, 2H), 1.96-1.80 (m, 4H) ppm.

Intermediate 37



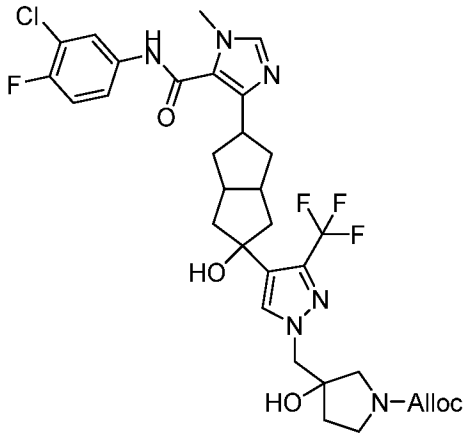
Allyl 3-methylenepyrrolidine-1-carboxylate. A solution of tert-butyl 3-methylenepyrrolidine-1-carboxylate (1.83 g, 10.0 mmol) in dichloromethane (50 mL) was treated with TFA (10 mL). The reaction mixture was stirred at room temperature overnight and concentrated in vacuo to provide 3-methylenepyrrolidine. To a solution of crude 3-methylenepyrrolidine in dichloromethane (50 mL) was added allyl carbonochloridate (1.32 g, 11.0 mmol) and triethylamine (3.03 g, 30.0 mmol). The mixture was stirred at room temperature overnight then concentrated in vacuo. The residue was purified by chromatography on silica gel (eluting with petroleum ether/ethyl acetate = 20/1 (v/v)) to provide the title compound as a clear oil.

Intermediate 38



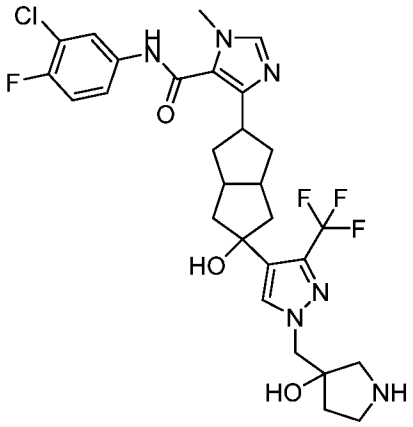
Allyl 1-oxa-5-azaspiro[2.4]heptane-5-carboxylate. To a solution of allyl 3-methylenepyrrolidine-1-carboxylate (1.67g, 10.0 mmol) in dichloromethane (150 mL) was added m-CPBA (1.72 g, 10.0 mmol). The mixture was stirred at room temperature overnight. To the reaction was added 100 mL saturated $NaHCO_3$ and the mixture stirred for 10 min. The dichloromethane phase was separated and dried over $MgSO_4$ for 10 min. The dichloromethane phase was filtered through Celite to remove $MgSO_4$. The filtrate was concentrated in vacuo to provide crude product as a residue which was used for the next step directly.

Intermediate 39



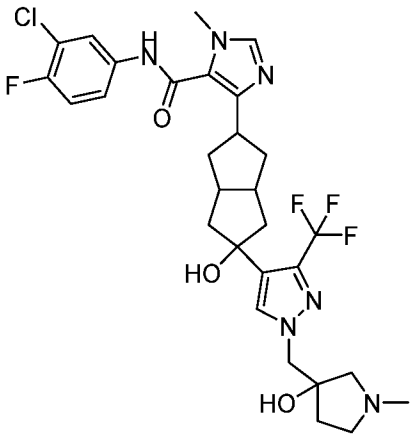
Allyl 3-((4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)-3-hydroxypyrrolidine-1-carboxylate. To a solution of crude allyl 1-oxa-5-azaspiro[2.4]heptane-5-carboxylate in acetonitrile was added compound N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (1.1 g, 0.22 mmol) and potassium carbonate powder (1.36 g, 10 mmol). The mixture was heated to 75°C and stirred overnight. After cooling, the mixture was filtered through Celite to remove potassium carbonate. The filtrate was concentrated in vacuo and the residue purified by pre-HPLC to provide the title compound as white solid. MS calcd. for $C_{32}H_{35}ClF_4N_6O_5$: 678.2; Found: 679.3 $[M+1]^+$.

Intermediate 40



N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxypyrrolidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of allyl 3-((4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)-3-hydroxypyrrolidine-1-carboxylate (200 mg, 0.3 mmol) in THF (20 mL) was added $Pd(PPh_3)_4$ (20 mg) and $NaBH_4$ powder (50 mg). The mixture was stirred at room temperature overnight. The reaction mixture was acidified using 1N HCl to pH 1.0 and the crude product used for the next step as a mixture of diastereomers. MS calcd. for $C_{28}H_{31}ClF_4N_6O_3$: 610.2; Found: 611.3 $[M+1]^+$.

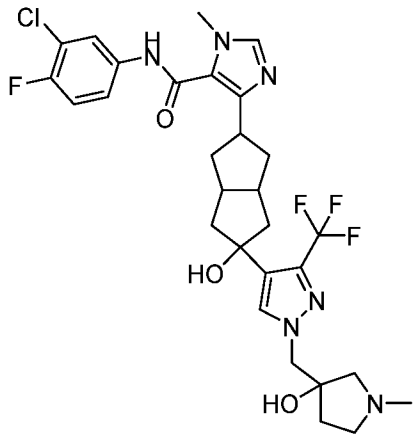
Example 159



N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxy-1-methylpyrrolidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-

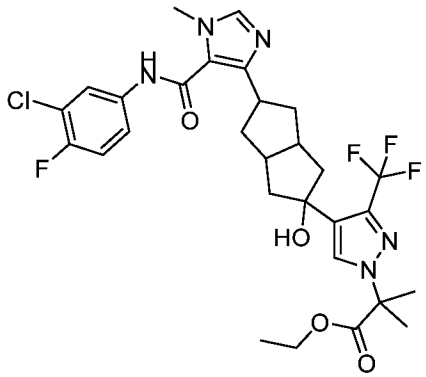
imidazole-5-carboxamide Isomer I. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxypyrrolidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide was treated with HCHO (30% H_2O, 2 mL) and stirred at room temperature overnight. To this solution was added $NaBH_4$ powder (100 mg) and the reaction stirred for 20 min. The mixture was purified by prep-HPLC and chiral HPLC to provide N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxy-1-methylpyrrolidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I and Isomer II. Isomer I; MS calcd. for $C_{29}H_{33}ClF_4N_6O_3$: 624.22; Found: 607.0 $[M^+-18+1]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.86 (dd, J = 6.8, 2.8 Hz, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 7.51-7.50 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.21 (s, 2H), 3.76 (s, 3H), 3.33-3.31 (m, 1H), 2.82-2.73 (m, 2H), 2.59-2.57 (m, 3H), 2.44 (d, J = 10.8, 1H), 2.46-2.43 (m, 5H), 2.36-2.21 (m, 2H), 2.09-2.02 (m, 1H), 1.95-1.88 (m, 4H), 1.77-1.70 (m, 1H) ppm.

Example 160



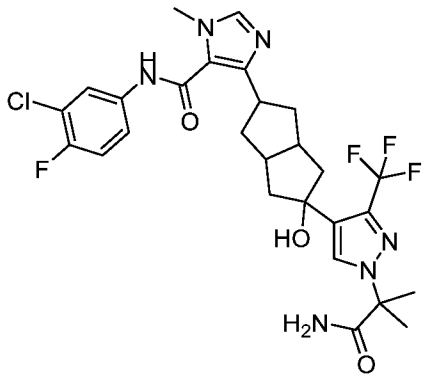
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxy-1-methylpyrrolidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II. MS calcd. for $C_{29}H_{33}ClF_4N_6O_3$: 624.22; Found: 607.0 $[M-18+1]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.86 (dd, J = 6.8, 2.8 Hz, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 7.50-7.49 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.21 (s, 2H), 3.76 (s, 3H), 3.33-3.30 (m, 1H), 2.84-2.78 (m, 2H), 2.64-2.57 (m, 3H), 2.47 (d, J = 10.8 Hz, 1H), 2.37-2.31 (m, 5H), 2.25-2.22 (m, 2H), 2.10-2.03 (m, 1H), 1.94-1.85 (m, 4H), 1.79-1.72 (m, 1H) ppm.

Example 161



Ethyl 2-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-2-methylpropanoate. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (80.0 mg, 0.15 mmol) in DMF (3 mL) was added ethyl 2-bromo-2-methylpropanoate (91.0 mg, 0.47 mmol), Cs_2CO_3 (250.0 mg, 0.78 mmol) and NaI (45.0 mg, 0.3 mmol). The reaction was stirred at 50°C overnight. Water was added and the solution extracted with ethyl acetate, dried over Na_2SO_4 then concentrated to give the crude product, which was purified by column chromatography to afford the title compound as a brown solid. TLC: 7% MeOH/dichloromethane (R_f: 0.6), MS calcd. for $C_{29}H_{32}ClF_4N_5O_4$: 625.2; Found: 625.9 $[M + 1]^+$.

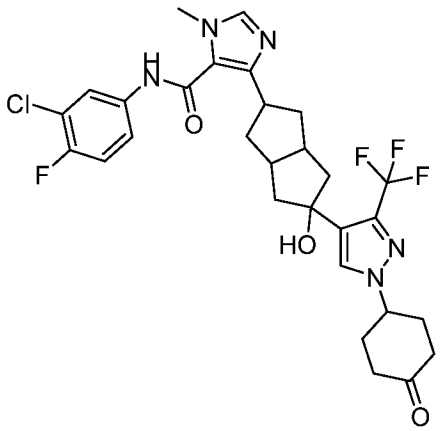
Example 162



4-(5-(1-(1-Amino-2-methyl-1-oxopropan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-

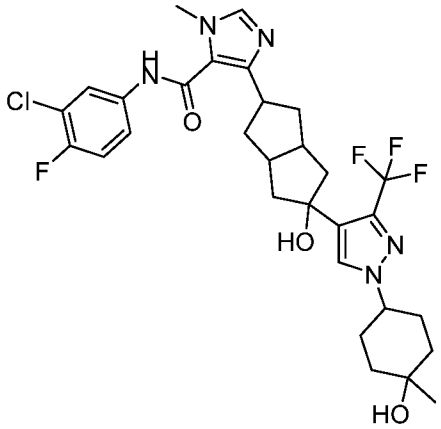
imidazole-5-carboxamide. A solution of ethyl 2-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-2-methylpropanoate (60.0 mg, 0.1 mmol) and NH_3/CH_3OH (3 mL) was stirred at 50°C overnight. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography and prep-HPLC to the title compound as a white solid. TLC: 9% MeOH/dichloromethane (R_f: 0.2), MS calcd. for $C_{27}H_{29}ClF_4N_6O_3$: 597.0; Found: 579.0 $[M -18 + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.79 (s, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 7.27 (s, 1H), 7.05 (s, 1H), 4.86 (s, 1H), 3.67 (s, 3H), 3.50-3.43 (m, 2H), 3.25-3.19 (m, 1H), 2.16-2.06 (m, 4H), 1.93-1.82 (m, 4H), 1.70 (s, 6H) ppm.

Example 163



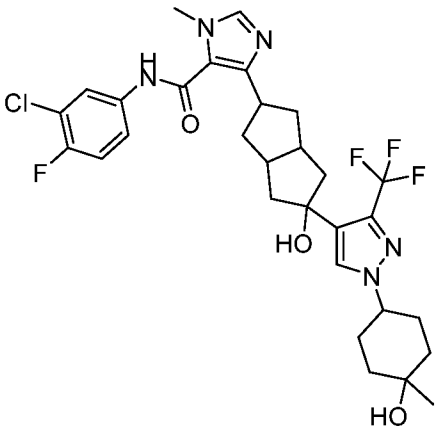
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(4-oxocyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. (CP-AIA-1422-6): To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(4-hydroxycyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (560 mg, 0.92 mmol) in acetone (15 mL) was added Dess-Martin Periodinane (1.17 g, 2.76 mmol) and Na_2CO_3, and the mixture stirred at 65 °C for 30 min. The reaction was quenched with Na_2SO_3 (aq). The suspension was extracted with ethyl acetate. The combined organic layers were dried and concentrated *in vacuo* and purified by column chromatography on silica gel with 9-18 % of MeOH in dichloromethane to afford the title compound as a white solid (230 mg, 41.0 %) TLC: 10% MeOH/dichloromethane (Rf: 0.4); MS calcd. for $C_{29}H_{30}ClF_4N_5O_3$: 607.2; Found: 590.0 $[M – 18 + 1]^+$.

Example 164



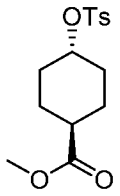
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(4-hydroxy-4-methylcyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(4-oxocyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (230 mg, 0.38 mmol) in dry THF (10 mL) at 65 °C was added 3.0 M (hexane) CH_3MgI (2.5 mL, 7.6 mmol) slowly and the reaction stirred for 2 hours. The reaction was quenched with H_2O and the suspension extracted with ethyl acetate (3x25 mL). The combined organic layers were dried and concentrated *in vacuo* to give the crude product which was purified by reversed phase prep-HPLC and chiral-SFC to afford N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(4-hydroxy-4-methylcyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I and Isomer II. Isomer I; TLC**:** 10% MeOH/dichloromethane (R_f: 0.5); MS calcd. for $C_{30}H_{34}ClF_4N_5O_3$: 624.1; Found: 606 $[M - 18]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.79 (s, 1H), 7.65 (s, 1H), 7.59-7.53 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 4.84 (s, 1H), 4.21 (s, 1H),4.09 (brs, 1H), 3.67 (s, 3H), 3.26-3.20 (m, 1H), 2.41-2.33 (m, 2H), 2.13-2.02 (m, 6H), 1.92-1.61 (m, 10H), 1.13 (s, 3H) ppm.

Example 165



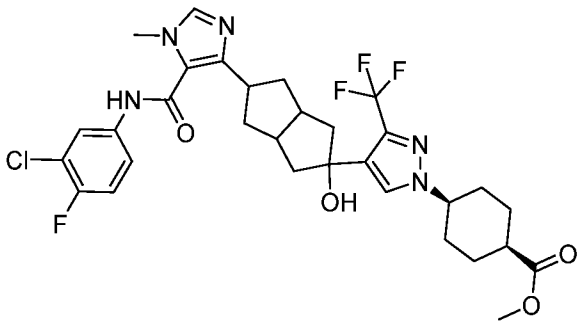
N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(4-hydroxy-4-methylcyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II. TLC: 10% MeOH/dichloromethane (*Rf*: 0.5); MS calcd. for $C_{30}H_{34}ClF_4N_5O_3$: 623.2; Found: 606 $[M - 18 + 1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.87 (s, 1H), 7.65 (s, 1H), 7.59-7.56 (m, 1H), 7.41 (t, J = 8.8 Hz, 1H), 4.84 (s, 1H), 4.42 (s, 1H), 3.33 (brs, 1H), 3.67 (s, 3H), 3.27-3.22 (m, 2H), 2.51-2.49 (m, 2H), 2.13-2.06 (m, 4H), 1.91-1.80 (m, 8H), 1.61-1.51 (m, 4H), 1.19 (s, 3H) ppm.

Intermediate 41



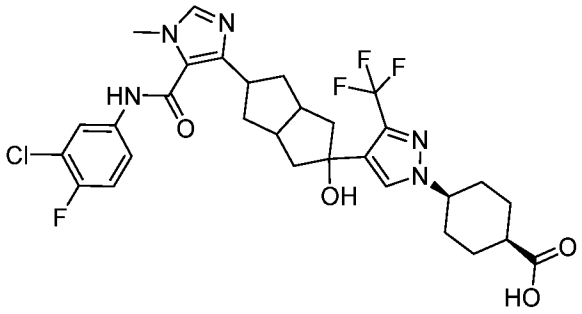
(1r,4r)-Methyl 4-(tosyloxy)cyclohexanecarboxylate. To a solution of (1r,4r)-methyl 4-hydroxycyclohexanecarboxylate (1.0 g, 6.3 mmol) in dichloromethane (15 mL) was added TsCl (3.0 g, 15.8 mmol), NEt_3 (1.9 g, 18.9 mmol) and DMAP (154 mg, 1.3 mmol). The mixture was stirred at 25 °C overnight. The solvent was removed under reduce pressure to give the crude product, which was purified by silica gel column chromatography to afford the title compound as a white solid. TLC: 11% ethyl acetate/petroleum ether (Rf: 0.4); MS calcd. for $C_{15}H_{20}O_5S$: 312.1; Found: 313.3 $[M + 1]^+$.

Example 166



Methyl (1s,4s)-4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexane-1-carboxylate. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (200 mg, 0.4 mmol) in DMF (5 ml) was added (1r,4r)-methyl 4-(tosyloxy)cyclohexanecarboxylate (370 mg, 1.2 mmol) and Cs_2CO_3 (140 mg, 0.4 mmol). The mixture was stirred at 50°C overnight. Water (50 ml) was added, and the mixture extracted with ethyl acetate. The organic layer was dried and concentrated. The crude product was purified by prep-HPLC to afford the title compound as a white solid. TLC: 9% MeOH/dichloromethane (R_f: 0.5); MS calcd. for $C_{31}H_{34}ClF_4N_5O_4$: 651.2; Found: 652.3 [M+1]$^+$. ^{1}H NMR (400 MHz, MeOH-d4): 7.88-7.86 (dd, J = 6.8, 2.4 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.65 (s, 1H), 7.52-7.48 (m, 1H), 7.26-7.21 (t, J = 9.2 Hz, 1H), 4.20-4.18 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.34-3.28 (m, 1H), 2.70-2.68 (m, 1H), 2.57-2.54 (m, 2H), 2.35-2.30 (m, 2H), 2.27-2.17 (m, 4H), 2.00-1.86 (m, 8H), 1.77-1.73 (m, 2H) ppm.

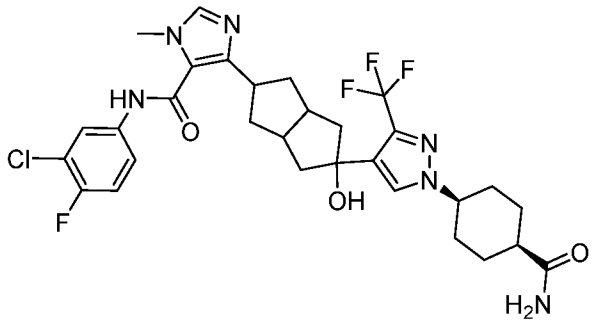
Intermediate 42



(1s,4s)-4-(4-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-

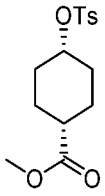
yl)cyclohexane-1-carboxylic acid. To a solution of methyl (1s,4s)-4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexane-1-carboxylate (30 mg, 0.05 mmol) in THF (1 mL) and H_2O (0.5 mL) was added NaOH aq. (3 M, 1.5 mL). The mixture was stirred at room temperature overnight. HCl aq. (1M) was added dropwise to reach pH < 4. Water (20 mL) was added, and the solution extracted with ethyl acetate. The organic layer was dried and concentrated under reduced pressure to give the title compound as colorless oil. TLC: 12% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{30}H_{32}ClF_4N_5O_4$: 637.2; Found: 638.3 [M + 1]$^+$.

Example 167



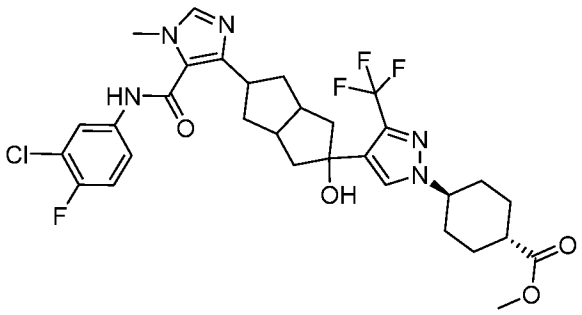
4-(5-(1-((1s,4s)-4-Carbamoylcyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of (1s,4s)-4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexane-1-carboxylic acid (25 mg, 0.04 mmol) in THF(3 mL) was added NH_4Cl (10 mg, 0.2 mmol) and diisopropyl-ethylamine (40 mg, 0.31 mmol). The mixture was stirred at room temperature for 0.5 h then HATU (44 mg, 0.12 mmol) added and stirring continued overnight. Water (20 ml) was added, and the mixture extracted with ethyl acetate. The organic layer was dried and concentrated under reduced pressure. The crude product was purified by prep-HPLC to afford the title compound as a white solid. TLC: 5% MeOH/dichloromethane (R_f: 0.3). MS calcd. for $C_{30}H_{33}ClF_4N_6O_3$: 636.2; Found: 619.0 [M - 18 + 1]$^+$. ^{1}H-NMR (400 MHz, MeOD): 7.89-7.86 (dd, J = 6.8, 2.4 Hz, 1H), 7.70 (d, J = 0.4 Hz, 1H), 7.65 (s, 1H), 7.52-7.48 (m, 1H), 7.26-7.21 (m, 1H), 4.26-4.21 (m, 1H), 3.76 (s, 3H), 3.35-3.30 (m, 1H), 2.58-2.51 (m, 3H), 2.37-2.31 (m, 2H), 2.27-2.19 (m, 4H), 2.03-1.86 (m, 8H), 1.76-1.71 (m, 2H) ppm.

Intermediate 43



(1s,4s)-Methyl 4-(tosyloxy)cyclohexanecarboxylate. To a solution of methyl (1s,4s)-4-hydroxycyclohexane-1-carboxylate (2.0 g, 12.66 mmol) in dichloromethane (100 mL) was added DMAP (1.5g, 12.66 mmol), Et_3N (2.8 g,31.65 mmol) and TsCl (3.6 g,18.99 mmol) and the reaction stirred for 16 hours at room temperature. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using 0-20% EtOAc in petroleum ether to afford the title compound as a white solid. TLC**:** 25% ethyl acetate/petroleum ether (R_f: 0.4), MS calcd. for $C_{15}H_{20}O_5S$: 312.1; Found: 330.1 $[M+18]^+$.

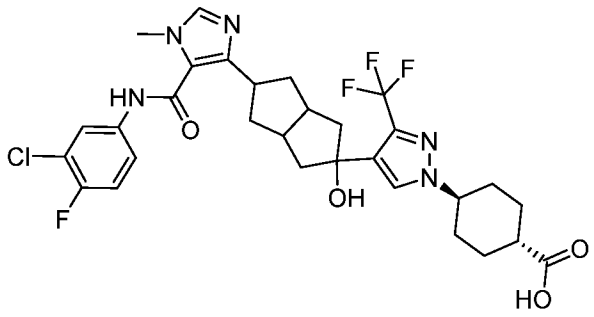
Example 168



Methyl (1r,4r)-4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexane-1-carboxylate. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (250.0 mg, 0.49 mmol) in DMF (15 ml) was added (1s,4s)-methyl 4-(tosyloxy)cyclohexanecarboxylate (610.0 mg, 1.96 mmol) and K_2CO_3 (74.0 mg,0.54mmol) and the reaction heated to 100°C and stirred for 16 hours .The reaction mixture was cooled to room temperature and quenched with H_2O (50 ml) and, extracted with EtOAc (30 ml x 3). The combined organic layers were washed with brine (30mL), dried over sodium sulfate, and

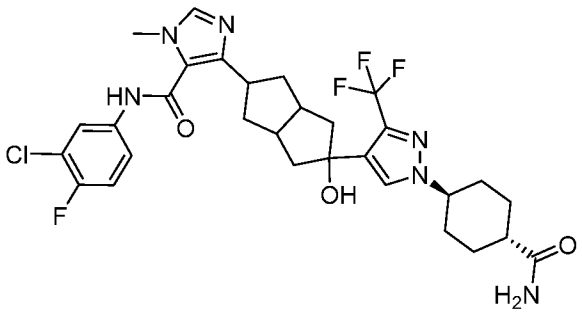
concentrated to dryness. The resulting residue was purified by column chromatography using 0-10% methanol in dichloromethane to afford the title compound as a white solid. TLC: 7% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{31}H_{34}ClF_4N_5O_4$: 651.2; Found: 634.0 [M – 18 + 1]$^+$. ^{1}H NMR (400 MHz, MeOH-d4): δ 7.88 (dd, J = 6.8, 2.4 Hz, 1H), 7.70 (s, 1H), 7.64 (s, 1H), 7.51-7.48 (m, 1H), 7.25 (t, J = 8.8 Hz, 1H), 4.17-4.13 (m, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.34-3.31 (m, 1H), 3.30-3.29 (m, 2H), 2.59-2.56 (m, 2H), 2.44-2.40 (m, 1H), 2.35-2.30 (m, 2H), 2.24-2.22 (m, 2H), 2.13-2.10 (m, 4H), 1.93-1.83 (m, 6H), 1.62-1.58 (m, 2H) ppm.

Intermediate 44



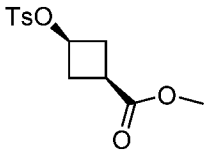
(1r,4r)-4-(4-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexane-1-carboxylic acid. To a solution of methyl (1r,4r)-4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexane-1-carboxylate (30.0 mg, 0.045 mmol) in THF/H_2O = 2/1 (v/v) (15 ml) was added NaOH (30 mg,0.75 mmol). The reaction stirred for 16 hours in room temperature then acidified with HCl (aq.) to pH 4. The solution was extracted with EtOAc (30 ml x 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, and concentrated to dryness. The resulting residue was purified by column chromatography using 0-20% methanol in dichloromethane to afford the title compound as a white solid. TLC**:** 20% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{30}H_{32}ClF_4N_5O_4$: 637.2; Found: 619.8 [M – 18 + 1]$^+$.

Example 169



4-(5-(1-((1r,4r)-4-Carbamoylcyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide To a solution of (1r,4r)-4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexane-1-carboxylic acid (25.0 mg, 0.039mmol) in DMF (5 mL) was added HATU (44.46 mg,0.117 mmol), NH_4Cl (3.2 mg,0.0585 mmol) and diisopropyl-ethylamine (15.09mg,0.117 mmol). The mixture was stirred for 4 h at room temperature then quenched with H_2O (20 ml) and extracted with EtOAc (10 ml x 3). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, and concentrated to dryness, The residue was purified by column chromatography using 0-20% methanol in dichloromethane and prep-HPLC to afford the title compound as a white solid. TLC: 20% MeOH/dichloromethane (R_f: 0.4). MS calcd. for $C_{30}H_{33}ClF_4N_6O_3$: 636.2; Found: 619.0 [M – 18 + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.97 (dd, J = 6.8, 2.8 Hz, 1H), 7.83 (s, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.43 (t, J = 9.2 Hz, 1H), 7.27 (s, 1H), 6.75 (s,1H), 4.86 (s, 1H), 4.16-4.12 (m, 1H), 3.67 (s, 3H), 3.22-3.16 (m, 1H), 2.49-2.46 (m, 2H), 2.13-1.99 (m, 7H), 1.91-1.79 (m, 6H), 1.73-1.69 (m, 2H), 1.50-1.46 (m, 2H) ppm.

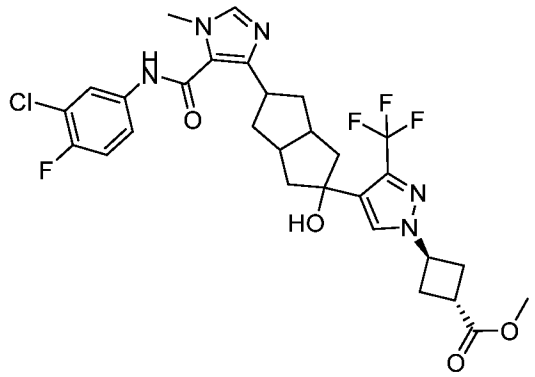
Intermediate 45



(1*s*,3*s*)-Methyl 3-(tosyloxy)cyclobutanecarboxylate To a solution of (1s,3s)-methyl 3-hydroxycyclobutanecarboxylate (1.0 g, 15.4 mmol), triethylamine (3.1 g, 30.8 mmol) and DMAP (188 mg, 1.5 mmol) in dichloromethane (30 mL) was added TosCl (2.5 g, 23.1

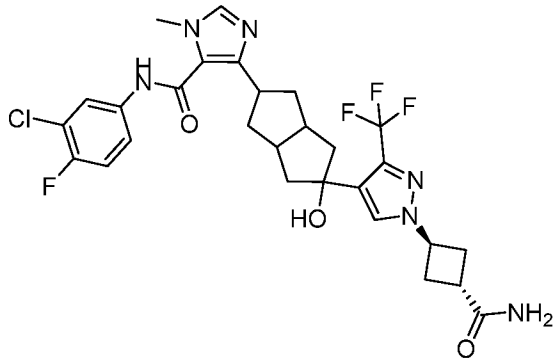
mmol). The mixture was stirred at room temperature for 16 h. The reaction was treated with $NaHCO_3$ solution (50 mL) and extracted with dichloromethane (3 x 50 mL), the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 3/1 (v/v)) to afford oil (3.0 g, 68.6%). MS calcd. for $C_{13}H_{16}O_5S$: 284.1; Found: 302.2 $[M+18]^+$.

Example 170



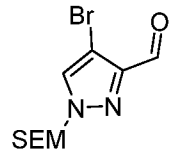
Methyl (1r,3r)-3-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclobutane-1-carboxylate. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (250 mg , 0.49 mmol) and Cs_2CO_3 (175 mg, 0.54 mmol) in DMF (2.5 mL) was added (1s,3s)-methyl 3-(tosyloxy)cyclobutanecarboxylate (417 mg, 1.47 mmol). The mixture was stirred for 16 hours at 50 °C. The reaction was treated with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine, dried, and concentrated *in vacuo*. The residue was purified by column chromatography (dichloromethane/MeOH = 15/1 (v/v)) to afford the title compound as a white solid. MS calcd. for $C_{29}H_{30}ClF_4N_5O_4$: 623.2; Found: 624.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.4, 2.4 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.65 (s, 1H), 7.53-7.47 (m, 1H), 7.23 (t, J = 8.8 Hz, 1H), 5.08-4.98 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.37-3.32 (m, 1H), 3.25-3.16 (m, 1H), 2.90-2.78 (m, 2H), 2.75-2.65 (m, 2H), 2.62-2.50 (m, 2H), 2.38-2.18 (m, 4H), 1.96-1.82 (m, 4 H) ppm.

Example 171



4-(5-(1-((1r,3r)-3-Carbamoylcyclobutyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of methyl (1r,3r)-3-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclobutane-1-carboxylate (50 mg , 0.08 mmol) was added NH_3 in MeOH (2 mL).The mixture was stirred at 50 °C for 24 hours. The reaction mixture was concentrated *in vacuo*. The residue was purified by reversed phase column chromatography afford the title compound. MS calcd. for $C_{28}H_{29}ClF_4N_6O_3$: 608.2; Found: 609.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.8 Hz, 1H), 7.73 (s 1H), 7.65 (s, 1 H), 7.53-7.46 (m, 1H), 7.23 (t, J = 8.8 Hz, 1H), 5.07-4.98 (m, 1H), 3.76 (s, 3H), 3.37-3.32 (m, 1 H), 3.22-3.12 (m, 1H), 2.84-2.73 (m, 2H), 2.71-2.62 (m, 2H), 2.60-2.50 (m, 2H), 2.37-2.18 (m, 4H), 1.95-1.80 (m, 4 H) ppm.

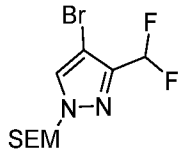
Intermediate 46



4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carbaldehyde A 100 mL flask was charged with 4-bromo-1H-pyrazole-3-carbaldehyde (3 g, 17 mmol) and THF (40 mL), added NaH (1 g, 26 mmol) slowly at 0 °C, the reaction mixture was stirred at 0 °C for 0.5 h. Then added 2-(trimethylsilyl)ethoxymethyl chloride (3.6 mL, 20 mmol), stirred at

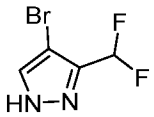
room temperature overnight. The mixture was quenched with H_2O (20 mL) and extracted with ethyl acetate (30 ml x 3), combined organic layer was dried over Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (petroleum ether: ethyl acetate = 60 :1, then petroleum ether: ethyl acetate = 30:1) to afford the title compound as a colorless oil. TLC: petroleum ether/ethyl acetate = 10/1 (v/v), R_f = 0.4.

Intermediate 47



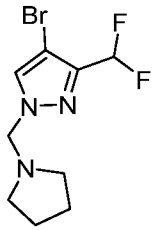
4-Bromo-3-(difluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole. A 100 mL flask was charged with 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carbaldehyde (3.07 g, 10 mmol) and dichloromethane (30 mL). DAST (5.5 mL, 40 mmol) was added slowly at 0 °C and the reaction warmed to room temperature slowly and stirred for 6 h. The mixture was extracted with ethyl acetate (30 ml x 3). The combined organic layer was dried over Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography to afford the title compound as a colorless oil. TLC: dichloromethane, R_f = 0.9.

Intermediate 48



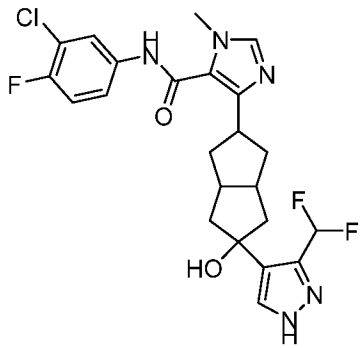
4-Bromo-3-(difluoromethyl)-1H-pyrazole A 100 mL flask was charged with 4-bromo-3-(difluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (2.7 g, 8.3 mmol) and CF_3COOH/dichloromethane (10 mL/20 mL). The mixture was stirred at room temperature for 4 h. The pH was adjusted to 8.0 with $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (30 ml x 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the title compound as a white solid.

Intermediate 49



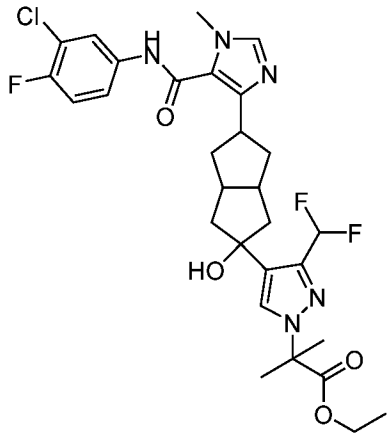
4-Bromo-3-(difluoromethyl)-1-(pyrrolidin-1-ylmethyl)-1H-pyrazole. A 100 mL flask was charged with 4-bromo-3-(difluoromethyl)-1H-pyrazole (1.6 g, 8.2 mmol), HCHO (674 mg, 9 mmol), pyrrolidine (640 mg, 9 mmol) and EtOH (25 mL). The mixture was stirred overnight at room temperature. The mixture was extracted with ethyl acetate (30 ml x 3) and the combined organic layer dried over Na_2SO_4, filtered, and concentrated to afford the title compound as a colorless oil.

Example 172



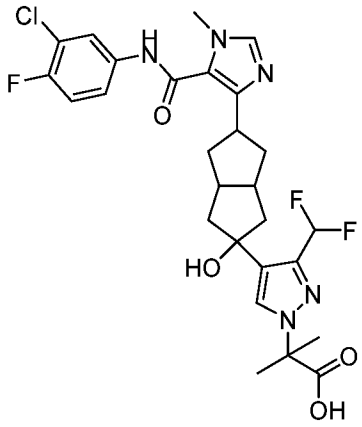
N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. A 100 mL flask was charged with 4-bromo-3-(difluoromethyl)-1-(pyrrolidin-1-ylmethyl)-1H-pyrazole (1.76 g, 6.3 mmol) and THF (40 mL). *n*-BuLi (2.5 mL, 6.3 mmol) slowly added at - 78 °C under an Argon atmosphere and the mixture stirred at - 78 °C for 2 min. N-(3-Chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (300 mg, 0.8 mmol) was then added at - 78 °C. The mixture was stirred at - 78 °C for 3 h under Argon. The mixture was quenched with H_2O (20 mL) and extracted with ethyl acetate (30 ml x 3). The combined organic layer was dried over Na_2SO_4, filtered, concentrated, and purified by prep-HPLC to afford the title compound as a white solid. TLC: dichloromethane/MeOH = 10/1, Rf = 0.5. MS calcd. for $C_{23}H_{23}ClF_3N_5O_2$: 493.2; Found: 494 $[M + 1]^+$.

Example 173



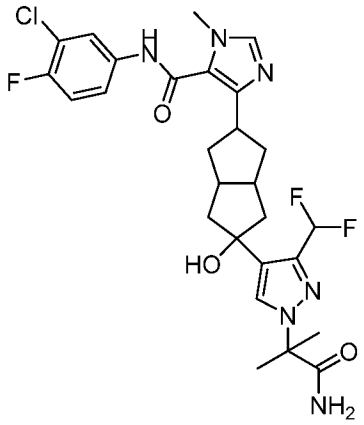
Ethyl 2-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)-2-methylpropanoate. A 100 mL flask was charged with N-(3-chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (150 mg, 0.3 mmol), ethyl 2-bromo-2-methylpropanoate (60 mg, 1.8 mmol), Cs_2CO_3 (90 mg, 0.3 mmol) and DMF (20 mL). The mixture was warmed up to 50 °C and stirred overnight. The reaction mixture was extracted with ethyl acetate (30 ml x 3). The combined organic layer was washed with H_2O three times. The organic layer was dried over Na_2SO_4, filtered, concentrated and the crude product purified by prep-HPLC to afford the title compound as a white solid. TLC: dichloromethane/MeOH = 10/1 (v/v), R_f = 0.6. MS calcd. for $C_{29}H_{33}ClF_3N_5O_4$: 607.22; Found: 590 $[M - 18+1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8 Hz, 2.8 Hz, 1H), 7.79 (s, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 7.14 (t, J = 54.4 Hz, 1H), 5.06 (s, 1H), 4.09 (q, J = 6.8 Hz, 2H), 3.67 (s, 3H), 3.27-3.20 (m, 1H), 2.50-2.49 (m, 2H), 2.12-2.07 (m, 4H), 1.92-1.79 (m, 4H), 1.74 (s, 6H), 1.11 (t, J = 7.2 Hz, 3H) ppm.

Example 174



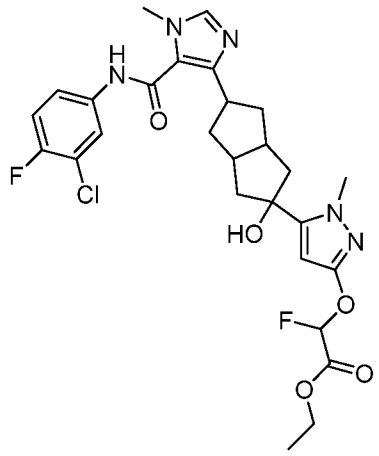
2-(4-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)-2-methylpropanoic acid. A 50 mL flask was charged with ethyl 2-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)-2-methylpropanoate (30 mg, 0.05 mmol), NaOH (8 mg, 0.20 mmol) and MeOH (10 mL), The mixture was stirred at room temperature overnight. The pH value was adjusted to 8.0 with HCl (1M). The mixture was extracted with ethyl acetate (30 ml x 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to afford the title compound as a white solid. MS calcd. for $C_{27}H_{29}ClF_3N_5O_4$: 579.19; Found: 580 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.71 (s, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.41 (t, J = 8.8 Hz, 1H), 7.13 (t, J = 54.4 Hz, 1H), 5.01 (s, 1H), 3.67 (s, 3H), 3.28-3.21 (m, 1H), 2.51-2.50 (m, 2H), 2.10-2.06 (m, 4H), 1.94-1.80 (m, 4H), 1.67 (s, 6H) ppm.

Example 175



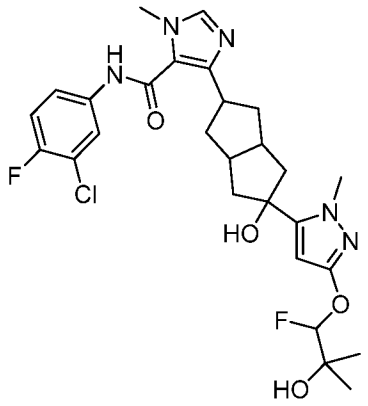
4-(5-(1-(1-Amino-2-methyl-1-oxopropan-2-yl)-3-(difluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a mixture of 2-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)-2-methylpropanoic acid (15 mg, 0.03 mmol), NH_4Cl (7 mg, 0.15 mmol), diisopropyl ethylamine (15 mg, 0.12 mmol) and DMF (4 mL) was added HATU (49 mg, 0.13 mmol) the reaction stirred at room temperature for 5 h. The mixture was extracted with ethyl acetate (30 ml x 3). The combined organic layer was dried over Na_2SO_4, filtered, concentrated then purified by prep-HPLC to afford the title compound as a white solid. MS calcd. for $C_{27}H_{30}ClF_3N_6O_3$: 578.20; Found: 561 $[M - 18 + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.4 Hz, 2.4 Hz, 1H), 7.69 (s, 1H), 7.65(s, 1H), 7.59-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 7.23 (s 1H), 7.14 (t, J = 54.4 Hz, 1H), 6.89 (s, 1H), 5.01 (s, 1H), 3.67 (s, 3H), 3.26-3.20 (m, 1H), 2.50-2.43 (m, 2H), 2.12-2.07 (m, 4H), 1.93-1.79 (m, 4H), 1.68 (s, 6H) ppm.

Intermediate 50



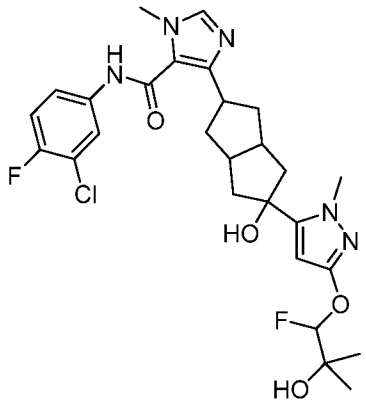
Ethyl 2-((5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)oxy)-2-fluoroacetate. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (450.2 mg , 0.95 mmol) in dry DMF (10 mL) was added cesium carbonate (619.1 mg, 1.9 mmol). Ethyl 2-bromo-2-fluoroacetate (192.4 mg, 1.04 mmol) in DMF (5 mL) was slowly added at 0°C and the reaction mixture stirred at 0°C overnight under a N_2-atmosphere. After completion, the reaction mixture was quenched with ice cold water (100 mL) and extracted with EtOAc (3x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (eluting with CH_3OH/DCM, 1:13 (v/v)) to provide the title compound as a yellow solid. TLC: 5% MeOH/DCM (R_f: 0.5). MS calcd. for $C_{27}H_{30}ClF_2N_5O_5$: 577.2; Found: 559.9 [M-18+1]$^+$.

Example 176



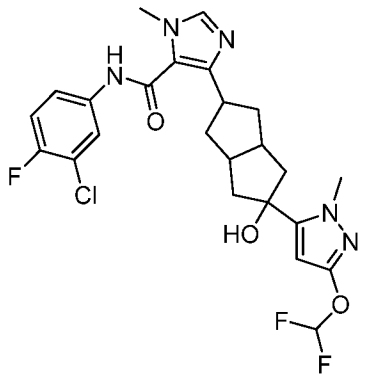
N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(1-fluoro-2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I. Methyl magnesium bromide (2.5M in THF, 0.6 mL, 1.8 mmol) was slowly added to a solution of ethyl 2-((5-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazol-3-yl)oxy)-2-fluoroacetate (202.3 mg, 0.35 mmol) in dry THF (10 mL) at 0 °C under a N_2-atmosphere. The reaction mixture was stirred at room temperature for 10 mins. After completion, the reaction mixture was quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (3x20mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (eluting with CH_3OH/DCM, 1:13 (v/v)) followed by chromatographic chiral separation to provide N-(3-chloro-4-fluorophenyl)-4-(5-(3-(1-fluoro-2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I and Isomer II. Isomer I: TLC: 5% MeOH/DCM (R*f*: 0.4). MS calcd. for $C_{27}H_{32}ClF_2N_5O_4$: 563.21; Found: 564.0 $[M+1]^+$, 546.0 $[M-18+1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H), 7.96 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.65 (s, 1H), 7.58-7.56 (m, 1H), 7.40 (t, *J* = 8.8 Hz, 1H), 5.73 (s, 1H), 5.59 (d, *J* = 61.2 Hz, 1H), 5.29 (s, 1H), 4.94 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.28-3.22 (m, 1H), 2.50-2.24 (m, 2H, merged), 2.20-2.07 (m, 4H), 1.86 (m, 4H), 1.14 (s , 6H) ppm.

Example 177



N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(1-fluoro-2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II. TLC: 5% MeOH/DCM (R*f*: 0.4). MS calcd. for $C_{27}H_{32}ClF_2N_5O_4$: 563.2; Found: 564.0 $[M+1]^+$, 546.0 $[M-18+1]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 7.96 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.40 (t, *J* = 8.8 Hz, 1H), 5.73 (s, 1H), 5.70 (d, *J* = 61.2 Hz, 1H), 5.26 (s, 1H), 4.92 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.28-3.22 (m, 1H), 2.50-2.24 (m, 2H, merged), 2.21-2.08 (m, 4H), 1.89-1.84 (m, 4H), 1.14 (s , 6H) ppm.

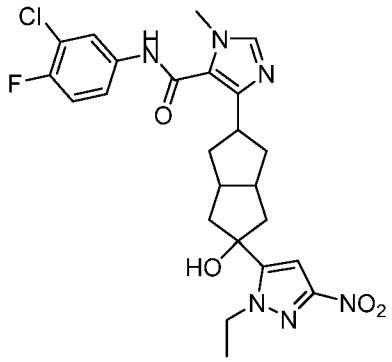
Example 178



N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethoxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. A solution of N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (199.1 mg , 0.42 mmol) in dry DMF (3 mL) was added DBU (127.9 mg, 0.84 mmol) and ethyl 2-bromo-2,2-

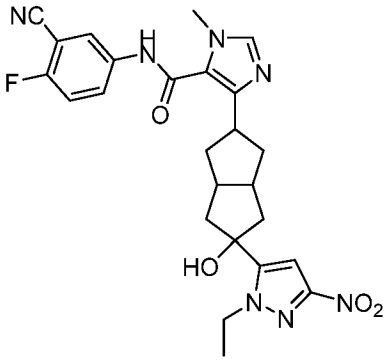
difluoroacetate (127.9 mg, 0.63 mmol) at 0°C. The reaction mixture was stirred at 70°C overnight under a N_2-atmosphere. The progress of reaction was monitored by LCMS. After completion, the reaction mixture was quenched with ice cold water (30 mL) and extracted with EtOAc (3x10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (eluting with CH_3OH/DCM, 1:15 v/v) followed by prep-HPLC to provide the title compound as a white solid. TLC: 5% MeOH/DCM (R*f*: 0.6). MS calcd. for $C_{24}H_{25}ClF_3N_5O_3$: 523.16; Found: 524.2 $[M+1]^+$, 506.2 $[M-18+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 7.88 (dd, J = 6.8, 2.8 Hz, 1H), 7.65 (s, 1H), 7.51-7.48 (m, 1H), 7.23 (t, J =9.2 Hz, 1H), 6.85 (t, J =74 Hz, 1H), 5.84 (s, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.33-3.31 (m, 1H), 2.59-2.57 (m, 2H), 2.39-2.34 (m, 2H), 2.27-2.24 (m, 2H), 1.98-1.87 (m, 4H) ppm.

Example 179



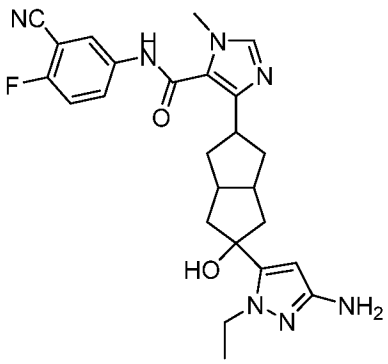
N-(3-Chloro-4-fluorophenyl)-4-(5-(1-ethyl-3-nitro-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of 1-ethyl-3-nitro-1H-pyrazole (1.0 mg, 7.09 mmol) in 100 mL of THF was added LDA(7 mL, 11.5 mmol). After addition, the reaction was stirred at -78 °C for 0.5 h. N-(3-Chloro-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide (324.4 mg, 0.88 mmol) was added and the reaction mixture warmed to room temperature and stirred for another 2 h. The reaction was quenched with water and extracted with ethyl acetate (100 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by prep-HPLC to afford the title compound as a yellow solid.

Example 180



N-(3-Cyano-4-fluorophenyl)-4-(5-(1-ethyl-3-nitro-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of N-(3-chloro-4-fluorophenyl)-4-(5-(1-ethyl-3-nitro-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (100.0 mg, 0.194 mmol) in dioxane(10 ml) and H_2O(5 ml) was added $Zn(CN)_2$ (114 mg, 0.968 mmol), t-BuXPhos (42 mg, 0.097 mmol), and 3rd generation t-BuXPhos-pre-catalyst (78 mg, 0.097 mmol). The reaction was stirred at 60 °C overnight. The reaction was quenched with water and extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by CC to afford the title compound as a white solid.

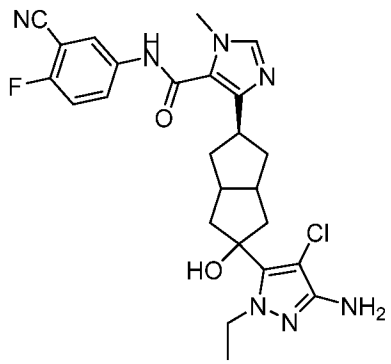
Example 181



4-(5-(3-Amino-1-ethyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-cyano-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of N-(3-cyano-4-fluorophenyl)-4-(5-(1-ethyl-3-nitro-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide (50.0 mg, 0.1 mmol) in EtOH(1 ml) was added $SnCl_2$ (60 mg, 0.27 mmol) and the solution stirred at 85

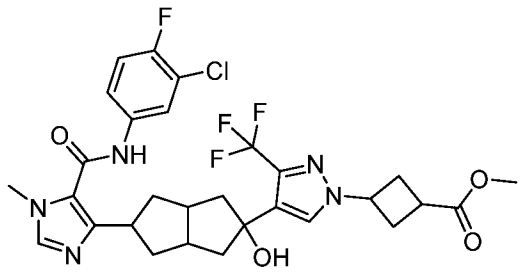
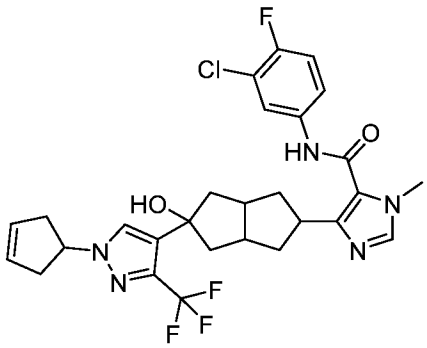
°C for 1 h. The reaction was quenched with saturated NaOH (aq), concentrated, and purified by column chromatography (DCM/MeOH, 30:1 (v/v)) to afford the title compound as a white solid.

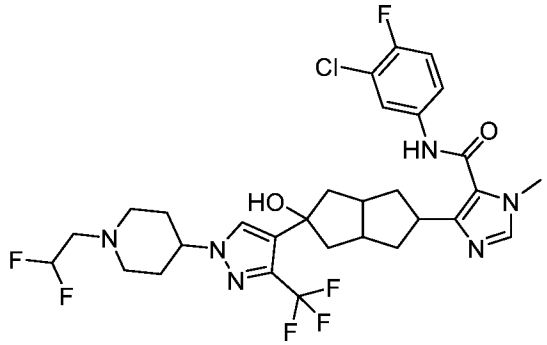
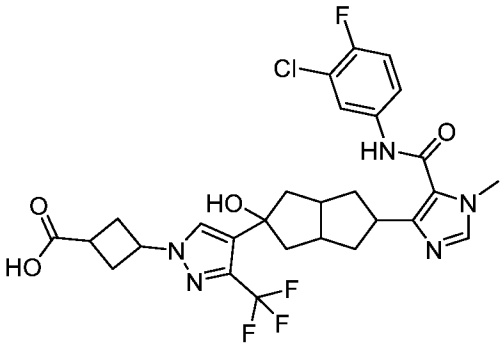
Example 182

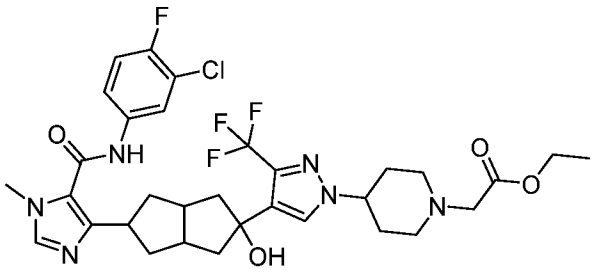
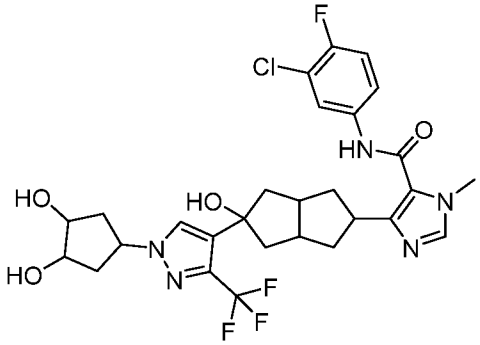


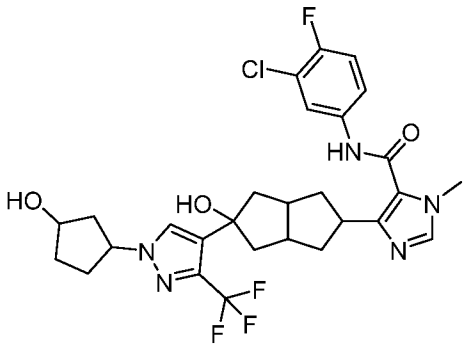
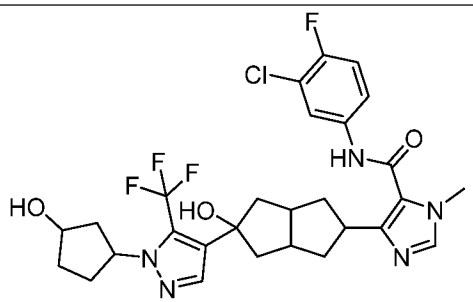
4-(5-(3-Amino-4-chloro-1-ethyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-cyano-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. To a solution of 4-(5-(3-amino-1-ethyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-cyano-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide (30.0 mg, 0.06 mmol) in dichloromethane (2 ml), was added N-chlorosuccinimide (10 mg, 0.072 mmol) and the reaction stirred at room temperature for 2 h. The reaction was quenched with water and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layer was concentrated and purified by prep-HPLC to afford the title compound as a white solid. MS calcd. for $C_{25}H_{27}ClFN_7O_2$: 511; Found: 512 $[M + 1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.36 (s, 1H), 8.17 (dd, J = 5.6 Hz, 2.8 Hz, 1H), 7.95-7.91 (m, 1H), 7.66 (s, 1H), 7.53 (t, J = 9.2 Hz, 1H), 5.31 (s, 1H), 4.59 (s, 2H), 4.11 (dd,J=7.2,6.8 Hz, 2H), 3.68 (s, 3H), 3.27-3.22 (m, 1H), 2.39-2.34 (m, 2H), 2.10-1.92 (m, 8H)), 1.25 (t, J=6.85 Hz, 3H) ppm.

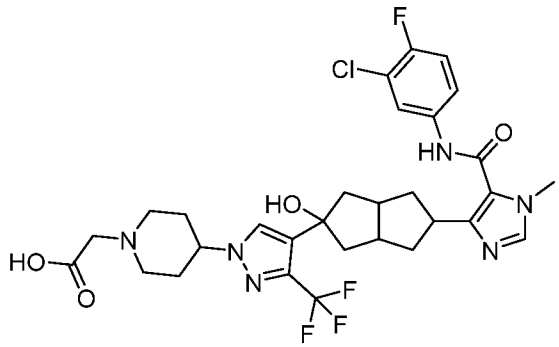
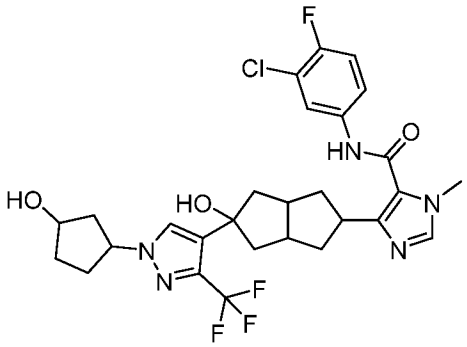
Table 5. Examples 183-302 were synthesized according to the methods described elsewhere in this case

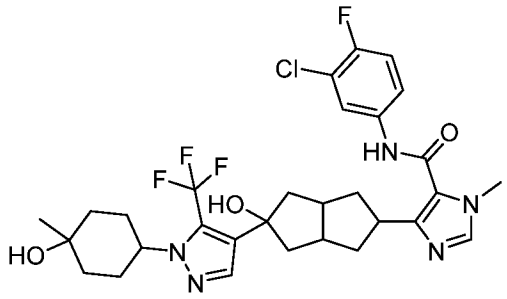
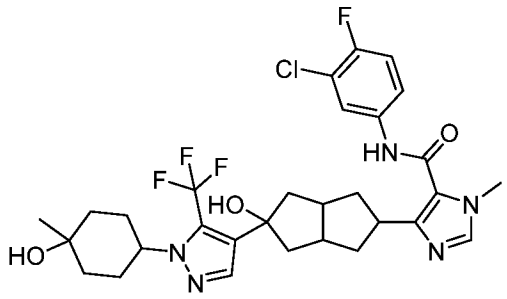
Example	Structure, ^{1}H NMR, and MS
183	 **Methyl 3-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclobutane-1-carboxylate** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.4, 2.4 Hz, 1H), 7.74 (s, 1H), 7.65 (s, 1H), 7.53-7.47 (m, 1H), 7.24 (t, J = 8.8 Hz, 1H), 4.81-4.68 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.28-3.22 (m, 1H), 3.05-2.95 (m, 1H), 2.78-2.68 (m, 4H), 2.62-2.50 (m, 2H), 2.40-2.29 (m, 2H), 2.28-2.18 (m, 2H), 1.96-1.80 (m, 4 H) ppm. MS calcd. for $C_{29}H_{30}ClF_4N_5O_4$: 623.2; Found: 624 $[M+1]^+$.
184	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(cyclopent-3-en-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.97 (dd, J = 6.8, 2.8 Hz, 1H), 7.79 (s, 1H), 7.64 (s, 1H), 7.59-7.55 (m, 1H), 7.43 (t, J = 8.8 Hz, 1H), 5.76 (s, 2H), 5.07-5.03 (m, 1H), 4.85 (s, 1H), 3.67 (s, 3H), 3.23-3.20 (m, 1H), 2.87-2.81 (m, 2H), 2.67-2.59 (m, 2H), 2.49-2.41 (m, 2H), 2.12-2.05 (m,

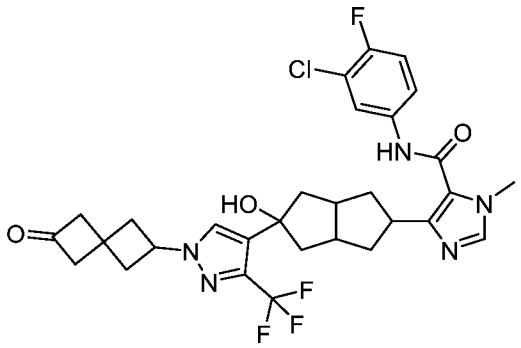
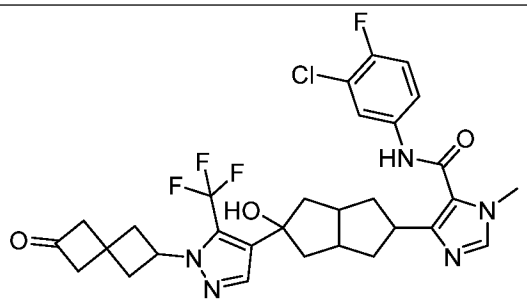
	4H), 1.92-1.80 (m, 4H) ppm. MS calcd. for $C_{28}H_{28}ClF_4N_5O_2$: 577.2; Found: 559.9 $[M-18+H]^+$.
185	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.87 (s, 1H), 7.65 (s, 1H),7.60-7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 6.27 (t, J = 4.4 Hz, 0.26 H), 6.13 (t, J = 4.4 Hz, 0.43 H), 5.99 (t, J = 4.4 Hz, 0.2 H), 4.86 (s, 1H), 4.22-4.10 (m, 1H), 3.67 (s, 3H), 3.28-3.15(m, 1H), 2.98 (d, J = 11.6 Hz, 2H), 2.76 (dt, J = 16.0, 4.4 Hz, 2H), 2.47-2.40 (m, 2H), 2.37-2.25 (m, 2H), 2.14-2.04 (m, 4H), 2.00-1.78 (m, 8H) ppm. MS calcd. for $C_{30}H_{33}ClF_6N_6O_2$: 658.2; Found: 659 $[M+1]^+$.
186	 **3-(4-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclobutane-1-carboxylic acid** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.74 (s 1H), 7.65 (s, 1H), 7.53-7.47 (m, 1H), 7.23 (t, J = 8.8 Hz, 1H), 5.08-4.98 (m, 1H), 3.76 (s, 3H), 3.28-3.22 (m, 1H), 3.18-3.10 (m, 1H), 2.87-2.77 (m, 2H),

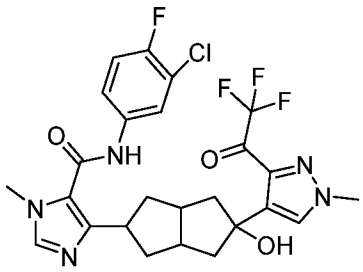
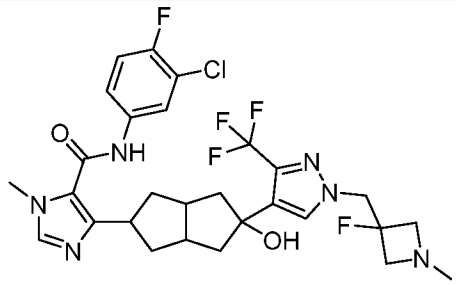
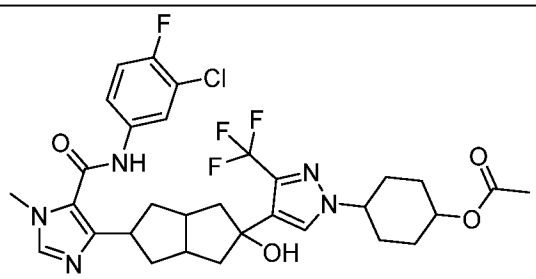
	2.75-2.65 (m, 2H), 2.62-2.50 (m, 2H), 2.37-2.18 (m, 4H), 1.97-1.83 (m, 4 H) ppm. MS calcd. for $C_{28}H_{28}ClF_4N_5O_4$: 609.2; Found: 610.1 $[M+1]^+$.
187	 **Ethyl 2-(4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)piperidin-1-yl)acetate** ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.87 (s, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 9.0 Hz, 1H), 4.85 (s, 1H), 4.20-4.05 (m, 3H), 3.67 (s, 3H), 3.26 (s, 2H), 3.24-3.16 (m, 1H), 2.92 (d, J = 11.2 Hz, 2H), 2.48-2.41 (m, 2H), 2.38-2.29 (m, 2H), 2.15-2.02 (m, 4H), 1.97-1.78 (m, 8H), 1.19 (t, J = 7.2 Hz, 3H) ppm. MS calcd. for $C_{32}H_{37}ClF_4N_6O_4$: 680.3; Found: 681.9 $[M+1]^+$.
188	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(3,4-dihydroxycyclopentyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.22 (s, 1H), 7.97 (dd, J = 6.8, 2.8 Hz, 1H), 7.84 (s, 1H), 7.64 (s, 1H), 7.59-7.55 (m, 1H), 7.43 (t, J = 8.8 Hz, 1H), 4.93-4.84 (m, 2H), 4.63 (d, J = 3.6 Hz, 2H), 4.11 (s, 2H), 3.67 (s, 3H), 3.22-3.21 (m, 1H), 2.50-2.46 (m, 2H), 2.12-2.05 (m, 6H), 1.99-1.94 (m, 2H), 1.91-1.79 (m, 4H) ppm. MS calcd. for $C_{28}H_{30}ClF_4N_5O_4$: 611.2; Found: 593.9 $[M - 18 + 1]^+$.

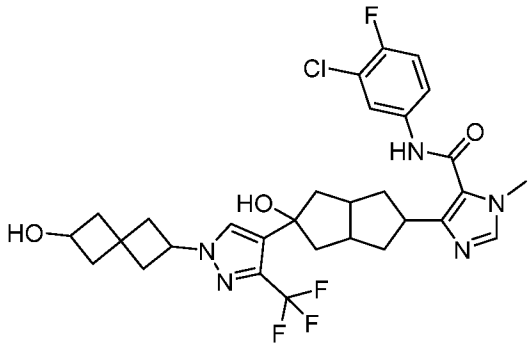
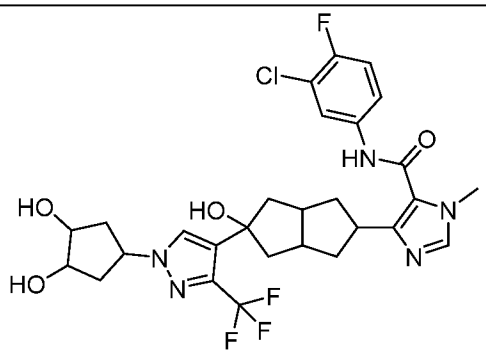
189	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(3-hydroxycyclopentyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.53-7.50 (m, 1H), 7.23 (t, *J* = 9.2 Hz, 1H), 4.87-4.73 (m, 1H), 4.32-4.30 (m, 1H), 3.76 (s, 3H), 3.36-3.31 (m, 1H), 2.61-2.56 (m, 2H), 2.50-2.41 (m, 1H), 2.36-2.31 (m, 2H), 2.25-2.14 (m, 3H), 2.08-2.03 (m, 1H), 1.94-1.85 (m, 7H) ppm. MS calcd. for $C_{28}H_{30}ClF_4N_5O_3$: 595.2; Found: 577.9 $[M-18+1]^+$.
190	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(3-hydroxycyclopentyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.88 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 7.50-7.48 (m, 1H), 7.23 (t, *J* = 8.8 Hz, 1H), 4.96-4.92 (m, 1H), 4.31-4.27 (m, 1H), 3.76 (s, 3H), 3.36-3.31 (m, 1H), 2.61-2.52 (m, 2H), 2.42-2.36 (m, 3H), 2.26-2.23 (m, 2H), 2.18-2.03 (m, 3H), 1.96-1.85 (s, 6H) ppm. MS calcd. for $C_{28}H_{30}ClF_4N_5O_3$: 595.2; Found: 577.9 $[M-18+1]^+$.

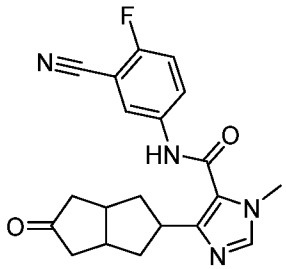
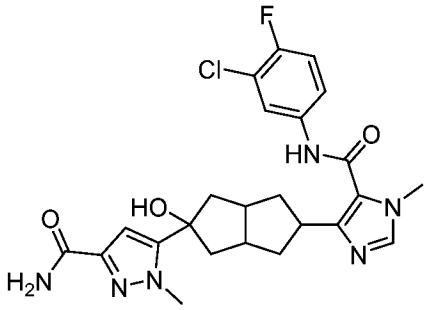
191	 **2-(4-(4-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)piperidin-1-yl)acetic acid** ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.86 (s, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 4.87 (d, J = 1.6 Hz, 1H), 4.22-4.12 (m, 1H), 3.67 (s, 3H), 3.43 (brs, 1H), 3.27-3.17 (m, 1H), 3.16 (s, 2H), 3.02 (d, J = 11.6 Hz, 2H), 2.48-2.37 (m, 4H), 2.15-2.02 (m, 4H), 2.01-1.94 (m, 4H), 1.92-1.77 (m, 4H) ppm. MS calcd. for $C_{30}H_{33}ClF_4N_6O_4$: 652.2; Found: 634.9 $[M-18+1]^+$.
192	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(3-hydroxycyclopentyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamideIsomer II** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 7.51-7.48 (m, 1H), 7.24 (t, *J* = 8.8 Hz, 1H), 4.93-4.91 (m, 1H), 4.47-4.46 (m, 1H), 3.76 (s, 3H), 3.36-3.31 (m, 1H), 2.62-2.50 (m, 2H), 2.36-2.31 (m, 3H), 2.25-2.13 (m, 5H), 1.96-1.89 (m, 5H), 1.73-1.64 (m, 1H) ppm. MS calcd. for $C_{28}H_{30}ClF_4N_5O_3$: 595.2; Found: 577.9 $[M-18+1]^+$.

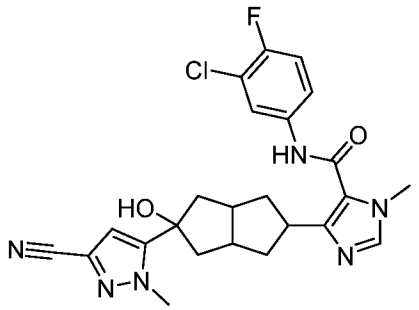
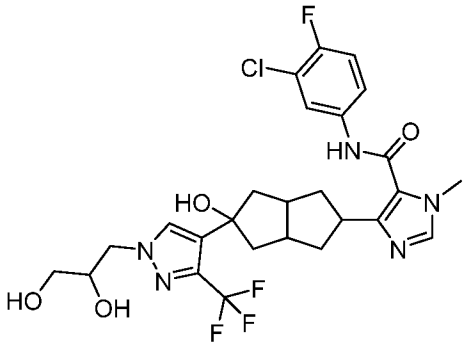
193	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(4-hydroxy-4-methylcyclohexyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.22 (brs, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.87 (s, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 2H), 7.41 (t, J = 8.8 Hz, 1H), 4.97 (s, 1H), 4.20 (s, 1H), 4.17-4.12 (m, 1H), 3.67 (s, 3H), 3.27-3.22 (m, 1H), 2.45-2.43 (m, 2H), 2.39-2.04 (m, 8H), 1.88-1.81 (m, 4H), 1.65-1.43 (m, 6H), 1.13 (s, 3H) ppm. MS calcd for $C_{30}H_{34}ClF_4N_5O_3$: 623.2; Found: 606 $[M-18+1]^+$.
194	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(4-hydroxy-4-methylcyclohexyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (brs, 1H), 8.07 (s, 0.5 H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.56-7.55 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 4.99 (s, 1H), 4.66 (s, 0.5H), 4.47 (s, 1H), 4.21 (brs, 1H), 3.67 (s, 3H), 3.27-3.22 (m, 1H), 2.45-2.43 (m, 2H), 2.19-1.88 (m, 8H), 1.85-1.78 (m, 4H), 1.69-1.49 (m, 6H), 1.19 (s, 3H) ppm. MS calcd. for $C_{30}H_{34}ClF_4N_5O_3$: 623.2; Found: 606 $[M-18+1]^+$.

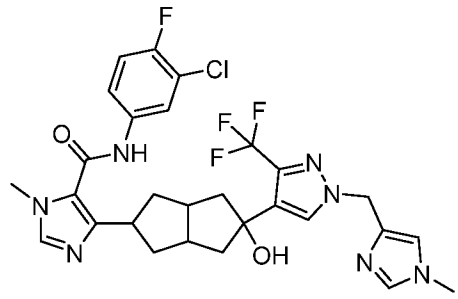
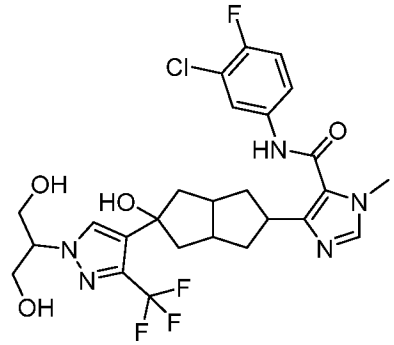
195	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(6-oxospiro[3.3]heptan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.88-7.86 (dd, J = 6.8, 2.4 Hz, 1H), 7.74 (d, J = 0.8 Hz, 1H), 7.65 (s, 1H), 7.52-7.48 (m, 1H), 7.25-7.21 (t, J = 8.8 Hz, 1H), 4.88-4.83 (m, 1H), 3.76 (s, 3H), 3.33-3.30 (m, 1H), 3.29-3.20 (m, 2H), 3.16-3.15 (m, 2H), 2.87-2.81 (m, 2H), 2.73-2.68 (m, 2H), 2.58-2.54 (m, 2H), 2.36-2.31 (m, 2H), 2.27-2.21 (m, 2H), 1.94-1.88 (m, 4H) ppm. MS calcd. for $C_{30}H_{30}ClF_4N_5O_3$: 619.2; Found: 620.7 $[M+1]^+$.
196	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(6-oxospiro[3.3]heptan-2-yl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89-7.86 (dd, J = 6.8, 2.8 Hz, 1H), 7.65 (s, 1H), 7.60 (s, 1H), 7.51-7.25 (m, 1H), 7.25-7.21 (t, J = 8.8 Hz, 1H), 4.99 (m, 1H), 3.76 (s, 3H), 3.34-3.30 (m, 1H), 3.25-3.23 (m, 2H), 3.16-3.15 (m, 2H), 2.99-2.94 (m, 2H), 2.72-2.67 (m, 2H), 2.56-2.55 (m, 2H), 2.41-2.36 (m, 2H), 2.28-2.23 (m, 2H), 1.96-1.89 (m, 4H) ppm. MS calcd. for $C_{30}H_{30}ClF_4N_5O_3$: 619.2; Found: 620.1 $[M+1]^+$.

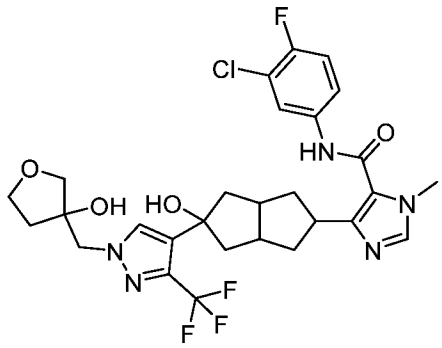
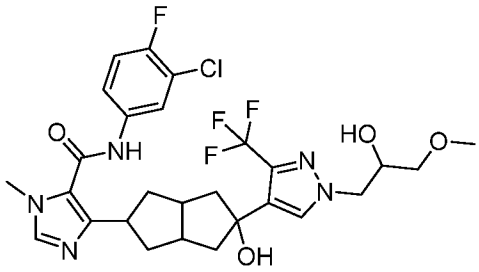
197	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(2,2,2-trifluoroacetyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.25 (s, 1H), 7.97-7.95 (m, 1H), 7.86 (s, 1H), 7.67-7.62 (m, 1H), 7.59-7.55 (m, 1H), 7.43-7.38 (m, 1H), 4.82 (s, 1H), 3.96 (s, 3H), 3.85 (s, 1H), 3.67 (s, 3H), 3.26-3.20 (m, 1H), 2.50-2.49 (m, 1H), 2.27-2.22 (m, 2H), 2.09-2.06 (m, 2H), 1.98-1.79 (m, 2H), 1.76-1.65 (m, 2H) ppm. MS calcd. for $C_{25}H_{24}ClF_4N_5O_3$: 553.2; Found: 554 $[M+1]^+$.
198	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-((3-fluoro-1-methylazetidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.86 (dd, J = 6.4, 2.4 Hz, 1H), 7.68 (s 1H), 7.64 (s, 1H), 7.53-7.47 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.57 (s, 1H), 4.52 (s, 1H), 3.76 (s, 3 H), 3.68-3.58 (m, 2H), 3.36-3.32 (m, 1H), 3.28-3.21 (m, 2H), 2.62-2.50 (m, 2H), 2.41 (s, 3H), 2.35-2.18 (m, 4H), 1.97-1.84 (m, 4 H) ppm. MS calcd. for $C_{28}H_{30}ClF_5N_6O_2$: 612.2; Found: 613.2 $[M+1]^+$.
199	

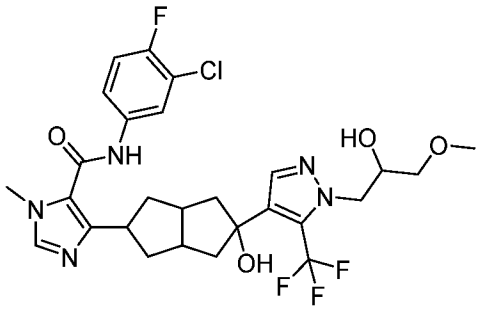
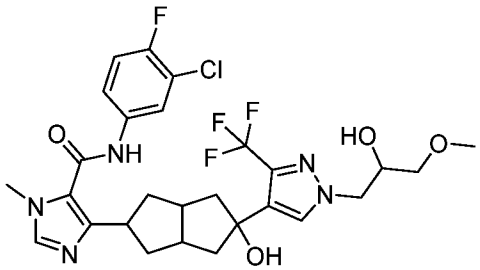
	4-(4-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl acetate ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.84 (s, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 9.0 Hz, 1H), 4.87 (s, 1H), 4.73-4.62 (m, 1H), 4.28-4.18 (m, 1H), 3.67 (s, 3H), 3.28-3.16 (m, 1H), 2.48-2.42 (m, 2H), 2.15-1.95 (m, 11H), 1.93-1.78 (m, 6H), 1.57-1.44 (m, 2H) ppm. MS calcd. for $C_{31}H_{34}ClF_4N_5O_4$: 651.2; Found: 651.9 $[M+1]^+$.
200	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(6-hydroxyspiro[3.3]heptan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.88-7.86 (dd, J = 6.8, 2.4 Hz, 1H), 7.68-7.65 (m, 2H), 7.52-7.48 (m, 1H), 7.25-7.21 (t, J = 8.8 Hz, 1H), 4.72-4.68 (m, 1H), 4.15-4.09 (m, 2H), 3.76 (s, 3H), 3.31-3.27 (m, 1H), 2.57-2.48 (m, 6H), 2.44-2.29 (m, 4H), 2.26-2.22 (m, 2H), 2.03-1.92 (m, 3H), 1.90-1.25 (m, 4H) ppm. MS calcd. for $C_{30}H_{32}ClF_4N_5O_3$: 621.2; Found: 604.0 $[M-18+1]^+$.
201	

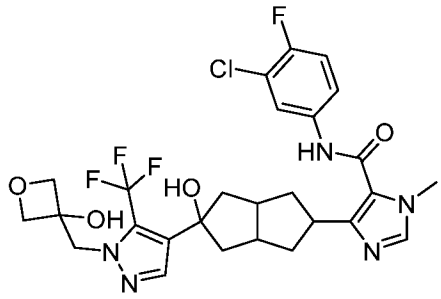
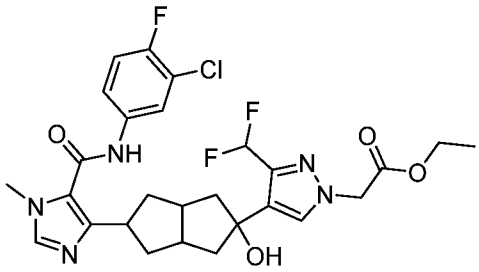
	N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(3,4-dihydroxycyclopentyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.97 (dd, J = 6.8, 2.8 Hz, 1H), 7.86 (d, J = 94.4 Hz, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.43 (t, J = 8.8 Hz, 1H), 4.99 (d, J = 42.0 Hz, 1H), 4.75-4.60 (m, 3H), 3.87-3.85 (m, 2H), 3.67 (s, 3H), 3.25-3.19 (m, 1H), 2.45 (s, 2H), 2.36-2.15 (m, 3H), 2.08-1.99 (m, 4H), 1.92-1.82 (m, 5H) ppm. MS calcd. for $C_{28}H_{30}ClF_4N_5O_4$: 611.2; Found: 594.0 [M - 18 + 1]$^+$.
202	 **N-(3-Cyano-4-fluorophenyl)-1-methyl-4-(5-oxooctahydropentalen-2-yl)-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 8.10 (dd, J = 5.6, 2.8 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.68 (s, 1H), 7.37 (t, J = 9.2 Hz, 1H), 3.76 (s, 3H), 3.51 – 3.43 (m, 1H), 2.86 – 2.77 (m, 2H), 2.56 – 2.45 (m, 2H), 2.39 – 2.31 (m, 2H), 2.25 – 2.16 (m, 2H), 1.75 – 1.65 (m, 2H) ppm. MS calcd. for $C_{20}H_{19}FN_4O_2$: 366.1; Found: 367 [M+1]$^+$.
203	 **5-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-3-carboxamide** ^{1}H -NMR (400 MHz, DMSO-d6): δ 10.20 (s, 1H), 7.93 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.63 (s, 1H), 7.55-7.51 (m, 1H), 7.37 (t, J = 9.2 Hz, 1H), 7.08 (s,

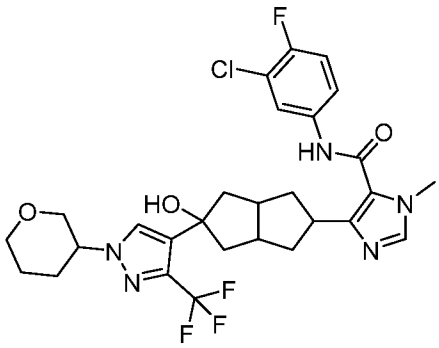
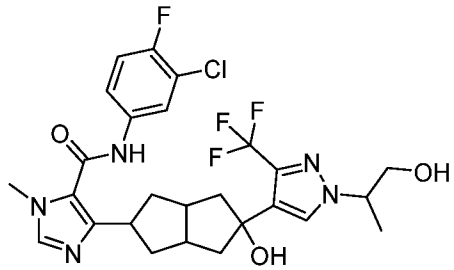
	1H), 6.43 (s, 1H), 5.33 (s, 1H), 3.92 (s, 3H), 3.64 (s, 3H), 3.26-3.20 (m, 1H), 2.40-2.47 (m, 2H), 2.22-2.17 (m, 2H), 2.10-2.06 (m, 2H), 1.87-1.78 (m, 4H) ppm. MS calcd. for $C_{24}H_{26}ClFN_6O_3$: 500.2; Found: 501 $[M+1]^+$.
204	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-cyano-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H -NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H),7.92 (dd, J = 6.8, 2.4 Hz, 1H), 7.63 (s, 1H), 7.56-7.52 (m, 1H), 7.38 (t, J = 9.2 Hz, 1H), 6.85 (s, 1H), 5.50 (s, 1H), 3.99 (s, 3H), 3.64 (s, 3H), 3.26-3.20 (m, 1H), 2.52-2.50 (m, 2H), 2.21-2.15 (m, 2H), 2.10-2.06 (m, 2H), 1.88-1.77 (m, 4H) ppm. MS calcd. for $C_{24}H_{24}ClFN_6O_2$: 482.2; Found: 483 $[M+1]^+$.
205	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(2,3-dihydroxypropyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): 7.78-7.76 (dd, J = 6.8, 2.4 Hz, 1H), 7.60-7.56 (m, 2H), 7.42-7.39 (m, 1H), 7.14 (t, J = 9.2 Hz, 1H), 4.19-4.15 (m, 1H), 4.02-3.96 (m, 1H), 3.87-3.84 (m, 1H), 3.66 (s, 3H), 3.41-3.39 (dd, J = 5.2, 1.6 Hz, 2H), 2.48-2.45 (m, 2H), 2.27-2.21 (m, 2H), 2.17-2.11 (m, 2H), 1.85-1.75 (m, 4H) ppm. MS calcd. for $C_{26}H_{28}ClF_4N_5O_4$: 585.2; Found: 586.9 $[M+1]^+$.

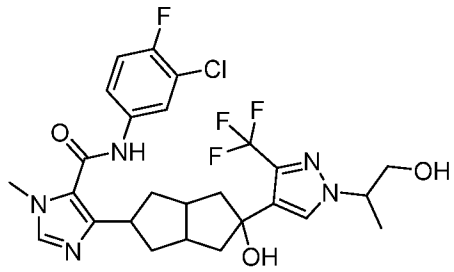
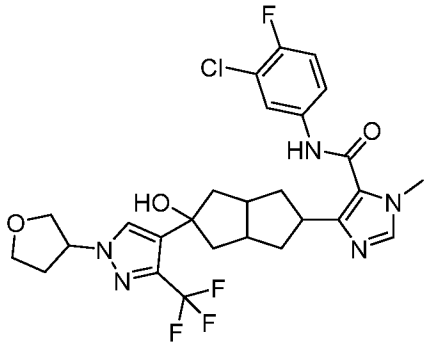
206	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1-methyl-1H-imidazol-4-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.76-7.78 (dd, J = 6.8, 2.8 Hz, 1H), 7.38-7.58 (m, 4H), 7.13 (t, J = 8.8 Hz, 1H), 7.03(s, 1H), 5.06(s, 2H), 3.65 (s, 3H), 3.59(s, 3H), 3.16-3.24 (m, 1H), 2.40-2.49 (m, 2H), 2.17-2.22 (m, 4H), 1.77-1.82 (m, 2H) ppm. MS calcd. for $C_{28}H_{28}ClF_4N_7O_2$: 605.2; Found: 587.9 [M-18+1]$^+$.
207	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(1,3-dihydroxypropan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.60 – 7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 4.93 (t, J = 5.2 Hz, 2H), 4.86 (s, 1H), 4.28 – 4.20 (m, 1H), 3.73 – 3.65 (m, 7H), 3.27 – 3.16 (m, 1H), 2.48 – 2.40 (m, 2H), 2.14 – 2.02 (m, 4H), 1.93 – 1.80 (m, 4H) ppm. MS calcd. for $C_{26}H_{28}ClF_4N_5O_4$: 585.2; Found: 585.8 [M+1]$^+$.

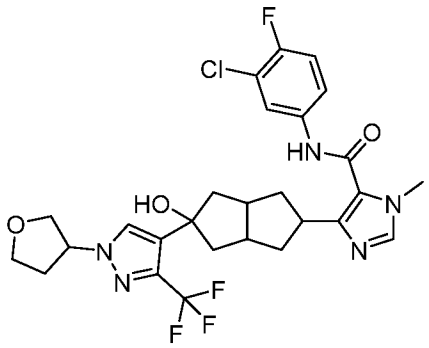
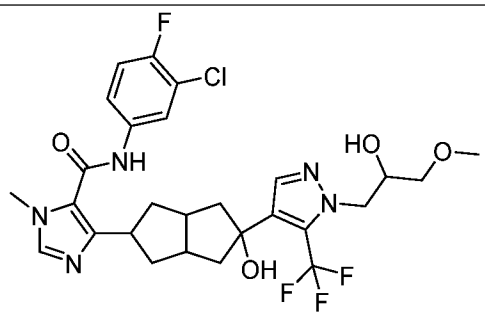
208	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxytetrahydrofuran-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.72 (s, 1H), 7.65 (s, 1H), 7.60 – 7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 5.21 (s, 1H), 4.91 (s, 1H), 4.23 (s, 2H), 3.84 – 3.72 (m, 2H), 3.70 – 3.65 (m, 4H), 3.42 (d, J = 8.8 Hz, 1H), 3.26 – 3.17 (m, 1H), 2.48 – 2.39 (m, 2H), 2.14 – 2.02 (m, 4H), 1.97 – 1.80 (m, 5H), 1.77 – 1.69 (m, 1H) ppm. MS calcd. for $C_{28}H_{30}ClF_4N_5O_4$: 611.2; Found: 611.9 $[M+1]^+$.
209	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-hydroxy-3-methoxypropyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.78-7.76 (dd, J = 6.8, 2.4 Hz, 1H), 7.57-7.56 (m, 2H), 7.42-7.39 (m, 1H), 7.14 (t, J = 9.2 Hz, 1H), 4.16-4.13 (m, 1H), 4.12-3.96 (m, 2H), 3.66 (s, 3H), 3.29-3.27 (m, 6H), 2.48-2.47 (m, 2H), 2.27-2.21 (m, 2H), 2.15-2.13 (m, 2H), 1.85-1.78 (m, 4H) ppm. MS calcd. for $C_{27}H_{30}ClF_4N_5O_4$: 599.2; Found: 601.8 $[M+1]^+$.

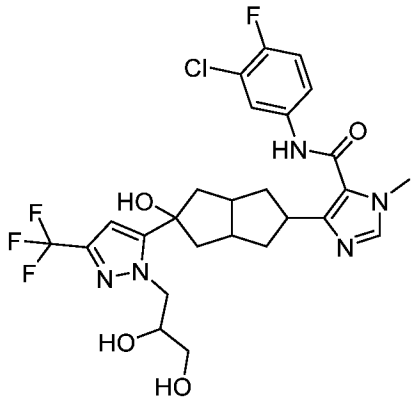
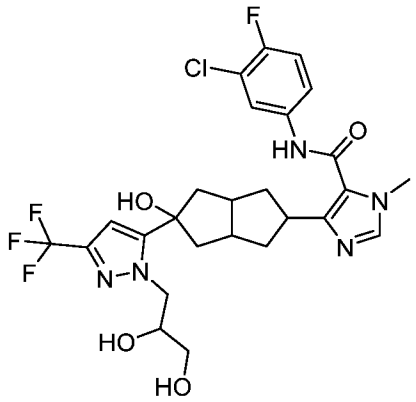
210	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-hydroxy-3-methoxypropyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.79-7.77 (dd, J = 6.8, 2.4 Hz, 1H), 7.56 (s, 1H), 7.48 (s, 1H), 7.42-7.38 (m, 1H), 7.14 (t, J = 9.2 Hz, 1H), 4.24-4.22 (m, 1H), 4.18-4.08 (m, 2H), 3.66 (s, 3H), 3.30-3.25 (m, 6H), 2.47-2.46 (m, 2H), 2.31-2.26 (m, 2H), 2.16-2.13 (m, 2H), 1.87-1.77 (m, 4H) ppm. MS calcd. for $C_{27}H_{30}ClF_4N_5O_4$: 599.2; Found: 601.8 $[M+1]^+$.
211	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-hydroxy-3-methoxypropyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.78-7.76 (dd, J = 6.8, 2.4 Hz, 1H), 7.57-7.56 (m, 2H), 7.43-7.39 (m, 1H), 7.14 (t, J = 9.2 Hz, 1H), 4.16-4.12 (m, 1H), 4.04-3.97 (m, 2H), 3.66 (s, 3H), 3.27-3.24 (m, 6H), 2.48-2.47 (m, 2H), 2.26-2.21 (m, 2H), 2.15-2.13 (m, 2H), 1.85-1.78 (m, 4H) ppm. MS calcd. for $C_{27}H_{30}ClF_4N_5O_4$: 599.2; Found: 601.8 $[M+1]^+$.

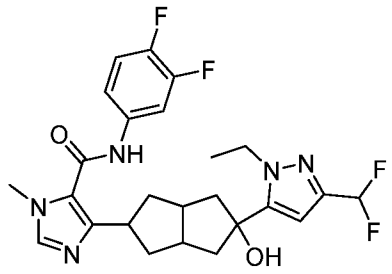
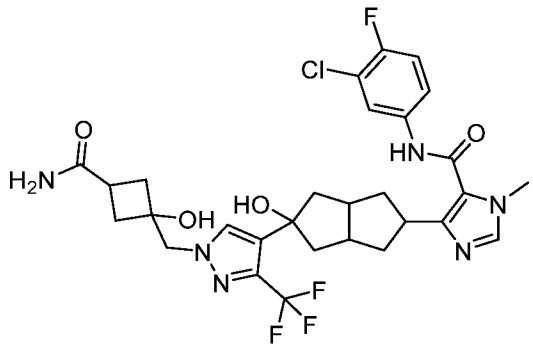
212	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxyoxetan-3-yl)methyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.79-7.77 (dd, J = 6.8, 2.4 Hz, 1H), 7.56 (s, 1H), 7.47 (s, 1H), 7.42-7.38 (m, 1H), 7.14 (t, J = 9.2 Hz, 1H), 4.68-4.66 (d, J = 7.2 Hz, 2H), 4.45-4.43 (m, 4H), 3.66 (s, 3H), 3.26-3.23 (m, 1H), 2.47-2.46 (m, 2H), 2.31-2.26 (m, 2H), 2.18-2.12 (m, 2H), 1.85-1.74 (m, 4H) ppm. MS calcd. for $C_{27}H_{28}ClF_4N_5O_4$: 597.2; Found: 598 $[M+1]^+$.
213	 **Ethyl 2-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)acetate** ^{1}H -NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.93 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.56-7.52 (m, 1H), 7.38 (t, J = 8.8 Hz, 1H), 7.11 (t, J = 54.4 Hz, 1H), 5.10 (s, 1H), 5.01 (s, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.65 (s, 3H), 3.22-3.19 (m, 1H), 2.48-2.47 (m, 2H), 2.07-1.99 (m, 4H), 1.87-1.76 (m, 4H), 1.18 (t, J = 7.2 Hz, 3H) ppm. MS calcd. for $C_{27}H_{29}ClF_3N_5O_4$: 579.2; Found:80 $[M+1]^+$.

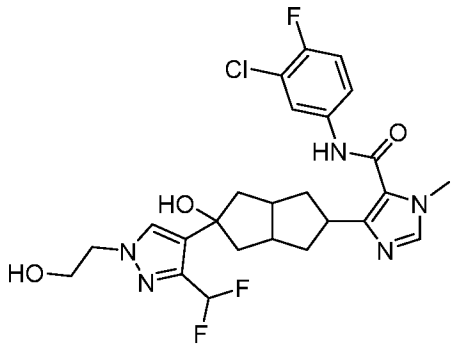
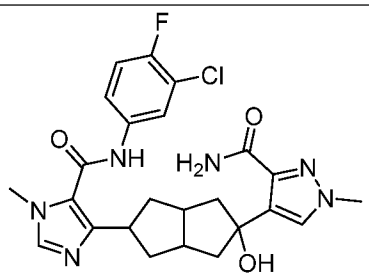
214	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(tetrahydro-2H-pyran-3-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.8 Hz, 1H), 7.85 (d, J = 0.8 Hz, 1H),7.65 (s, 1H), 7.53-7.47 (m, 1H), 7.24 (t, J = 9.2 Hz, 1H), 4.34-4.26 (m, 1H), 4.04-3.97 (m, 1H), 3.88-3.81 (m, 1H), 3.76 (s, 3H), 3.75-3.68 (m, 1H), 3.59-3.49 (m, 1H), 3.37-3.32 (m, 1H), 2.63-2.50 (m, 2H), 2.38-2.29 (m, 2H), 2.28-2.20 (m, 2H), 2.19-2.07 (m, 2H), 1.96-1.84 (m, 4H), 1.82-1.68 (m, 2H) ppm. MS calcd for $C_{28}H_{30}ClF_4N_5O_3$: 595.2; Found: 595.9 $[M+1]^+$.
215	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(1-hydroxypropan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.21 (brs, 1H), 7.93 (dd, J = 6.4, 2.4 Hz, 1H), 7.70 (brs, 1H), 7.62 (brs, 1H), 7.57-7.52 (m, 1H), 7.38 (t, J = 8.8 Hz, 1H), 4.94-4.89 (m, 1H), 4.85 (brs, 1H), 4.05-3.87 (m, 3H), 3.65 (s, 3H), 3.25-3.13 (m, 1H), 2.45-2.36 (m, 2H), 2.15-2.00 (m, 4H), 1.90-1.75 (m, 4H), 1.05- 0.95 (m, 3H) ppm. MS calcd. for $C_{26}H_{28}ClF_4N_5O_3$: 569.2; Found: 570.2 $[M+1]^+$.

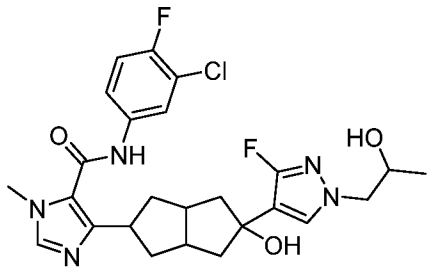
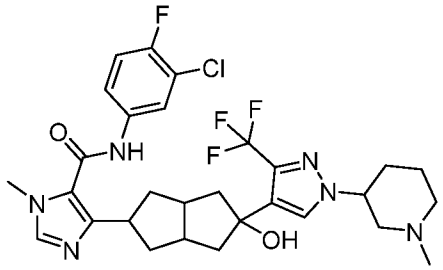
216	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(1-hydroxypropan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.20 (brs, 1H), 7.93 (dd, J = 6.8, 2.4 Hz, 1H), 7.70 (brs, 1H), 7.62 (s, 1H), 7.57-7.52 (m, 1H), 7.38 (t, J = 9.2 Hz, 1H), 4.92-4.88 (m, 1H), 4.84 (brs, 1H), 4.05-3.90 (m, 3H), 3.65 (s, 3H), 3.25-3.14 (m, 1H), 2.43-2.32 (m, 2H), 2.11-2.00 (m, 4H), 1.92-1.75 (m, 4H), 1.04-0.97(m, 3H) ppm. MS calcd. for $C_{26}H_{28}ClF_4N_5O_3$: 569.2; Found: 570 $[M+1]^+$.
217	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(tetrahydrofuran-3-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamideIsomer I** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.78 (dd, J = 6.8, 2.4 Hz, 1H), 7.61 (brs, 1H),7.55 (s, 1H), 7.43-7.37 (m, 1H), 7.17-7.09 (m, 1H), 4.95-4.85 (m, 1H), 4.05-3.95 (m, 1H), 3.93-3.88 (m, 2H), 3.87-3.75 (m, 1H), 3.66 (s, 3H), 3.28-3.22 (m, 1H), 2.52-2.42 (m, 2H), 2.40-2.30 (m, 1H), 2.26-2.10 (m, 5H), 1.88-1.72 (m, 4H) ppm. MS calcd for $C_{27}H_{28}ClF_4N_5O_3$: 581.2; Found: 582 $[M+1]^+$.

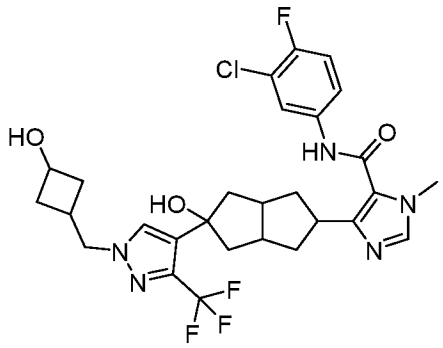
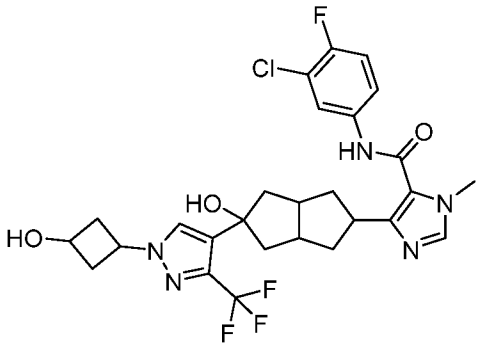
218	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(tetrahydrofuran-3-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.78 (dd, J = 6.8, 2.4 Hz, 1H), 7.61 (brs, 1H),7.55 (s, 1H), 7.43-7.38 (m, 1H), 7.14 (t, J = 8.8 Hz 1H), 4.94-4.87 (m, 1H), 4.03-3.95 (m, 1H), 3.93-3.88 (m, 2H), 3.83-3.75 (m, 1H), 3.66 (s, 3H), 3.27-3.22 (m, 1H), 2.52-2.42 (m, 2H), 2.40-2.30 (m, 1H), 2.28-2.10 (m, 5H), 1.88-1.75 (m, 4H) ppm. MS calcd for $C_{27}H_{28}ClF_4N_5O_3$: 581.2; Found: 582 $[M+1]^+$.
219	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-hydroxy-3-methoxypropyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.79-7.77 (dd, J = 6.8, 2.4 Hz, 1H), 7.56 (s, 1H), 7.48 (s, 1H), 7.42-7.38 (m, 1H), 7.14 (t, J = 9.2 Hz, 1H), 4.24-4.22 (m, 1H), 4.16-4.08 (m, 2H), 3.66 (s, 3H), 3.30-3.25 (m, 6H), 2.47-2.46 (m, 2H), 2.31-2.26 (m, 2H), 2.16-2.14 (m, 2H), 1.87-1.76 (m, 4H) ppm. MS calcd. for $C_{27}H_{30}ClF_4N_5O_4$: 599.2; Found:601.8 $[M+1]^+$.

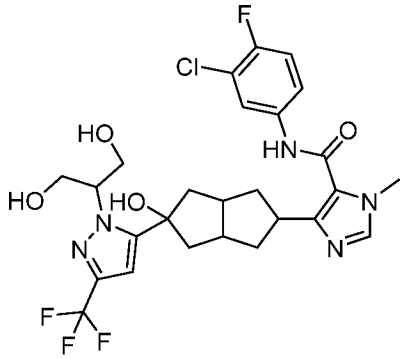
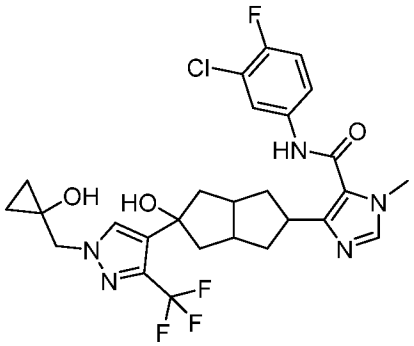
220	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(2,3-dihydroxypropyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamideIsomer I** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.93 (dd, J = 6.8, 4.4 Hz, 1H), 7.63 (s, 1H), 7.56-7.52 (m, 1H), 7.38 (t, J = 9.2 Hz, 1H), 6.53 (s, 1H), 5.48 (s, 1H), 4.97 (d, J = 5.2 Hz, 1H), 4.72 (t, J = 5.6 Hz, 1H), 4.47-4.41 (m, 1H), 4.25-4.21 (m, 1H), 4.02 (brs, 1H), 3.65 (s, 3H), 3.41-3.37 (m, 2H), 3.25-3.21 (m, 1H), 2.47-2.40 (m, 2H), 2.30-2.25 (m, 2H), 2.09-2.04 (m, 2H), 1.91-1.78 (m, 4H) ppm. MS calcd. for $C_{26}H_{28}ClF_4N_5O_4$: 585.2; Found: 586 $[M+1]^+$.
221	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(2,3-dihydroxypropyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamideIsomer II** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.93 (dd, J = 6.8, 4.4 Hz, 1H), 7.63 (s, 1H), 7.56-7.52 (m, 1H), 7.38 (t, J = 9.2 Hz, 1H), 6.53 (s, 1H), 5.48 (s, 1H), 4.96 (d, J = 5.2 Hz, 1H), 4.72 (t, J = 5.6 Hz, 1H), 4.47-4.41 (m, 1H), 4.27-4.21 (m, 1H), 4.03 (brs, 1H), 3.65 (s, 3H), 3.41-3.37 (m, 2H),

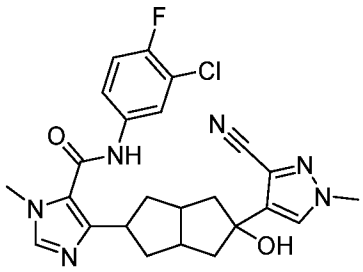
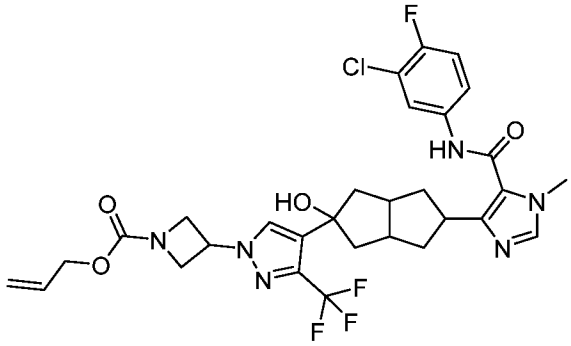
	3.24-3.20 (m, 1H), 2.51-2.47 (m, 2H), 2.32-2.25 (m, 2H), 2.09-2.04 (m, 2H), 1.91-1.75 (m, 4H) ppm. MS calcd. for $C_{26}H_{28}ClF_4N_5O_4$: 585.2; Found: 586 $[M+1]^+$.
222	 **4-(5-(3-(Difluoromethyl)-1-ethyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3,4-difluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.78 – 7.71 (m, 1H), 7.65 (s, 1H), 7.33 – 7.17 (m, 2H), 6.63 (t, J = 54.8 Hz, 1H), 6.33 (s, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.75 (s, 3H), 3.37 – 3.31 (m, 1H), 2.64 – 2.51 (m, 2H), 2.44 – 2.32 (m, 2H), 2.28 – 2.17 (m, 2H), 2.04 – 1.83 (m, 4H), 1.42 (t, J = 6.8 Hz, 3H) ppm. MS calcd. for $C_{25}H_{27}F_4N_5O_2$: 505. Found: 506 $[M+1]^+$.
223	 **4-(5-(1-((3-Carbamoyl-1-hydroxycyclobutyl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 7.59-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 7.24 (s, 1H), 6.80 (s, 1H), 5.38 (s, 1H), 4.88 (s, 1H), 4.18 (s, 2H), 3.67 (s, 3H), 3.23-3.20 (m, 1H), 2.97-2.92 (m, 1H), 2.54-2.50 (m, 2H), 2.33-2.28 (m, 2H), 2.10-1.99 (m, 6H), 1.92-1.81 (m, 4H) ppm. MS calcd. for $C_{29}H_{31}ClF_4N_6O_4$: 638.2; Found: 620.9 $[M-18+1]^+$.

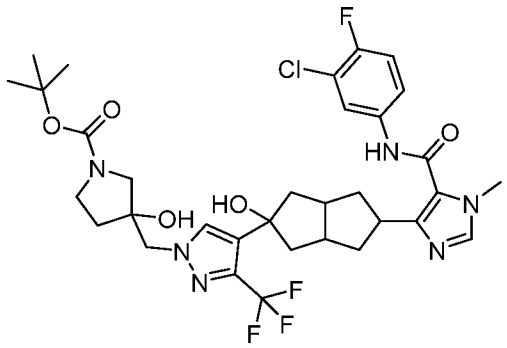
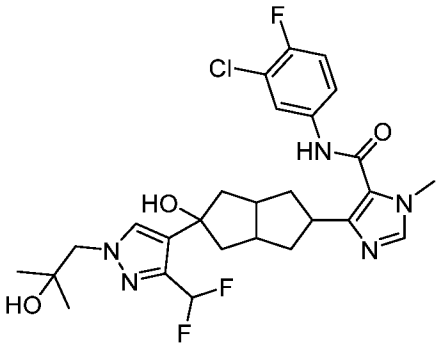
224	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.93 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.63 (s, 1H), 7.61 (s, 1H), 7.56-7.52 (m, 1H), 7.38 (t, J = 9.4 Hz, 1H), 7.10 (t, J = 54.4 Hz, 1H), 5.00 (s, 1H), 4.88 (t, J = 5.2 Hz, 1H), 4.07 (t, J = 5.2 Hz, 2H), 3.71-3.65 (m, 5H), 3.23-3.17 (m, 1H), 2.51-2.47 (m, 2H), 2.08-1.99 (m, 4H), 1.89-1.75 (m, 4H) ppm. MS calcd. for $C_{25}H_{27}ClF_3N_5O_3$: 537.2; Found: 538 $[M+1]^+$.
225	 **4-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-pyrazole-3-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.92 (dd, J = 6.8 Hz, 2.8 Hz, 1H), 7.79 (s, 1H), 7.64-7.52 (m, 4H), 7.38(t, J = 9.0 Hz, 1H), 6.61 (s, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 3.23-3.17 (m, 1H), 2.39 (s, 2H), 2.07-1.99 (m, 4H), 1.84-1.70 (m, 4H) ppm. MS calcd. for $C_{24}H_{26}ClFN_6O_3$: 500.2; Found: 501 $[M+1]^+$.

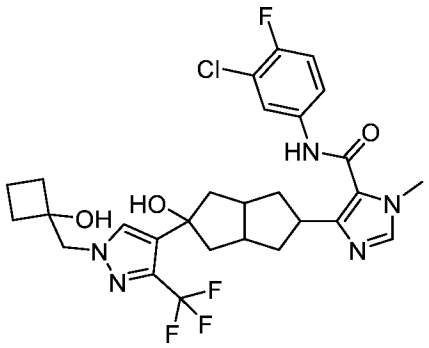
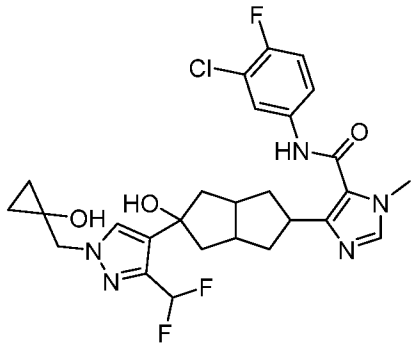
226	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-fluoro-1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.70 (s, 1H), 7.52 – 7.46 (m, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.07 – 3.98 (m, 1H), 3.91 – 3.79 (m, 2H), 3.76 (s, 3H), 3.34 – 3.25 (m, 1H), 2.59 – 2.48 (m, 2H), 2.37 – 2.29 (m, 2H), 2.27 – 2.18 (m, 2H), 1.90 – 1.80 (m, 4H), 1.12 (d, J = 6.4 Hz, 3H) ppm. MS calcd. for $C_{25}H_{28}ClF_2N_5O_3$: 519.2; Found: 502.1 $[M-18+1]^+$.
227	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(1-methylpiperidin-3-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.85 (dd, J = 6.8, 2.8 Hz, 1H), 7.74 (s, 1H), 7.65 (s, 1H), 7.52-7.48 (m, 1H), 7.23 (t, J = 8.8 Hz, 1H), 4.21 (dd, J = 13.6, 6.0 Hz, 1H), 3.75 (s, 3H), 3.36-3.34 (m, 1H), 3.06-3.04 (m, 1H), 2.77-2.74 (m, 1H), 2.55 (s, 2H), 2.35-2.20 (m, 8H), 1.93-1.83 (m, 5H), 1.76-1.50 (m, 4H) ppm. MS calcd. for $C_{29}H_{33}ClF_4N_6O_2$: 608.2; Found: 305.1 $[M/2+1]^+$.

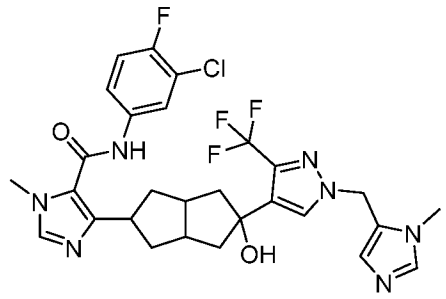
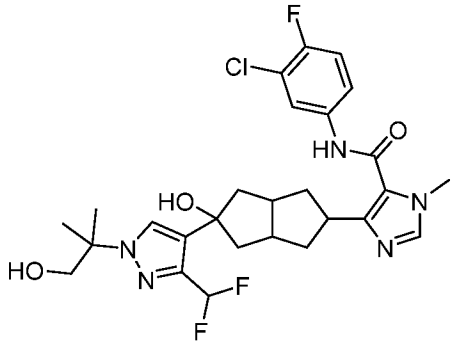
228	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxycyclobutyl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.86 (dd, J = 6.8, 2.8Hz, 1H), 7.66 (d, J = 0.8 Hz, 1H),7.64 (s, 1H), 7.52-7.46 (m, 1H), 7.23 (t, J = 10.0 Hz, 1H), 4.17-4.09 (m, 2H), 4.08-3.99 (m, 1H), 3.75 (s, 3H), 3.37-3.31 (m, 1H), 2.62-2.48 (m, 2H), 2.40-2.18 (m, 7H), 1.98-2.18 (m, 4H), 1.70-1.58 (m, 2H) ppm. MS calcd. for $C_{28}H_{30}ClF_4N_5O_3$: 595.2; Found: 596 $[M+1]^+$.
229	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(3-hydroxycyclobutyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.93 (dd, J = 6.8, 2.4 Hz, 1H), 7.84 (s, 1H), 7.62 (s, 1H), 7.57-7.52 (m, 1H), 7.38 (t, J = 9.0 Hz, 1H), 5.21 (d, J = 5.2 Hz, 1H), 4.96-4.87 (m, 1H), 4.83 (s, 1H), 4.42-4.33 (m, 1H), 3.64 (s, 3H), 3.25-3.13 (m, 1H), 2.61-2.52 (m, 2 H), 2.45-2.39 (m, 2H), 2.33-2.25 (m, 2H), 2.11-2.00 (m, 4H), 1.90-1.75 (m, 4H) ppm. MS calcd. for $C_{27}H_{28}ClF_4N_5O_3$: 581.2; Found: 582 $[M+1]^+$.

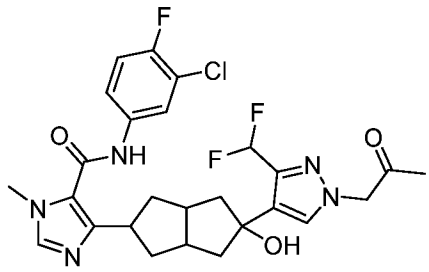
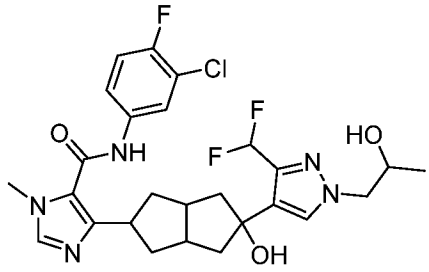
230	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(1,3-dihydroxypropan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.52 – 7.45 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 6.47 (s, 1H), 5.20 – 5.11 (m, 1H), 3.96 – 3.87 (m, 4H), 3.76 (s, 3H), 3.38 – 3.32 (m, 1H), 2.63 – 2.48 (m, 4H), 2.31 – 2.20 (m, 2H), 2.05 – 1.96 (m, 2H), 1.94 – 1.82 (m, 2H) ppm. MS calcd. for $C_{26}H_{28}ClF_4N_5O_4$: 585.2; Found: 586 $[M+1]^+$.
231	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1-hydroxycyclopropyl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4,): δ 7.86 (dd, J = 6.8, 2.8 Hz, 1H), 7.32 (d, J = 1.2 Hz, 1H), 7.65 (s, 1H), 7.51-7.47 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.18 (s, 2H), 3.75 (s, 3H), 3.32-3.29 (m, 1H), 2.61-2.52 (m, 2H), 2.40-2.20 (m, 4H), 1.97-1.87 (m, 4H), 0.78-0.72 (m, 4H) ppm. MS calcd. for $C_{27}H_{28}ClF_4N_5O_3$: 581.2; Found: 564 $[M-18+1]^+$.

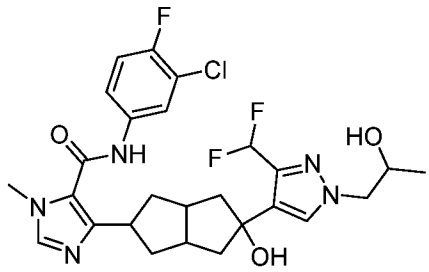
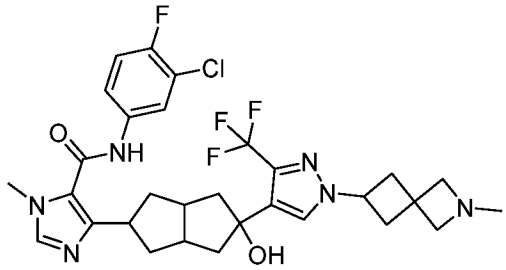
232	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-cyano-1-methyl-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H),7.93 (dd, J = 6.8, 2.4 Hz, 1H), 7.82 (s, 1H), 7.62 (s, 1H), 7.56-7.52 (m, 1 H), 7.38 (t, J = 9.2 Hz, 1H), 5.17 (s, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 3.20-3.17 (m, 1H), 2.49-2.46 (m, 2H), 2.09-2.02 (m, 4H), 1.89-1.78(m, 4H) ppm. MS calcd. for $C_{24}H_{24}ClFN_6O_2$: 482.2; Found: 483 $[M+1]^+$.
233	 **Allyl 3-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)azetidine-1-carboxylate** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 8.03 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.60-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 5.97-5.86 (m, 1H), 5.34-5.23 (m, 2H), 5.22-5.17 (m, 1H), 4.93 (s, 1H), 4.55-4.51 (m, 2H), 4.45-4.30 (m, 2H), 4.25-4.13 (m, 2H), 3.68 (s, 3H), 3.28-3.19 (m, 1H), 2.48-2.42 (m, 2 H), 2.15-2.04 (m, 4H), 1.92-1.79 (m, 4H) ppm. MS calcd. for $C_{30}H_{31}ClF_4N_6O_4$: 650.2; Found: 650.9 $[M+1]^+$.

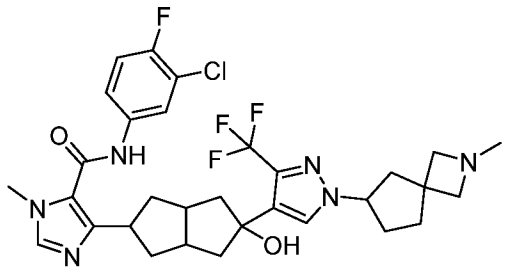
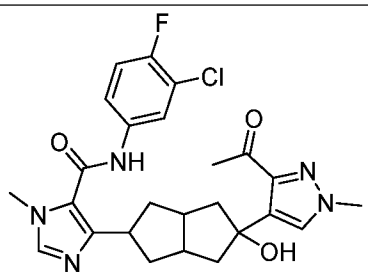
234	 **tert-Butyl 3-((4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)-3-hydroxypyrrolidine-1-carboxylate. Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.85-7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.68 (s, 1H), 7.64 (s, 1H),7.48-7.51(m, 1H), 7.22 (t, J = 8.8 Hz, 1H), 4.25(d, J = 8.8 Hz, 2H), 2.55-2.61 (m, 2H), 2.30-2.36 (m, 2H), 2.19-2.29 (m, 2H), 1.80-2.04 (m, 6H), 1.41 (d, J = 9.2 Hz, 9H) ppm. MS calcd. for $C_{33}H_{39}ClF_4N_6O_5$: 710.3; Found: 711 $[M+1]^+$.
235	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.4, 2.4 Hz, 1H), 7.66 (s, 1H), 7.58 (s, 1H), 7.53 – 7.46 (m, 1H), 7.23 (t, J = 8.8 Hz, 1H), 7.04 (t, J = 54.4 Hz, 1H), 4.04 (s, 2H), 3.76 (s, 3H), 3.38 – 3.32 (m, 1H), 2.66 – 2.51 (m, 2H), 2.31 – 2.18 (m, 4H), 1.96 – 1.83 (m, 4H) ppm. MS calcd. for $C_{27}H_{31}ClF_3N_5O_3$: 565.2; Found: 566.2 $[M+1]^+$.

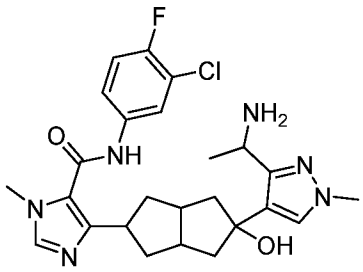
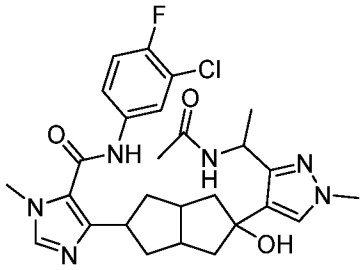
236	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1-hydroxycyclobutyl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 7.2, 2.8 Hz, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 5.40 (s, 1H), 4.90 (s, 1H), 4.15 (s, 2H), 3.67 (s, 3H), 3.34-3.21 (m, 1H), 3.23-3.19 (m, 1H), 2.51-2.49 (m, 2H), 2.08-2.03 (m, 5H), 1.93-1.80 (m, 6H), 1.62-1.59 (m, 1H), 1.50-1.47 (m, 1H) ppm. MS calcd. for $C_{28}H_{30}ClF_4N_5O_3$: 595.2; Found: 578 $[M-18+1]^+$.
237	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1-((1-hydroxycyclopropyl)methyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.59-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 7.13 (t, J = 54.4 Hz, 1H), 5.54 (s, 1H), 5.04 (s, 1H), 4.12 (s, 2H), 3.68 (s, 3H), 3.24-3.20 (m, 1H), 2.54-2.50 (m, 2H), 2.08-2.06 (m, 4H), 1.93-1.80 (m, 4H) ppm. MS calcd. for $C_{27}H_{29}ClF_3N_5O_3$: 563.2; Found: 546.2 $[M-18+1]^+$.

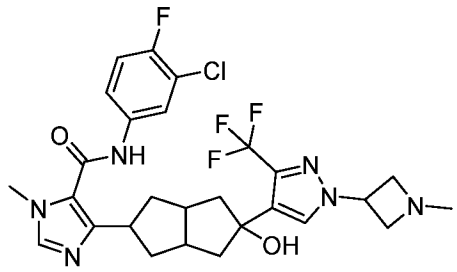
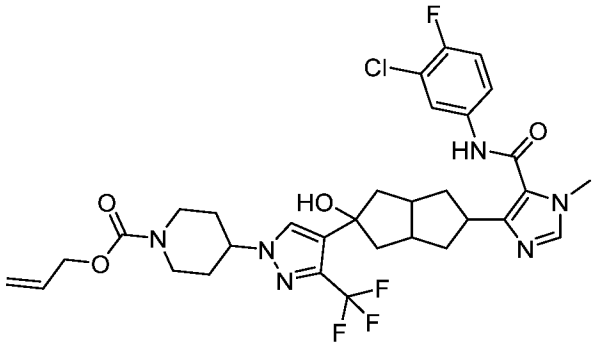
238	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1-methyl-1H-imidazol-5-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.88-7.86 (dd, J = 6.8, 2.4 Hz, 1H), 7.68 (s, 1H), 7.64-7.62 (m, 2H), 7.52-7.48 (m, 1H), 7.14 (t, J = 8.8 Hz, 1H), 7.06 (s, 1H), 5.38 (s, 2H), 3.75 (s, 3H), 3.66 (s, 3H), 3.31-3.28 (m, 1H), 2.55-2.54 (m, 2H), 2.32-2.21 (m, 4H), 1.93-1.88 (m, 4H) ppm. MS calcd. for $C_{28}H_{28}ClF_4N_7O_2$: 605.2; Found: 606 $[M+1]^+$.
239	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.63 (s, 1H), 7.53 – 7.46 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 6.99 (t, J = 54.4 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 2H), 3.37 – 3.31 (m, 1H), 2.64 – 2.55 (m, 2H), 2.35 – 2.18 (m, 4H), 1.96 – 1.84 (m, 4H), 1.52 (s, 6H) ppm. MS calcd. for $C_{27}H_{31}ClF_3N_5O_3$: 565.2; Found: 548.0 $[M-18+1]^+$.

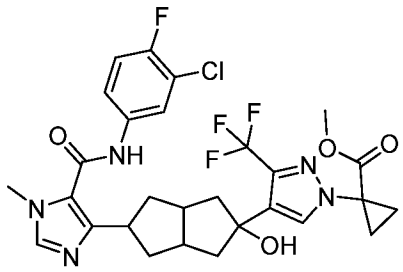
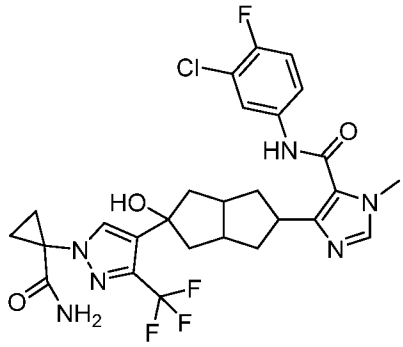
240	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1-(2-oxopropyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4,): δ 7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.52-7.48 (m,1H), 7.25 (t, J = 8.8 Hz, 1H), 7.18 (t, J = 54.4 Hz, 1H), 5.03 (s, 1H), 3.76 (s, 3H), 3.34-3.31 (m, 1H), 3.30-3.29 (m, 3H), 2.58 (s, 2H), 2.30-2.20 (m, 4H), 2.14 (s, 3H), 1.93-1.84 (m, 4H) ppm. MS calcd. for $C_{26}H_{27}ClF_3N_5O_3$: 549.2; Found: 532 $[M-18+1]^+$.
241	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.97 (dd, J = 6.8, 2.4 Hz, 1H), 7.64 (s, 1H), 7.60 (s,1H), 7.58-7.54 (m, 1H), 7.42 (t, J = 9.2 Hz, 1H), 7.26 (t, J = 57.2 Hz, 1H), 5.03 (s, 1H), 4.92-4.91 (m, 1H), 3.95 (s, 3H), 3.67 (s, 3H), 3.26-3.20 (m, 1H), 2.51-2.47 (m, 2H),2.10-2.02 (m, 4H), 1.90-1.77 (m, 4H), 1.02 (t, J = 2.8 Hz 3H) ppm. MS calcd. for $C_{26}H_{29}ClF_3N_5O_3$: 551.2; Found: 534 $[M-18+1]^+$.

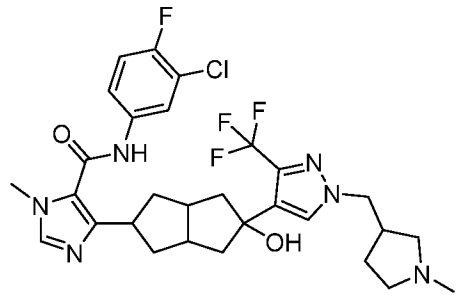
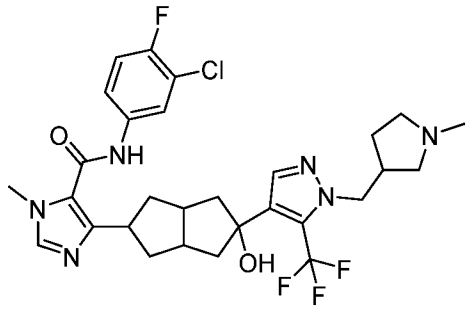
242	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.97 (dd, J = 6.8, 2.4 Hz, 1H), 7.64 (s, 1H), 7.60 (s,1H), 7.58-7.54 (m, 1H), 7.42 (t, J = 9.2 Hz, 1H), 7.26 (t, J = 57.2 Hz, 1H), 5.03 (s, 2H), 3.95 (s, 3H), 3.67 (s, 3H), 3.25-3.22 (m, 1H), 2.51-2.47 (m, 2H),2.10-2.02 (m, 4H), 1.90-1.78 (m, 4H), 1.02 (t, J = 2.8 Hz, 3H) ppm. MS calcd. for $C_{26}H_{29}ClF_3N_5O_3$: 551.2; Found: 534 [M-18+1]$^+$.
243	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-methyl-2-azaspiro[3.3]heptan-6-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.4, 2.4 Hz, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 7.52-7.48 (m, 1H), 7.24 (t, J = 9.2 Hz, 1H), 4.72-4.68 (m, 1H), 3.76 (s, 3H), 3.44 (s, 2H), 3.37 (s, 2H), 3.34-3.30 (m, 1H), 2.66-2.62 (m, 4H), 2.55 (brs, 2H), 2.35 (s, 3H), 2.35-2.20 (m, 4H), 1.91-1.85 (m, 4H) ppm. MS calcd. for $C_{30}H_{33}ClF_4N_6O_2$: 620.2; Found: 311[M/2+H]$^+$.

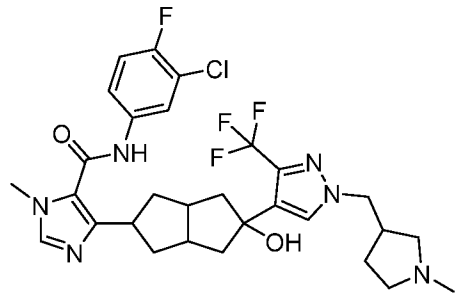
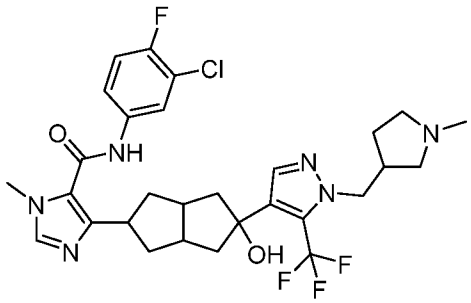
244	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-methyl-2-azaspiro[3.3]heptan-6-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.25 (s, 1H), 7.95 (dd, J = 6.4, 2.4 Hz, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.57-7.56 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 4.86 (s, 1H), 4.66 (t, J = 7.6 Hz, 1H), 3.67 (s, 3H), 3.26-3.20 (m, 1H), 3.07-3.01 (m, 4H), 2.50-2.40 (m, 2H), 2.29-2.24 (m, 1H), 2.18 (m, 3H), 2.12-2.05 (m, 6H), 1.99-1.94 (m, 1H), 1.86-1.77 (m, 6H) ppm. MS calcd. for $C_{31}H_{35}ClF_4N_6O_2$: 634.2; Found: 318 $[M/2+H]^+$.
245	 **4-(5-(3-Acetyl-1-methyl-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.22 (s, 1H), 7.93 (dd, J = 6.8, 2.4 Hz, 1H), 7.72 (s, 1H),7.62 (s, 1H), 7.56-7.52 (m, 1H), 7.38 (t, 9.2 Hz, 1H), 5.30 (s, 1H), 3.85 (s, 3H), 3.64 (s, 3H), 3.29-3.17 (m, 1H), 2.51 (s, 3H), 2.48-2.41 (m, 2H), 2.10-2.03 (m, 4H), 1.84-1.71 (m, 2H), 1.70-1.67 (m, 2H) ppm; MS calcd. for $C_{25}H_{27}ClFN_5O_3$: 499.2; Found: 500 $[M+1]^+$.

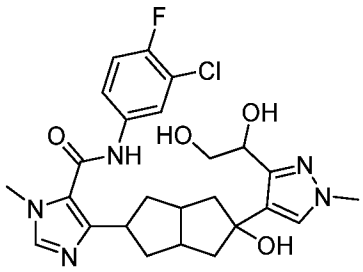
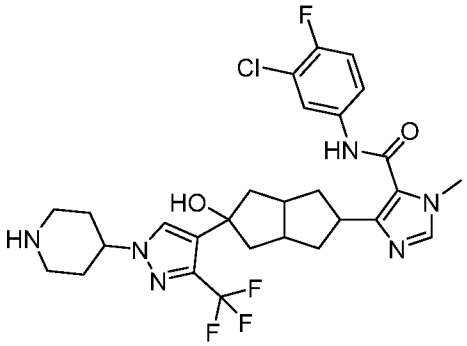
246	 **4-(5-(3-(1-Aminoethyl)-1-methyl-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H -NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H),7.93 (dd, J = 6.8, 2.4 Hz, 1H), 7.62 (s, 1H), 7.56-7.52 (m, 1 H), 7.40-7.35 (m, 2H), 4.05-4.03 (m, 1H), 3.65 (s, 6H), 3.22-3.16 (m, 1H), 2.34-2.28 (m, 2H), 2.11-1.95 (m, 4H), 1.83-1.70(m, 4H), 1.34 (d, 6.4 Hz, 3H) ppm; MS calcd. for $C_{25}H_{30}ClFN_6O_2$: 500.2; Found: 501 $[M+1]^+$.
247	 **4-(5-(3-(1-Acetamidoethyl)-1-methyl-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.96 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 5.24-5.19 (m, 1H), 4.96 (s, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.33-3.19 (m, 1H), 2.41-2.36 (m, 2H), 2.10-2.03 (m, 4H), 1.88-1.74 (m, 7H), 1.31 (d, J = 6.8 Hz, 3H) ppm. MS calcd. for $C_{27}H_{32}ClFN_6O_3$: 542.2; Found: 525 $[M+1]^+$.

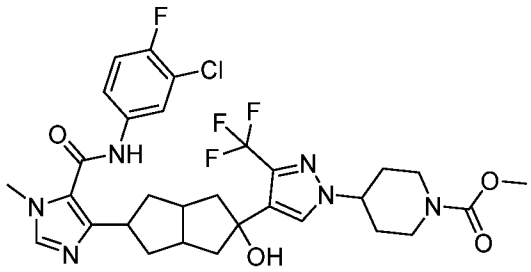
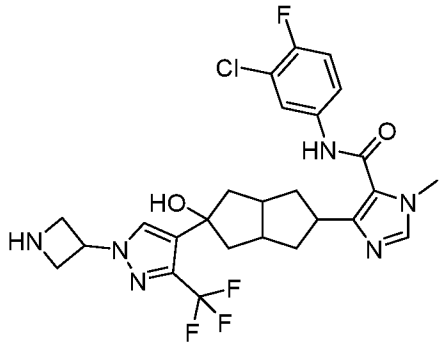
248	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(1-methylazetidin-3-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.98-7.93 (m, 2H), 7.65 (s, 1H), 7.60-7.55 (m, 1H), 7.41 (t, J = 9.0 Hz, 1H), 4.97-4.90 (m, 1H), 4.90 (s, 1H), 3.70-3.61 (m, 5H), 3.34-3.30 (m, 2H), 3.28-3.18 (m, 1H), 2.48-2.42 (m, 2H), 2.30 (s, 3H), 2.15-2.03 (m, 4H), 1.93-1.79 (m, 4H) ppm. MS calcd. for $C_{27}H_{29}ClF_4N_6O_2$: 580.2; Found: 581 $[M+1]^+$.
249	 **Allyl 4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.8 Hz, 1H), 7.44 (d, J= 0.8 Hz, 1H),7.65 (s, 1H), 7.54-7.46 (m, 1H), 7.24 (t, J =9.2 Hz, 1H),6.02-5.90 (m, 1H), 5.35-5.26 (m, 1H), 5.24-5.17 (m, 1H), 4.62-4.50 (m, 2H), 4.42-4.32 (m, 1H), 4.30-4.18 (m, 2H), 3.76 (s, 3H), 3.38-3.32 (m, 1H), 3.14-2.85 (m, 2H), 2.62-2.48 (m, 2H), 2.38-2.18 (m, 4H), 2.10-2.00 (m, 2H), 1.98-1.80 (m, 6H) ppm. MS calcd. for $C_{32}H_{35}ClF_4N_6O_4$: 678.2; Found: 660.8 $[M-18+1]^+$.

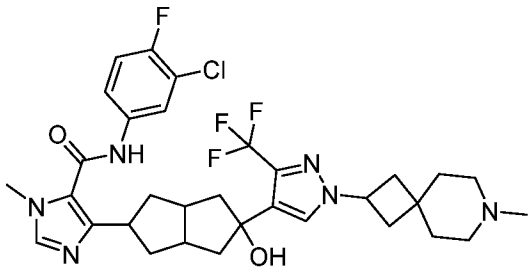
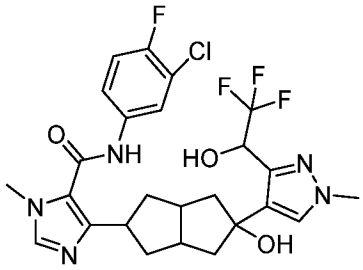
250	 **Methyl 1-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclopropane-1-carboxylate** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.88-7.84 (m, 2H), 7.65 (s, 1H), 7.53-7.49 (m, 1H), 7.26-7.21 (t, J = 8.8 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 3.34-3.30 (m, 1H), 2.60-2.58 (m, 2H), 2.35-2.21 (m, 4H), 1.95-1.88 (m, 4H), 1.82-1.78 (m, 2H), 1.68-1.64 (m, 2H) ppm. MS calcd. for $C_{28}H_{28}ClF_4N_5O_4$: 609.2; Found: 610.8 $[M+1]^+$.
251	 **4-(5-(1-(1-Carbamoylcyclopropyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.90-7.86 (m, 2H), 7.65 (s, 1H), 7.52-7.48 (m, 1H), 7.26-7.21 (t, J = 8.8 Hz, 1H), 3.76 (s, 3H), 3.31-3.30 (m, 1H), 2.59-2.58 (m, 2H), 2.38-2.32 (m, 2H), 2.26-2.22 (m, 2H), 1.96-1.88 (m, 4H), 1.75-1.72 (m, 2H), 1.54-1.28 (m, 2H) ppm. MS calcd. for $C_{27}H_{27}ClF_4N_6O_3$: 594.2; Found: 594.9 $[M+1]^+$.

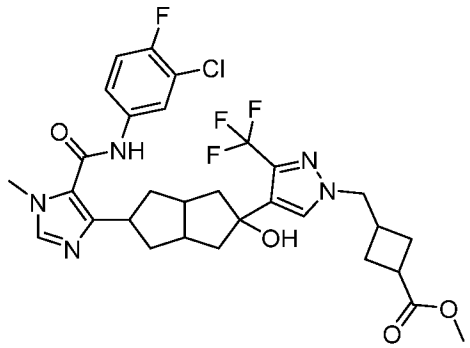
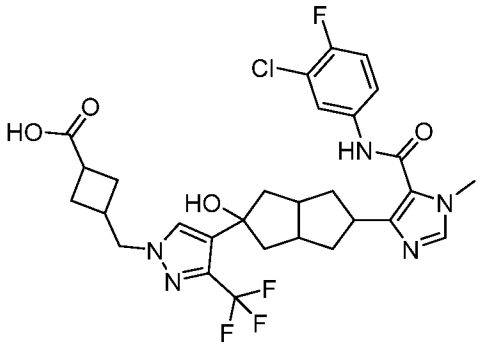
252	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1-methylpyrrolidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.83 (s, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.43 (t, J = 9.2 Hz, 1H), 4.88 (s, 1H), 4.04 (d, J = 6.8 Hz, 2H), 3.67 (s, 3H), 3.31-3.20 (m,2H), 2.65-2.55 (m, 1H), 2.47-2.45 (m, 2H), 2.39-2.32 (m, 2H), 2.24-2.22 (m, 1H), 2.20 (s, 3H), 2.11-2.07 (m, 4H), 1.90-1.77 (m, 5H), 1.43-1.42 (m, 1H) ppm. MS calcd. for $C_{29}H_{33}ClF_4N_6O_2$: 608.2; Found: 305.1 $[M/2+H]^+$.
253	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1-methylpyrrolidin-3-yl)methyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 2H), 7.42 (t, J = 9.2 Hz, 1H), 5.00 (s, 1H), 4.16 (dd, J = 12.8, 5.2 Hz, 2H), 3.67 (s, 3H), 3.27-3.16 (m, 1H), 2.66-2.63 (m, 1H), 2.55-2.53 (m, 1H), 2.43 (s, 2H), 2.35-2.27 (m, 3H), 2.20-2.11 (m, 5H), 2.09-2.04 (m, 2H), 1.89-1.78 (m, 5H), 1.47-1.42 (m, 1H) ppm. MS calcd. for $C_{29}H_{33}ClF_4N_6O_2$: 608.2; Found: 305 $[M/2+H]^+$.

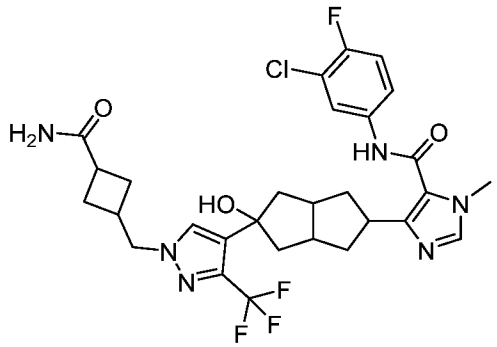
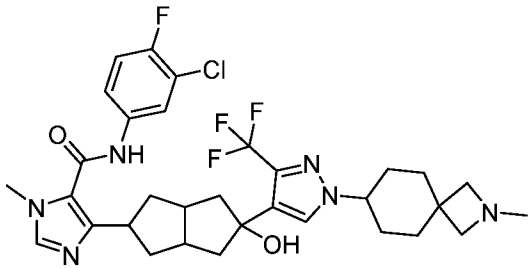
254	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1-methylpyrrolidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.84 (s, 1H), 7.65 (s, 1H), 7.59-7.52 (m, 1H), 7.43 (t, J = 9.2 Hz, 1H), 4.88 (s, 1H), 4.04 (d, J = 6.0 Hz, 2H), 3.67 (s, 3H), 3.23-3.20 (m, 1H), 2.61-2.58 (m, 1H), 2.48-2.44 (m, 3H), 2.39-2.30 (m, 2H), 2.24-2.19 (m, 4H), 2.12-2.07 (m, 4H), 1.90-1.79 (m, 5H), 1.45-1.42 (m, 1H) ppm. MS calcd. for $C_{29}H_{33}ClF_4N_6O_2$: 608.2; Found: 305.1 [M/2+H].
255	 **N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((1-methylpyrrolidin-3-yl)methyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamideIsomer II** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.97 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 2H), 7.42 (t, J = 9.2 Hz, 1H), 4.99 (s, 1H), 4.15 (t, J = 6.0 Hz, 2H), 3.67 (s, 3H), 3.26-3.20 (m, 1H), 2.66-2.63 (m, 1H), 2.54-2.52 (m, 1H), 2.44 (s, 2H), 2.34-2.27 (m, 3H), 2.20-2.13 (m, 5H), 2.11-2.06 (m, 2H), 1.85-1.81 (m, 5H), 1.47-1.44 (m, 1H) ppm. MS calcd. for $C_{29}H_{33}ClF_4N_6O_2$: 608.2; Found: 305.1 $[M/2+H]^+$.

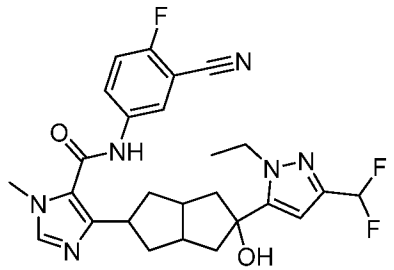
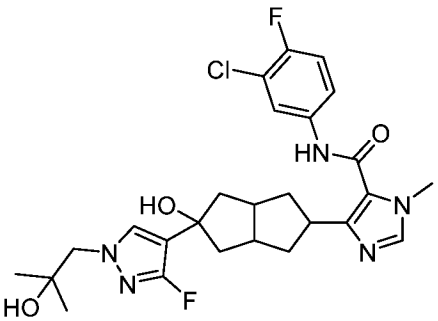
256	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(1,2-dihydroxyethyl)-1-methyl-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.65 (s, 1H), 7.59-7.55 (m, 1H), 7.44-7.39 (m, 2H), 5.33 (d, J = 4.8 Hz, 1H), 5.18 (s, 1H), 4.76-4.74 (m, 1H), 4.56 (t, J = 6.0 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.64-3.60 (m, 2H), 3.24-3.21 (m, 1H), 2.49-2.44 (m, 2H), 2.14-2.06 (m, 4H), 1.85-1.77 (m, 4H) ppm. MS calcd. for $C_{25}H_{29}ClFN_5O_4$: 517.2; Found: 500 $[M-18+1]^+$.
257	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(piperidin-4-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.72 (brs, 1H),7.65 (s, 1H), 7.55-7.47 (m, 1H), 7.23 (t, J =9.2 Hz, 1H), 4.33-4.22 (m, 1H), 3.76 (s, 3H), 3.38-3.32 (m, 1H), 3.20-3.10 (m, 2H), 2.80-2.67 (m, 2H), 2.39-2.15 (m, 4H), 2.10-2.00 (m, 2H), 1.99-1.80 (m, 6H) ppm. MS calcd. for $C_{28}H_{31}ClF_4N_6O_2$: 594.2; Found: 298.2 $[M/2+H]^+$.

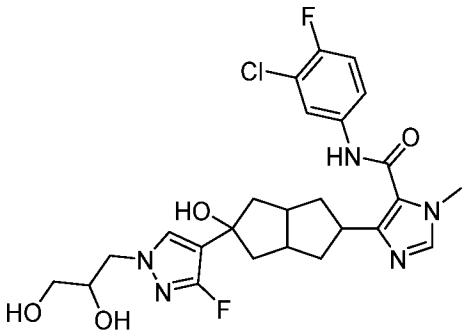
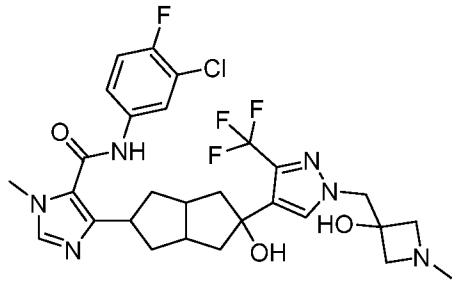
258	 **Methyl 4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.8 Hz, 1H), 7.74 (brs, 1H),7.65 (s, 1H), 7.53-7.47 (m, 1H), 7.24 (t, J = 8.8 Hz, 1H), 4.28-4.15 (m, 2H), 3.76 (s, 3H), 3.70 (s, 3H), 3.08-2.90 (m, 2H), 2.62-2.50 (m, 2H), 2.40-2.18 (m, 4H), 2.10-2.00 (m, 2H), 1.98-1.82 (m, 6H) ppm. MS calcd. for $C_{30}H_{33}ClF_4N_6O_4$: 652.2; Found: 653.2 $[M+1]^+$.
259	 **4-(5-(1-(Azetidin-3-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.94 (s, 1H), 7.65 (s, 1H), 7.60-7.55 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 5.22-5.13 (m, 1H), 4.90 (s, 1H), 3.86 (t, J = 7.6 Hz, 2H), 3.72-3.65 (m, 5H), 3.35 (brs, 1H), 3.28-3.16 (m, 1H), 2.48-2.42 (m, 2H), 2.15-2.03 (m, 4H), 1.93-1.78 (m, 4H) ppm. MS calcd. for $C_{26}H_{27}ClF_4N_6O_2$: 566.2; Found: 566.8 $[M+1]^+$.

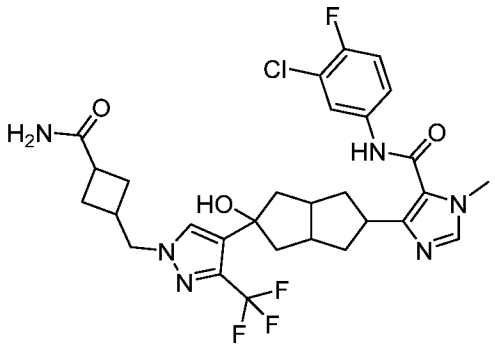
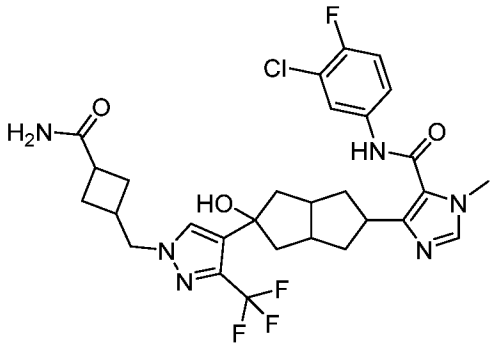
260	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(7-methyl-7-azaspiro[3.5]nonan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.26 (s, 1H), 7.97 – 7.95 (m, 1H), 7.87 (s, 1H), 7.64 (s, 1H), 7.59 – 7.50 (m, 1H), 7.39 (t, J = 9.2 Hz, 1H), 4.94 – 4.76 (m, 2H), 3.68 (s, 3H), 3.26 – 3.18 (m, 1H), 2.36 – 2.24 (m, 4H), 2.21 – 2.02 (m, 11H), 1.97 – 1.73 (m, 5H), 1.70 – 1.51 (m, 5H) ppm. MS calcd. for $C_{32}H_{37}ClF_4N_6O_2$: 648.3; Found: 649.2 $[M+1]^+$.
261	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(2,2,2-trifluoro-1-hydroxyethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.25 (S, 1H), 7.96 (dd, J = 6.8 Hz, 2.8 Hz, 1H), 7.66 (s, 1H), 7.60-7.54 (m,2H), 7.41 (t, J = 9.2 Hz, 1H), 6.53 (d, J = 7.6 Hz, 1H), 5.49-5.45 (m, 1H), 5.14 (s, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.34-3.22 (m, 1H), 2.44-2.39 (m, 2H), 2.12-2.07 (m, 4H), 1.88-1.75 (m, 4H) ppm. MS calcd. for $C_{25}H_{26}ClF_4N_5O_3$: 555.2; Found: 556.2 $[M+1]^+$.

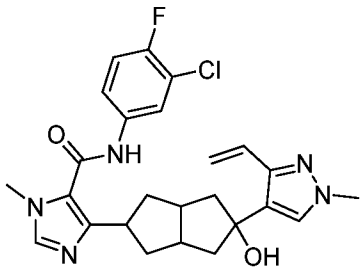
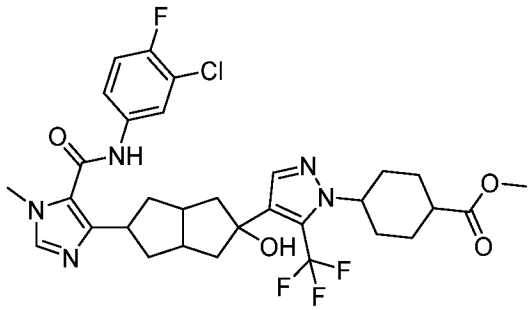
262	 **Methyl 3-((4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)cyclobutane-1-carboxylate. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.25 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.83 (s, 0.4H), 7.79 (s, 0.6H), 7.67 (s, 1H), 7.60-7.55 (m, 1H), 7.41 (t, J = 9.0 Hz, 1H), 4.89 (s, 0.4H), 4.88 (s, 0.5H), 4.20 (d, J = 7.6 Hz, 0.9H), 4.08 (d, J = 7.2 Hz, 1.2H), 3.68 (s, 3H), 3.59 (s, 1.2H), 3.57 (s, 1.8H), 3.28-3.12 (m, 1.5H), 3.08-2.98 (m, 0.6H), 2.75-2.60 (m, 1H), 2.47-2.40 (m, 2H), 2.26-2.14 (m, 2H), 2.14-2.04 (m, 4H), 2.03-1.92 (m, 2H), 1.92-1.77 (m, 4H) ppm. MS calcd. for $C_{30}H_{32}ClF_4N_5O_4$: 637.2; Found: 637.8 $[M+1]^+$.
263	 **3-((4-(5-(5-((3-Chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)cyclobutane-1-carboxylic acid. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.81 (s, 0.4H), 7.77 (s, 0.5H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 9.0 Hz, 1H), 4.89 (s, 0.4H), 4.88 (s, 0.5H), 4.17 (d, J = 7.6 Hz, 0.9H), 4.07 (d, J = 7.6 Hz, 1.2H), 3.67 (s, 3H), 3.28-3.16 (m, 2H), 3.03-2.93 (m, 0.5H),

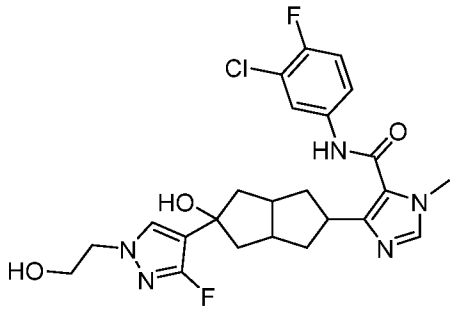
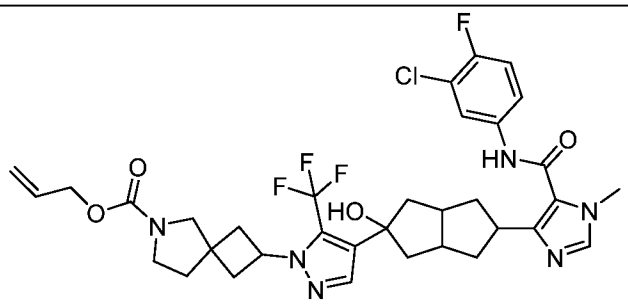
	2.88-2.78 (m, 0.6H), 2.66-2.54 (m, 1H), 2.47-2.40 (m, 2H), 2.21-2.03 (m, 6H), 1.96-1.77 (m, 6H) ppm. MS calcd. for $C_{29}H_{30}ClF_4N_5O_4$: 623.2; Found: 623.8 $[M+1]^+$.
264	 **4-(5-(1-((3-Carbamoylcyclobutyl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.81 (s, 0.4H), 7.77 (s, 0.5H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 7.16 (s, 1H), 6.73 (s, 1H), 4.89 (s, 0.4H), 4.88 (s, 0.5H), 4.16 (d, J = 7.6 Hz, 0.8H), 4.07 (d, J = 7.2 Hz, 1.1H), 3.67 (s, 3H), 3.28-3.16 (m, 1H), 3.02-2.92 (m, 0.4H), 2.87-2.76 (m, 0.6H), 2.70-2.55 (m, 1H), 2.47-2.40 (m, 2H), 2.19-2.00 (m, 6H), 1.93-1.77 (m, 6H) ppm. MS calcd. for $C_{29}H_{31}ClF_4N_6O_3$: 622.2; Found: 622.8 $[M+1]^+$.
265	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-methyl-2-azaspiro[3.5]nonan-7-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 8.40 (s, 1H), 7.91 (dd, J = 6.8, 2.4 Hz, 1H), 7.73 (s, 1H), 7.56-7.52 (m, 1H), 7.27 (t, J = 9.2 Hz, 1H), 4.24-4.14 (m, 2H), 4.03-4.00 (m, 1H), 3.91-3.81 (m, 2H), 3.87 (s, 3H), 3.38-3.31 (m, 2H), 2.95 (s, 3H), 2.69 (brs, 2H), 2.36-2.24 (m, 4H), 2.21-2.15 (m, 4H), 2.07-1.89

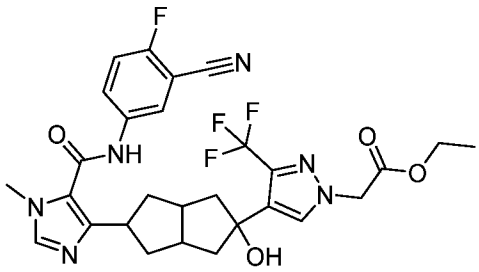
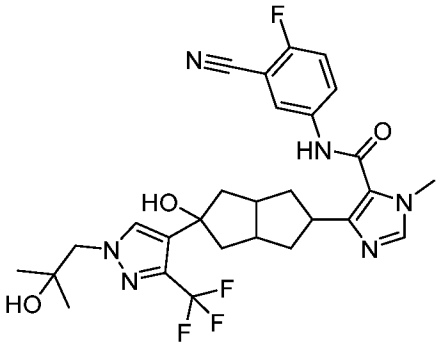
	(m, 4H), 1.81-1.74 (m, 3H) ppm. MS calcd. for $C_{32}H_{37}ClF_4N_6O_2$: 648.3; Found: 325.0 $[M/2+1]^+$.
266	 **N-(3-Cyano-4-fluorophenyl)-4-(5-(3-(difluoromethyl)-1-ethyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.78-7.74 (m, 1H), 7.69 (dd, J = 6.4, 2.4 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.26 (t, J = 9.2 Hz, 1H), 6.73 (t, J = 54.8 Hz, 1H), 6.44 (s, 1H), 4.68 (q, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.53-3.49 (m, 1H), 2.84-2.76 (m, 2H), 2.55-2.48 (m, 2H), 2.39-2.32 (m, 2H), 2.23-2.17 (m, 2H), 1.74-1.66 (m, 2H), 1.45 (t, J = 7.2 Hz, 3H) ppm. MS calcd. for $C_{26}H_{27}F_3N_6O_2$: 512.2; Found: 513 $[M+1]^+$.
267	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-fluoro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.53 – 7.47 (m, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.23 (t, J = 9.2 Hz, 1H), 3.86 (s, 2H), 3.76 (s, 3H), 3.34 – 3.25 (m, 1H), 2.60 – 2.49 (m, 2H), 2.40 – 2.30 (m, 2H), 2.28 – 2.17 (m, 2H), 1.91 – 1.80 (m, 4H), 1.14 (s, 6H) ppm. MS calcd. for $C_{26}H_{30}ClF_2N_5O_3$: 533.2; Found: 516.0 $[M-18+1]^+$.

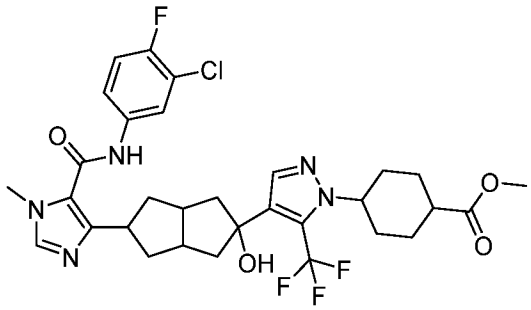
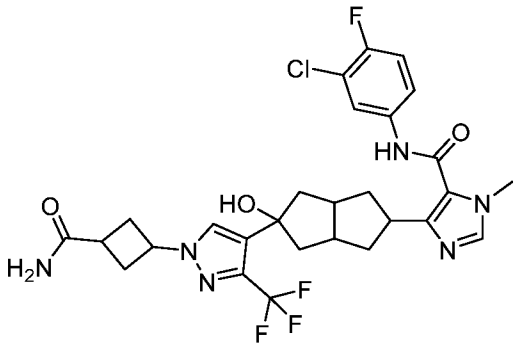
268	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(1-(2,3-dihydroxypropyl)-3-fluoro-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide. Mixture of diastereomers** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.53 – 7.47 (m, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.11 – 4.02 (m, 1H), 3.93 – 3.85 (m, 2H), 3.76 (s, 3H), 3.52 – 3.42 (m, 2H), 3.35 – 3.26 (m, 1H), 2.59 – 2.49 (m, 2H), 2.39 – 2.30 (m, 2H), 2.28 – 2.17 (m, 2H), 1.91 – 1.79 (m, 4H) ppm. MS calcd. for $C_{25}H_{28}ClF_2N_5O_4$: 535.2; Found: 518.0 $[M-18+1]^+$.
269	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-((3-hydroxy-1-methylazetidin-3-yl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4,): δ 7.86 (dd, J = 6.4, 2.4 Hz, 1H), 7.66-7.65 (m, 2H), 7.52-7.48 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.35 (s, 2H), 3.76 (s, 3H), 3.57 (d, J = 9.6 Hz, 2H), 2.98 (d, J = 9.2 Hz, 2H), 2.57-2.56 (m, 2H), 2.38 (s, 3H), 2.35-2.20 (m, 4H), 1.93-1.87 (m, 4H) ppm. MS calcd. for $C_{28}H_{31}ClF_4N_6O_3$: 610.2; Found: 306.1 $[M/2+1]^+$.

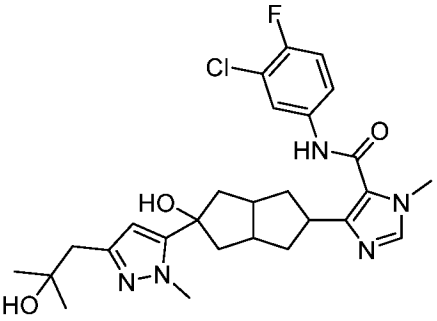
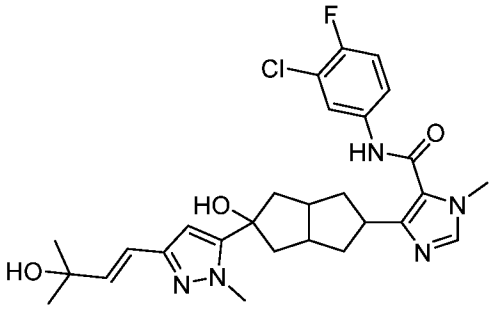
270	 **4-(5-(1-((3-Carbamoylcyclobutyl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d6,): δ 10.22 (s, 1H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.76 (s, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 7.14 (s, 1H), 6.71 (s, 1H), 4.86 (s, 1H), 4.07 (d, J = 7.2 Hz, 2H), 3.67 (s, 3H), 3.28-3.17 (m, 1H), 2.87-2.76 (m, 1H), 2.65-2.55 (m, 1H), 2.48-2.40 (m, 2H), 2.13-2.01 (m, 6H), 1.93-1.77 (m, 6H) ppm. MS calcd. for $C_{29}H_{31}ClF_4N_6O_3$: 622.2; Found: 604.9 $[M-18+1]^+$.
271	 **4-(5-(1-((3-Carbamoylcyclobutyl)methyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H -NMR (400 MHz, DMSO-d6): δ 10.22 (s, 1H), 7.96 (d, J = 4.8 Hz, 1H), 7.80 (s, 1H), 7.65 (s, 1H), 7.60-7.54 (m, 1H), 7.41 (t, J = 9.2 Hz, 1H), 7.15 (s, 1H), 6.73 (s, 1H), 4.88 (s, 1H), 4.16 (d, J = 7.2 Hz, 2H), 3.67 (s, 3H), 3.28-3.15 (m, 1H), 3.03-2.92 (m, 1H), 2.71-2.60 (m, 1H), 2.47-2.40 (m, 2H), 2.19-2.02 (m, 6H), 1.94-1.78 (m, 6H) ppm. MS calcd. for $C_{29}H_{31}ClF_4N_6O_3$: 622.2; Found: 622.9 $[M+1]^+$.

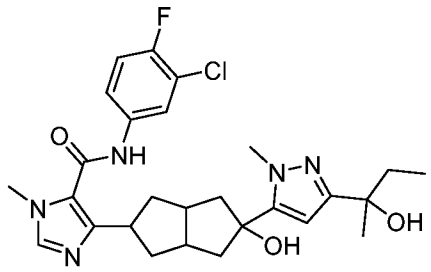
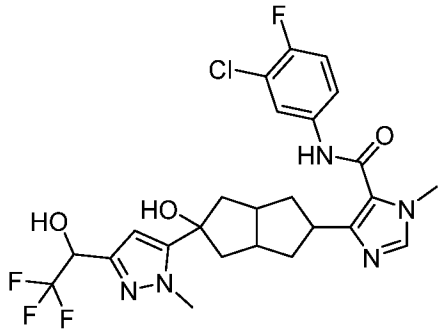
272	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-vinyl-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.66 (s, 1H), 7.59-7.55 (m, 1H), 7.48 (s, 1H), 7.41 (t, J = 9.2 Hz, 1H), 6.93-6.86 (m,1H), 5.73 (dd, J = 17.6 Hz, 2.8 Hz, 1H), 5.66 (dd, J 11.2 Hz, 2.4 Hz, 1H), 4.81 (s, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.24-3.21 (m, 1H), 2.38-2.37 (m, 2H), 2.13-2.04 (m, 4H), 1.84-1.72 (m, 4H) ppm. MS calcd. for $C_{25}H_{27}ClFN_5O_2$: 483.2; Found: 466 $[M-18+1]^+$.
273	 **Methyl 4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexane-1-carboxylate Isomer I** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.88 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.56 (s, 1H), 7.51-7.47 (m, 1H), 7.25 (t, J = 8.8 Hz, 1H), 4.30-4.26 (m, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.34-3.31 (m, 1H), 3.30-3.29 (m, 2H), 2.55-2.52 (m, 2H), 2.42-2.35 (m, 3H), 2.25-2.21 (m, 2H), 2.14-2.11 (m, 2H), 2.05-1.84 (m, 8H), 1.60-1.56 (m, 2H) ppm. MS calcd. for $C_{31}H_{34}ClF_4N_5O_4$: 651.2; Found: 634 $[M-18+1]^+$.

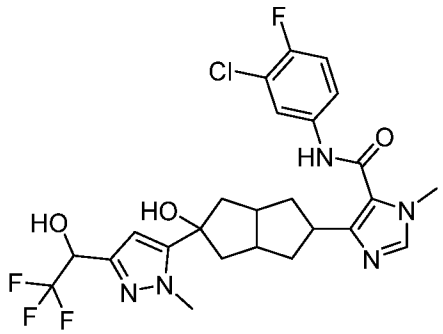
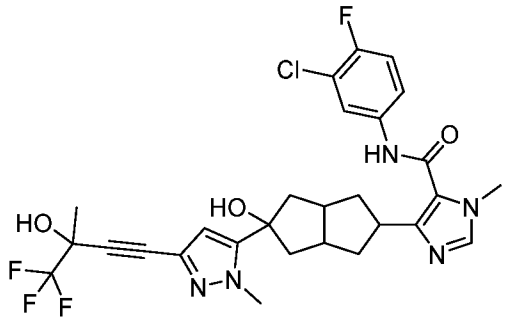
274	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-fluoro-1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.87 (dd, J = 6.8, 2.4 Hz, 1H), 7.64 (s, 1H), 7.52 – 7.47 (m, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.00 (t, J = 5.2 Hz, 2H), 3.80 (t, J = 5.2 Hz, 2H), 3.76 (s, 3H), 3.35 – 3.25 (m, 1H), 2.60 – 2.49 (m, 2H), 2.40 – 2.29 (m, 2H), 2.28 – 2.17 (m, 2H), 1.92 – 1.80 (m, 4H) ppm. MS calcd. for $C_{24}H_{26}ClF_2N_5O_3$: 505.2; Found: 488.0 [M-18+1]$^+$.
275	 **Allyl 2-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-6-azaspiro[3.4]octane-6-carboxylate** ^{1}H NMR (400 MHz, MeOH-d4): 7.88-7.86 (dd, J = 6.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.60 (s, 1H), 7.52-7.48 (m, 1H), 7.25-7.21 (t, J = 9.2 Hz, 1H), 5.98-5.91 (m, 1H), 5.34-5.28 (m, 1H), 5.21-5.18 (m, 1H), 5.02-4.98 (m, 1H), 4.56-4.55 (m, 2H), 3.76 (s, 3H), 3.52-3.30 (m, 5H), 2.72-2.67 (m, 2H), 2.55-2.44 (m, 4H), 2.40-2.35 (m, 2H), 2.28-2.21 (m, 2H), 2.09-2.02 (m, 2H), 1.99-1.83 (m, 4H) ppm. MS calcd. for $C_{34}H_{37}ClF_4N_6O_4$: 704.3; Found: 705.8 [M+1]$^+$.

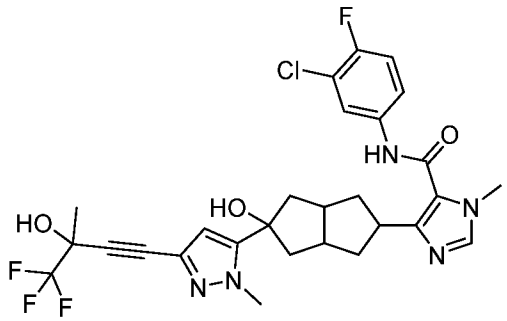
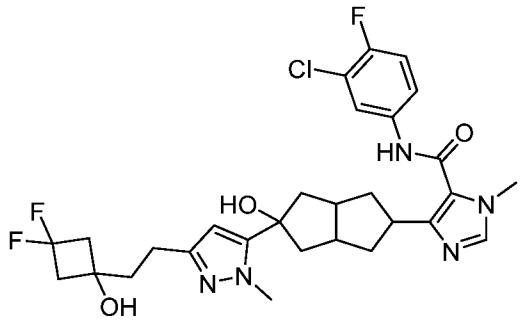
276	 **Ethyl 2-(4-(5-(5-((3-cyano-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetate** ^{1}H NMR (400 MHz, DMSO-d6,): δ 10.36 (s, 1H), 8.16-8.14 (m, 1H), 7.95-7.91 (m, 1H), 7.82 (s, 1H),7.67 (s, 1H), 7.53 (t, J = 9.2 Hz, 1H), 5.08(s, 2H), 4.97 (s, 1H), 4.18-4.13 (m, 2H),3.67 (s, 3H), 3.27-3.22 (m, 1H), 2.11-2.06(m, 4H), 1.85-1.81(m, 6H), 1.20 (t, J =7.2 Hz, 3H) ppm. MS calcd. for $C_{28}H_{28}F_4N_6O_4$: 588.2; Found: 571 $[M-18+1]^+$.
277	 **N-(3-Cyano-4-fluorophenyl)-4-(5-hydroxy-5-(1-(2-hydroxy-2-methylpropyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.36 (s, 1H), 8.16 (dd, J = 6.8, 2.4 Hz, 1H), 7.95-7.91 (m, 1H), 7.67 (s, 1H), 7.54 (t, J = 9.2 Hz, 1H), 4.90 (s, 1H), 4.73 (s, 1H), 4.00 (s, 2H), 3.68 (s, 3H), 3.27-3.21 (m, 1H), 2.46-2.42 (m, 2H), 2.13-2.07 (m, 4H), 1.92-1.81 (m, 4H), 1.05 (s, 6H) ppm. MS calcd. for $C_{28}H_{30}F_4N_6O_3$: 574.2; Found: 557 $[M-18+1]^+$.

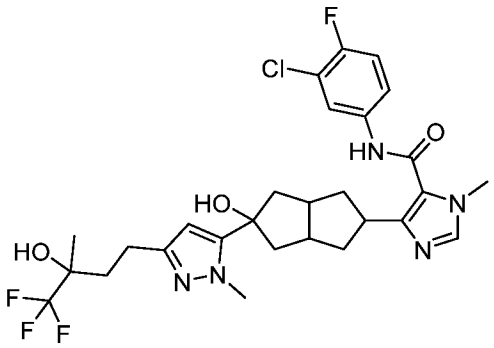
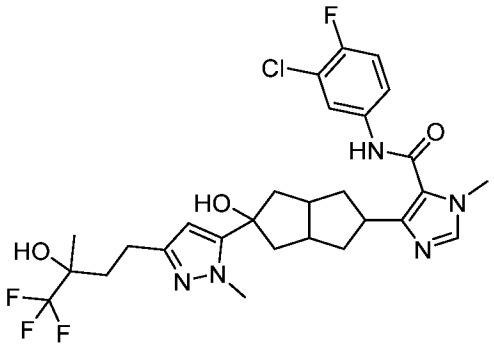
278	 **Methyl 4-(4-(5-(5-((3-chloro-4-fluorophenyl)carbamoyl)-1-methyl-1H-imidazol-4-yl)-2-hydroxyoctahydropentalen-2-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexane-1-carboxylate Isomer II** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89-7.86 (dd, J = 6.8, 2.8 Hz, 1H), 7.65 (s, 1H), 7.54 (s, 1H), 7.51-7.47 (m, 1H), 7.25-7.21 (t, J = 9.2 Hz, 1H), 4.33-4.31 (m, 1H), 3.76-3.73 (m, 6H), 3.34-3.30 (m, 1H), 2.72 (s, 1H), 2.54-2.53 (m, 2H), 2.41-2.31 (m, 4H), 2.27-2.21 (m, 2H), 2.08-2.01 (m, 2H), 1.95-1.80 (m, 6H), 1.74-1.66 (m, 2H) ppm. MS calcd. for $C_{31}H_{34}ClF_4N_5O_4$: 651.2; Found: 651.8 $[M+1]^+$.
279	 **4-(5-(1-(3-Carbamoylcyclobutyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.87 (dd, J = 6.4, 2.4 Hz, 1H), 7.83 (s, 1H), 7.65 (s, 1H), 7.53-7.47 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.80-4.70 (m, 1H), 3.76 (s, 3H), 3.38-3.32 (m, 1H), 2.97-2.86 (m, 1H), 2.71-2.63 (m, 4H), 2.62-2.51 (m, 2H), 2.40-2.30 (m, 2H), 2.28-2.18 (m, 2H), 1.96-1.83(m, 4H) ppm. MS calcd. for $C_{28}H_{29}ClF_4N_6O_3$: 608.2; Found: 609.2 $[M+H]^+$.

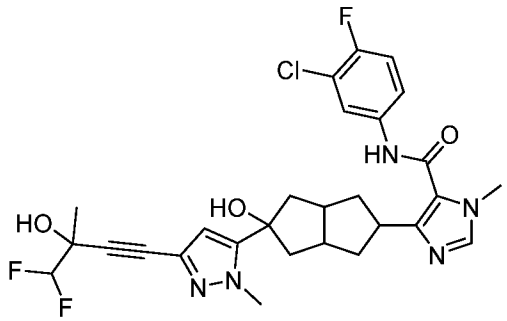
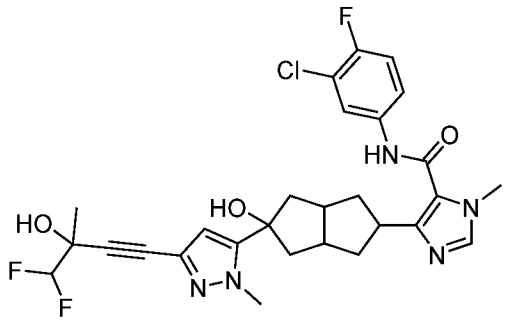
280	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-hydroxy-2-methylpropyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H-NMR (400 MHz, MeOH-d4): δ 7.87 (dd, *J* = 2.8 Hz, 6.8 Hz, 1H), 7.66 (s, 1H), 7.53-7.47 (m, 1H), 7.23 (t, J = 9.0 Hz, 1H), 6.06 (s, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 3.34-3.20 (m, 1H), 2.53-2.67 (m, 4H), 2.45-2.37 (m, 2H), 2.30-2.21 (m, 2H), 1.98-1.81 (m, 4H), 1.17 (s, 6H) ppm. MS calcd. for $C_{27}H_{33}ClFN_5O_3$: 529.2; Found: 530.3 $[M+1]^+$.
281	 **(E)-N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxy-3-methylbut-1-en-1-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** 1H NMR (400 MHz, MeOH-d_4): δ 7.88 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.73-7.65 (m, 1H), 7.53-7.45 (m, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.44-6.40 (m, 1H), 6.33-6.29 (m, 2H), 3.93 (s, 3H), 3.77 (s, 3H), 3.40-3.33 (m, 1H), 2.65-2.52 (m, 2H), 2.46-2.35 (m, 2H), 2.32-2.22(m, 2H), 2.00-1.80 (m, 4H), 1.97-1.80 (m, 4H), 1.36 (s, 6H) ppm. MS calcd. for $C_{28}H_{33}ClFN_5O_3$: 541.2; Found: 542.2 $[M+1]^+$.

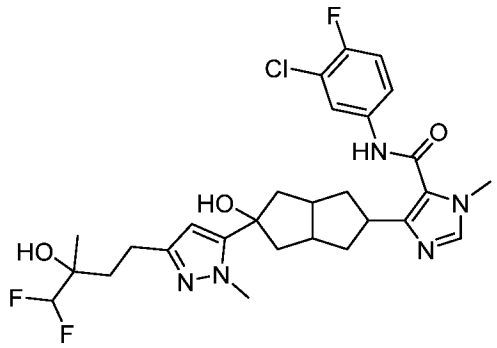
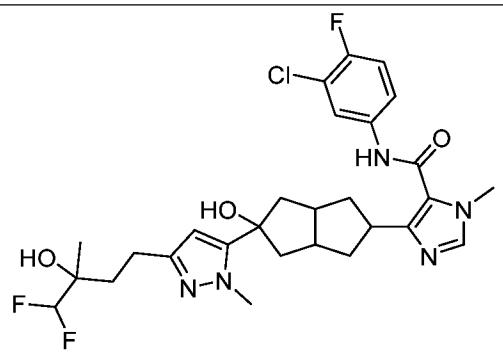
282	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-hydroxybutan-2-yl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H-NMR (400 MHz, MeOH-d4): δ 7.87 (dd, *J* = 2.4 Hz, 6.4 Hz, 1H), 7.67 (s, 1H), 7.53-7.47 (m, 1H), 7.23 (t, J = 8.8 Hz, 1H), 6.14 (s, 1H), 3.94 (s, 3H), 3.76 (s, 3H), 3.34-3.20 (m, 1H), 2.53-2.62 (m, 2H), 2.44-2.36 (m, 2H), 2.28-2.21 (m, 2H), 1.97-1.72 (m, 6H), 1.43 (s, 3H), 0.82-0.74 (m, 3H) ppm. MS calcd. for $C_{27}H_{33}ClFN_5O_3$: 529.2; Found: 530.3 $[M+1]^+$.
283	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(2,2,2-trifluoro-1-hydroxyethyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, J = 6.7, 2.6 Hz, 1H), 7.66 (s, 1H), 7.52 (ddd, J = 9.1, 4.2, 2.6 Hz, 1H), 7.30 (s, 1H), 7.25 (t, J = 8.9 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.37 (q, J = 6.2 Hz, 1H), 2.71 – 2.49 (m, 4H), 2.27 (dd, J = 12.3, 6.1 Hz, 2H), 1.94 (td, J = 12.7, 6.1 Hz, 4H), 1.63 (s, 3H) ppm. MS calcd. for $C_{25}H_{26}ClF_4N_5O_3$: 555.2; Found: 554.0 $[M-H]^-$.

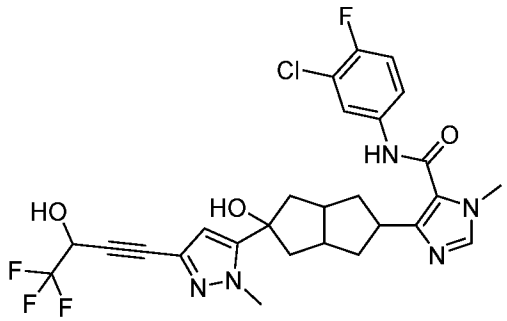
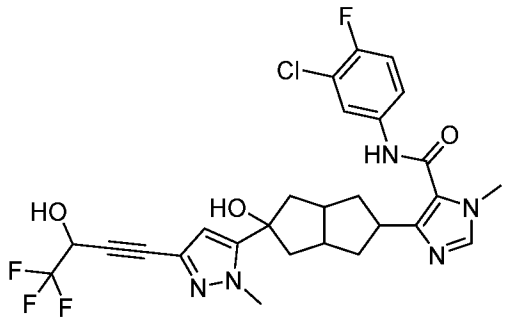
284	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(2,2,2-trifluoro-1-hydroxyethyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, J = 6.7, 2.6 Hz, 1H), 7.66 (s, 1H), 7.52 (ddd, J = 9.0, 4.2, 2.6 Hz, 1H), 7.30 (s, 1H), 7.24 (t, J = 9.0 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.37 (d, J = 5.6 Hz, 1H), 2.68 – 2.49 (m, 4H), 2.26 (dt, J = 13.2, 6.4 Hz, 2H), 2.02 – 1.81 (m, 4H), 1.63 (s, 3H) ppm. MS calcd. for $C_{25}H_{26}ClF_4N_5O_3$: 555.2; Found: 554.0 $[M-H]^-$.
285	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(4,4,4-trifluoro-3-hydroxy-3-methylbut-1-yn-1-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, J = 6.7, 2.6 Hz, 1H), 7.65 (s, 1H), 7.57 – 7.46 (m, 1H), 7.25 (t, J = 8.9 Hz, 1H), 5.62 (t, J = 56.4 Hz, 1H), 3.77 (s, 3H), 3.42 – 3.34 (m, 1H), 2.69 (s, 2H), 2.23 (dd, J = 12.3, 6.6 Hz, 4H), 1.80 (dd, J = 13.2, 8.2 Hz, 4H), 1.43 (t, J = 1.6 Hz, 3H) ppm. MS calcd. for $C_{28}H_{28}ClF_4N_5O_3$: 593.2; Found: 494.2 $[M-H]^-$.

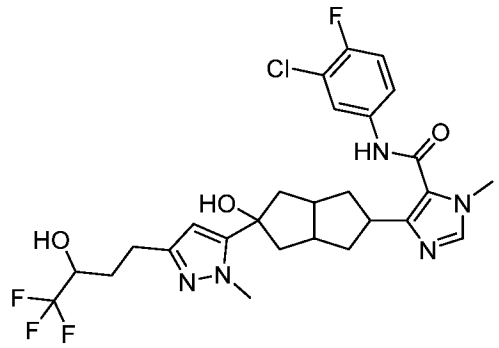
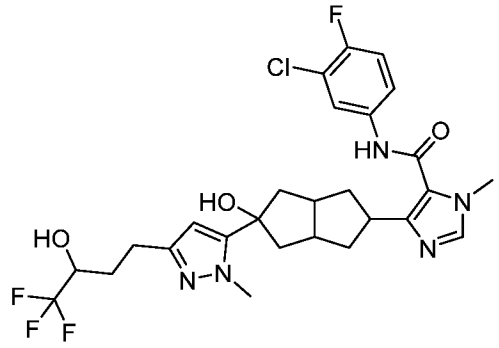
286	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(4,4,4-trifluoro-3-hydroxy-3-methylbut-1-yn-1-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.96 (dd, J = 6.8, 2.5 Hz, 1H), 7.65 (s, 1H), 7.57 (ddd, J = 9.1, 4.3, 2.5 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 6.22 (s, 1H), 5.40 (d, J = 5.3 Hz, 1H), 5.33 (s, 1H), 4.53 (p, J = 6.3 Hz, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 3.28 – 3.20 (m, 1H), 2.44 (s, 2H), 2.19 (dd, J = 13.1, 7.0 Hz, 2H), 2.08 (d, J = 8.3 Hz, 2H), 1.94 – 1.69 (m, 4H), 1.34 (d, J = 6.6 Hz, 3H) ppm. MS calcd. for $C_{28}H_{28}ClF_4N_5O_3$: 593.2; Found:; 524.2 $[M-H]^-$.
287	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(2-(3,3-difluoro-1-hydroxycyclobutyl)ethyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, J = 6.7, 2.6 Hz, 1H), 7.66 (s, 1H), 7.51 (ddd, J = 9.0, 4.2, 2.7 Hz, 1H), 7.24 (t, J = 9.0 Hz, 1H), 6.03 (s, 1H), 3.92 (s, 3H), 3.78 (s, 3H), 3.40 – 3.33 (m, 1H), 2.73 – 2.47 (m, 8H), 2.41 (dd, J = 13.2, 7.3 Hz, 2H), 2.26 (dt, J = 13.4, 7.0 Hz, 2H), 2.02 – 1.78 (m, 6H) ppm. MS calcd. for $C_{29}H_{33}ClF_3N_5O_3$: 591.2; Found: 590.2 $[M-H]^-$.

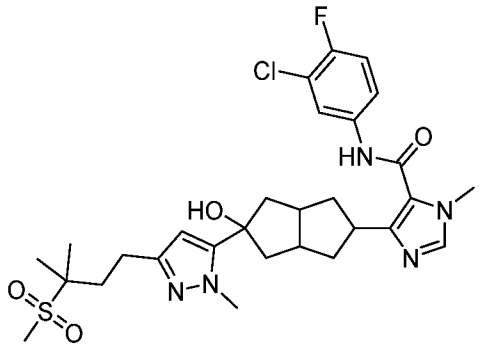
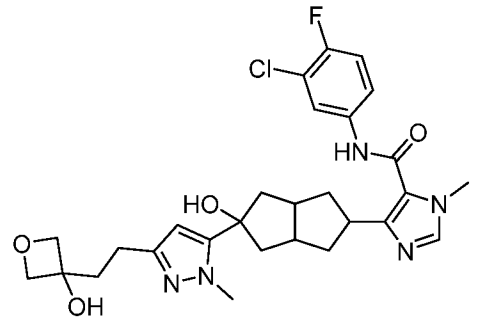
288	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (600 MHz, MeOH-d4): δ 7.87 (dd, J = 6.7, 2.6 Hz, 1H), 7.65 (s, 1H), 7.50 (ddd, J = 9.0, 4.2, 2.7 Hz, 1H), 7.23 (t, J = 8.9 Hz, 1H), 6.02 (s, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 3.35 (dd, J = 12.2, 6.2 Hz, 1H), 2.75 – 2.60 (m, 3H), 2.56 (s, 2H), 2.39 (dd, J = 13.1, 7.7 Hz, 2H), 2.29 – 2.20 (m, 2H), 2.00 – 1.91 (m, 3H), 1.91 – 1.82 (m, 3H), 1.33 (s, 3H) ppm. MS calcd. for $C_{28}H_{32}ClF_4N_5O_3$: 597.2; Found: 596.0 $[M-H]^-$.
289	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (600 MHz, MeOH-d4): δ 7.87 (dd, J = 6.6, 2.6 Hz, 1H), 7.65 (s, 1H), 7.50 (dt, J = 9.1, 3.4 Hz, 1H), 7.23 (t, J = 8.9 Hz, 1H), 6.02 (s, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 3.37 – 3.33 (m, 1H), 2.66 (q, J = 10.2, 9.5 Hz, 3H), 2.56 (s, 2H), 2.39 (dd, J = 12.9, 7.2 Hz, 2H), 2.28 – 2.21 (m, 2H), 1.95 (td, J = 13.1, 12.6, 5.3 Hz, 3H), 1.87 (q, J = 11.5 Hz, 3H), 1.33 (s, 3H) ppm. MS calcd. for $C_{28}H_{32}ClF_4N_5O_3$: 597.2; Found: 596.0 $[M-H]^-$.

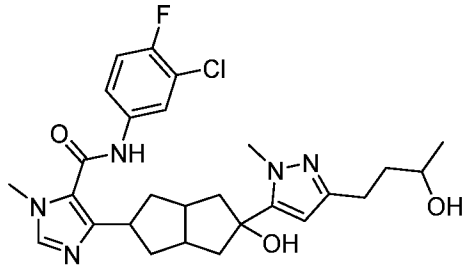
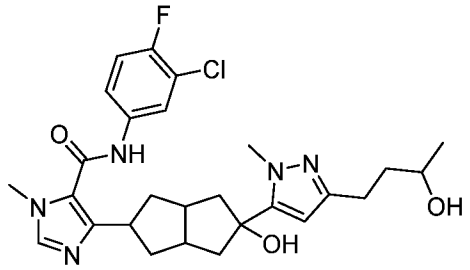
290	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(4,4-difluoro-3-hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (600 MHz, MeOH-d4): δ 7.88 (dd, J = 6.8, 2.6 Hz, 1H), 7.67 (s, 1H), 7.49 (dt, J = 7.4, 3.3 Hz, 1H), 7.23 (t, J = 8.9 Hz, 1H), 6.33 (s, 1H), 5.70 (t, J = 56.4 Hz, 1H), 3.97 (s, 3H), 3.76 (s, 3H), 3.38 – 3.32 (m, 1H), 2.61 (d, J = 47.5 Hz, 2H), 2.37 (dd, J = 13.3, 7.3 Hz, 2H), 2.31 – 2.14 (m, 2H), 1.97 (dd, J = 13.3, 5.2 Hz, 2H), 1.88 (q, J = 11.5 Hz, 2H), 1.51 (s, 3H) ppm. MS calcd. for $C_{28}H_{29}ClF_3N_5O_3$: 575.2; Found: 575.0 $[M-H]^-$.
291	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(4,4-difluoro-3-hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (600 MHz, MeOH-d4): δ 7.87 (dd, J = 6.7, 2.6 Hz, 1H), 7.65 (s, 1H), 7.49 (dt, J = 8.8, 3.4 Hz, 1H), 7.23 (t, J = 8.9 Hz, 1H), 6.32 (s, 1H), 5.69 (t, J = 56.3 Hz, 1H), 3.97 (s, 3H), 3.76 (s, 3H), 3.38 – 3.32 (m, 1H), 2.61 (d, J = 48.8 Hz, 2H), 2.37 (dd, J = 13.2, 7.6 Hz, 2H), 2.26 (dd, J = 12.6, 6.4 Hz, 2H), 1.97 (dd, J = 13.3, 5.3 Hz, 2H), 1.94 – 1.74 (m, 2H), 1.50 (d, J = 1.8 Hz, 3H) ppm. MS calcd. for $C_{28}H_{29}ClF_3N_5O_3$: 575.2; Found: 574.2 $[M-H]^-$.

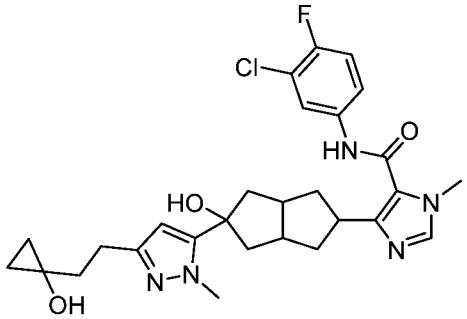
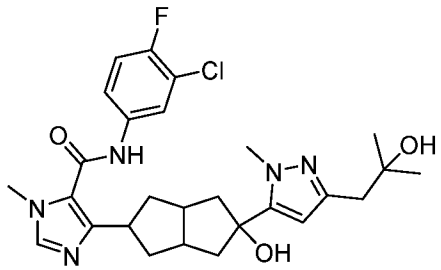
292	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(4,4-difluoro-3-hydroxy-3-methylbutyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.20 (s, 1H), 7.96 (dd, J = 6.9, 2.5 Hz, 1H), 7.65 (s, 1H), 7.57 (ddd, J = 9.1, 4.3, 2.6 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.88 (s, 1H), 5.71 (t, J = 56.3 Hz, 1H), 5.16 (d, J = 5.5 Hz, 2H), 3.81 (s, 3H), 3.67 (s, 3H), 3.24 (dd, J = 12.3, 5.8 Hz, 1H), 2.48 (s, 4H), 2.18 (dd, J = 12.7, 6.9 Hz, 2H), 2.14 – 2.02 (m, 2H), 1.84 (d, J = 11.1 Hz, 4H), 1.77 – 1.60 (m, 2H), 1.11 (s, 3H) ppm. MS calcd. for $C_{28}H_{33}ClF_3N_5O_3$: 579.2; Found: 578.0 $[M-H]^-$.
293	 **N-(3-Chloro-4-fluorophenyl)-4-(5-(3-(4,4-difluoro-3-hydroxy-3-methylbutyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.20 (s, 1H), 7.95 (dd, J = 6.8, 2.6 Hz, 1H), 7.65 (s, 1H), 7.61 – 7.52 (m, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.88 (s, 1H), 5.71 (t, J = 56.3 Hz, 1H), 5.16 (d, J = 5.5 Hz, 2H), 3.81 (s, 3H), 3.67 (s, 3H), 3.28 – 3.22 (m, 1H), 2.49 – 2.42 (m, 4H), 2.24 – 2.15 (m, 2H), 2.14 – 2.05 (m, 2H), 1.84 (d, J = 10.5 Hz, 4H), 1.76 – 1.62 (m, 2H), 1.11 (s, 3H) ppm. MS calcd. for $C_{28}H_{33}ClF_3N_5O_3$: 579.2; Found: 578.0 $[M-H]^-$.

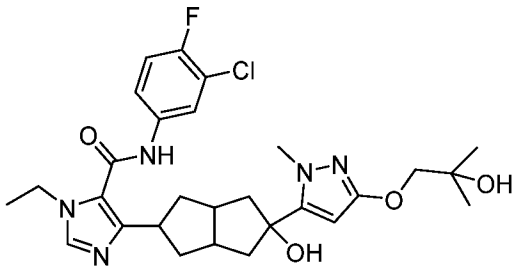
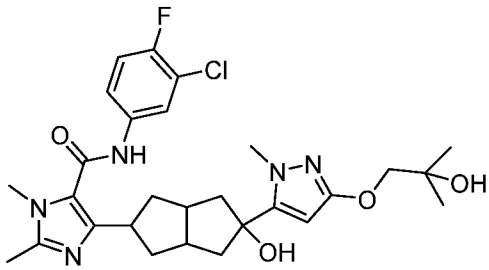
294	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (600 MHz, MeOH-d4): δ 7.88 (dd, J = 6.7, 2.6 Hz, 1H), 7.65 (s, 1H), 7.49 (dt, J = 9.0, 3.5 Hz, 1H), 7.23 (t, J = 8.9 Hz, 1H), 6.37 (s, 1H), 4.96 (t, J = 6.2 Hz, 1H), 3.98 (s, 3H), 3.76 (s, 3H), 3.35 (d, J = 6.1 Hz, 1H), 2.57 (d, J = 6.1 Hz, 2H), 2.37 (dd, J = 13.2, 7.7 Hz, 2H), 2.26 (dd, J = 12.7, 6.6 Hz, 2H), 1.97 (dd, J = 13.2, 5.3 Hz, 2H), 1.89 (td, J = 12.1, 8.4 Hz, 2H) ppm. MS calcd. for $C_{27}H_{26}ClF_4N_5O_3$: 579.2; Found: 578.0 $[M-H]^-$.
295	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, J = 6.7, 2.6 Hz, 1H), 7.65 (s, 1H), 7.57 – 7.46 (m, 1H), 7.25 (t, J = 8.9 Hz, 1H), 5.62 (t, J = 56.4 Hz, 1H), 3.77 (s, 3H), 3.42 – 3.34 (m, 1H), 2.69 (s, 2H), 2.23 (dd, J = 12.3, 6.6 Hz, 4H), 1.80 (dd, J = 13.2, 8.2 Hz, 4H), 1.43 (t, J = 1.6 Hz, 3H) ppm. MS calcd. for $C_{27}H_{26}ClF_4N_5O_3$: 579.2; Found: 494.2 $[M-H]^-$.

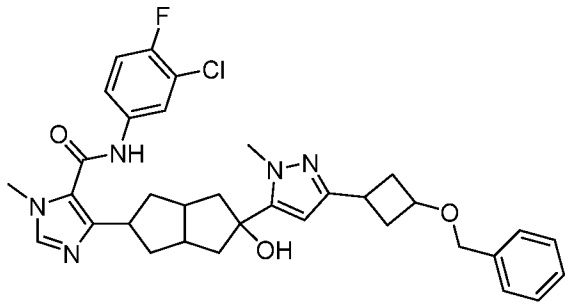
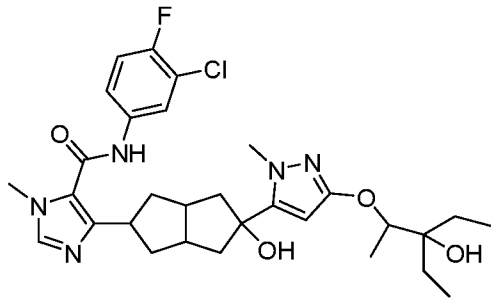
	
296	**N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(4,4,4-trifluoro-3-hydroxybutyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.97 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.28 – 7.12 (m, 3H), 7.08 (d, J = 7.0 Hz, 1H), 7.01 – 6.90 (m, 2H), 4.39 (s, 2H), 4.12 (s, 2H), 3.39 (t, J = 5.1 Hz, 4H), 3.15 (s, 2H), 2.71 (t, J = 5.0 Hz, 4H) ppm. MS calcd. for $C_{27}H_{30}ClF_4N_5O_3$: 583.2; Found: 589.2 $[M-H]^-$.
	
297	**N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(4,4,4-trifluoro-3-hydroxybutyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.97 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.61 (t, J = 2.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.26 – 7.11 (m, 4H), 7.08 (d, J = 7.1 Hz, 1H), 4.39 (s, 2H), 4.12 (s, 2H), 3.29 (t, J = 5.1 Hz, 4H), 3.17 (s, 2H), 2.74 (t, J = 4.9 Hz, 4H), 2.04 (s, 1H) ppm. MS calcd. for $C_{27}H_{30}ClF_4N_5O_3$: 583.2; Found: 589.0 $[M-H]^-$.

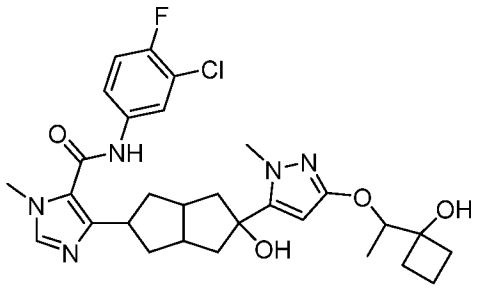
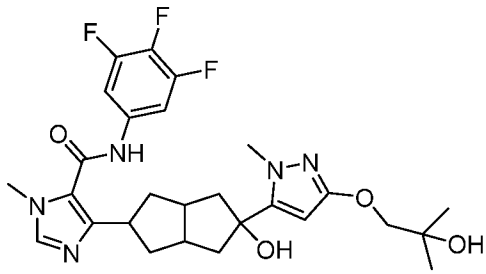
298	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(1-methyl-3-(3-methyl-3-(methylsulfonyl)butyl)-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, J = 6.7, 2.6 Hz, 1H), 7.66 (s, 1H), 7.51 (ddd, J = 9.0, 4.1, 2.6 Hz, 1H), 7.24 (t, J = 9.0 Hz, 1H), 6.07 (s, 1H), 3.93 (s, 3H), 3.77 (s, 3H), 3.37 (dd, J = 12.2, 6.1 Hz, 1H), 2.89 (s, 3H), 2.71 – 2.64 (m, 2H), 2.57 (s, 2H), 2.41 (dd, J = 13.2, 7.6 Hz, 2H), 2.30 – 2.22 (m, 2H), 2.09 – 2.03 (m, 2H), 1.98 – 1.81 (m, 4H), 1.42 (s, 6H) ppm. MS calcd. for $C_{29}H_{37}ClFN_5O_4S$: 605.2; Found: 604.2 $[M-H]^-$.
299	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-(3-hydroxyoxetan-3-yl)ethyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, DMSO-d6): δ 10.20 (s, 1H), 7.96 (dd, J = 6.8, 2.5 Hz, 1H), 7.65 (s, 1H), 7.57 (ddd, J = 9.0, 4.4, 2.7 Hz, 1H), 7.40 (t, J = 9.1 Hz, 1H), 5.91 (s, 1H), 5.59 (s, 1H), 5.18 (s, 1H), 4.39 (d, J = 6.1 Hz, 2H), 4.30 (d, J = 6.2 Hz, 2H), 4.09 (q, J = 5.2 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.17 (d, J = 5.2 Hz, 2H), 2.45 (s, 2H), 2.19 (dd, J = 13.2, 7.2 Hz, 2H), 2.10 (t, J = 6.5 Hz, 2H), 2.01 – 1.92 (m, 2H), 1.85 (d, J = 11.7 Hz, 4H) ppm. MS calcd. for $C_{28}H_{33}ClFN_5O_4$: 557.2; Found: 556.2 $[M-H]^-$.

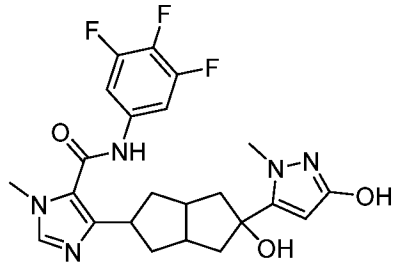
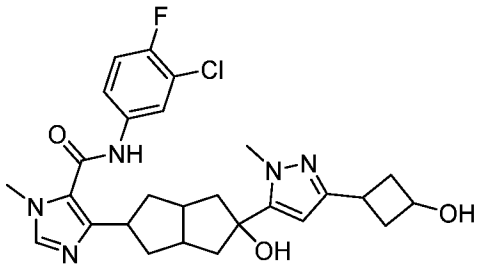
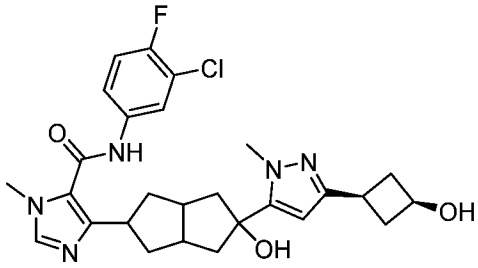
300	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxybutyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer I** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, J = 6.7, 2.7 Hz, 1H), 7.68 (s, 1H), 7.51 (dt, J = 9.1, 3.4 Hz, 1H), 7.25 (t, J = 9.0 Hz, 1H), 6.02 (s, 1H), 3.92 (s, 3H), 3.78 (s, 3H), 3.72 (p, J = 6.1 Hz, 1H), 3.41 – 3.34 (m, 1H), 2.72 – 2.52 (m, 4H), 2.41 (dd, J = 12.7, 7.9 Hz, 2H), 2.34 – 2.21 (m, 2H), 2.01 – 1.81 (m, 4H), 1.77 – 1.58 (m, 2H), 1.18 (d, J = 6.2 Hz, 3H) ppm. MS calcd. for $C_{27}H_{33}ClFN_5O_3$: 529.2; Found: 528.2 $[M-H]^-$.
301	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxybutyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide Isomer II** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, J = 6.7, 2.6 Hz, 1H), 7.66 (s, 1H), 7.51 (ddd, J = 8.9, 4.1, 2.6 Hz, 1H), 7.24 (t, J = 8.9 Hz, 1H), 6.01 (s, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 3.75 – 3.67 (m, 1H), 3.37 (dt, J = 12.0, 6.0 Hz, 1H), 2.68 – 2.49 (m, 4H), 2.40 (dd, J = 12.6, 7.7 Hz, 2H), 2.26 (dt, J = 13.2, 6.6 Hz, 2H), 2.02 – 1.79 (m, 4H), 1.79 – 1.64 (m, 2H), 1.17 (d, J = 6.2 Hz, 3H) ppm. MS calcd. for $C_{27}H_{33}ClFN_5O_3$: 529.2; Found: 528.2 $[M-H]^-$.

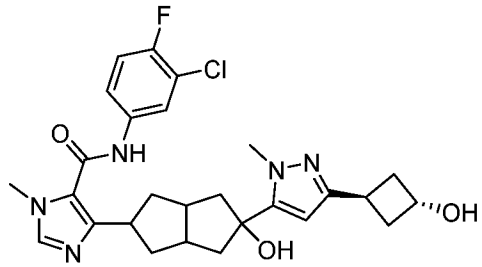
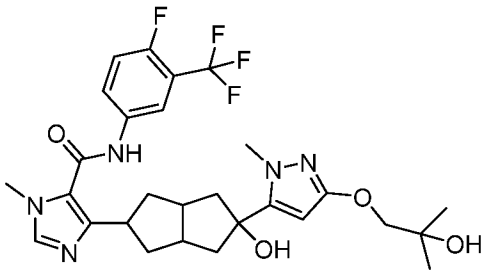
302	 **N-(3-Chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-(1-hydroxycyclopropyl)ethyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** ^{1}H NMR (400 MHz, MeOH-d4): δ 7.89 (dd, J = 6.7, 2.6 Hz, 1H), 7.67 (s, 1H), 7.51 (ddd, J = 8.9, 4.2, 2.6 Hz, 1H), 7.24 (t, J = 9.0 Hz, 1H), 6.02 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.35 (s, 1H), 2.81 – 2.71 (m, 2H), 2.56 (d, J = 6.4 Hz, 2H), 2.41 (dd, J = 12.7, 7.3 Hz, 2H), 2.27 (dd, J = 12.4, 6.5 Hz, 2H), 2.03 – 1.73 (m, 6H), 0.74 – 0.55 (m, 2H), 0.44 (t, J = 3.4 Hz, 2H) ppm. MS calcd. for $C_{28}H_{33}ClFN_5O_3$: 541.2; Found: 540.2 $[M-H]^-$.
303	 **N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-hydroxy-2-methylpropyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{27}H_{33}ClFN_5O_3$: 529; Found: 530 $[M+1]^+$. ^{1}H NMR (400 MHz, CD_3OD): δ 7.87 (dd, J = 2.8 Hz, 6.8 Hz, 1H), 7.66 (s, 1H), 7.53-7.47 (m, 1H), 7.23 (t, J = 9.0 Hz, 1H), 6.06 (s, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 3.34-3.20 (m, 1H), 2.53-2.67 (m, 4H), 2.45-2.37 (m, 2H), 2.30-2.21 (m, 2H), 1.98-1.81 (m, 4H), 1.17 (s, 6H) ppm.

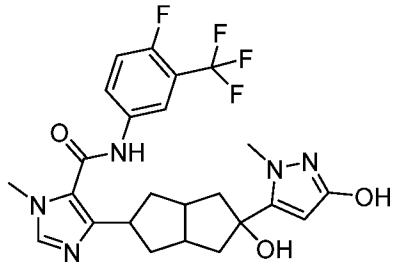
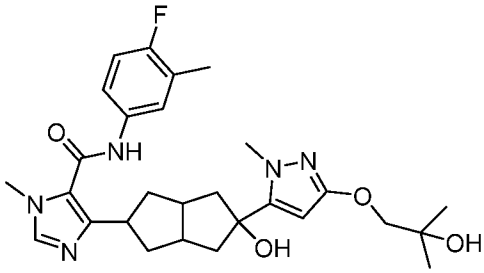
304	 **N-(3-chloro-4-fluorophenyl)-1-ethyl-4-(5-hydroxy-5-(3-(2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1H-imidazole-5-carboxamide** MS calcd. for $C_{28}H_{35}ClFN_5O_4$: 559; Found: 560 $[M+1]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, J = 2.4 Hz, 6.4 Hz, 1H), 7.66 (s, 1H), 7.57 (s, 1H), 7.37-7.34 (m, 1H), 7.15 (t, J = 8.8 Hz, 1H), 5.53 (s, 1H), 4.25 (q, J = 7.2 Hz, 6.4 Hz, 2H), 3.96 (s, 2H), 3.86 (s, 3H), 3.31-3.25 (m, 1H), 2.75-2.71 (m, 2H), 2.33-2.19 (m, 4H), 2.02-1.99 (m, 4H), 1.44 (t, J = 7.2 Hz, 3H), 1.29 (s, 6H) ppm.
305	 **N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1,2-dimethyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{28}H_{35}ClFN_5O_4$: 559; Found: 560 $[M+1]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.87 (dd, J = 6.4, 2.4 Hz, 1H), 7.51-7.47 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 5.64 (s, 1H), 3.81 (d, J = 3.2 Hz, 5H), 3.64 (s, 3H), 3.30-3.28 (m, 1H), 2.55-2.54 (m, 2H), 2.41-2.35 (m, 5H), 2.23-2.20 (m, 2H), 1.94-1.82 (m, 4H), 1.25 (s, 6H) ppm.

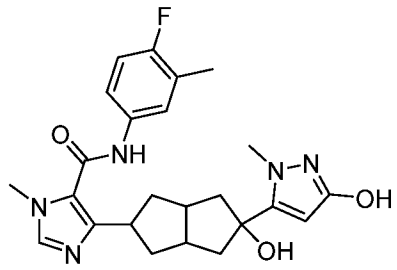
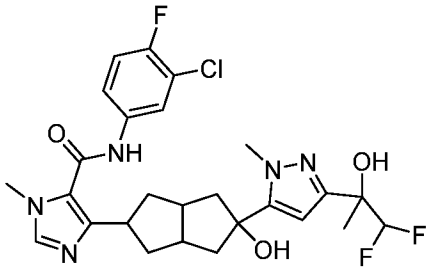
306	 **4-(5-(3-(3-(benzyloxy)cyclobutyl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-N-(3-chloro-4-fluorophenyl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{34}H_{37}ClFN_5O_3$: 617; Found: 618 $[M+1]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.87-7.33 (m, 1H), 7.32 (s, 1H), 7.31-7.29 (m, 1H), 7.28-7.21 (m, 6H), 6.17-6.15 (m, 1H), 4.43 (s, 2H), 4.04 (s, 3H), 3.75 (s, 3H), 3.31-3.30 (m, 1H), 2.63-2.58 (m, 4H), 2.42-2.40 (m, 2H), 2.24-2.21 (m, 2H), 2.09-2.06 (m, 2H), 1.90-1.87 (m, 2H), 1.85-1.74 (m, 2H), 1.53-1.48 (m, 2H) ppm. (One aliphatic proton was merged in solvent peak)
307	 **N-(3-chloro-4-fluorophenyl)-4-(5-(3-((3-ethyl-3-hydroxypentan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{30}H_{39}ClFN_5O_4$: 587; Found: 588 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.96 (dd, J = 2.4, 6.8 Hz, 1H), 7.65 (s, 1H), 7.60 - 7.54 (m, 1H), 7.43 - 7.37 (m, 1H), 5.46 (s, 1H), 5.20 (s, 1H), 4.39 (q, J = 6.3 Hz, 1H), 4.02 (brs, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.25 - 3.18 (m, 1H), 2.47 - 2.42 (m, 2H), 2.20 - 2.04 (m, 4H), 1.91 - 1.79 (m, 4H), 1.55 - 1.32 (m, 4H), 1.15 (d, J = 6.1 Hz, 3H), 0.82 - 0.75 (m, 6H) ppm.

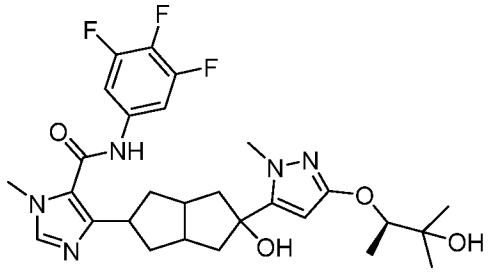
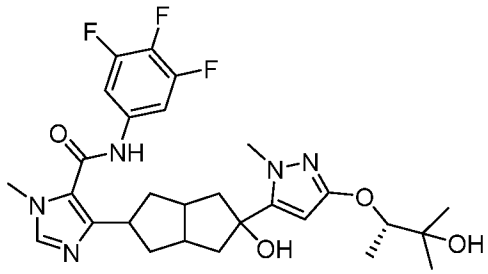
308	 **N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(1-(1-hydroxycyclobutyl)ethoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{29}H_{35}ClFN_5O_4$: 571; Found: 572 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.66 (brs, 1H), 8.62 (br s, 1H), 7.96 (dd, J = 6.6 Hz, 2.2 Hz, 1H), 7.60 - 7.54 (m, 1H), 7.48 - 7.41 (m, 1H), 5.51 (s, 1H), 5.30 (brs, 1H), 5.0 (brs, 1H), 4.44 (q, J = 5.9 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 2.27 - 1.98 (m, 6H), 1.93 - 1.63 (m, 8H), 1.56 - 1.45 (m, 2H), 1.12 (d, J = 5.9 Hz, 3H) ppm. (One aliphatic proton was merged in solvent peak)
309	 **4-(5-hydroxy-5-(3-(2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-N-(3,4,5-trifluorophenyl)-1H-imidazole-5-carboxamide** MS calcd. for $C_{27}H_{32}F_3N_5O_4$: 547; Found: 548 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.35 (s, 1H), 7.67 (s, 1H), 7.60-7.55 (m, 2H), 5.52 (s, 1H), 5.21 (brs, 1H), 4.51 (brs ,1H), 3.72 - 3.71 (m, 5H), 3.67 (s, 3H), 2.46 - 2.42 (m, 2H), 2.22 - 2.13 (m, 2H), 2.12 - 2.03 (m, 2H), 1.90 - 1.79 (m, 4H), 1.13 (s, 6H) ppm. (One aliphatic proton was merged in solvent peak)

310	 **4-(5-hydroxy-5-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-N-(3,4,5-trifluorophenyl)-1H-imidazole-5-carboxamide** MS calcd. for $C_{23}H_{24}F_3N_5O_3$: 475; Found: 476 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.34 (s, 1H), 9.28 (s, 1H), 7.66 (s, 1H), 7.63 - 7.52 (m, 2H), 5.28 (s, 1H), 5.14 (s, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.27 - 3.15 (m, 1H), 2.47 - 2.40 (m, 2H), 2.18 - 2.03 (m, 4H), 1.91 - 1.77 (m, 4H) ppm
311	 **N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-(3-hydroxycyclobutyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{27}H_{31}ClFN_5O_3$: 527; Found: 528 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.24 (d, J = 15.2 Hz, 1H), 7.99 - 7.94 (m, 1H), 7.68 - 7.36 (m, 4H), 6.06 (s, 1H), 5.09 - 4.97 (m, 2H), 3.96 (s, 3H), 3.67 (s, 3H), 3.25 - 3.12 (m, 2H), 2.26 - 1.97 (m, 5H), 1.97 - 1.80 (m, 5H), 1.77 - 1.60 (m, 2H), 1.39 - 1.29 (m, 1H), 1.03 - 0.88 (m, 1H) ppm
312	

	N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1s,3s)-3-hydroxycyclobutyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide MS calcd. for $C_{27}H_{31}ClFN_5O_3$: 527; Found: 528 $[M+1]^+$. 1H NMR (400 MHz, DMSO-d6): δ 10.20 (s, 1H), 7.96 (dd, J = 6.8 Hz, 2.8 Hz, 1H), 7.64 (s, 1H), 7.58-7.55 (m, 1H), 7.42-7.37 (m, 1H), 5.91 (s, 1H), 5.16 (s, 1H), 4.99 (brs, 1H), 3.96-3.92 (m, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.24-3.16 (m, 1H), 2.71-2.64 (m, 1H), 2.50-2.41 (m, 4H), 2.21-2.07 (m, 4H), 1.91-1.70 (m, 6H) ppm
313	 **N-(3-chloro-4-fluorophenyl)-4-(5-hydroxy-5-(3-((1r,3r)-3-hydroxycyclobutyl)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{27}H_{31}ClFN_5O_3$: 527; Found: 528 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 7.96 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.59-7.55 (m, 1H), 7.52-7.51 (m, 1H), 7.42-7.37 (m, 1H), 6.05 (s, 1H), 5.39-5.36 (m, 1H), 5.03-4.98 (m, 1H), 4.75 (s, 1H), 3.99 (s, 3H), 3.64 (s, 3H), 3.32-3.15 (m, 1H), 2.82-2.73 (m, 1H), 2.59-2.53 (m, 1H), 2.49-2.40 (m, 2H), 2.29-2.23 (m, 1H), 2.21-2.14 (m, 2H), 2.08-2.02 (m, 2H), 1.92-1.85 (m, 4H), 1.37-1.23 (m, 2H) ppm
314	 **N-(4-fluoro-3-(trifluoromethyl)phenyl)-4-(5-hydroxy-5-(3-(2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide**

	MS calcd. for $C_{28}H_{33}F_4N_5O_4$: 579; Found: 580 $[M+1]^+$. 1H NMR (400 MHz, DMSO-d6) δ 10.33 (s, 1H), 8.17 (dd, J = 2.5, 6.4 Hz, 1H), 7.92 - 7.86 (m, 1H), 7.66 (s, 1H), 7.55 - 7.46 (m, 1H), 5.51 (s, 1H), 5.22 (s, 1H), 4.52 (s, 1H), 3.76 - 3.70 (m, 5H), 3.67 (s, 3H), 2.46 - 2.40 (m, 2H), 2.25 - 2.04 (m, 4H), 1.89 - 1.77 (m, 4H), 1.13 (s, 6H) ppm. (One aliphatic proton was merged in solvent peak)
315	 **N-(4-fluoro-3-(trifluoromethyl)phenyl)-4-(5-hydroxy-5-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{24}H_{25}F_4N_5O_3$: 507; Found: 508 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d6): δ 10.33 (s, 1H), 9.29 (s, 1H), 8.17 (dd, J = 2.6, 6.5 Hz, 1H), 7.92 - 7.86 (m, 1H), 7.66 (s, 1H), 7.54 - 7.47 (m, 1H), 5.28 (s, 1H), 5.15 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.29 - 3.21 (m, 1H), 2.47 - 2.40 (m, 2H), 2.18 - 2.04 (m, 4H), 1.92 - 1.78 (m, 4H) ppm
316	 **N-(4-fluoro-3-methylphenyl)-4-(5-hydroxy-5-(3-(2-hydroxy-2-methylpropoxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{28}H_{36}FN_5O_4$: 525; Found: 526 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d6): δ 9.98 (s, 1H), 7.66 - 7.55 (m, 2H), 7.49 - 7.40 (m, 1H), 7.15 - 7.04 (m, 1H), 5.51 (s, 1H), 5.22 (s, 1H), 4.52 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.66 (s, 2H), 2.22 (s, 3H), 2.17 - 1.94 (m, 4H), 1.89 - 1.75 (m, 4H), 1.13 (s, 6H) ppm. (Three aliphatic protons were merged in solvent peak)

317	 **N-(4-fluoro-3-methylphenyl)-4-(5-hydroxy-5-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{24}H_{28}FN_5O_3$: 453; Found: 454 $[M+1]^+$. 1H NMR (400 MHz, DMSO-d6): δ 9.97 (s, 1H), 9.28 (s, 1H), 7.62 (s, 1H), 7.61 - 7.56 (m, 1H), 7.48 - 7.42 (m, 1H), 7.15 - 7.04 (m, 1H), 5.28 (s, 1H), 5.14 (s, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.26 - 3.15 (m, 1H), 2.47 - 2.38 (m, 2H), 2.22 (s, 3H), 2.18 - 2.03 (m, 4H), 1.91 - 1.76 (m, 4H) ppm
318	 **N-(3-chloro-4-fluorophenyl)-4-(5-(3-(1,1-difluoro-2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-5-yl)-5-hydroxyoctahydropentalen-2-yl)-1-methyl-1H-imidazole-5-carboxamide** MS calcd. for $C_{26}H_{29}ClF_3N_5O_3$: 551; Found: 552 $[M+1]^+$. 1H NMR (400 MHz, DMSO-d6): δ10.49 (br s, 1H), 7.96 (dd, J = 2.5, 6.8 Hz, 1H), 7.60 - 7.54 (m, 1H), 7.47 - 7.40 (m, 1H), 6.14 (s, 1H), 5.91 (s, 1H), 5.78 - 5.76 (m, 1H), 5.76 - 5.73 (m, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 2.25 - 2.13 (m, 4H), 1.93 - 1.77 (m, 4H), 1.42 (s, 3H) ppm. (Three aliphatic protons were merged in solvent peak and imidazole -CH was not observed)

319	 (Single diastereomer, the stereochemistry of the chiral either was arbitrarily assigned) **4-(5-hydroxy-5-(3-(((R)-3-hydroxy-3-methylbutan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-N-(3,4,5-trifluorophenyl)-1H-imidazole-5-carboxamide** MS calcd. for $C_{28}H_{34}F_3N_5O_4$: 561; Found: 562 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 10.34 (s, 1H), 7.66 (s, 1H), 7.57 (dd, J = 10 Hz, 6.4 Hz, 2H), 5.47 (s, 1H), 5.19 (s, 1H), 4.34 (s, 1H), 4.26 (q, J = 6.0 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.25-3.21 (m, 1H), 2.46-2.45 (m, 2H), 2.18 - 2.04 (m, 4H), 1.88-1.80 (m, 4H), 1.14 (d, J = 6.0 Hz, 3H), 1.07 (s, 3H), 1.05 (s, 3H) ppm
320	 (Single diastereomer, the stereochemistry of the chiral either was arbitrarily assigned) **4-(5-hydroxy-5-(3-(((S)-3-hydroxy-3-methylbutan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)octahydropentalen-2-yl)-1-methyl-N-(3,4,5-trifluorophenyl)-1H-imidazole-5-carboxamide** MS calcd. for $C_{28}H_{34}F_3N_5O_4$: 561; Found: 562 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.34 (s, 1H), 7.66 (s, 1H), 7.57 (dd, J = 10 Hz, 6.4 Hz, 2H), 5.47 (s, 1H), 5.19 (s, 1H), 4.34 (s, 1H), 4.26 (q, J = 6.0 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.25-3.18 (m, 1H), 2.46-2.45 (m, 2H), 2.18 - 2.05 (m, 4H), 1.85-1.80 (m, 4H), 1.14 (d, J = 6.4 Hz, 3H), 1.10 (s, 3H), 1.07 (s, 3H) ppm

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 6 gives the viral load lowering EC_{50} values for exemplified compounds of the invention. In the table, A; $EC_{50} \leq 10$ nM, B; EC_{50} >10, ≤ 100 nM and C; EC_{50} >100, ≤ 500 nM.

Table 6.

Example	**EC_{50}**
Example 2	A
Example 3	A
Example 4	A
Example 5	A
Example 6	A
Example 7	A
Example 8	A
Example 9	A
Example 10	A
Example 11	B
Example 12	A
Example 13	A
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	A
Example 28	A
Example 29	A
Example 30	B
Example 31	B
Example32	A
Example 33	A
Example 34	A
Example 35	A
Example 36	A
Example 37	A
Example 38	A
Example 39	A
Example 40	A
Example 41	A
Example 42	A
Example 43	B
Example 44	A
Example 45	A
Example 46	A
Example 47	A
Example 48	A
Example 49	A
Example 50	A
Example 51	A
Example 52	A
Example 53	A
Example 54	A
Example 55	A
Example 56	A

Example 57	A
Example 58	A
Example 59	A
Example 60	A
Example 61	A
Example 62	A
Example 63	A
Example 64	A
Example 65	A
Example 66	A
Example 67	A
Example 68	A
Example 69	A
Example 70	A
Example 71	A
Example 72	A
Example 73	A
Example 74	A
Example 75	A
Example 76	A
Example 77	A
Example 78	A
Example 79	A
Example 80	A
Example 81	A
Example 82	A
Example 83	A
Example 84	A
Example 85	A
Example 86	A
Example 87	A
Example 88	A

Example 89	A
Example 90	A
Example 91	B
Example 92	A
Example 93	A
Example 94	A
Example 95	B
Example 96	A
Example 97	A
Example 98	A
Example 99	A
Example 100	A
Example 101	A
Example 102	A
Example 103	A
Example 104	A
Example 105	A
Example 106	A
Example 107	A
Example 108	A
Example 109	A
Example 110	A
Example 111	A
Example 112	A
Example 113	A
Example 114	B
Example 115	A
Example 116	A
Example 117	A
Example 118	B
Example 119	A
Example 120	A

Example 121	A
Example 122	A
Example 123	A
Example 124	A
Example 125	A
Example 126	A
Example 127	A
Example 128	A
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Example 131	A
Example 132	A
Example 133	A
Example 134	A
Example 135	A
Example 136	A
Example 137	A
Example 138	A
Example 139	B
Example 140	A
Example 141	A
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Example 146	A
Example 147	A
Example 148	B
Example 149	A
Example 150	A
Example 151	A
Example 152	A

Example 153	A
Example 154	A
Example 155	A
Example 156	A
Example 157	A
Example 158	A
Example 159	A
Example 160	A
Example 161	C
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Example 164	A
Example 165	A
Example 166	B
Example 167	A
Example 168	B
Example 169	A
Example 170	C
Example 171	A
Example 172	A
Example 173	C
Example 174	C
Example 175	A
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Example 177	A
Example 178	A
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Example 182	A
Example 183	C
Example 184	A

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Example 187	A
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Example 280	A

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Example 304	A
Example 305	A
Example 306	A
Example 307	A
Example 308	A
Example 309	B
Example 310	A
Example 311	A
Example 312	A

Example 313	A
Example 314	A
Example 315	A
Example 316	A
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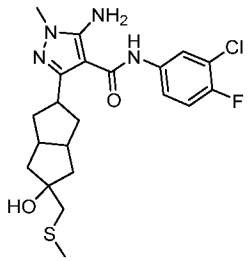
Example 318	A
Example 319	A
Example 320	A

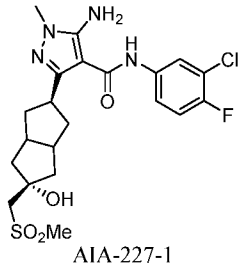
VI. Stereochemistry of Examples

AIA-225

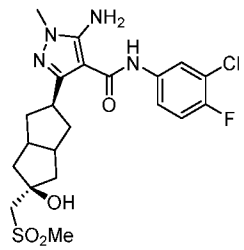


5-Amino-N-(3-chloro-4-fluorophenyl)-3-(5-hydroxy-5-(methylthiomethyl)octahydropentalen-2-yl)-1-methyl-1H-pyrazole-4-carboxamide. To a solution of 5-amino-N-(3-chloro-4-fluorophenyl)-3-(hexahydro-1'H-spiro[oxirane-2,2'-pentalene]-5'-yl)-1-methyl-1H-pyrazole-4-carboxamide (200 mg, 0.495 mmol) in THF/H_2O (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 (*v/v*) 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. for $C_{21}H_{26}ClFN_4O_2S$: 452; Found: 453 $[M+1]^+$.

AIA-227-1, AIA-227-2



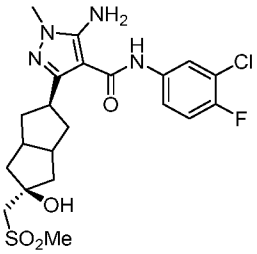
AIA-227-1



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. for $C_{21}H_{26}ClFN_4O_4S$: 484, Found: 485 $[M+1]^+$. 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. for $C_{21}H_{26}ClFN_4O_4S$: 484; Found: 485 $[M+1]^+$. ^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), 5.98 (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

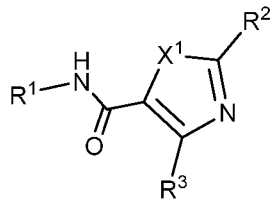
While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification. The full scope of the disclosure should be determined 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^1 is a bond, C_{1-4}alkylene, C_{1-4}alkenylene, C_{1-4}alkynylene, haloC_{1-4}alkylene, hydroxyC_{1-4}alkylene, NR^cC_{1-4}alkyl, OC_{1-4}alkyl, O, NR^c, C(O), C(O)O, C(O)NR^c, $S(O)_t$, $S(O)_tNR^c$, $S(O)_tC_{1-4}$alkyl, and $S(O)_t$haloC_{1-4}alkyl;

L^3 is C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, wherein the C_{1-6}alkylene, C_{2-6}alkenylene, C_{2-6}alkynylene is optionally substituted with 1-10 substituents independently selected from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, R^aR^bN-C_{1-6}alkoxy, and haloC_{1-6}alkylNR^c-;

X^1 is NR^{x1}, O or S;

X^4 is O or S;

X^5 is O, S or NR^{6a};

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

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;

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^{6a} is hydrogen or C_{1-4} alkyl, haloC_{1-4}alkyl or C_{3-4}cycloalkyl;

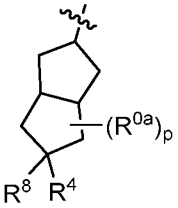
R^{6b} is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl is optionally substituted with 1-10 substituents independently selected from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, R^aR^bN-C_{1-6}alkoxy, and haloC_{1-6}alkylNR^c-;

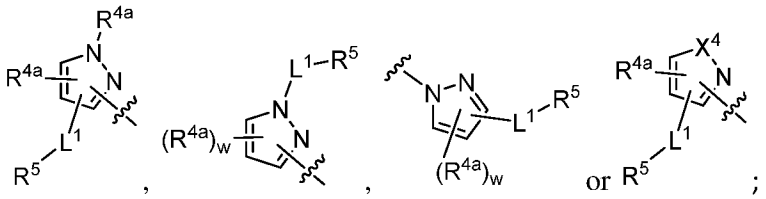
R^0, R^{4a}, R^6 and R^{11} are independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, R^dN=, hydrazino, formyl, azido, silyl,

siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, R^{6b}, $R^{6b}C(O)$-, $R^{6b}C(O)O$-, $R^{6b}C(O)NR^c$-, $R^{6b}S(O)_tNR^c$-, $R^{6b}S(O)_t$-, $R^{6b}O$-, $R^{6b}NR^c$-, $R^{6b}C(O)$-L^3-, and $R^{6b}C(O)O$-L^3-, $R^{6b}C(O)NR^c$-L^3-, $R^{6b}S(O)_tNR^c$-L^3-, $R^{6b}S(O)_q$-L^3-, $R^{6b}O$-L^3-, and $R^{6b}NR^c$-L^3-;

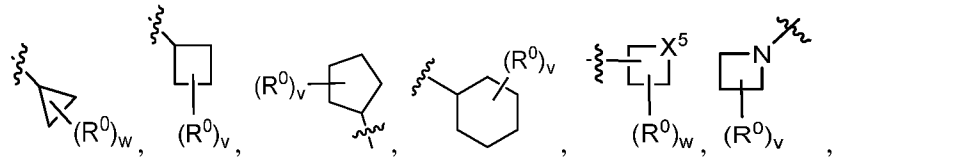
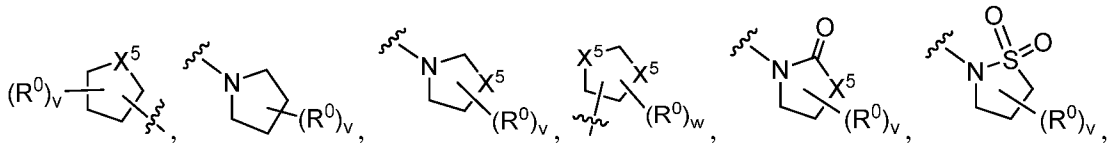
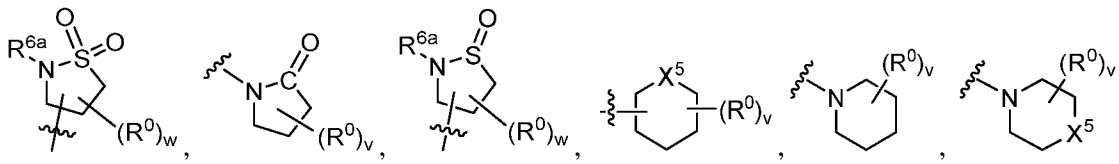
R^1 is a phenyl or 5-6 membered monocyclic heteroaryl, wherein the phenyl or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

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;

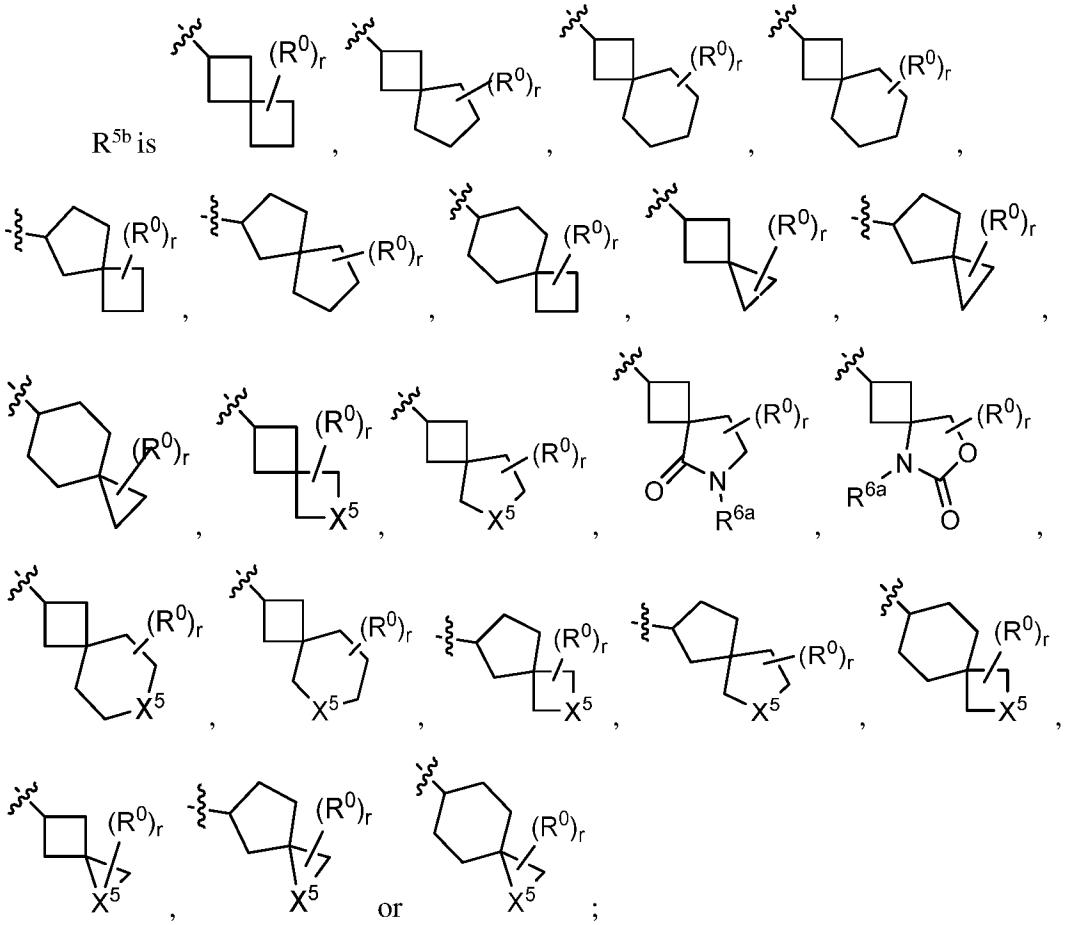
R^3 is  ;

R^4 is  ;

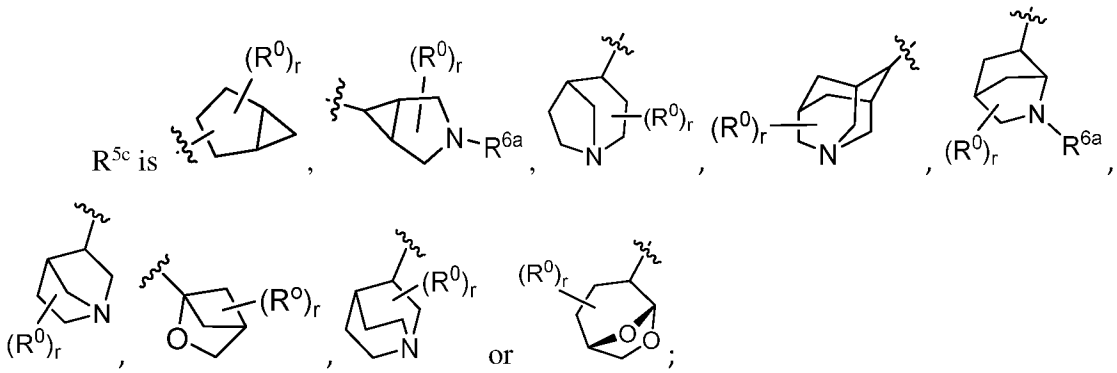
R^5 is R^{5a}, R^{5b}, R^{5c}, R^{5d} or R^6;

R^{5a} is  ,  ,  ,  ;

or ;

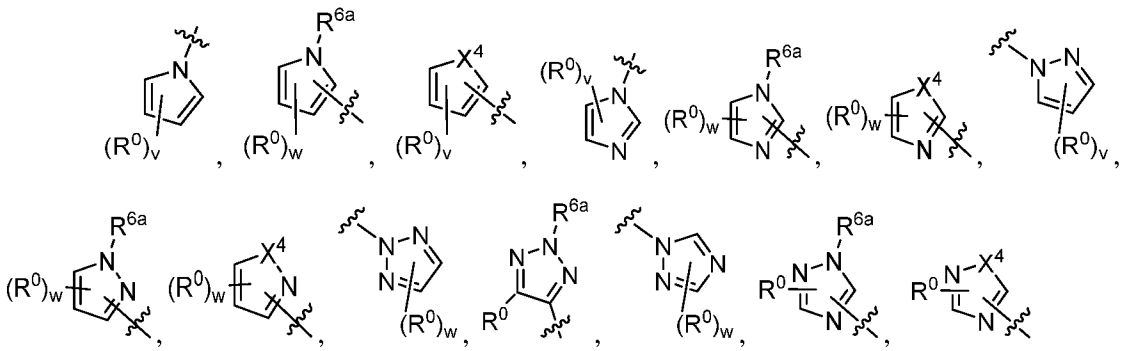
R^{5b} is 

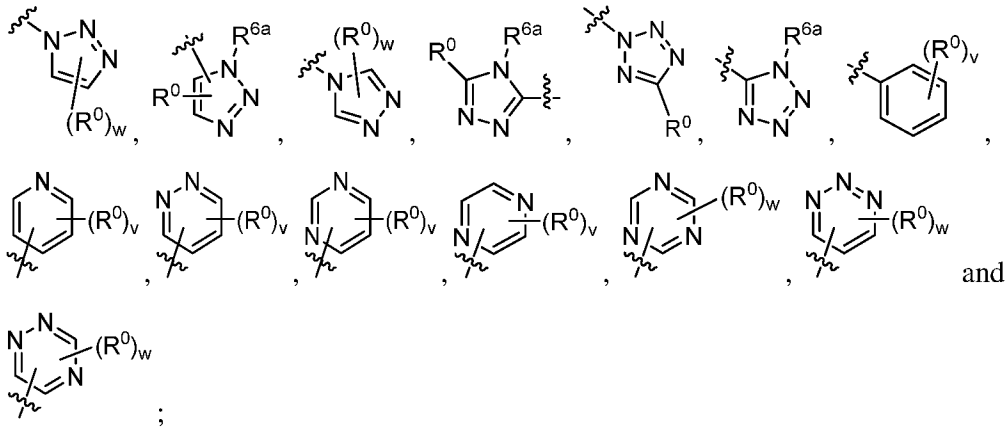
or ;

R^{5c} is 

or ;

R^{5d} is selected from the group consisting of:





;

p is independently selected for each occurrence from the group consisting of 0, 1, 2 and 3;

r is independently selected for each occurrence from the group consisting of 0, 1 and 2;

t is independently selected for each occurrence from the group consisting of 0, 1 and 2;

v is independently selected for each occurrence from the group consisting of 0, 1, 2 and 3; and

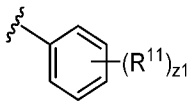
w is independently selected for each occurrence from the group consisting of 0, 1 and 2.

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

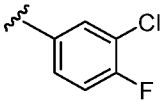
3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R^{x1} is methyl.

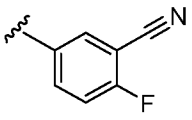
4. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein p is 0.

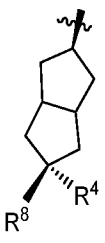
5. The compound according to any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

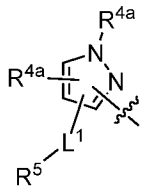
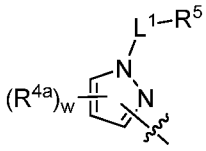
6. The compound according to any one of Claims 1-5, or a pharmaceutically acceptable salt thereof, wherein: R^1 is  ; R^{11} is independently selected for each occurrence from the group consisting of halogen, CN, $C_{1\text{-}6}$alkyl and halo$C_{1\text{-}6}$ alkyl; and z1 is 0, 1, 2 or 3.

7. The compound of Claim 6, 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.

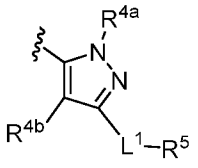
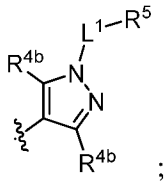
8. The compound of Claim 7, or a pharmaceutically acceptable salt thereof, wherein R^1 is  .

9. The compound of Claim 7, 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 R^3 is  .

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

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is  or  ;

R^{4b} is 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-, $R^aR^bNS(O)_t$-, $R^aR^bNC(O)$-, 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-, C_{1-6}alkylC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkylC(O)NR^c-, C_{1-6}alkyl$S(O)_t$-, C_{1-6}alkyl$S(O)_tNR^c$-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, $R^aR^bNC_{1-6}$alkoxy-, $R^aR^bNC_{1-6}$alkylNR^c-, C_{1-6}alkylNR^aC_{1-6}alkyleneNR^c-, C_{1-6}alkoxyC_{1-6}alkylene-, haloC_{1-6}alkoxyC_{1-6}alkylene-, C_{1-6}alkoxyC(O)-, C_{1-6}alkyl$S(O)_tC_{1-6}$alkylene-, C_{1-6}alkyl$S(O)_tNR^aC_{1-6}$alkylene-, C_{1-6}alkylC(O)C_{1-6}alkylene-, C_{1-6}alkylC(O)OC_{1-6}alkylene- and R^9;

R^9 is $R^{12}S(O)_t$-C_{1-6}alkylene-, $R^{12}S(O)_tNH$-C_{1-6}alkylene-, $R^{12}C(O)NH$-C_{1-6}alkylene-, $R^{12}S(O)_t$-haloC_{1-6}alkylene-, $R^{12}S(O)_tNH$-haloC_{1-6}alkylene-, or $R^{12}C(O)NH$-haloC_{1-6}alkylene-; and

R^{12} is R^aR^bN-, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, or C_{1-6}haloalkoxy.

13. The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^5 is In certain embodiments, R^5 is R^{5a}, R^{5d} or R^6.

14. The compound according to any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein L^1 is a bond.

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

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

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.

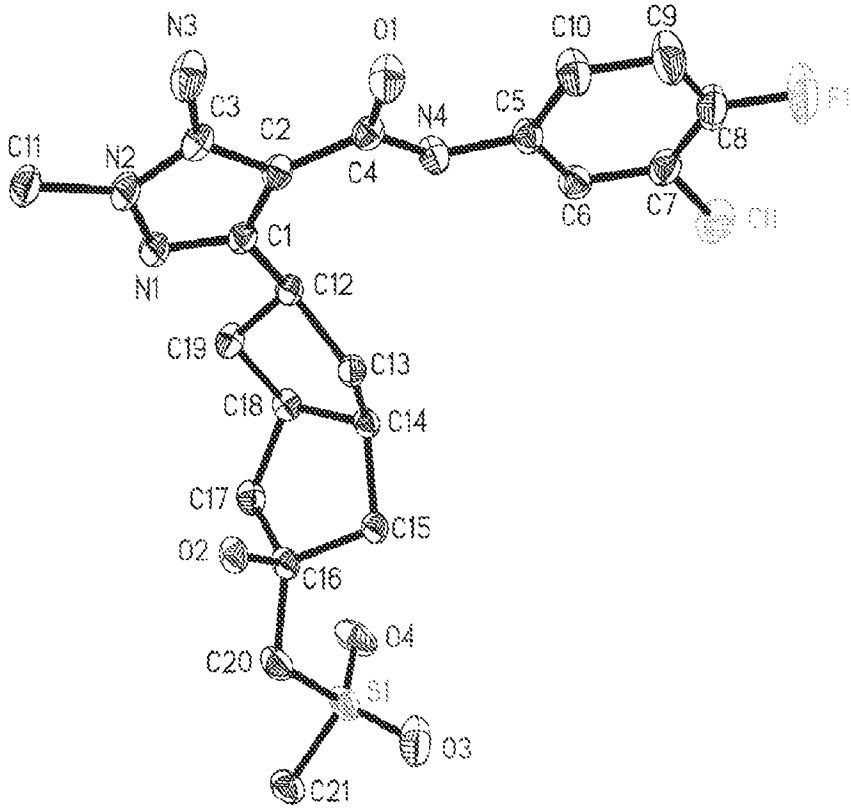


Fig. 1 The ORTEP plot for compound AIA-227-2

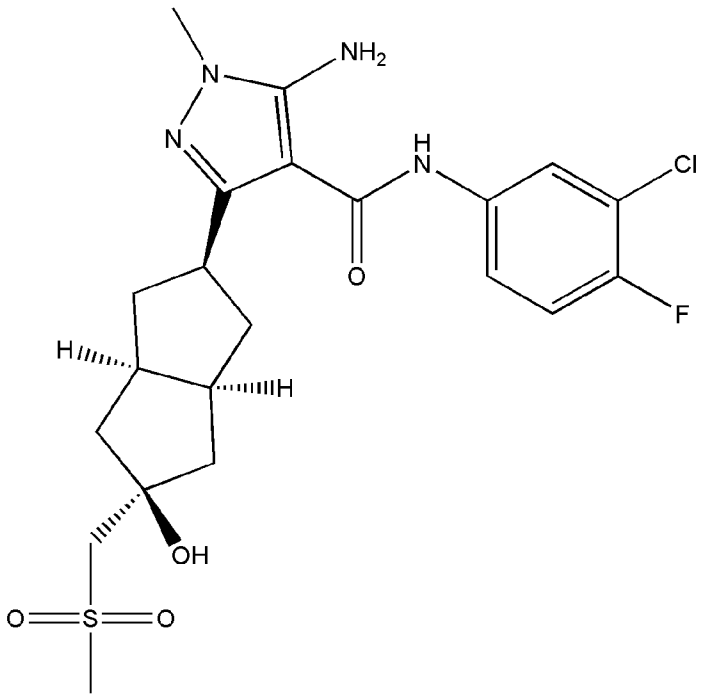


Fig. 2 The relative stereochemistry scheme of compound AIA-227-2.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/047169

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/04 C07D401/14 C07D403/14 C07D405/14 A61P31/22
A61K31/4178
ADD.
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)
A61P C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/086533 A1 (ASSEMBLY BIOSCIENCES INC [US]) 30 April 2020 (2020-04-30) page 2, line 12 - line 14; claim 1; compounds AIA-225, AIA-227	1-19
X,P	WO 2021/216656 A1 (ASSEMBLY BIOSCIENCES INC [US]) 28 October 2021 (2021-10-28) claim 1; examples 1-223; table 8	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2023	14/02/2023

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	Seelmann, Ingo

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/047169

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