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(71) Applicant: **GASHERBRUM BIO, INC.** [US/US]; 601 Gateway Blvd. Suite 900, South San Francisco, California 94080 (US).

(72) Inventor; and
(71) Applicant *(for SC only)*: **HUANG, Wei** [CN/CN]; 5 F, JLABS@Shanghai, No. 1 South Bldg., Jin Chuang, 4560 JinKe Rd, Zhangjiang Hi-Tech Park, Pudong New Area, Shanghai 200003 (CN).

(72) Inventors: **LEI, Hui**; 5 F, JLABS@Shanghai, No. 1 South Bldg., Jin Chuang, 4560 JinKe Rd, Zhangjiang Hi-Tech Park, Pudong New Area, Shanghai 200003 (CN). **LU, Chunliang**; 5 F, JLABS@Shanghai, No. 1 South Bldg., Jin Chuang, 4560 JinKe Rd, Zhangjiang Hi-Tech Park, Pudong New Area, Shanghai 200003 (CN). **ZHANG, Haizhen**; 5 F, JLABS@Shanghai, No. 1 South Bldg., Jin Chuang, 4560 JinKe Rd, Zhangjiang Hi-Tech Park, Pudong New Area, Shanghai 200003 (CN).

(74) Agent: **WU, FENG & ZHANG**; 3FL, Building 4, Yard 38, LinFengErLu Road, Greenland Central Square, Haidian District, Beijing 100089 (CN).

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(54) Title: HETEROCYCLIC GLP-1 AGONISTS

(57) Abstract: The present disclosure relates generally to glucagon-like peptide-1 (GLP-1) agonists and pharmaceutical compositions comprising the same, as well as methods for treating a GLP-1 associated disease, disorder, or condition.

Description

Title of Invention: HETEROCYCLIC GLP-1 AGONISTS

[0001] CROSS REFERENCE TO RELATED APPLICATIONS

[0002] The application claims the benefit of International Patent Application Number PCT/CN2023/076495, filed on February 16, 2023, International Patent Application Number PCT/CN2023/113565, filed on August 17, 2023, and International Patent Application Number PCT/CN2023/141034, filed December 22, 2023, each of which is incorporated herein by reference in its entirety.

FIELD

[0003] This disclosure relates to GLP-1 agonists, pharmaceutical compositions, and methods of use thereof.

BACKGROUND

[0004] Incretin metabolic hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) , are important in the regulation of glucose homeostasis. Medicaments targeting this family of intestinal peptides, such as GLP-1 agonists, have been shown to suppress glucagon production, decrease gastric motility, and increase satiety.

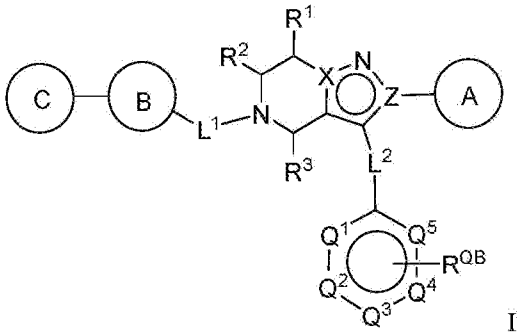
[0005] Diabetes mellitus refers to a group of metabolic disorders characterized by persistent hyperglycemia. The most common form, type 2 diabetes mellitus (T2DM) is an acquired condition that accounts for more than 90%of diabetes cases. Typical onset occurs in obese or otherwise sedentary adults and begins with insulin resistance. Though lifestyle changes can be useful in management of this disorder, patients with T2DM may be required to take antidiabetic medications, including dipeptidyl peptidase-4 inhibitors, SGLT2 inhibitors, and sulfonylureas, among others.

[0006] In healthy individuals, the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) provide tandem modulation of insulin secretory response to glucose ingestion. While this incretin effect is significantly diminished (if at all present) in cases of T2DM, GLP-1 retains insulinotropic properties, even as endocrine pancreatic response to GIP is effectively halted. As such, incretin mimetics and other GLP-1–based therapies can help stimulate insulin production in T2DM patients.

SUMMARY

[0007] The present application describes heterocyclic GLP-1 agonists, as well as pharmaceutical compositions comprising the compounds disclosed herein. Also provided are methods for treating GLP-1–associated diseases, disorders, and conditions.

[0008] In one aspect, provided are compounds of Formula I:



I

[0009] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein ring A, ring B, ring C, X, Z, Q^1, Q^2, Q^3, Q^4, Q^5, L^1, L^2, R^1, R^2, R^3, and R^{QB} are each independently as defined herein.

[0010] This disclosure also provides pharmaceutical compositions comprising one or more compounds of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable excipient.

[0011] Also provided herein are pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable excipient.

[0012] Also provided herein are methods for treating type 2 diabetes mellitus in a patient in need thereof, the methods comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a pharmaceutical composition thereof.

[0013] Also provided herein are methods for treating type 2 diabetes mellitus in a patient, the methods comprising administering to a patient identified or diagnosed as having type 2 diabetes mellitus a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a pharmaceutical composition thereof.

[0014] Also provided herein are methods for treating diabetes mellitus in a patient, the methods comprising determining that the patient has type 2 diabetes mellitus; and administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a pharmaceutical composition thereof. In some embodiments, the step of determining that the patient has type 2 diabetes mellitus includes performing an assay to determine the level of an analyte in a sample from the patient, wherein the analyte is selected from the group consisting of hemogl

obin A1c (HbA1c) , fasting plasma glucose, non-fasting plasma glucose, or any com bination thereof. In some embodiments, the level of HbA1c is greater than or about 6. 5%. In some embodiments, the level of fasting plasma glucose is greater than or about 126 mg/dL. In some embodiments, the level of non-fasting plasma glucose is greater than or about 200 mg/dL.

[0015] In some embodiments, the methods further comprise obtaining a sample from the patient. In some embodiments, the sample is a body fluid s ample. In some embodiments, the patient is about 40 to about 70 years old and is over weight or obese. In some embodiments, the patient has a body mass in dex (BMI) greater than or about 22 kg/m^2. In some embodiments, the patient has a BMI greater than or about 30 kg/m^2.

[0016] In some embodiments, the methods for the treatment of type 2 diabete s mellitus comprise a reduction in fasting plasma glucose levels. In some embodiments , the fasting plasma glucose levels are reduced to about or below 100 mg/dL.

[0017] In some embodiments, the methods for the treatment of type 2 diabete s mellitus comprise a reduction in HbA1c levels. In some embodiments , the HbA1c levels are reduced to about or below 5.7 %.

[0018] In some embodiments, the methods for the treatment of type 2 diabete s mellitus comprise a reduction in glucagon levels.

[0019] In some embodiments, the methods for the treatment of type 2 diabete s mellitus comprise an increase in insulin levels.

[0020] In some embodiments, the methods for the treatment of type 2 diabete s mellitus comprise a decrease in BMI. In some embodiments, the BMI is decreased to about or below 25 kg/m^2.

[0021] In some embodiments, the compound of Formula I, or a pharmaceuticall y acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisome rs, or prodrug thereof, or a pharmaceutical composition thereof, is administered orally.

[0022] In some embodiments, the methods of treatment for type 2 diabetes mellitus further comprise administering an additional therapy or therapeutic agent to the patient. In some embodiments, the additional therapy or therapeutic agent is selected from the group consisting of an antidiabetic agent, an anti-obesity agent, a GLP-1 receptor agonist, an agent to treat non-alcoholic steatohepatitis (NASH) , anti-emetic agent, gastric electrical stimulation, dietary monitoring, physical activity, or any combinations thereof. In some embodiments, the antidiabetic agent is selected from the group consisting of a biguanide, a sulfonylurea, a glitazar, a thiazolidinedione, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a meglitinide, a sodium-glucose linked transporter 2 (SGLT2) inhibitor, a glitazone, a GRP40 agonist, a

glucose-dependent insulinotropic peptide (GIP) , an insulin or insulin analogue, an alpha glucosidase inhibitor, a sodium-glucose linked transporter 1 (SGLT1) inhibitor, or any combinations thereof. In some embodiments, the biguanide is metformin. In some embodiments, the anti-obesity agent is selected from the group consisting of neuropeptide Y receptor type 2 (NPYR2) agonist, a NPYR1 or NPYR5 antagonist, a human proislet peptide (HIP) , a cannabinoid receptor type 1 (CB1R) antagonist, a lipase inhibitor, a melanocortin receptor 4 agonist, a farnesoid X receptor (FXR) agonist, phentermine, zonisamide, a norepinephrine/dopamine reuptake inhibitor, a GDF-15 analog, an opioid receptor antagonist, a cholecystokinin agonist, a serotonergic agent, a methionine aminopeptidase 2 (MetAP2) inhibitor, diethylpropion, phendimetrazine, benzphetamine, a fibroblast growth factor receptor (FGFR) modulator, an AMP-activated protein kinase (AMPK) activator, or any combinations thereof. In some embodiments, the GLP-1 receptor agonist is selected from the group consisting of liraglutide, exenatide, dulaglutide, albiglutide, taspoglutide, lixisenatide, semaglutide, or any combinations thereof. In some embodiments, the agent to treat NASH is selected from the group consisting of an FXR agonist, PF-05221304, a synthetic fatty acid-bile conjugate, an anti-lysyl oxidase homologue 2 (LOXL2) monoclonal antibody, a caspase inhibitor, a MAPK5 inhibitor, a galectin 3 inhibitor, a fibroblast growth factor 21 (FGF21) agonist, a niacin analogue, a leukotriene D4 (LTD4) receptor antagonist, an acetyl-CoA carboxylase (ACC) inhibitor, a ketohexokinase (KHK) inhibitor, an ileal bile acid transporter (IBAT) inhibitor, an apoptosis signal-regulating kinase 1 (ASK1) inhibitor, or any combinations thereof. In some embodiments, the compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a pharmaceutical composition thereof, and the additional therapeutic agent are administered as separate dosages sequentially in any order.

[0023] Also provided herein are methods for modulating insulin levels in a patient in need o f such modulating, the method comprising administering to the patient an effective am ount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a pha rmaceutical composition thereof. In some embodiments, the modulation results in an in crease of insulin levels.

[0024] Also provided herein are methods for modulating glucose levels in a patient in need o f such modulating, the method comprising administering to the patient an effective am ount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a pha rmaceutical composition thereof. In some embodiments, the modulation results in a decrease of glucose levels.

[0025] Also provided herein are methods for treating a GLP-1 associated disease, disorder, or condition, the method comprising administering to a patient in need thereof an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a pharmaceutical composition thereof. In some embodiments, the disease, disorder, or condition is selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, early onset type 2 diabetes mellitus, idiopathic type 1 diabetes mellitus (Type 1b) , youth-onset atypical diabetes (YOAD) , maturity onset diabetes of the young (MODY) , latent autoimmune diabetes in adults (LADA) , obesity, weight gain from use of other agents, gout, excessive sugar craving, hypertriglyceridemia, dyslipidemia, malnutrition-related diabetes, gestational diabetes, kidney disease, adipocyte dysfunction, sleep apnea, visceral adipose deposition, eating disorders, cardiovascular disease, congestive heart failure, myocardial infarction, left ventricular hypertrophy, peripheral arterial disease, stroke, hemorrhagic stroke, ischemic stroke, transient ischemic attacks, atherosclerotic cardiovascular disease, traumatic brain injury, peripheral vascular disease, endothelial dysfunction, impaired vascular compliance, vascular restenosis, thrombosis, hypertension, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis, hyperinsulinemia, impaired glucose metabolism, insulin resistance, hepatic insulin resistance, alcohol use disorder, chronic renal failure, metabolic syndrome, syndrome X, smoking cessation, premenstrual syndrome, angina pectoris, diabetic nephropathy, impaired glucose tolerance, diabetic neuropathy, diabetic retinopathy, macular degeneration, cataract, glomerulosclerosis, arthritis, osteoporosis, treatment of addiction, cocaine dependence, bipolar disorder/major depressive disorder, skin and connective tissue disorders, foot ulcerations, psoriasis, primary polydipsia, non-alcoholic steatohepatitis (NASH) , non-alcoholic fatty liver disease (NAFLD) , ulcerative colitis, inflammatory bowel disease, colitis, irritable bowel syndrome, Crohn's disease, short bowel syndrome, Parkinson's, Alzheimer's disease, impaired cognition, schizophrenia, Polycystic Ovary Syndrome (PCOS) , or any combination thereof. In some embodiments, the disease, disorder, or condition is selected from the group consisting of type 2 diabetes mellitus, early onset type 2 diabetes mellitus, obesity, weight gain from use of other agents, gout, excessive sugar craving, hypertriglyceridemia, dyslipidemia, gestational diabetes, kidney disease, adipocyte dysfunction, sleep apnea, visceral adipose deposition, eating disorders, cardiovascular disease, congestive heart failure, myocardial infarction, left ventricular hypertrophy, peripheral arterial disease, stroke, hemorrhagic stroke, ischemic stroke, transient ischemic attacks, atherosclerotic cardiovascular disease, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis, hyperinsulinemia, impaired glucose

metabolism, insulin resistance, hepatic insulin resistance, alcohol use disorder, chronic renal failure, metabolic syndrome, syndrome X, smoking cessation, premenstrual syndrome, angina pectoris, diabetic nephropathy, impaired glucose tolerance, diabetic neuropathy, diabetic retinopathy, bipolar disorder/major depressive disorder, skin and connective tissue disorders, foot ulcerations, psoriasis, primary polydipsia, non-alcoholic steatohepatitis (NASH) , non-alcoholic fatty liver disease (NAFLD) , short bowel syndrome, Parkinson's disease, Polycystic Ovary Syndrome (PCOS) , or any combination thereof. In some embodiments, the disease, disorder, or condition includes, but is not limited to type 2 diabetes mellitus, early onset type 2 diabetes mellitus, obesity, weight gain from use of other agents, gout, excessive sugar craving, hypertriglyceridemia, dyslipidemia, gestational diabetes, adipocyte dysfunction, visceral adipose deposition, myocardial infarction, peripheral arterial disease, stroke, transient ischemic attacks, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis, hyperinsulinemia, impaired glucose metabolism, insulin resistance, hepatic insulin resistance, chronic renal failure, syndrome X, angina pectoris, diabetic nephropathy, impaired glucose tolerance, diabetic neuropathy, diabetic retinopathy, skin and connective tissue disorders, foot ulcerations, or any combination thereof.

[0026] All publications, patents, and patent applications mentioned in this specification ar e herein incorporated by reference to the same extent as if each individual publicati on, patent, or patent application was specifically and individually indicated to be i ncorporated by reference. To the extent publications and patents or patent applicatio ns incorporated by reference contradict the disclosure contained in the specification , the specification is intended to supersede and/or take precedence over any such con tradictory material.

DESCRIPTION

[0027] Before the present compounds and methods are described, it is to be understood that t he disclosure is not limited to the methodologies, protocols, cell lines, assays, and reagents described, as these may vary. It is also to be understood that the terminol ogy used herein is intended to describe embodiments of the present disclosure, and is in no way intended to limit the scope of the present disclosure as set forth in the appended claims.

[0028] Definitions

[0029] Provided herein are heterocyclic GLP-1 agonists for use in the manageme nt of T2DM and other conditions where activation of GLP-1 activity is useful.

[0030] Before the present compounds and methods are described, it is to be understood that t he disclosure is not limited to the methodologies, protocols, cell lines, assays, and reagents described, as these may vary. It is also to be understood that the terminol

ogy used herein is intended to describe embodiments of the present disclosure, and is in no way intended to limit the scope of the present disclosure as set forth in the appended claims.

[0031] Definitions

[0032] The following description sets forth exemplary embodiments of the pr esent technology. It should be recognized, however, that such description is not inte nded as a limitation on the scope of the present disclosure but is instead provided a s a description of exemplary embodiments.

[0033] As used in the present specification, the following words, phrases and symbols are ge nerally intended to have the meanings as set forth below, except to the extent that t he context in which they are used indicates otherwise.

[0034] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -C (O) NH_2 is attached thro ugh the carbon atom. A dash at the front or end of a chemical group is a matter of co nvenience; chemical groups may be depicted with or without one or mo re dashes without losing their ordinary meaning. A wavy line or a dashed line drawn t hrough a line in a structure indicates a specified point of attachment of a group. Un less chemically or structurally required, no directionality or stereochemistry is ind icated or implied by the order in which a chemical group is written or named.

[0035] The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. F or example, "C_{1-6} alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0036] Reference to "about" a value or parameter herein includes (and descr ibes) embodiments that are directed to that value or parameter per se. In certain emb odiments, the term "about" includes the indicated amount ± 10%. In o ther embodiments, the term "about" includes the indicated amount ± 5%. In certain oth er embodiments, the term "about" includes the indicated amount ± 1%. Also, to the ter m "about x" includes description of "x" . Also, the singular forms "a" and "the" incl ude plural references unless the context clearly dictates otherwise. Thus, e.g., refe rence to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to thos e skilled in the art.

[0037] "Alkyl" refers to an unbranched or branched saturated hydrocarbon ch ain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C_{1-20} alkyl) , 1 to 12 carbon atoms (i.e., C_{1-12} alkyl) , 1 to 8 carbon atoms (i.e., C_{1-8} alkyl) , 1 to 6 carbon atoms (i.e., C_{1-6} alkyl) , or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl) . Example s of alkyl groups include, e.g., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-

hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carb ons is named by chemical name or identified by molecular formula, all positional isom ers having that number of carbons may be encompassed; thus, for exam ple, “butyl” includes n-butyl (i.e., - $(CH_2)_3CH_3$) , sec-butyl (i.e., -CH (CH_3) CH_2CH_3) , isobutyl (i.e., -$CH_2CH(CH_3)_2$) , and tert-butyl (i.e., -C $(CH_3)_3$) , and “propyl” includes n-propyl (i.e., - $(CH_2)_2CH_3$) , and isopropyl (i.e., -CH $(CH_3)_2$) .

[0038] “Alkenyl” refers to an alkyl group containing at least one (e.g., 1-3, or 1) carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkenyl) , 2 to 12 carbon atoms (i.e., C_{2-12} alkenyl) , 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl) , 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl) , or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl) . Examp les of alkenyl groups include, e.g., ethenyl, propenyl, butadienyl (including 1, 2-butadienyl, and 1, 3-butadienyl) .

[0039] “Alkynyl” refers to an alkyl group containing at least one (e.g., 1-3, or 1) carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkynyl) , 2 to 12 carbon atoms (i.e., C_{2-12} alkynyl) , 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl) , 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl) , or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl) . The t erm “alkynyl” also includes those groups having one triple bond and one double bond.

[0040] Certain commonly used alternative chemical names may be used. For ex ample, a divalent group such as a divalent “alkyl” group, a divalent “aryl” group, et c., may also be referred to as an “alkylene” group or an “alkylenyl” group, an “aryle ne” group or an “arylenyl” group, respectively.

[0041] “Alkoxy” refers to the group “alkyl-O-” . Examples of alkoxy groups incl ude, e.g., methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1, 2-dimethylbutoxy.

[0042] “Thioalkoxy” refers to the group “alkyl-S-” .

[0043] “Haloalkyl” refers to an unbranched or branched alkyl group as defin ed above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, i t may be referred to by using a prefix corresponding to the number of halogen moietie s attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be, but are not necessarily, the same halo gen. Examples of haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluorometh yl, trichloromethyl, 2, 2, 2-trifluoroethyl, 1, 2-difluoroethyl, 3-bromo-2-fluoropropyl, 1, 2-dibromoethyl, and the like.

[0044] “Haloalkoxy” refers to an alkoxy group as defined above, wherein one or more (e.g., 1 to 6, or 1 to 3) hydrogen atoms are replaced by a halogen.

[0045] "Hydroxyalkyl" refers to an alkyl group as defined above, wherein on e or more (e.g., 1 to 6, or 1 to 3) hydrogen atoms are replaced by a hydroxy group.

[0046] "Cyanoalkyl" refers to an alkyl group as defined above, wherein one, or one or more (e.g., 1 to 6, or 1 to 3) hydrogen atoms are replaced by a hydroxy gr oup.

[0047] "Alkylthio" refers to the group "alkyl-S-" .

[0048] "Acyl" refers to a group -C (O) R, wherein R is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally subst ituted, as defined herein. Examples of acyl include formyl, acetyl, cylcohexylcarbony l, cyclohexylmethyl-carbonyl, and benzoyl.

[0049] "Amido" refers to both a "C-amido" group which refers to the group -C (O) NR^yR^z and an "N-amido" group which refers to the group $-NR^yC(O)R^z$, wherein R^y and R ^{z} are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a cycloalkyl or heterocyclyl; each of wh ich may be optionally substituted, as defined herein.

[0050] "Amino" refers to the group $-NR^yR^z$ wherein R^y and R^z are independentl y hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0051] "Amidino" refers to -C (NR^y) (NR^z_2) , wherein R^y and R^z are independentl y hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0052] "Aryl" refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used he rein, aryl has 6 to 20 ring carbon atoms (i.e., C_{6-20} aryl) , 6 to 12 carbon ring atoms (i.e., C_{6-12} aryl) , or 6 to 10 carbon ring atoms (i.e., C_{6-10} aryl) . Examples of aryl groups include, e.g., phenyl, naphthyl, fluorenyl, and anthryl. Aryl, howeve r, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl regardless of point of attachment. If one or more aryl groups are fused with a heter ocyclyl, the resulting ring system is heterocyclyl regardless of point of attachment. If one or more aryl groups are fused with a cycloalkyl, the resulting ring system is cycloalkyl regardless of point of attachment.

[0053] "Carbamoyl" refers to both an "O-carbamoyl" group which refers to the group -O-C (O) NR^yR^z and an "N-carbamoyl" group which refers to the group $-NR^yC(O)OR^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, he

terocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substit uted, as defined herein.

[0054] "Carboxyl ester" or "ester" refer to both -OC (O) R^x and -C (O) OR^x, wherein R ^{x} is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroar yl; each of which may be optionally substituted, as defined herein.

[0055] "Cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. Th e term "cycloalkyl" includes cycloalkenyl groups (i.e., the cyclic group having at le ast one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring) . As used herein, cycloalkyl has fro m 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl) , 3 to 14 ring carbon atoms (i.e., C $_{3-12}$ cycloalkyl) , 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl) , 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl) , 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl) , or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl) . Monocyclic groups include, for examp le, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Po lycyclic groups include, for example, bicyclo [2.2.1] heptanyl, bicyclo [2.2.2] octan yl, adamantyl, norbornyl, decalinyl, 7, 7-dimethyl-bicyclo [2.2.1] heptanyl, and the like. Further, the term cycloalkyl is intended to encompass any non-aromatic ring whi ch may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule. Still further, cycloalkyl also includes "spirocycloalkyl" when there are t wo positions for substitution on the same carbon atom, for example spiro [2.5] octany l, spiro [4.5] decanyl, or spiro [5.5] undecanyl.

[0056] "Imino" refers to a group -C (NR^y) R^z, wherein R^y and R^z are each indepen dently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl , or heteroaryl; each of which may be optionally substituted, as defined herein.

[0057] "Halogen" or "halo" refers to atoms occupying group VIIA of the peri odic table, such as fluoro, chloro, bromo, or iodo.

[0058] "Heteroalkyl" refers to an alkyl group in which one or more of the c arbon atoms (and any associated hydrogen atoms) are each independent ly replaced with the same or different heteroatomic group. The term "heteroalkyl " includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be indepe ndently replaced with the same or different heteroatomic group. Heteroatomic groups i nclude, but are not limited to, -NR-, -O-, -S-, -S (O) -, -S (O) $_2$-, and the like, w here R is H, alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl or heterocyclyl, each o f which may be optionally substituted. Examples of heteroalkyl groups include - OCH_3, $-CH_2OCH_3$, $-SCH_3$, $-CH_2SCH_3$, $-NRCH_3$, and $-CH_2NRCH_3$, where R is hydr

ogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be option ally substituted. As used herein, heteroalkyl include 1 to 10 carbon atoms, 1 to 8 ca rbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0059] "Heteroalkylene" refers to a divalent heteroalkyl group. "Heteroalky lene" groups must have at least one carbon and at least one heteroatomic group within the chain. The term "heteroalkylene" includes unbranched or branche d saturated chain having carbon and heteroatoms. By way of example, 1, 2, or 3 carbon atoms may be independently replaced with the same or different hete roatomic group. Heteroatomic groups include, but are not limited to, -NR^y-, -O- , -S-, -S (O) -, -S $(O)_2$-, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alky nyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkylene groups include, e.g., -CH_2OCH_2-, -CH (CH_3) OCH_2-, -$CH_2CH_2OCH_2$-, -OCH_2-, -CH (CH_3) O-, -CH $_2CH_2O$-, -$CH_2CH_2OCH_2CH_2OCH_2$-, -$CH_2CH_2OCH_2CH_2O$-, -CH_2SCH_2-, -CH (CH $_3$) SCH_2-, -$CH_2CH_2SCH_2$-, -$CH_2CH_2SCH_2CH_2SCH_2$-, -SCH_2-, -CH (CH_3) S-, -CH_2 CH_2S-, -$CH_2CH_2SCH_2CH_2S$-, -CH_2S $(O)_2CH_2$-, -CH (CH_3) S $(O)_2CH_2$-, -CH_2CH_2 S $(O)_2CH_2$-, -CH_2CH_2S $(O)_2CH_2CH_2OCH_2$-, -$CH_2NR^yCH_2$-, -CH (CH_3) NR^yCH_2- , -$CH_2CH_2NR^yCH_2$-, -$CH_2CH_2NR^yCH_2CH_2NR^yCH_2$-, etc., where R^y is hydrogen, alk yl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; eac h of which may be optionally substituted, as defined herein) . As used herein, hetero alkylene includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom. As used herein, the term "heteroalkylene" does not include groups such as amides or other functional groups h aving an oxo present on one or more carbon atoms.

[0060] "Heteroaryl" refers to an aromatic group having a single ring or multiple fused rings , with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C_{1-20} heteroaryl) , 3 to 12 ring carbon atoms (i.e., C_{3-12} heteroaryl) , or 3 to 8 carbon ri ng atoms (i.e., C_{3-8} heteroaryl) , and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. In certain instances, heteroaryl include s 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring s ystems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, ox ygen, and sulfur. Examples of heteroaryl groups include, e.g., acridinyl, benzimidazo lyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, be

nzonaphthofuranyl, benzoxazolyl, benzothienyl, benzotriazolyl, benzo [4, 6] imidazo [1, 2-a] pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, diben zothienyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindol yl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1 -oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phth alazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl , pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, thienyl, triazolyl, tetrazolyl, and triazinyl. Examples of t he fused-heteroaryl rings include, but are not limited to, benzo [d] thiazoly l, quinolinyl, isoquinolinyl, benzo [b] thienyl, indazolyl, benzo [d] imidazolyl, pyr azolo [1, 5-a] pyridinyl, and imidazo [1, 5-a] pyridinyl, where the heteroaryl can be bound via either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroa ryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings) . Heteroaryl does not encompass or overlap with aryl as defin ed above.

[0061] "Heterocyclyl" refers to a saturated or partially unsaturated cyclic alkyl group, wit h one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulf ur. The term "heterocyclyl" includes heterocycloalkenyl groups (i.e., the heterocycly l group having at least one double bond) , bridged-heterocyclyl groups, fused-heterocyclyl groups, and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro, a nd may comprise one or more (e.g., 1 to 3) oxo (=O) or N-oxide ($-O^-$) moieties. Any n on-aromatic ring or fused ring system containing at least one heteroatom and one non-aromatic ring is considered a heterocyclyl, regardless of the attachment to the remai nder of the molecule. For example, fused ring systems such as decahydroquinazolinyl, 1, 2, 3, 4-tetrahydroquinazolinyl, and 5, 6, 7, 8-tetrahydroquinazolinyl are heteroc yclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a he teroatom) . Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to a cycloa lkyl, an aryl, or heteroaryl ring, regardless of the attachment to the remainder of t he molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms (i.e., C_{2-20} heterocyclyl) , 2 to 12 ring carbon atoms (i.e., C_{2-12} heterocyclyl) , 2 to 10 ring carb on atoms (i.e., C_{2-10} heterocyclyl) , 2 to 8 ring carbon atoms (i.e., C_{2-8} heterocyclyl) , 3 to 12 ring carbon atoms (i.e., C_{3-12} heterocyclyl) , 3 to 8 ring carbon atoms (i.e., C_{3-8} heterocyclyl) , or 3 to 6 ring carbon atoms (i.e., C_{3-6} heterocyclyl) ; having 1 to 5 rin g heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroat

oms, or 1 ring heteroatom independently selected from nitrogen, sulfur, or oxygen. Examples of heterocyclyl groups include, e.g., azetidinyl, azepinyl, benzodioxolyl, benzo [b] [1, 4] dioxepinyl, 1, 4-benzodioxanyl, benzopyranyl, benzodioxinyl, benzopyranonyl, benzofuranonyl, dioxolanyl, dihydropyranyl, hydropyranyl, thienyl [1, 3] dithianyl, decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, indolinyl, indolizinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, oxetanyl, phenothiazinyl, phenoxazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, tetrahydropyranyl, trithianyl, tetrahydroquinolinyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1, 1-dioxo-thiomorpholinyl. The term "heterocyclyl" also includes "spiroheterocyclyl" when there are two positions for substitution on the same carbon atom. Examples of the spiro-heterocyclyl rings include, e.g., bicyclic and tricyclic ring systems, such as oxabicyclo [2.2.2] octanyl, 2-oxa-7-azaspiro [3.5] nonanyl, 2-oxa-6-azaspiro [3.4] octanyl, and 6-oxa-1-azaspiro [3.3] heptanyl. Examples of the fused-heterocyclyl rings include, but are not limited to, 1, 2, 3, 4-tetrahydroisoquinolinyl, 4, 5, 6, 7-tetrahydrothieno [2, 3-c] pyridinyl, indolinyl, and isoindolinyl, where the heterocyclyl can be bound via either ring of the fused system. The term "heterocyclyl" also includes rings comprising the sulfoximine moiety of R^{QB} (e.g., when R^a and R^b of R^{QB} is fused to the ring comprising Q^1-Q^5, e.g., when R^a and R^{QA}, or R^b and R^{QA}, form a ring), such as, but not limited to, 3, 4-dihydro-1λ^6, 2-thiazine 1-oxide, 1λ^6, 2-thiazine 1-oxide, 4, 5-dihydro-3H-1λ^6-isothiazole 1-oxide, 1- (imino) tetrahydro-1H-1λ^6-thiophene 1-oxide, 4, 5-dihydro-3H-1λ^6, 2-thiazepine 1-oxide, and the like. See, e.g., Cram, et. al., J. Org. Chem., 1973, 38 (1), 20-26.

[0062] "Sulfonyl" refers to the group -S (O) $_2R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0063] "Alkylsulfonyl" refers to the group -S (O) $_2$R, where R is alkyl.

[0064] "Alkylsulfinyl" refers to the group -S (O) R, where R is alkyl.

[0065] The terms "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term "optionally substituted" refers to any one or more (e.g., 1 to 5, or 1 to 3) hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0066] As used herein, the term “compound, ” is meant to include any or all stereoisomers, g eometric isomers, tautomers, and isotopically enriched analogs (e.g., deuterated anal ogs) of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

[0067] Some of the compounds exist as tautomers. Tautomers are in equilibri um with one another. For example, amide containing compounds may exi st in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown, and regardless of the nature of the equilibrium among tautomers, the compounds are un derstood by one of ordinary skill in the art to comprise both amide and imidic acid t automers. Thus, the amide containing compounds are understood to inc lude their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[0068] Any compound or structure given herein, is also intended to represen t unlabeled forms as well as isotopically labeled forms of the compounds. These forms of compounds may also be referred to as “isotopically enriched analogs. ” Isotopicall y labeled compounds have structures depicted herein, except that one or more atoms ar e replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include is otopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and io dine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Various isotopically labeled compounds of the present disclosure, fo r example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporate d. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomograph y (PET) or single-photon emission computed tomography (SPECT) includi ng drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0069] The term “isotopically enriched analogs” includes “deuterated analog s” of compounds described herein in which one or more hydrogens is/ are replaced by deuterium, such as a hydrogen on a carbon atom. Such compounds exhibit increased resistance to metabolism and are thus us eful for increasing the half-life of any compound when administered to a mammal, particularly a human. See, for example, Foster, “Deuterium Isotope Effects in Studie s of Drug Metabolism, ” Trends Pharmacol. Sci. 5 (12) : 524-527 (1984) . Such compounds are synthesized by means well known in the art, for examp le by employing starting materials in which one or more hydrogens ha ve been replaced by deuterium.

[0070] Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and excretion (ADME) . Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life, reduced dosage requirements, and/or an improvement in therapeutic index. An ^{18}F, ^{3}H, ^{11}C labeled compound may be useful for PET or SPECT or other imaging studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in a compound described herein.

[0071] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen, " the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0072] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0073] Provided are also pharmaceutically acceptable salts, hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein. "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0074] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that

may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include, e.g., acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of NH_3, or primary, secondary, tertiary amines, such as salts derived from a N-containing heterocycle, a N-containing heteroaryl, or derived from an amine of formula $N(R^N)_3$ (e.g., $HN^+(R^N)_3$ or (alkyl) $N^+(R^N)_3$) where each R^N is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each is optionally substituted, such as by one or more (e.g., 1-5 or 1-3) substituents (e.g., halo, cyano, hydroxy, amino, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, or haloalkoxy) . Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri (iso-propyl) amine, tri (n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0075] The term “substituted” means that any one or more hydrogen atoms on the designated atom or group is replaced with one or more substituents other than hydrogen, provided that the designated atom’s normal valence is not exceeded. The one or more substituents include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, hydroxy, hydrazino, imino, oxo, nitro, alkylsulfinyl, sulfonic acid, alkylsulfonyl, thiocyanate, thiol, thione, or combinations thereof. In some embodiments, the one or more substituents include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkylalkyl, guanidino, halo, haloalkyl, hydroxyalkyl, haloalkoxy, haloalkoxyalkyl, heteroalkyl, heteroaryl, heterocyclyl, hydroxy, hydrazino, imino, imido, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, thione, or combinations thereof.

[0076] Polymers or similar indefinite structures arrived at by defining substituents with fu rther substituents appended ad infinitum (e.g., a substituted aryl having a substitut ed alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substi tutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((subs tituted aryl) substituted aryl) substituted aryl. Similarly, the above definitions ar e not intended to include impermissible substitution patterns (e.g., methyl substitut ed with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms) . Suc h impermissible substitution patterns are well known to the skilled artisan. When use d to modify a chemical group, the term "substituted" may describe other chemical grou ps defined herein. Unless specified otherwise, where a group is described as optional ly substituted, any substituents of the group are themselves unsubstituted. For examp le, in some embodiments, the term "substituted alkyl" refers to an alkyl group having one or more substituents including hydroxyl, halo, alkoxy, cycloalkyl, heterocyclyl, aryl, and heteroaryl. In other embodiments, the one or more substituents may be furt her substituted with halo, alkyl, haloalkyl, hydroxyl, alkoxy, cycloalkyl, heterocycl yl, aryl, or heteroaryl, each of which is substituted. In other embodiments, the subs tituents may be further substituted with halo, alkyl, haloalkyl, alkoxy, hydroxyl, cy cloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is unsubstituted.

[0077] As used herein, "pharmaceutically acceptable carrier" or "pharmaceut ically acceptable excipient" includes any and all solvents, dispersion media, coating s, antibacterial and antifungal agents, isotonic and absorption delaying agents and t he like. The use of such media and agents for pharmaceutically active substances is w ell known in the art. Except insofar as any conventional media or agent is incompatib le with the active ingredient, its use in the therapeutic compositions is contemplate d. Supplementary active ingredients can also be incorporated into the compositions.

[0078] A "solvate" is formed by the interaction of a solvent and a compound . Solvates of salts of the compounds described herein are also provided. Hydrates of the compounds described herein are also provided.

[0079] As used herein, when a ring is described as being "aromatic, " it means the ring has a continuous, delocalized π-electron system. Typically, the number of out of plane π-electrons corresponds to the Hückel rule (4n+2) . Examples of such rings include: ben zene, pyridine, pyrimidine, pyrazine, pyridazine, pyridone, pyrrole, pyrazole, oxazole, thiazole, isoxazole, isothiazole, and the like. When a ring system comprisi ng at least two rings is described as "aromatic, " it means the ring system comprises one or more aromatic ring (s) . Accordingly, when a ring system comprising at least

two rings is described as “non-aromatic, ” none of the constituent rings of the ri ng system is aromatic.

[0080] As used herein, when a ring is described as being “partially unsaturated, ” it means the ring has one or more additional degrees of unsaturation (in addition to the degre e of unsaturation attributed to the ring itself; e.g., one or more double bonds betwe en constituent ring atoms) , provided that the ring is not aromatic. Examples of such rings include: cyclopentene, cyclohexene, cycloheptene, dihydropyridine, tetrahydrop yridine, dihydropyrrole, dihydrofuran, dihydrothiophene, and the like. When a ring sy stem comprising at least two rings is described as “partially unsaturated, ” it means the ring system comprises one or more partially unsaturated ring (s) , provided that none of the constituent rings of the ring system is aromatic.

[0081] As used herein, the term “compound, ” is meant to include all stereo isomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compo unds herein identified by name or structure as one particular tautomeric form are int ended to include other tautomeric forms unless otherwise specified.

[0082] The term “tautomer” as used herein refers to compounds whose structu res differ markedly in arrangement of atoms, but which exist in easy and rapid equili brium, and it is to be understood that compounds provided herein may be depicted as different tautomers, and when compounds have tautomeric forms, all ta utomeric forms are intended to be within the scope of the disclosure, and the naming of the compounds does not exclude any tautomer.

[0083] The term “GLP-1R” or “GLP-1 receptor” as used herein is meant to include, wit hout limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisens e polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous, and/or orthologous GLP-1R molecules, isoforms, precursors , mutants, variants, derivatives, splice variants, alleles, different species, and ac tive fragments thereof.

[0084] The term “GLP-1 associated disease” as used herein is meant to include, without li mitation, all those diseases, disorders, or conditions in which modulating glucagon-like peptide-1 (GLP-1) receptor signaling can alter the pathology and/o r symptoms and/or progression of the disease, disorder, or condition.

[0085] The term “GLP-1 agonist” or “GLP-1 RA” as used herein refers to an agonist of the glucagon-like peptide-1 (GLP-1) receptor. GLP-1 RAs enhance glu cose-dependent insulin secretion; suppress inappropriately elevated gluca gon levels, both in fasting and postprandial states; and slow gastric emptying. Karla et al., Glucagon-like peptide-1 receptor agonists in the treatment of type 2 diab etes: Past, present, and future, Indian J Endocrinol Metab. 2016 Mar-Apr; 20 (2) : 254 –267. GLP-1 RAs have been shown to treat type 2 diabetes. Examples of GLP-

1 RAs include, but are not limited to, albiglutide (Tanzeum®), dulaglutide (LY21 89265, Trulicity®) , efpeglenatide, exenatide (Byetta®, Bydureon®, Exendin-4) , liraglutide (Victoza®, NN2211) , lixisenatide (Lyxumia®), semaglutide (Ozempic®), tirzepatide, ZP29 29, NNC0113-0987, BPI-3016, and TT401.

[0086] The term “pharmaceutically acceptable” as used herein indicates that the compound, or salt or composition thereof is compatible chemically and/or toxicol ogically with the other ingredients comprising a formulation and/or the subject being treated therewith.

[0087] The term “administration” or “administering” refers to a method of g iving a dosage of a compound or pharmaceutical composition to a vertebrate or inverte brate, including a mammal, a bird, a fish, or an amphibian. The method of administrat ion can vary depending on various factors, e.g., the components of the pharmaceutical composition, the site of the disease, and the severity of the disease.

[0088] The terms “effective amount” or “effective dosage” or “pharmaceutica lly effective amount” or “therapeutically effective amount, ” as used herein, refer t o a sufficient amount of a chemical entity (e.g., a compound of Formula I, or a pharm aceutically acceptable salt or solvate thereof) being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated , and can include curing the disease. “Curing” means that the symptoms of active dise ase are eliminated. The result includes reduction and/or alleviation of the signs, sy mptoms, or causes of a disease, or any other desired alteration of a biological syste m. For example, an “effective amount” for therapeutic uses is the amount of the compo sition comprising a compound as disclosed herein required to provide a clinically sig nificant decrease in disease symptoms. An appropriate “effective” am ount in any individual case is determined using any suitable technique, such as a dos e escalation study. In some embodiments, a “therapeutically effective amount” of a co mpound as provided herein refers to an amount of the compound that is effective as a monotherapy or combination therapy.

[0089] The term “excipient” or “pharmaceutically acceptable excipient” mean s a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In some embodiments, each component is “pharmaceutically acceptable” i n the sense of being compatible with the other ingredients of a pharmaceutical formul ation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/ri sk ratio. See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.; Lippi ncott Williams & Wilkins: Philadelphia, PA, 2005; Handbook of Pharma

ceutical Excipients, 6th ed.; Rowe et al., Eds.; The Pharmaceutical Press and the Ame rican Pharmaceutical Association: 2009; Handbook of Pharmaceutical A dditives, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; Pharmaceutical Preformulation and Formulation, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

[0090] The term “pharmaceutical composition” refers to a mixture of a compo und of Formula I, or a pharmaceutically acceptable salt or solvate thereof as provide d herein with other chemical components (referred to collectively herein as “excipien ts”) , such as carriers, stabilizers, diluents, dispersing agents , and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administerin g a compound exist in the art including, but not limited to, rectal, oral, intravenou s, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

[0091] The terms “treat, ” “treating, ” and “treatment, ” in the context of treating a disea se, disorder, or condition, are meant to include alleviating or abrogating a disorder , disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or to slowing the progression, spread or worsening of a disea se, disorder or condition or of one or more symptoms thereof.

[0092] The term “preventing, ” as used herein, is the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a s ymptom thereof.

[0093] The terms “subject, ” “patient, ” or “individual, ” as used herein, are used intercha ngeably and refers to any animal, including mammals such as mice, rats, other rodents , rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some em bodiments, the term refers to a subject, particularly a mammalian subject, for whom d iagnosis, prognosis, or therapy is desired or needed. In some embodiments, the subjec t is a human. In some embodiments, the subject has experienced and/or exhibited at le ast one symptom of the disease, disorder, or condition to be treated and/or prevented.

[0094] The terms “treatment regimen” and “dosing regimen” are used intercha ngeably to refer to the dose and timing of administration of each therapeutic agent i n a combination.

[0095] The term “pharmaceutical combination, ” as used herein, refers to a pharmaceutical tr eatment resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients.

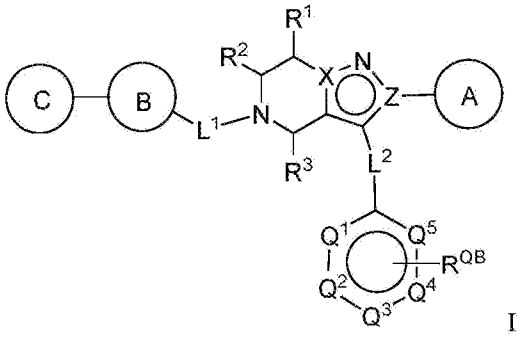
[0096] The term “combination therapy” as used herein refers to a dosing reg imen of two different therapeutically active agents (i.e., the components or combinat ion partners of the combination) , wherein the therapeutically active agents are admi

nistered together or separately in a manner prescribed by a medical care taker or acc ording to a regulatory agency as defined herein.

[0097] The term “modulate, ” “modulating, ” or “modulation, ” as used herein, refers to a re gulation or an adjustment (e.g., increase or decrease) and can include, for example a gonism, partial agonism or antagonism.

[0098] Compounds

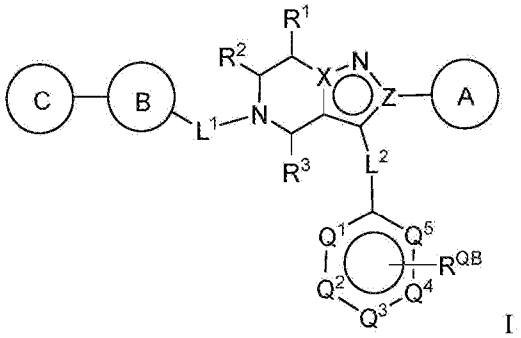
[0099] Provided herein are compounds of Formula I:



I

[0100] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mi xture of stereoisomers, or prodrug thereof, wherein ring A, ring B, ring C, X, Z, Q^1, Q^2 , Q^3, Q^4, Q^5, L^1, L^2, R^1, R^2, R^3, and R^{QB} are each independently as defined herein.

[0101] In one aspect, provided herein are compounds of Formula I:



I

[0102] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mi xture of stereoisomers, or prodrug thereof, wherein:

[0103] X is C and Z is N, or X is N and Z is C;

[0104] Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2, Q^3, and Q^4 are each indepen dently N, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, and Q^4 is CR^{QB}; or

[0105] Q^1 is a bond; and Q^2, Q^3, Q^4, and Q^5 are each independently O, S, N, NH, NR^c, CR^{QA} , or CR^{QB}, provided that at least one of Q^2, Q^3, Q^4, and Q^5 is CR^{QB};

[0106] provided that the ring including Q^1-Q^5 is aromatic;

[0107] R^{QB} is –S (O) (=NR^a) R^b, – (CR^iR^j) $_n$–S (O) (=NR^a) R^b, –N=S (O) (R^{1a}) R^b, or – O– (CR^iR^j) $_n$–S (O) (=NR^a) R^b;

[0108] R^{1a} is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0109] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0110] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0111] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0112] n is 1, 2, 3, 4, 5, or 6;

[0113] each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

[0114] or R^a and R^i, or R^b and R^i, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0115] each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

[0116] or one R^i and one R^j, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0117] or one R^i and one R^j on adjacent carbon atoms taken together with the atom (s) to which each is attached form an alkene, wherein said alkene is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

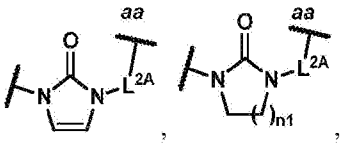
[0118] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each in

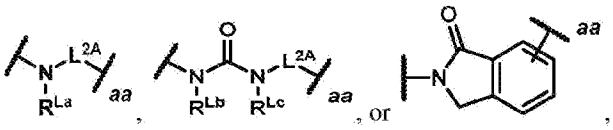
dependently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

[0119] or two R^{QA} on adjacent carbon atoms, taken together with the atom to which eac h is attached form a 5-8 membered heterocyclyl, wherein said ring is optio nally substituted with 1-2 independently selected R^h;

[0120] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

[0121] L^2 is C_{6-10} aryl optionally substituted with 1-2 independently selected R^h, 5-10 membered heteroaryl optionally substituted with 1-2 independently selected R^h,





wherein aa represents the point of attachment to the ring containing Q^1-Q^5;

[0122] n1 is 1, 2, or 3;

[0123] L^{2A} is a bond or C_{1-10} alkylene;

[0124] R^{La} is hydrogen, C_{1-6} alkyl, or -C (O) (C_{1-6} alkyl) ;

[0125] each of R^{Lb} and R^{Lc} is independently hydrogen or C_{1-6} alkyl;

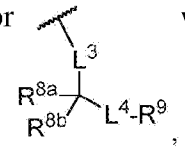
[0126] Ring A is C_{6-10} aryl, C_{5-7} cycloalkyl, 5-7 membered heterocyclyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-5 independently selected R^A;

[0127] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0128] R^1, R^2, and R^3 are each independently hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the group consisting of h alo, hydroxy, and C_{1-6} alkoxy;

[0129] L^1 is -C (O) -, -CH_2-, -CH (C_{1-6} alkyl) -, or -S (O) $_2$-;

[0130] Ring B is a 5, 6-fused heteroaryl having from 5 to 8 carbon atoms and from 1 to 3 het eroatoms independently selected from O, S, and N, wherein Ring B is substituted with R^8 and optionally substituted with 1 to 4 substituents independently selected from halo , oxo, and C_{1-6} alkyl;

[0131] R^8 is phenyl, 5-6 membered heteroaryl, or  wherein the phenyl or 5-6 membered heteroaryl are substituted with R^{8c}, and are optionally further substituted with 1-3 independently selected R^h;

[0132] L^3 is a bond or C_{1-3} alkylene;

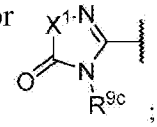
[0133] L^4 is a bond or C_{1-5} alkylene;

[0134] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{3-15} cycloalkyl; or

[0135] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted with 1-3 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently selected R^f;

[0136] each R^{8c} is independently -C (O) OH, -S (O) $_2$OH, -S (O) $_2$$NH_2$, -$L^5$-$C_{1-6}$ alkyl, -L^5-C_{3-6} cycloalkyl, -L^5-C_{6-10} aryl, -L^5-5-6 membered heterocyclyl, -L^5- (5-6 membered heteroaryl) , wherein each is optionally substituted with 1-6 substituents independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0137] each L^5 is independently -C (O) -, -C (O) O-, -OC (O) -, -S (O) $_{1-2}$-, -S (O) $_2$O-, -S (O) $_2$NH-, or -NHS (O) $_2$-;

[0138] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally substituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0139] X^1 is O or S;

[0140] R^{9a} is hydrogen or C_{1-6} alkyl;

[0141] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0142] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0143] Ring C is 3-12 membered heterocyclyl, C_{3-15} cycloalkyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-3 R^{Ca};

[0144] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0145] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0146] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

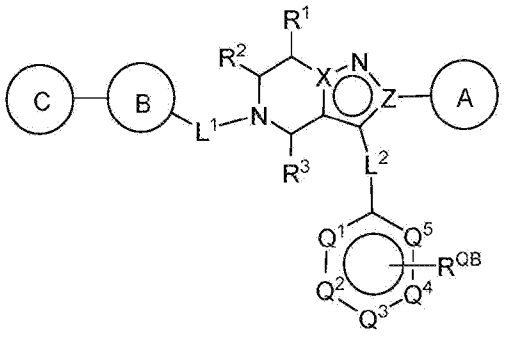
[0147] R^e is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0148] each R^f is independently halo, hydroxy, -NR^cR^d, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0149] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, -NR^cR^d, or 3 to 12 memb ered heterocyclyl optionally substituted with one or more substituents each independe ntly selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0150] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, -NH_2, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0151] In one aspect, provided herein are compounds of Formula I:



I

[0152] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mi xture of stereoisomers, or prodrug thereof, wherein:

[0153] X is C and Z is N, or X is N and Z is C;

[0154] Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2, Q^3, and Q^4 are each indepen dently N, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, and Q^4 is CR^{QB}; or

[0155] Q^1 is a bond; and Q^2, Q^3, Q^4, and Q^5 are each independently O, S, N, NH, NR^c, CR^{QA} , or CR^{QB}, provided that at least one of Q^2, Q^3, Q^4, and Q^5 is CR^{QB};

[0156] provided that the ring including Q^1-Q^5 is aromatic;

[0157] R^{QB} is –S (O) (=NR^a) R^b or – (CR^iR^j) $_n$–S (O) (=NR^a) R^b;

[0158] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0159] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0160] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0161] n is 1, 2, 3, 4, 5, or 6;

[0162] each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

[0163] or R^a and R^i, or R^b and R^i, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0164] each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

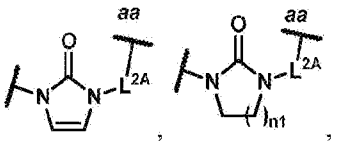
[0165] or one R^i and one R^j, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

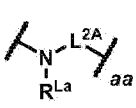
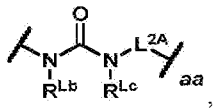
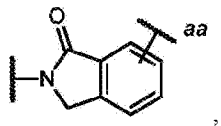
[0166] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and $-C(O)(C_{1-6}$ alkyl), C_{6-10} aryl optionally substituted with 1-3 independently selected $-C(O)(C_{1-6}$ alkyl), and 5-10 membered heteroaryl optionally substituted with 1-6 independently selected R^g;

[0167] or two R^{QA} on adjacent carbon atoms, taken together with the atom to which each is attached form a 5-8 membered heterocyclyl, wherein said ring is optionally substituted with 1-2 independently selected R^h;

[0168] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

[0169] L^2 is C_{6-10} aryl optionally substituted with 1-2 independently selected R^h, 5-10 membered heteroaryl optionally substituted with 1-2 independently selected R^h,



wherein aa represents the point of attachment to the ring containing Q^1-Q^5;

[0170] n1 is 1, 2, or 3;

[0171] L^{2A} is a bond or C_{1-10} alkylene;

[0172] R^{La} is hydrogen, C_{1-6} alkyl, or -C (O) (C_{1-6} alkyl) ;

[0173] each of R^{Lb} and R^{Lc} is independently hydrogen or C_{1-6} alkyl;

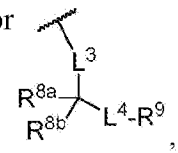
[0174] Ring A is C_{6-10} aryl, C_{5-7} cycloalkyl, 5-7 membered heterocyclyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-5 independently selected R^A;

[0175] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0176] R^1, R^2, and R^3 are each independently hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the group consisting of h alo, hydroxy, and C_{1-6} alkoxy;

[0177] L^1 is -C (O) -, -CH_2-, -CH (C_{1-6} alkyl) -, or -S (O) $_2$-;

[0178] Ring B is a 5, 6-fused heteroaryl having from 5 to 8 carbon atoms and from 1 to 3 het eroatoms independently selected from O, S, and N, wherein Ring B is substituted with R^8 and optionally substituted with 1 to 4 substituents independently selected from halo , oxo, and C_{1-6} alkyl;

[0179] R^8 is phenyl, 5-6 membered heteroaryl, or  wherein the phenyl or 5-6 membered heteroaryl are substituted with R^{8c}, and are optionally further subst ituted with 1-3 independently selected R^h;

[0180] L^3 is a bond or C_{1-3} alkylene;

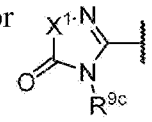
[0181] L^4 is a bond or C_{1-5} alkylene;

[0182] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo an d C_{3-15} cycloalkyl; or

[0183] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted with 1-3 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0184] each R^{8c} is independently -C (O) OH, -S (O) $_2$OH, -S (O) $_2$$NH_2$, -$L^5$-$C_{1-6}$ alkyl, -L^5-C_{3-6} cycloalkyl, -L^5-C_{6-10} aryl, -L^5-5-6 membered heterocyclyl, -L^5- (5-6 membered hetero aryl) , wherein each is optionally substituted with 1-6 substituents independently selec ted from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0185] each L^5 is independently -C (O) -, -C (O) O-, -OC (O) -, -S (O) $_{1-2}$-, -S (O) $_2$O-, -S (O) $_2$NH-, or -NHS (O) $_2$-;

[0186] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0187] X^1 is O or S;

[0188] R^{9a} is hydrogen or C_{1-6} alkyl;

[0189] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0190] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0191] Ring C is 3-12 membered heterocyclyl, C_{3-15} cycloalkyl, or 5-10 membered heter oaryl, each of which is optionally substituted with 1-3 R^{Ca};

[0192] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0193] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0194] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are

each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

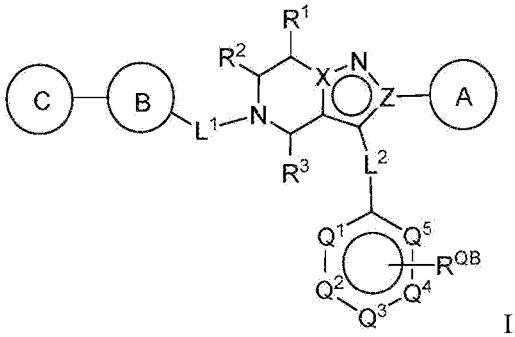
[0195] R^e is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0196] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0197] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 memb ered heterocyclyl optionally substituted with one or more substituents each independe ntly selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0198] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0199] In one aspect, provided herein are compounds of Formula I:



I

[0200] or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0201] X is C and Z is N, or X is N and Z is C;

[0202] Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2, Q^3, and Q^4 are each indepen dently N, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, and Q^4 is CR^{QB}; or

[0203] Q^1 is a bond; and Q^2, Q^3, Q^4, and Q^5 are each independently O, S, N, NH, NR^c, CR^{QA} , or CR^{QB}, provided that at least one of Q^2, Q^3, Q^4, and Q^5 is CR^{QB};

[0204] provided that the ring including Q^1-Q^5 is aromatic;

[0205] R^{QB} is –S (O) (=NR^a) R^b or – (CR^iR^j) $_n$–S (O) (=NR^a) R^b;

[0206] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C $_{1-6}$ alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0207] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents ea ch independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6}

cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents ea ch independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0208] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said ring is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0209] n is 1, 2, 3, 4, 5, or 6;

[0210] each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

[0211] or R^a and R^i, or R^b and R^i, taken together with the atoms to which each is at tached form a 5-8 membered heterocyclyl, wherein said ring is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

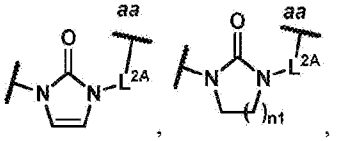
[0212] each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

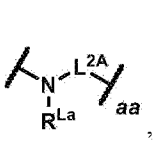
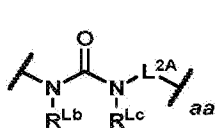
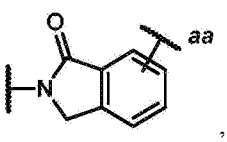
[0213] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each in dependently selected from the group consisting of C_{1-6} alkyl and $-C(O)(C_{1-6}$ alkyl), C_{6-10} aryl optionally substituted with 1-3 independently selected $-C(O)(C_{1-6}$ alkyl), and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

[0214] or two R^{QA} on adjacent carbon atoms, taken together with the atom to which eac h is attached form a 5-8 membered heterocyclyl, wherein said ring is optio nally substituted with 1-2 independently selected R^h;

[0215] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said ring is optio nally substituted with 1-2 independently selected R^h;

[0216] L^2 is C_{6-10} aryl optionally substituted with 1-2 independently selected R^h, 5-10 membered heteroaryl optionally substituted with 1-2 independently selected R^h,



wherein aa represents the point of attachment to the ring containing Q^1-Q^5;

[0217] n1 is 1, 2, or 3;

[0218] L^{2A} is a bond or C_{1-10} alkylene;

[0219] R^{La} is hydrogen, C_{1-6} alkyl, or -C (O) (C_{1-6} alkyl) ;

[0220] each of R^{Lb} and R^{Lc} is independently hydrogen or C_{1-6} alkyl;

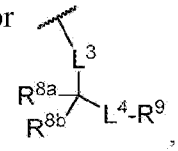
[0221] Ring A is C_{6-10} aryl, C_{5-7} cycloalkyl, 5-7 membered heterocyclyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-5 independently selected R^A;

[0222] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0223] R^1, R^2, and R^3 are each independently hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the group consisting of h alo, hydroxy, and C_{1-6} alkoxy;

[0224] L^1 is -C (O) -, -CH_2-, -CH (C_{1-6} alkyl) -, or -S (O) $_2$-;

[0225] Ring B is a 5, 6fused heteroaryl having from 5 to 8 carbon atoms and from 1 to 3 heteroatoms independently selected from O, S, and N, wherein Ring B is s ubstituted with R^8 and optionally substituted with 1 to 4 substituents independently s elected from halo, oxo, and C_{1-6} alkyl;

[0226] R^8 is phenyl, 5-6 membered heteroaryl, or  , wherein the phenyl or 5-6 membered heteroaryl are substituted with R^{8c} and are optionally further substi tuted with 1-3 independently selected R^h;

[0227] L^3 is a bond or C_{1-3} alkylene;

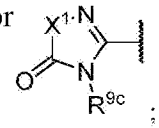
[0228] L^4 is a bond or C_{1-5} alkylene;

[0229] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo an d C_{3-15} cycloalkyl; or

[0230] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C $_{3-15}$ cycloalkyl ring which is optionally substituted with 1-3 independently selected C $_{1-6}$ alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0231] each R^{8c} is independently -C (O) OH, -S (O) $_2$OH, -S (O) $_2NH_2$, -L^5-C_{1-6} alkyl, -L^5-C_{3-6} cycloalkyl, -L^5-C_{6-10} aryl, -L^5-5-6 membered heterocyclyl, -L^5- (5-6 membered hetero aryl) , wherein each is optionally substituted with 1-6 substituents independently selec ted from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0232] each L^5 is independently -C (O) -, -C (O) O-, -OC (O) -, -S (O) $_{1-2}$-, -S (O) $_2$O-, -S (O) $_2$NH-, or -NHS (O) $_2$-;

[0233] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, or  ;

[0234] X^1 is O or S;

[0235] R^{9a} is hydrogen or C_{1-6} alkyl;

[0236] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0237] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0238] Ring C is 3-12 membered heterocyclyl, C_{3-15} cycloalkyl, or 5-10 membered heter oaryl, each of which is optionally substituted with 1-3 R^{Ca};

[0239] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0240] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0241] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

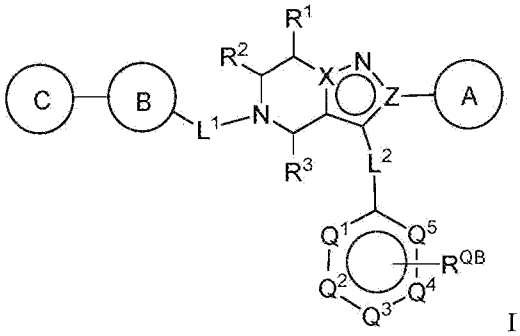
[0242] R^e is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0243] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0244] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 memb ered heterocyclyl optionally substituted with one or more substituents each independe ntly selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0245] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0246] In one aspect, provided herein are compounds of Formula I:



I

[0247] or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0248] X is C and Z is N, or X is N and Z is C;

[0249] Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2, Q^3, and Q^4 are each independently N, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, and Q^4 is CR^{QB}; or

[0250] Q^1 is a bond; and Q^2, Q^3, Q^4, and Q^5 are each independently O, S, N, NH, NR^c, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, Q^4, and Q^5 is CR^{QB};

[0251] provided that the ring including Q^1-Q^5 is aromatic;

[0252] R^{QB} is –S (O) (=NR^a) R^b or – (CR^iR^j) $_n$–S (O) (=NR^a) R^b;

[0253] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0254] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0255] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said ring is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0256] n is 1, 2, 3, 4, 5, or 6;

[0257] each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

[0258] or R^a and R^i, or R^b and R^i, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said ring is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

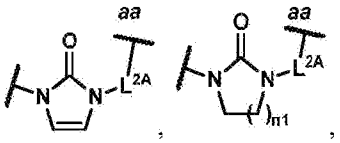
[0259] each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

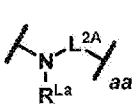
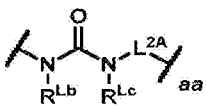
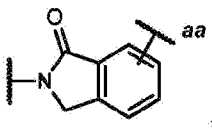
[0260] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, -C (O) NR^c R^d, -S (O) $_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

[0261] or two R^{QA} on adjacent carbon atoms, taken together with the atom to which eac h is attached form a 5-8 membered heterocyclyl, wherein said ring is optio nally substituted with 1-2 independently selected R^h;

[0262] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said ring is optio nally substituted with 1-2 independently selected R^h;

[0263] L^2 is C_{6-10} aryl optionally substituted with 1-2 independently selected R^h, 5-10 membered heteroaryl optionally substituted with 1-2 independently selected R^h,






wherein aa represents the point of attachment to the ring containing Q^1-Q^5;

[0264] n1 is 1, 2, or 3;

[0265] L^{2A} is a bond or C_{1-10} alkylene;

[0266] R^{La} is hydrogen, C_{1-6} alkyl, or -C (O) (C_{1-6} alkyl) ;

[0267] each of R^{Lb} and R^{Lc} is independently hydrogen or C_{1-6} alkyl;

[0268] Ring A is C_{6-10} aryl, C_{5-7} cycloalkyl, 5-7 membered heterocyclyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-5 independently selected R^A;

[0269] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

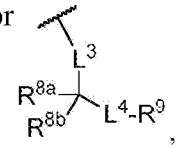
[0270] R^1, R^2, and R^3 are each independently hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the group consisting of h alo, hydroxy, and C_{1-6} alkoxy;

[0271] L^1 is -C (O) -, -CH_2-, -CH (C_{1-6} alkyl) -, or -S (O) $_2$-;

[0272] Ring B is a 5, 6-fused heteroaryl having from 5 to 8 carbon atoms and from 1 to 3 het eroatoms independently selected from O, S, and N, wherein Ring B is optionally substi tuted with 1 to 4 substituents independently selected from halo, oxo, and C_{1-6} alkyl;

[0273] wherein bb represents point of attachment to L^1;

[0274] R^4, R^5, R^6, and R^7 are each independently hydrogen, halo, or C_{1-6} alkyl;

[0275] R^8 is phenyl, 5-6 membered heteroaryl, or  wherein the phenyl or 5-6 membered heteroaryl are substituted with R^{8c} and are optionally further substi tuted with 1-3 independently selected R^h;

[0276] L^3 is a bond or C_{1-3} alkylene;

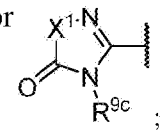
[0277] L^4 is a bond or C_{1-5} alkylene;

[0278] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo an d C_{3-15} cycloalkyl; or

[0279] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C $_{3-15}$ cycloalkyl ring which is optionally substituted with 1-3 independently selected C $_{1-6}$ alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0280] each R^{8c} is independently -C (O) OH, -S (O) $_2$OH, -S (O) $_2NH_2$, -L^5-C_{1-6} alkyl, -L^5-C_{3-6} cycloalkyl, -L^5-C_{6-10} aryl, -L^5-5-6 membered heterocyclyl, -L^5- (5-6 membered hetero aryl) , wherein each is optionally substituted with 1-6 substituents independently selec ted from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0281] each L^5 is independently -C (O) -, -C (O) O-, -OC (O) -, -S (O) $_{1-2}$-, -S (O) $_2$O-, -S (O) $_2$NH-, or -NHS (O) $_2$-;

[0282] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, or  ;

[0283] X^1 is O or S;

[0284] R^{9a} is hydrogen or C_{1-6} alkyl;

[0285] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0286] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0287] Ring C is 3-12 membered heterocyclyl, C_{3-15} cycloalkyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-3 R^{Ca};

[0288] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0289] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring atom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0290] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

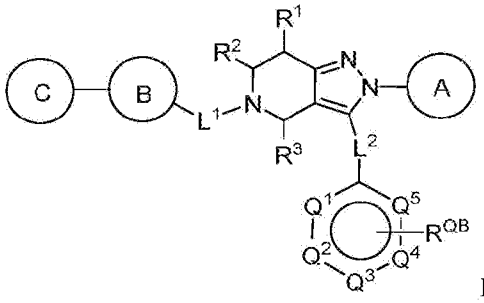
[0291] R^e is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0292] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3-12 membered heterocyclyl which is optionally substituted with 1-4 substituents each independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0293] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0294] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

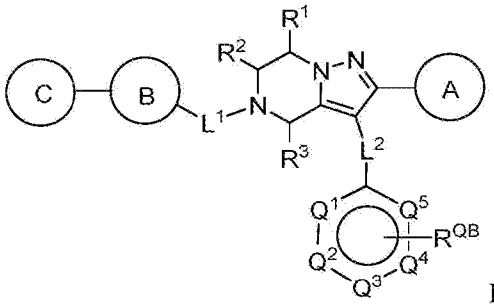
[0295] In some embodiments, provided herein is a compound of Formula II:



II

[0296] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein ring A, ring B, ring C, Q^1, Q^2, Q^3, Q^4, Q^5, L^1, L^2, R^1, R^2, R^3, and R^{QB} are each independently as defined herein.

[0297] In some embodiments, provided herein is a compound of Formula III:



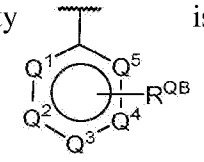
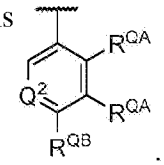
III

[0298] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein ring A, ring B, ring C, Q^1, Q^2, Q^3, Q^4, Q^5, L^1, L^2, R^1, R^2, R^3, and R^{QB} are each independently as defined herein.

[0299] In some embodiments, Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2, Q^3, and Q^4 are each independently N, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, and Q^4 is CR^{QB}.

[0300] In some embodiments, Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2 and Q^3 are each independently N or CR^{QA}, and Q^4 is CR^{QB}. In some embodiments, Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2 and Q^4 are each independently N or CR^{QA}, and Q^3 is CR^{QB}. In some embodiments, Q^1 and Q^5 are each independently N or CR^{QA}; and Q^3 and Q^4 are each independently N or CR^{QA}, and Q^2 is CR^{QB}.

[0301] In some embodiments, Q^1 and Q^5 are each independently CR^{QA}; and Q^2 and Q^3 are each independently N or CR^{QA}, and Q^4 is CR^{QB}. In some embodiments, Q^1 and Q^5 are each independently CR^{QA}; and Q^2 and Q^4 are each independently N or CR^{QA}, and Q^3 is CR^{QB}. In some embodiments, Q^1 and Q^5 are each independently CR^{QA}; and Q^3 and Q^4 are each independently N or CR^{QA}, and Q^2 is CR^{QB}.

[0302] In some embodiments, the moiety  is  .

[0303] In some embodiments, each R^{QA} is independently hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or $-NR^cR^d$.

[0304] In some embodiments, R^c and R^d are each independently hydrogen or C_{1-6} alkyl.

[0305] In some embodiments, Q^1 and Q^5 are each independently CR^{QA}; where each R^{QA} is independently hydrogen or halo.

[0306] In some embodiments, one of Q^2, Q^3, and Q^4 is N.

[0307] In some embodiments, Q^2, Q^3, and Q^4 are each independently CR^{QA} or CR^{QB}, provided that at least one of Q^2, Q^3, and Q^4 is CR^{QB}.

[0308] In some embodiments, R^{QB} is $-S(O)(=NR^a)R^b$.

[0309] In some embodiments, R^{QB} is –S (O) (=NR^a) R^b; R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents ea ch independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl; and R^b is C $_{1-6}$ alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C $_{3-6}$ cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl.

[0310] In some embodiments, R^{QB} is –S (O) (=NR^a) R^b; and R^a and R^b taken together w ith the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein s aid heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl.

[0311] In some embodiments, R^{QB} is –S (O) (=NR^a) R^b; and R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[0312] In some embodiments, R^{QB} is –S (O) (=NR^a) R^b; and R^a and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[0313] In some embodiments, R^{QB} is –S (O) (=NR^a) R^b; and R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[0314] In some embodiments, R^{QB} is – (CR^iR^j) $_n$–S (O) (=NR^a) R^b.

[0315] In some embodiments, R^{QB} is – (CR^iR^j) $_n$–S (O) (=NR^a) R^b; n is 1, 2, 3, 4 , 5, or 6; R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C $_{1-6}$ alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C $_{1-3}$ alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently s elected C_{1-3} alkyl; and R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C $_{3-6}$ cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents ea

ch independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl.

[0316] In some embodiments, R^{QB} is $-(CR^iR^j)_n-S(O)(=NR^a)R^b$; and R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl.

[0317] In some embodiments, R^{QB} is $-(CR^iR^j)_n-S(O)(=NR^a)R^b$; n is 1, 2, 3, 4, 5, or 6; and each R^i is independently hydrogen, halo, or C_{1-6} alkyl; and each R^j is independently hydrogen, halo, or C_{1-6} alkyl.

[0318] In some embodiments, R^{QB} is $-(CR^iR^j)_n-S(O)(=NR^a)R^b$; and one R^i and one R^j, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl.

[0319] In some embodiments, R^{QB} is $-(CR^iR^j)_n-S(O)(=NR^a)R^b$; n is 1, 2, 3, 4, 5, or 6; and R^a and R^i, or R^b and R^i, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl.

[0320] In some embodiments, R^{QB} is $-(CR^iR^j)_n-S(O)(=NR^a)R^b$; and R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[0321] In some embodiments, R^{QB} is $-(CR^iR^j)_n-S(O)(=NR^a)R^b$; R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h; and one R^i and one R^j on adjacent carbon atoms taken together with the atom (s) to which each is attached form an alkene, wherein said alkene is optionally substituted with 1-3 independently selected C_{1-6} alkyl.

[0322] In some embodiments, R^{QB} is $-(CR^iR^j)_n-S(O)(=NR^a)R^b$; and R^a and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[0323] In some embodiments, R^{QB} is $-(CR^iR^j)_n-S(O)(=NR^a)R^b$; and R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[0324] In some embodiments, R^{QB} is $-N=S(O)(R^{1a})R^b$.

[0325] In some embodiments, R^{QB} is –N=S (O) (R^{1a}) R^b; R^{1a} is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl; and R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl.

[0326] In some embodiments, R^{QB} is –O- $(CR^iR^j)_n$–S (O) (=NR^a) R^b.

[0327] In some embodiments, R^{QB} is –O– $(CR^iR^j)_n$–S (O) (=NR^a) R^b; n is 1, 2, 3, 4, 5, or 6; R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl; and R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl.

[0328] In some embodiments, R^{QB} is –O– $(CR^iR^j)_n$–S (O) (=NR^a) R^b; and R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl.

[0329] In some embodiments, R^{QB} is –O– $(CR^iR^j)_n$–S (O) (=NR^a) R^b; n is 1, 2, 3, 4, 5, or 6; and each R^i is independently hydrogen, halo, or C_{1-6} alkyl; and each R^j is independently hydrogen, halo, or C_{1-6} alkyl.

[0330] In some embodiments, R^{QB} is –O– $(CR^iR^j)_n$–S (O) (=NR^a) R^b; and one R^i and one R^j, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl.

[0331] In some embodiments, R^{QB} is –O– $(CR^iR^j)_n$–S (O) (=NR^a) R^b; n is 1, 2, 3, 4, 5, or 6; and R^a and R^i, or R^b and R^i, taken together with the atoms to which each is at

tached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally sub stituted with 1-3 independently selected C_{1-6} alkyl.

[0332] In some embodiments, R^{QB} is –O– $(CR^iR^j)_n$–S (O) (=NR^a) R^b; and R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[0333] In some embodiments, R^{QB} is –O– $(CR^iR^j)_n$–S (O) (=NR^a) R^b; and R^a and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

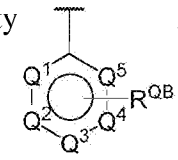
[0334] In some embodiments, R^{QB} is –O– $(CR^iR^j)_n$–S (O) (=NR^a) R^b; and R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

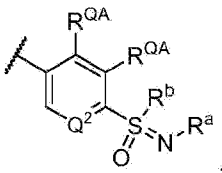
[0335] In some embodiments, R^{QB} is –S (O) (=NR^a) R^b or –C_{1-6} alkyl-S (O) (=NR^a) R^b.

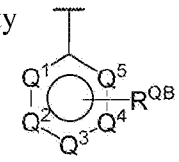
[0336] In some embodiments, R^{QB} is–C_{1-6} alkyl-S (O) (=NR^a) R^b.

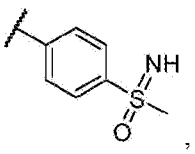
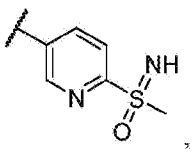
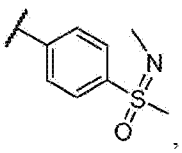
[0337] In some embodiments, R^{QB} is –S (O) (=NR^a) R^b or –CH_2-S (O) (=NR^a) R^b.

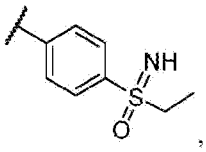
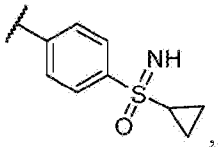
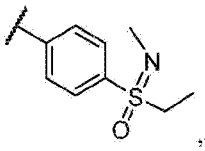
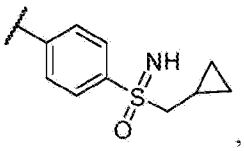
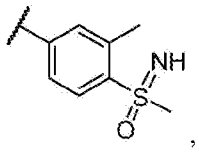
[0338] In some embodiments, R^{QB} is –CH_2-S (O) (=NR^a) R^b.

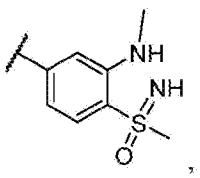
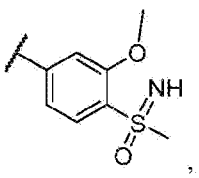
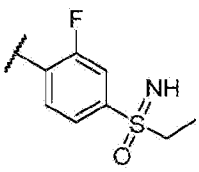
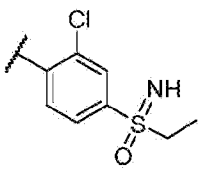
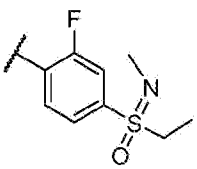
[0339] In some embodiments, the moiety  is

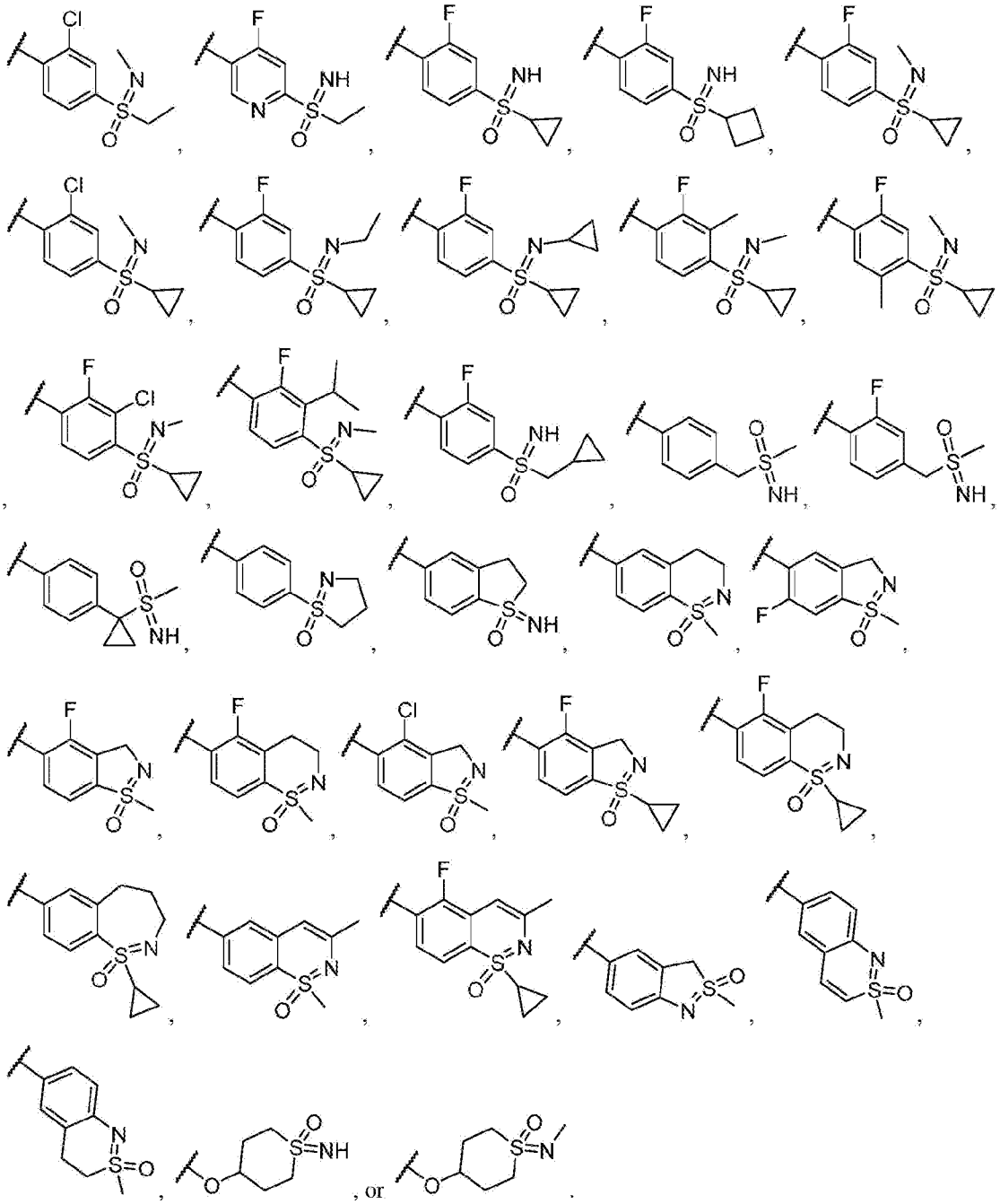
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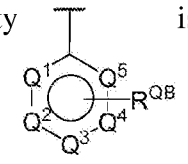
In some embodiments, the moiety  is

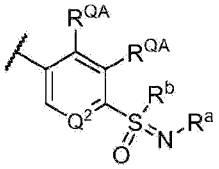
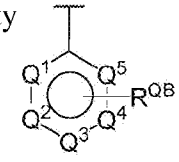
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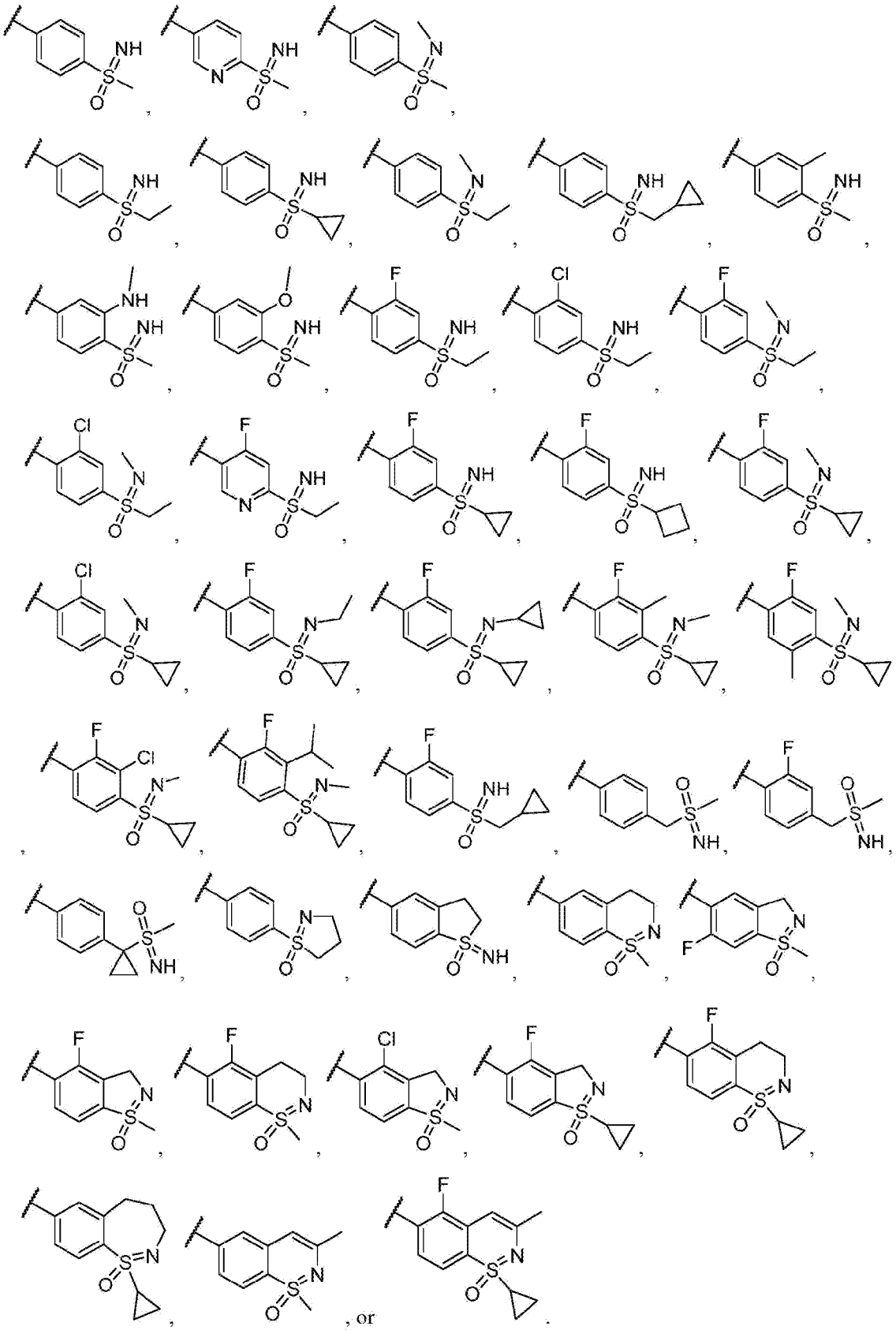
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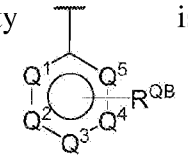
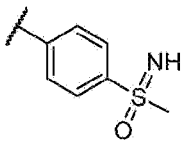
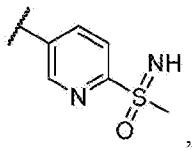
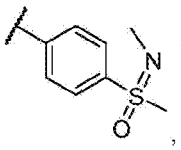
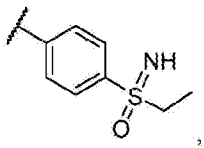
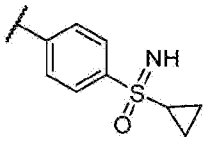
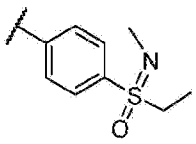
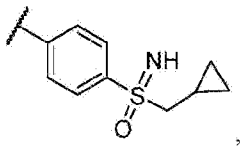
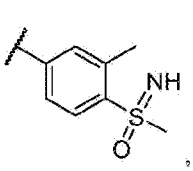
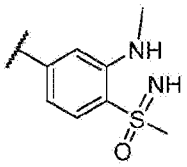
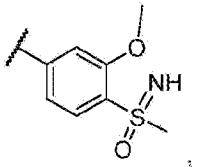
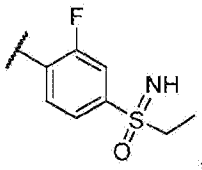
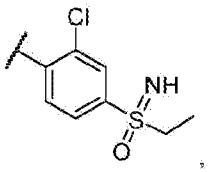
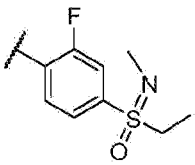
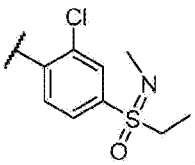
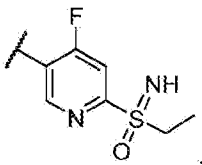
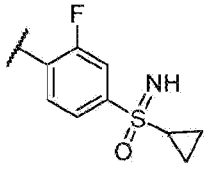
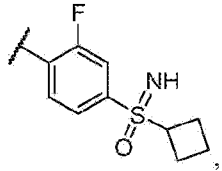
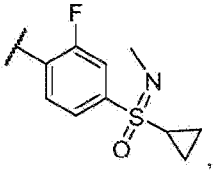
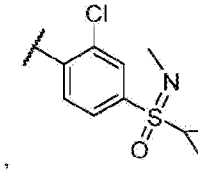
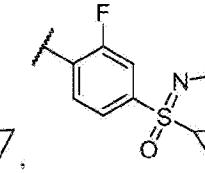
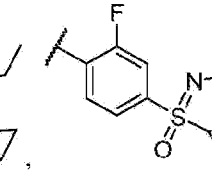
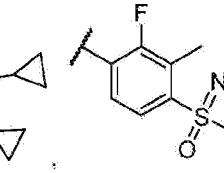
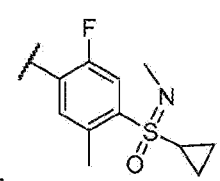
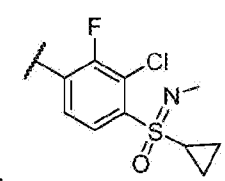
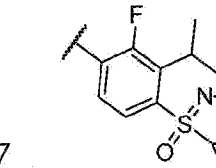
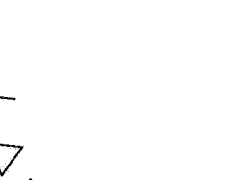
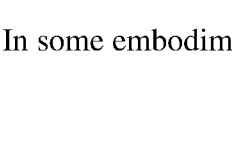
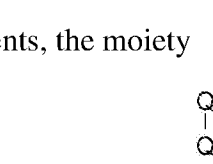
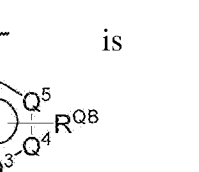
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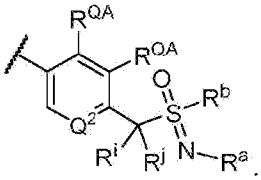
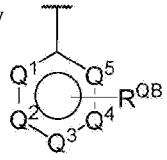
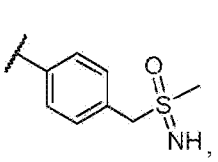
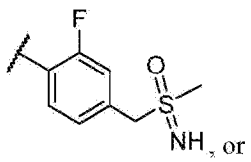
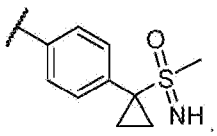


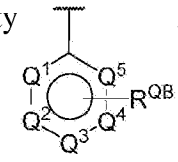
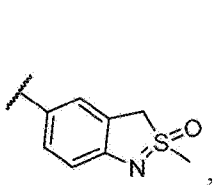
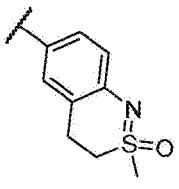
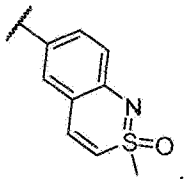
[0340] In some embodiments, the moiety  is

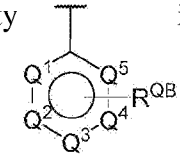
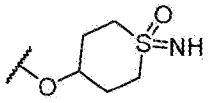
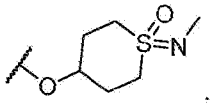
 . In some embodiments, the moiety  is

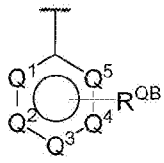
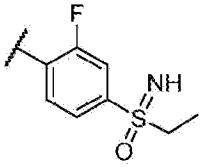
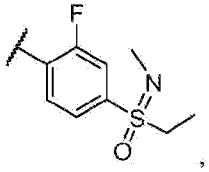
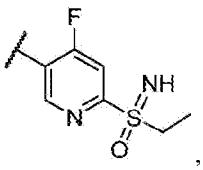
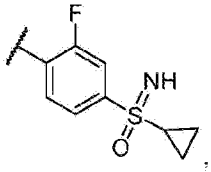
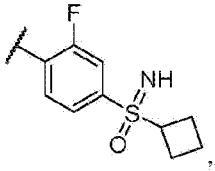
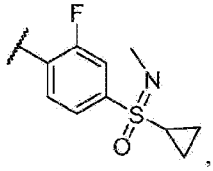
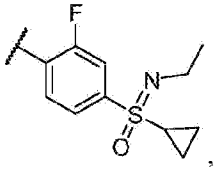
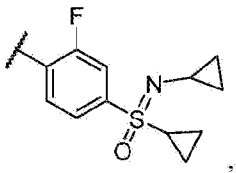
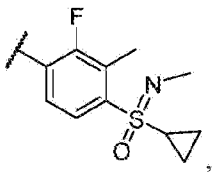
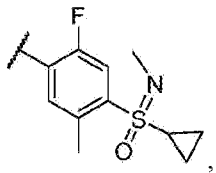
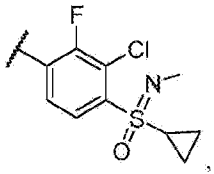
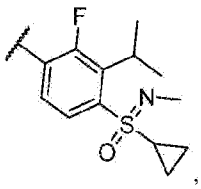
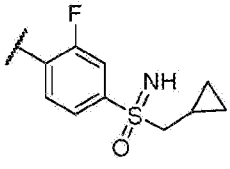
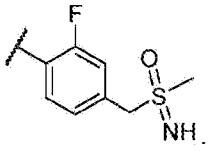


[0341] In some embodiments, the moiety  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  , or .

[0342] In some embodiments, the moiety is  . In some embodiments, the moiety  is  ,  , or  .

[0343] In some embodiments, the moiety  is  ,  , or  .

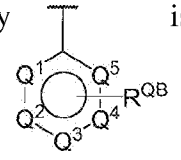
[0344] In some embodiments, the moiety  is  or  .

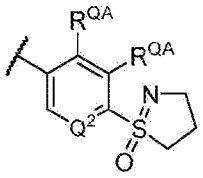
[0345] In some embodiments, the moiety  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

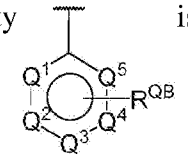
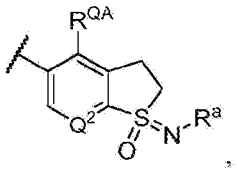
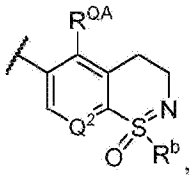
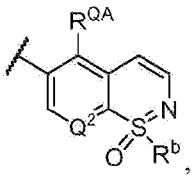
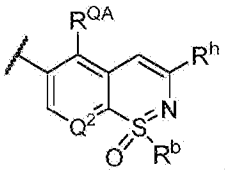
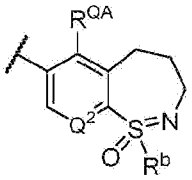
[0346] In some embodiments, R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substit uted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl.

[0347] In some embodiments, R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, or C_{3-6} cycloalkyl.

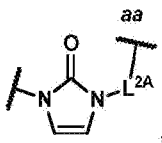
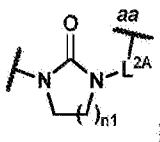
[0348] In some embodiments, R^a and R^b taken together with the atoms to which each is att ached form a 5-8 membered heterocyclyl. In some embodiments, R^a and R^b

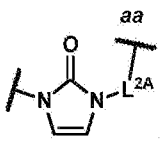
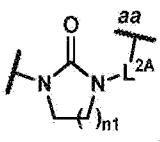
taken together with the atoms to which each is attached form a 5 membered heterocycl yl. In some embodiments, the moiety is 

 .

[0349] In some embodiments, R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein s aid ring is optionally substituted with 1-2 independently selected R^h. In some embodim ents, the moiety is   ,    , or  .

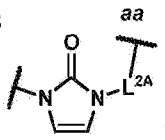
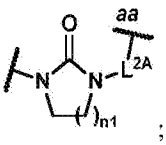
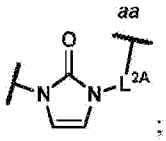
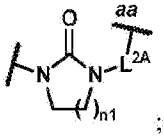
[0350] In some embodiments, R^a and R^i, or R^b and R^i, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said ring is optio nally substituted with 1-3 independently selected C_{1-6} alkyl.

[0351] In some embodiments, L^2 is C_{6-10} aryl optionally substituted with 1-2 independently s elected R^h, 5-10 membered heteroaryl optionally substituted with 1-2 independently s elected R^h,  , or  ; wherein aa represents the point of attachment to the ring containing Q^1-Q^5.

[0352] In some embodiments, L^2 is C_{6-10} aryl optionally substituted with 1-2 independently s elected R^h,  , or  ; wherein aa represents the point of attachment to the ring containing Q^1-Q^5.

[0353] In some embodiments, L^2 is C_{6-10} aryl optionally substituted with 1-2 independently s elected R^h.

[0354] In some embodiments, L^2 is 5-10 membered heteroaryl optionally substituted with 1-2 independently selected R^h.

[0355] In some embodiments, L^2 is  or  ; wherein aa repres ents the point of attachment to the ring containing Q^1-Q^5. In some embodiments, L^2 is  ; wherein aa represents the point of attachment to the ring containing Q^1-Q^5. In some embodiments, L^2 is  ; wherein aa represents the point of attachment to the ring containing Q^1-Q^5.

[0356] In some embodiments, L^{2A} is a bond.

[0357] In some embodiments, R^1 is hydrogen. In some embodiments, R^2 is hydrogen. In some embodiments, R^1 and R^2 are each hydrogen.

[0358] In some embodiments, R^3 is hydrogen or C_{1-6} alkyl. In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is C_{1-6} alkyl. In some embodiments, R^3 is hydrogen or methyl. In some embodiments, R^3 is methyl. In some embodiments, R^3 is methyl and is connected to the ring to which it is attached in the (S) -configuration. In some embodiments, R^3 is hydrogen or methyl, where the methyl is connected to the ring to which it is attached in the (S) -configuration.

[0359] In some embodiments, L^1 is -C (O) -,

[0360] In some embodiments, Ring A is C_{6-10} aryl optionally substituted with 1-5 independently selected R^A. In some embodiments, Ring A is C_{5-7} cycloalkyl optionally substituted with 1-5 independently selected R^A. In some embodiments, Ring A is 5-7 membered heterocyclyl optionally substituted with 1-5 independently selected R^A. In some embodiments, Ring A is 5-10 membered heteroaryl optionally substituted with 1-5 independently selected R^A.

[0361] In some embodiments, each R^A is independently halo, C_{1-6} alkyl, or C_{3-6} cycloalkyl.

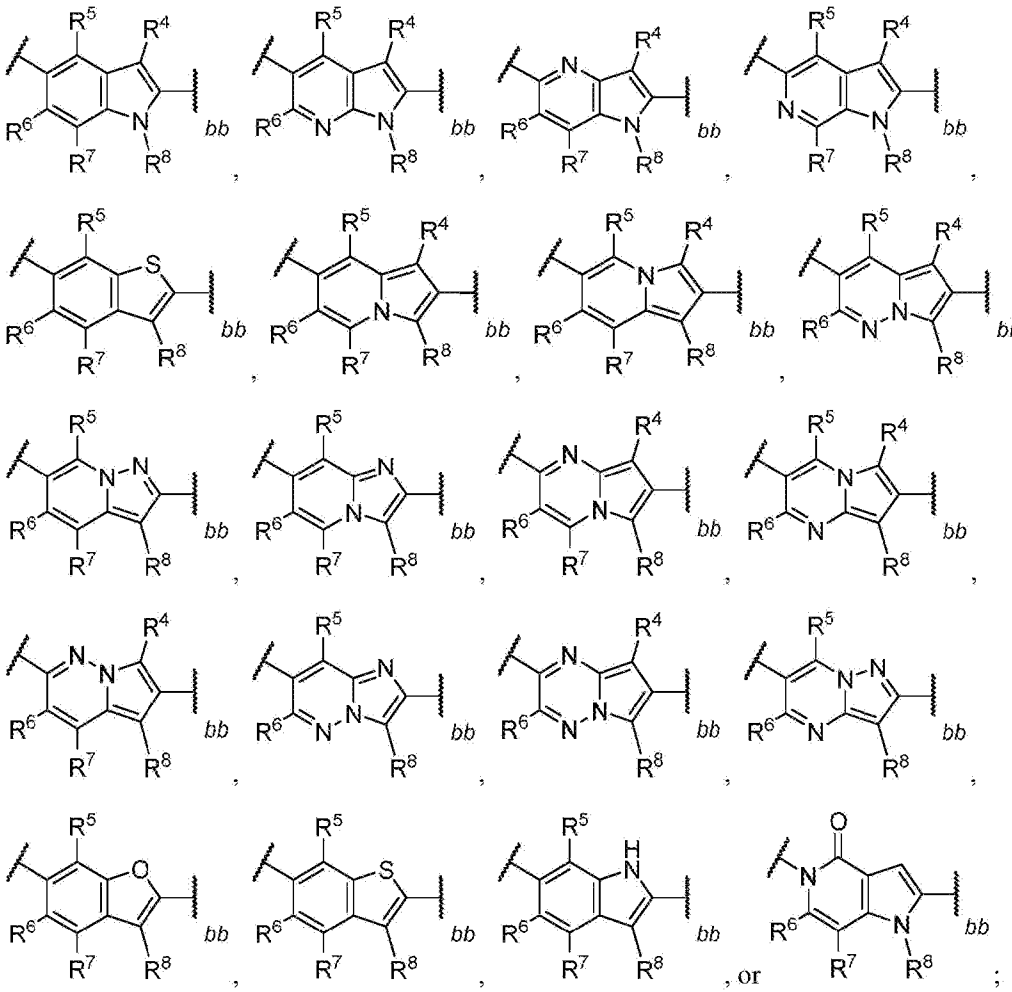
[0362] In some embodiments, Ring A is C_{6-10} aryl which is optionally substituted with 1-5 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl.

[0363] In some embodiments, Ring A is phenyl substituted with 2-3 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, and C_{3-6} cycloalkyl.

[0364] In some embodiments, Ring B is a 5, 6-fused heteroaryl having from 5 to 8 carbon atoms and from 1 to 3 heteroatoms independently selected fr om O, S, and N, wherein Ring B is substituted with R^8 and optionally s ubstituted with 1 to 4 substituents independently selected from halo, oxo, and C $_{1-6}$ alkyl; and the 5-membered ring of the 5, 6-fused heteroaryl is bonded to L ^{1}. In some embodiments, Ring B is a 5, 6-fused heteroaryl having from 5 to 8 carbon atoms and from 1 to 3 heteroatoms independently selected fr om O, S, and N, wherein Ring B is substituted with R^8 and optionally s ubstituted with 1 to 4 substituents independently selected from halo, oxo, and C_{1-6} alkyl; the 5-membered ring of the 5, 6-fused heteroaryl is bonded to L^1; and ring C is b onded to the 6-membered ring of the 5, 6-fused heteroaryl.

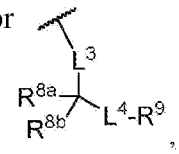
[0365] In some embodiments, Ring B is a 5, 6-fused heteroaryl having from 5 to 8 carbon atoms and from 1 to 3 heteroatoms independently selected fr om O, S, and N, wherein Ring B is optionally substituted with 1 to 4 substituents ind ependently selected from halo, oxo, and C_{1-6} alkyl; and the 5-membered ring of the 5, 6-fused heteroaryl is bonded to L^1. In some embodiments, Ring B is a 5, 6-fused heteroaryl having from 5 to 8 carbon atoms and from 1 to 3 het eroatoms independently selected from O, S, and N, wherein Ring B is optionally substi tuted with 1 to 4 substituents independently selected from halo, oxo, and C_{1-6} alkyl; the 5-membered ring of the 5, 6-fused heteroaryl is bonded to L^1; and ring C is b onded to the 6-membered ring of the 5, 6-fused heteroaryl.

[0366] In some embodiments, Ring B is:



[0367] wherein bb represents point of attachment to L^1;

[0368] R^4, R^5, R^6, and R^7 are each independently hydrogen, halo, or C_{1-6} alkyl;

[0369] R^8 is phenyl, 5-6 membered heteroaryl, or  wherein the phenyl or 5-6 membered heteroaryl are substituted with R^{8c} and are optionally further substituted with 1-3 independently selected R^h;

[0370] L^3 is a bond or C_{1-3} alkylene;

[0371] L^4 is a bond or C_{1-5} alkylene;

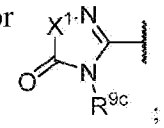
[0372] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{3-15} cycloalkyl; or

[0373] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted with 1-3 independently selected C

$_{1-6}$ alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0374] each R^{8c} is independently -C (O) OH, -S (O) $_2$OH, -S (O) $_2$NH$_2$, -L^5-C_{1-6} alkyl, -L^5-C_{3-6} cycloalkyl, -L^5-C_{6-10} aryl, -L^5-5-6 membered heterocyclyl, -L^5- (5-6 membered hetero aryl) , wherein each is optionally substituted with 1-6 substituents independently selec ted from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0375] each L^5 is independently -C (O) -, -C (O) O-, -OC (O) -, -S (O) $_{1-2}$-, -S (O) $_2$O-, -S (O) $_2$NH-, or -NHS (O) $_2$-;

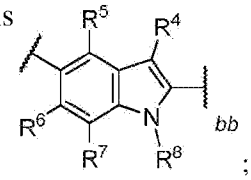
[0376] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, or  ;

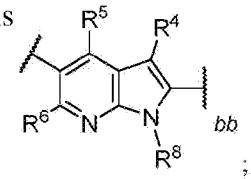
[0377] X^1 is O or S;

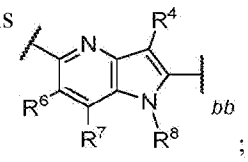
[0378] R^{9a} is hydrogen or C_{1-6} alkyl;

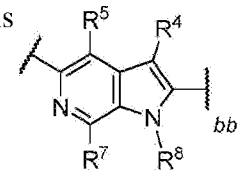
[0379] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

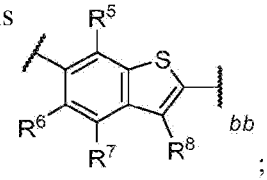
[0380] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) .

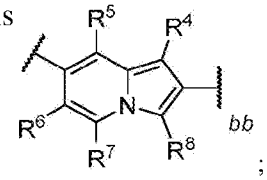
[0381] In some embodiments, Ring B is  wherein bb represents point of att achment to L^1.

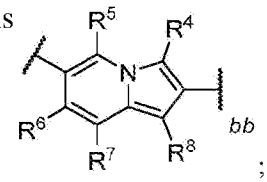
[0382] In some embodiments, Ring B is  wherein bb represents point of att achment to L^1.

[0383] In some embodiments, Ring B is  wherein bb represents point of att achment to L^1.

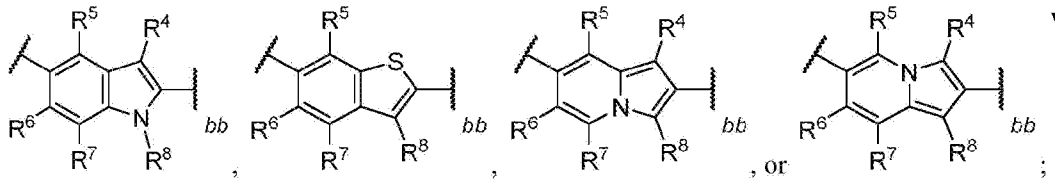
[0384] In some embodiments, Ring B is  wherein bb represents point of attachment to L^1.

[0385] In some embodiments, Ring B is  wherein bb represents point of attachment to L^1.

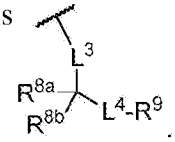
[0386] In some embodiments, Ring B is  wherein bb represents point of attachment to L^1.

[0387] In some embodiments, Ring B is  wherein bb represents point of attachment to L^1.

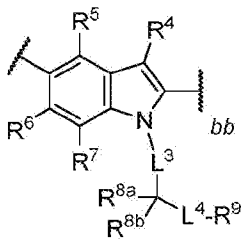
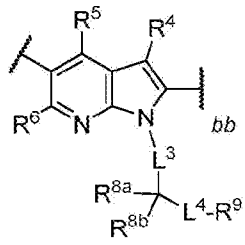
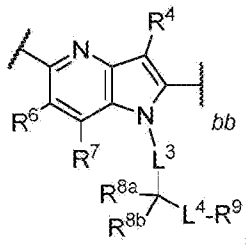
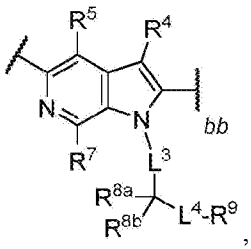
[0388] In some embodiments, Ring B is:

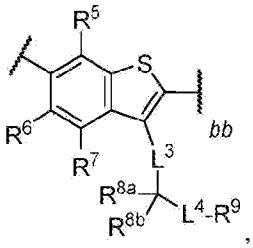
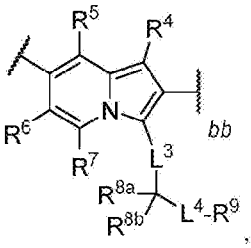
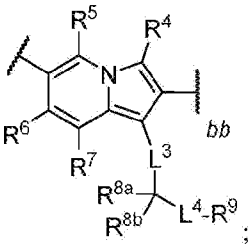
[0389]  wherein bb represents point of attachment to L^1;

[0390] In some embodiments, R^8 is phenyl substituted with R^{8c}. In some embodiments, R^8 is 5-6 membered heteroaryl substituted with R^{8c}. In some embodiments, R^8 is pyridyl substituted with R^{8c}. In some embodiments, R^8 is phenyl substituted with R^{8c} or pyridyl substituted with R^{8c}.

[0391] In some embodiments, R^8 is  .

[0392] In some embodiments, Ring B is:

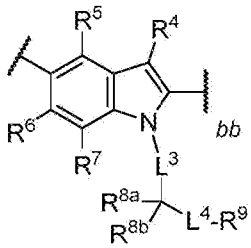
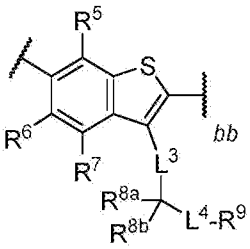
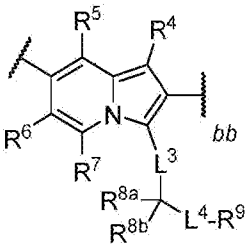
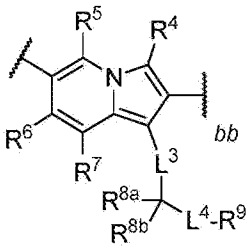





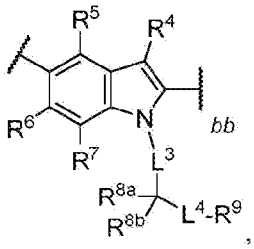
wherein bb repres

ents point of attachment to L^1.

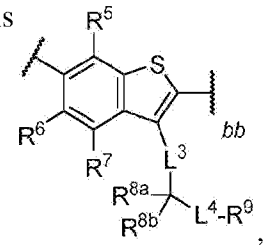
[0393] In some embodiments, Ring B is:

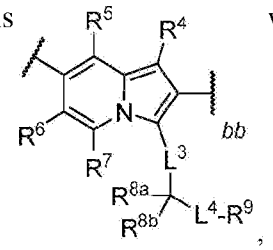
[0394] wherein bb represents point of attachment to L^1.

[0395] In some embodiments, Ring B is  wherein bb repres

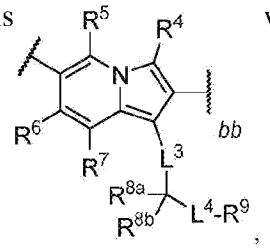
ents point of attachment to L^1.

[0396] In some embodiments, Ring B is  wherein bb repres

ents point of attachment to L^1.

[0397] In some embodiments, Ring B is  wherein bb repres

ents point of attachment to L^1.

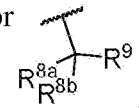
[0398] In some embodiments, Ring B is  wherein bb repres

ents point of attachment to L^1.

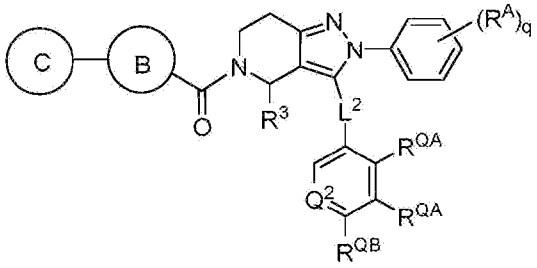
[0399] In some embodiments, L^3 is a bond.

[0400] In some embodiments, L^4 is a bond.

[0401] In some embodiments, L^3 is a bond and L^4 is a bond.

[0402] In some embodiments, R^8 is phenyl substituted with R^{8c}, 5-6 membered hetero aryl substituted with R^{8c}, or  .

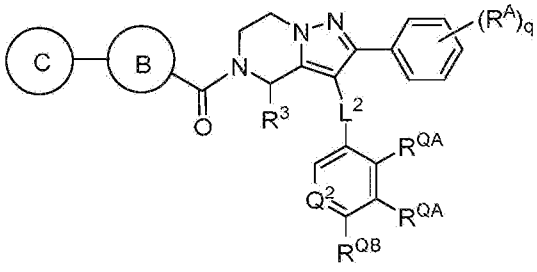
[0403] In some embodiments, provided herein is a compound of Formula IIA:



IIA

[0404] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mi xture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; and rin g B, ring C, Q^2, L^2, R^A, R^3, R^{QA}, and R^{QB} are each independently as defined herein.

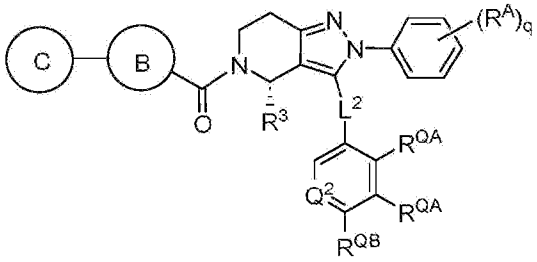
[0405] In some embodiments, provided herein is a compound of Formula IIB:



IIB

[0406] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; and ring B, ring C, Q^2, L^2, R^A, R^3, R^{QA}, and R^{QB} are each independently as defined herein.

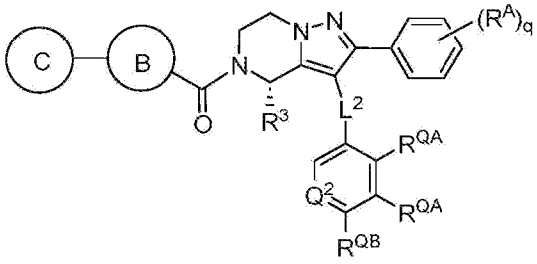
[0407] In some embodiments, provided herein is a compound of Formula IIA- (S) :



IIA-(*S*)

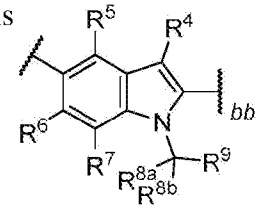
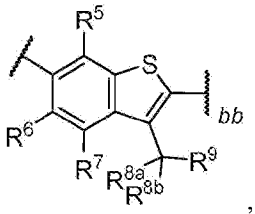
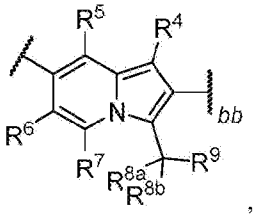
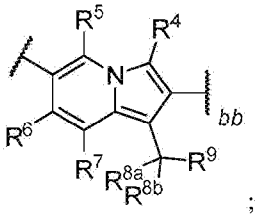
[0408] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; and ring B, ring C, Q^2, L^2, R^A, R^3, R^{QA}, and R^{QB} are each independently as defined herein.

[0409] In some embodiments, provided herein is a compound of Formula IIB- (S) :



IIB-(*S*)

[0410] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; and ring B, ring C, Q^2, L^2, R^A, R^3, R^{QA}, and R^{QB} are each independently as defined herein.

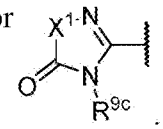
[0411] In some embodiments, Ring B is  ,  ,  , or  ; wherein bb represents point of attachment to L^1.

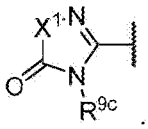
[0412] In some embodiments, R^4 is hydrogen or halo.

[0413] In some embodiments, R^5, R^6, and R^7 are each hydrogen.

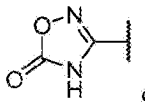
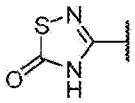
[0414] In some embodiments, R^{8a} and R^{8b} are each independently hydrogen.

[0415] In some embodiments, R^{8a} and R^{8b} taken together with the carbon at om to which each is attached forms a C_{3-15} cycloalkyl ring which is optional ly substituted C_{1-6} alkyl.

[0416] In some embodiments, R^9 is a 5-6 membered heteroaryl optionally substituted with 1 -3 independently selected R^{9c}, or  In some embodiments, R^9 is a 5-

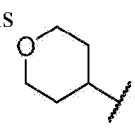
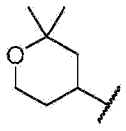
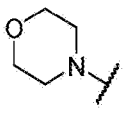
6 membered heteroaryl optionally substituted with 1-3 independently selected R^{9c} . In some embodiments, R^9 is 

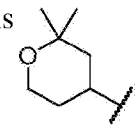
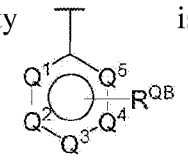
[0417] In some embodiments, R^9 is a 6 membered heteroaryl.

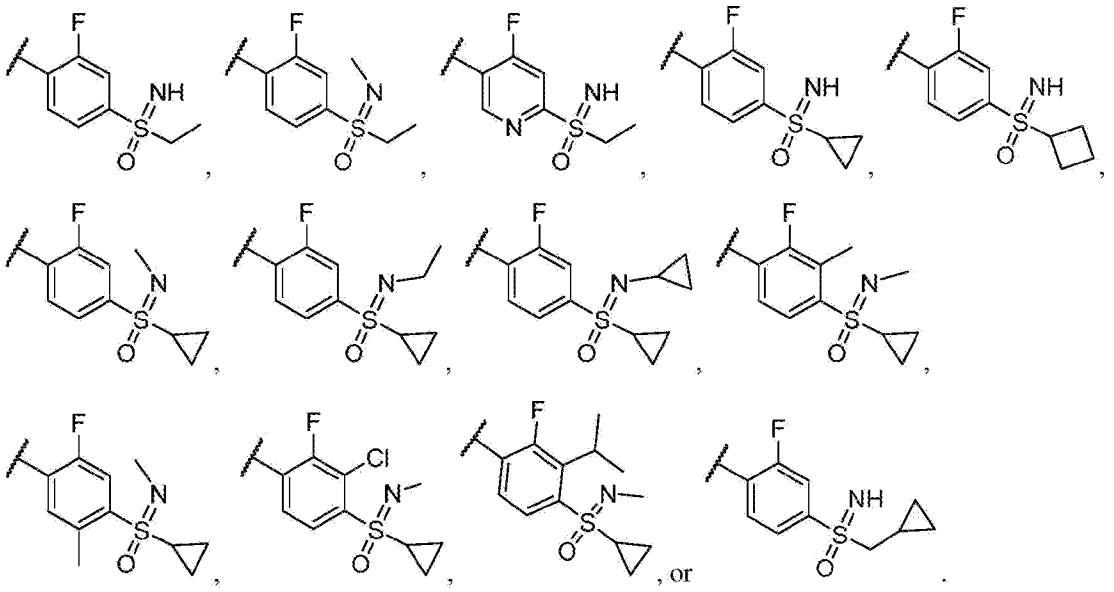
[0418] In some embodiments, R^9 is  or 

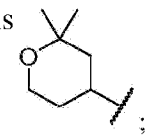
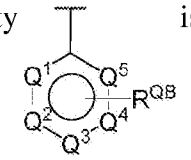
[0419] In some embodiments, Ring C is 3-12 membered heterocyclyl optionall y substituted with 1-3 R^{Ca}. In some embodiments, Ring C is a 6 membered heter ocyclyl optionally substituted with 1-3 R^{Ca}.

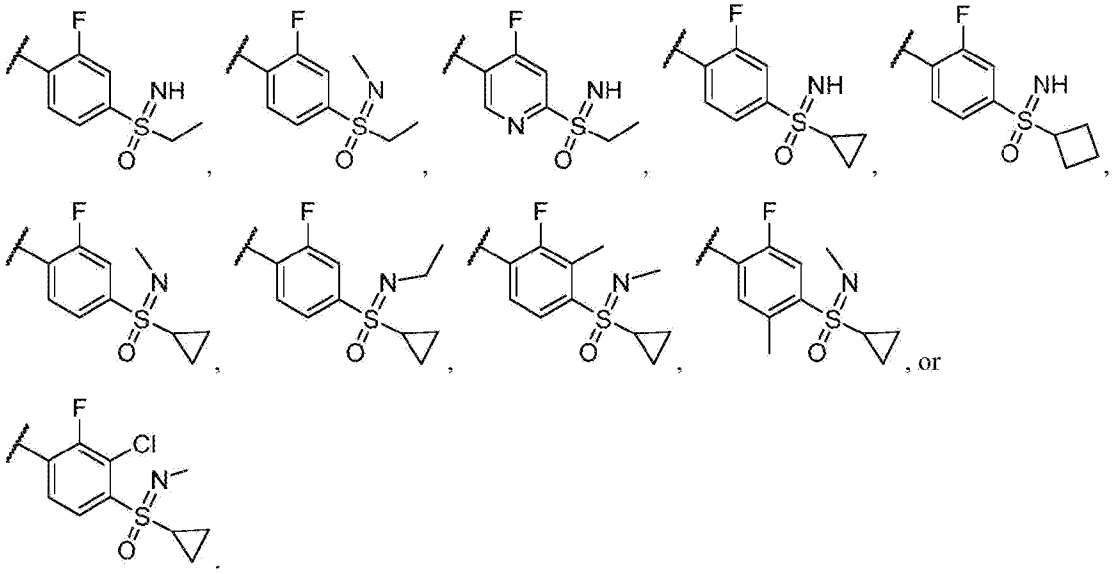
[0420] In some embodiments, each R^{Ca} is C_{1-6} alkyl.

[0421] In some embodiments, Ring C is  ,  , or  .

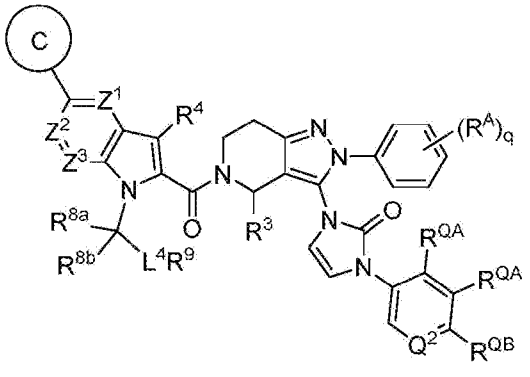
[0422] In some embodiments, Ring C is  ; and the moiety  is:



[0423] In some embodiments, Ring C is  and the moiety  is:



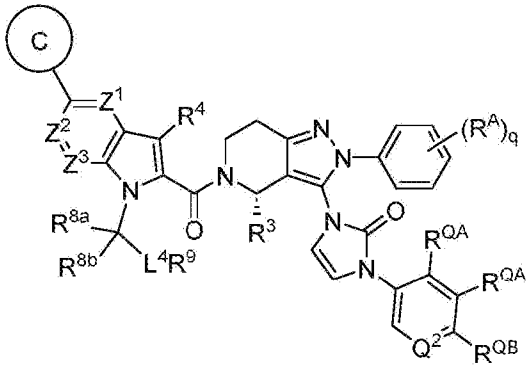
[0424] In some embodiments, provided herein is a compound of Formula IIC:



IIC

[0425] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; Z^1 is N or CR^5; Z^2 is N or CR^6; Z^3 is N or CR^7; R^4, R^5, R^6, and R^7 are each independently hydrogen, halo, or C_{1-6} alkyl; and ring C, R^{8a}, R^{8b}, L^4, R^9, R^A, R^3, Q^2, R^{QA}, and R^{QB} are each independently as defined herein.

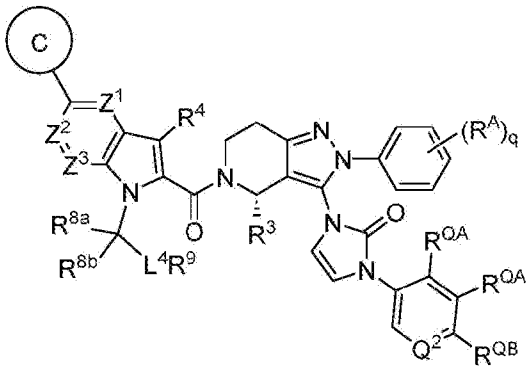
[0426] In some embodiments, provided herein is a compound of Formula IIC- (S) :



IIC-(*S*)

[0427] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; Z^1 is N or CR^5; Z^2 is N or CR^6; Z^3 is N or CR^7; R^4, R^5, R^6, and R^7 are each independently hydrogen, halo, or C_{1-6} alkyl; and ring C, R^{8a}, R^{8b}, L^4, R^9, R^A, R^3, Q^2, R^{QA}, and R^{QB} are each independently as defined herein.

[0428] In one aspect, provided herein are compounds of Formula IIC- (S) :



IIC-(*S*)

[0429] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0430] Q^2 is N or CR^{QA};

[0431] R^{QB} is –S (O) (=NR^a) R^b, – (CR^iR^j) $_n$–S (O) (=NR^a) R^b, –N=S (O) (R^{1a}) R^b, or – O– (CR^iR^j) $_n$–S (O) (=NR^a) R^b;

[0432] R^{1a} is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0433] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0434] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0435] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0436] n is 1, 2, 3, 4, 5, or 6;

[0437] each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

[0438] or R^a and R^i, or R^b and R^i, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0439] each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

[0440] or one R^i and one R^j, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0441] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, -NR^cR^d, -C (O) NR^cR^d, -S (O) $_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently

selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

[0442] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

[0443] q is 0, 1, 2, 3, 4, or 5;

[0444] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0445] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents in dependently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0446] Z^1 is N or CR^5;

[0447] Z^2 is N or CR^6;

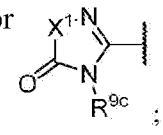
[0448] Z^3 is N or CR^7;

[0449] R^4, R^5, R^6, and R^7 are each independently hydrogen, halo, or C_{1-6} alkyl;

[0450] L^4 is a bond or C_{1-5} alkylene;

[0451] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo an d C_{3-15} cycloalkyl; or

[0452] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted with 1-3 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0453] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0454] X^1 is O or S;

[0455] R^{9a} is hydrogen or C_{1-6} alkyl;

[0456] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0457] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0458] Ring C is 3-12 membered heterocyclyl, C_{3-15} cycloalkyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-3 R^{Ca};

[0459] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0460] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring atom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0461] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

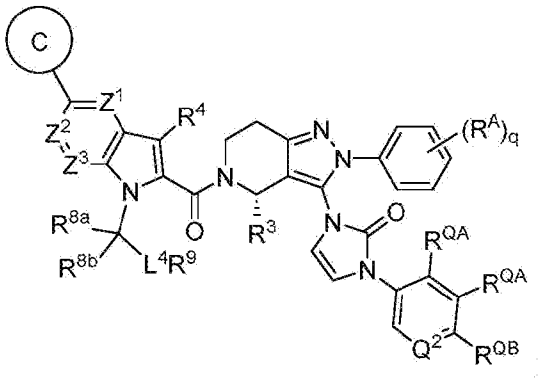
[0462] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0463] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3-12 membered heterocyclyl which is optionally substituted with 1-4 substituents each independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0464] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0465] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0466] In one aspect, provided herein are compounds of Formula IIC- (S) :



IIC-(*S*)

[0467] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0468] Q^2 is N or CR^{QA};

[0469] R^{QB} is –S (O) (=NR^a) R^b or – (CR^iR^j) $_n$–S (O) (=NR^a) R^b;

[0470] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0471] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0472] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0473] n is 1, 2, 3, 4, 5, or 6;

[0474] each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

[0475] or R^a and R^i, or R^b and R^i, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0476] each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

[0477] or one R^i and one R^j, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0478] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and $-C(O)(C_{1-6}$ alkyl), C_{6-10} aryl optionally substituted with 1-3 independently selected $-C(O)(C_{1-6}$ alkyl), and 5-10 membered heteroaryl optionally substituted with 1-6 independently selected R^g;

[0479] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

[0480] q is 0, 1, 2, 3, 4, or 5;

[0481] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0482] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents in dependently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0483] Z^1 is N or CR^5;

[0484] Z^2 is N or CR^6;

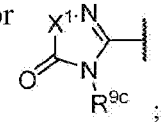
[0485] Z^3 is N or CR^7;

[0486] R^4, R^5, R^6, and R^7 are each independently hydrogen, halo, or C_{1-6} alkyl;

[0487] L^4 is a bond or C_{1-5} alkylene;

[0488] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo an d C_{3-15} cycloalkyl; or

[0489] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted with 1-3 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0490] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0491] X^1 is O or S;

[0492] R^{9a} is hydrogen or C_{1-6} alkyl;

[0493] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0494] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0495] Ring C is 3-12 membered heterocyclyl, C_{3-15} cycloalkyl, or 5-10 membered heter oaryl, each of which is optionally substituted with 1-3 R^{Ca};

[0496] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0497] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0498] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -

C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0499] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0500] each R^f is independently halo, hydroxy, -NR^cR^d, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0501] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, -NR^cR^d, or 3 to 12 memb ered heterocyclyl optionally substituted with one or more substituents each independe ntly selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0502] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, -NH_2, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0503] In some embodiments, R^4 is hydrogen. In some embodiments, R^4, R^5, R^6, and R^7 are each hydrogen.

[0504] In some embodiments, Z^1 is CH. In some embodiments, Z^1 is N.

[0505] In some embodiments, Z^2 is CH. In some embodiments, Z^2 is N.

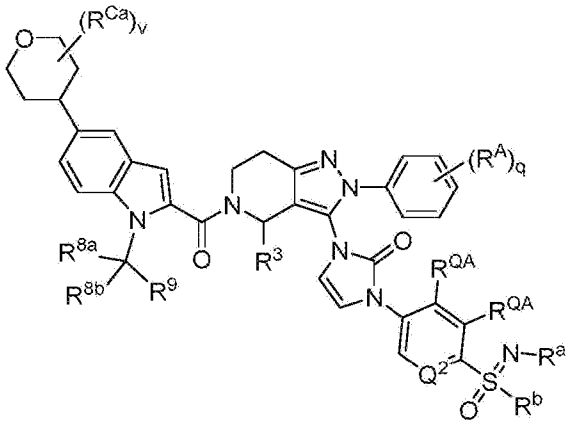
[0506] In some embodiments, Z^3 is CH. In some embodiments, Z^3 is N.

[0507] In some embodiments, one of Z^1, Z^2, and Z^3 is N or CH, and the other two of Z ^{1}, Z^2, and Z^3 are CH. In some embodiments, one of Z^1, Z^2, and Z^3 is N, and the ot her two of Z^1, Z^2, and Z^3 are CH. In some embodiments, Z^1, Z^2, and Z^3 are each CH.

[0508] In some embodiments, R^4 is hydrogen; and one of Z^1, Z^2, and Z^3 is N or CH, and the other two of Z^1, Z^2, and Z^3 are CH. In some embodiments, R^4 is hydrogen; and one of Z^1, Z^2, and Z^3 is N, and the other two of Z^1, Z^2, and Z^3 are CH. In some embodiments, R^4 is hydrogen; and Z^1, Z^2, and Z^3 are each CH.

[0509] In some embodiments, R^{QB} is –S (O) (=NR^a) R^b.

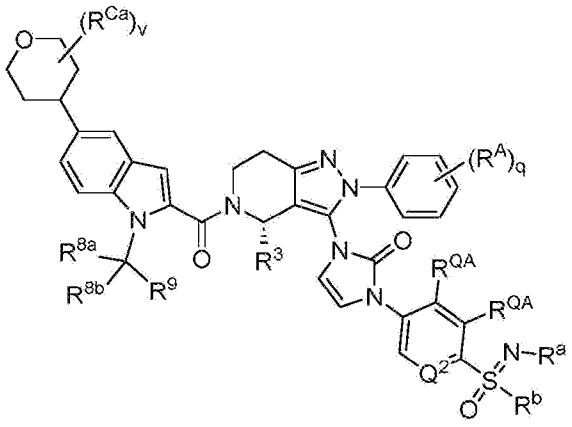
[0510] In some embodiments, provided herein is a compound of Formula IID:



IID

[0511] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; and R^a, R^b, R^{Ca}, R^{8a}, R^{8b}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

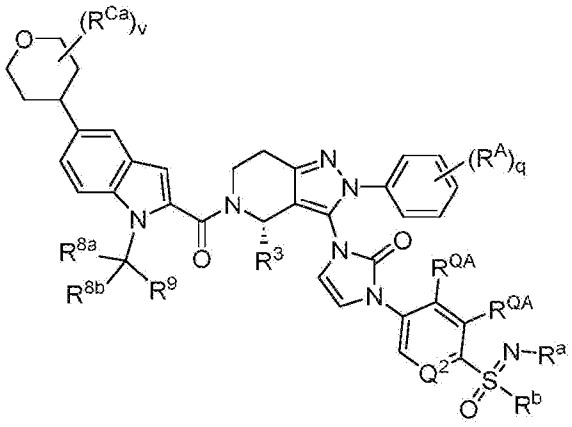
[0512] In some embodiments, provided herein is a compound of Formula IID- (S) :



IID-(*S*)

[0513] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; and R^a, R^b, R^{Ca}, R^{8a}, R^{8b}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

[0514] In one aspect, provided herein are compounds of Formula IID- (S) :



IID-(*S*)

[0515] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0516] Q^2 is N or CR^{QA};

[0517] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3}

alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0518] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents ea ch independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents ea ch independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0519] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0520] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each in dependently selected from the group consisting of C_{1-6} alkyl and $-C(O)(C_{1-6}$ alkyl), C_{6-10} aryl optionally substituted with 1-3 independently selected $-C(O)(C_{1-6}$ alkyl), and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

[0521] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

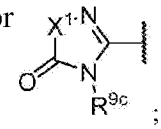
[0522] q is 0, 1, 2, 3, 4, or 5;

[0523] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0524] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents in dependently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0525] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo an d C_{3-15} cycloalkyl; or

[0526] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted with 1-3 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0527] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0528] X^1 is O or S;

[0529] R^{9a} is hydrogen or C_{1-6} alkyl;

[0530] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0531] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0532] v is 0, 1, 2, or 3;

[0533] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0534] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0535] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

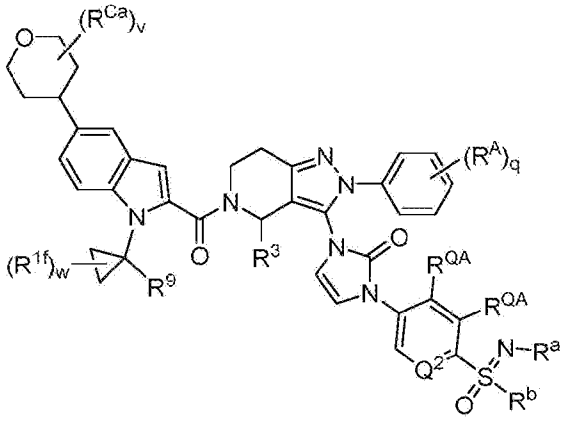
[0536] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0537] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0538] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 memb ered heterocyclyl optionally substituted with one or more substituents each independe ntly selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0539] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

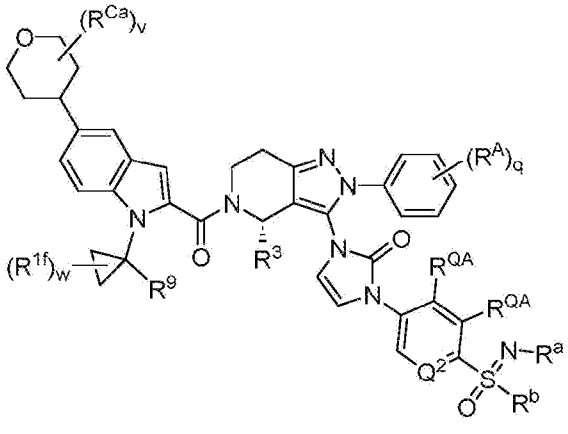
[0540] In some embodiments, provided herein is a compound of Formula IIE:



IIE

[0541] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; w is 0, 1, 2, or 3; each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is independently optionally substituted with 1-6 independently selected R^f; and R^a, R^b, R^{Ca}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

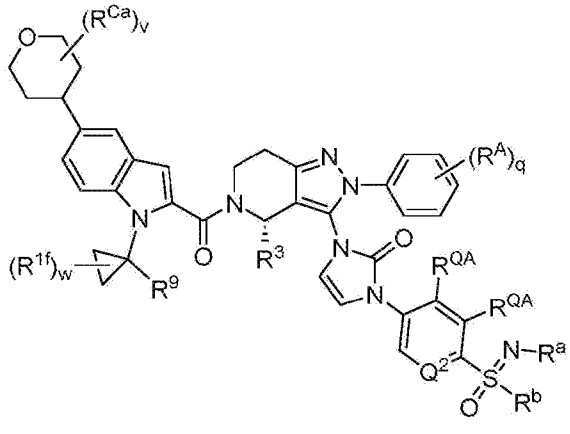
[0542] In some embodiments, provided herein is a compound of Formula IIE- (S) :



IIE-(*S*)

[0543] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; w is 0, 1, 2, or 3; R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is independently optionally substituted with 1-6 independently selected R^f; and R^a, R^b, R^{Ca}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

[0544] In one aspect, provided herein are compounds of Formula IIE- (S) :



IIE-(*S*)

[0545] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0546] Q^2 is N or CR^{QA};

[0547] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0548] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0549] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

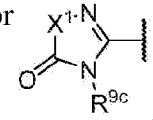
[0550] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and $-C(O)(C_{1-6}$ alkyl), C_{6-10} aryl optionally substituted with 1-3 independently selected $-C(O)(C_{1-6}$ alkyl), and 5-10 membered heteroaryl optionally substituted with 1-6 independently selected R^g;

[0551] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

[0552] q is 0, 1, 2, 3, 4, or 5;

[0553] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0554] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents in dependently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0555] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0556] X^1 is O or S;

[0557] R^{9a} is hydrogen or C_{1-6} alkyl;

[0558] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0559] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0560] v is 0, 1, 2, or 3;

[0561] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0562] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0563] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0564] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0565] w is 0, 1, 2, or 3;

[0566] each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is indepen dently optionally substituted with 1-6 independently selected R^f;

[0567] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea

ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

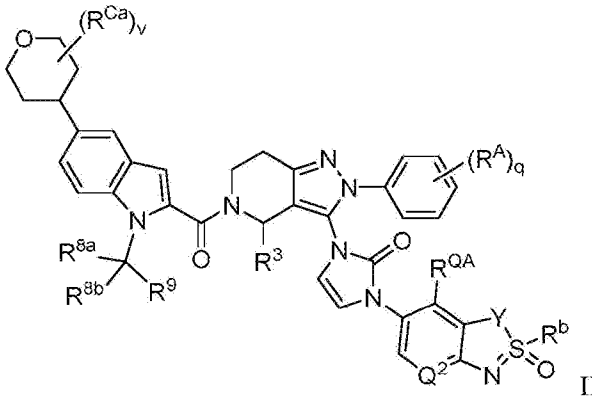
[0568] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0569] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0570] In some embodiments, R^{QB} is $-(CR^iR^j)_n-S(O)(=NR^a)R^b$. In some embodiments, n is 1 or 2. In some embodiments, n is 1. In some embodiments, n is 2.

[0571] In some embodiments, R^a and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

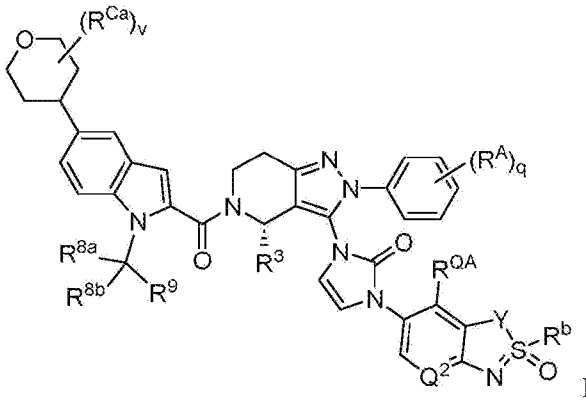
[0572] In some embodiments, provided herein is a compound of Formula IIF:



IIF

[0573] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein Y is $-(CR^iR^j)_n-$; q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; and n, R^b, R^i, R^j, R^{Ca}, R^{8a}, R^{8b}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

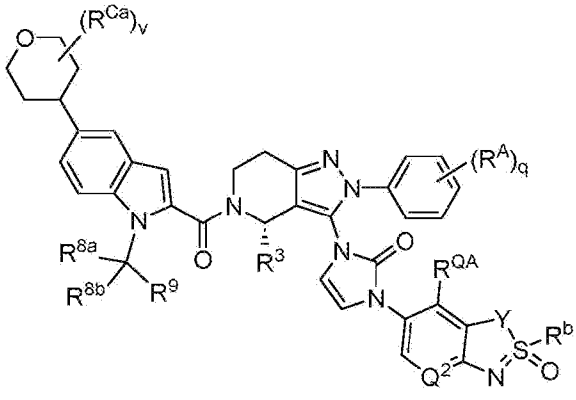
[0574] In some embodiments, provided herein is a compound of Formula IIF- (S) :



IIF-(*S*)

[0575] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein Y is - $(CR^iR^j)_n$-; q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; and n, R^b, R^i, R^j, R^{Ca}, R^{8a}, R^{8b}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

[0576] In one aspect, provided herein are compounds of Formula IIF- (S) :



IIF-(*S*)

[0577] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0578] Q^2 is N or CR^{QA};

[0579] Y is - $(CR^iR^j)_n$-;

[0580] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0581] n is 1, 2, 3, 4, 5, or 6;

[0582] each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

[0583] each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

[0584] or one R^i and one R^j on adjacent carbon atoms taken together with the atom (s) to which each is attached form an alkene, wherein said alkene is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0585] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, -NR^cR^d, -C (O) NR^cR^d, -S $(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6}

alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

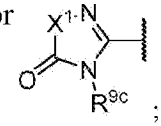
[0586] q is 0, 1, 2, 3, 4, or 5;

[0587] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0588] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents in dependently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0589] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo an d C_{3-15} cycloalkyl; or

[0590] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C $_{3-15}$ cycloalkyl ring which is optionally substituted with 1-3 independently selected C $_{1-6}$ alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0591] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0592] X^1 is O or S;

[0593] R^{9a} is hydrogen or C_{1-6} alkyl;

[0594] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0595] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0596] v is 0, 1, 2, or 3;

[0597] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0598] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0599] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C $_{3-6}$ cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

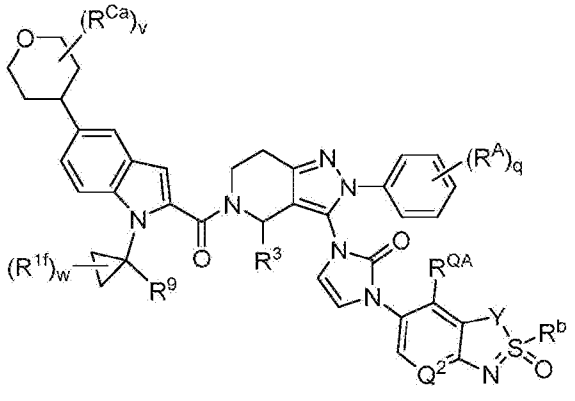
[0600] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0601] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3-12 membered heterocyclyl which is optionally substituted with 1-4 substituents each independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0602] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0603] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

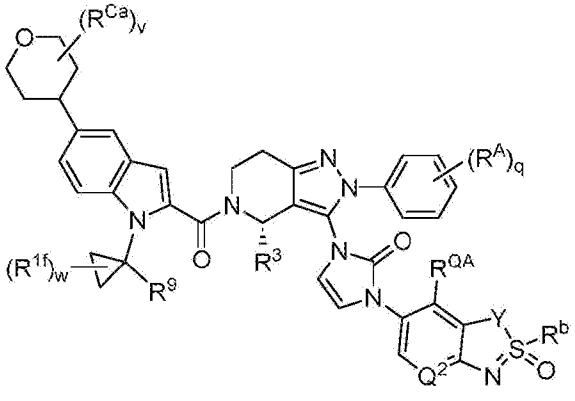
[0604] In some embodiments, provided herein is a compound of Formula IIG:



IIG

[0605] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein Y is - (CR^iR^j) $_n$-; q is 0, 1, 2, 3, 4, or 5; w is 0, 1, 2, or 3; v is 0, 1, 2, or 3; each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is independently optionally substituted with 1-6 independently selected R^f; and n, R^b, R^i, R^j, R^{Ca}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

[0606] In some embodiments, provided herein is a compound of Formula IIG- (S) :

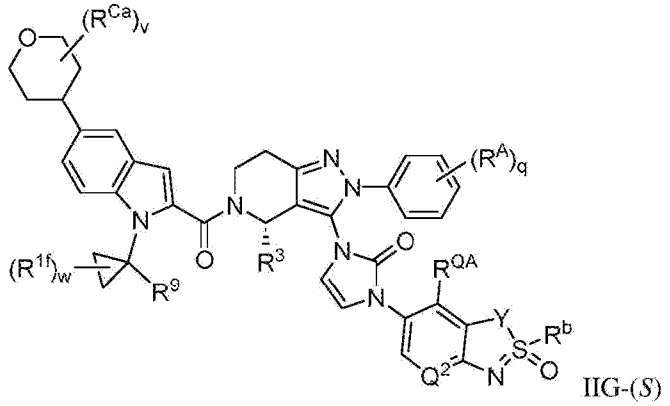


IIG-(*S*)

[0607] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein Y is - (CR^iR^j) $_n$-; q is 0, 1, 2, 3

, 4, or 5; w is 0, 1, 2, or 3; v is 0, 1, 2, or 3; each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is independently optionally substituted with 1-6 independently selected R^f; and n, R^b, R^i, R^j, R^{Ca}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

[0608] In one aspect, provided herein are compounds of Formula IIG- (S) :



IIG-(*S*)

[0609] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0610] Q^2 is N or CR^{QA};

[0611] Y is - $(CR^iR^j)_n$-;

[0612] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0613] n is 1, 2, 3, 4, 5, or 6;

[0614] each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

[0615] each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

[0616] or one R^i and one R^j on adjacent carbon atoms taken together with the atom (s) to which each is attached form an alkene, wherein said alkene is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

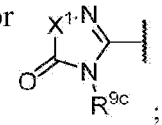
[0617] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, -C (O) NR^cR^d, -S $(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6}

alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

[0618] q is 0, 1, 2, 3, 4, or 5;

[0619] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0620] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents in dependently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0621] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0622] X^1 is O or S;

[0623] R^{9a} is hydrogen or C_{1-6} alkyl;

[0624] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0625] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0626] v is 0, 1, 2, or 3;

[0627] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0628] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0629] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0630] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0631] w is 0, 1, 2, or 3;

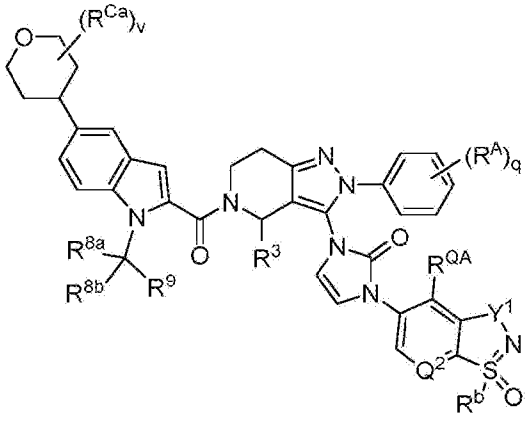
[0632] each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is indepen dently optionally substituted with 1-6 independently selected R^f;

[0633] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0634] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, -NR^cR^d, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0635] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, -NH_2, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

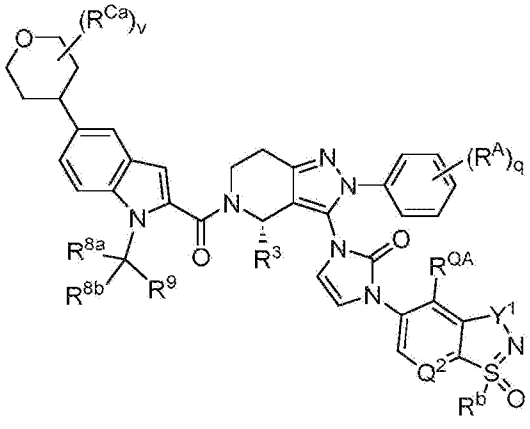
[0636] In some embodiments, provided herein is a compound of Formula IIH:



IIH

[0637] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein Y^1 is C_{1-3} alkylene or C_2 alkenylene, wherein the C_{1-3} alkylene or C_2 alkenylene is optionally substituted with 1-2 independently selected R^h; q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; and R^b, R^{Ca}, R^{8a}, R^{8b}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

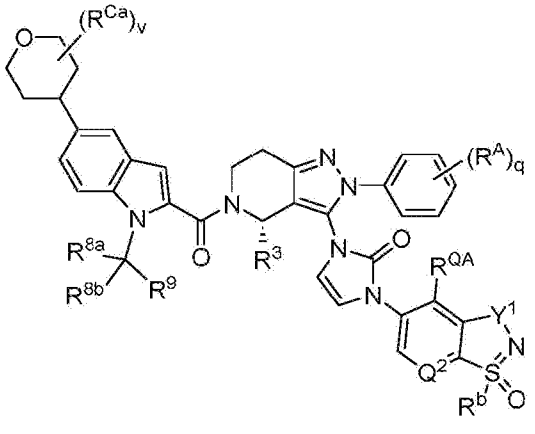
[0638] In some embodiments, provided herein is a compound of Formula IIH- (S) :



IIH-(*S*)

[0639] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein Y^1 is C_{1-3} alkylene or C_2 alkenylene, wherein the C_{1-3} alkylene or C_2 alkenylene is optionally substituted with 1-2 independently selected R^h; q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; and R^b, R^{Ca}, R^{8a}, R^{8b}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

[0640] In one aspect, provided herein are compounds of Formula IIH- (S) :



IIH-(*S*)

[0641] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0642] Q^2 is N or CR^{QA};

[0643] Y^1 is C_{1-3} alkylene or C_2 alkenylene, wherein the C_{1-3} alkylene or C_2 alkenylene is optionally substituted with 1-2 independently selected R^h;

[0644] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0645] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and $-C(O)(C_{1-6}$ alkyl), C_{6-10} aryl optionally substituted with 1-3 independently selected $-C(O)(C_{1-6}$ alkyl), and 5-10 membered heteroaryl optionally substituted with 1-6 independently selected R^g;

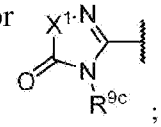
[0646] q is 0, 1, 2, 3, 4, or 5;

[0647] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0648] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0649] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{3-15} cycloalkyl; or

[0650] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted with 1-3 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0651] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0652] X^1 is O or S;

[0653] R^{9a} is hydrogen or C_{1-6} alkyl;

[0654] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0655] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0656] v is 0, 1, 2, or 3;

[0657] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0658] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0659] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

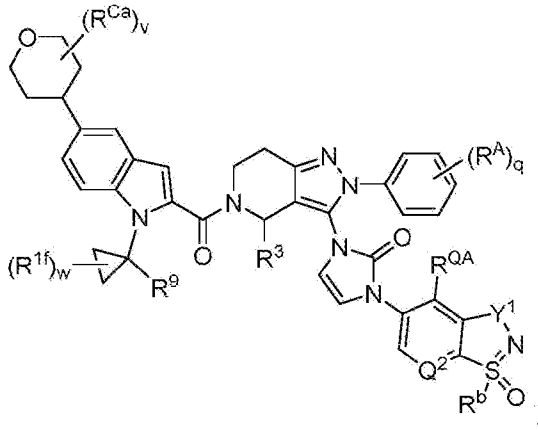
[0660] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0661] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0662] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 memb ered heterocyclyl optionally substituted with one or more substituents each independe ntly selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0663] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

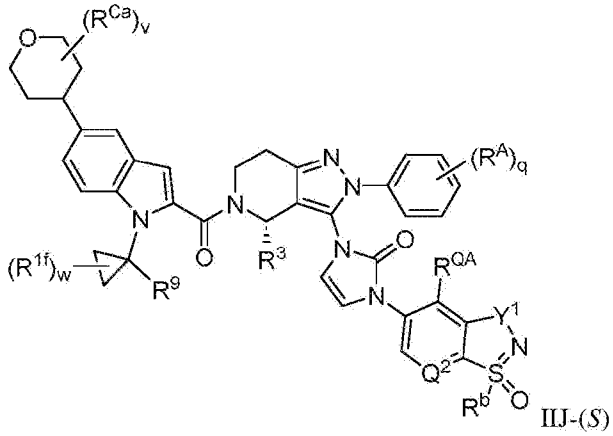
[0664] In some embodiments, provided herein is a compound of Formula IIJ:



IIJ

[0665] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein Y^1 is C_{1-3} alkylene or C_2 alkenylene, wherein the C_{1-3} alkylene or C_2 alkenylene is optionally substituted with 1-2 independently selected R^h; q is 0, 1, 2, 3, 4, or 5; w is 0, 1, 2, or 3; v is 0, 1, 2, or 3; each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is independently optionally substituted with 1-6 independently selected R^f; and R^b, R^{Ca}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

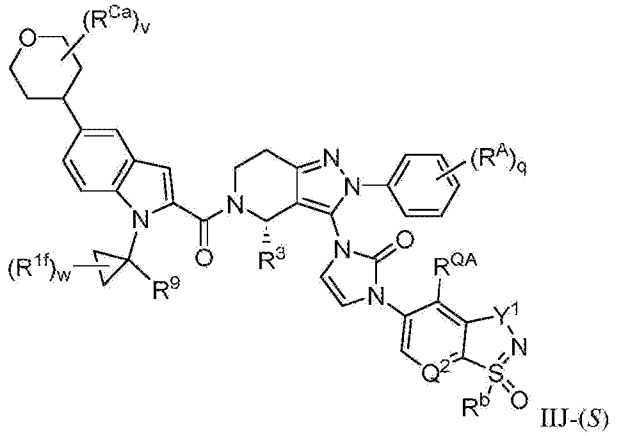
[0666] In some embodiments, provided herein is a compound of Formula IIJ- (S) :



IIJ-(*S*)

[0667] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein Y^1 is C_{1-3} alkylene or C_2 alkenylene, wherein the C_{1-3} alkylene or C_2 alkenylene is optionally substituted with 1-2 independently selected R^h; q is 0, 1, 2, 3, 4, or 5; w is 0, 1, 2, or 3; v is 0, 1, 2, or 3; each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is independently optionally substituted with 1-6 independently selected R^f; and R^b, R^{Ca}, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

[0668] In one aspect, provided herein are compounds of Formula IIJ- (S) :



IIJ-(*S*)

[0669] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0670] Q^2 is N or CR^{QA};

[0671] Y^1 is C_{1-3} alkylene or C_2 alkenylene, wherein the C_{1-3} alkylene or C_2 alkenylene is optionally substituted with 1-2 independently selected R^h;

[0672] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0673] n is 1, 2, 3, 4, 5, or 6;

[0674] each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

[0675] each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

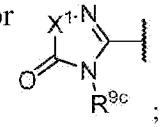
[0676] or one R^i and one R^j on adjacent carbon atoms taken together with the atom (s) to which each is attached form an alkene, wherein said alkene is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0677] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, -C (O) NR^cR^d, -S (O) $_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently selected R^g;

[0678] q is 0, 1, 2, 3, 4, or 5;

[0679] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0680] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents in dependently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0681] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0682] X^1 is O or S;

[0683] R^{9a} is hydrogen or C_{1-6} alkyl;

[0684] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0685] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0686] v is 0, 1, 2, or 3;

[0687] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0688] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0689] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0690] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0691] w is 0, 1, 2, or 3;

[0692] each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is indepen dently optionally substituted with 1-6 independently selected R^f;

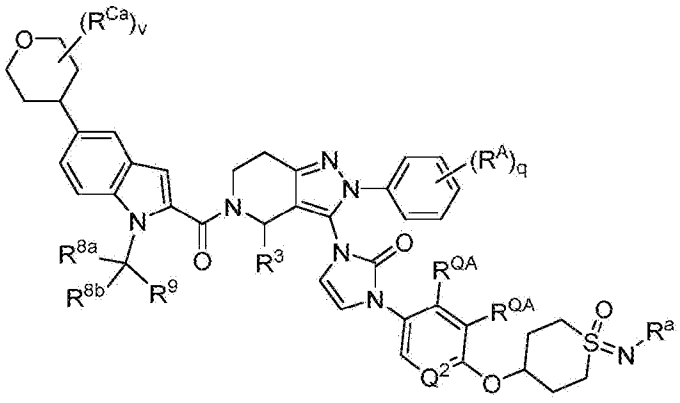
[0693] each R^f is independently halo, hydroxy, -NR^cR^d, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0694] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, -NR^cR^d, or 3 to 12 memb ered heterocyclyl optionally substituted with one or more substituents each independe ntly selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0695] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0696] In some embodiments, R^{QB} is –O- (CR^iR^j) $_n$–S (O) (=NR^a) R^b. In some embodim ents, n is 3. In some embodiments, R^b and R^i, taken together with the atoms to which each is attached, form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl.

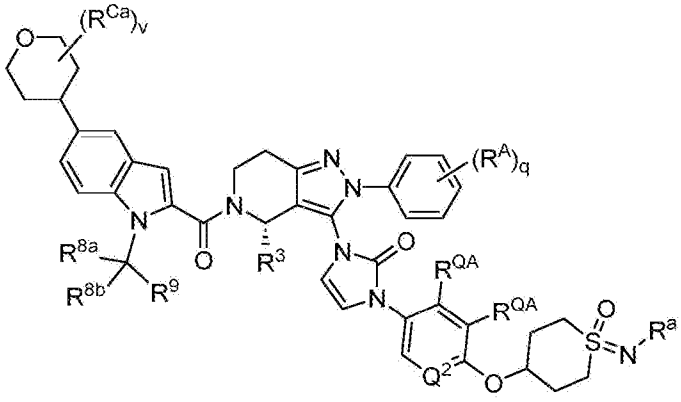
[0697] In some embodiments, provided herein is a compound of Formula IIK:



IIK

[0698] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mi xture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; and R^a, R^{Ca}, R^{8a}, R^{8b}, R^9, R^A, R^3, Q^2, and R^{QA} are each indepen dently as defined herein.

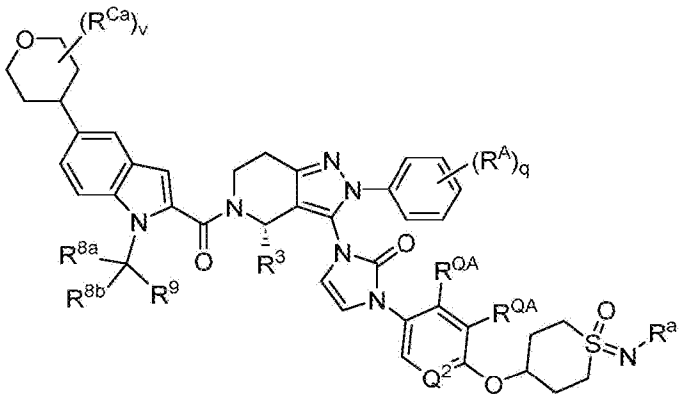
[0699] In some embodiments, provided herein is a compound of Formula IIK- (S) :



IIK-(*S*)

[0700] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mi xture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; and R^a, R^{Ca}, R^{8a}, R^{8b}, R^9, R^A, R^3, Q^2, and R^{QA} are each indepen dently as defined herein.

[0701] In one aspect, provided herein are compounds of Formula IIF- (S) :



IIK-(*S*)

[0702] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0703] Q^2 is N or CR^{QA};

[0704] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0705] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, -C (O) NR^cR^d, -S $(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently selected R^g;

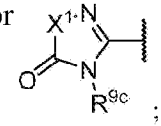
[0706] q is 0, 1, 2, 3, 4, or 5;

[0707] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0708] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0709] R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{3-15} cycloalkyl; or

[0710] R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted with 1-3 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-6 independently s elected R^f;

[0711] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0712] X^1 is O or S;

[0713] R^{9a} is hydrogen or C_{1-6} alkyl;

[0714] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0715] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0716] v is 0, 1, 2, or 3;

[0717] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0718] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0719] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

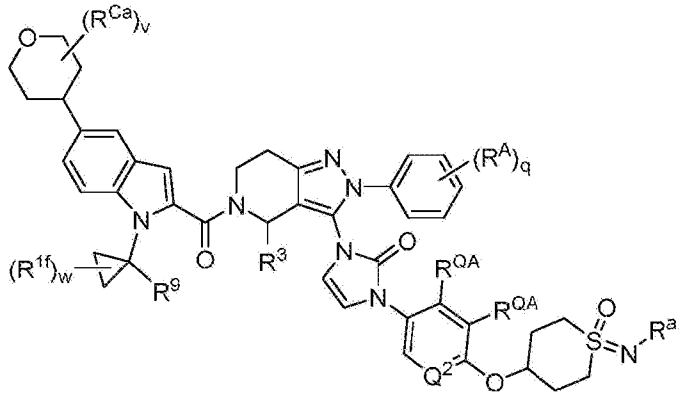
[0720] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0721] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0722] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 memb ered heterocyclyl optionally substituted with one or more substituents each independe ntly selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0723] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

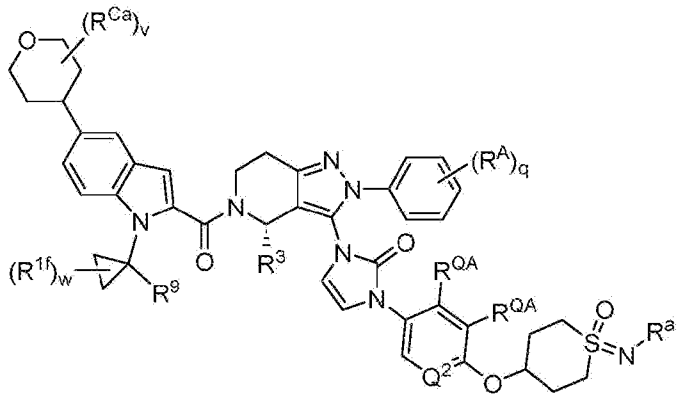
[0724] In some embodiments, provided herein is a compound of Formula IIL:



IIL

[0725] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is independently optionally substituted with 1-6 independently selected R^f; q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; w is 0, 1, 2, or 3; and R^a, R^{Ca}, R^f, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

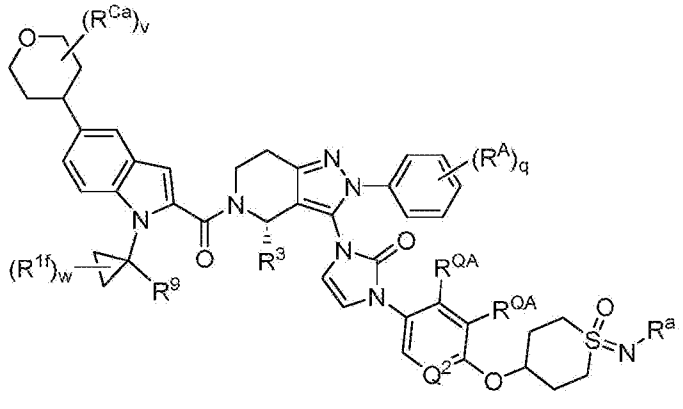
[0726] In some embodiments, provided herein is a compound of Formula IIL- (S) :



IIL-(*S*)

[0727] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is independently optionally substituted with 1-6 independently selected R^f; q is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, or 3; w is 0, 1, 2, or 3; and R^a, R^{Ca}, R^f, R^9, R^A, R^3, Q^2, and R^{QA} are each independently as defined herein.

[0728] In one aspect, provided herein are compounds of Formula IIL- (S) :



IIL-(*S*)

[0729] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0730] Q^2 is N or CR^{QA};

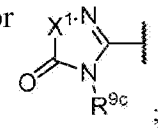
[0731] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0732] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, -C (O) NR^cR^d, -S $(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently selected R^g;

[0733] q is 0, 1, 2, 3, 4, or 5;

[0734] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0735] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0736] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0737] X^1 is O or S;

[0738] R^{9a} is hydrogen or C_{1-6} alkyl;

[0739] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0740] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0741] v is 0, 1, 2, or 3;

[0742] each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

[0743] or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring a tom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

[0744] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0745] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0746] w is 0, 1, 2, or 3;

[0747] each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is indepen dently optionally substituted with 1-6 independently selected R^f;

[0748] each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0749] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 memb ered heterocyclyl optionally substituted with one or more substituents each independe ntly selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0750] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0751] In some embodiments, R^3 is methyl.

[0752] In some embodiments, q is 2 or 3.

[0753] In some embodiments, each R^A is independently halo, C_{1-6} alkyl, or C_{3-6} cycloalkyl. In some embodiments, each R^A is independently fluoro, chloro, methyl, or cyclopropyl.

[0754] In some embodiments, q is 2 or 3; and each R^A is independently halo, C_{1-6} alkyl, or C_{3-6} cycloalkyl. In some embodiments, q is 2 or 3; and each R^A is independently fluoro, chloro, methyl, or cyclopropyl.

[0755] In some embodiments, Q^2 is N. In some embodiments, Q^2 is CR^{QA}.

[0756] In some embodiments, each R^{QA} is independently hydrogen, halo, -NH (C_{1-6} alkyl) , C_{1-6} alkyl, or C_{1-6} alkoxy. In some embodiments, each R^{QA} is independently hydrogen, fluoro, chloro, $-NHCH_3$, methyl, isopropyl, or $-OCH_3$.

[0757] In some embodiments, Q^2 is CR^{QA}; and each R^{QA} is independently hydrogen, halo, -NH (C_{1-6} alkyl) , C_{1-6} alkyl, or C_{1-6} alkoxy.

[0758] In some embodiments, Q^2 is CR^{QA}; and R^a or R^b and R^{QA} are taken together with the atom to which each is attached to form a 5-7 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[0759] In some embodiments, R^a is hydrogen, cyano, C_{1-6} alkyl, or C_{3-6} cycloalkyl.

[0760] In some embodiments, R^b is C_{1-6} alkyl optionally substituted with C_{3-6} cycloalkyl, or C_{3-6} cycloalkyl. In some embodiments, R^b is C_{1-6} alkyl. In some embodiments, R^b is C_{1-6} alkyl substituted with C_{3-6} cycloalkyl. In some embodiments, R^b is C_{3-6} cycloalkyl.

[0761] In some embodiments, R^a is hydrogen, cyano, C_{1-6} alkyl, or C_{3-6} cycloalkyl; and R^b is C_{1-6} alkyl optionally substituted with C_{3-6} cycloalkyl, or C_{3-6} cycloalkyl. In some embodiments, R^a is hydrogen, cyano, methyl, or cyclopropyl; and R^b is methyl, ethyl, $-CH_2$-cyclopropyl, cyclopropyl, or cyclobutyl.

[0762] In some embodiments, R^a and R^b are taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl.

[0763] In some embodiments, R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-7 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[0764] In In some embodiments, w is 0 or 1. In some embodiments, w is 0. In some embodiments, w is 1. In some embodiments, each R^f is independently C_{1-6} alkyl.

[0765] In some embodiments, w is 0 or 1; and R^f is methyl.

[0766] In some embodiments, R^a is hydrogen, cyano, C_{1-6} alkyl, or C_{3-6} cycloalkyl; and R^b is C_{1-6} alkyl optionally substituted with C_{3-6} cycloalkyl, or C_{3-6} cycloalkyl; or R

^{a} and R^{b} are taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl; or

[0767] R^{a} is hydrogen, cyano, C_{1-6} alkyl, or C_{3-6} cycloalkyl; and R^{b} and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-7 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^{h}; or

[0768] R^{a} and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-7 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^{h}; and R^{b} is C_{1-6} alkyl optionally substituted with C_{3-6} cycloalkyl, or C_{3-6} cycloalkyl.

[0769] In some embodiments, each R^{h} is independently C_{1-6} alkyl. In some e mbodiments, each R^{h} is independently methyl.

[0770] In some embodiments, each R^{i} and each R^{j} are hydrogen; or R^{a} or R^{b} and R^{i}, taken together with the atoms to which each is attached form a 5-8 membered hetero cyclyl; or one R^{i} and one R^{j}, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl.

[0771] In some embodiments, R^{3} is methyl;

[0772] q is 2 or 3;

[0773] each R^{A} is independently halo, C_{1-6} alkyl, or C_{3-6} cycloalkyl;

[0774] each R^{QA} is independently hydrogen, halo, -NH (C_{1-6} alkyl) , C_{1-6} alkyl, or C_{1-6} alkoxy;

[0775] R^{a} is hydrogen, cyano, C_{1-6} alkyl, or C_{3-6} cycloalkyl; and R^{b} is C_{1-6} alkyl optionally substituted with C_{3-6} cycloalkyl, or C_{3-6} cycloalkyl; or R^{a} and R^{b} are taken togeth er with the atoms to which each is attached form a 5-8 membered heterocyclyl; or

[0776] R^{a} is hydrogen, cyano, C_{1-6} alkyl, or C_{3-6} cycloalkyl; and R^{b} and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-7 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^{h}; or

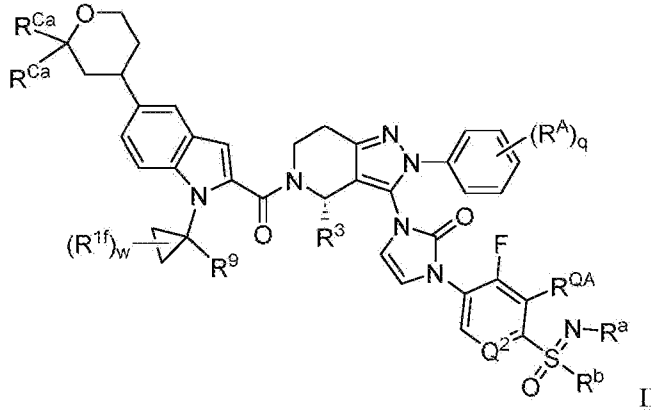
[0777] R^{a} and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-7 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^{h}; and R^{b} is C_{1-6} alkyl optionally substituted with C_{3-6} cycloalkyl, or C_{3-6} cycloalkyl;

[0778] each R^{h} is independently C_{1-6} alkyl; and

[0779] each R^{i} and each R^{j} are hydrogen; or R^{a} and R^{i}, or R^{b} and R^{i}, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl; or one R

^{i} and one R^{j}, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl.

[0780] In one aspect, provided herein are compounds of Formula IIIA:



IIIA

[0781] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0782] Q^2 is N or CR^{QA};

[0783] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0784] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0785] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0786] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and $-C(O)(C_{1-6}$ alkyl), C_{6-10} aryl optionally substituted with 1-3 independently selected $-C(O)(C_{1-6}$

alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

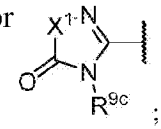
[0787] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

[0788] each R^{Ca} is independently C_{1-6} alkyl;

[0789] q is 0, 1, 2, 3, 4, or 5;

[0790] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0791] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents in dependently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0792] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0793] X^1 is O or S;

[0794] R^{9a} is hydrogen or C_{1-6} alkyl;

[0795] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0796] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0797] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0798] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0799] w is 0, 1, 2, or 3;

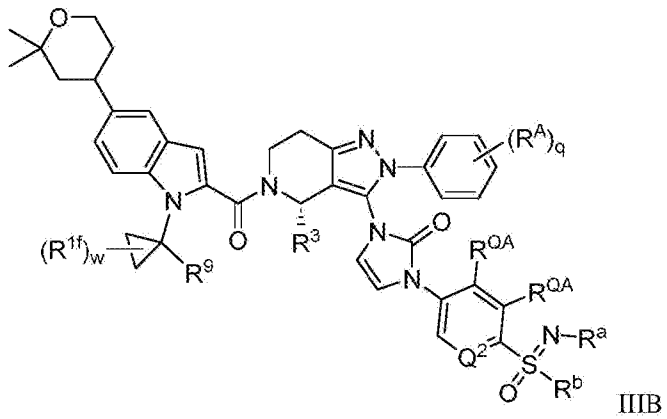
[0800] each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is indepen dently optionally substituted with 1-6 independently selected R^f;

[0801] each R^f is independently halo, hydroxy, -NR^cR^d, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0802] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

[0803] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0804] In one aspect, provided herein are compounds of Formula IIIB:



IIIB

[0805] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0806] Q^2 is N or CR^{QA};

[0807] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0808] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0809] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

[0810] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, -C (O) NR^cR^d, -S (O) $_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-

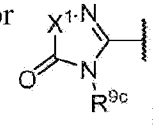
12 membered heterocyclyl optionally substituted with one or more substituents each in dependently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

[0811] or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

[0812] q is 0, 1, 2, 3, 4, or 5;

[0813] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0814] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents in dependently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0815] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0816] X^1 is O or S;

[0817] R^{9a} is hydrogen or C_{1-6} alkyl;

[0818] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0819] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0820] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0821] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0822] w is 0, 1, 2, or 3;

[0823] each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is indepen dently optionally substituted with 1-6 independently selected R^f;

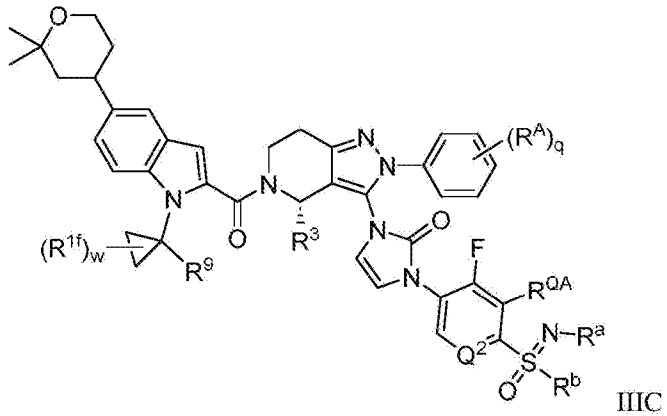
[0824] each R^f is independently halo, hydroxy, -NR^cR^d, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3 -12 membered heterocyclyl which is optionally substituted with 1-4 substituents ea

ch independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

[0825] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and $-C(O)C_{1-6}$ alkyl; and

[0826] each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, $-NH(C_{1-3}\text{ alkyl})$, $-N(C_{1-3}\text{ alkyl})_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[0827] In one aspect, provided herein are compounds of Formula IIIC:



IIIC

[0828] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0829] Q^2 is N or CR^{QA};

[0830] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0831] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0832] or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

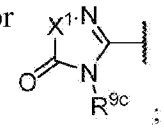
[0833] each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R

f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently s elected R^g;

[0834] q is 0, 1, 2, 3, 4, or 5;

[0835] each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

[0836] R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

[0837] R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally s ubstituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

[0838] X^1 is O or S;

[0839] R^{9a} is hydrogen or C_{1-6} alkyl;

[0840] R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

[0841] each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

[0842] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0843] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

[0844] w is 0, 1, 2, or 3;

[0845] each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is independently optionally substituted with 1-6 independently selected R^f;

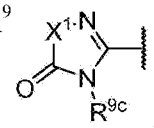
[0846] each R^f is independently halo, hydroxy, -NR^cR^d, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3-12 membered heterocyclyl which is optionally substituted with 1-4 substituents each independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl; and

[0847] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl.

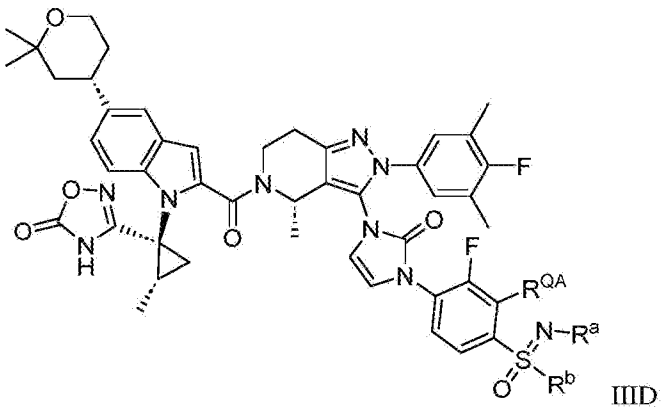
[0848] In certain embodiments, such as of Formula IIIA or IIIB, R^3 is C_{1-6} alkyl. In certain embodiments, such as of Formula IIIA or IIIB, R^3 is methyl.

[0849] In certain embodiments, such as of Formula IIIA or IIIB, Q^2 is CH. such as of Formula IIIA or IIIB, R^3 is methyl.

[0850] In certain embodiments, such as of Formula IIIA or IIIB, q is 2 or 3.

[0851] In certain embodiments, such as of Formula IIIA or IIIB, R^9  .

[0852] In one aspect, provided herein are compounds of Formula IIID:



IIID

[0853] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

[0854] R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0855] R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

[0856] R^{QA} is hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, -C (O) NR^cR^d, -S (O) $_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionall

y substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently selected R^g;

[0857] each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

[0858] each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; and

[0859] each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, -NR^cR^d, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl.

[0860] In certain embodiments, such as of Formula IIIA, IIIB, or IIIC, R^{QA} is hydrogen, halo, -NR^cR^d, or C_{1-6} alkyl. In certain embodiments, such as of Formula IIIA, IIIB, or IIIC, R^{QA} is hydrogen, halo, -$NHCH_3$, or methyl.

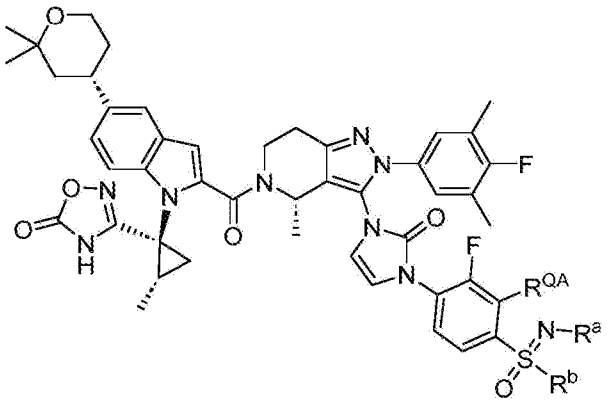
[0861] In certain embodiments, such as of Formula IIIA, IIIB, or IIIC, R^a is hydrogen or C_{1-6} alkyl. In certain embodiments, such as of Formula IIIA, IIIB, or IIIC, R^a is hydrogen, methyl, or ethyl.

[0862] In certain embodiments, such as of Formula IIIA, IIIB, or IIIC, R^b is C_{1-6} alkyl or C_{3-6} cycloalkyl. In certain embodiments, such as of Formula IIIA, IIIB, or IIIC, R^b is methyl, ethyl, cyclopropyl, or cyclobutyl.

[0863] In certain embodiments, such as of Formula IIIA, IIIB, or IIIC, R^a is hydrogen or C_{1-6} alkyl; and R^b is C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0864] In certain embodiments, such as of Formula IIIA, IIIB, or IIIC, R^a is hydrogen, methyl, or ethyl; and R^b is methyl, ethyl, cyclopropyl, or cyclobutyl.

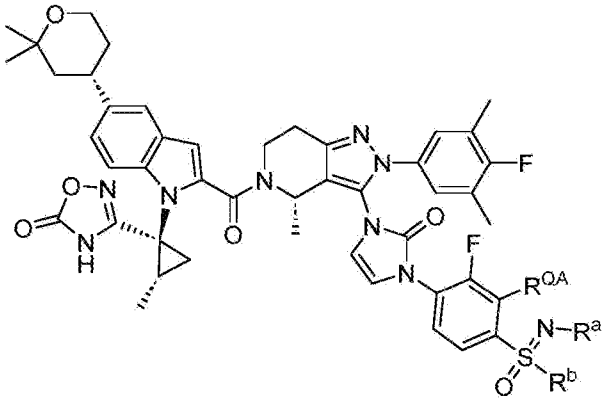
[0865] In one aspect, provided herein are compounds of Formula IIID:



IIID

[0866] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein: R^{QA} is hydrogen, halo, $-NR^cR^d$, or C_{1-6} alkyl; R^a is hydrogen or C_{1-6} alkyl; and R^b is C_{1-6} alkyl or C_{3-6} cycloalkyl.

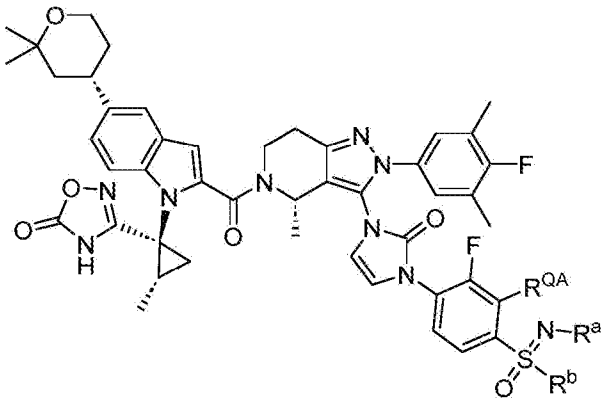
[0867] In one aspect, provided herein are compounds of Formula IIID:



IIID

[0868] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein: R^{QA} is hydrogen, halo, $-NHCH_3$, or methyl; R^a is hydrogen, methyl, or ethyl; and R^b is methyl, ethyl, cyclopropyl, or cyclobutyl.

[0869] In one aspect, provided herein are compounds of Formula IIID:

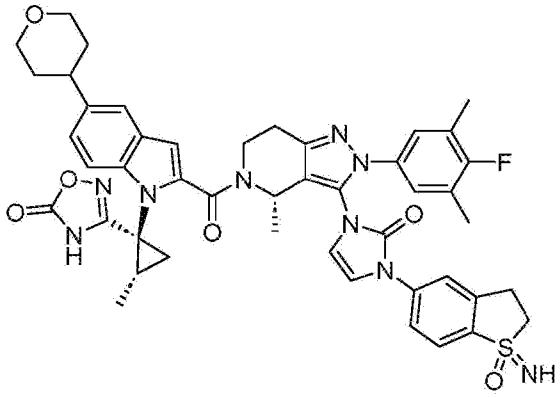
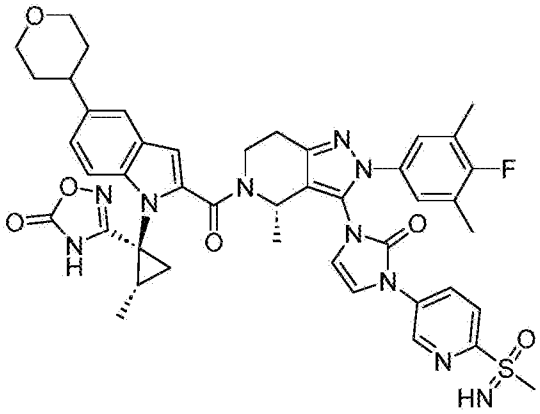
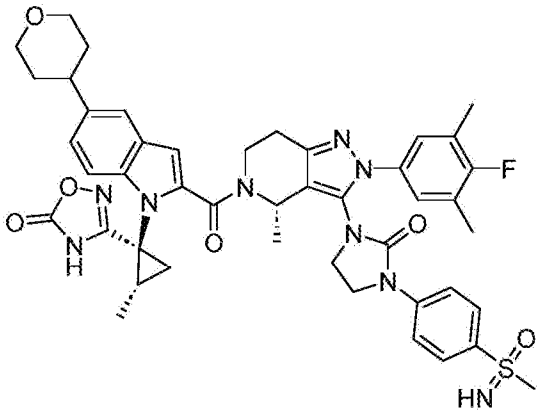


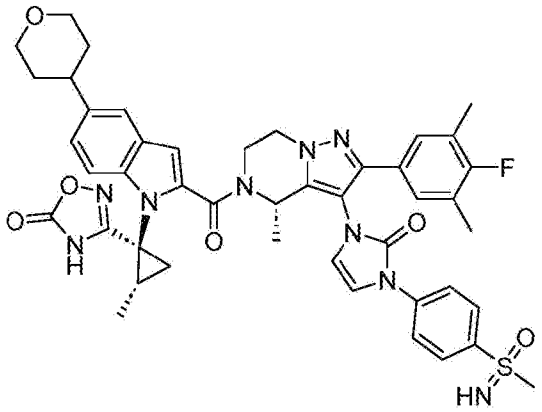
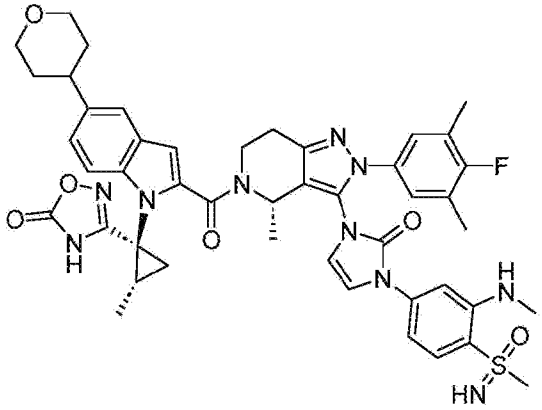
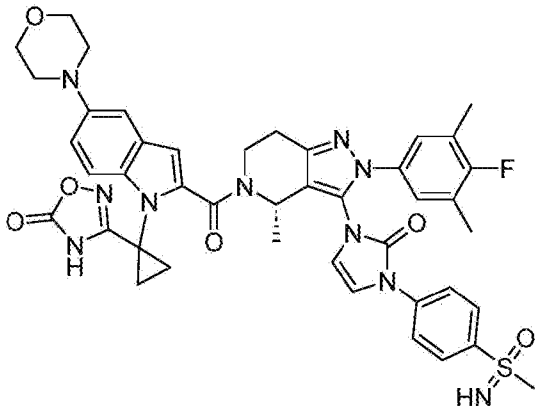
IIID

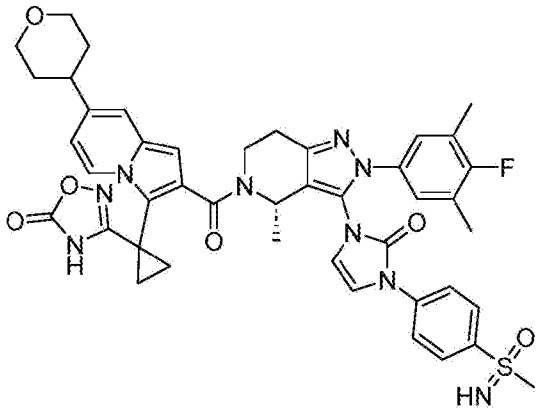
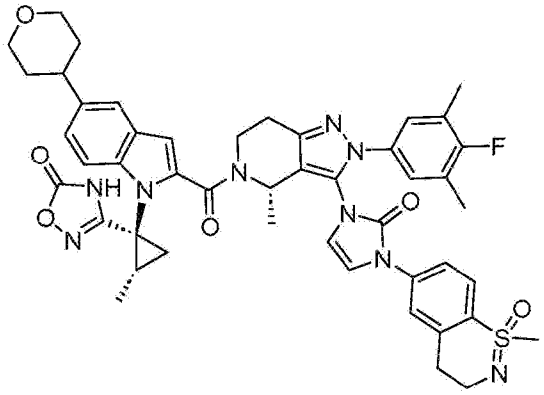
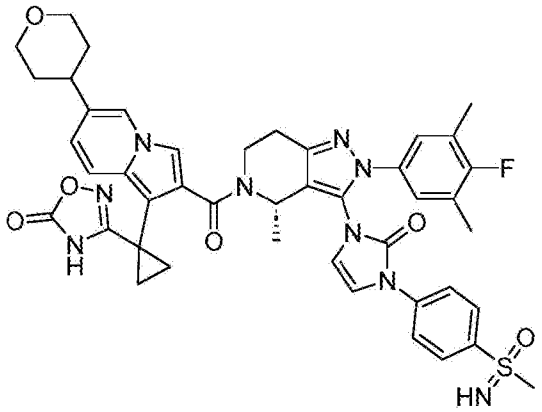
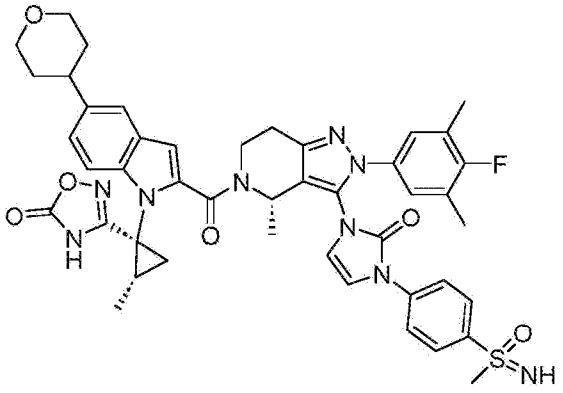
[0870] or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein: R^{QA} is hydrogen, halo, -$NHCH_3$, or methyl; R^a is methyl or ethyl; and R^b is ethyl or cyclopropyl or cyclobutyl.

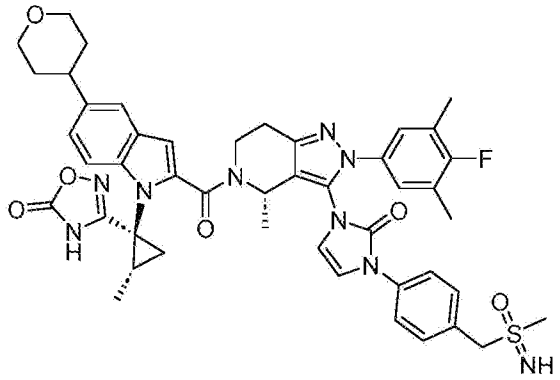
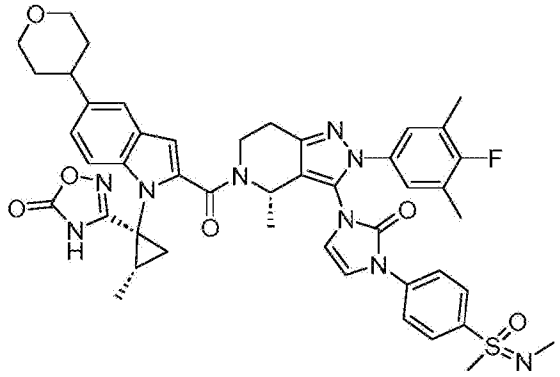
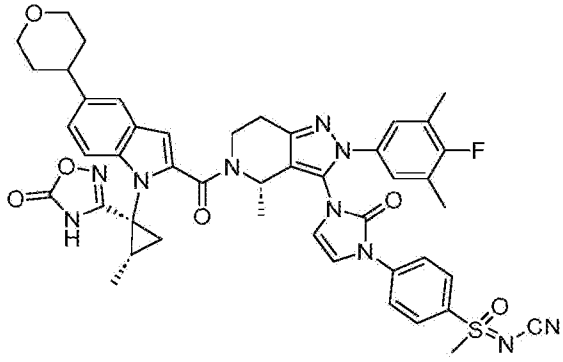
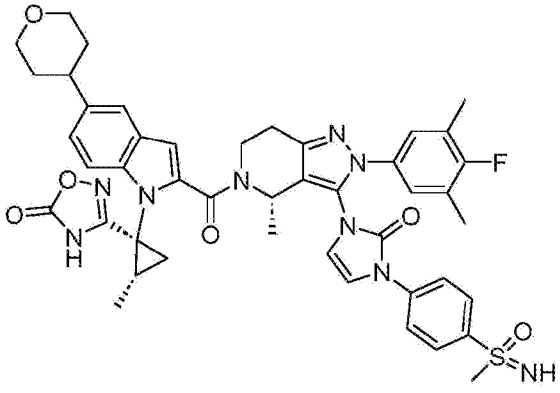
[0871] In certain embodiments, provided is a compound selected from Table 1, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof:

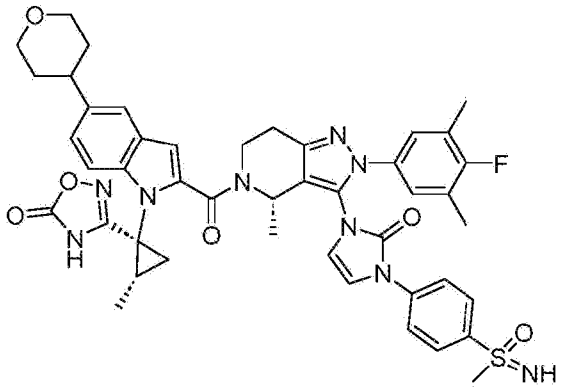
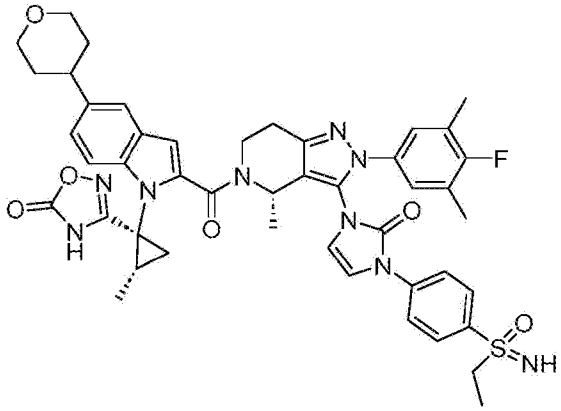
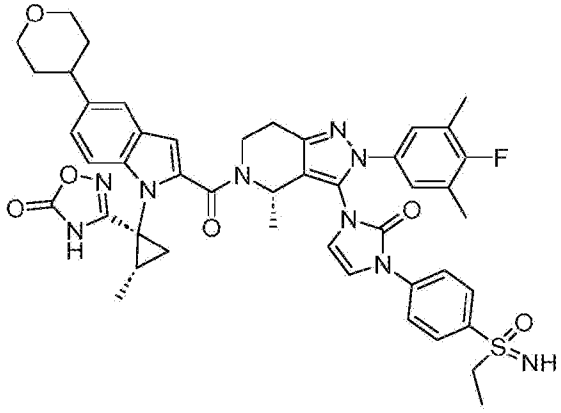
[0872] Table 1

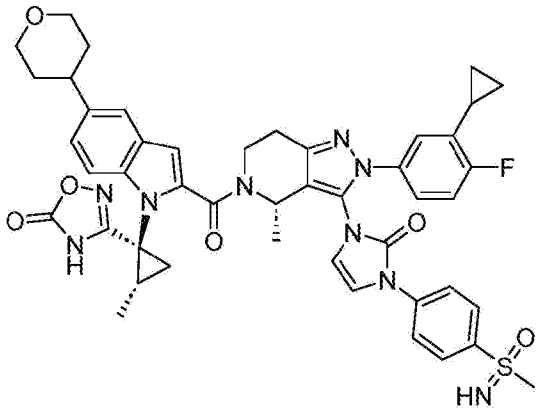
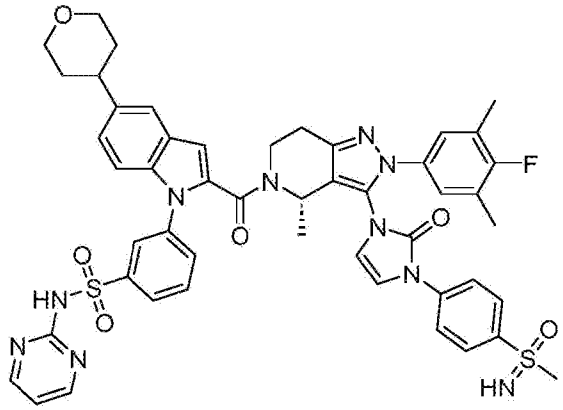
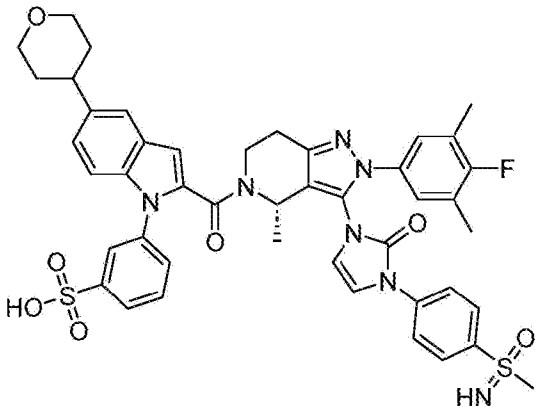
Compound No.	Structure
101	
102	
103	

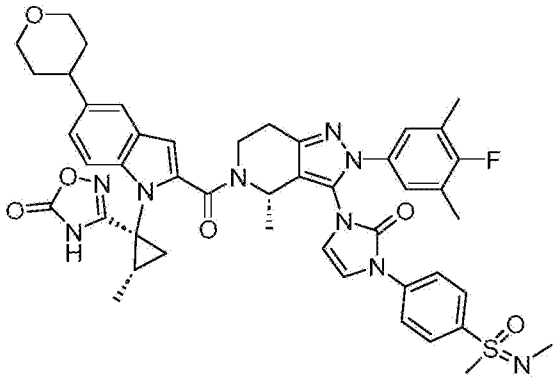
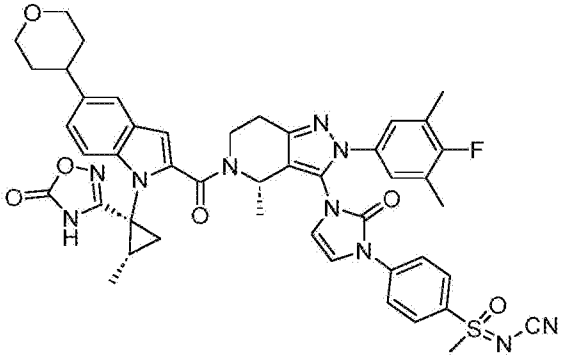
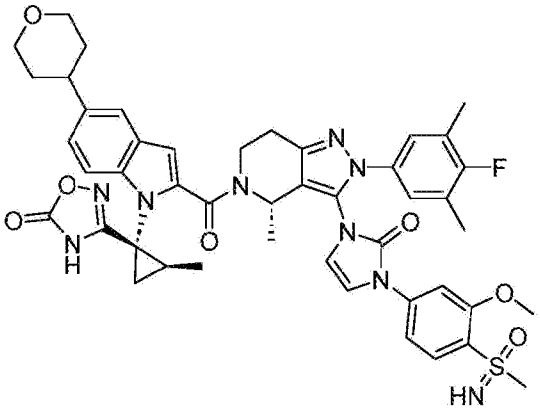
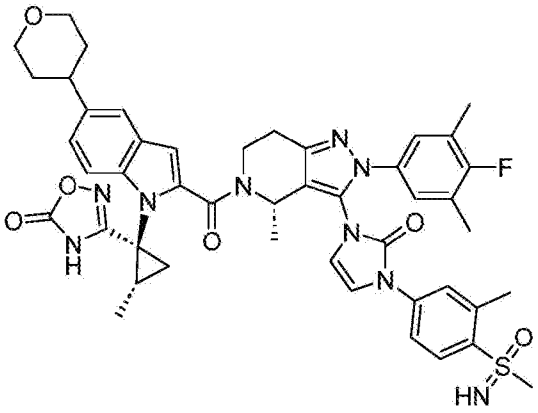
Compound No.	Structure
104	
105	
106	

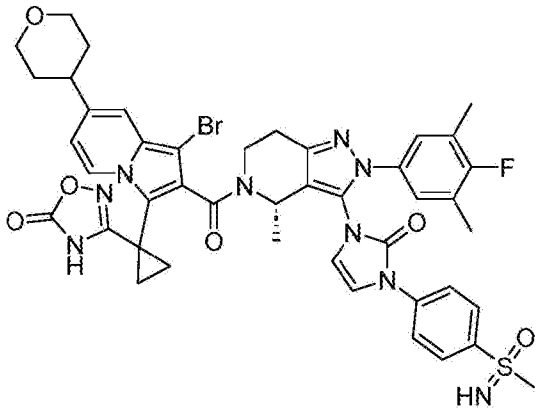
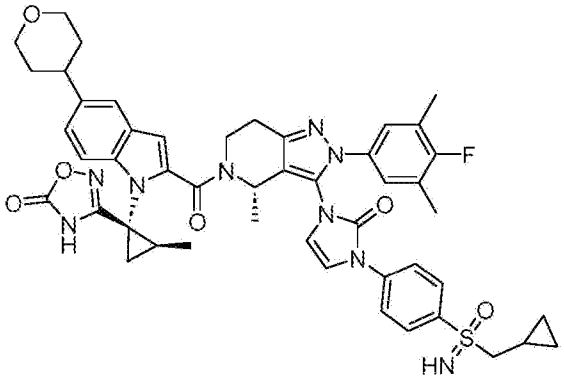
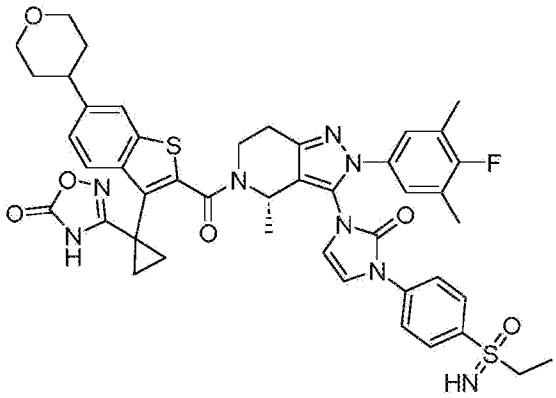
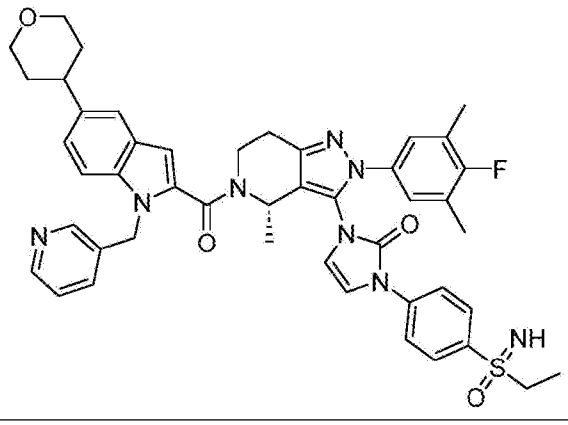
Compound No.	Structure
107	
108	
109	
110	

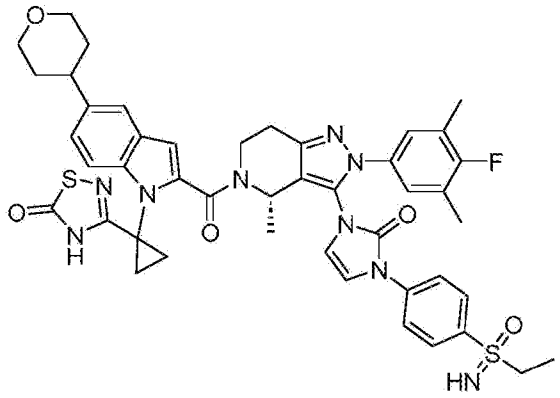
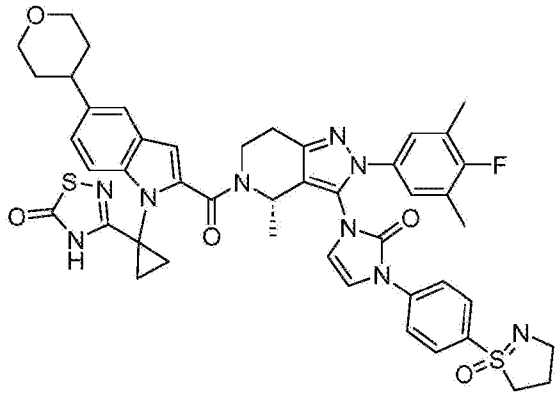
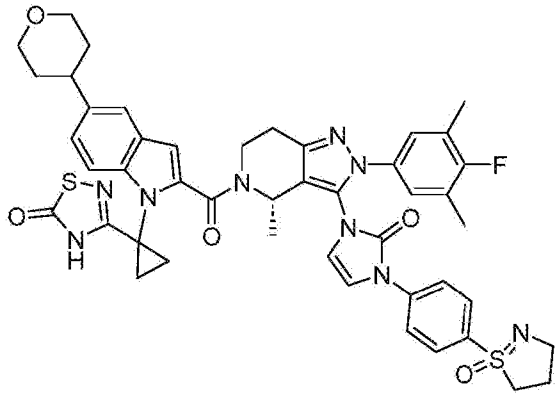
Compound No.	Structure
111	
112	 Enantiomer 1
113	 Enantiomer 1
114	 Enantiomer 1

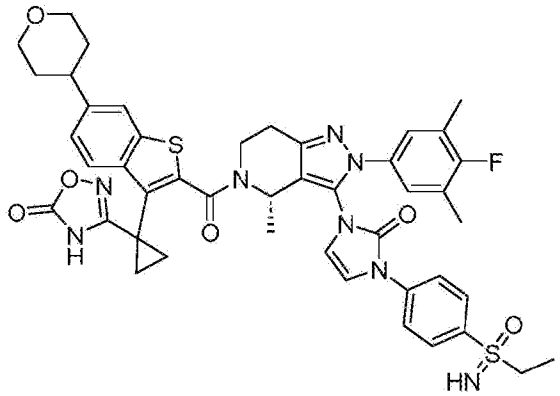
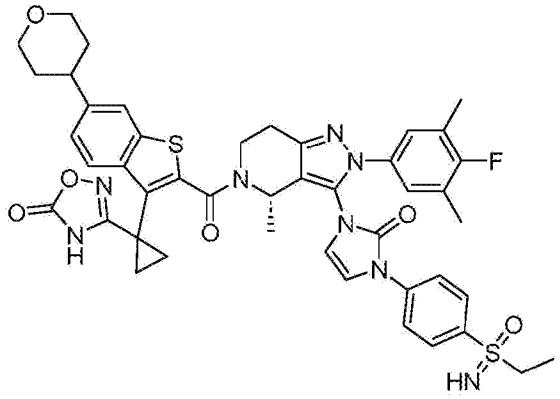
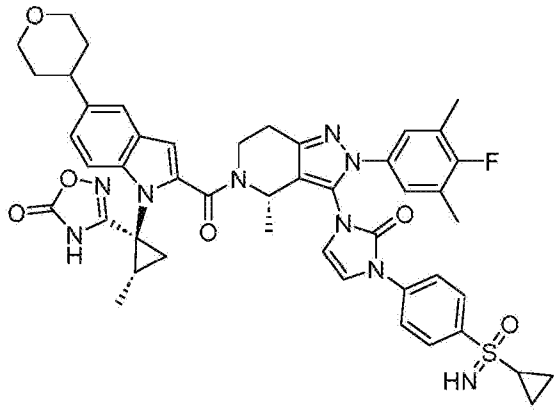
Compound No.	Structure
115	 Enantiomer 2
116	 Enantiomer 1
117	 Enantiomer 2

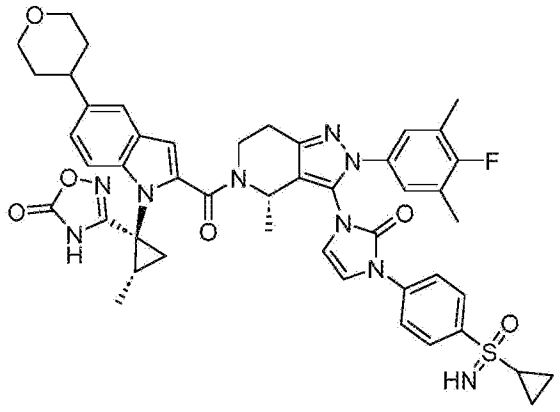
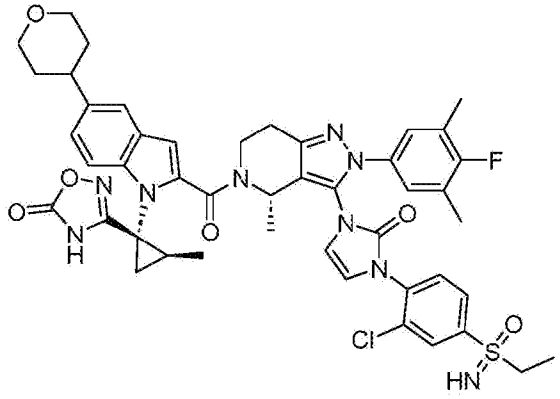
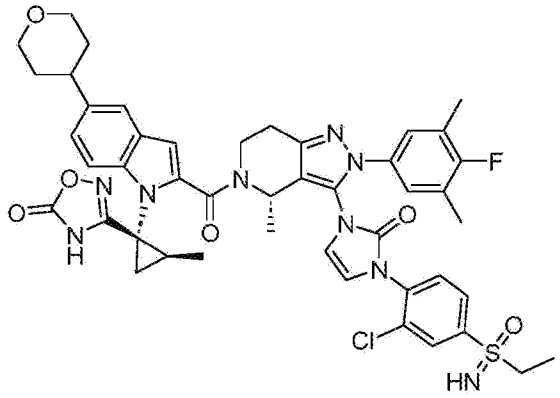
Compound No.	Structure
118	
119	
120	

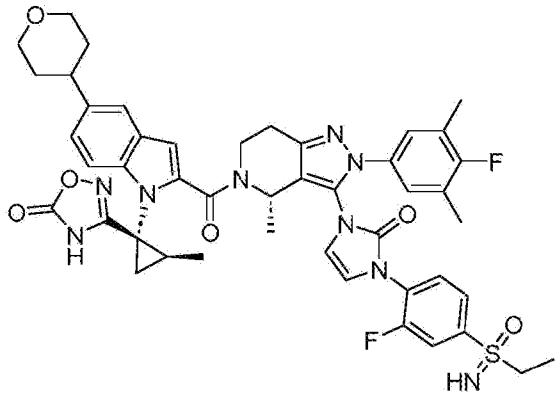
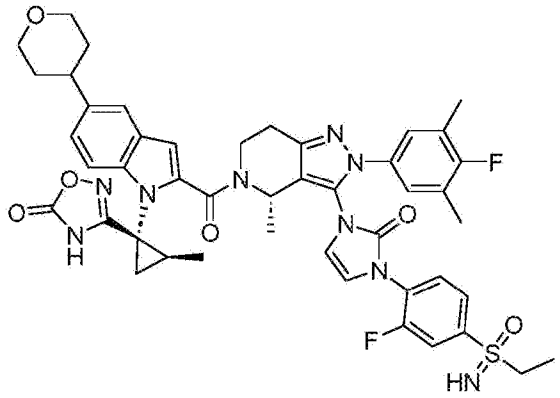
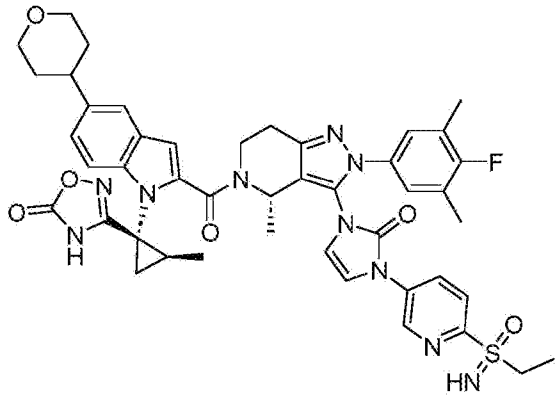
Compound No.	Structure
121	 Enantiomer 2
122	 Enantiomer 2
123	
124	

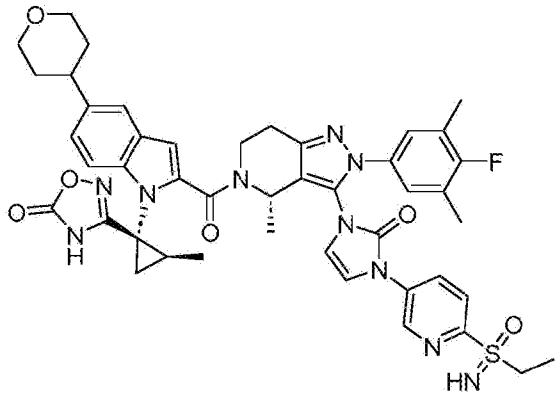
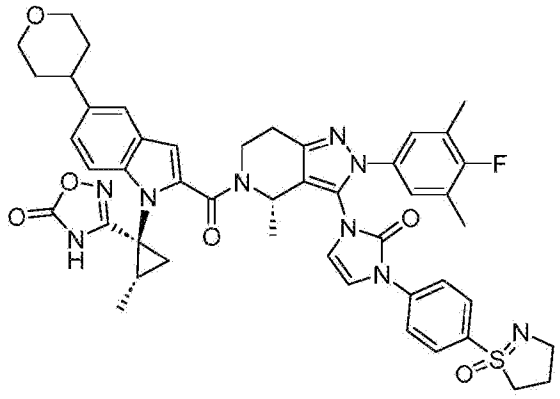
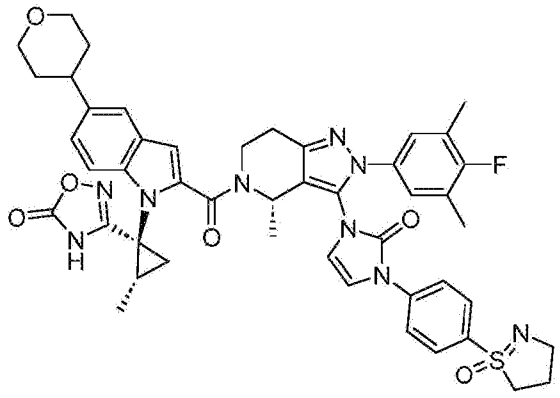
Compound No.	Structure
125	
126	
127	
128	

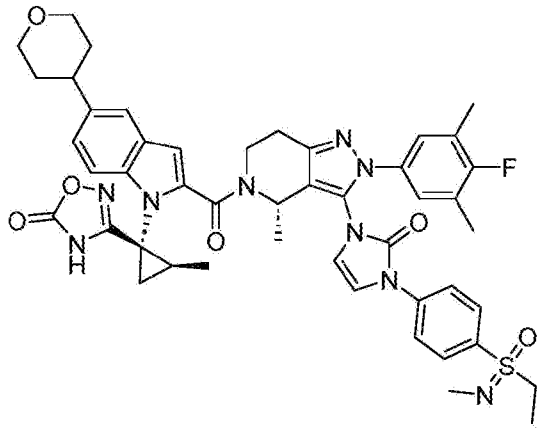
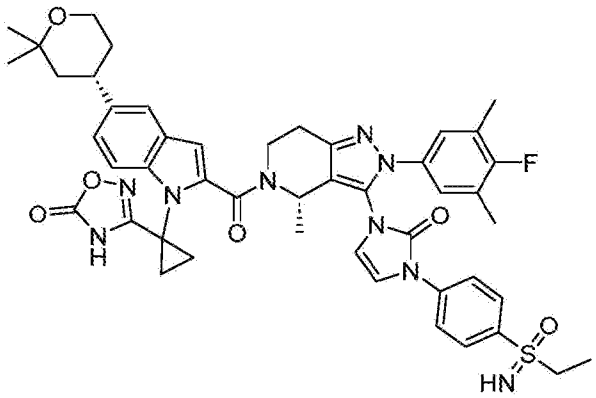
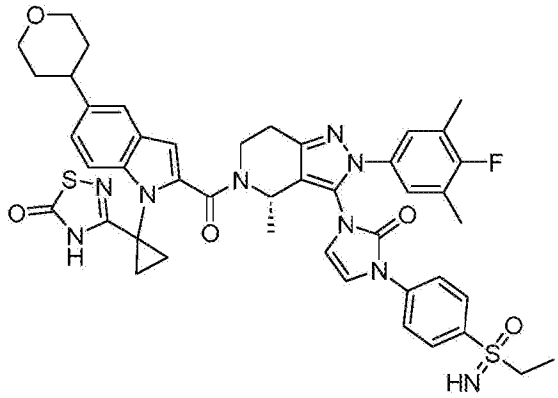
Compound No.	Structure
129	
130	 Enantiomer 1
131	 Enantiomer 2

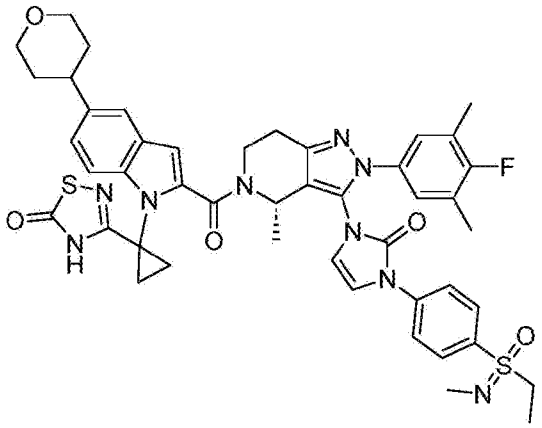
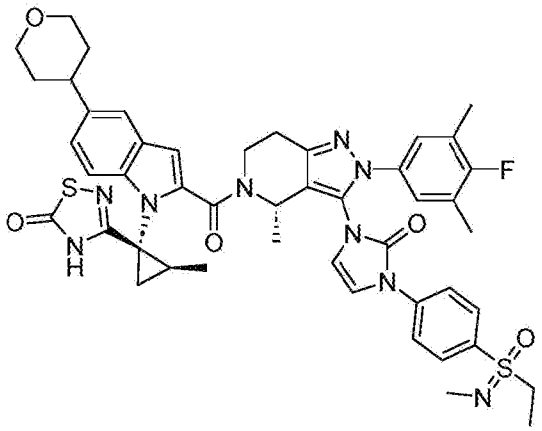
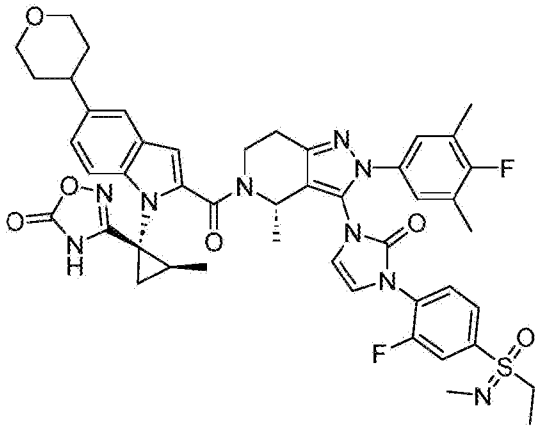
Compound No.	Structure
132	 Enantiomer 1
133	 Enantiomer 2
134	 Enantiomer 1

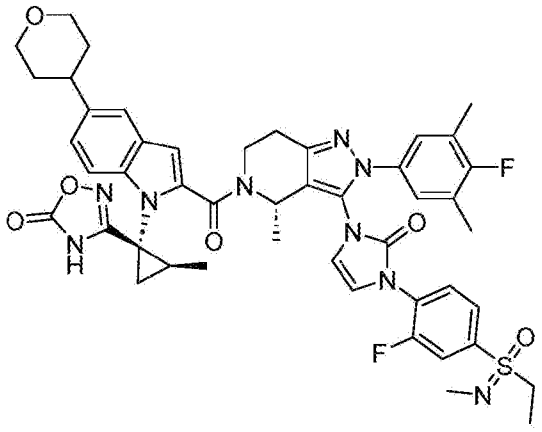
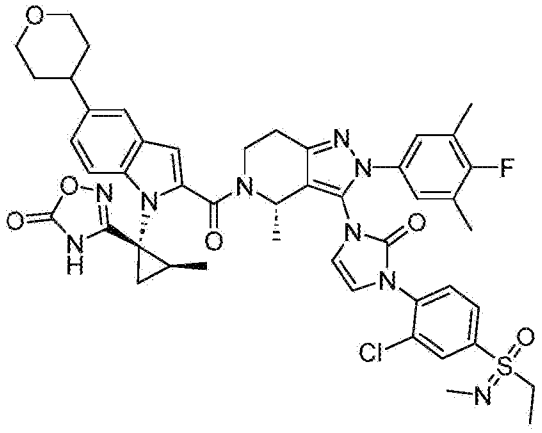
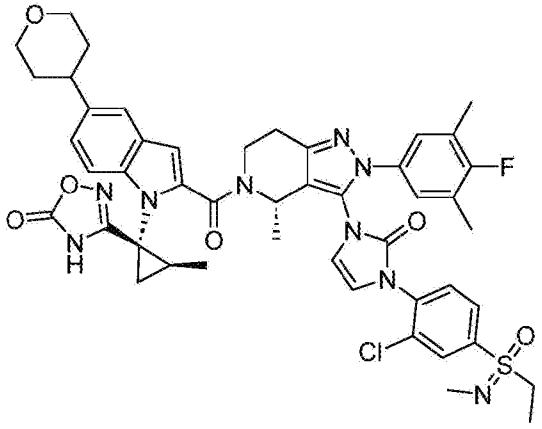
Compound No.	Structure
135	 Enantiomer 2
136	 Enantiomer 1
137	 Enantiomer 2

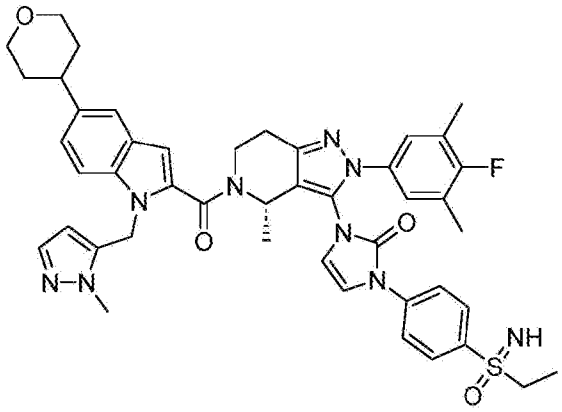
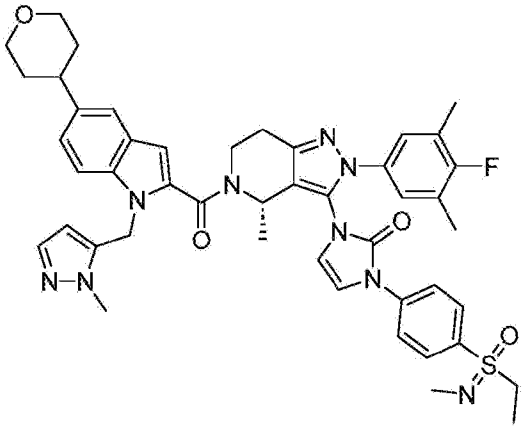
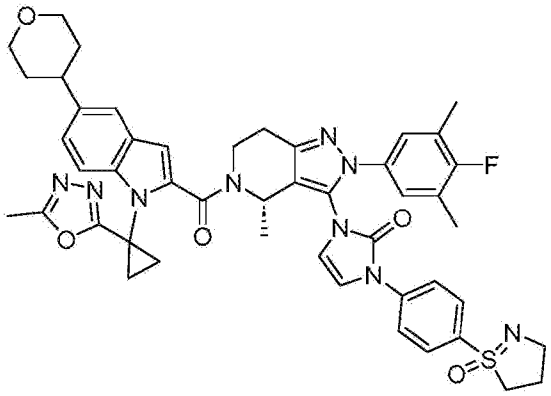
Compound No.	Structure
138	
139	 Enantiomer 2
140	 Enantiomer 1

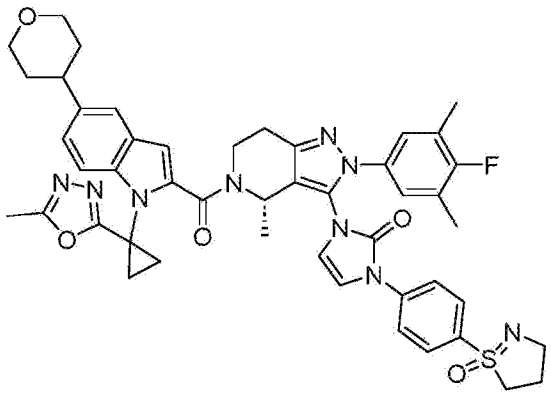
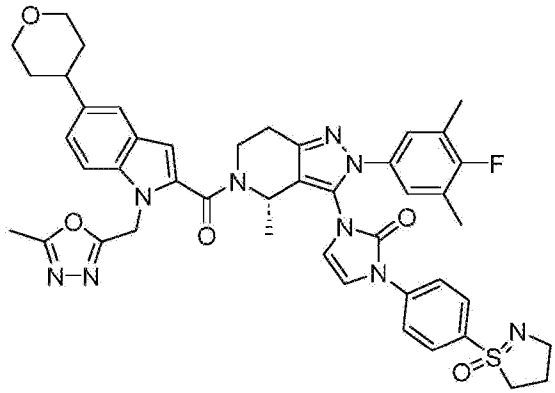
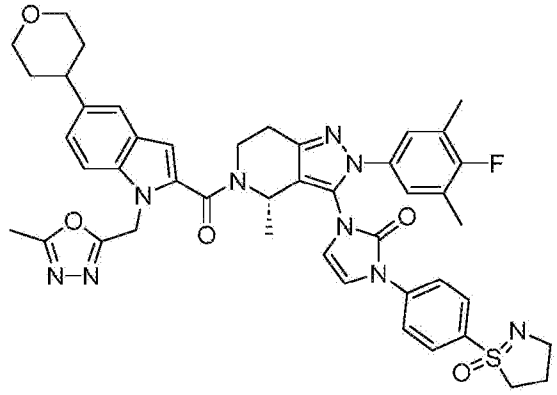
Compound No.	Structure
141	 Enantiomer 2
142	 Enantiomer 1
143	 Enantiomer 2

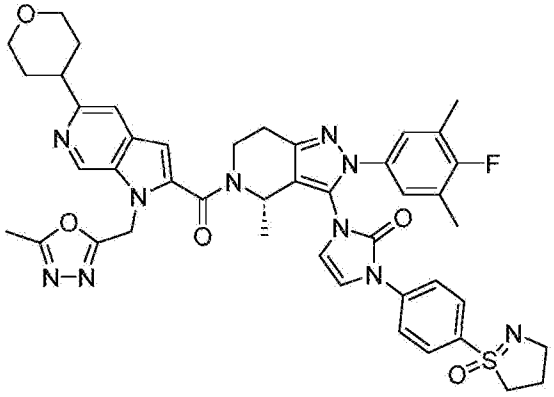
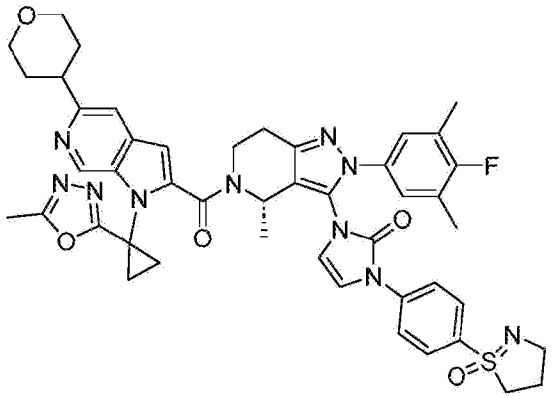
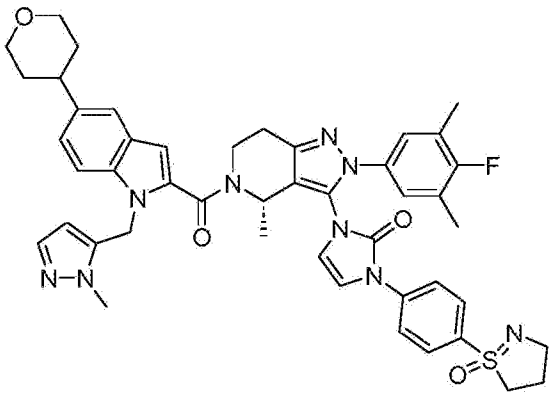
Compound No.	Structure
144	 Single unknown enantiomer
145	 Single unknown enantiomer
146	 Single unknown enantiomer

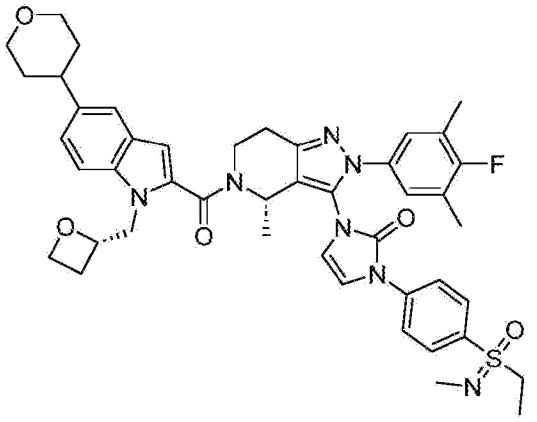
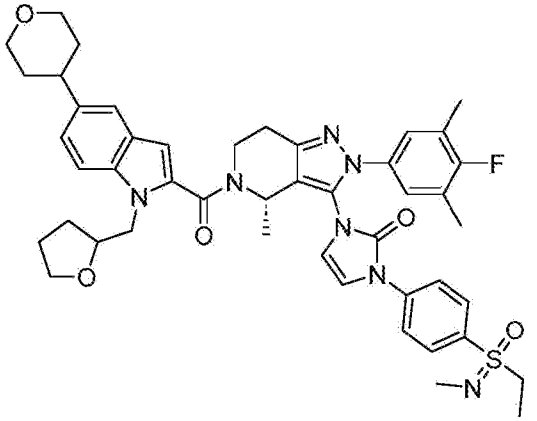
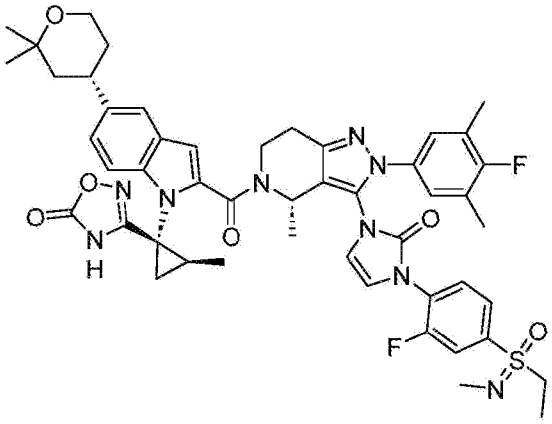
Compound No.	Structure
147	 Single unknown enantiomer
148	 Single unknown enantiomer
149	 Enantiomer 1

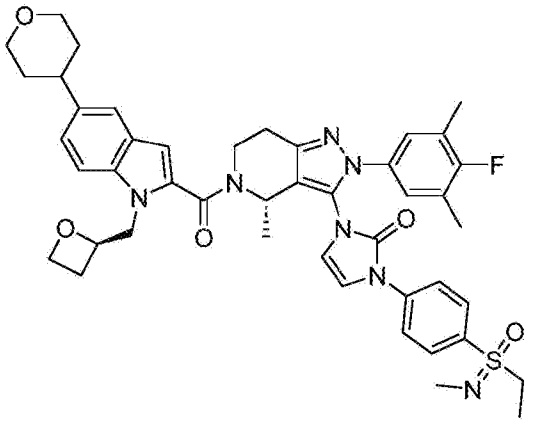
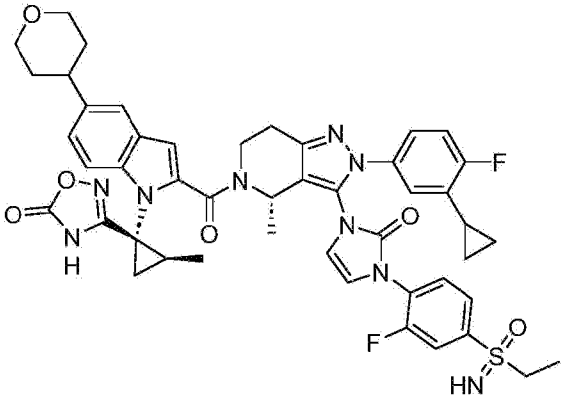
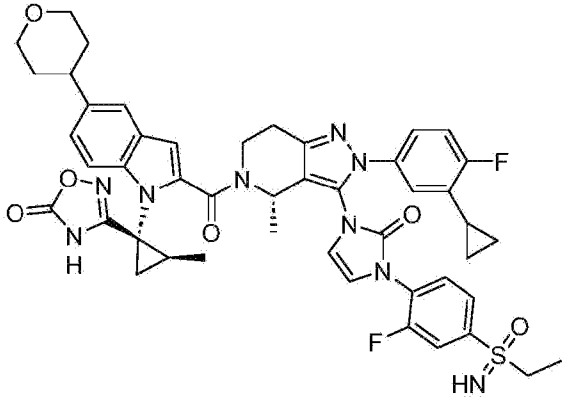
Compound No.	Structure
150	 Enantiomer 2
151	 Enantiomer 1
152	 Enantiomer 2

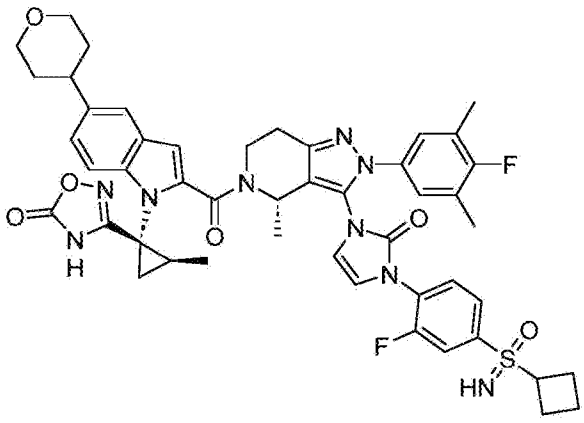
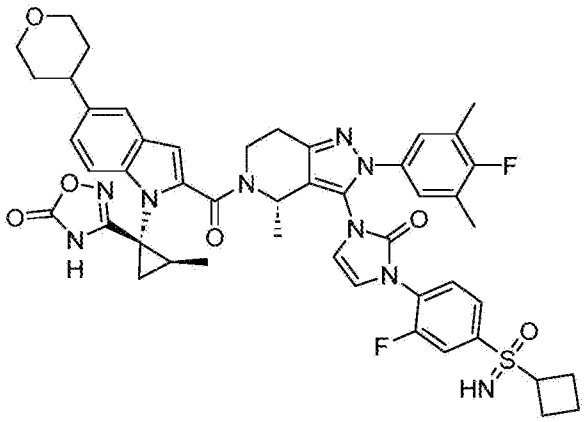
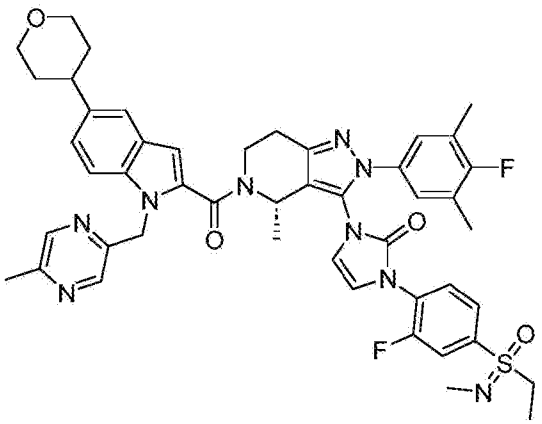
Compound No.	Structure
153	 Enantiomer 1
154	 Enantiomer 2
155	 Enantiomer 2

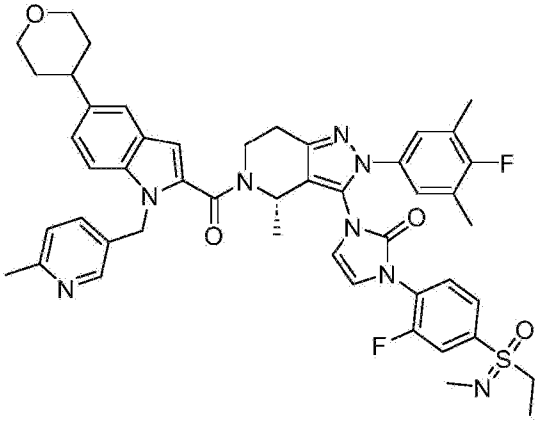
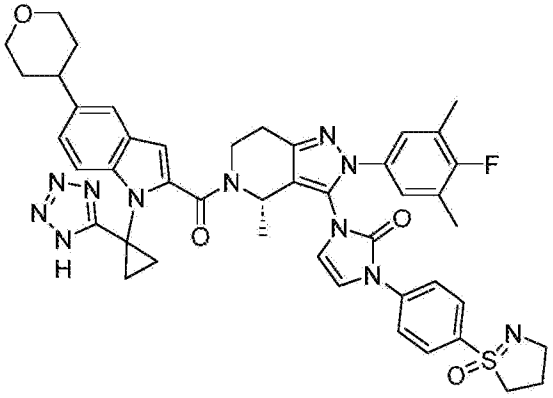
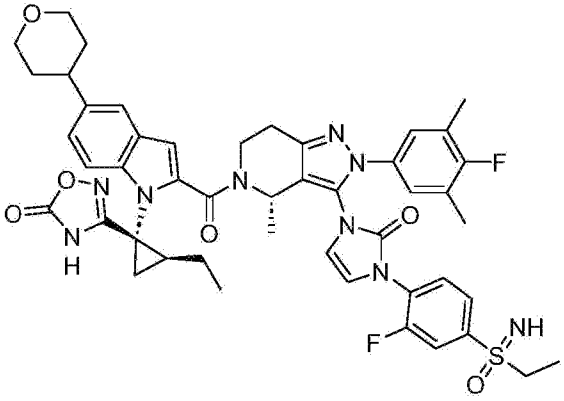
Compound No.	Structure
156	 Enantiomer 1
157	 Enantiomer 1
158	 Enantiomer 2

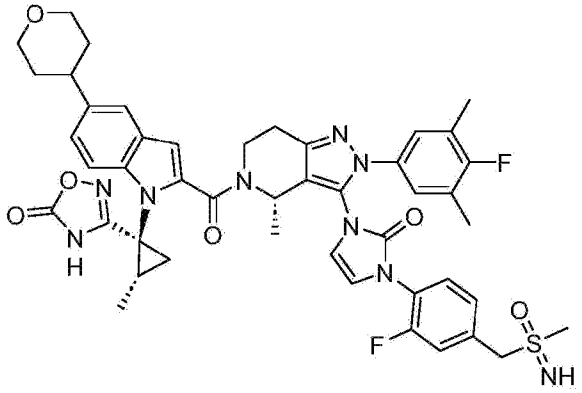
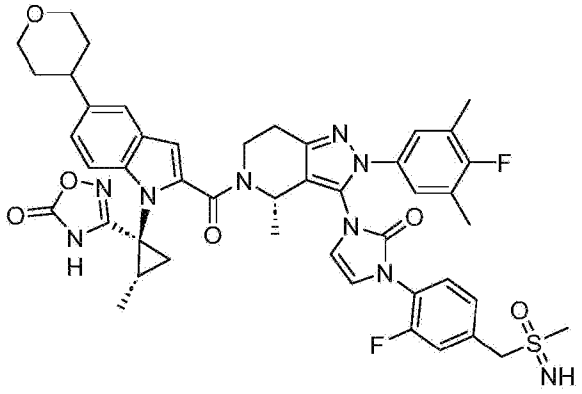
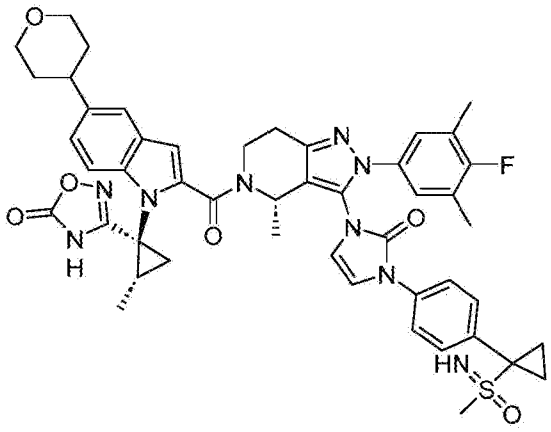
Compound No.	Structure
159	 Single unknown enantiomer
160	 Single unknown enantiomer
161	 Single unknown enantiomer

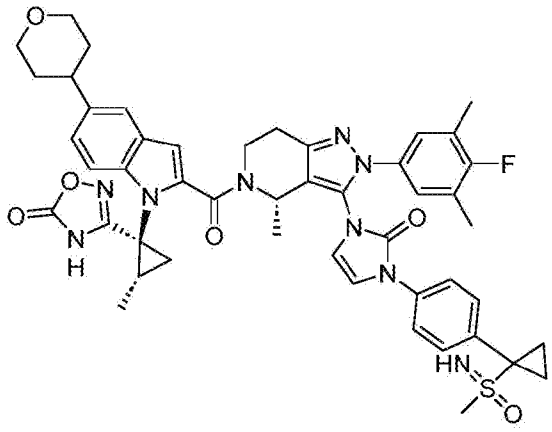
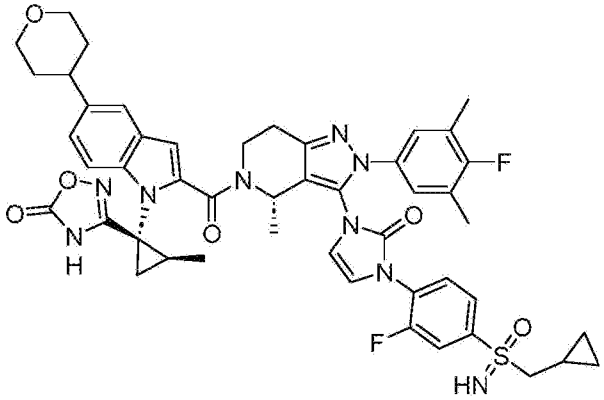
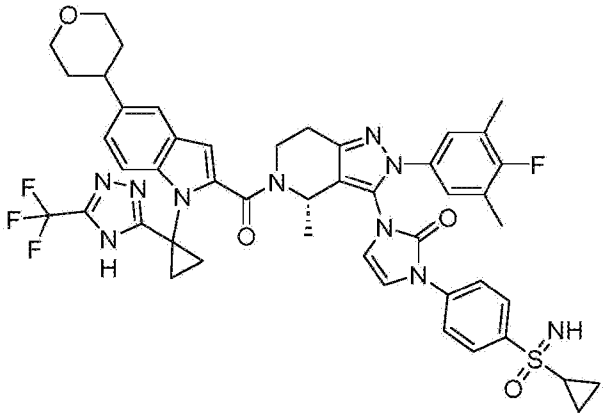
Compound No.	Structure
162	 Single unknown enantiomer
163	
164	 Single unknown enantiomer

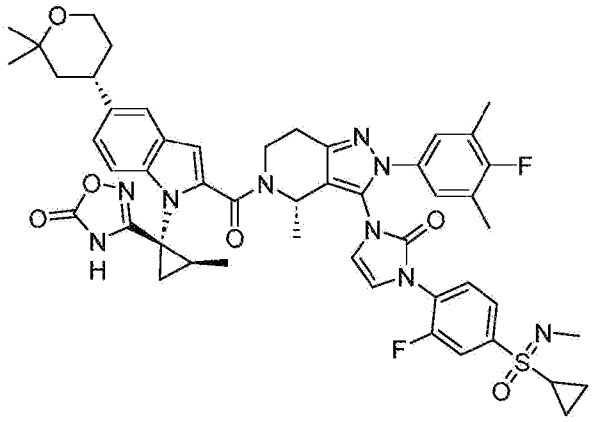
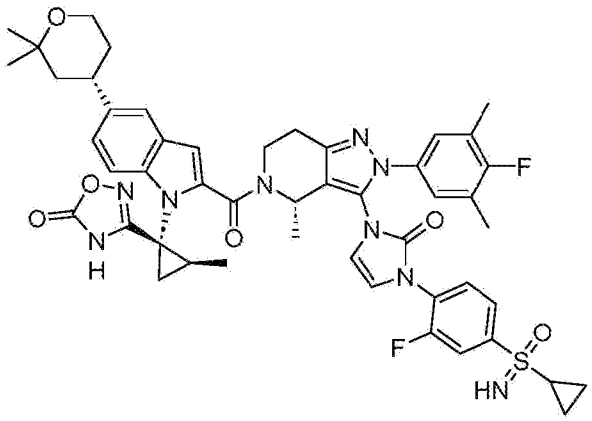
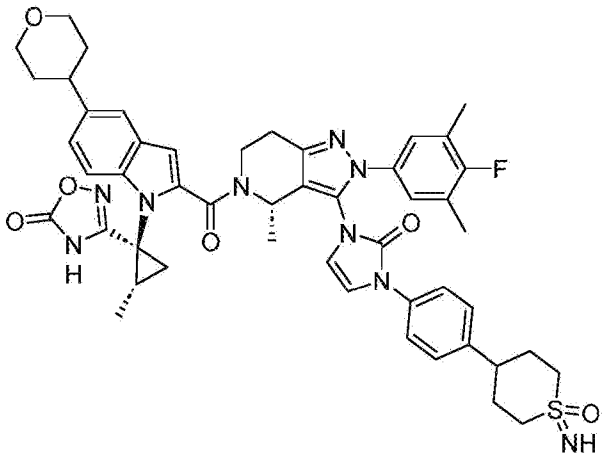
Compound No.	Structure
165	 Single unknown enantiomer
166	 Enantiomer 1
167	 Enantiomer 2

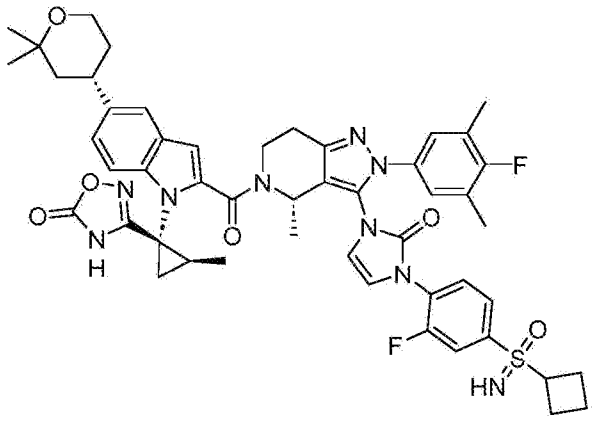
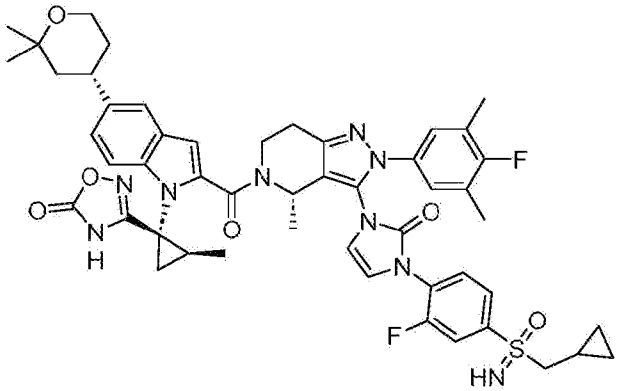
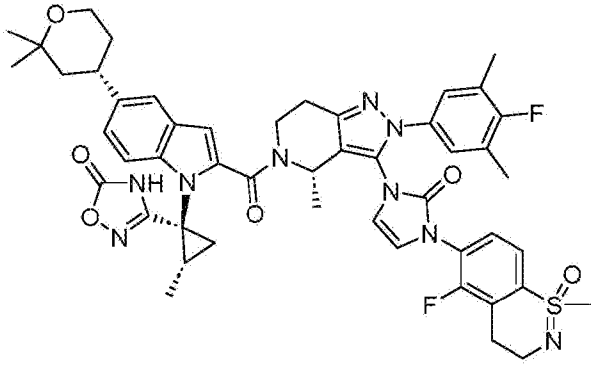
Compound No.	Structure
168	 Enantiomer 1
169	 Enantiomer 2
170	 Single unknown enantiomer

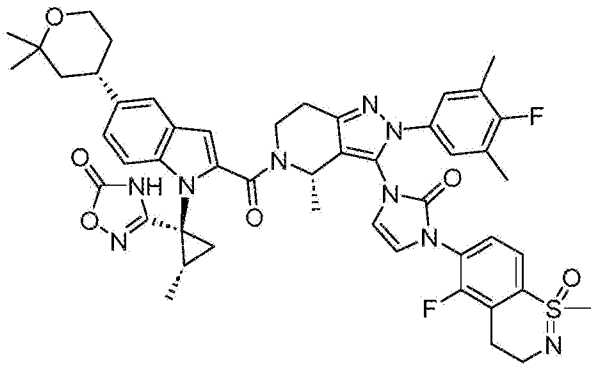
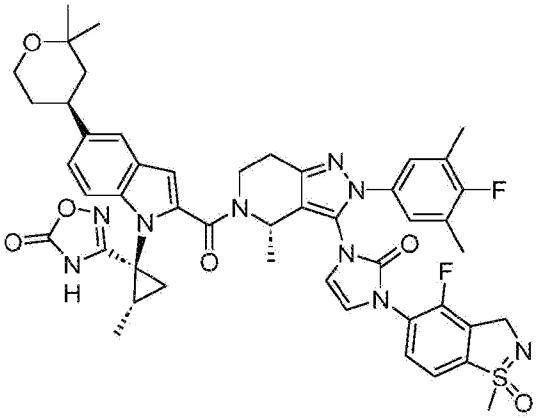
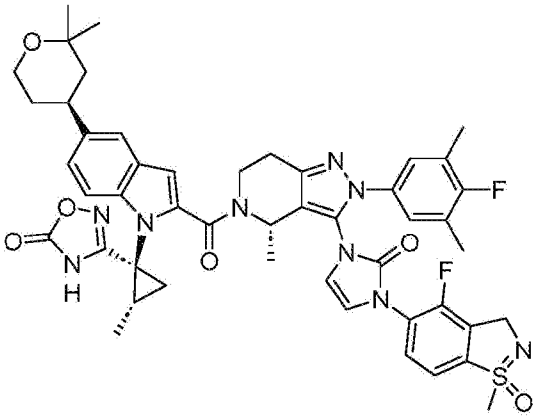
Compound No.	Structure
171	 Single unknown enantiomer
172	 Single unknown enantiomer
173	 Single unknown enantiomer

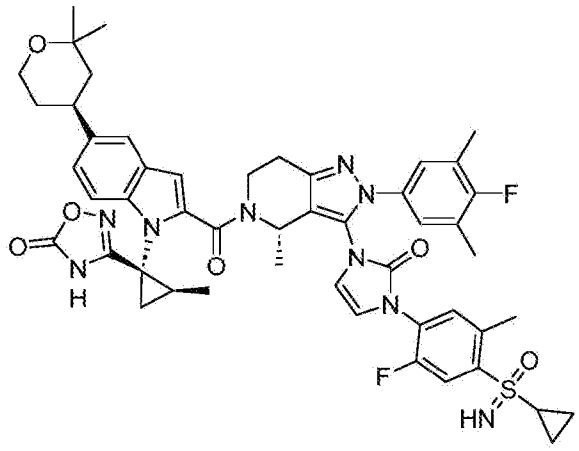
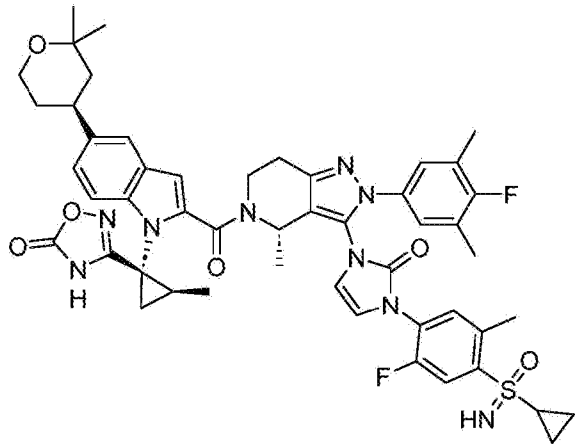
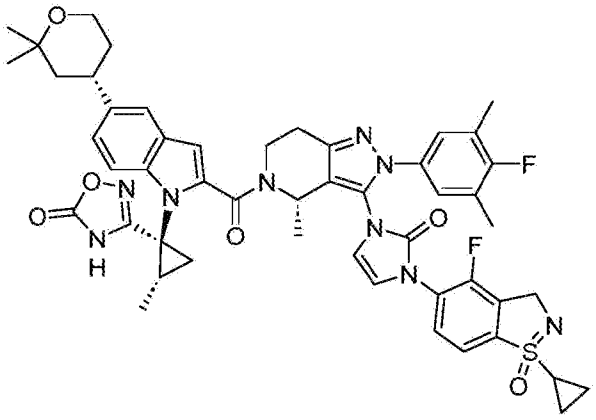
Compound No.	Structure
174	 Enantiomer 1
175	 Enantiomer 2
176	 Enantiomer 1

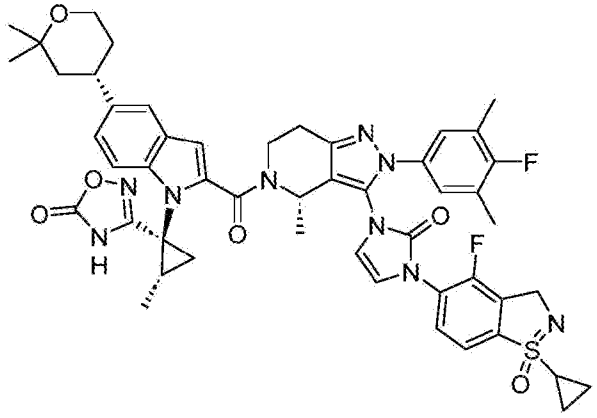
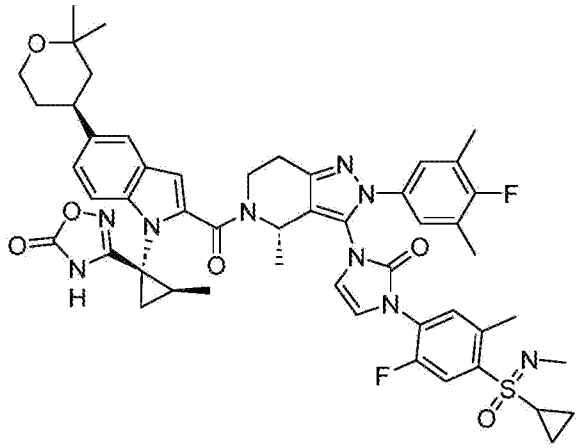
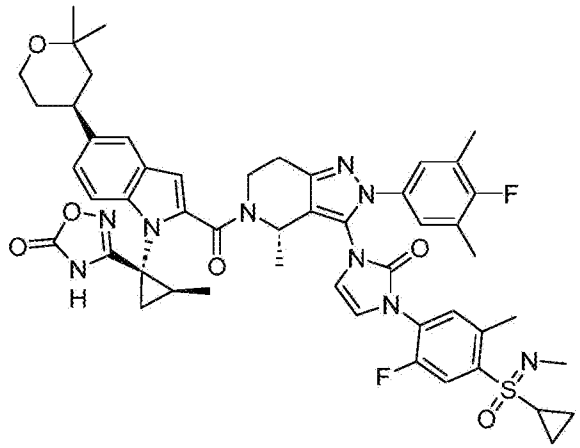
Compound No.	Structure
177	 Enantiomer 2
178	 Single unknown enantiomer
179	 Single unknown enantiomer

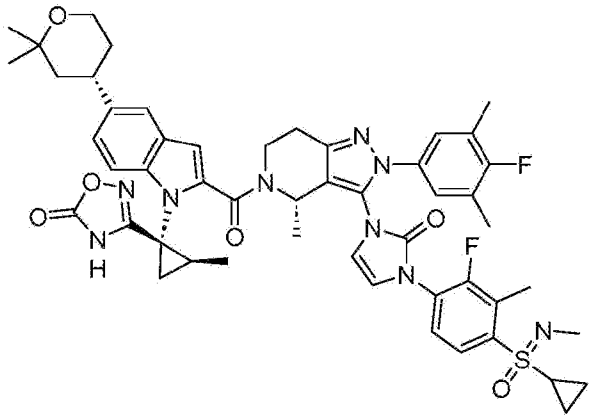
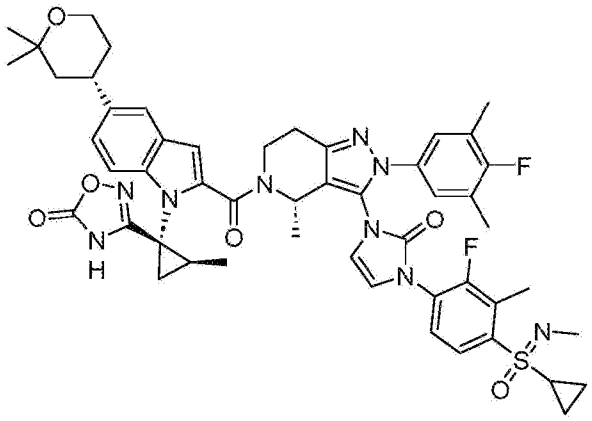
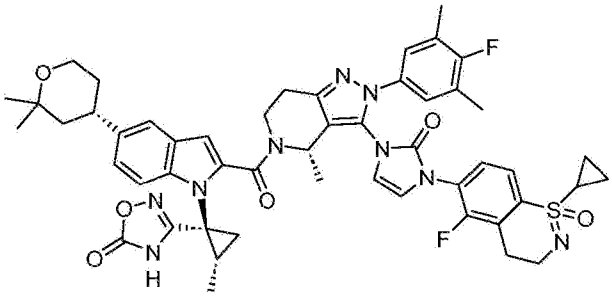
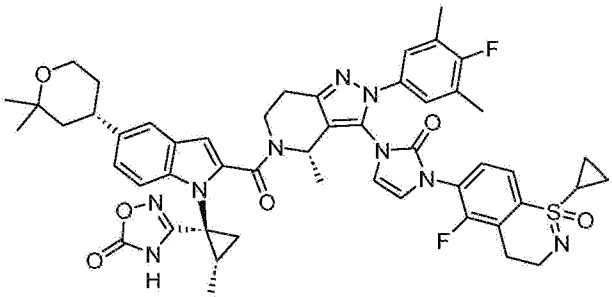
Compound No.	Structure
180	 Single unknown enantiomer
181	 Single unknown enantiomer
182	

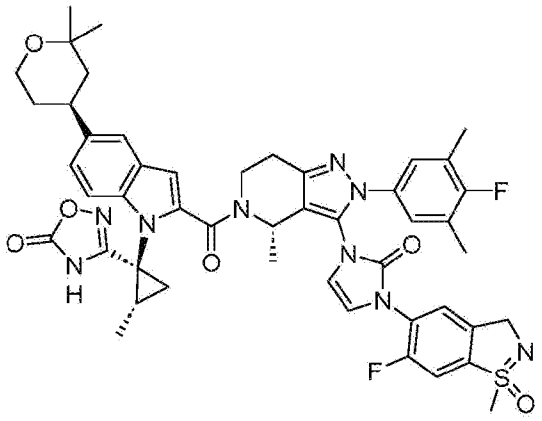
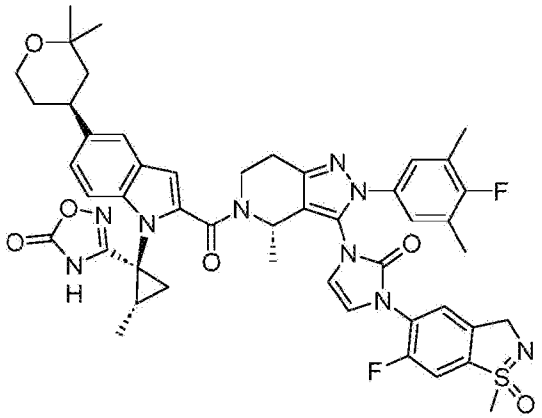
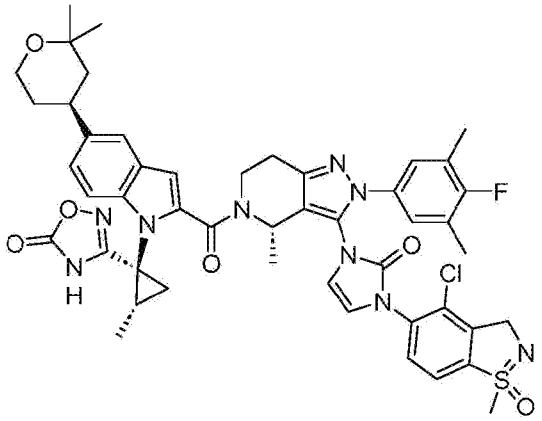
Compound No.	Structure
183	 Single unknown enantiomer
184	 Single unknown enantiomer
185	 Enantiomer 1

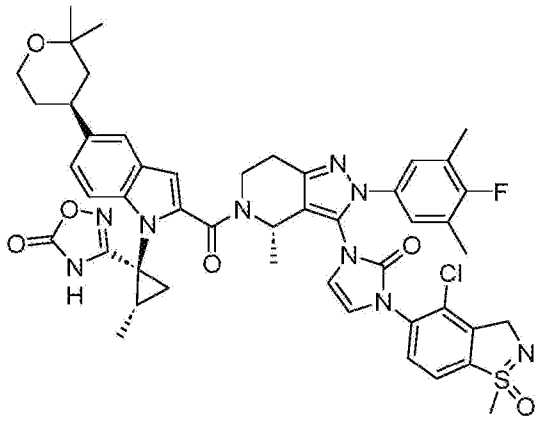
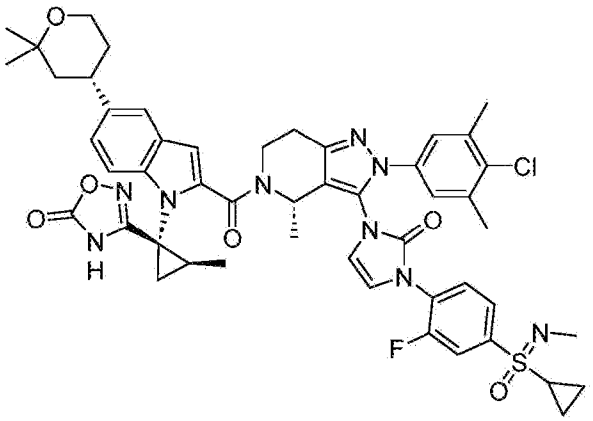
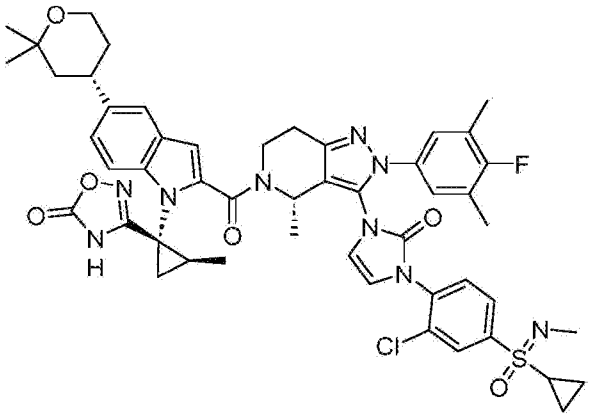
Compound No.	Structure
186	 Enantiomer 2
187	 Enantiomer 1
188	 Enantiomer 2

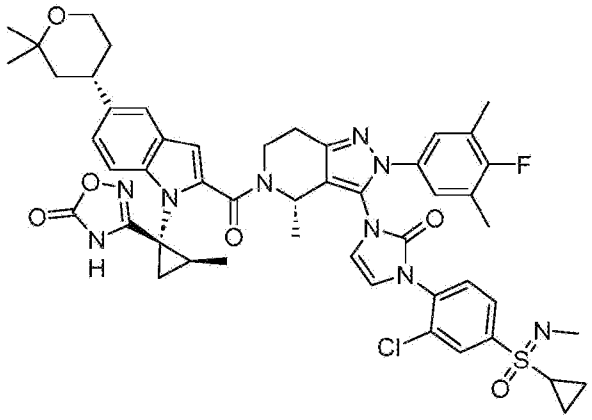
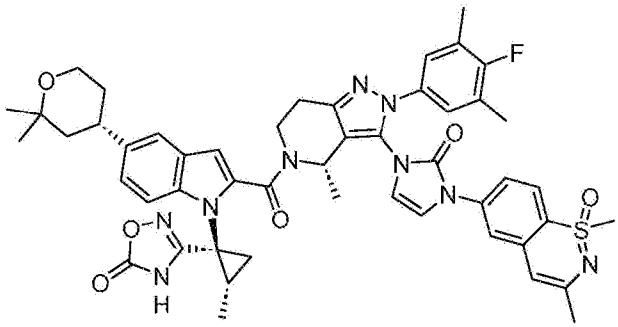
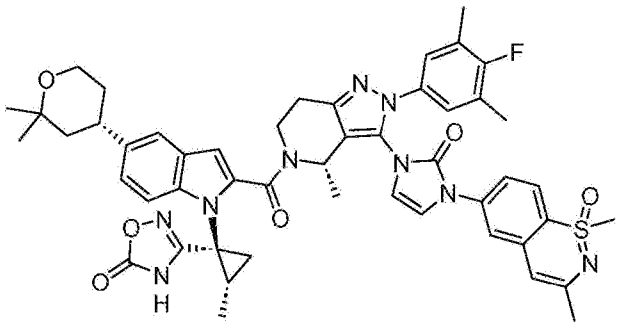
Compound No.	Structure
189	 Enantiomer 1
190	 Enantiomer 2
191	 Enantiomer 1

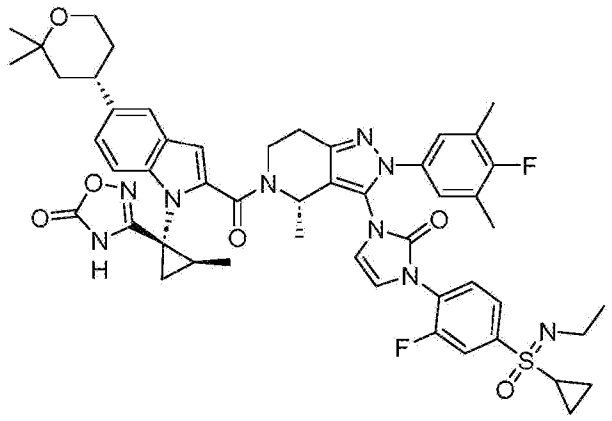
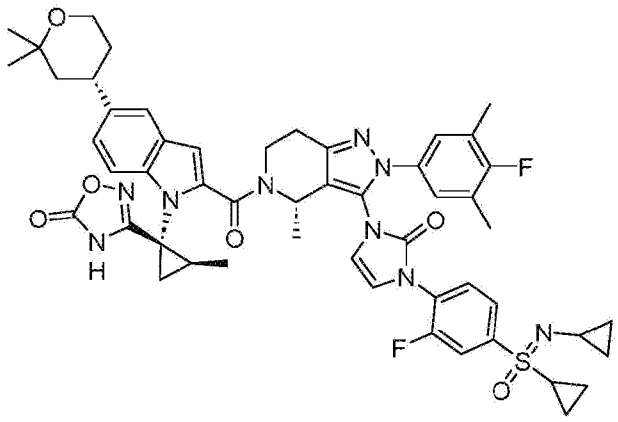
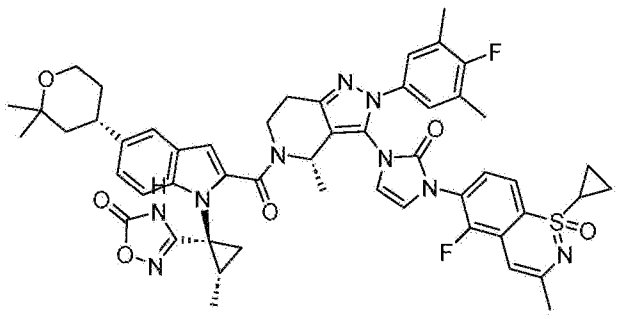
Compound No.	Structure
192	 Enantiomer 2
193	 Enantiomer 1
194	 Enantiomer 2

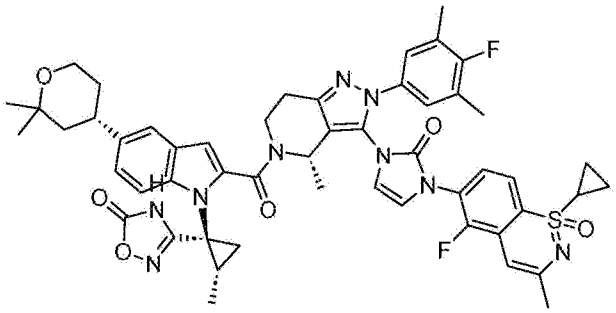
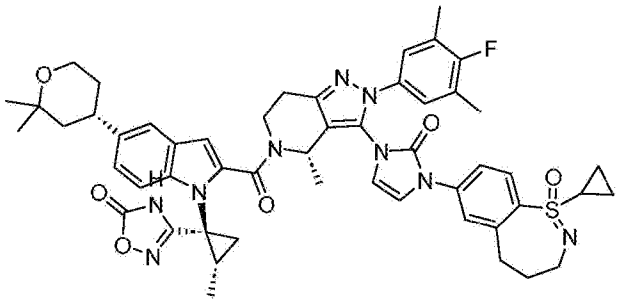
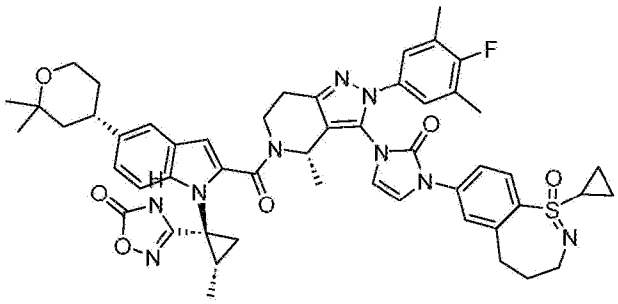
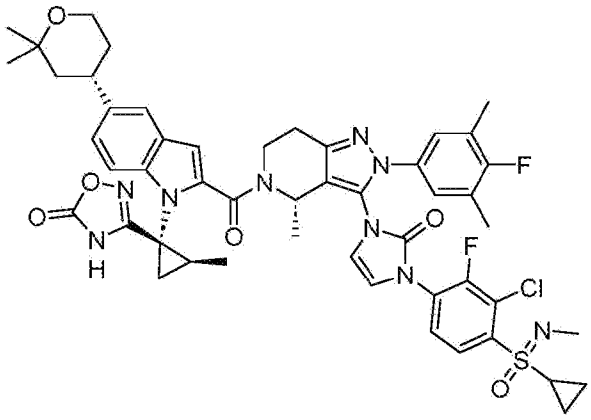
Compound No.	Structure
195	 Enantiomer 1
196	 Enantiomer 2
197	 Enantiomer 1
198	 Enantiomer 2

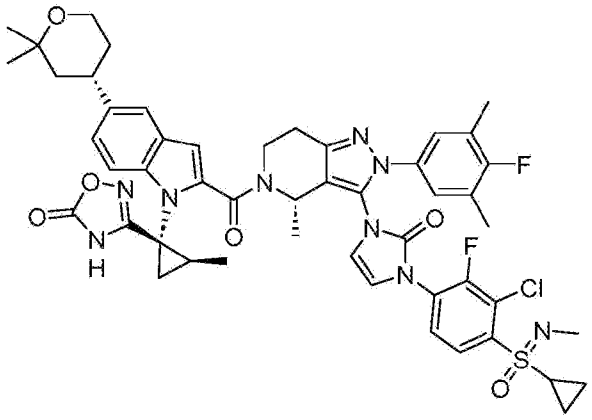
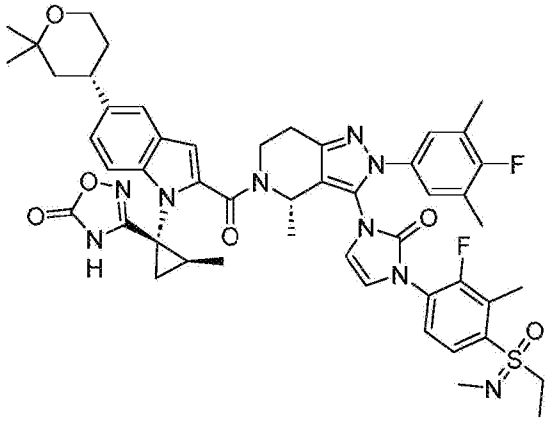
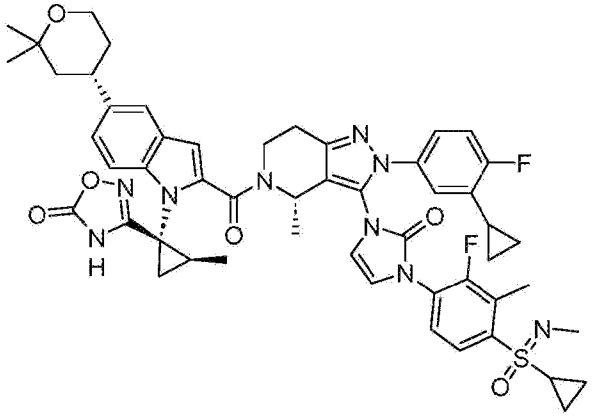
Compound No.	Structure
199	 Enantiomer 1
200	 Enantiomer 2
201	 Enantiomer 1

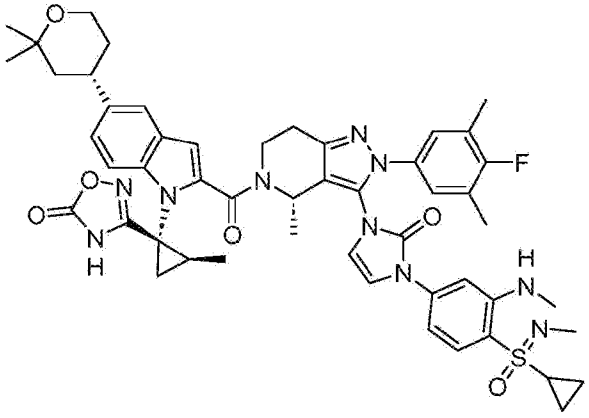
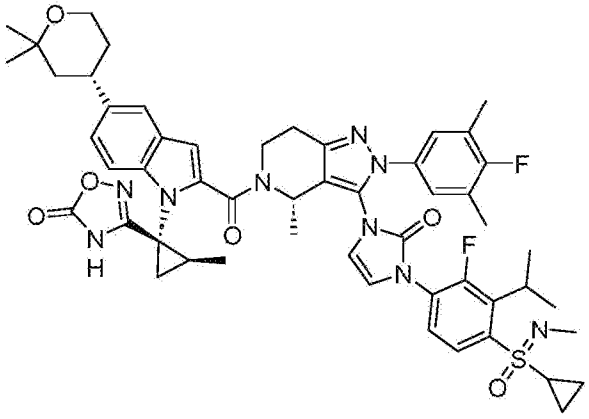
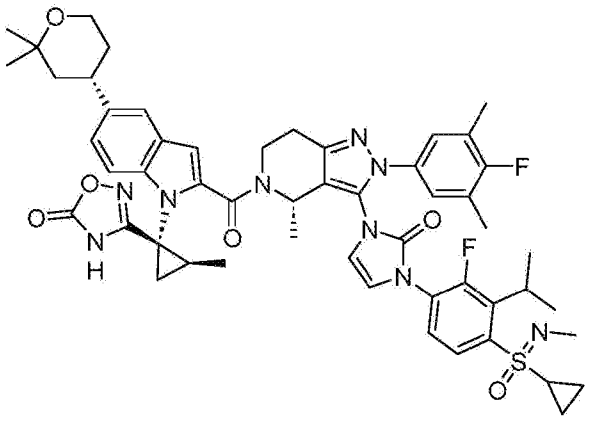
Compound No.	Structure
202	 Enantiomer 2
203	 Single unknown enantiomer
204	 Enantiomer 1

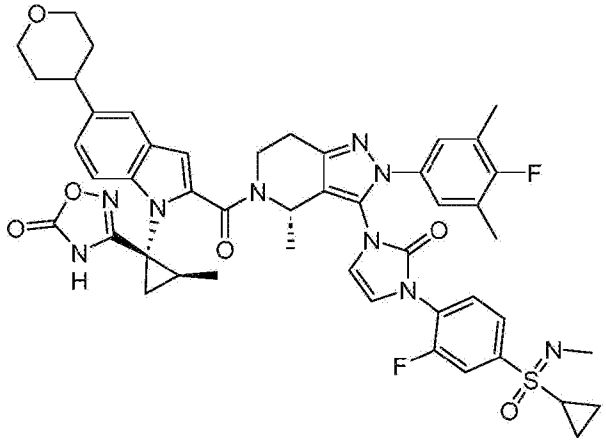
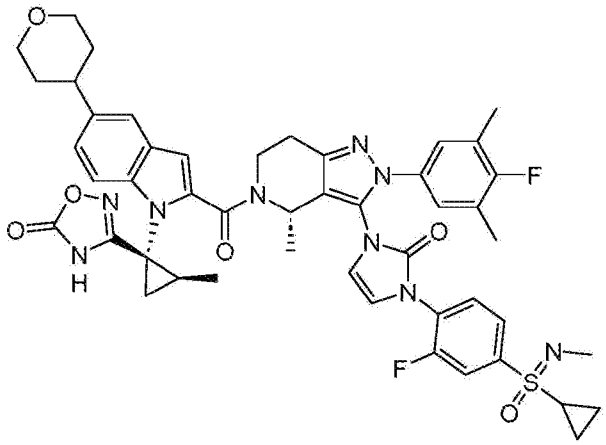
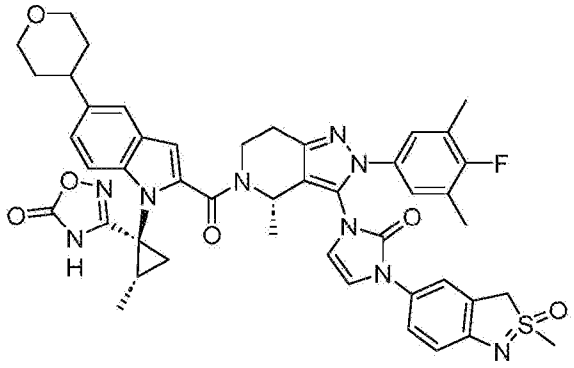
Compound No.	Structure
205	 Enantiomer 2
206	 Enantiomer 1
207	 Enantiomer 2

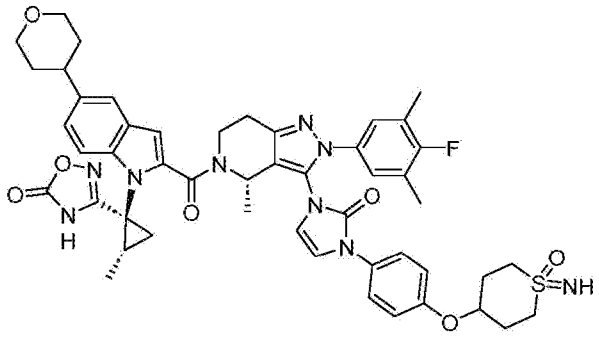
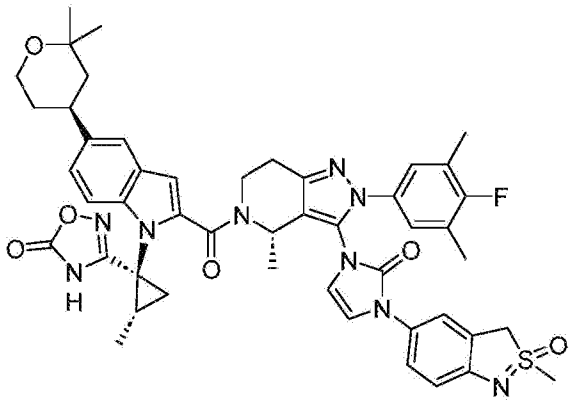
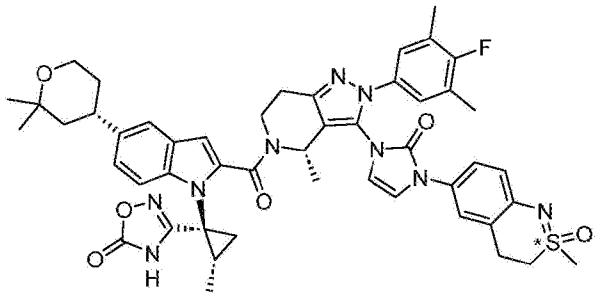
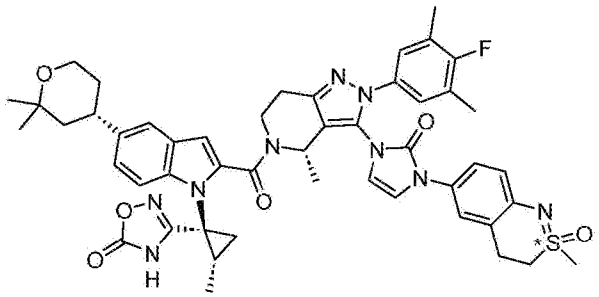
Compound No.	Structure
208	 Single unknown enantiomer
209	 Single unknown enantiomer
210	 Enantiomer 1

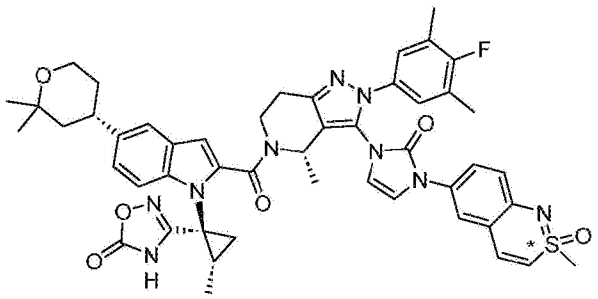
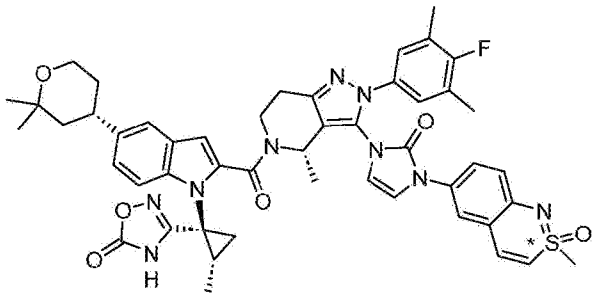
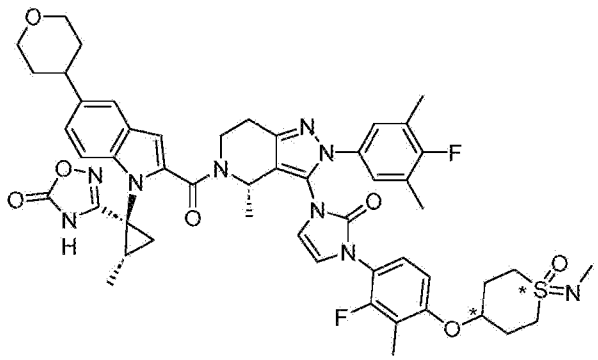
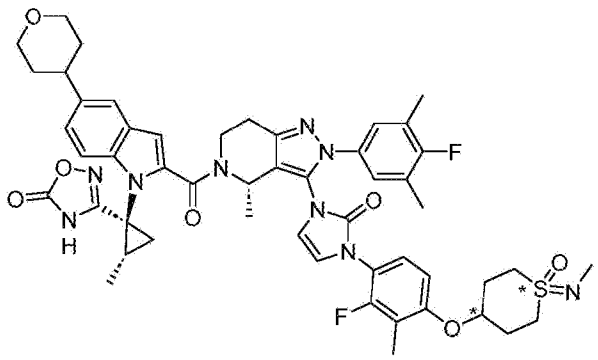
Compound No.	Structure
211	 Enantiomer 2
212	 Enantiomer 1
213	 Enantiomer 2
214	 Enantiomer 1

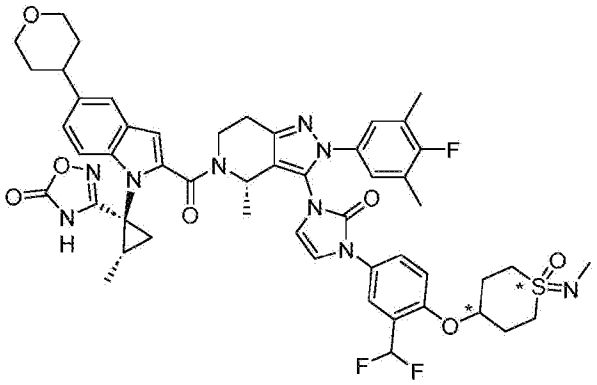
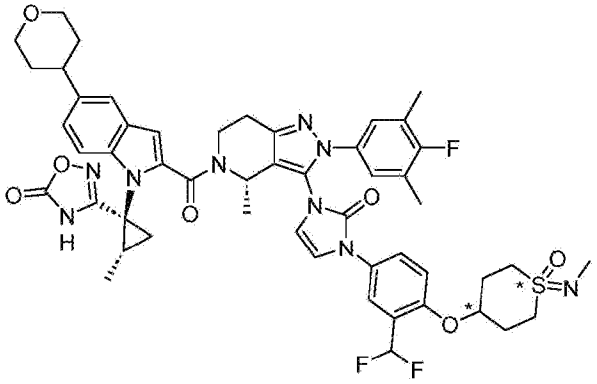
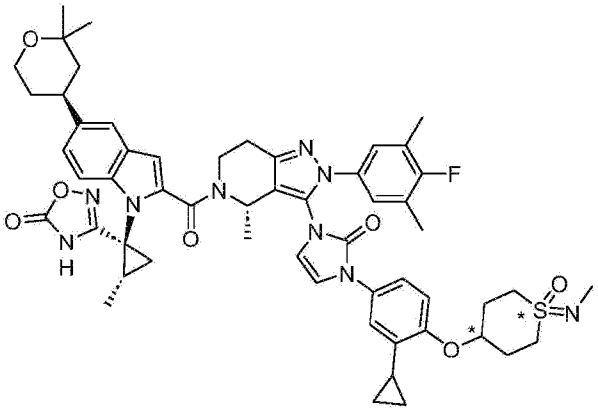
Compound No.	Structure
215	 Enantiomer 2
216	 Single unknown enantiomer
217	 Single unknown enantiomer

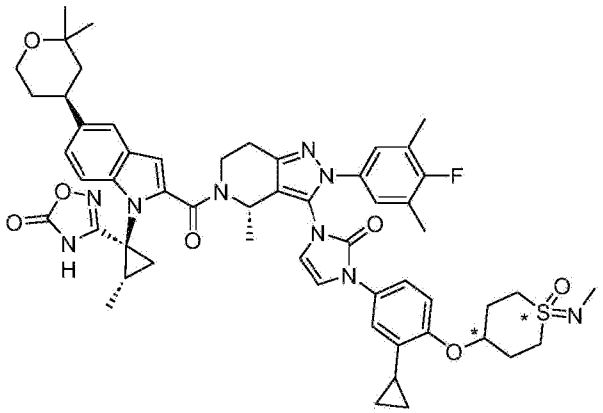
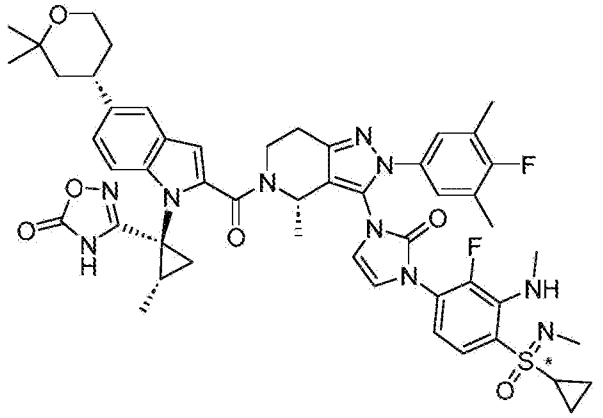
Compound No.	Structure
218	 Single unknown enantiomer
219	 Enantiomer 1
220	 Enantiomer 2

Compound No.	Structure
221	 Enantiomer 1
222	 Enantiomer 2
225	

Compound No.	Structure
226	
227	
228	 Enantiomer 1
229	 Enantiomer 2

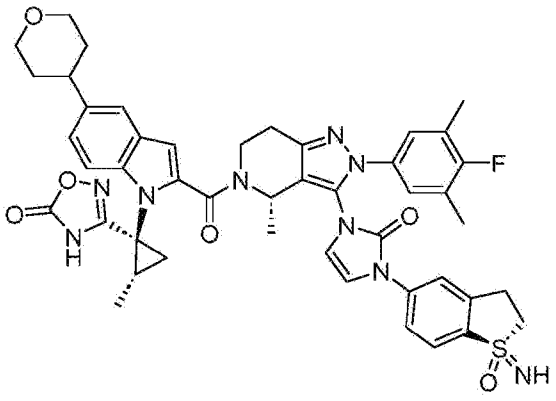
Compound No.	Structure
230	 Enantiomer 1
231	 Enantiomer 2
232	 Enantiomer 1
233	 Enantiomer 2

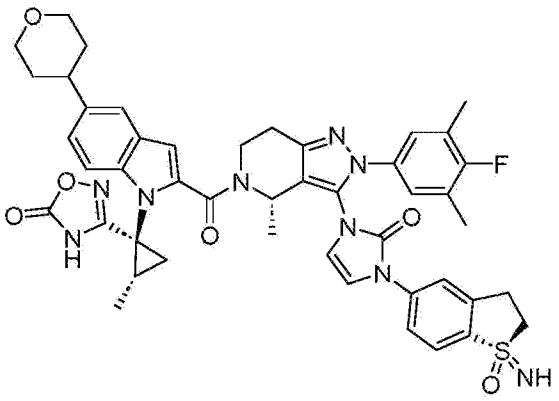
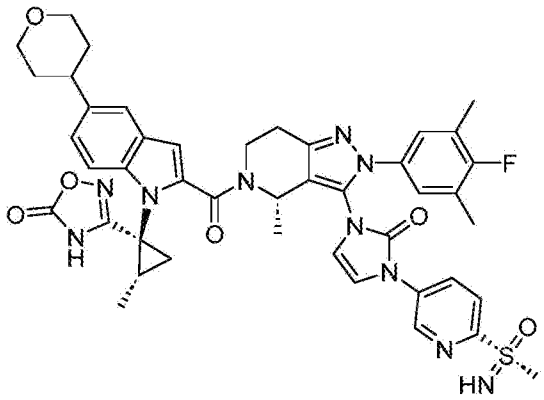
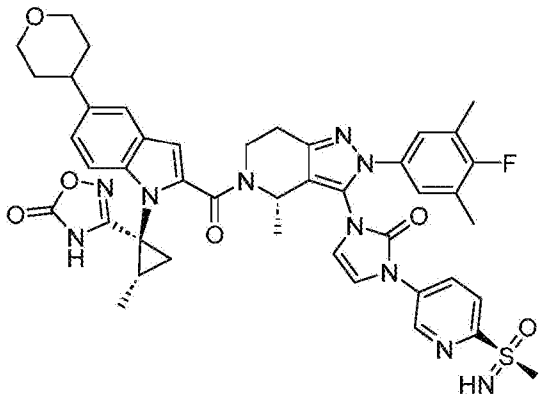
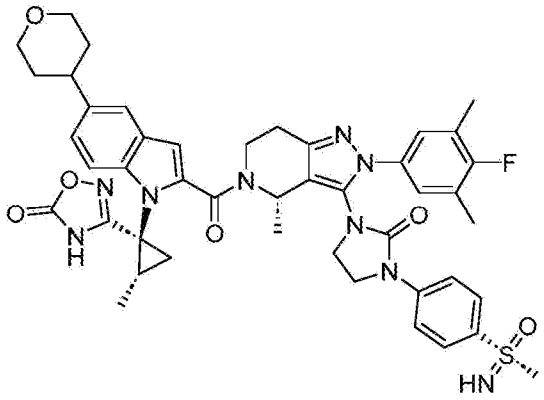
Compound No.	Structure
234	 Enantiomer 1
235	 Enantiomer 2
236	 Enantiomer 1

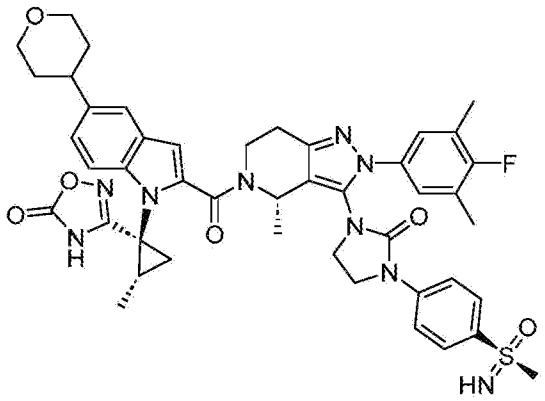
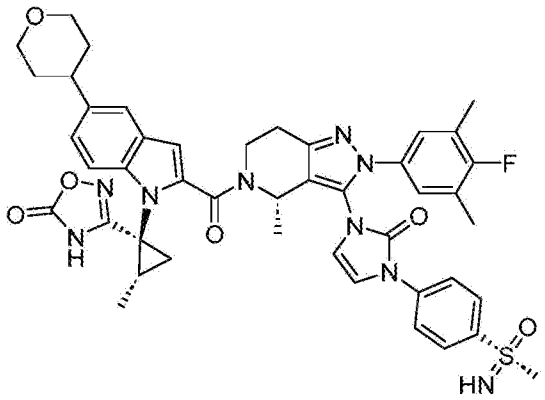
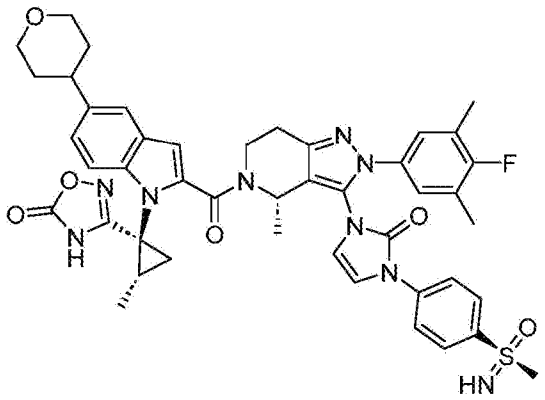
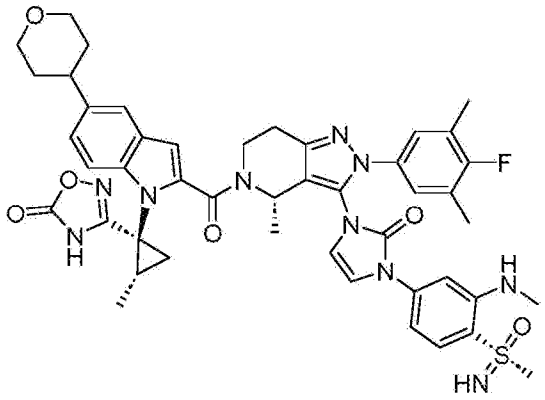
Compound No.	Structure
237	 Enantiomer 2
238	

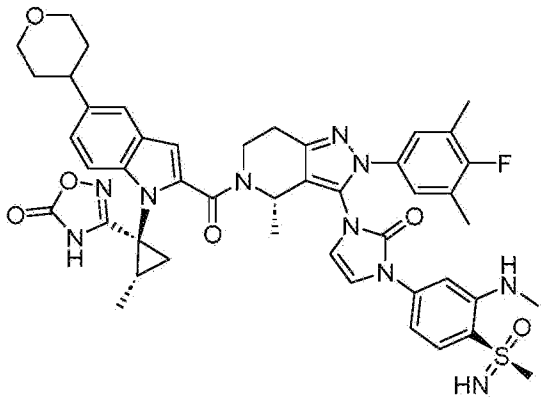
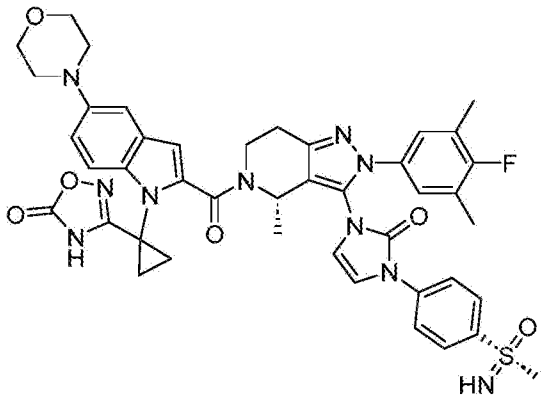
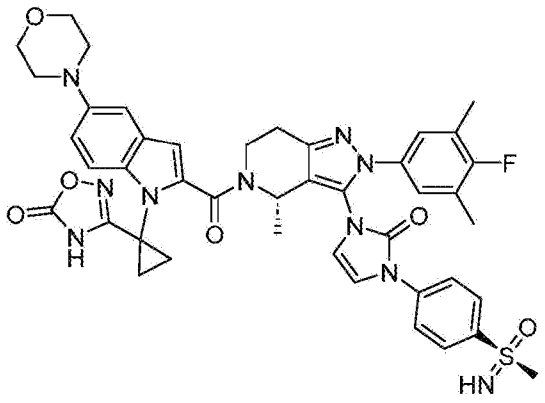
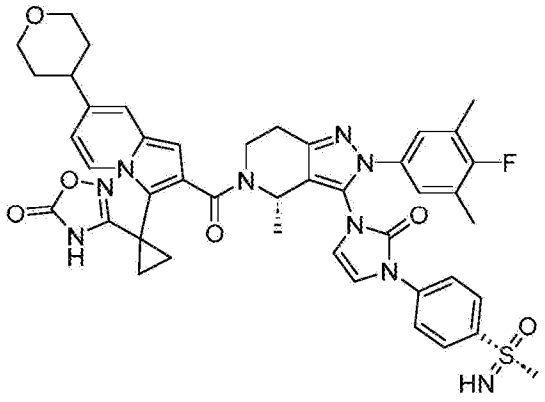
[0873] In certain embodiments, provided is a compound selected from Table 2 , or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof:

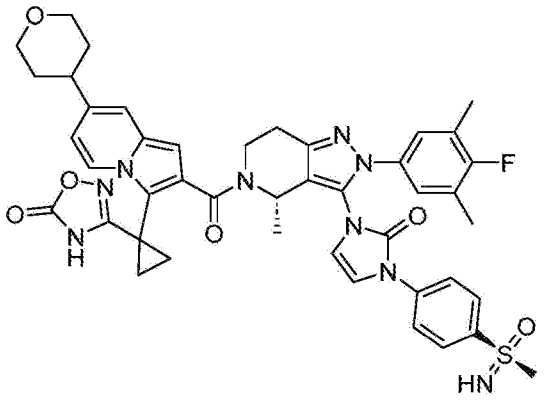
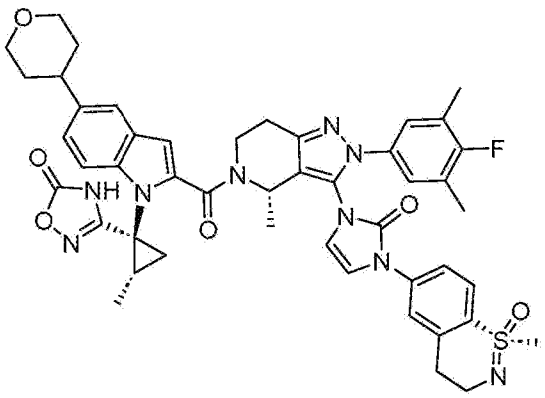
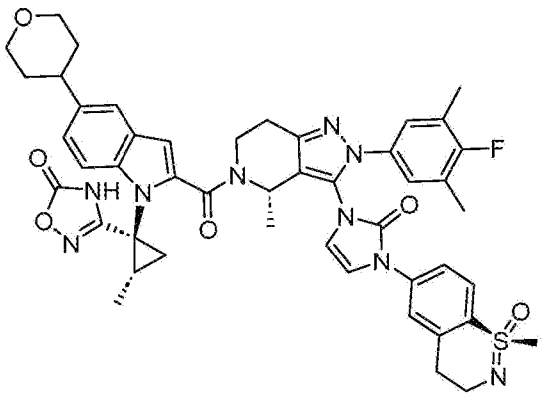
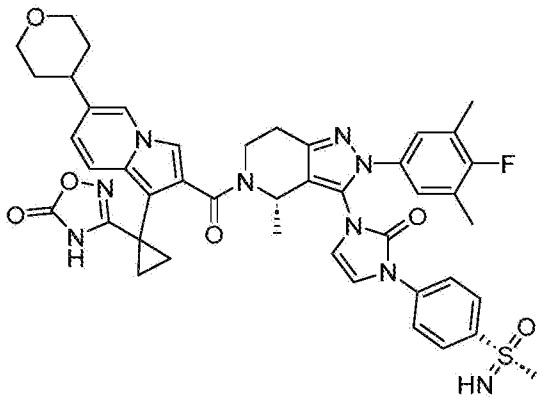
[0874] Table 2

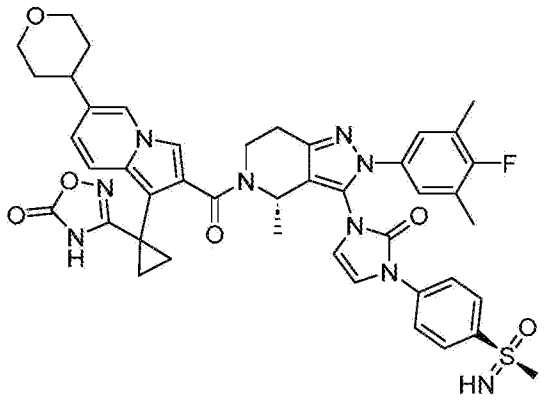
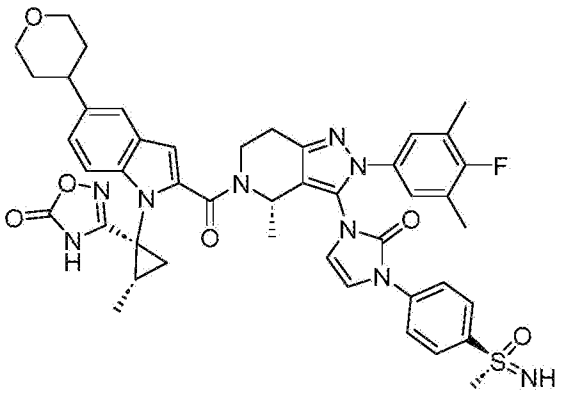
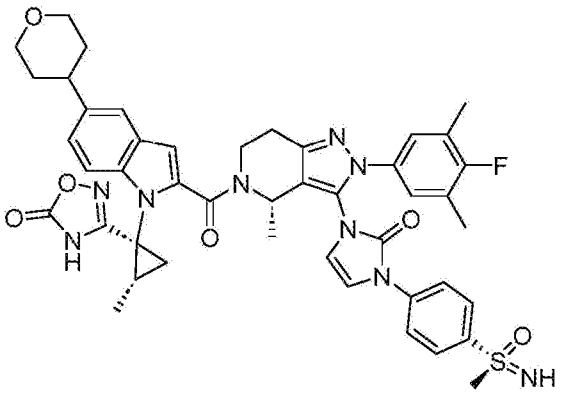
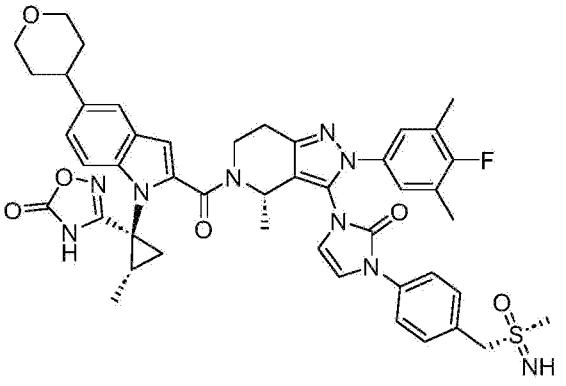
Structure


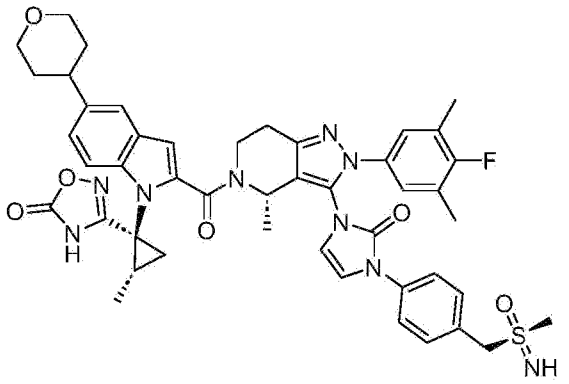
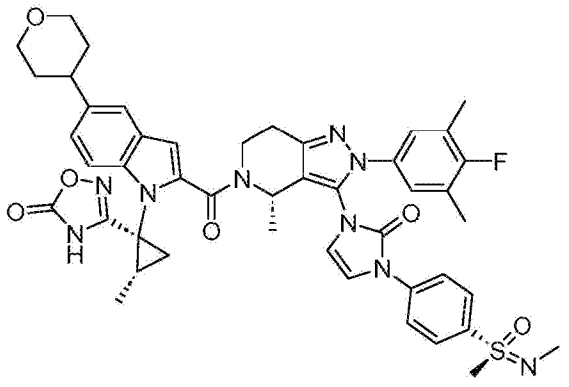
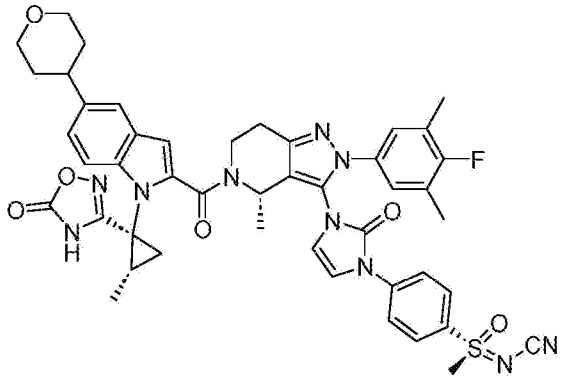
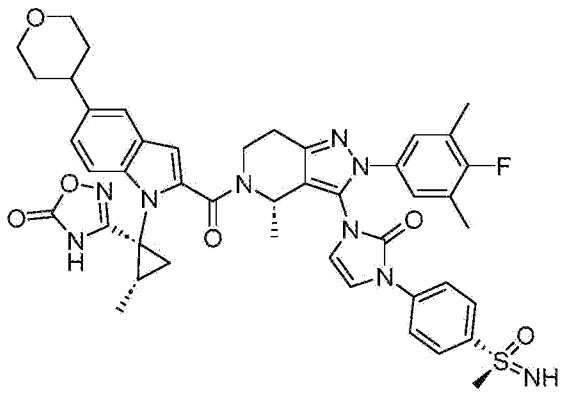
Structure





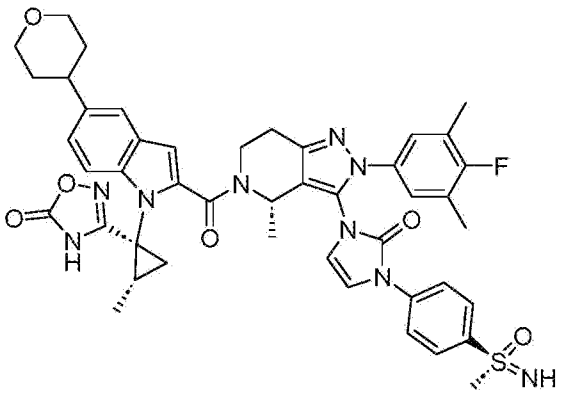
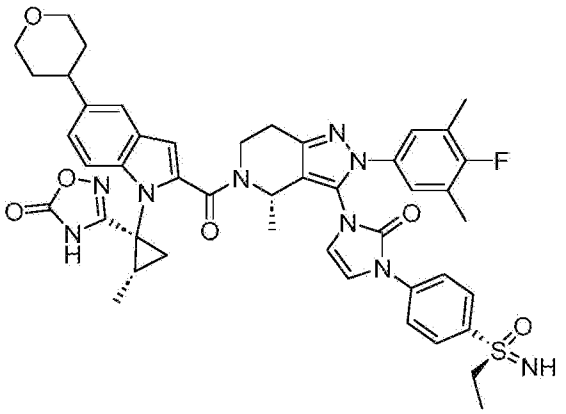
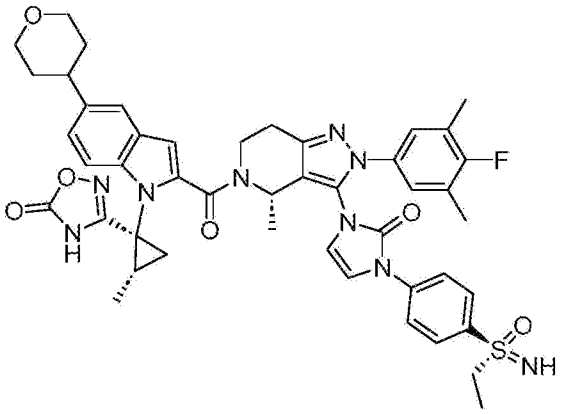
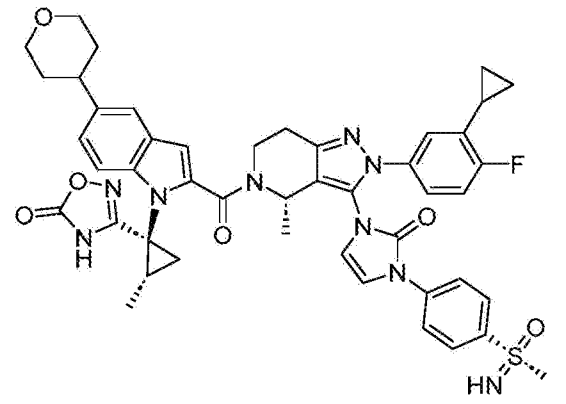
Structure





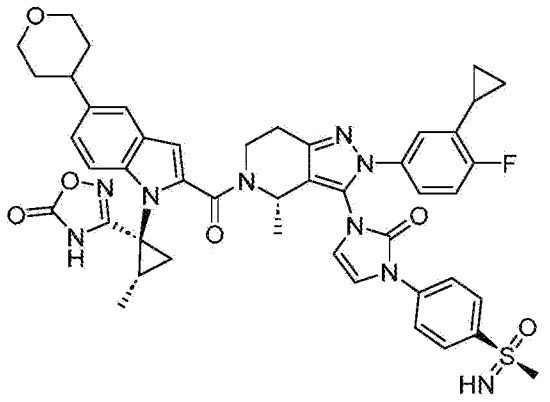
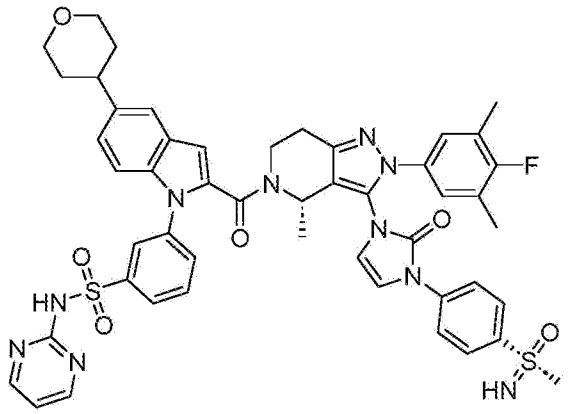
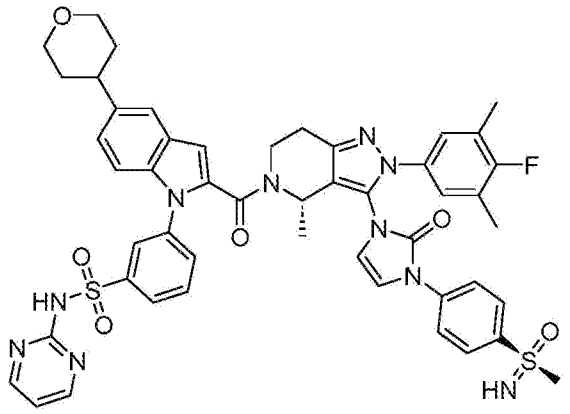
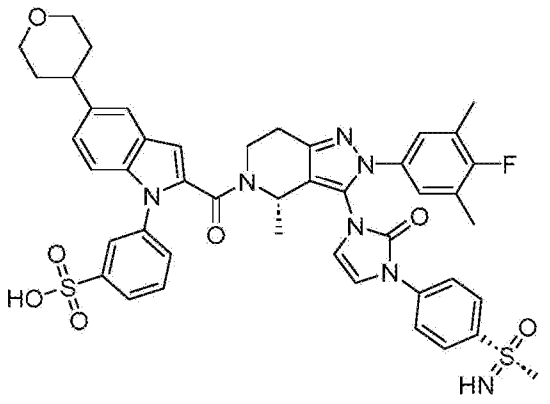
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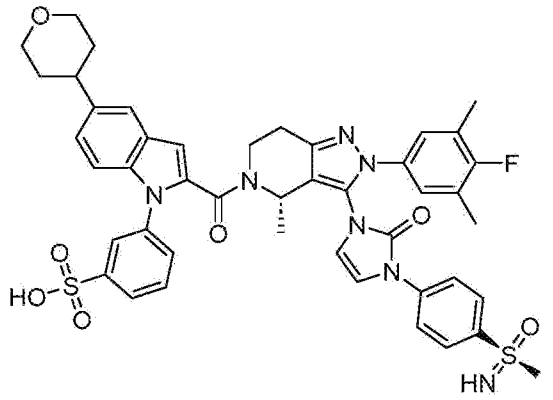
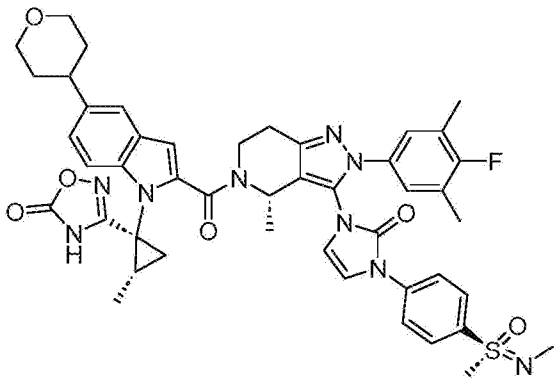
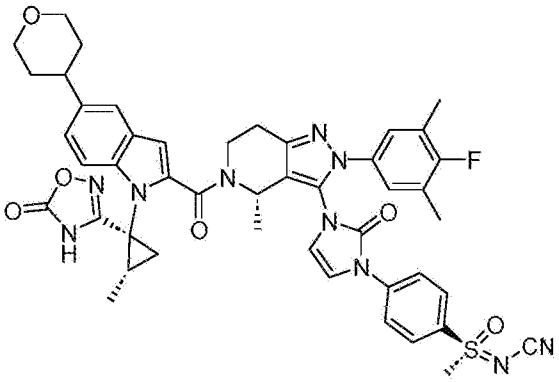
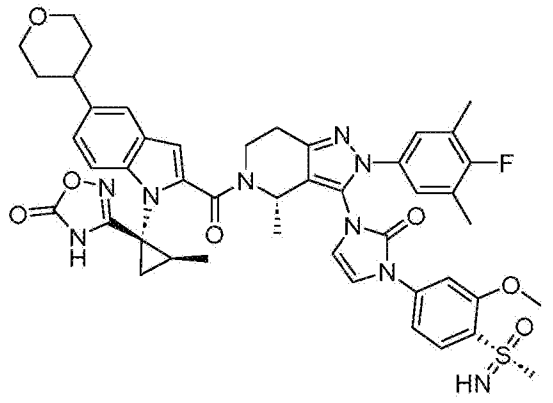
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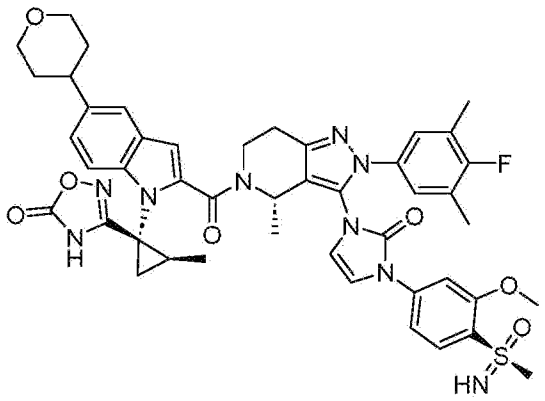
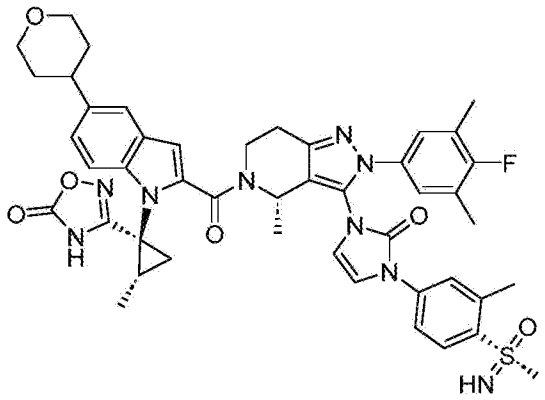
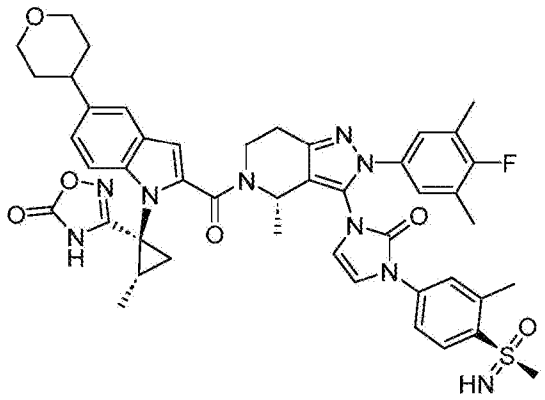
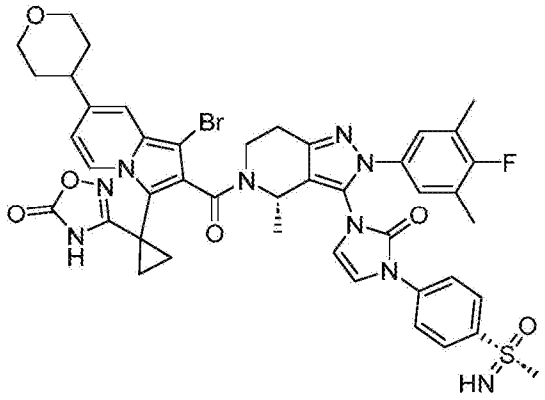
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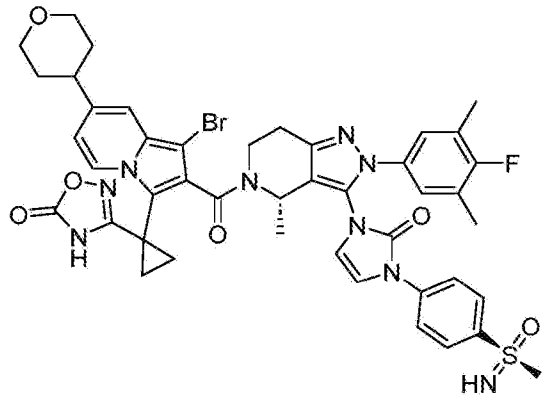
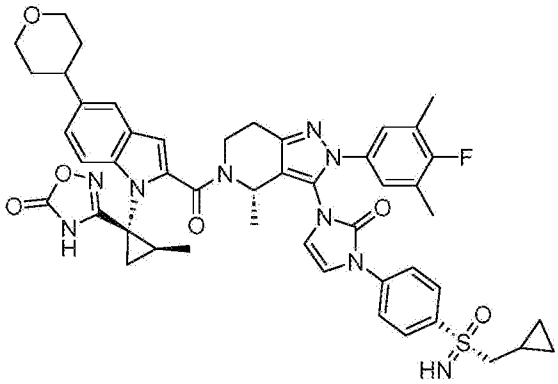
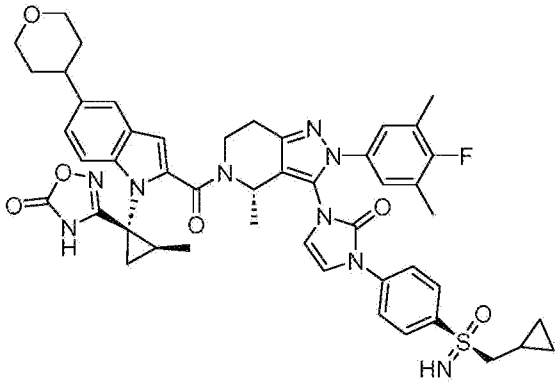
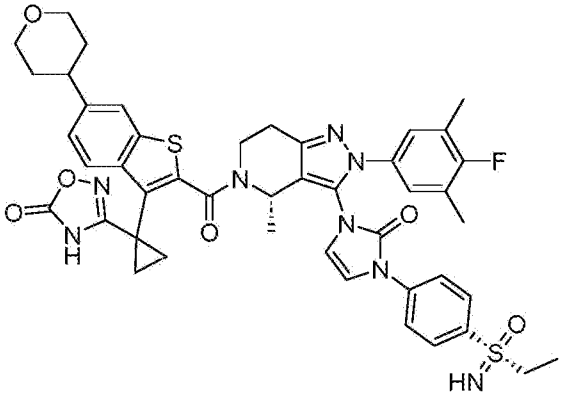
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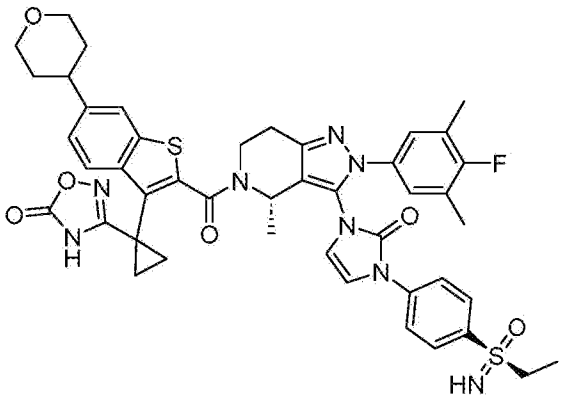
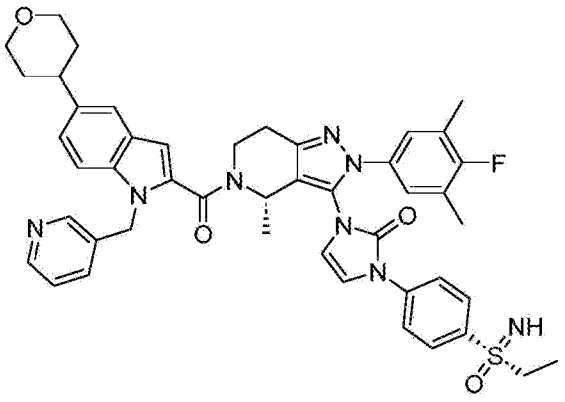
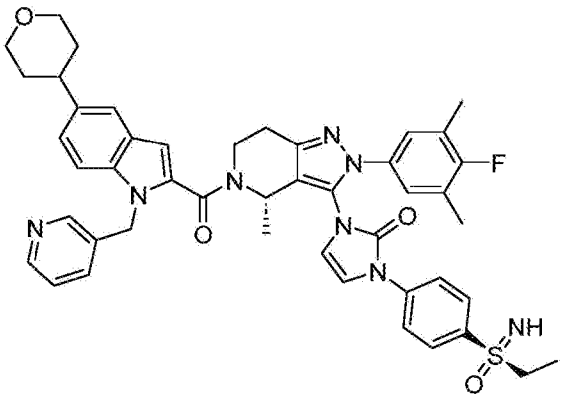
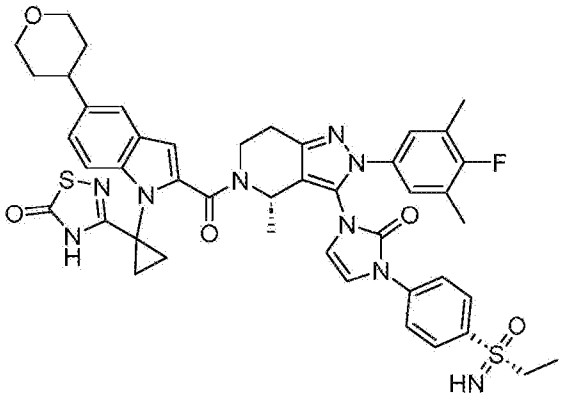
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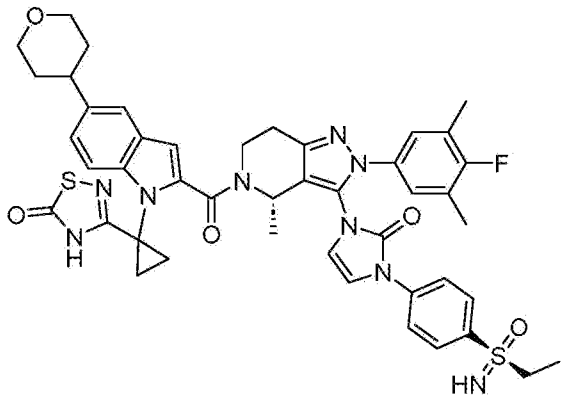
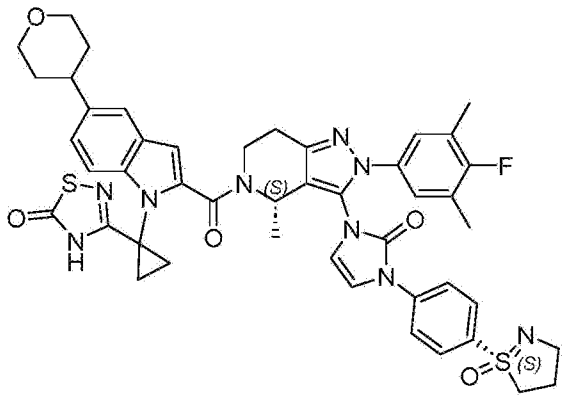
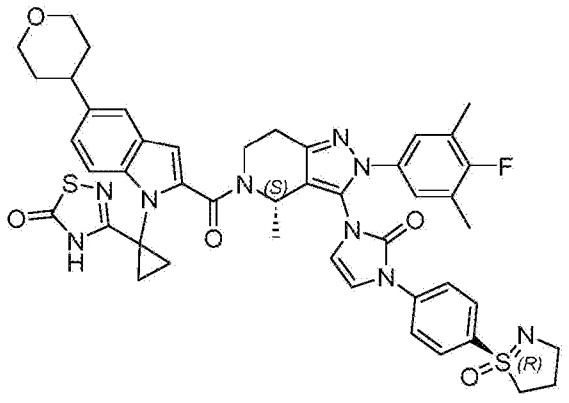
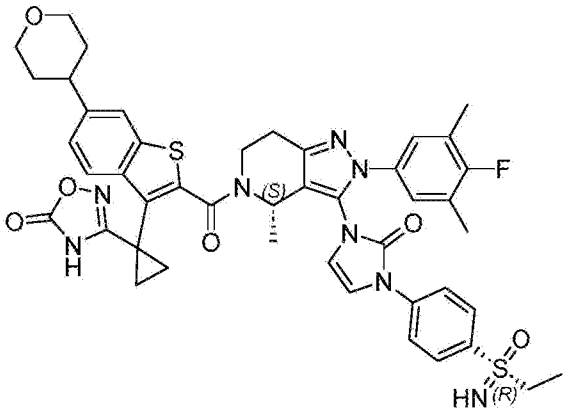
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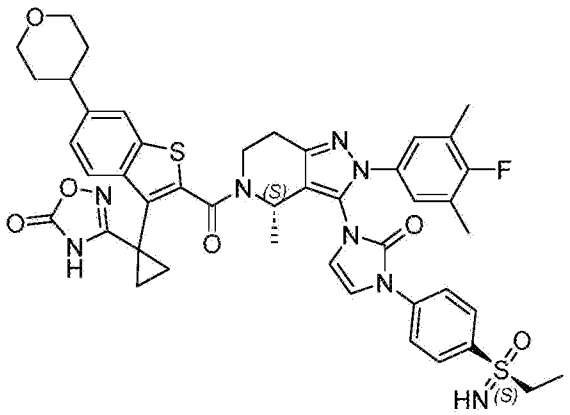
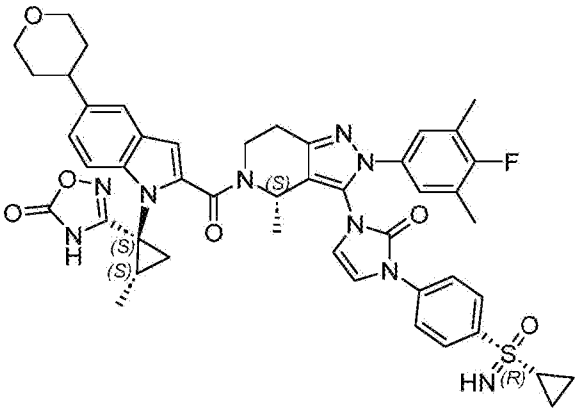
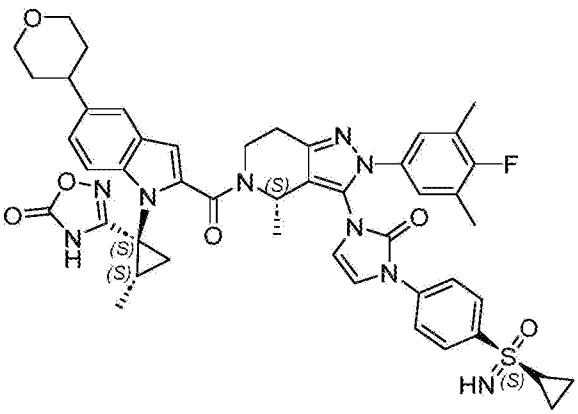
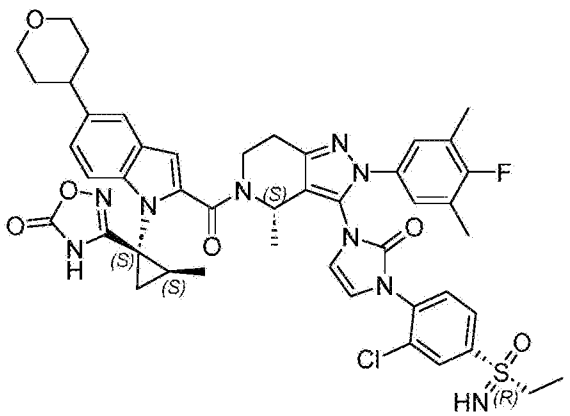
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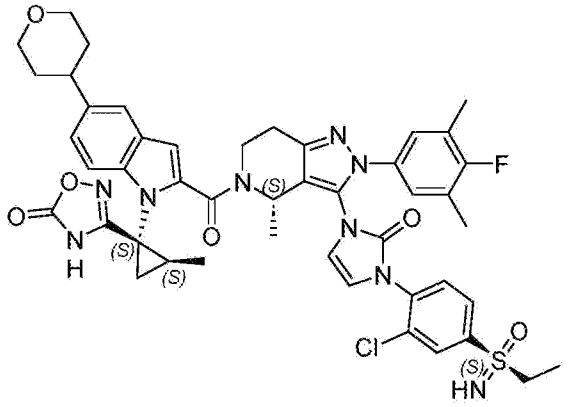
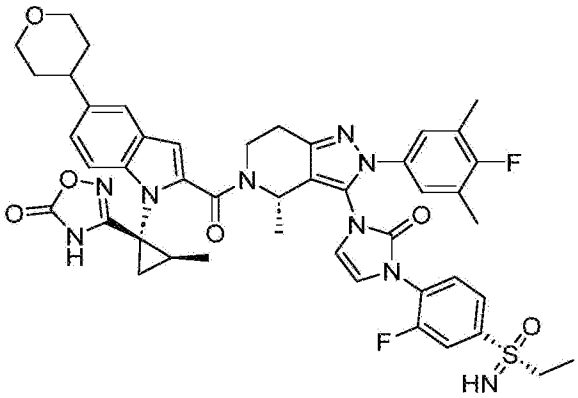
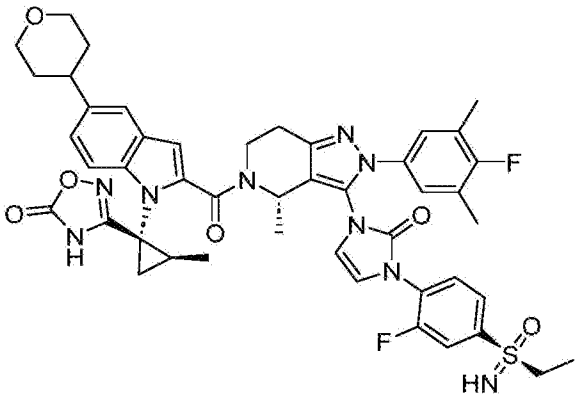
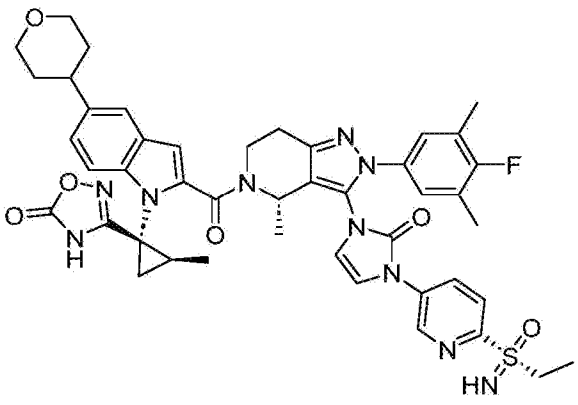
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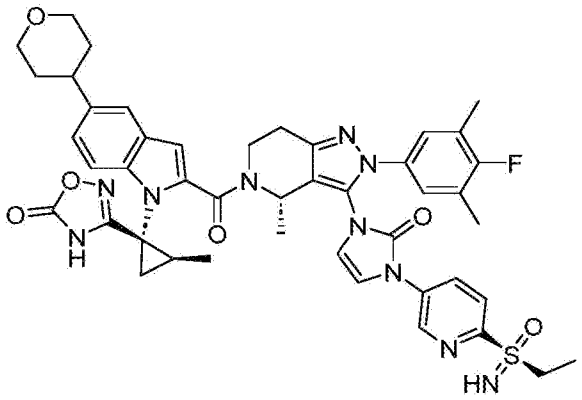
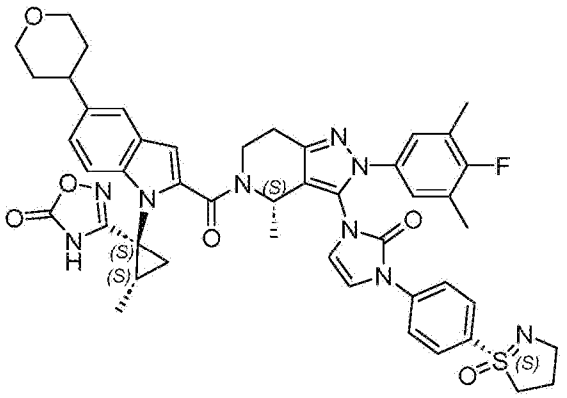
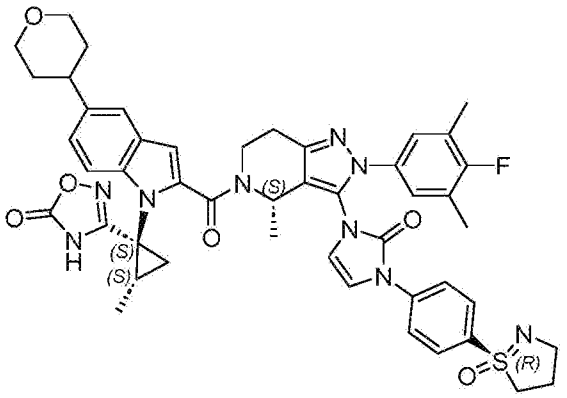
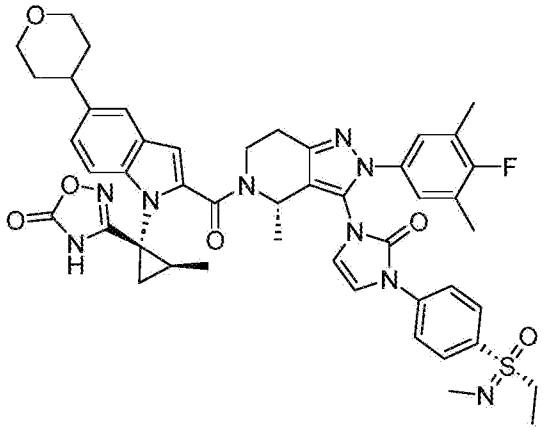
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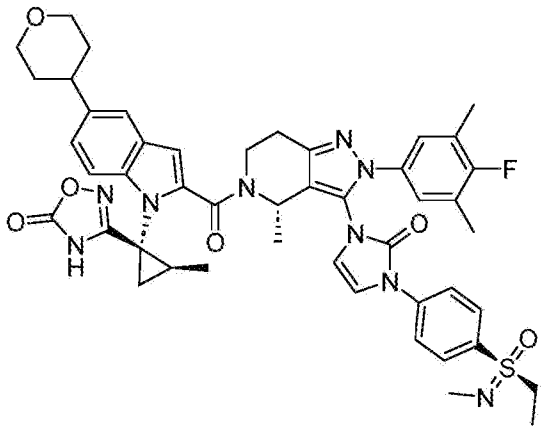
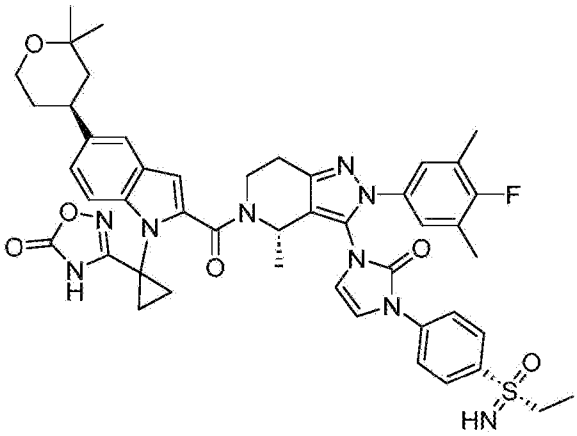
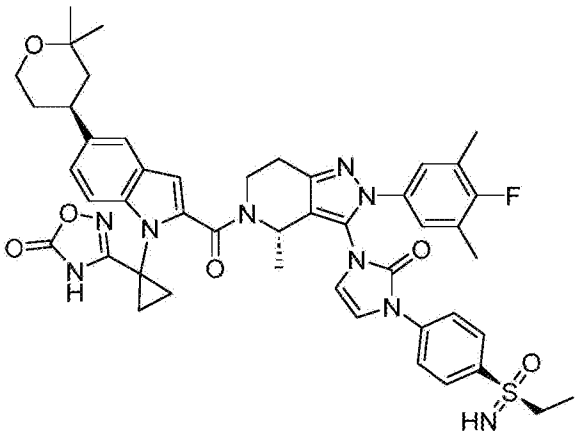
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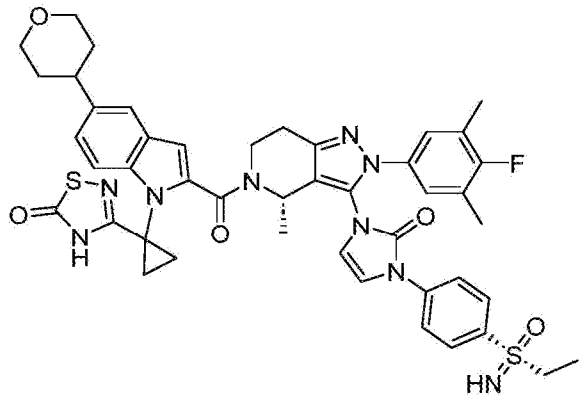
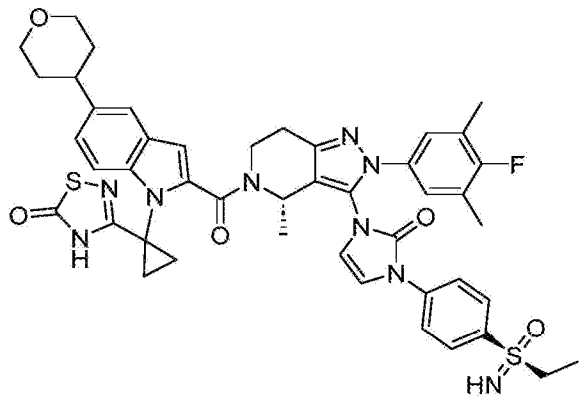
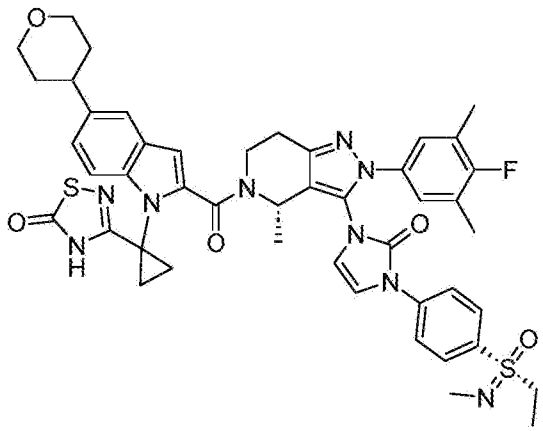
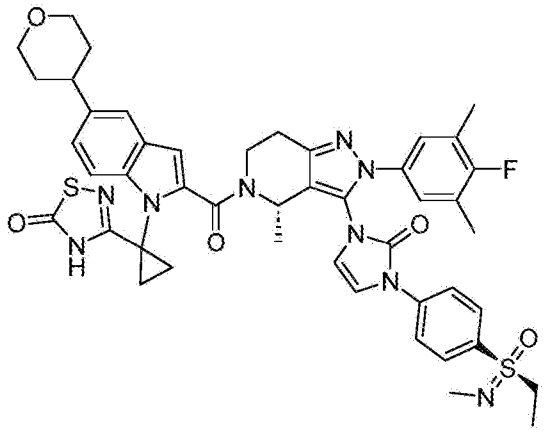
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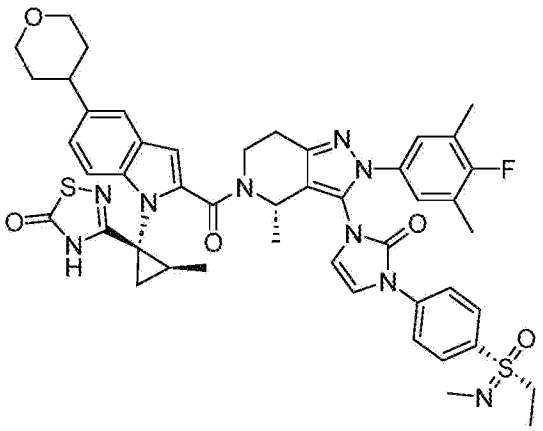
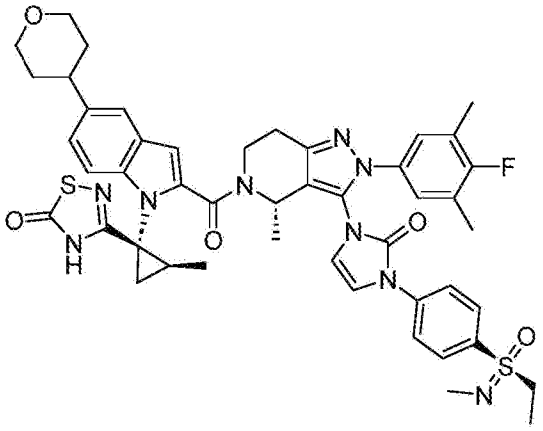
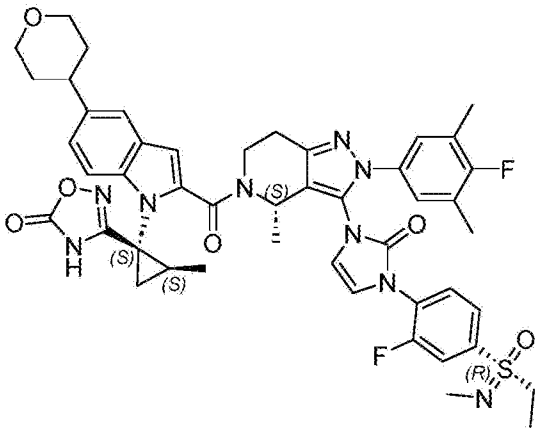
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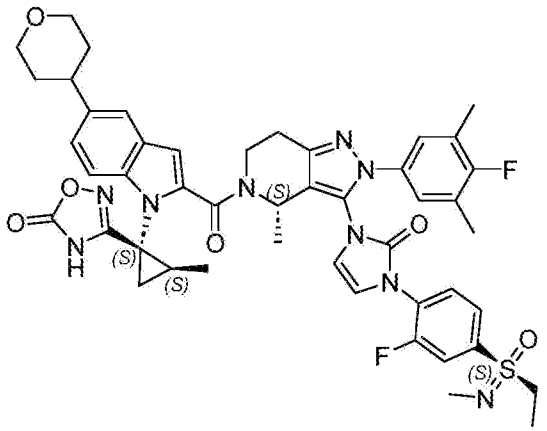
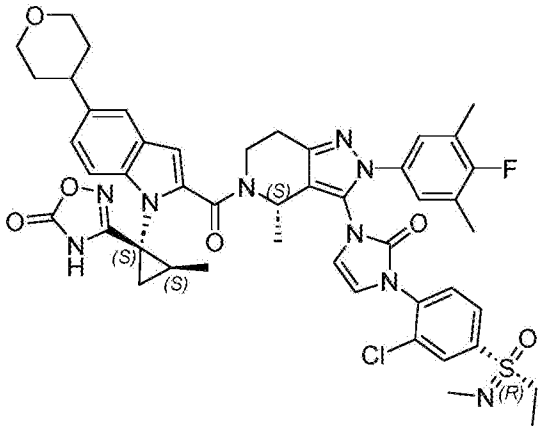
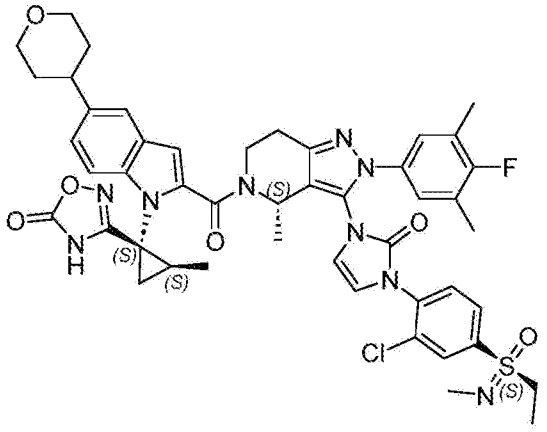
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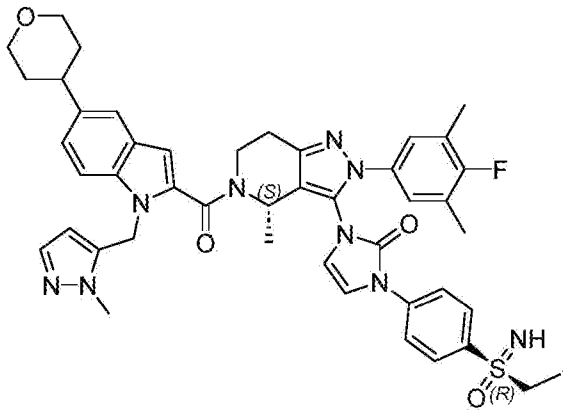
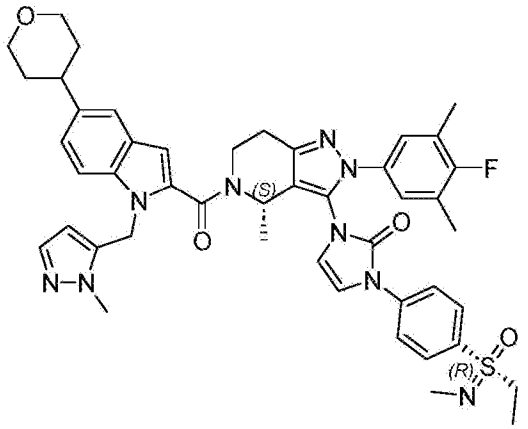
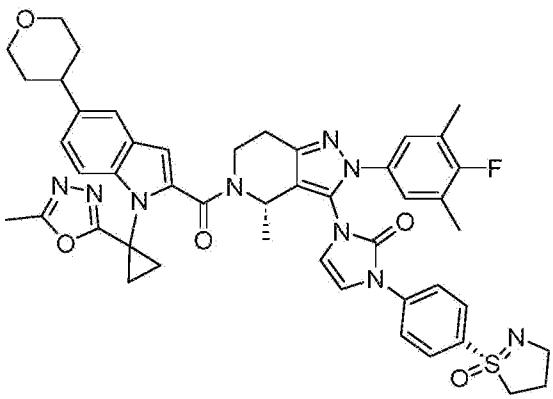
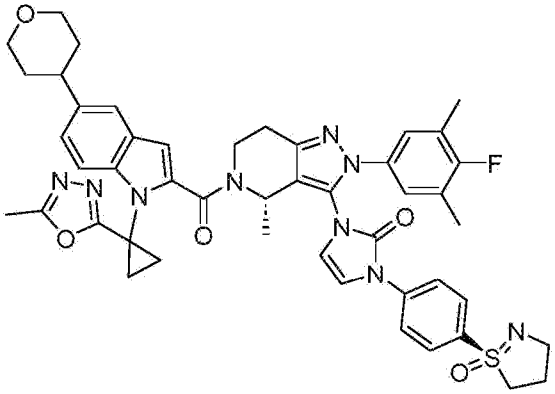
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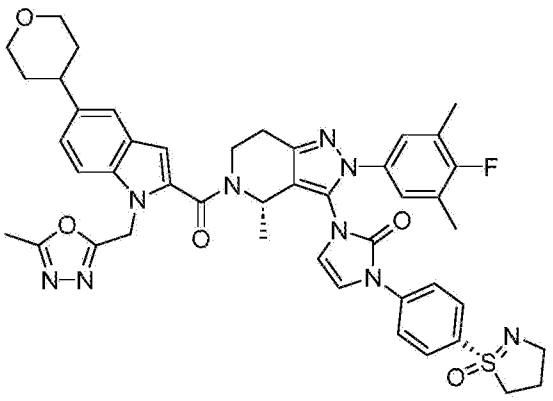
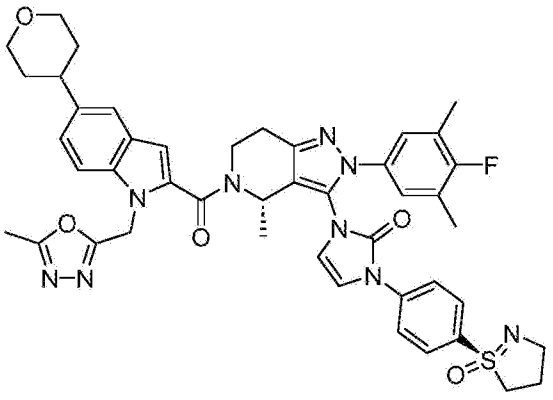
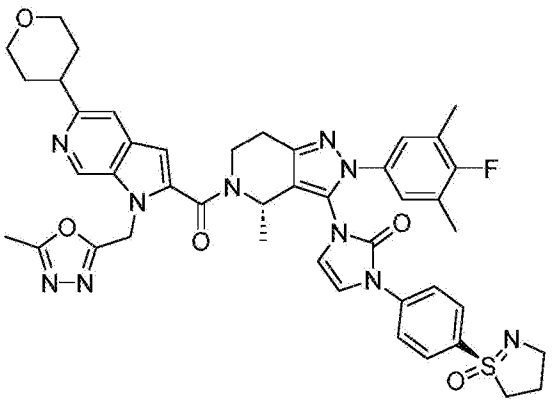
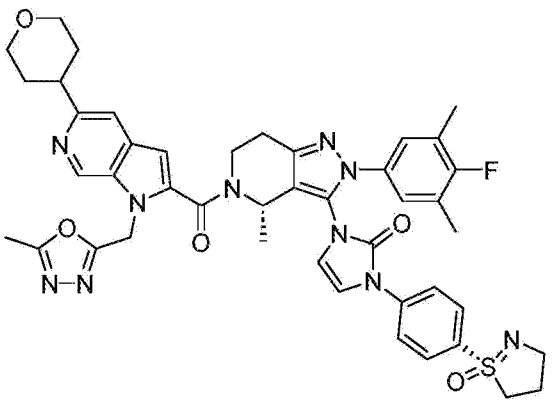
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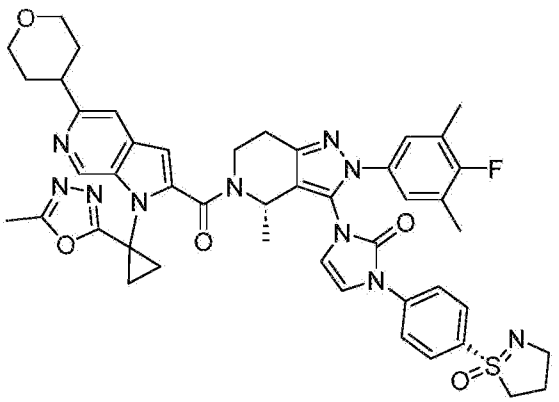
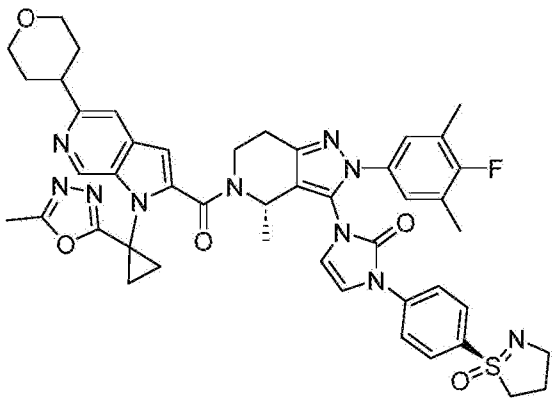
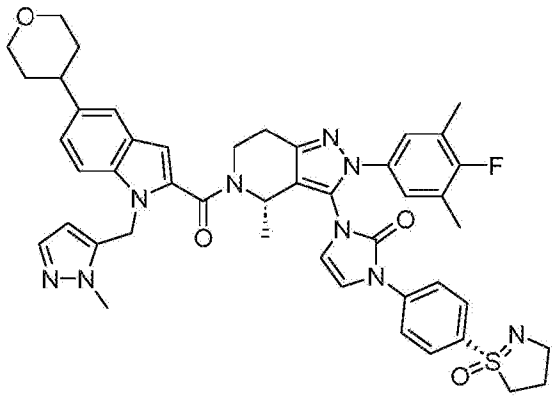
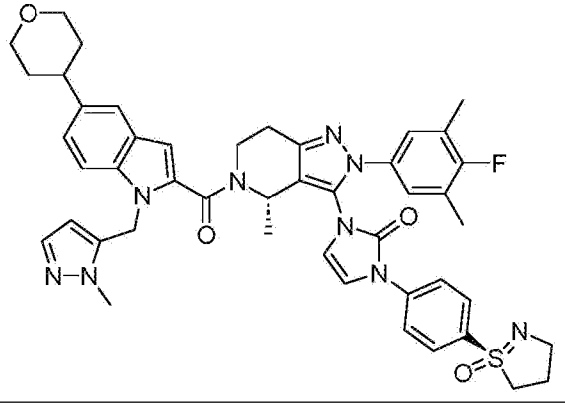
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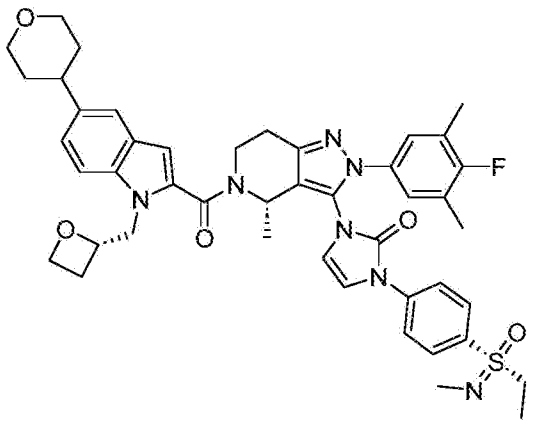
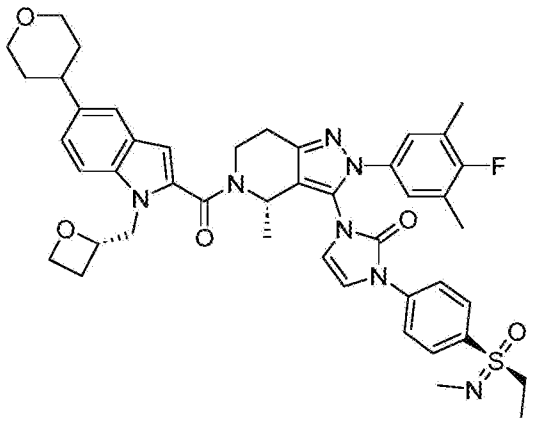
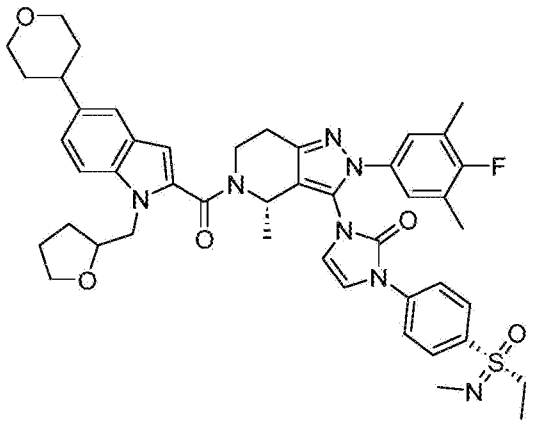
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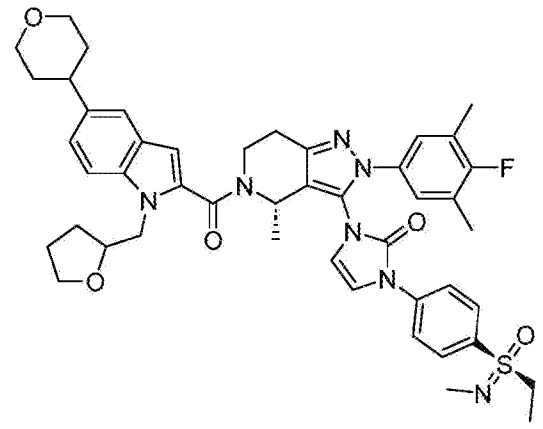
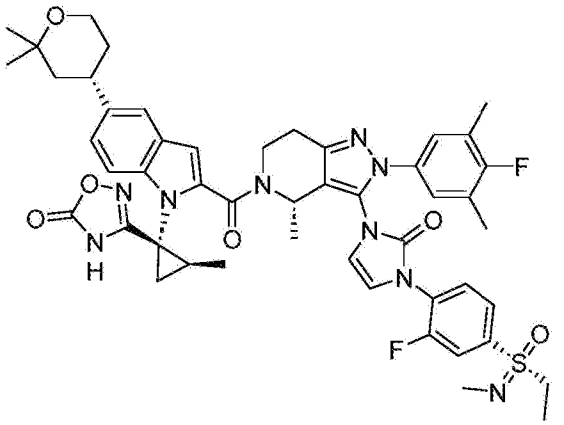
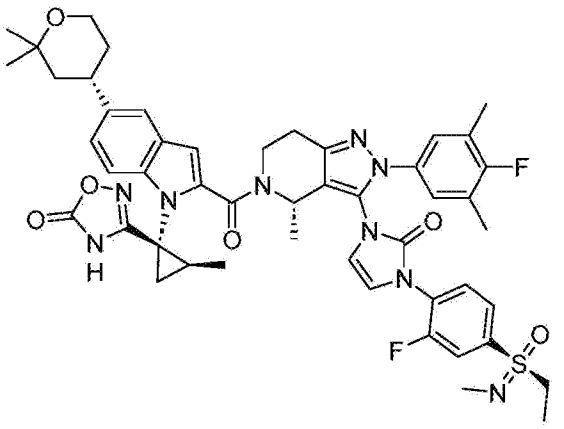
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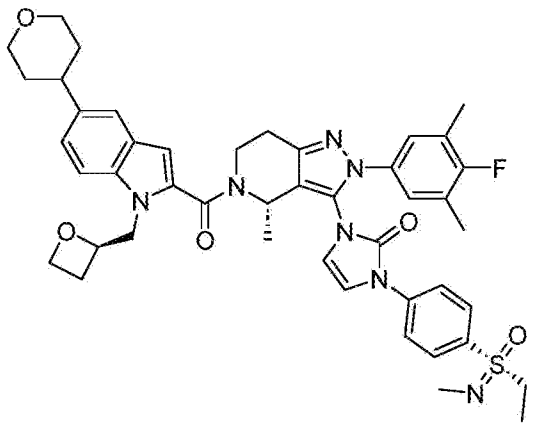
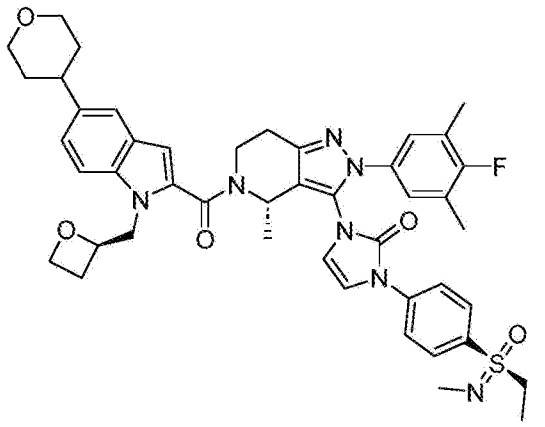
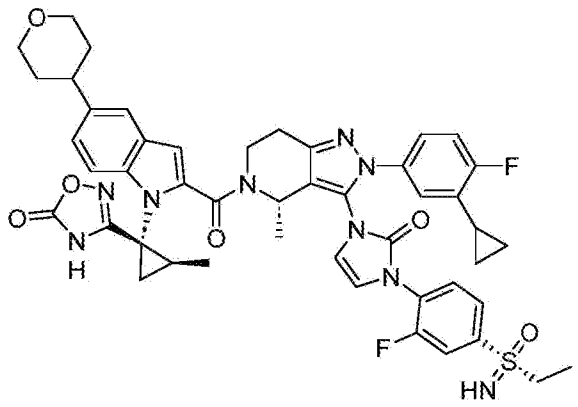
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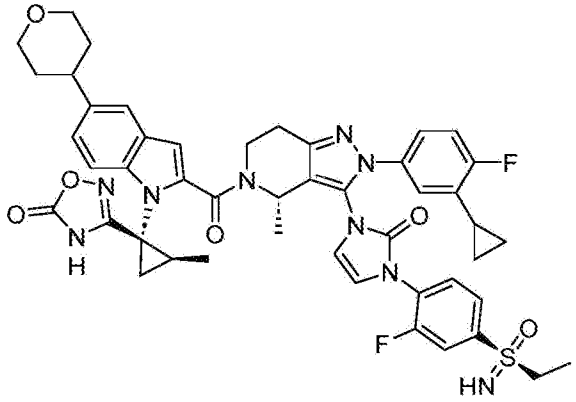
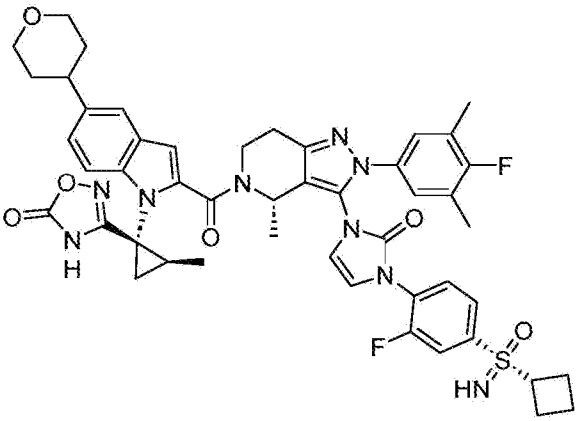
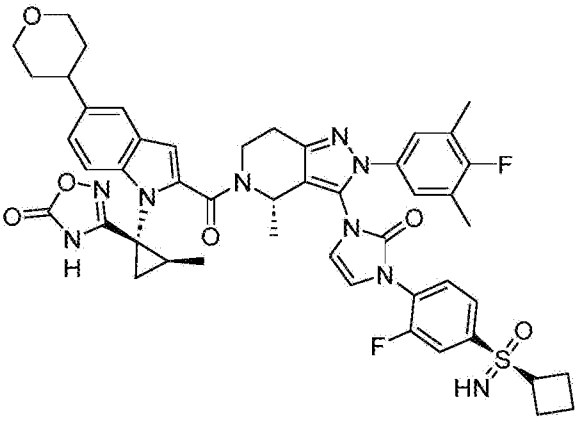
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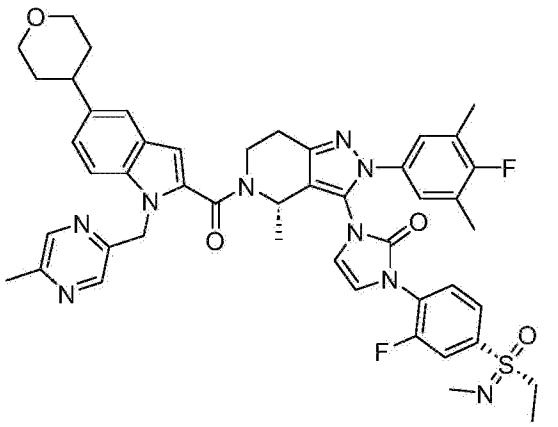
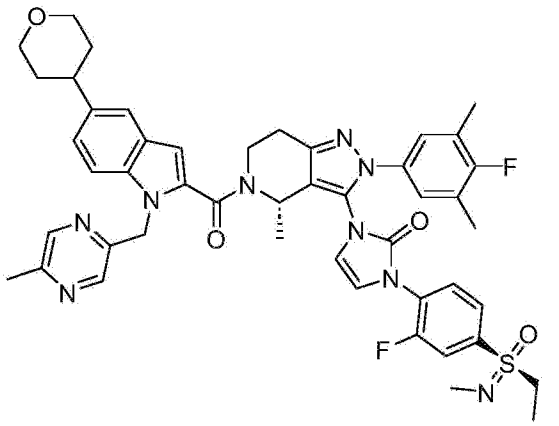
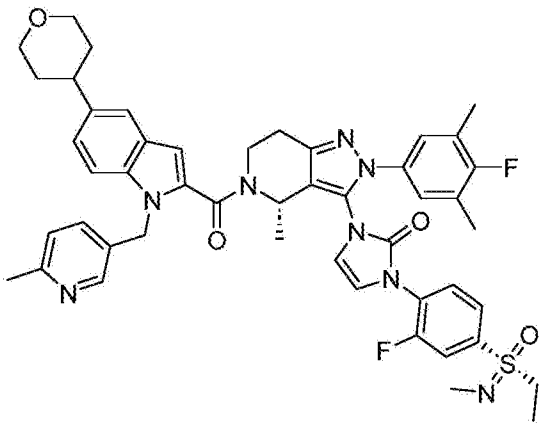
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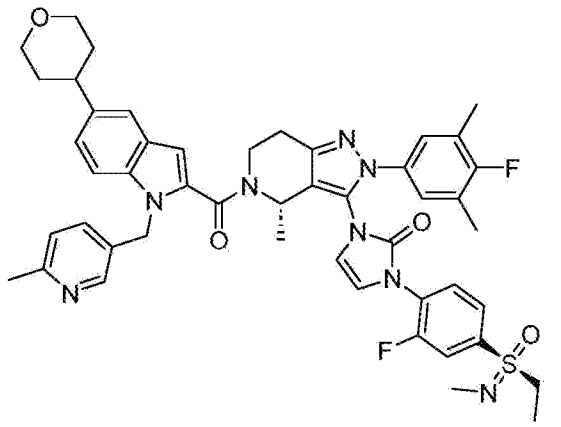
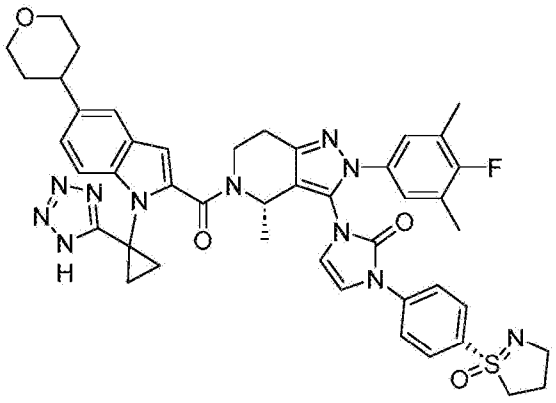
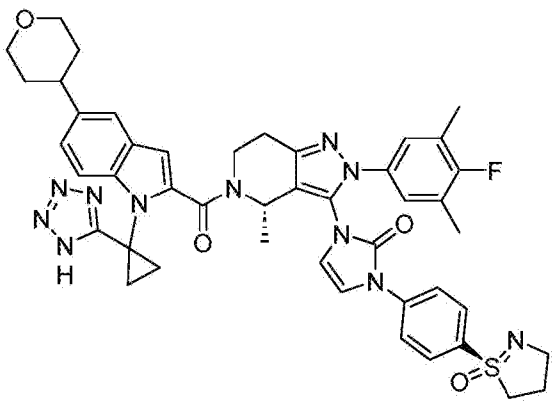
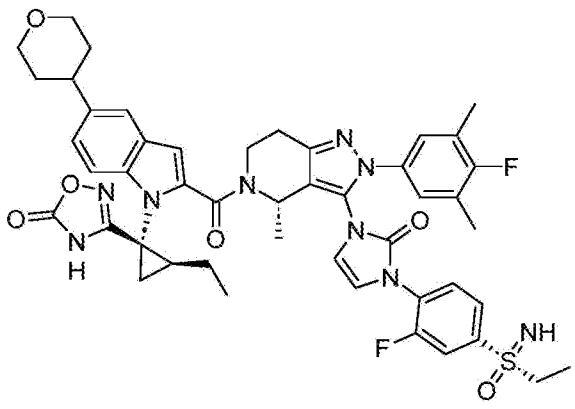
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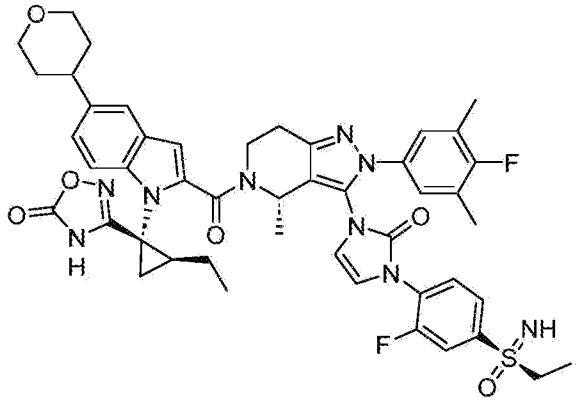
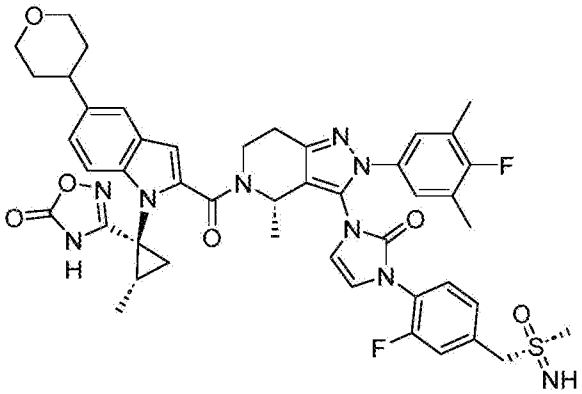
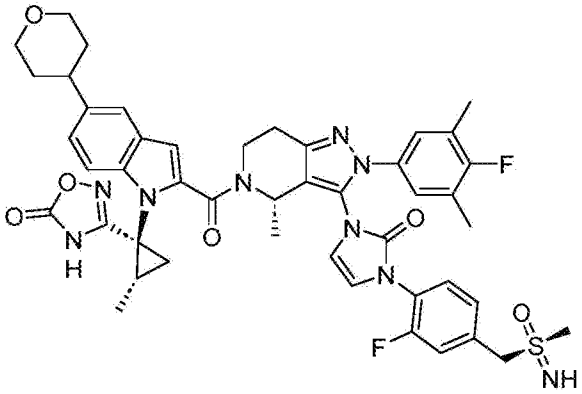
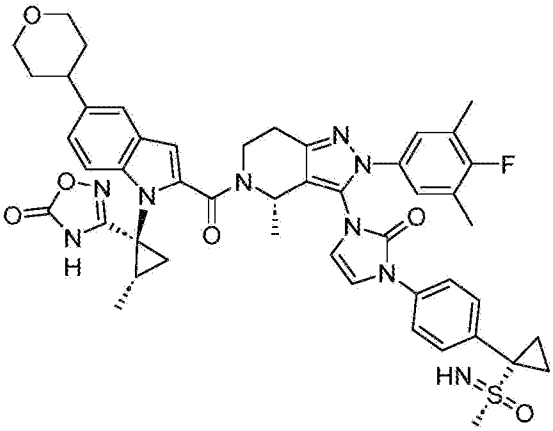
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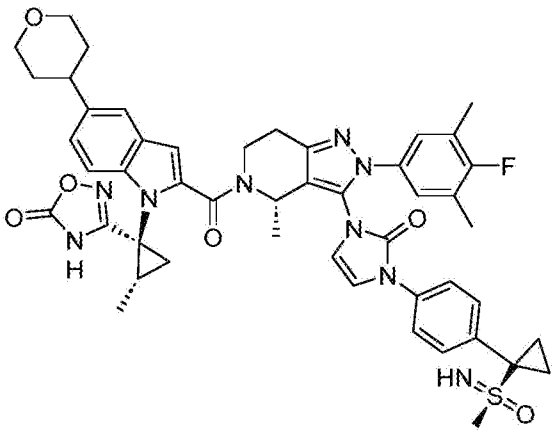
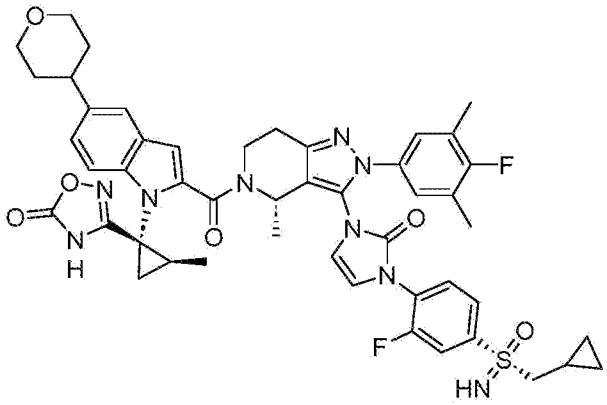
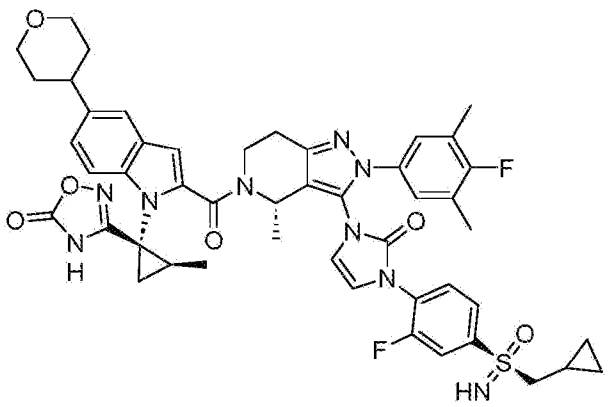
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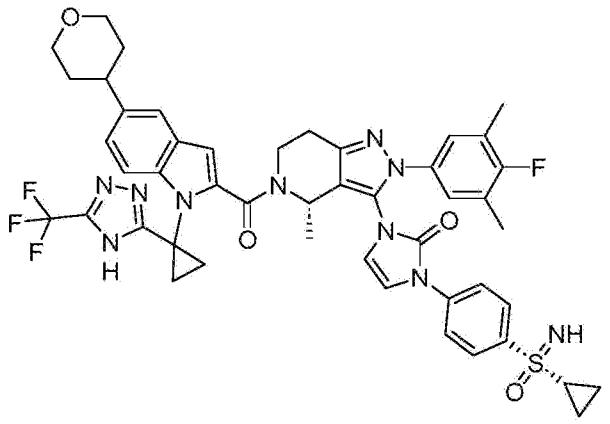
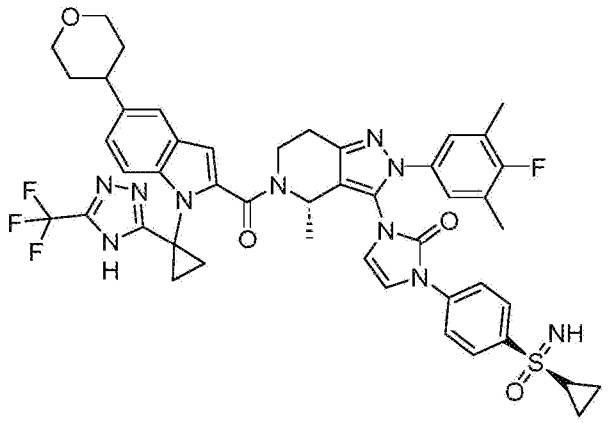
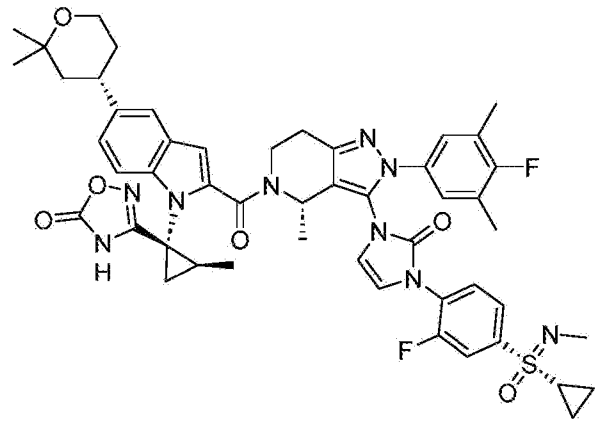
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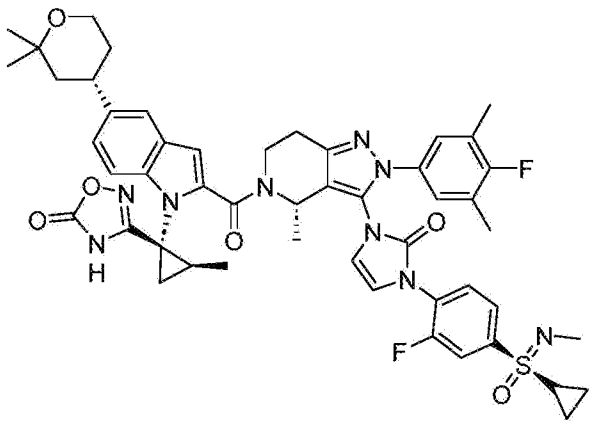
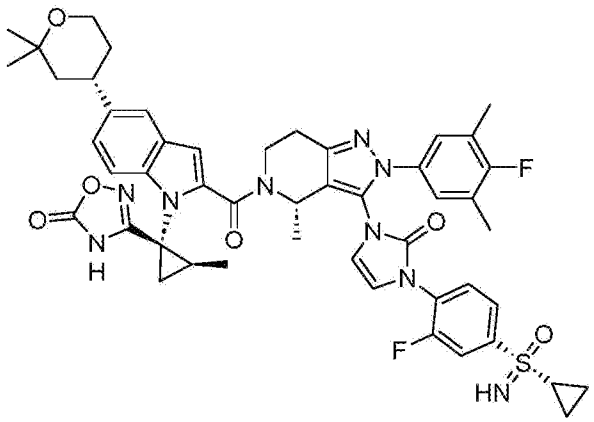
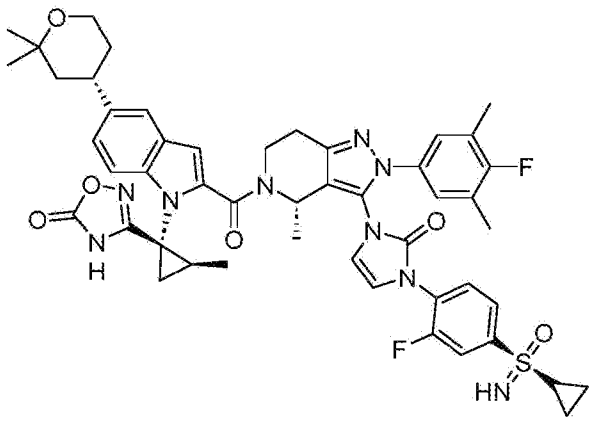
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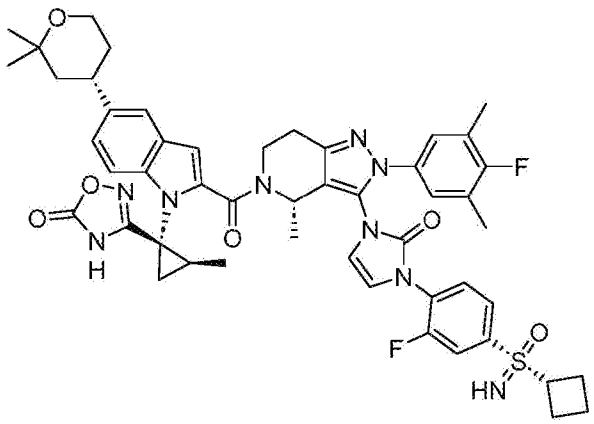
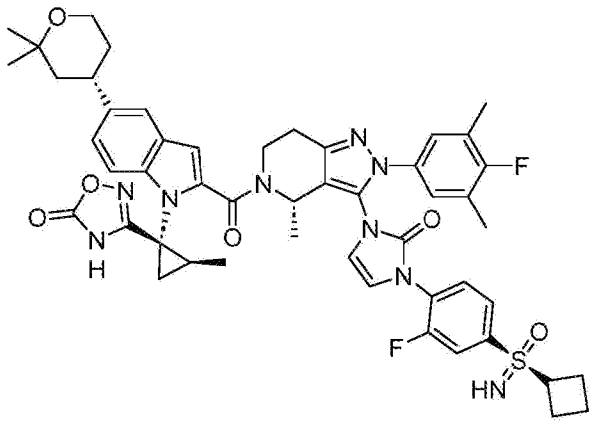
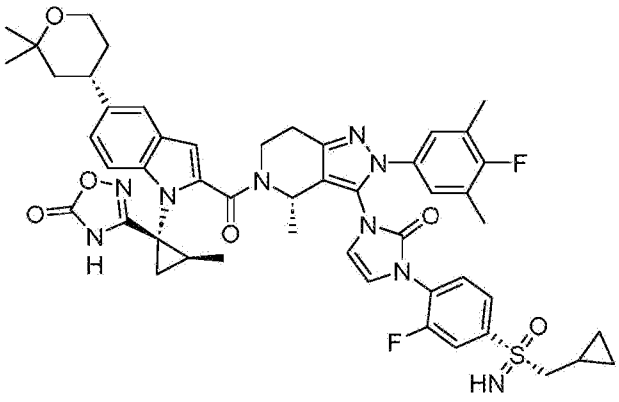
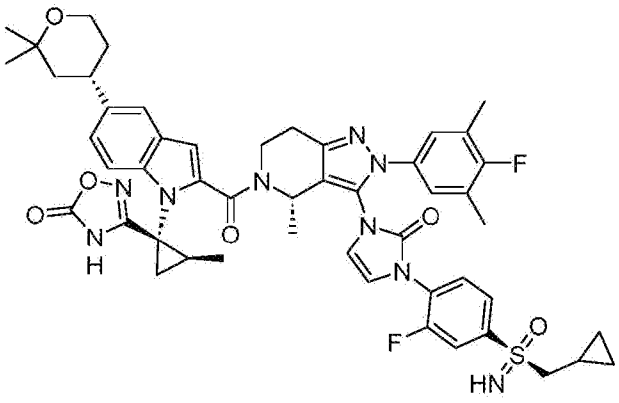
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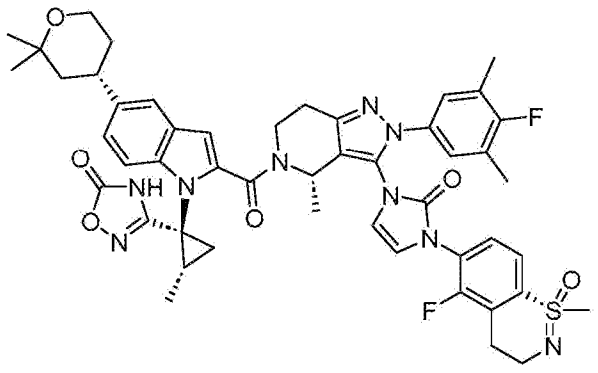
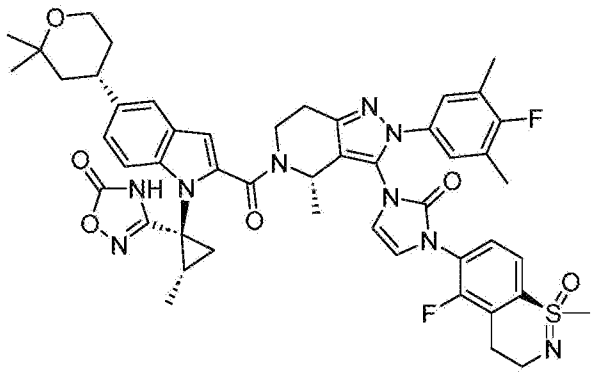
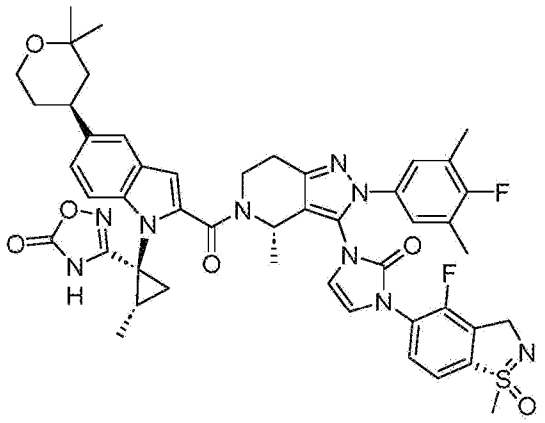
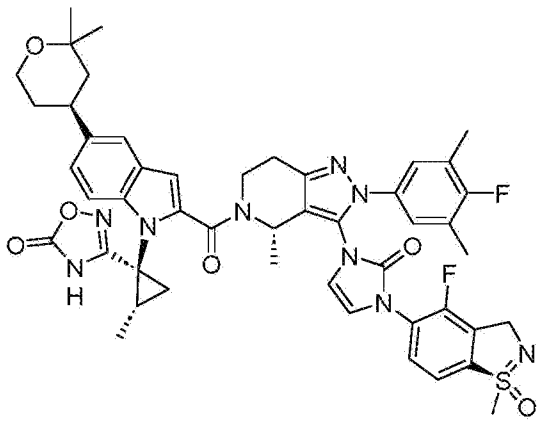
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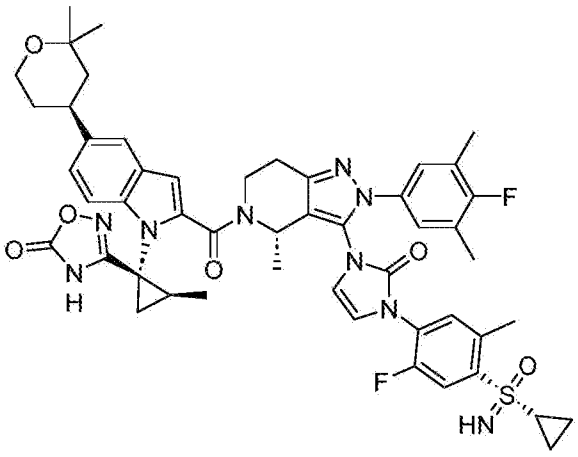
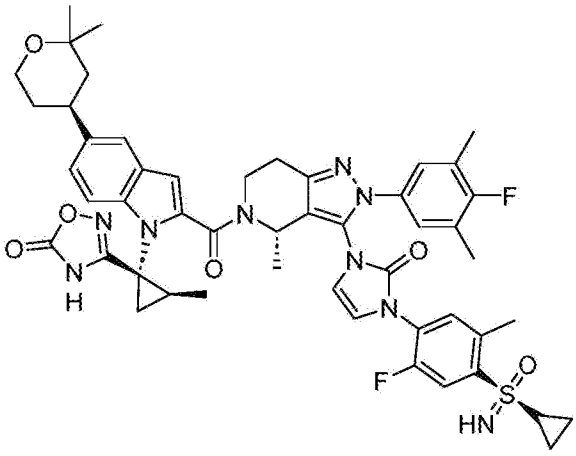
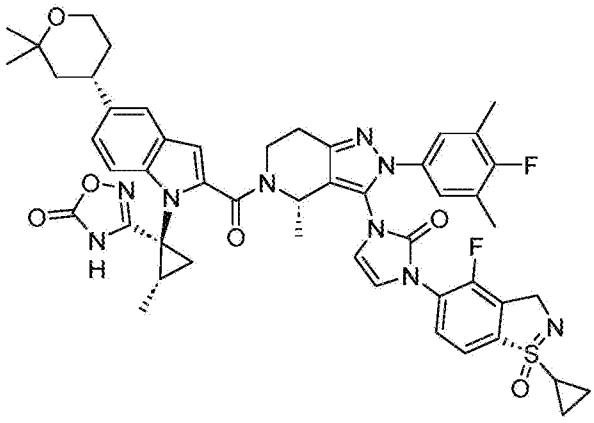
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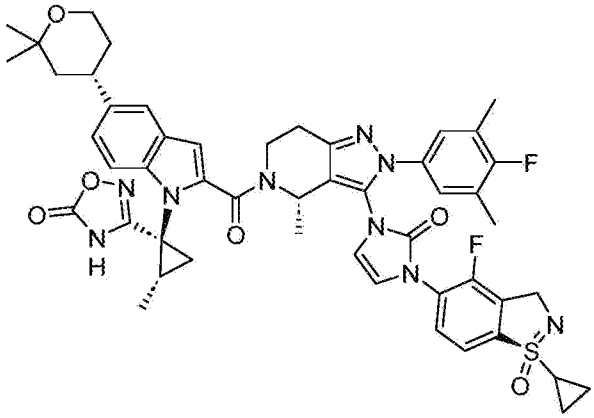
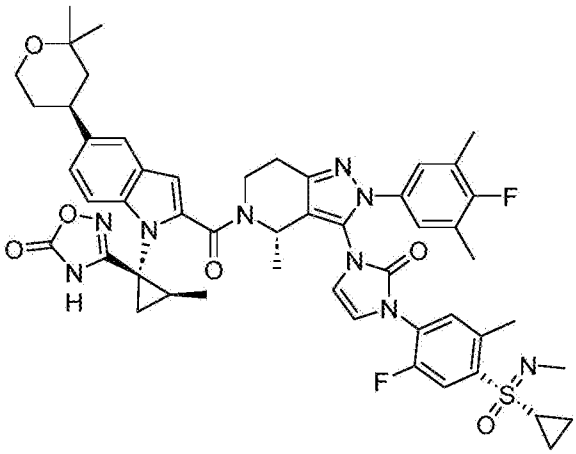
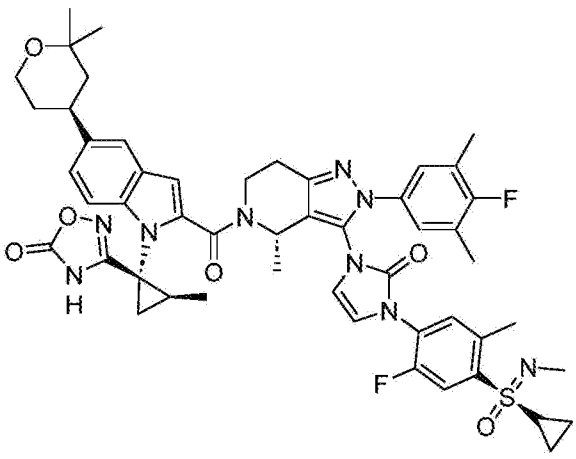
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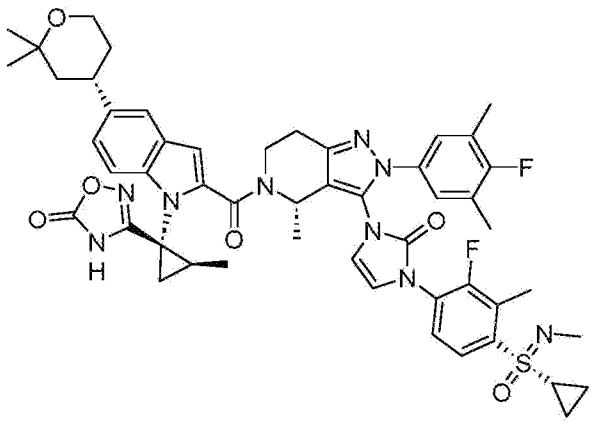
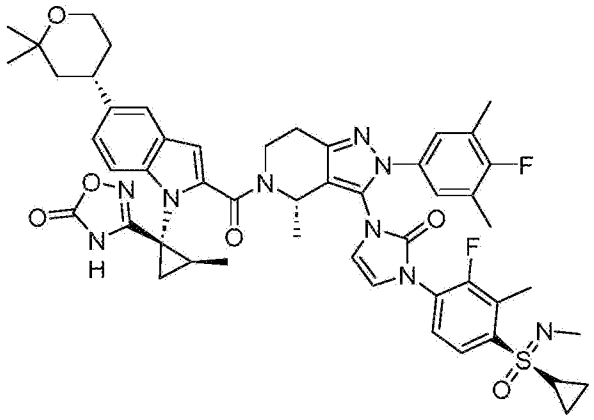
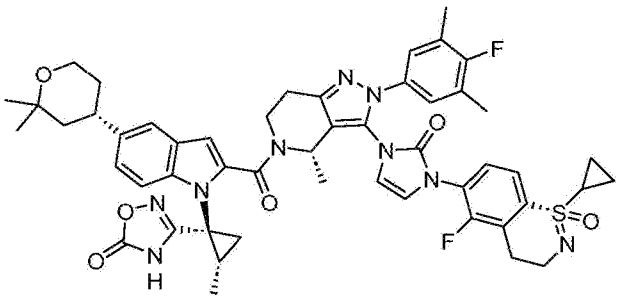
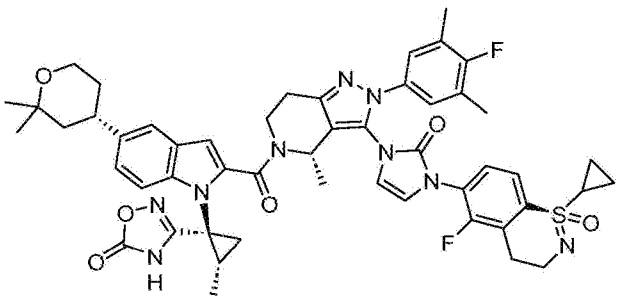
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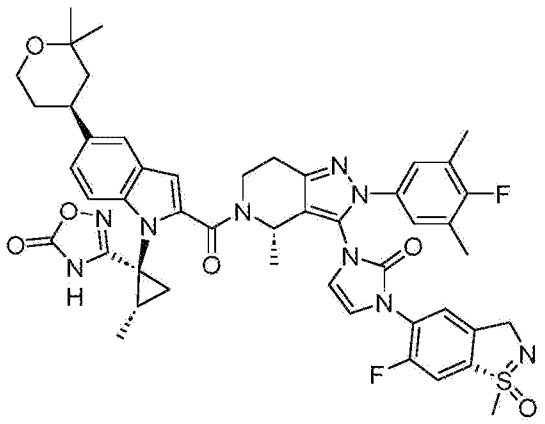
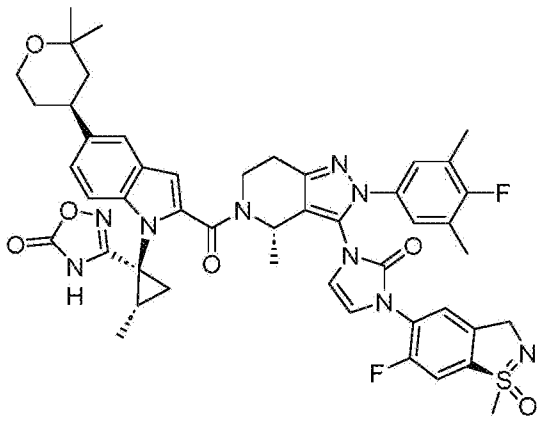
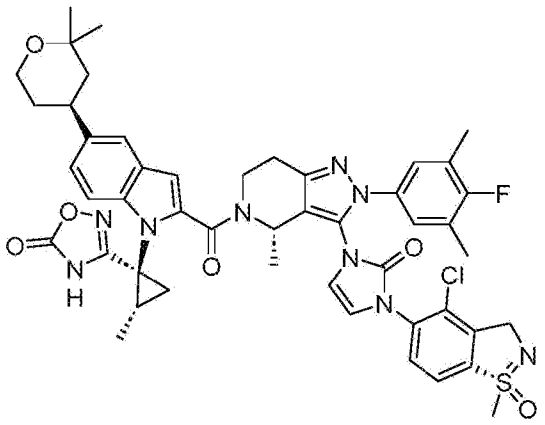
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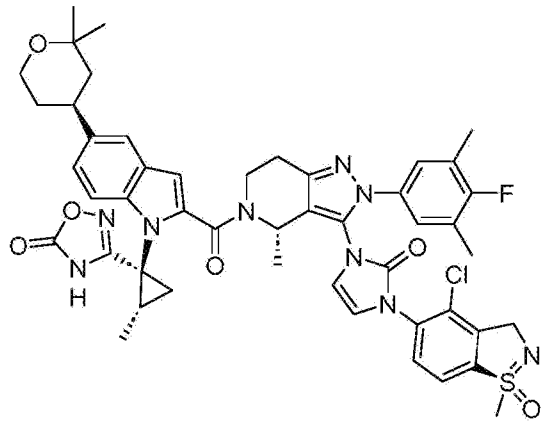
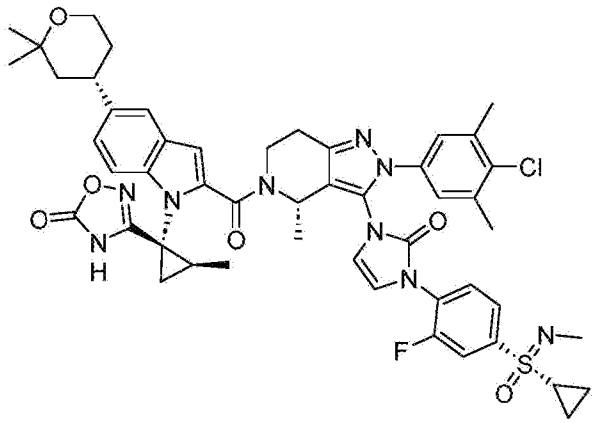
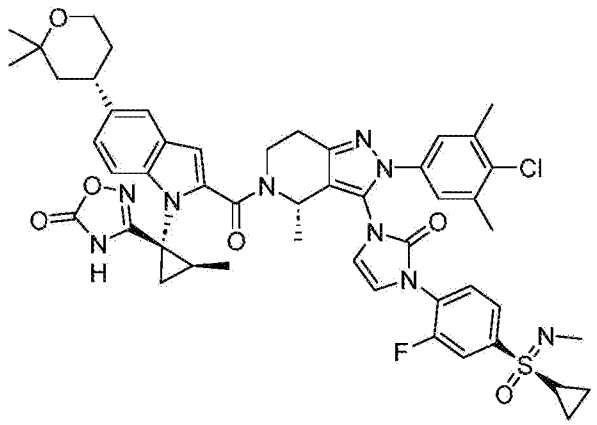
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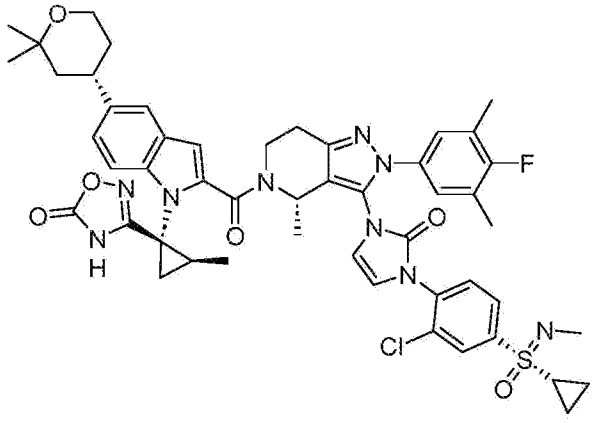
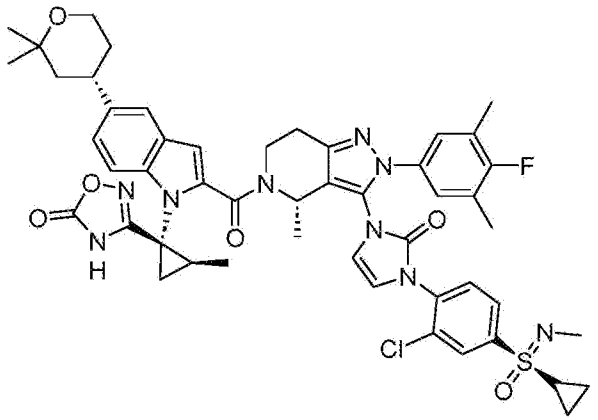
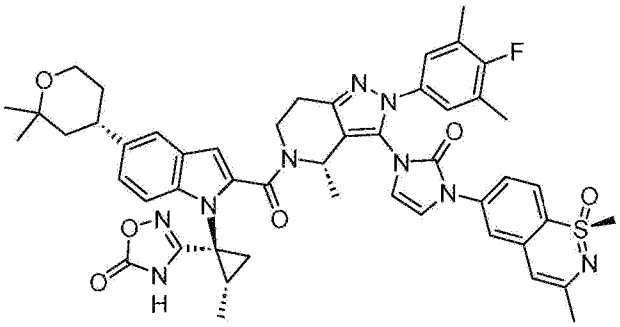
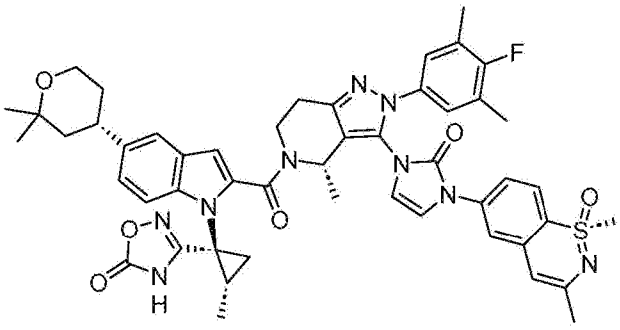
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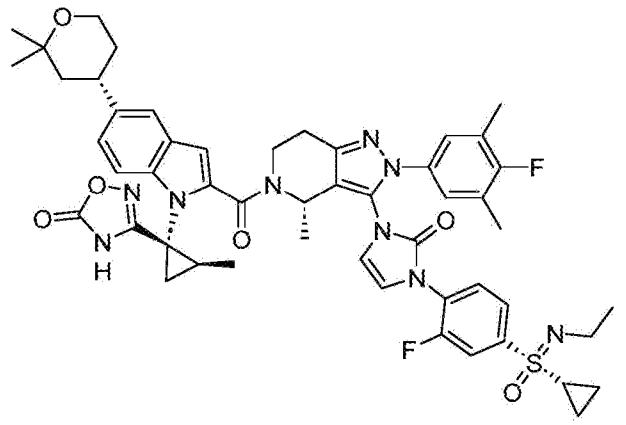
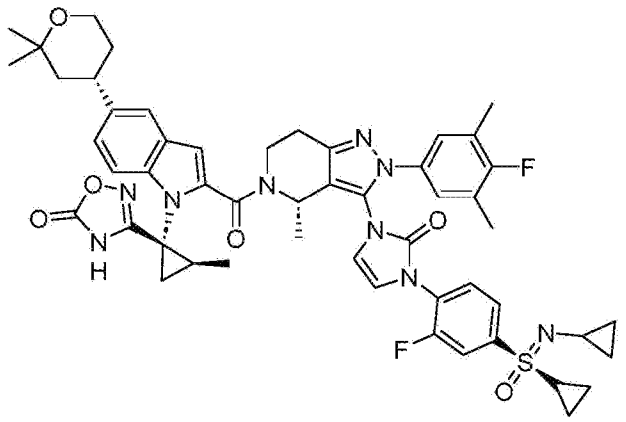
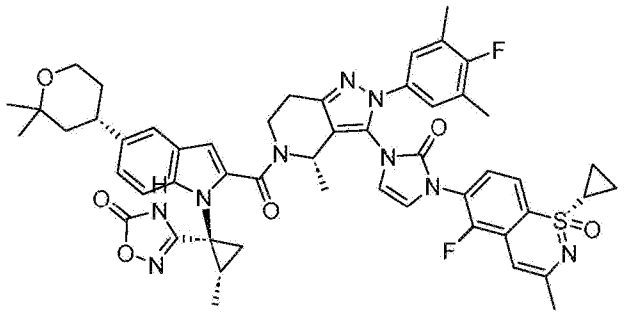
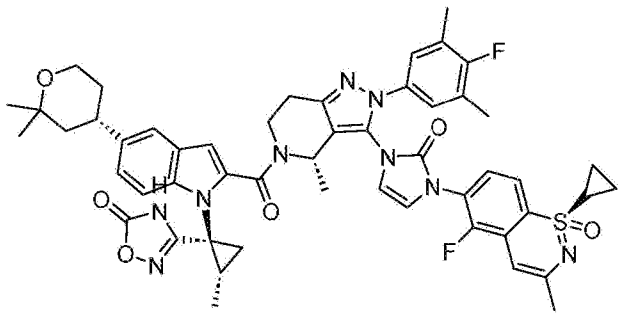
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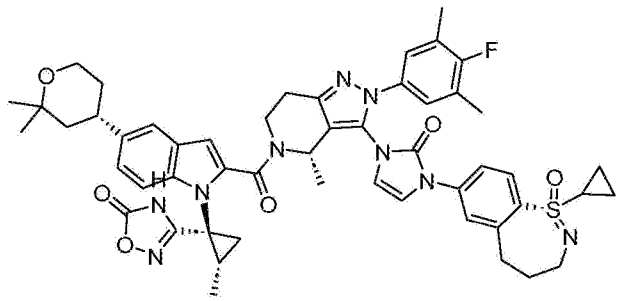
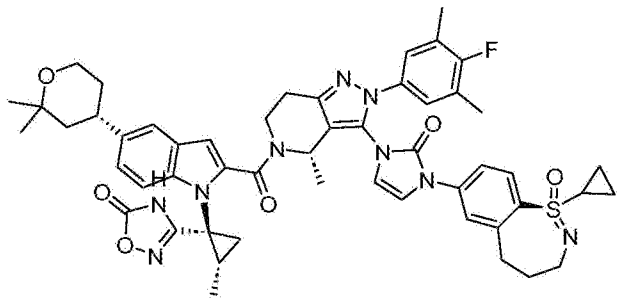
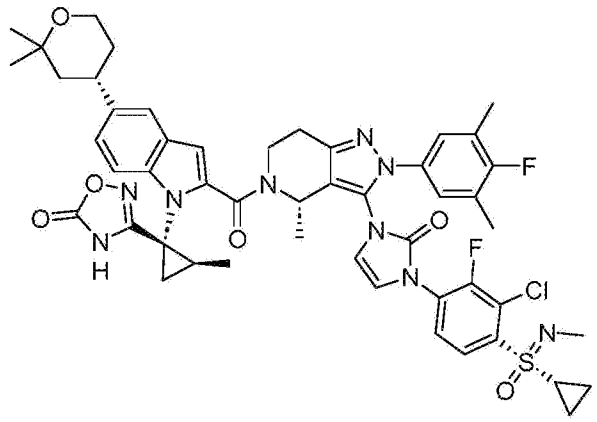
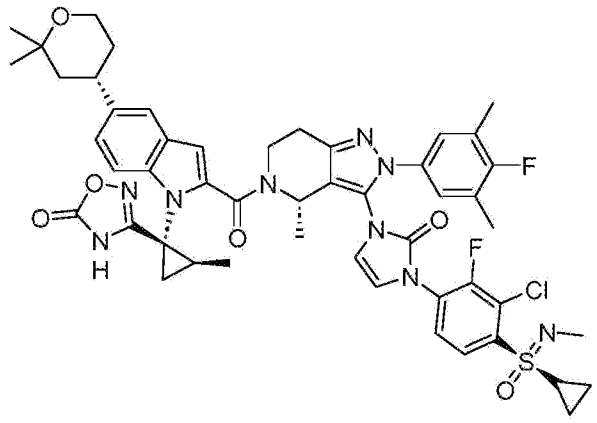
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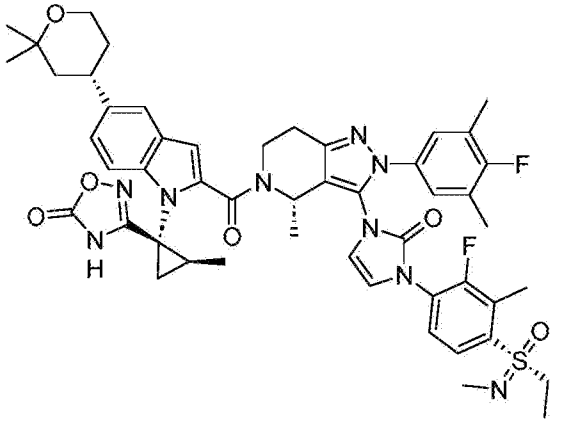
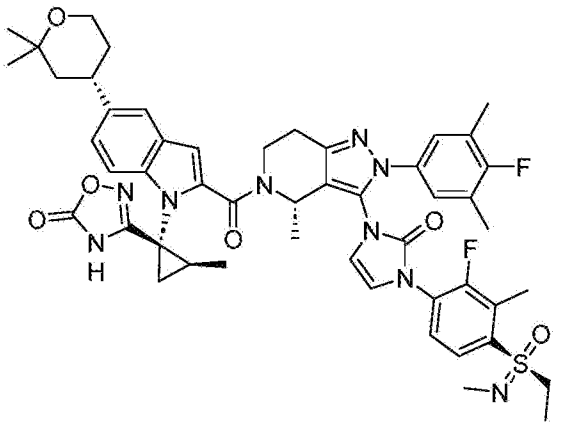
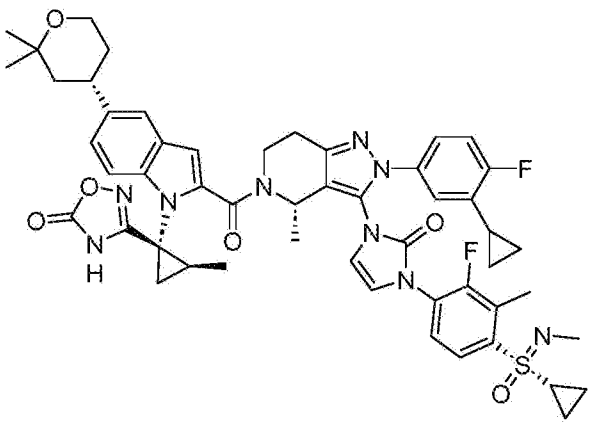
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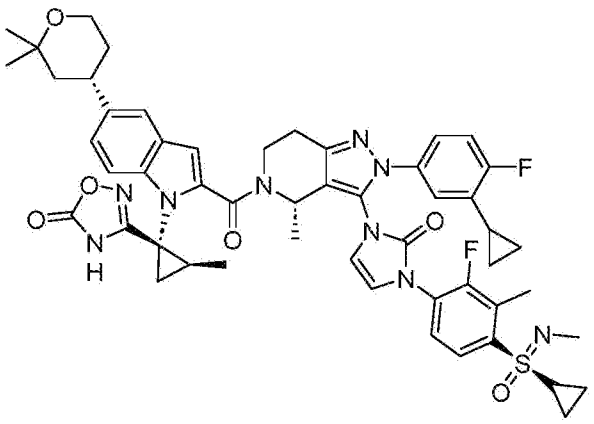
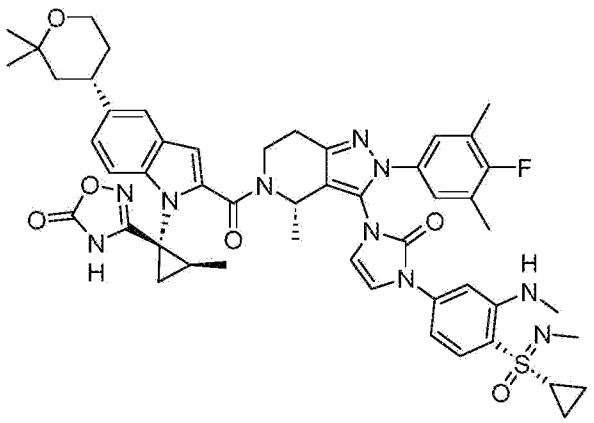
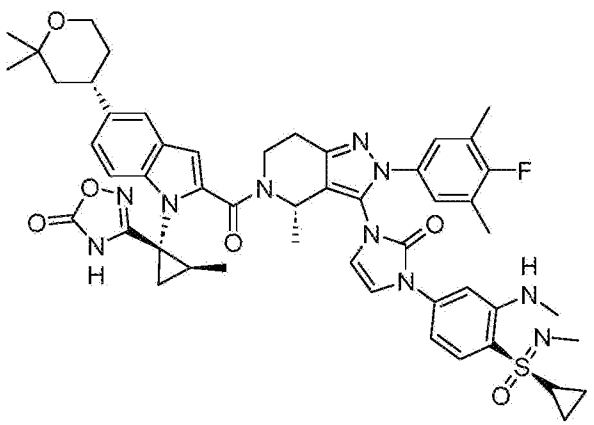
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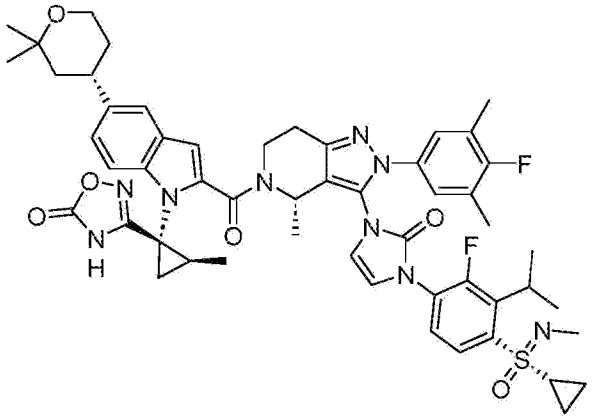
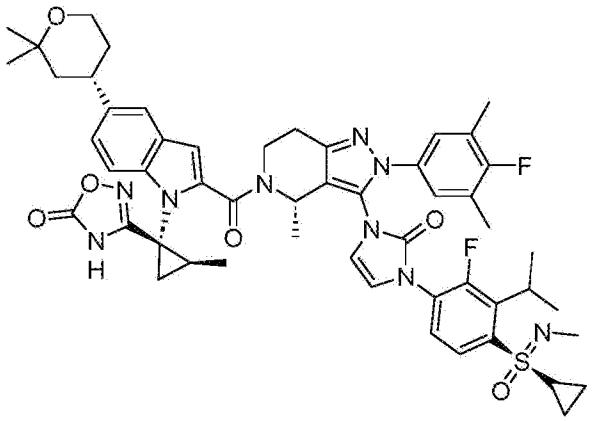
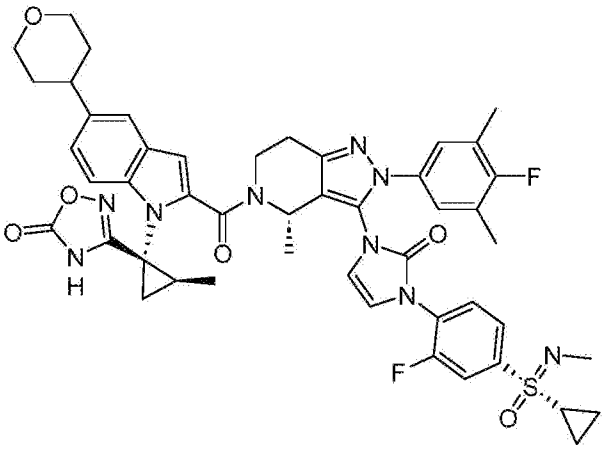
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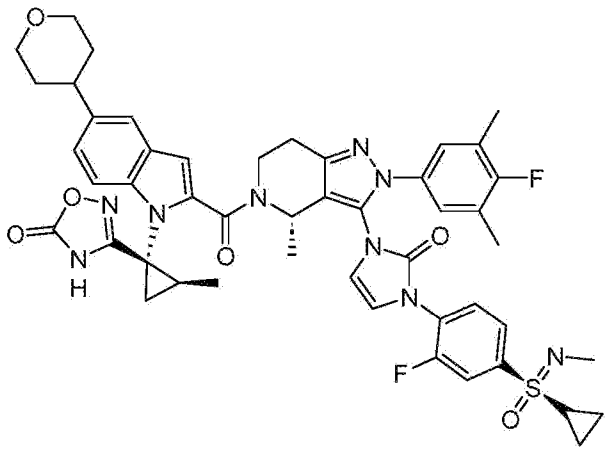
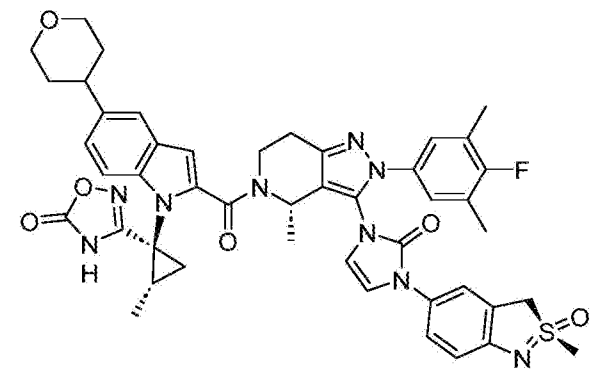
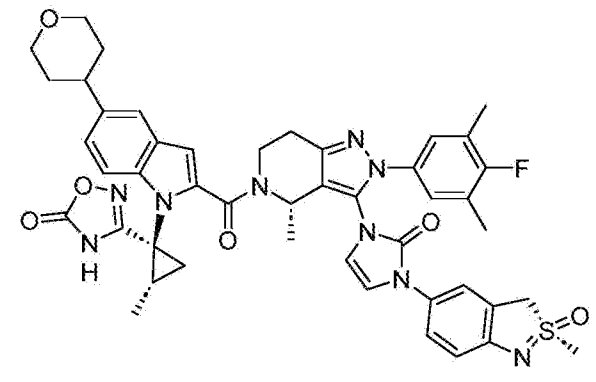
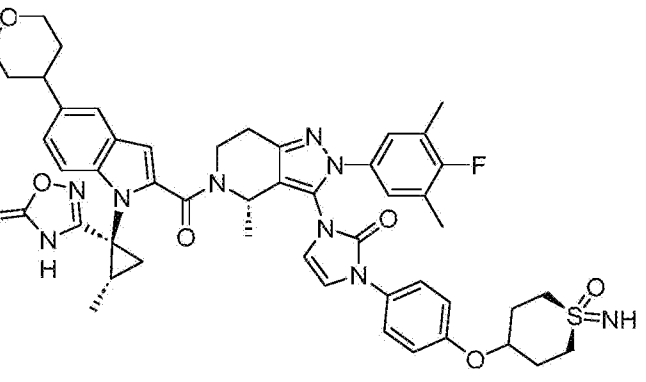
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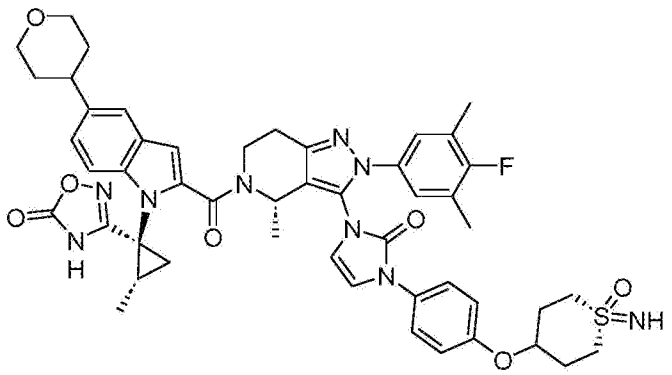
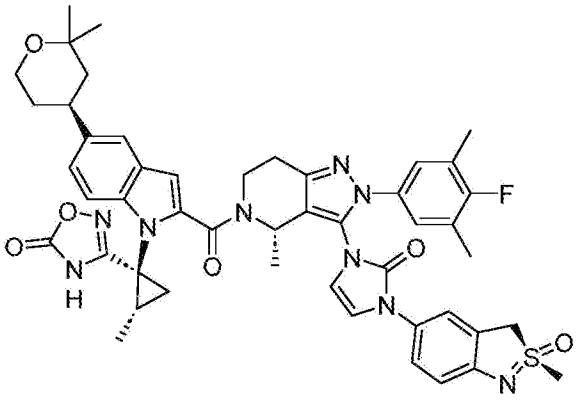
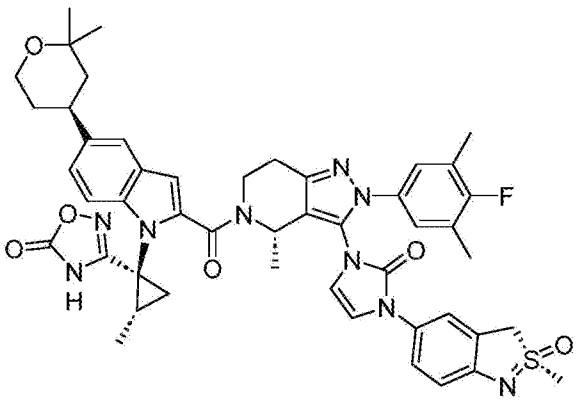
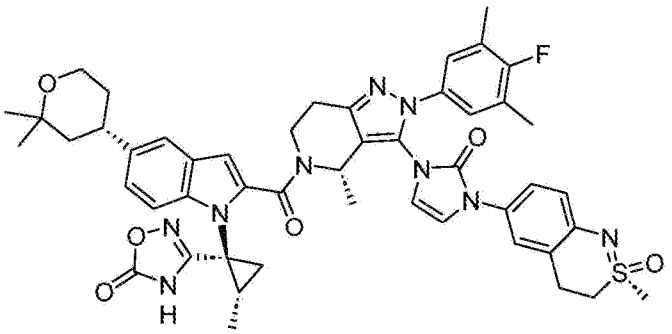
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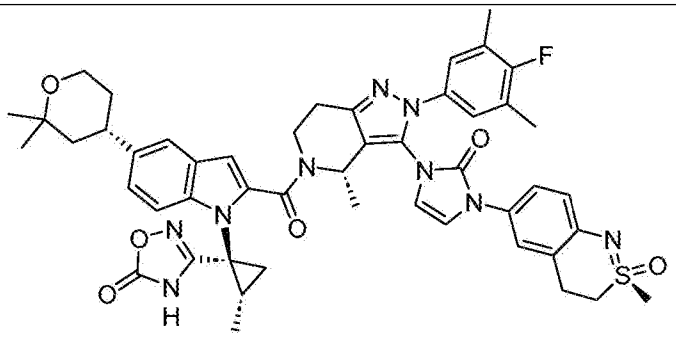
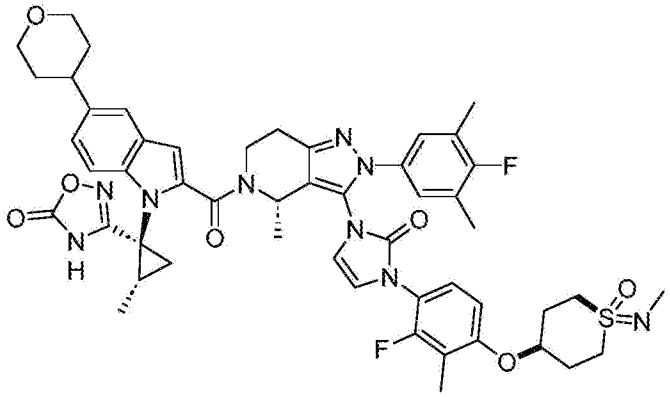
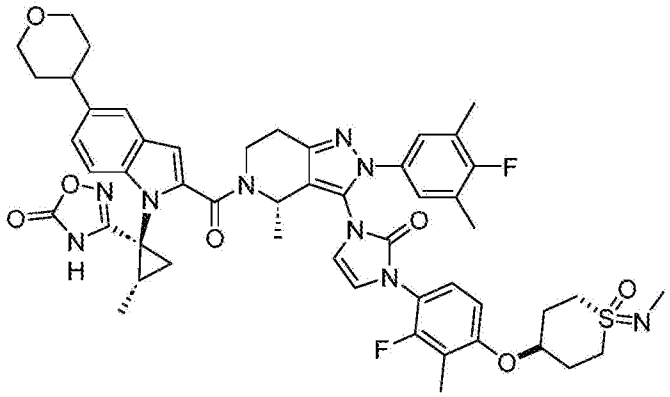
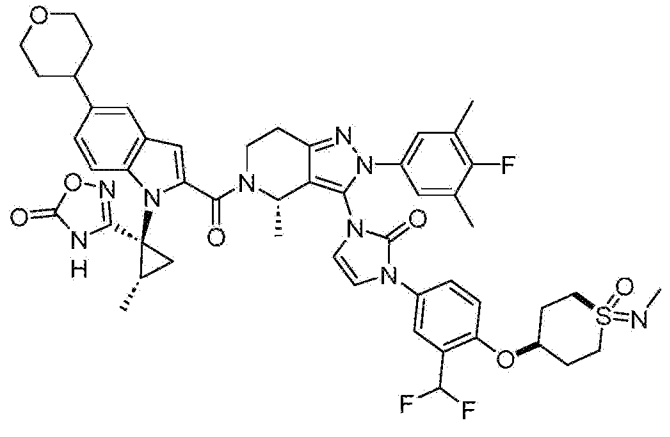
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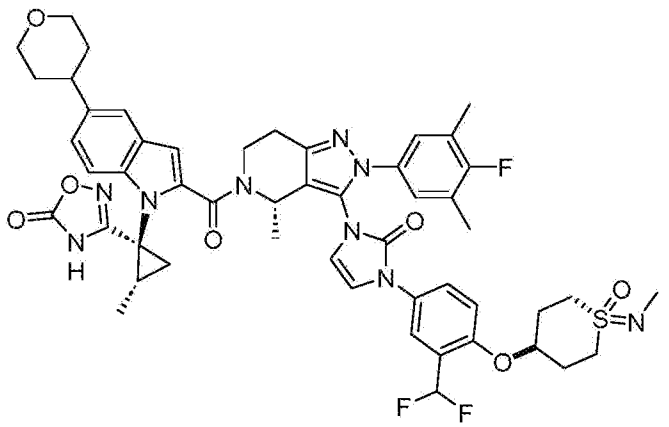
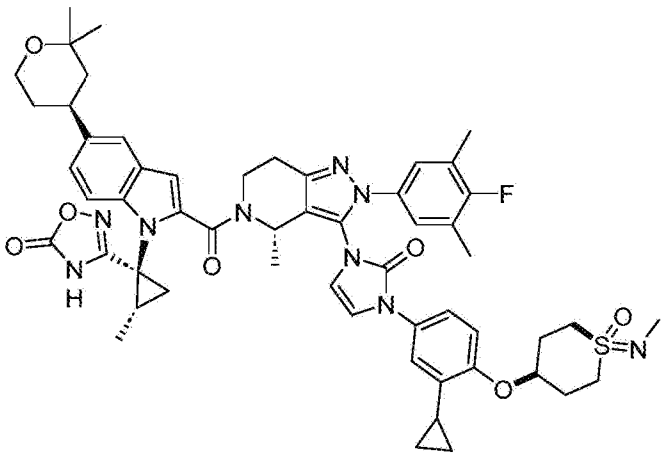
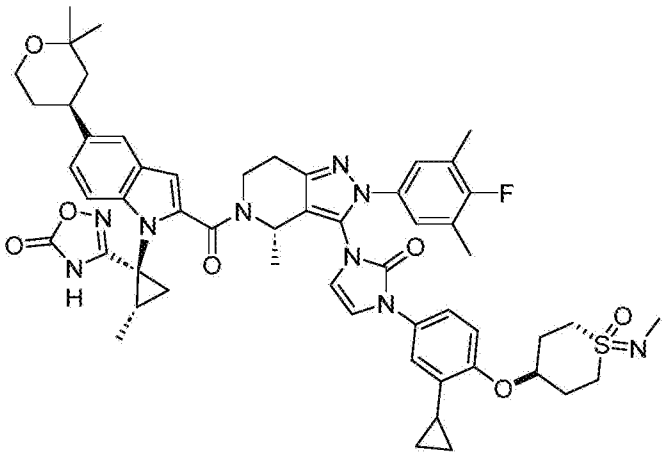
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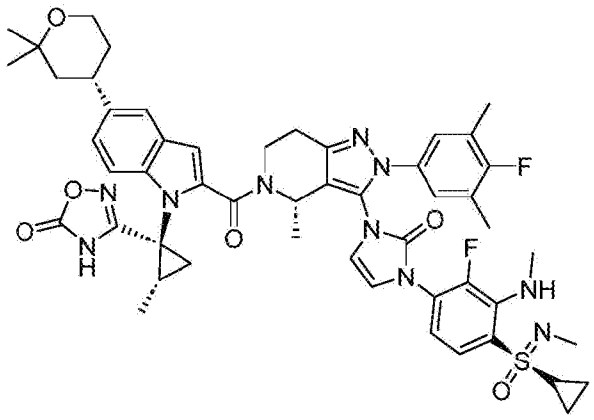
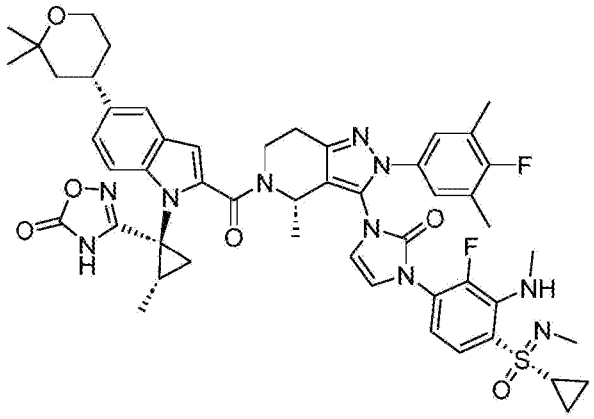
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[0875] The compounds of Formula I include pharmaceutically acceptable salts thereof. In addition, the compounds of Formula I also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/ or purifying compounds of Formula I and/or for separating enantiomers of com pounds of Formula I. Non-limiting examples of pharmaceutically acceptable sa lts of compounds of Formula I include trifluoroacetic acid salts.

[0876] It will further be appreciated that the compounds of Formula I or their salts may be isolated in the form of solvates, and accordingly that any such solvate is included w ithin the scope of the present disclosure. For example, compounds of Formula I and sa lts thereof can exist in unsolvated as well as solvated forms with pharmaceutically a cceptable solvents such as water, ethanol, and the like.

[0877] Pharmaceutical Compositions and Administration

[0878] When employed as pharmaceuticals, compounds as described herein (e.g ., a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enric hed analog, stereoisomer, mixture of stereoisomers, or prodrug thereof) can be admini stered in the form of a pharmaceutical compositions. These compositions can be prepar ed in a manner well known in the pharmaceutical art, and can be administered by a var

iety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (including transderm al, epidermal, ophthalmic and to mucous membranes including intranas al, vaginal and rectal delivery) , pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal) , oral or p arenteral. Oral administration can include a dosage form formulated for once-daily or twice-daily (BID) administration. Parenteral administration includes intra venous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or in fusion; or intracranial, e.g., intrathecal or intraventricular, administration. Paren teral administration can be in the form of a single bolus dose, or can be, for exampl e, by a continuous perfusion pump. Pharmaceutical compositions and f ormulations for topical administration can include transdermal patches, ointments, lo tions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may b e necessary or desirable.

[0879] Also provided herein are pharmaceutical compositions which contain, as the active ingredient, a compound of Formula I, or a pharmaceutic ally acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereois omers, or prodrug thereof, in combination with one or more pharmaceu tically acceptable excipients (carriers) . For example, a pharmaceutical composition prepared using a compound of Formula I, or a pharmaceutically acceptable salt, isotop ically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof. I n some embodiments, the composition is suitable for topical administration. In making the compositions provided herein, the active ingredient is typically mixed with an e xcipient, diluted by an excipient or enclosed within such a carrier in the form of, f or example, a capsule, sachet, paper, or other container. When the excipient serves a s a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the fo rm of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emul sions, solutions, syrups, aerosols (as a solid or in a liquid medium) , ointments con taining, for example, up to 10%by weight of the active compound, soft and hard gelati n capsules, suppositories, sterile injectable solutions, and sterile packaged powders . In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is a solid oral formulation. In some embodiments, the c omposition is formulated as a tablet or capsule.

[0880] Further provided herein are pharmaceutical compositions containing a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof with a pharmaceuti

cally acceptable excipient. Pharmaceutical compositions containing a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof as the active ingr edient can be prepared by intimately mixing the compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral) . In some embodiments, the composition is a solid oral composition.

[0881] Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers can be found in The Handbook of Pharmaceutical Excipients, published by the Ameri can Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

[0882] Methods of formulating pharmaceutical compositions have been describ ed in numerous publications such as Pharmaceutical Dosage Forms: Tab lets, Second Edition, Revised and Expanded, Volumes 1–3, edited by L ieberman et al; Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1– 2, edited by Avis et al; and Pharmaceutical Dosage Forms: Disperse Systems , Volumes 1–2, edited by Lieberman et al; published by Marcel Dekker, Inc.

[0883] In some embodiments, the compound or pharmaceutical composition can be administered in combination with one or more conventional pharmac eutical excipients. Pharmaceutically acceptable excipients include, but are not limit ed to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 100 0 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, suc h as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty aci ds, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosph ate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal si lica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethyl ene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α- , β, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalky lcyclodextrins, including 2-and 3-hydroxypropyl-β-cyclodextrins, or other solubilize d derivatives can also be used to enhance delivery of compounds described herein. Dos age forms or compositions containing a chemical entity as described herein in the ran ge of 0.005%to 100%with the balance made up from non-toxic excipient m

ay be prepared. The contemplated compositions may contain 0.001%-100%of a chemical entity provided herein, in one embodiment 0.1-95%, in another e mbodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing s uch dosage forms are known, or will be apparent, to those skilled in this art; for ex ample, see Remington: The Science and Practice of Pharmacy, 22nd Edi tion (Pharmaceutical Press, London, UK. 2012) .

[0884] In some embodiments, the compounds and pharmaceutical compositions d escribed herein or a pharmaceutical composition thereof can be administered to patien t in need thereof by any accepted route of administration. Acceptable routes of admin istration include, but are not limited to, buccal, cutaneous, endocervical, endosinus ial, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabr onchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intr aductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intra gingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspina l, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauter ine, intravascular, intravenous, nasal (e.g., intranasal) , nasogastric, oral, parent eral, percutaneous, peridural, rectal, respiratory (inhalation) , subcutaneous, subli ngual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, ureth ral and vaginal. In some embodiments, a route of administration is parenteral (e.g., intratumoral) .

[0885] In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers , or prodrug thereof as described herein or pharmaceutical compositions thereof can b e formulated for parenteral administration, e.g., formulated for injection via the in traarterial, intrasternal, intracranial, intravenous, intramuscular, sub-cutaneous, or int raperitoneal routes. For example, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for u se to prepare solutions or suspensions upon the addition of a liquid prior to injecti on can also be prepared; and the preparations can also be emulsified. The preparation of such formulations will be known to those of skill in the art in light of the pres ent disclosure. In some embodiments, devices are used for parenteral administration. For example, such devices may include needle injectors, microneedle injectors, needle-free injectors, and infusion techniques.

[0886] In some embodiments, the pharmaceutical forms suitable for injectabl e use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporan eous preparation of sterile injectable solutions or dispersions. In some embodiments,

the form must be sterile and must be fluid to the extent that it may be easily injec ted. In some embodiments, the form should be stable under the condit ions of manufacture and storage and must be preserved against the contaminating actio n of microorganisms, such as bacteria and fungi.

[0887] In some embodiments, the carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example , glycerol, propylene glycol, and liquid polyethylene glycol, and the like) , suitabl e mixtures thereof, and vegetable oils. In some embodiments, the proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the mainten ance of the required particle size in the case of dispersion, and by the use of surfa ctants. In some embodiments, the prevention of the action of microor ganisms can be brought about by various antibacterial and antifungal agents, for exam ple, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In some embodiments, isotonic agents, for example, sugars or sodium chloride are included. In some embodiments, prolonged absorption of the injectable compositio ns can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0888] In some embodiments, sterile injectable solutions are prepared by in corporating a compound of Formula I, or a pharmaceutically acceptable salt, isotopica lly enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof in th e required amount in the appropriate solvent with various of the other ingredients en umerated above, as required, followed by filtered sterilization. In some embodiments, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required ot her ingredients from those enumerated above. In some embodiments, st erile powders are used for the preparation of sterile injectable solutions. In some e mbodiments, the methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0889] In some embodiments, pharmacologically acceptable excipients usable in a rectal composition as a gel, cream, enema, or rectal suppository, include, witho ut limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments) , glycerine, glycerinated gelatin, hy drogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various mo lecular weights and fatty acid esters of polyethylene glycol, Vaseline, anhydrous lan olin, shark liver oil, sodium saccharinate, menthol, sweet almond oil, sorbitol, sodi um benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbome

rs, carbopol, methyloxybenzoate, macrogol cetostearyl ether, cocoyl caprylocaprate, i sopropyl alcohol, propylene glycol, liquid paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium metabisulfite, grapefruit s eed extract, methyl sulfonyl methane (MSM) , lactic acid, glycine, vitamins, such as vitamin A and E and potassium acetate.

[0890] In some embodiments, suppositories can be prepared by mixing a compo und of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog , stereoisomer, mixture of stereoisomers, or prodrug thereof, or pharmaceutical compo sitions as described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at amb ient temperature but liquid at body temperature and therefore melt in the rectum and release the active compound. In some embodiments, compositions for r ectal administration are in the form of an enema.

[0891] In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers , or prodrug thereof, as described herein or a pharmaceutical composition thereof is formulated for local delivery to the digestive or GI tract by way of oral administrat ion (e.g., solid or liquid dosage forms.) .

[0892] In some embodiments, solid dosage forms for oral administration incl ude capsules, tablets, pills, powders, and granules. In some embodim ents, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically en riched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, is mixed with one or more pharmaceutically acceptable excipients, such as sodiu m citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, la ctose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and aca cia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, a nd sodium carbonate, e) solution retarding agents such as paraffin, f) absorption acc elerators such as quaternary ammonium compounds, g) wetting agents s uch as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as k aolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. F or example, in the case of capsules, tablets and pills, the dosage form may also comp rise buffering agents. In some embodiments, solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene gl ycols and the like.

[0893] In some embodiments, the pharmaceutical compositions will take the f orm of a unit dosage form such as a pill or tablet and thus the composition may conta in, along with a compound of Formula I, or a pharmaceutically acceptable salt, isotop ically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof as provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the lik e; a lubricant such as magnesium stearate or the like; and a binder such as starch, g um acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the lik e. In some embodiments, another solid dosage form, a powder, marume, solution or suspension (e.g., in propylene carbonate, vegetable oils, PEG's, poloxam er 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base caps ule) . In some embodiments, unit dosage forms in which one or more c ompounds and pharmaceutical compositions as provided herein or addit ional active agents are physically separated are also contemplated; e.g., capsules wi th granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. In some embodiments, enteric coated or delayed release ora l dosage forms are also contemplated.

[0894] In some embodiments, other physiologically acceptable compounds may include wetting agents, emulsifying agents, dispersing agents or preservatives that a re particularly useful for preventing the growth or action of microorganisms. For exa mple, various preservatives are well known and include, for example, phenol and ascor bic acid.

[0895] In some embodiments, the excipients are sterile and generally free o f undesirable matter. For example, these compositions can be sterilized by convention al, well-known sterilization techniques. In some embodiments, for various ora l dosage form excipients such as tablets and capsules, sterility is not required. For example, the United States Pharmacopeia/National Formulary (USP/NF) standard can be sufficient.

[0896] In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers , or prodrug thereof as described herein or a pharmaceutical composition thereof is f ormulated for ocular administration. In some embodiments, ocular com positions can include, without limitation, one or more of any of the following: visco gens (e.g., carboxymethylcellulose, glycerin, polyvinylpyrrolidone, polyethylene glyc ol) ; stabilizers (e.g., Pluronic (triblock copolymers) , cyclodextrins) ; preservati ves (e.g., benzalkonium chloride, EDTA, SofZia (boric acid, propylene glycol, sorbito l, and zinc chloride; Alcon Laboratories, Inc.) , Purite (stabilized oxychloro compl ex; Allergan, Inc.)) .

[0897] In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers , or prodrug thereof as described herein or a pharmaceutical composition thereof is f ormulated for topical administration to the skin or mucosa (e.g., dermally or transde rmally) . In some embodiments, topical compositions can include oint ments and creams. In some embodiments, ointments are semisolid prepa rations that are typically based on petrolatum or other petroleum derivatives. In som e embodiments, creams containing the selected active agent are typically viscous liqu id or semisolid emulsions, often either oil-in-water or water-in-oil. For example, cream bases are typically water-washable, and contain an oil phase, an emulsifier a nd an aqueous phase. For example, the oil phase, also sometimes called the “internal” phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or ste aryl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil ph ase in volume, and generally contains a humectant. In some embodimen ts, the emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. In some embodiments, as with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing.

[0898] In any of the foregoing embodiments, pharmaceutical compositions as described herein can include one or more one or more of the following: lipids, interb ilayer crosslinked multilamellar vesicles, biodegradable poly (D, L-lactic-co-glycolic acid) (PLGA) -based or poly anhydride-based nanoparticles or micropartic les, and nanoporous particle-supported lipid bilayers.

[0899] The amount of the compound in a pharmaceutical composition or formul ation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt %of a compound of this disclosure based on the total formulation, with the b alance being one or more suitable pharmaceutical excipients. In one embodiment, the c ompound is present at a level of about 1-80 wt %. Representative pharmaceut ical formulations are described below.

[0900] Formulation Example 1 -Tablet formulation

[0901] The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this disclosure	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

[0902] Formulation Example 2 -Capsule formulation

[0903] The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule

Ingredient	Quantity per capsule, mg
compound of this disclosure	200
lactose, spray-dried	148
magnesium stearate	2

[0904] Formulation Example 3 -Suspension formulation

[0905] The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this disclosure	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.0 g
sorbitol (70% solution)	13.00 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 mL
coloring	0.5 mg
distilled water	q.s. to 100 mL

[0906] Formulation Example 4 -Injectable formulation

[0907] The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this disclosure	0.2 mg-20 mg
sodium acetate buffer solution, 0.4 M	2.0 mL
HCl (1N) or NaOH (1N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 mL

[0908] Formulation Example 5 -Suppository Formulation

[0909] A suppository of total weight 2.5 g is prepared by mixing the compound of this disclosure with Witepsol®H-15 (triglycerides of saturated vegetable fatty acid ; Riches-Nelson, Inc., New York) , and has the following composition:

Ingredient	Amount
compound of this disclosure	500 mg
Witepsol® H-15	balance

[0910] In some embodiments, the dosage for a compound of Formula I, or a ph armaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture o f stereoisomers, or prodrug thereof, is determined based on a multiple factors includ ing, but not limited to, type, age, weight, sex, medical condition of the patient, se verity of the medical condition of the patient, route of administration, and activity of the compound or pharmaceutically acceptable salt, isotopically enriched analog, s tereoisomer, mixture of stereoisomers, or prodrug thereof. In some e mbodiments, proper dosage for a particular situation can be determined by one skilled in the medical arts. In some embodiments, the total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery .

[0911] In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers , or prodrug thereof, is administered at a dose from about 0.01 to about 1000 mg. For example, from about 0.1 to about 30 mg, about 10 to about 80 mg, about 0.5 to about 15 mg, about 50 mg to about 200 mg, about 100 mg to about 300 mg, ab out 200 to about 400 mg, about 300 mg to about 500 mg, about 400 mg to about 600 mg, about 500 mg to about 800 mg, about 600 mg to about 900 mg, or about 700 mg to about 1000 mg. In some embodiments, the dose is a therapeutically effective amount.

[0912] In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers , or prodrug thereof as described herein is administered at a dosage of from ab out 0.0002 mg/Kg to about 100 mg/Kg (e.g., from about 0.0002 mg/Kg t o about 50 mg/Kg; from about 0.0002 mg/Kg to about 25 mg/Kg; from ab out 0.0002 mg/Kg to about 10 mg/Kg; from about 0.0002 mg/Kg to about 5 mg/ Kg; from about 0.0002 mg/Kg to about 1 mg/Kg; from about 0.0002 mg/Kg to about 0.5 mg/Kg; from about 0.0002 mg/Kg to about 0.1 mg/Kg; from about 0.001 mg/ Kg to about 50 mg/Kg; from about 0.001 mg/Kg to about 25 mg/Kg; from about 0.0 01 mg/Kg to about 10 mg/Kg; from about 0.001 mg/Kg to about 5 mg/Kg; from about 0.001 mg/Kg to about 1 mg/Kg; from about 0.001 mg/Kg to about 0.5 mg/ Kg; from about 0.001 mg/Kg to about 0.1 mg/Kg; from about 0.01 mg/Kg to about 50 mg/Kg; from about 0.01 mg/Kg to about 25 mg/Kg; from about 0.01 mg/ Kg to about 10 mg/Kg; from about 0.01 mg/Kg to about 5 mg/Kg; from about 0.01 mg/Kg to about 1 mg/Kg; from about 0.01 mg/Kg to about 0.5 mg/Kg; f rom about 0.01 mg/Kg to about 0.1 mg/Kg; from about 0.1 mg/Kg to about 50 mg/ Kg; from about 0.1 mg/Kg to about 25 mg/Kg; from about 0.1 mg/Kg to about 10 mg/ Kg; from about 0.1 mg/Kg to about 5 mg/Kg; from about 0.1 mg/Kg to about 1 mg/

Kg; from about 0.1 mg/Kg to about 0.5 mg/Kg) . In some embodiments, a c ompound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched an alog, stereoisomer, mixture of stereoisomers, or prodrug thereof as described herein is administered as a dosage of about 100 mg/Kg.

[0913] In some embodiments, the foregoing dosages of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g. , every other day, every two days, every three days, once weekly, twice weeks, once e very two weeks, once a month) .

[0914] In some embodiments, the period of administration of a compound of F ormula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereo isomer, mixture of stereoisomers, or prodrug thereof as described herein is for 1 day , 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 wee ks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 mont hs, 6 months, 7 months, 8 months, 9 months, 10 months, 1 1 months, 1 2 months, or more. In some embodiments, a period of during which adm inistration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 wee ks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 1 1 weeks, 12 week s, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 mo nths, 1 1 months, 12 months, or more. In some embodiments, a compoun d of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof is administered to a patie nt for a period of time followed by a separate period of time where administration of the compound of Formula I, or a pharmaceutically acceptable salt, isotopically enric hed analog, stereoisomer, mixture of stereoisomers, or prodrug thereof is stopped. In some embodiments, a compound of Formula I, or a pharmaceutically ac ceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomer s, or prodrug thereof is administered for a first period and a second period followin g the first period, with administration stopped during the second period, followed by a third period where administration of the compound of Formula I, or a pharmaceutica lly acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoiso mers, or prodrug thereof is started and then a fourth period following the third peri od where administration is stopped. For example, the period of administration of a co mpound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched ana log, stereoisomer, mixture of stereoisomers, or prodrug thereof followed by a period

where administration is stopped is repeated for a determined or undetermined period o f time. In some embodiments, a period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 wee ks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 mo nths, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In some embodiments, a period of during which administration is stop ped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks , 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months , 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

[0915] In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers , or prodrug thereof, is orally administered to the patient one or more times per day (e.g., one time per day, two times per day, three times per day, four times per day per day or a single daily dose) .

[0916] In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers , or prodrug thereof, is administered by parenteral administration to the patient one or more times per day (e.g., 1 to 4 times, one time per day, two times per day, thre e times per day, four times per day or a single daily dose) .

[0917] In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers , or prodrug thereof, is administered by parenteral administration to the patient weekly.

[0918] Methods of Treatment

[0919] In some embodiments, this disclosure features methods for treating a patient (e.g., a human) having a disease, disorder, or condition in which modulation of GLP-1R (e.g., repressed or impaired and/or elevated or unwanted GLP-1R) is beneficial for the trea tment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. In some embodiments, the methods described herein can include or further include treating one or more conditions associated, co-morbid or sequela with any one or more of the conditions described herein.

[0920] Provided herein is a method for treating a GLP-1 associated disease, disorder, or condition, the method comprising administering to a patient in need thereof an effec tive amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotop ically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, o r a pharmaceutical composition as disclosed herein.

[0921] In some embodiments, the disease, disorder, or condition includes, but is not limited to type 1 diabetes mellitus, type 2 diabetes mellitus, early onset type 2 diabetes mellitus, idiopathic type 1 diabetes mellitus (Type 1b) , youth-onset atypical diabetes (YOAD) , maturity onset diabetes of the young (MODY) , latent autoimmune diabetes in adults (LADA) , obesity, weight gain from use of other agents, gout, excessive sugar craving, hypertriglyceridemia, dyslipidemia, malnutrition-related diabetes, gestational diabetes, kidney disease, adipocyte dysfunction, sleep apnea, visceral adipose deposition, eating disorders, cardiovascular disease, congestive heart failure, myocardial infarction, left ventricular hypertrophy, peripheral arterial disease, stroke, hemorrhagic stroke, ischemic stroke, transient ischemic attacks, atherosclerotic cardiovascular disease, traumatic brain injury, peripheral vascular disease, endothelial dysfunction, impaired vascular compliance, vascular restenosis, thrombosis, hypertension, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis, hyperinsulinemia, impaired glucose metabolism, insulin resistance, hepatic insulin resistance, alcohol use disorder, chronic renal failure, metabolic syndrome, syndrome X, smoking cessation, premenstrual syndrome, angina pectoris, diabetic nephropathy, impaired glucose tolerance, diabetic neuropathy, diabetic retinopathy, macular degeneration, cataract, glomerulosclerosis, arthritis, osteoporosis, treatment of addiction, cocaine dependence, bipolar disorder/major depressive disorder, skin and connective tissue disorders, foot ulcerations, psoriasis, primary polydipsia, non-alcoholic steatohepatitis (NASH) , non-alcoholic fatty liver disease (NAFLD) , ulcerative colitis, inflammatory bowel disease, colitis, irritable bowel syndrome, Crohn's disease, short bowel syndrome, Parkinson's, Alzheimer's disease, impaired cognition, schizophrenia, and Polycystic Ovary Syndrome (PCOS) .

[0922] In some embodiments, the disease, disorder, or condition includes, but is not limited to type 2 diabetes mellitus, early onset type 2 diabetes mellitus, obesity, weight g ain from use of other agents, gout, excessive sugar craving, hypertriglyceridemia, dy slipidemia, gestational diabetes, kidney disease, adipocyte dysfunction, sleep apnea, visceral adipose deposition, eating disorders, cardiovascular disease, congestive he art failure, myocardial infarction, left ventricular hypertrophy, peripheral arterial disease, stroke, hemorrhagic stroke, ischemic stroke, transient ischemic attacks, at herosclerotic cardiovascular disease, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis, hyperinsulinemia, impaired glucose metabolism, insulin resistance, hepatic insulin resistance, alcohol use disorder, chronic renal failure, metabolic syndrome, syndrome X, smoking cessation, premenstrual synd rome, angina pectoris, diabetic nephropathy, impaired glucose tolerance, diabetic neu ropathy, diabetic retinopathy, bipolar disorder/major depressive disorder, skin and c

onnective tissue disorders, foot ulcerations, psoriasis, primary polydipsia, non-alcoholic steatohepatitis (NASH) , non-alcoholic fatty liver disease (NAF LD) , short bowel syndrome, Parkinson's disease, Polycystic Ovary Sy ndrome (PCOS) , or any combination thereof.

[0923] In some embodiments, the disease, disorder, or condition includes, but is not limited to type 2 diabetes mellitus, early onset type 2 diabetes mellitus, obesity, weight g ain from use of other agents, gout, excessive sugar craving, hypertriglyceridemia, dy slipidemia, gestational diabetes, adipocyte dysfunction, visceral adipose deposition, myocardial infarction, peripheral arterial disease, stroke, transient ischemic attac ks, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis, hype rinsulinemia, impaired glucose metabolism, insulin resistance, hepatic insulin resist ance, chronic renal failure, syndrome X, angina pectoris, diabetic nephropathy, impai red glucose tolerance, diabetic neuropathy, diabetic retinopathy, skin and connective tissue disorders, foot ulcerations, or any combination thereof.

[0924] In some embodiments, the compounds and pharmaceutical compositions a nd methods for treating a patient described herein induce one or mor e of blood glucose reduction (e.g., reduce blood glucose levels) , reduce blood hemog lobin A1c (HbA1c) levels, promote insulin synthesis, stimulate insulin secretion, inc rease the mass of β-cells, modulate gastric acid secretion, modulate gastric emptying, d ecrease the body mass index (BMI) , and/or decrease glucagon production (e.g., level) . In certain embodiments, the compounds and pharmaceutical composit ions and methods for treating a patient described herein stabilize serum glucose and serum insulin levels (e.g., serum glucose and serum insulin concentrations) . Also pr ovided herein are methods for modulating glucose or insulin levels in a patient in ne ed of such modulating, the method comprising administering to the patient an effectiv e amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopica lly enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a pharmaceutical composition as disclosed herein.

[0925] In some embodiments, provided herein is a method for reducing the ri sk (e.g., by about at least 20%, at least 30%, at least 40%, at least 50%, at least 6 0%, at least 70%, or at least 80%) of major adverse cardiovascular events (MACE) in a patient in need thereof, the method comprising administering to the patient an effec tive amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotop ically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, o r a pharmaceutical composition as disclosed herein. In certain of these embodiments, the patient is an adult that has been diagnosed with type 2 diabetes (T2D) . In certa in embodiments, the patient is an adult that has been diagnosed with a heart disease. In certain embodiments, the patient is an adult that has been diagnosed with type 2

diabetes (T2D) and a heart disease. In certain embodiments, the patient is an adult t hat has type 2 diabetes (T2D) . In certain embodiments, the patient is an adult that has a heart disease. In certain embodiments, the patient has type 2 diabetes (T2D) an d a heart disease.

[0926] Indications

[0927] Obesity

[0928] In some embodiments, the condition, disease, or disorder is obesity and conditions, d iseases or disorders that are associated with or related to obesity. Non-limiting examples of obesity and obesity related conditions include symptomatic obesi ty, simple obesity, childhood obesity, morbid obesity, and abdominal obesity (central obesity characterized by abdominal adiposity) . Non-limiting examples of symptomatic obesity include endocrine obesity (e.g., Cushing syn drome, hypothyroidism, insulinoma, obese type II diabetes, pseudohyp oparathyroidism, hypogonadism) , hypothalamic obesity, hereditary obesity (e.g., Prad er-Willi syndrome, Laurence-Moon-Biedl syndrome) , and drug-induced obesity (e.g., steroid, phenothiazine, insulin, sulfonylurea agent, or β-blocker-induced obesity) .

[0929] In some embodiments, the condition, disease, or disorder is associated with obesity. Examples of such conditions, diseases or disorders include, without limitation, gluco se tolerance disorders, diabetes (e.g., type 2 diabetes, obese diabetes) , lipid meta bolism abnormality, hyperlipidemia, hypertension, cardiac failure, hyperuricemia, gou t, fatty liver (including non-alcoholic steatohepatitis (NASH)) , coronary heart disease (e.g., myocardial infarction, angina pectoris) , cerebral infarction (e.g., brain thrombosis, transient cerebral ischemic attack) , bone or articular disease (e. g., knee osteoarthritis, hip osteoarthritis, spondylitis deformans, lumbago) , sleep apnea syndrome, obesity hypoventilation syndrome (Pickwickian syndro me) , menstrual disorder (e.g., abnormal menstrual cycle, abnormality of menstrual fl ow and cycle, amenorrhea, abnormal catamenial symptom) , visceral ob esity syndrome, and metabolic syndrome. In some embodiments, the che mical compound and pharmaceutical compositions described herein can be used to treat patients exhibiting symptoms of both obesity and insulin deficiency.

[0930] Diabetes

[0931] In some embodiments, the condition, disease, or disorder is diabetes. Non-limiting examples of diabetes include type 1 diabetes mellitus, type 2 diabetes melli tus (e.g., diet-treated type 2-diabetes, sulfonylurea-treated type 2-diabetes, a far-advanced stage type 2-diabetes, long-term insulin-treated type 2-diabetes) , diabe tes mellitus (e.g., non-insulin-dependent diabetes mellitus, insulin-dependent diabete s mellitus) , gestational diabetes, obese diabetes, autoimmune diabetes, and borderli ne type diabetes. In some embodiments, the condition, disease, or disorder is type 2

diabetes mellitus (e.g., diet-treated type 2-diabetes, sulfonylurea-treated type 2-diabetes, a far-advanced stage type 2-diabetes, long-term insulin-treated type 2-diabetes) .

[0932] Provided herein is a method of treating a diabetes mellitus in a patient, the method comprising (a) determining that the patient has type 2 diabetes mellitus, and (b) adm inistering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer , mixture of stereoisomers, or prodrug thereof, or a pharmaceutical composition as di sclosed herein.

[0933] Provided herein is a method for treating type 2 diabetes mellitus in a patient, the m ethod comprising administering to a patient identified or diagnosed as having type 2 diabetes mellitus a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixtur e of stereoisomers, or prodrug thereof, or a pharmaceutical composition as disclosed herein.

[0934] Also provided herein is a method of treating type 2 diabetes mellitus in a patient in need thereof, the method comprising administering to the patient a therapeutically e ffective amount of a compound of Formula I, or a pharmaceutically acceptable salt, is otopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereo f, or a pharmaceutical composition as disclosed herein.

[0935] In some embodiments, the compounds and pharmaceutical compositions a nd methods for treating a patient with a condition, disease, or disorder (e.g., type 2 diabetes mellitus) described herein reduce fasting plasma glucose levels. In some e mbodiments, the compounds and pharmaceutical compositions and method s for treating a patient with a condition, disease, or disorder (e.g., type 2 diabete s mellitus) described herein reduce non-fasting plasma glucose levels. In some embodiments, the compounds and pharmaceutical compositions and methods for treating a patient with a condition, disease, or disorder (e.g., type 2 d iabetes mellitus) described herein reduce HbA1c levels. In some embo diments, the compounds and pharmaceutical compositions and methods f or treating a patient with a condition, disease, or disorder (e.g., type 2 diabetes m ellitus) described herein reduce glucagon levels. In some embodiment s, the compounds and pharmaceutical compositions and methods for tre ating a patient with a condition, disease, or disorder (e.g., type 2 diabetes mellitu s) described herein increase insulin levels. In some embodiments, the compounds and p harmaceutical compositions and methods for treating a patient with a condition, disea se, or disorder (e.g., type 2 diabetes mellitus) described herein reduce BMI.

[0936] In some embodiments, a reduction in fasting plasma glucose levels of about 5%to about 95%indicates treatment of type 2 diabetes mellitus . In some embodiments, a reduction in fasting plasma glucose levels of about 15%to about 80%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in fasting plasma glucose levels of about 25%to about 60%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in fasting plasma glucose levels to about or below 126 mg/dL, about or below 110 mg/dL, or about or below 90 mg/dL indicates treatment of the type 2 diabetes mellitus.

[0937] In some embodiments, a reduction in non-fasting plasma glucose levels of about 5%to about 95%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in non-fasting plasma glucose levels of about 15%to about 80%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in non-fasting plasma glucose levels of about 25%to about 60%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in non-fasting plasma glucose levels to about or below 200 mg/dL, about or below 150 mg/dL, or about or below 130 mg/dL indicates treatment of type 2 diabetes mellitus.

[0938] In some embodiments, a reduction in HbA1c levels of about 5%to about 95%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in HbA1c levels of about 15%to about 80%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in HbA1c levels of about 25%to about 60%indicates treatment of type 2 diabetes mellitus. In some embodiments, reduction in HbA1c levels to about or below 6.5%, about or below 6.0%, or about or below 5.0%indicates treatment of type 2 diabetes mellitus.

[0939] In some embodiments, a reduction in glucagon levels of about 5%to about 95%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in glucagon levels of about 15%to about 80%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in glucagon levels of about 25%to about 60%indicates treatment of type 2 diabetes mellitus. In some embodiments, an increase in insulin levels of about 5%to about 95%indicates treatment of type 2 diabetes mellitus. In some embodiments, an increase in insulin levels of about 15%to about 80%indicates treatment of type 2 diabetes mellitus. In some embodiments, an increase in insulin levels of about 25%to about 60%indicates treatment of type 2 diabetes mellitus.

[0940] In some embodiments, a reduction in BMI of about 5%to about 95%indicates treatment of type 2 diabetes mellitus. In some embodiments, a reduction in BMI of about 15%to about 80%indicates treatment of the type 2 diabetes mellitus. In some embodiments, a reduction in BMI of about 25%to about 60%indicates tre

atment of type 2 diabetes mellitus. In some embodiments, a reduction in BMI of about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40 %, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%indicates t reatment of type 2 diabetes mellitus. In some embodiments, a reduction in BMI to abou t or below 40, about or below 30, or about or below 20 indicates treatment of type 2 diabetes mellitus.

[0941] In some embodiments, the condition, disease, or disorder is associated with diabetes (e.g., a complication of diabetes) . Non-limiting examples of disorders ass ociated with diabetes include obesity, obesity-related disorders, metabolic syndr ome, neuropathy, nephropathy (e.g., diabetic nephropathy) , retinopathy, diabetic car diomyopathy, cataract, macroangiopathy, osteopenia, hyperosmolar dia betic coma, infectious disease (e.g., respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infections, inferior limb infection) , diabetic gangrene, xerostomia, hypacusis, cerebrovascular disorder, diabetic cachex ia, delayed wound healing, diabetic dyslipidemia peripheral blood circulation disorde r, cardiovascular risk factors. (e.g., coronary artery disease, peripheral artery dis ease, cerebrovascular disease, hypertension, and risk factors related to unmanaged ch olesterol and/or lipid levels, and/or inflammation) , NASH, bone fracture, and cognit ive dysfunction

[0942] Other non-limiting examples of disorders related to diabetes include pre-diabetes, hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, high LDL-cholesterolemia, low HDL-cholesterolemia, postprandial hyperlipemia) , metab olic syndrome (e.g., metabolic disorder where activation of GLP-1R is beneficial, metabolic syndrome X) , hypertension, impaired glucose tolerance (IGT) , insulin res istance, and sarcopenia.

[0943] In some embodiments, the condition, disease, or disorder is diabetes and obesity (dia besity) . In some embodiments, the compounds described herein are also useful in impr oving the therapeutic effectiveness of metformin.

[0944] Disorders of Metabolically Important Tissues

[0945] In some embodiments, the condition, disease, or disorder is a disorder of a metabolic ally important tissue. Non-limiting examples of metabolically important tissue s include liver, fat, pancreas, kidney, and gut.

[0946] In some embodiments, the condition, disease, or disorder is a fatty liver disease. Fa tty liver diseases include, but are not limited to, non-alcoholic fatty acid liver disease (NAFLD) , steatohepatitis, non-alcoholic steatohepatitis (NASH) , fatty liver dise ase resulting from hepatitis, fatty liver disease resulting from obesity, fatty liver disease resulting from diabetes, fatty liver disease resulting from insulin resistan

ce, fatty liver disease resulting from hypertriglyceridemia, Abetalipoproteinemia, gl ycogen storage diseases, Weber-Christian disease, Wolman's disease, acute fatty li ver of pregnancy, and lipodystrophy.

[0947] Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of disea se occurring in the absence of alcohol abuse and is typically characterized by the pr esence of steatosis (fat in the liver) . NAFLD is believed to be linked to a variety of conditions, e.g., metabolic syndrome (including obesity, diabetes and hypertriglyc eridemia) and insulin resistance. It can cause liver disease in adults and children a nd may ultimately lead to cirrhosis (Skelly et al., J Hepatol 2001; 35: 195- 9; Chitturi et al., Hepatology 2002; 35 (2) : 373-9) . The severity of NAFLD ranges from the relatively benign isolated predominantly macrovesicular steatosis (i.e., non alcoholic fatty liver or NAFL) to non-alcoholic steatohepatitis (NASH) (Angulo et al., J Gastroenterol Hepatol 2002; 17 Suppl: S186-90) . In some emb odiments, the patient is a pediatric patient. The term "pediatric patient" as used he rein refers to a patient under the age of 21 years at the time of diagnosis or treatm ent. The term "pediatric" can be further be divided into various subpopulations inclu ding: neonates (from birth through the first month of life) ; infants (1 month up to two years of age) ; children (two years of age up to 12 years of age) ; and adolescen ts (12 years of age through 21 years of age (up to, but not including, the twenty- second birthday)) . Berhman RE, Kliegman R, Arvin AM, Nelson WE. Ne lson Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Co mpany, 1996; Rudolph AM, et al. Rudolph's Pediatrics, 21st Ed. New Y ork: McGraw-Hill, 2002; and Avery MD, First LR. Pediatric Medicine, 2nd Ed. Balt imore: Williams & Wilkins; 1994. In some embodiments, a pediatric patient is fro m birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age throu gh 21 years of age (up to, but not including, the twenty-second birthday) . In some embodiments, a pediatric patient is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, f rom six months of age to less than 1 year of age, from 1 year of age to less than 2 y ears of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age t o less than 22 years of age. In some embodiments, the patient is an adult patient.

[0948] Other non-limiting examples of disorders in metabolically important tissues in clude joint disorders (e.g., osteoarthritis, secondary osteoarthritis) , steatosis (e

.g., in the liver) ; gall stones; gallbladder disorders; gastroesophageal reflux; sle ep apnea; hepatitis; fatty liver; bone disorder characterized by altered bone metabol ism, such as osteoporosis, including post-menopausal osteoporosis, poor bone strength, osteopenia, Paget's disease, osteolytic metastasis in cancer patients, ost eodistrophy in liver disease and the altered bone metabolism caused by renal failure or hemodialysis, bone fracture, bone surgery, aging, pregnancy, protection against bo ne fractures, and malnutrition polycystic ovary syndrome; renal disease (e.g., chroni c renal failure, glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hyperten sive nephrosclerosis, end-stage renal disease) ; muscular dystrophy, angina p ectoris, acute or chronic diarrhea, testicular dysfunction, respiratory dysfunction, frailty, sexual dysfunction (e.g., erectile dysfunction) , and geriatric syndrome. In some embodiments, the compounds and pharmaceutical compositions des cribed herein can be used for treating surgical trauma by improving recovery after su rgery and/or by preventing the catabolic reaction caused by surgical trauma.

[0949] Cardiovascular and Vascular Diseases

[0950] In some embodiments, the condition, disease, or disorder is a cardiovascular disease. Non-limiting examples of cardiovascular disease include congestive heart failure, atherosclerosis, arteriosclerosis, coronary heart disease, coronary artery disease, congestive heart failure, coronary heart disease, hypertension, cardiac fail ure, cerebrovascular disorder (e.g., cerebral infarction) , vascular dysfunction, myo cardial infarction, elevated blood pressure (e.g., 130/85 mm Hg or higher) , and prot hrombotic state (exemplified by high fibrinogen or plasminogen activator inhibitor in the blood) .

[0951] In some embodiments, the condition, disease, or disorder is related to a vascular dis ease. Non-limiting examples of vascular diseases include peripheral vascular d isease, macrovascular complications (e.g., stroke) , vascular dysfunction, peripheral artery disease, abdominal aortic aneurysm, carotid artery disease, cerebrovascular d isorder (e.g., cerebral infarction) , pulmonary embolism, chronic venous insufficienc y, critical limb ischemia, retinopathy, nephropathy, and neuropathy.

[0952] Neurological Diseases

[0953] In some embodiments, the condition, disease, or disorder is a neurological disorder (e.g., neurodegenerative disorder) or a psychiatric disorder. Non-limiting examples of neurological disorders include brain insulin resistance, mild cognitive impairmen t (MCI) , Alzheimer's disease (AD) , Parkinson's disease (PD) , anxiety, dementia (e. g., senile dementia) , traumatic brain injury, Huntington's chores, tardive dyskinesi a, hyperkinesia, mania, Morbus Parkinson, steel-Richard syndrome, Down's syndrome, myasthenia gravis, nerve trauma, brain trauma, vascular amyloidosis, cerebral hemorr hage I with amyloidosis, brain inflammation, Friedrich's ataxia, acute confusion diso

rder, amyotrophic lateral sclerosis (ALS) , glaucoma, and apoptosis-mediated degenera tive diseases of the central nervous system (e.g., Creutzfeld-Jakob Disease, bo vine spongiform encephalopathy (mad cow disease) , and chronic wasti ng syndrome) . See, e.g., US2006/0275288A1.

[0954] Non-limiting examples of psychiatric disorders include drug dependence/a ddiction (narcotics and amphetamines and attention deficit/hyperactivity disorder (AD HD) . The compounds and pharmaceutical compositions described herein can be useful in improving behavioral response to addictive drugs, decreasing drug d ependence, prevention drug abuse relapse, and relieving anxiety caused by the absence of a given addictive substance. See, e.g., US2012/0021979A1.

[0955] In some embodiments, the compounds and pharmaceutical compositions d escribed herein are useful in improving learning and memory by enhan cing neuronal plasticity and facilitation of cellular differentiation, and also in pr eserving dopamine neurons and motor function in Morbus Parkinson.

[0956] Insulin-Related Conditions and Disorders

[0957] In some embodiments, the condition, disease, or disorder is impaired fasting glucose (IFG) , impaired fasting glycemia (IFG) , hyperglycemia, insulin resistance (impaired glucose homeostasis) , hyperinsulinemia, elevated blood levels of fatty acids or gly cerol, a hypoglycemic condition, insulin resistant syndrome, paresthesia caused by hy perinsulinemia, hyperlipidemia, hypercholesteremia, impaired wound h ealing, leptin resistance, glucose intolerance, increased fasting glucose, dyslipidem ia (e.g., hyperlipidemia, atherogenic dyslipidemia characterized by high triglyceride s and low HDL cholesterol) , glucagonoma, hyperprolactinemia, hypogl ycemia (e.g., nighttime hypoglycemia) , and concomitant comatose end point associated with insulin.

[0958] In some embodiments, the compounds and pharmaceutical compositions d escribed herein can reduce or slow down the progression of borderline type, impaired fasting glucose or impaired fasting glycemia into diabetes.

[0959] Autoimmune Disorders

[0960] In some embodiments, the condition, disease, or disorder is an autoi mmune disorder. Non-limiting examples of autoimmune disorders include m ultiple sclerosis, experimental autoimmune encephalomyelitis, autoimmune disorder is associated with immune rejection, graft versus host disease, uveitis, op tic neuropathies, optic neuritis, transverse myelitis, inflammatory bowel disease, rh eumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, myasthenia gravis, and Graves' disease. See, e.g., US20120148586A1.

[0961] Stomach and Intestine-Related Disorders

[0962] In some embodiments, the condition, disease, or disorder is a stomach or intestine related disorder. Non-limiting examples of these disorders include ulcers of any etiology (e.g., peptic ulcers, Zollinger-Ellison syndrome, drug-induced ulcers, ulcers related to infections or other pathogens) , digestion disorders, malabsorption, short bowel syndrome, cul-de-sac syndrome, inflammatory bowel diseases (Crohn's disease and ulcerative colitis) , celiac sprue, hypogammaglobulinemic sprue, chemotherapy and/or radiation therapy-induced mucositis and diarrhea, gastrointestinal inflammation, short bowel syndrome, colitis ulcerosa, gastric mucosal injury (e.g., gastric mucosal injury caused by aspirin) , small intestinal mucosal injury, and cachexia (e.g., cancerous cachexia, tuberculous cachexia, cachexia associated with blood disease, cachexia associated with endocrine disease, cachexia associated with infectious disease, and cachexia caused by acquired immunodeficiency syndrome) .

[0963] Body Weight

[0964] In some embodiments, the compounds and pharmaceutical compositions described herein can be used to reduce body weight (e.g., excess body weight) , prevent body weight gain, induce weight loss, decrease body fat, or reduce food intake in a patient (e.g., a patient in need thereof) . In some embodiments, the weight increase in a patient may be attributed to excessive ingestion of food or unbalanced diets, or may be weight increase derived from a concomitant drug (e.g., insulin sensitizers having a PPARγ agonist-like action, such as troglitazone, rosiglitazone, englitazone, ciglitazone, pioglitazone and the like) . In some embodiments, the weight increase may be weight increase before reaching obesity, or may be weight increase in an obese patient. In some embodiments, the weight increase may also be medication-induced weight gain or weight gain subsequent to cessation of smoking.

[0965] In some embodiments, the condition, disease, or disorder is an eating disorder, such as hyperphagia, binge eating, bulimia, or compulsive eating.

[0966] Inflammatory Diseases

[0967] In some embodiments, the condition, disease, or disorder is an inflammatory disorder. Non-limiting examples of inflammatory disorders include chronic rheumatoid arthritis, spondylitis deformans, arthritis deformans, lumbago, gout, post-operational or post-traumatic inflammation, bloating, neuralgia, laryngopharyngitis, cystitis, pneumonia, pancreatitis, enteritis, inflammatory bowel disease (including inflammatory large bowel disease) , inflammation in metabolically important tissues including liver, fat, pancreas, kidney and gut, and a proinflammatory state (e.g., elevated levels of proinflammatory cytokines or markers of inflammation-like C-reactive protein in the blood) .

[0968] Cancer

[0969] In some embodiments, the condition, disease, or disorder is cancer. Suitable examples of cancer include breast cancer (e.g., invasive ductal breast cancer, noninvasive ductal breast cancer, inflammatory breast cancer) , prostate cancer (e.g., hormone-dependent prostate cancer, hormone-independent prostate cancer) , pancreatic cancer (e.g., ductal pancreatic cancer) , gastric cancer (e.g., papillary adenocarcinoma, mucous adenocarcinoma, adenosquamous carcinoma) , lung cancer (e.g., non-small cell lung cancer, small-cell lung cancer, malignant mesothelioma) , colon cancer (e.g., gastrointestinal stromal tumor) , rectal cancer (e.g., gastrointestinal stromal tumor) , colorectal cancer (e.g., familial colorectal cancer, hereditary non-polyposis colorectal cancer, gastrointestinal stromal tumor) , small intestinal cancer (e.g., non-Hodgkin's lymphoma, gastrointestinal stromal tumor) , esophageal cancer, duodenal cancer, tongue cancer, pharyngeal cancer (e.g., nasopharyngeal cancer, oropharynx cancer, hypopharyngeal cancer) , salivary gland cancer, brain tumor (e.g., pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma) , neurilemmoma, liver cancer (e.g., primary liver cancer, extrahepatic bile duct cancer) , renal cancer (e.g., renal cell cancer, transitional cell cancer of the renal pelvis and ureter) , bile duct cancer, endometrial cancer, uterine cervical cancer, ovarian cancer (e.g., epithelial ovarian cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian tumor of low malignant potential) , bladder cancer, urethral cancer, skin cancer (e.g., intraocular (ocular) melanoma, Merkel cell carcinoma) , hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer (e.g., medullary thyroid cancer) , parathyroid cancer, nasal cavity cancer, sinus cancer, bone tumor (e.g., osteosarcoma, Ewing tumor, uterine sarcoma, soft tissue sarcoma) , angiofibroma, sarcoma of the retina, penis cancer, testicular tumor, pediatric solid tumor (e.g., Wilms' tumor, childhood kidney tumor) , Kaposi's sarcoma, Kaposi's sarcoma caused by AIDS, tumor of maxillary sinus, fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, and leukemia (e.g., acute myeloid leukemia, acute lymphoblastic leukemia) .

[0970] Hypothalamic-pituitary disorders

[0971] In some embodiments, the condition, disease, or disorder is related to the hypothalam ic-pituitary-gonadal axis. For example, the condition, disease, or disorder is re lated to the hypothalamus-pituitary-ovary axis. In another example, the condition, dise ase, or disorder is related to the hypothalamus-pituitary-testis axis. Hypothalamic-pituitary-gonadal axis diseases include, but are not limited to, hypogonadism, polycystic ovary syndrome, hypothyroidism, hypopituitarism, sexual dysfunction, and Cushing's disease.

[0972] In some embodiments, the condition, disease, or disorder associated with diabetes is related to the hypothalamic-pituitary-gonadal axis.

[0973] Pulmonary disease

[0974] In some embodiments, the condition, disease, or disorder is related to a pulmonary di sease. Pulmonary diseases include, but are not limited to, asthma, idiopathic pulmona ry fibrosis, pulmonary hypertension, obstructive sleep apnoea-hypopnoea syndrom e, and chronic obstructive pulmonary disease (COPD) (e.g., emphysema , chronic bronchitis, and refractory (non-reversible) asthma) .

[0975] In some embodiments, the condition, disease, or disorder associated with diabetes is a pulmonary disease.

[0976] Combination Therapy

[0977] In some embodiments, this disclosure contemplates both monotherapy r egimens as well as combination therapy regimens.

[0978] In some embodiments, the methods described herein can further includ e administering one or more additional therapies (e.g., one or more additional therap eutic agents and/or one or more therapeutic regimens) in combination with administrat ion of the compounds described herein.

[0979] In some embodiments, the methods described herein include administer ing a compound described herein in combination with one or more of a diet therapy (e. g., dietary monitoring, diet therapy for diabetes) , an exercise therapy (e.g., physi cal activity) , blood sugar monitoring, gastric electrical stimulation (e.g., TANTALUS®) , and diet modifications.

[0980] In some embodiments, the compounds of Formula I, or a pharmaceutical ly acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisom ers, or prodrug thereof as described herein can be administered in combination with o ne or more additional therapeutic agents.

[0981] Representative additional therapeutic agents include, but are not limited to, anti-obesity agents, therapeutic agents for diabetes, therapeutic agents for diabetic comp lications, therapeutic agents for hyperlipidemia, antihypertensive agents, diuretics, chemotherapeutics, immunotherapeutics, anti-inflammatory drugs, antithrombotic agents, anti-oxidants, therapeutic agents for osteoporosis, vitamins, antidementi a drugs, erectile dysfunction drugs, therapeutic drugs for urinary frequency or urina ry incontinence, therapeutic agents for NAFLD, therapeutic agents fo r NASH, therapeutic agents for dysuria and anti-emetic agents.

[0982] In some embodiments, the one or more additional therapeutic agents i nclude those useful, for example, as anti-obesity agents. Non-limiting examples include monoamine uptake inhibitors (e.g., tramadol, phentermine, sibutramine, mazin dol, fluoxetine, tesofensine) , serotonin 2C receptor agonists (e.g., lorcaserin) , s erotonin 6 receptor antagonists, histamine H3 receptor modulator, GA BA modulator (e.g., topiramate) , including GABA receptor agonists (e.g., gabapentin,

pregabalin) , neuropeptide Y antagonists (e.g., velneperit) , cannabinoid receptor a ntagonists (e.g., rimonabant, taranabant) , ghrelin antagonists, ghrelin receptor ant agonists, ghrelin acylation enzyme inhibitors, opioid receptor antagonists (e.g., GSK -1521498) , orexin receptor antagonists, melanocortin 4 receptor agonists, 11β-hydroxysteroid dehydrogenase inhibitors (e.g., AZD-4017, BVT-3498, INCB-13739) , pancreatic lipase inhibitors (e.g., orlistat, cetilistat) , β3 agonists (e.g ., N-5984) , diacylglycerol acyltransferase 1 (DGAT1) inhibitors, acetylCoA c arboxylase (ACC) inhibitors, stearoyl-CoA desaturated enzyme inhibitors, microsomal triglyceride transfer protein inhibitors (e.g., R-256918) , sodium-glucose cotransporter 2 (SGLT-2) inhibitors (e.g., JNJ-28431754, dapagli flozin, AVE2268, TS-033, YM543, TA-7284, ASP1941, remogliflozin) , NF K inhibitors (e.g., HE-3286) , PPAR agonists (e.g., GFT-505, DRF-11605, gemfibrozi l and fenofibrate) , phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate, t rodusquemin) , GPR119 agonists (e.g., PSN-821, MBX-2982, APD597) , g lucokinase activators (e.g., piragliatin, AZD-1656, AZD6370, TTP-355, compounds de scribed in W0006/112549, W0007/028135, W0008/047821, W0008/050821, W 0008/136428 and W0008/156757) , leptin, leptin derivatives (e.g., metreleptin) , lept in resistance improving drugs, CNTF (ciliary neurotrophic factor) , BDNF (brain-derived neurotrophic factor) , cholecystokinin agonists, amylin preparations (e.g., p ramlintide, AC-2307) , neuropeptide Y agonists (e.g., PYY3-36, derivatives o f PYY3-36, obineptide, TM-30339, TM-30335) , oxyntomodulin (OXM) prepa rations, appetite suppressants (e.g., ephedrine) , FGF21 preparations (e.g., animal F GF21 preparations extracted from the pancreas of bovine or swine; hu man FGF21 preparations genetically synthesized using Escherichia coli or yeast; fragm ents or derivatives of FGF21) , anorexigenic agents (e.g., P-57) , human prois let peptide (HIP) , farnesoid X receptor (FXR) agonist, phentermine, zonisamide, nore pinephrine/dopamine reuptake inhibitor, GDF-15 analog, methionine aminopeptida se 2 (MetAP2) inhibitor, diethylpropion, phendimetrazine, benzphetam ine, fibroblast growth factor receptor (FGFR) modulator, and AMP-activated protein kinase (AMPK) activator.

[0983] In some embodiments, the one or more additional therapeutic agents i nclude those useful, for example, as anti-diabetic agents. Non-limiting examples include insulin and insulin preparations (e.g., animal insulin preparations extracte d from the pancreas of bovine or swine; human insulin preparations genetically synthe sized using Escherichia coli or yeast; zinc insulin; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1) , oral insulin preparation, synthetic human insu lin) , insulin sensitizers (e.g., pioglitazone or a salt thereof) , biguanides (e.g., metformin, buformin or a salt thereof (e.g., hydrochloride, fumarate, succinate)) ,

glucagon analogs (e.g., any of glucagon analogs described, e.g., in WO 2010/011439) , agents which antagonize the actions of or reduce secretion of glucagon, sulfonylure a agents (e.g., chlorpropamide, tolazamide, gliclazide, glimepiride, tolbutamide, gli benclamide, gliclazide, acetohexamide, glyclopyramide, glybuzole, glyburide) , thiazo lidinedione agents (e.g., rosiglitazone or pioglitazone) , α-glucosidase inhib itors (e.g., voglibose, acarbose, miglitol, emiglitate) , insulin secretagogues, such as prandial glucose regulators (sometimes called "short-acting secretagog ues") , e.g., meglitinides (e.g., repaglinide and nateglinide) , cholinesterase inhi bitors (e.g., donepezil, galantamine, rivastigmine, tacrine) , NMDA receptor antagoni sts, dual GLP-1/GIP receptor agonists (e.g., LBT-2000, ZPD1-70) , GLP-1R agonists (e.g., exenatide, liraglutide, albiglutide, dulaglutide, abiglutide, tasp oglutide, lixisenatide, semaglutide, AVE-0010, S4P and Boc5) , and dipeptid yl peptidase IV (DPP-4) inhibitors (e.g., vildagliptin, dutogliptin, gemigliptin, aloglip tin, saxagliptin, sitagliptin, linagliptin, berberine, adogliptin, BI1356, GRC8200, MP-513, PF-00734200, PHX1149, SK-0403, ALS2-0426, TA-6666, TS-021, KRP-104, trelagliptin) .

[0984] In some embodiments, the one or more additional therapeutic agents i nclude those useful, for example, for treating NAFL and NASH. Non-limiting examples include FXR agonists, PF-05221304, a synthetic fatty acid-bile conjugate, an anti-lysyl oxidase homologue 2 (LOXL2) monoclonal antibo dy, a caspase inhibitor, a MAPK5 inhibitor, a galectin 3 inhibitor, a fibroblast grow th factor 21 (FGF21) , a niacin analogue, a leukotriene D4 (LTD4) receptor antagonist , an acetyl-CoA carboxylase (ACC) inhibitor, a ketohexokinase (KHK) inhibitor, a n apoptosis signal-regulating kinase 1 (ASK1) inhibitor, an ileal bile acid transporter (IBAT) inhibitor, glycyrrhizin, Schisandra extract, ascorbic acid, glutathione, sily marin, lipoic acid, and d-alpha-tocopherol, ascorbic acid, glutathione, vitamin B-complex, glitazones/thiazolidinediones (e.g., troglitazone, rosiglitazone, pioglitazo ne) , metformin, cysteamine, sulfonylureas, alpha-glucosidase inhibitors, meglitinid es, vitamin E, tetrahydrolipstatin, milk thistle protein, anti-virals, and anti-oxidants.

[0985] In some embodiments, the one or more additional therapeutic agents i nclude those useful, for example, for treating diabetic complications. Non-limiting examples include aldose reductase inhibitors (e.g., tolrestat, epalrestat, z opolrestat, fidarestat, CT-112, ranirestat, lidorestat) , neurotrophic factor and increasing agents thereof (e.g., NGF, NT-3, BDNF, neurotrophic production/s ecretion promoting agents described in WO01/14372 (e.g., 4- (4-chlorophenyl) -2- (2-methyl-1-imidazolyl) -5- [3- (2-methylphenoxyl) propyl] oxazole) , compounds descri bed in WO2004/039365) , PKC inhibitors (e.g., ruboxistaurin mesylate) , AGE inhibitors (e.g., ALT946, N-phenacylthiazolium bromide (ALT766) , EXO-

226, pyridorin, pyridoxamine) , serotonin and noradrenalin reuptake inhibitors (e.g., duloxetine) , sodium channel inhibitors (e.g., lacosamide) , active oxygen scavengers (e.g., thioctic acid) , cerebral vasodilators (e.g., tiapuride, mexiletine) , somatostatin receptor agonists (e.g., BIM23190) , and apoptosis signal regulating kinase-1 (ASK-1) inhibitors.

[0986] In some embodiments, the one or more additional therapeutic agents include those useful, for example, for treating hyperlipidemia. Non-limiting examples include HMG-COA reductase inhibitors (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, rosuvastatin, pitavastatin or a salt thereof (e.g., sodium salt, calcium salt)) , squalene synthase inhibitors (e.g., compounds described in WO97/10224, e.g., N- [[(3R, 5S) -1- (3-acetoxy-2, 2-dimethylpropyl) -7-chloro-5- (2, 3-dimethoxyphenyl) -2-oxo-1, 2, 3, 5-tetrahydro-4, 1-benzoxazepin-3-yl] acetyl] piperidin-4-acetic acid) , fibrate compounds (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate) , anion exchange resin (e.g., colestyramine) , nicotinic acid drugs (e.g., nicomol, niceritrol, niaspan) , phytosterols (e.g., soy sterol, gamma oryzanol (γ-oryzanol)) , cholesterol absorption inhibitors (e.g., zechia) , CETP inhibitors (e.g., dalcetrapib, anacetrapib) and ω-3 fatty acid preparations (e.g., ω-3-fatty acid ethyl esters 90) .

[0987] In some embodiments, the one or more additional therapeutic agents include those useful, for example, as anti-hypertensive agents. Non-limiting examples include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril) , angiotensin II antagonists (e.g., candesartan cilexetil, candesartan, losartan, losartan potassium, eprosartan, valsartan, telmisartan, irbesartan, tasosartan, olmesartan, olmesartan medoxomil, azilsartan, azilsartan medoxomil) , calcium antagonists (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine, cilnidipine) and β-blockers (e.g., metoprolol, atenolol, propranolol, carvedilol, pindolol) .

[0988] In some embodiments, the one or more additional therapeutic agents include those useful, for example, as diuretics. Non-limiting examples include xanthine derivatives (e.g., theobromine sodium salicylate, theobromine calcium salicylate) , thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penfluthiazide, polythiazide, methyclothiazide) , antialdosterone preparations (e.g., spironolactone, triamterene) , carbonic anhydrase inhibitors (e.g., acetazolamide) and chlorobenzenesulfonamide agents (e.g., chlortalidone, mefruside, indapamide) .

[0989] In some embodiments, the one or more additional therapeutic agents include those useful, for example, as immunotherapeutic agents. Non-limiting examples include microbial or bacterial compounds (e.g., muramyl dipeptide derivative, picibanil) , polysaccharides having immunoenhancing activity (e.g., lentinan, sizofiran, kr

estin) , cytokines obtained by genetic engineering approaches (e.g., interferon, inte rleukin (IL) such as IL-1, IL-2, IL-12) , and colony-stimulating factors (e.g., granulo cyte colony-stimulating factor, erythropoietin) .

[0990] In some embodiments, the one or more additional therapeutic agents i nclude those useful, for example, as anti-thrombotic agents. Non-limiting examples include heparins (e.g., heparin sodium, heparin calcium, enoxaparin sodium, daltepar in sodium) warfarin (e.g., warfarin potassium) ; anti-thrombin drugs (e.g., aragatroban, dabigatran) FXa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, betrixaban, YM150 , compounds described in WO02/06234, WO2004/048363, WO2005/030740, W O2005/058823, and WO2005/113504) thrombolytic agents (e.g., urokinas e, tisokinase, alteplase, nateplase, monteplase, pamiteplase) , and platelet aggregat ion inhibitors (e.g., ticlopidine hydrochloride, clopidogrel, prasugrel, E5555, SHC53 0348, cilostazol, ethyl icosapentate, beraprost sodium, and sarpogrelate hydrochlorid e) .

[0991] In some embodiments, the one or more additional therapeutic agents i nclude those useful, for example, for treating osteoporosis. Non-limiting examples include alfacalcidol, calcitriol, elcatonin, calcitonin salmon, estriol, ipriflavone , pamidronate disodium, alendronate sodium hydrate, incadronate diso dium, and risedronate disodium. Suitable examples of vitamins includ e vitamin B1 and vitamin B12. Suitable examples of erectile dysfunction drugs include apomorphine and sildenafil citrate. Suitable examples of therapeutic agents for urin ary frequency or urinary incontinence include flavorxate hydrochlori de, oxybutynin hydrochloride and propiverine hydrochloride. Suitable examples of ther apeutic agents for dysuria include acetylcholine esterase inhibitors (e.g., distigmin e) . Suitable examples of anti-inflammatory agents include nonsteroidal anti-inflammatory drugs such as aspirin, acetaminophen, indomethacin.

[0992] Other exemplary additional therapeutic agents include agents that modulate hepatic glucose balance (e.g., fructose 1, 6-bisphosphatase inhibitors, glycogen phosphorylase inhibitors, glycogen synthase kinase inhibitors, glucokinase activators) , agents designed to treat the complications of prolonged hyperglycemia, such as aldose reductase inhibitors (e.g., epalrestat and ranirestat) , agents used to treat complications related to micro-angiopathies, anti-dyslipidemia agents, such as HMG-CoA reductase inhibitors (statins, e.g., rosuvastatin) , cholesterol-lowering agents, bile acid sequestrants (e.g., cholestyramine) , cholesterol absorption inhibitors (e.g., plant sterols such as phytosterols) , cholesteryl ester transfer protein (CETP) inhibitors, inhibitors of the ileal bile acid transport system (IBAT inhibitors) , bile acid binding resins, nicotinic acid (niacin) and analogues thereof, anti-oxidants (e.g., probucol) , omega-3 fatty acids, antihypertensive agents, including adrenergic

receptor antagonists, such as beta blockers (e.g., atenolol) , alpha blockers (e.g., doxazosin) , and mixed alpha/beta blockers (e.g., labetalol) , adrenergic receptor agonists, including alpha-2 agonists (e.g., clonidine) , angiotensin converting enzyme (ACE) inhibitors (e.g., lisinopril) , calcium channel blockers, such as dihydropyridines (e.g., nifedipine) , phenylalkylamines (e.g., verapamil) , and benzothiazepines (e.g., diltiazem) , angiotensin II receptor antagonists (e.g., candesartan) , aldosterone receptor antagonists (e.g., eplerenone) , centrally acting adrenergic drugs, such as central alpha agonists (e.g., clonidine) , diuretic agents (e.g., furosemide) , haemostasis modulators, including antithrombotics (e.g., activators of fibrinolysis) , thrombin antagonists, factor VIIa inhibitors, anticoagulants (e.g., vitamin K antagonists such as warfarin) , heparin and low molecular weight analogues thereof, factor Xa inhibitors, and direct thrombin inhibitors (e.g., argatroban) , antiplatelet agents (e.g., cyclooxygenase inhibitors (e.g., aspirin)) , adenosine diphosphate (ADP) receptor inhibitors (e.g., clopidogrel) , phosphodiesterase inhibitors (e.g., cilostazol) , glycoprotein IIB/IIA inhibitors (e.g., tirofiban) , adenosine reuptake inhibitors (e.g., dipyridamole) , noradrenergic agents (e.g., phentermine) , serotonergic agents (e.g., sibutramine) , diacyl glycerolacyltransferase (DGAT) inhibitors, feeding behavior modifying agents, pyruvate dehydrogenase kinase (PDK) modulators, serotonin receptor modulators, monoamine transmission-modulating agents, such as selective serotonin reuptake inhibitors (SSRI) (e.g., fluoxetine) , noradrenaline reuptake inhibitors (NARI) , noradrenaline-serotonin reuptake inhibitors (SNRI) , and monoamine oxidase inhibitors (MAOI) (e.g., toloxatone and amiflamine) , compounds described in W0007/013694, WO2007/018314, WO2008/093639 and WO2008/099794, GPR40 agonists (e.g., fasiglifam or a hydrate thereof, compounds described in WO2004/041266, WO2004/106276, WO2005/063729, WO2005/063725, WO2005/087710, WO2005/095338, WO2007/013689 and WO2008/001931) , SGLT1 inhibitors, adiponectin or agonist thereof, IKK inhibitors (e.g., AS-2868) , somatostatin receptor agonists, ACC2 inhibitors, cachexia-ameliorating agents, such as a cyclooxygenase inhibitors (e.g., indomethacin) , progesterone derivatives (e.g., megestrol acetate) , glucocorticoids (e.g., dexamethasone) , metoclopramide agents, tetrahydrocannabinol agents, agents for improving fat metabolism (e.g., eicosapentaenoic acid) , growth hormones, IGF-1, antibodies against a cachexia-inducing factor TNF-α, LIF, IL-6, and oncostatin M, metabolism-modifying proteins or peptides such as glucokinase (GK) , glucokinase regulatory protein (GKRP) , uncoupling proteins 2 and 3 (UCP2 and UCP3) , peroxisome proliferator-activated receptor α (PPARα) , MC4r agonists, insulin receptor agonist, PDE 5 inhibitors, glycation inhibitors (e.g., ALT-711) , nerve regeneration-promoting drugs (e.g., Y-128, VX853, prosaptide) , antidepressants (e.g., desipramine, amitriptyline, imipramine) ,

antiepileptic drugs (e.g., lamotrigine, trileptal, keppra, zonegran, pregabalin, harkoseride, carbamazepine) , antiarrhythmic drugs (e.g., mexiletine) , acetylcholine receptor ligands (e.g., ABT-594) , endothelin receptor antagonists (e.g., ABT-627) , narcotic analgesics (e.g., morphine) , α2 receptor agonists (e.g., clonidine) , local analgesics (e.g., capsaicin) , antianxiety drugs (e.g., benzothiazepine) , phosphodiesterase inhibitors (e.g., sildenafil) , dopamine receptor agonists (e.g., apomorphine) , cytotoxic antibodies (e.g., T-cell receptor and IL-2 receptor-specific antibodies) , B cell depleting therapies (e.g., anti-CD20 antibody (e.g., rituxan) , i-BLyS antibody) , drugs affecting T cell migration (e.g., anti-integrin alpha 4/beta 1 antibody (e.g., tysabri) , drugs that act on immunophilins (e.g., cyclosporine, tacrolimus, sirolimus, rapamicin) , interferons (e.g., IFN-β) , immunomodulators (e.g., glatiramer) , TNF-binding proteins (e.g., circulating receptors) , immunosupressants (e.g., mycophenolate) , and metaglidasen, AMG-131, balaglitazone, MBX-2044, rivoglitazone, aleglitazar, chiglitazar, lobeglitazone, PLX-204, PN-2034, GFT-505, THR-0921, exenatide, exendin-4, memantine, midazolam, ketoconazole, ethyl icosapentate, clonidine, azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide, etoposide, piroxicam, NO donating agents (e.g., organonitrates) , and NO promoting agents (e.g., phosphodiesterase inhibitors) .

[0993] In some embodiments, the one or more additional therapeutic agents i nclude those useful, for example, as anti-emetic agents. As used herein, an “anti-emetic” agent refers to any agent that counteracts (e.g., reduces or removes) nausea or emesis (vomiting) . It is to be understood that when referring to a therapeutically effective amount of an anti-emetic agent, the amount administe red is an amount needed to counteract (e.g., reduce or remove) nausea or emesis (vomi ting) . While not wishing to be bound by theory, it is believed that administering on e or more anti-emetic agents in combination with the formula (I) compounds describe d herein may allow higher dosages of the formula (I) compounds to be administered, e. g., because the patient may be able to have a normal food intake and thereby respond faster to the treatment.

[0994] Non-limiting examples of anti-emetic agents include 5HT3-receptor antagoni sts (serotonin receptor antagonists) , neuroleptics/anti-psychotics, antih istamines, anticholinergic agents, steroids (e.g., corticosteroids) , NK1 -receptor antagonists (e.g., Neurokinin 1 substance P receptor antagonists) , antidopa minergic agents/dopamine receptor antagonists, benzodiazepines, cannabinoids.

[0995] For example, the antiemetic agent can be selected from the group con sisting of; neuroleptics, antihistamines, anti-cholinergic agents, steroids, 5HT-3-receptor antagonists, NK1 -receptor antagonists, anti-dopaminergic agents/ dopamine receptor antagonists, benzodiazepines and non-psychoactive cannabinoids.

[0996] In some embodiments, the anti-emetic agent is a 5HT3-receptor antagonist (serotonin receptor antagonist) . Non-limiting examples of 5HT3-receptor antagonists (serotonin receptor antagonists) include: Granisetron (Kytril) , Dolasetron, Ondansetron (Zofran) , Tropisetron, Ramosetron, Palonosetron, Alosetron, azasetron, Bemesetron, Zatisetron, Batanopirde, MDL-73147EF; Metoclopramide, N-3389 (endo-3, 9-dimethyl-3, 9-diazabicyclo [3, 3, 1] non-7-yl-1 H-indazole-3-carboxamide dihydrochloride) , Y-25130 hydrochloride, MDL 72222, Tropanyl-3, 5-dimethylbenzoate, 3- (4-Allylpiperazin-1-yl) -2-quinoxalinecarbonitrile maleate, Zacopride hydrochloride, and Mirtazepine. Other non-limiting examples of 5HT3-receptor antagonists (serotonin receptor antagonists) include: cilansetron, clozapine, cyproheptadine, dazopride, hydroxyzine, lerisetron, metoclopramide, mianserin, olanzapine, palonosetron (+ netupitant) , quetiapine, qamosetron, ramosteron, ricasetron, risperidone, ziprasidone, and zatosetron.

[0997] In certain embodiments, the 5HT-3-receptor antagonist is Granisetron, Dolasetron, Ondansetron hydrochloride, Tropisetron, Ramosetron, Palonosetron, Alosetron, Bemesetron, Zatisetron, Batanopirde, MDL-73147EF, Metoclopramide, N-3389, Y-25130 hydrochloride, MDL 72222, Tropanyl-3, 5-dimethylbenzoate 3- (4-AIIyI-piperazin-1-yl) -2-quinoxalinecarbonitrile maleate, Zacopride hydrochloride and Mirtazepine.

[0998] In certain embodiments, the 5HT-3-receptor antagonist is Granisetron, Dolasetron, Ondansetron hydrochloride, Tropisetron, Ramosetron, Palonosetron, Alosetron, Bemesetron, and Zatisetron.

[0999] In certain embodiments, the 5HT-3-receptor antagonist is Granisetron, Dolasetron and Ondansetron.

[1000] In certain embodiments, the 5HT-3-receptor antagonist is Granisetron.

[1001] In certain embodiments, the 5HT-3-receptor antagonist is Ondansetron.

[1002] In some embodiments, the anti-emetic agent is an antihistamine. Non-limiting examples of antihistamines include: piperazine derivatives (e.g., cyclizine, meclizine, and cinnarizine) ; Promethazine; Dimenhydrinate (Dramamine, Gravol) ; Diphenhydramine; Hydroxyzine; Buclizine; and Meclizine hydrochloride (Bonine, Antivert) , doxylamine, and mirtazapine.

[1003] In some embodiments, the anti-emetic agent is an anticholinergic agent (Inhibitors of the acetylcholine receptors) . Non-limiting examples of anticholinergic agents include: atropine, Scopolamine, Glycopyrron, Hyoscine, Artane (Trihexy-5 trihexyphenidyl hydrochloride) , Cogentin (benztropine mesylate) , Akineton (biperiden hydrochloride) , Disipal (Norflex orphenadrine citrate) , diphenhydramine, hydroxyzine, hyoscyamine, and Kemadrin (procyclidine hydrochloride) .

[1004] In some embodiments, the anti-emetic agent is a steroid (e.g., a corticosteroid) . Non-limiting examples of steroids include: betamethasone, Dexamethasone, Methylprednisolone, Prednisone®, and Trimethobenzamide (Tigan) .

[1005] In some embodiments, the anti-emetic agent is an NK1 -receptor antagonists (e.g., Neurokinin 1 substance P receptor antagonists) . Non-limiting examples of NK1 -receptor antagonists include: aprepitant, casopitant, ezlopitant, fosaprepitant, maropitant, netupitant, rolapitant, and vestipitant.

[1006] Other non-limiting examples of NK1 -receptor antagonists include: MPC-4505, GW597599, MPC-4505, GR205171, L-759274, SR 140333, CP-96, 345, BIIF 1149, NKP 608C, NKP 608A, CGP 60829, SR 140333 (Nolpitantium besilate/chloride) , LY 303870 (Lanepitant) , MDL-105172A, MDL-103896, MEN-11149, MEN-11467, DNK 333A, YM-49244, YM-44778, ZM-274773, MEN-10930, S-19752, Neuronorm, YM-35375, DA-5018, MK-869, L-754030, CJ-11974, L-758298, DNK-33A, 6b-l, CJ-11974 j. Benserazide and carbidopa k. TAK-637 [(aR, 9R) -7- [3, 5-bis (trifluoromethyl) benzyl] -8, 9, 10, 11-tetrahydro-9-methyl-5- (4-methylphenyl) -7H- [1 , 4] diazocino [2, 1-g] [1 , 7] naphthyridine-6, 13-dione] , PD 154075, ([(2-benzofuran) -CH2OCO] - (R) -alpha-MeTrp- (S) -NHCH (CH_3) Ph) , FK888, and (D-Pro4, D-Trp7, 9, 10, Phe11) SP4-11.

[1007] In some embodiments, the anti-emetic agent is an anti-dopaminergic agents/dopamine receptor antagonist (e.g., dopamine receptor antagonist, e.g., D2 or D3 antagonists) . Non-limiting examples include phenothiazines (e.g., promethazine, chlorpromazine, prochlorperazine, perphenazine, hydroxyzine, thiethylperazine, metopimazine,) ; benzamides (e.g., Metoclopramide, domperidone) , butyrophenones (e.g., haloperidol, droperidol) ; alizapride, bromopride, clebopride, domperidone, itopride, metoclopramide, trimethobenzamide, and amisulpride.

[1008] In some embodiments, the anti-emetic agent is a non-psychoactive cannabinoids (e.g., Cannabidiol (CBD) , Cannabidiol dimethylheptyl (CBD-DMH) , Tetrahydro-cannabinol (THC) , Cannabinoid agonists such as WIN 55-212 (aCB1 and CB2 receptor agonist) , Dronabinol (Marinol®), and Nabilone (Cesamet)) .

[1009] Other exemplary anti-emetic agents include: c-9280 (Merck) ; benzodiazepines (diazepam, midazolam, lorazepam) ; neuroleptics/anti-psychotics (e.g., dixyrazine, haloperidol, and Prochlorperazine (Compazine®));cerium oxalate; propofol; sodium citrate; dextrose; fructose (Nauzene) ; orthophosphoric acid; fructose; glucose (Emetrol) ; bismuth subsalicylate (Pepto Bismol) ; ephedrine; vitamin B6;

[1010] peppermint, lavender, and lemon essential oils; and ginger.

[1011] Still other exemplary anti-emetic agents include those disclosed in US 2012010 1089A1; US 10,071,088 B2; US 6,673,792 B1; US 6,197,329 B1; US 10,82 8,297 B2; US 10,322,106 B2; US 10,525,033 B2; WO 2009080351

A1; WO 2019203753 A2; WO 2002020001 A2; US 8,119,697 B2; US 5,039,528; US20090305964A1; and WO 2006/111169, each of which is incorporated by reference in its entirety.

[1012] In some embodiments, the additional therapeutic agent or regimen is administered to the patient prior to contacting with or administering the compounds and pharmaceutical compositions (e.g., about one hour prior, or about 6 hours prior, or about 12 hours prior, or about 24 hours prior, or about 48 hours prior, or about 1 week prior, or about 1 month prior) .

[1013] In some embodiments, the additional therapeutic agent or regimen is administered to the patient at about the same time as contacting with or administering the compounds and pharmaceutical compositions. By way of example, the additional therapeutic agent or regimen and the compounds and pharmaceutical compositions are provided to the patient simultaneously in the same dosage form. As another example, the additional therapeutic agent or regimen and the compounds and pharmaceutical compositions are provided to the patient concurrently in separate dosage forms.

[1014] Patient Selection

[1015] In some embodiments, the methods described herein further include the step of identifying a patient (e.g., a subject) in need of such treatment (e.g., by way of blood assay, body mass index, or other conventional method known in the art) .

[1016] In some embodiments, the methods described herein further include the step of identifying a patient (e.g., patient) that has a disease, disorder, or condition as provided here (e.g., a GLP-1 associated disease, disorder, or condition) .

[1017] In some embodiments, the methods described herein further include the step of identifying a patient (e.g., patient) that has type 2 diabetes mellitus. In some embodiments, determining if the patient has type 2 diabetes mellitus includes performing an assay to determine the level of hemoglobin A1c (HbA1c), fasting plasma glucose, non-fasting plasma glucose, or any combination thereof. In some embodiments, the level of HbA1c is about 6.5%to about 24.0%. In some embodiments, the level of HbA1c is greater than or about 6.5%. In some embodiments, the level of HbA1c is greater than or about 8.0%. In some embodiments, the level of HbA1c is greater than or about 10.0%. In some embodiments, the level of HbA1c is greater than or about 12.0%. In some embodiments, the level of HbA1c is greater than or about 14.0%. In some embodiments, the level of HbA1c is greater than or about 16.0%. In some embodiments, the level of HbA1c is greater than or about 18.0%. In some embodiments, the level of HbA1c

is greater than or about 20.0%. In some embodiments, the level of HbA1c is greater th an or about 22.0%. In some embodiments, the level of HbA1c is greate r than or about 24.0%.

[1018] In some embodiments, the level of fasting plasma glucose is greater than or about 120 mg/dL to greater than or about 750 mg/dL. In some embodiments, the level of fasting plasma glucose is greater than or about 200 mg/ dL to greater than or about 500 mg/dL. In some embodiments, the level of fa sting plasma glucose is greater than or about 300 mg/dL to greater than or about 700 mg/dL.

[1019] In some embodiments, the level of non-fasting plasma glucose is greater than or about 190 mg/dL to greater than or about 750 mg/dL. In some embodiments, the level of non-fasting plasma glucose is greater than or about 250 mg/dL to greater than or about 450 mg/dL. In some embodiments, the level of non-fasting plasma glucose is greater than or about 400 mg/dL to greater than or about 70 0 mg/dL.

[1020] In some embodiments, determining if the patient has type 2 diabetes mellitus further includes determining the patient's BMI. In some embodiments, the BMI of the patient is greater than or about 22 kg/m2 to greater than or about 100 kg/ m2. In some embodiments, the BMI of the patient is greater than or about 30 kg/ m2 to greater than or about 90 kg/m2. In some embodiments, the BMI of the pat ient is greater than or about 40 kg/m2 to greater than or about 80 kg/m2. In some emb odiments, the BMI of the patient is greater than or about 50 kg/m2 to greater than or about 70 kg/m2.

[1021] In some embodiments, additional factors (e.g., risk factors) used for determining if the patient has type 2 diabetes mellitus further includes age and ethnicity of the patient. In some embodiments, the patient's age is greater than or about 10 years. In some embodiments, the patient's age is greater than or about 15 years. In some embodiments, the patient's age is greater than or about 20 years. In some embodiments, the patient's age is greater than or about 25 years. In some embodiments, the patient's age is greater than or about 30 years. In some embodiments, the patient's age is greater than or about 35 years. In some embodiments, the patient's age is greater than or about 40 years. In some embodiments, the patient's age is greater than or about 42 years. In some embodiments, the patient's age is greater than or about 44 years. In some embodiments, the patient's age is greater than or about 46 years. In some embodiments, the patient's age is greater than or about 48 years. In some embodiments, the patient's age is greater than or about 50 years. In some embodiments, the patient's age is greater than or about

52 years. In some embodiments, the patient's age is greater than or about 54 years. In some embodiments, the patient's age is greater than or about 56 years. In some embodiments, the patient's age is greater than or about 58 years. In some embodiments, the patient's age is greater than or about 60 years. In some embodiments, the patient's age is greater than or about 62 years. In some embodiments, the patient's age is greater than or about 64 years. In some embodiments, the patient's age is greater than or about 66 years. In some embodiments, the patient's age is greater than or about 68 years. In some embodiments, the patient's age is greater than or about 70 years. In some embodiments, the patient's age is greater than or about 72 years. In some embodiments, the patient's age is greater than or about 74 years. In some embodiments, the patient's age is greater than or about 76 years. In some embodiments, the patient's age is greater than or about 78 years. In some embodiments, the patient's age is greater than or about 80 years. In some embodiments, the patient's age is greater than or about 85 years. In some embodiments, the patient's age is greater than or about 90 years. In some embodiments, the patient's age is greater than or about 95 years. In some e mbodiments, the ethnicity of the patient may be African American, Am erican Indian or Alaska Native, Asian American, Hispanics or Latinos , or Native Hawaiian or Pacific Islander.

[1022] General Synthetic Methods

[1023] The compounds of this disclosure can be prepared from readily availa ble starting materials using, for example, the following general methods, and procedu res. It will be appreciated that where certain process conditions (i.e., reaction tem peratures, times, mole ratios of reactants, solvents, pressures, etc.) are given, ot her process conditions can also be used unless otherwise stated. Optimum reaction con ditions may vary with the reactants or solvent used, but such conditions can be deter mined by one skilled in the art by routine optimization procedures.

[1024] Additionally, as will be apparent to those skilled in the art, conventional protectin g groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional gro ups as well as suitable conditions for protecting and deprotecting certain functional groups are well known in the art. For example, numerous protecting groups are descri bed in T.W. Greene and G.M. Wuts (1999) Protecting Groups in Organic Synthesis, 3rd Edition, Wiley, New York, and references cited therein.

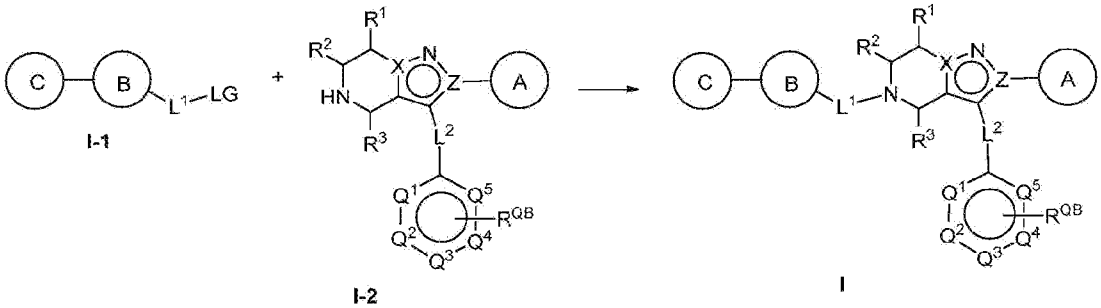
[1025] Furthermore, the compounds of this disclosure may contain one or mor e chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stere

oisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) ar e included within the scope of this disclosure, unless otherwise indicated. Pure ster eoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, r acemic mixtures of such compounds can be separated using, for exampl e, chiral column chromatography, chiral resolving agents, and the like.

[1026] The starting materials for the following reactions are generally kno wn compounds or can be prepared by known procedures or obvious modif ications thereof. For example, many of the starting materials are available from comm ercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA) , Bachem (Torrance CA USA) , EMKA-Chemie Gmbh & Co. KG (Eching Germany) , or Millipore Sigma (Burlington MA USA) . Othe rs may be prepared by procedures, or obvious modifications thereof, described in stan dard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volu mes 1-15 (John Wiley, and Sons, 1991) , Rodd's Chemistry of Carbon Compoun ds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989) , Organic R eactions, Volumes 1-40 (John Wiley, and Sons, 1991) , March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001) , and Larock's Com prehensive Organic Transformations (VCH Publishers Inc., 1989) .

[1027] Scheme I illustrates a general method which can be employed for the synthesis of compounds described herein, where ring A, ring B, ring C, X, Z, Q^1, Q^2, Q^3, Q^4, Q^5, L^1, L^2, R^1, R^2, R^3, and R^{QB} are each independently as define d herein, and LG is a leaving group, such as halo (e.g., hydroxy, alkoxy, halo, etc.) .

[1028] Scheme I



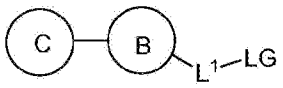
[1029] Compounds of Formula I can be provided by coupling compound I-1 with compound I-2 under suitable coupling reaction conditions, such as amide bond forming reaction conditions or nucleophilic substitution reaction cond itions reaction conditions. Further derivatization can be performed of the resulting product via methods and chemical transformations which are known to those of skill in the art can provide alternative compounds of Formula I. For example , when the leaving group is an electrophile, such as an aldehyde, the coupling reacti

on conditions may comprise reductive amination reaction conditions. Thus, the convers ion may comprise more than one reaction or set of reactants.

[1030] Upon reaction completion, compounds of Formula I can be recovered by conventional techniques such as neutralization, extraction, precipitation, chromatog raphy, filtration and the like. In certain embodiments, when control of stereochemist ry is desired, proper control of reaction conditions and selection of substituents fo r the reagents can at least partially dictate or preserve the formation of the variou s stereoisomers.

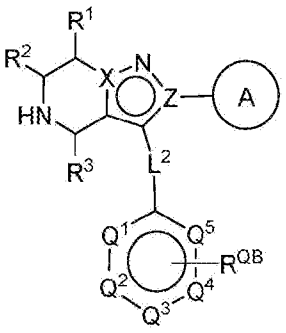
[1031] In some embodiments, the various substituents of Formula I-1 or I-2 are as defined herein. However, derivatization thereof prior to reacting in any step, and/or further derivatization of the resulting reaction product, provides various compounds of Form ula I. Appropriate starting materials and reagents can be purchased or prepared by me thods known to one of skill in the art. Upon each reaction completion, each of the in termediate or final compounds can be recovered, and optionally purified, by conventio nal techniques such as neutralization, extraction, precipitation, chromatography, fil tration, and the like. Other modifications to arrive at compounds of this disclosure are within the skill of the art.

[1032] In some embodiments, provided is a process for preparing a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, st ereoisomer, mixture of stereoisomers, or prodrug thereof, comprising contacting a com pound of Formula I-1:



I-1

[1033] with a compound of Formula I-2:



I-2

[1034] wherein ring A, ring B, ring C, X, Z, Q^1, Q^2, Q^3, Q^4, Q^5, L^1, L^2, R^1, R^2, R^3, and R^{QB} are as defined herein, and LG is a leaving group, under conditions sufficient to pro vide the compound of Formula I, or a pharmaceutically acceptable salt, isotopically e nriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[1035] In some embodiments, the process further comprises a hydrolysis or transesterificatio n step prior to or after the contacting. In some embodiments, the process comprises a base. In some embodiments, the process comprises elevated temperature.

[1036] EXAMPLES

[1037] This disclosure is further understood by reference to the following examples, which a re intended to be purely exemplary of the disclosure. The present disclosure is not l imited in scope by the exemplified embodiments, which are intended as illustrations o f single aspects of the disclosure only. Any methods that are functionally equivalent are within the scope of the disclosure. Various modifications of the disclosure in a ddition to those described herein will become apparent to those skilled in the art fr om the foregoing description and accompanying figures. Such modifica tions fall within the scope of the appended claims.

[1038] Abbreviations (as used herein) :

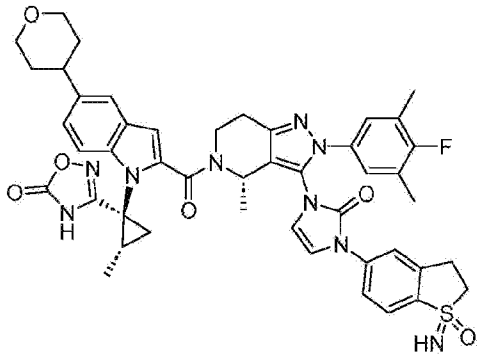
CCl_4	carbon tetrachloride
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
CuI	cuprous iodide
DCM or CH_2Cl_2	dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-dimethyl-formamide
EtOAc	ethyl acetate
EtOH	ethanol
h	hour

HATU	2-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl	hydrochloric acid
$H_2NCO_2NH_4$	ammonium carbamate
H_2O	water
K_2CO_3	potassium carbonate
LiHMDS	lithium bis(trimethylsilyl)amide
MeOH	methanol
MeSNa	sodium methanethiolate
MeI	iodomethane
$NaBH_4$	sodium borohydride
NaH	sodium hydride
Na_2SO_4	sodium sulfate
NMP	*N*-Methyl-2-pyrrolidone
$PhI(OAc)_2$	(diacetoxyiodo)benzene
PE	Petrol ether
prep. HPLC	Preparative High Performance Liquid Chromatography
rt	room temperature
SFC	Supercritical Fluid Chromatography
THF	tetrahydrofuran
TEA or Et_3N	triethylamine
TFA	trifluoroacetic acid

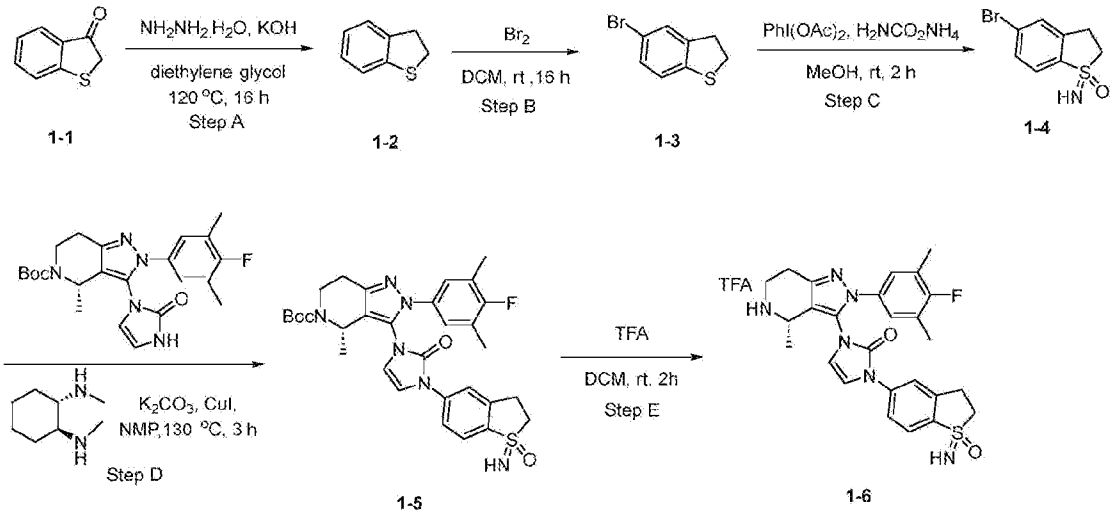
[1039] General information: All evaporations or concentrations were carried out in vacuo with a rotary evaporator. Analytical samples were dried in vacuo (1-5 mmHg) at rt. Thin layer chromatography (TLC) was performed on sili ca gel plates, spots were visualized by UV light (214 and 254 nm) . Purification by c olumn and flash chromatography was carried out using silica gel (100-200 mesh) . Solvent systems were reported as mixtures by volume. NMR spectra were recorded on a Bruker 400 or Varian (400 MHz) spectrometer. ^{1}H chemical shifts are reported in δ values in ppm with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s= sin glet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) , coupling co nstant (Hz) , integration. LCMS spectra were obtained on SHIMADZU LC 20-MS2020 or Agilent 1260 series 6125B mass spectrometer or Agilent 120 0 series, 6110 or 6120 mass spectrometer with electrospray ionization and excepted as otherwise indicated.

[1040] Example A1

[1041] 3- [(1S, 2S) -1- (2- { [(4S) -3- [3- (1-azanylidene-1-oxo-2, 3-dihydro-1λ^6-benzo [b] thiophen-5-yl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 101)

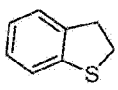


Compound 101



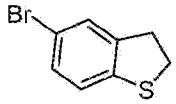
Compound 101

[1042] Step A 2, 3-dihydrobenzo [b] thiophene



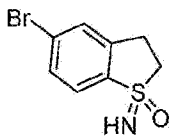
[1043] To a solution of 2, 3-dihydrobenzo [b] thiophen-3-one (500 mg, 3.32 9 mmol) in EtOH (8 mL) was added N_2H_4 hydrate (2.6 mL) . The mixture wa s heated to reflux and stir for 45 min. The mixture was allowed to cool to rt and the n concentrated. The residue was dissolved in diethylene glycol (20 m L) and KOH (560 mg, 9.987 mmol) was added. The resulting mixture was stirred at 120 ℃ for 16 h. The mixture was cooled to rt, diluted with EtOAc (50 mL) and the pH was adjusted with 1 M aq. HCl to pH <4. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated . The residue was purified by flash silica gel chromatography (Silica Flash Column, E luent of 0～10%EtOAc/PE gradient) to obtain 2, 3-dihydrobenzo [b] thiophene (347 mg, 76.5%yield) . ^{1}H NMR (400 MHz, DMSO-d6) δ 7.26 - 7.17 (m, 2H) , 7.11 (t, J = 7.6 Hz, 1H) , 7.00 (t, J = 7.2 Hz, 1H) , 3.38 -3.33 (m, 2H) , 3. 30 -3.25 (m, 2H) .

[1044] Step B 5-bromo-2, 3-dihydrobenzothiophene



[1045] To a solution of 2, 3-dihydrobenzothiophene (1350 mg, 9.911 mmol) in DCM (20 mL) was added Br_2 (0.463 mL, 8.424 mmol) at 0 ℃. The mixture was sti rred at rt for 16 h. The mixture was diluted with H_2O and extracted w ith DCM (50 mL x 2) . The combined organic layers were washed with b rine, dried over Na_2SO_4 and concentrated. The residue was purified by flas h silica gel chromatography (Silica Flash Column, Eluent of 0～10%EtOAc/ PE gradient) to obtain 5-bromo-2, 3-dihydrobenzothiophene (650 mg, 30.5%yield) . ^{1} H NMR (400 MHz, DMSO-d6) δ 7.30 (d, J_1 = 2.0 Hz, 1 H) , 7.23 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H) , 7.08 (d, J = 8.0 Hz, 1H) , 3.38 -3.33 (m, 2H) , 3.30 -3.25 (m, 2H) .

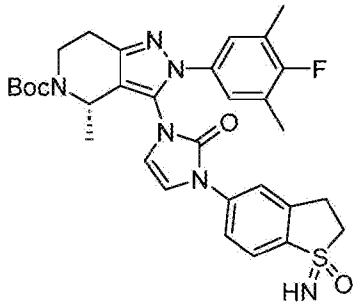
[1046] Step C 1-azanylidene-5-bromo-2, 3-dihydro-1λ^6-benzo [b] thiophen-1-one



[1047] To a solution of 5-bromo-2, 3-dihydrobenzo [b] thiophene (650 mg, 3.022 mmol) in MeOH (5 mL) was added PhI (OAc) $_2$ (1.96 g, 6.043 mmol) and $H_2NCO_2NH_4$ (472 mg, 6.043 mmol) . The mixture was stirred at rt for 2 h under N_2. Then the reacti on mixture was poured into water (100 mL) , extracted with DCM (100 mL x 2) . The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash silica gel chromatogra phy (Silica Flash Column, Eluent of 0～5%MeOH/DCM gradient) to obtain 1-

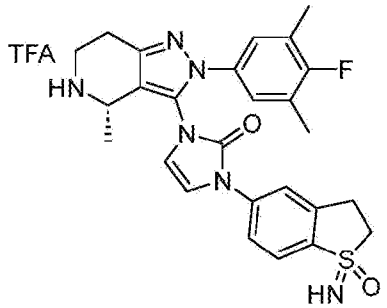
azanylidene-5-bromo-2, 3-dihydro-1λ^6-benzo [b] thiophen-1-one (450 mg, 60.5 %yield) . LC-MS: m/z: 246.1 (M+H) $^+$.

[1048] Step D tert-butyl (4S) -3- [3- (1-azanylidene-1-oxo-2, 3-dihydro-1λ^6-benzo [b] thiophen-5-yl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



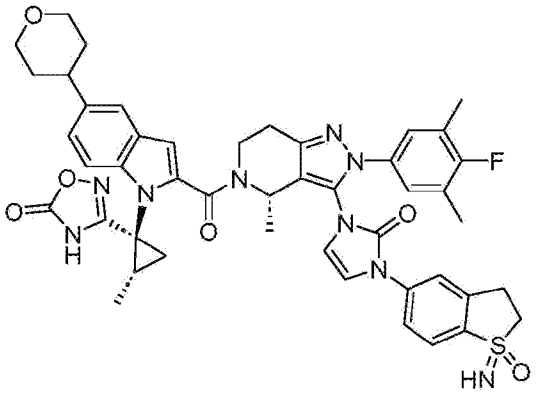
[1049] To a solution of 1-azanylidene-5-bromo-2, 3-dihydro-1λ^6-benzo [b] thiophen-1-one (290 mg, 1.178 mmol) in NMP (5 mL) was added methyl [(1R, 2R) -2- (methylamino) cyclohexyl] amine (67 mg, 0.471 mmol) , K_2CO_3 (488 mg, 3.535 m mol) , CuI (45 mg, 0.236 mmol) and tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-3H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazol o [4, 3-c] pyridine-5-carboxylate (520 mg, 1.178 mmol) . The reaction mix ture was stirred at 130 ℃ for 5 h under N_2. After cooling, the reaction mixt ure was diluted with EtOAc (50 mL) and water (25 mL) . The organic l ayer was separated, washed with brine, dried with Na_2SO_4 and concentrated . The residue was purified by flash silica gel chromatography (Silica Flash Column, E luent of 0～5%MeOH/DCM gradient) to obtain tert-butyl (4S) -3- [3- (1-azanylidene-1-oxo-2, 3-dihydro-1λ^6-benzo [b] thiophen-5-yl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (462 mg, 64.6%yield) . LC-MS: m/z 607.4 (M+H) $^+$.

[1050] Step E 3- (1-azanylidene-1-oxo-2, 3-dihydro-1λ^6-benzo [b] thiophen-5-yl) -1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2, 3-dihydro-1H-imidazol-2-one TFA salt



[1051] To a solution of tert-butyl (4S) -3- [3- (1-azanylidene-1-oxo-2, 3-dihydro-1λ^6-benzo [b] thiophen-5-yl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3- c] pyridine-5-carboxylate (528 mg, 0.870 mmol) in DCM (5 mL) was added TFA (3.3 mL) . The reaction mixture was stirred at rt for 2 h under N_2. The reaction mixture was concent rated to obtain 3- (1-azanylidene-1-oxo-2, 3-dihydro-1λ^6-benzo [b] thiophen-5-yl) -1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2, 3-dihydro-1H-imidazol-2-one TFA salt (265 mg, 49.0%yield) . LC-MS: m/z 507.3 $(M+H)^+$.

[1052] Step F 3- [(1S, 2S) -1- (2- { [(4S) -3- [3- (1-azanylidene-1-oxo-2, 3-dihydro-1λ^6-benzo [b] thiophen-5-yl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 101)

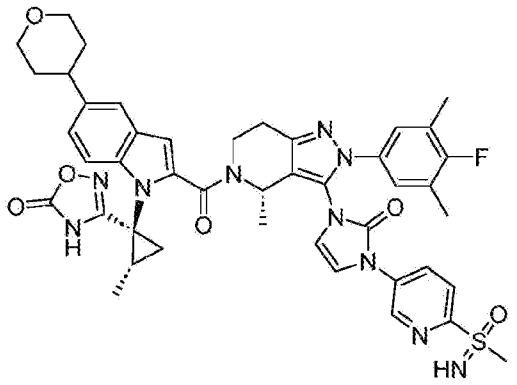


[1053] To a solution of 3- (1-azanylidene-1-oxo-2, 3-dihydro-1λ^6-benzo [b] thiophen-5-yl) -1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazol o [4, 3-c] pyridin-3-yl] -2, 3-dihydro-1H-imidazol-2-one TFA salt (100 mg, 0.197 mmol) in DMF (5 mL) was added 1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indole-2-carboxylic acid (75.7 mg, 0.197 mmol) , TEA (0.082 mL, 0.592 mmol) and HATU (112.6 mg, 0.296 mmol) . The reaction mixtu re was stirred at rt for 12 h under N_2. The mixture was filtered and the residue was puri fied by prep. HPLC (Column: Sunfire C18 19*250mm*10 μm; Mobile Phase A: Water (0.1%formic acid) , B: CH_3CN; Flow rate: 20 mL/min; Gradient : 58%B to 68%B; Retention Time: 8.7 min) to obtain 3- [(1S, 2S) -1- (2- { [(4S) -3- [3- (1-azanylidene-1-oxo-2, 3-dihydro-1λ^6-benzo [b] thiophen-5-yl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-

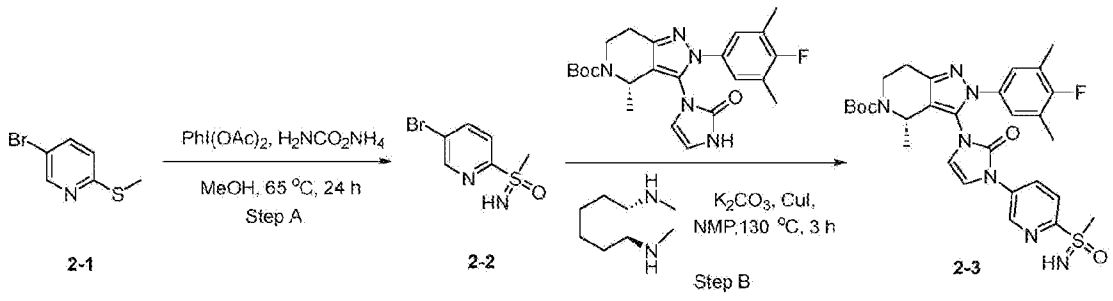
methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (4.89 mg, 2.84%yield) . LC-MS: m/z 872.4 (M+H) $^{+}$. ^{1}H NMR (400 MHz, DMSO-d6) δ7.74 -7.65 (m, 3H) , 7. 52 (s, 1H) , 7.50 -7.42 (m, 1H) , 7.28 -7.25 (m, 2H) , 7.14 (d, J = 6.0 Hz, 2H) , 6.91 - 6.81 (m, 2H) , 5.69 -5.44 (m, 1H) , 4.55 -4.27 (m, 1H) , 3.99 -3.94 (m, 2H) , 3. 50 -3.47 (m, 4H) , 3.32 -3.28 (m, 2H) , 2.92 -2.86 (m, 5H) , 2.22 (s, 6H) , 1.76 - 1.70 (m, 7H) , 1.43 (s, 3H) , 1.18 (s, 3H) .

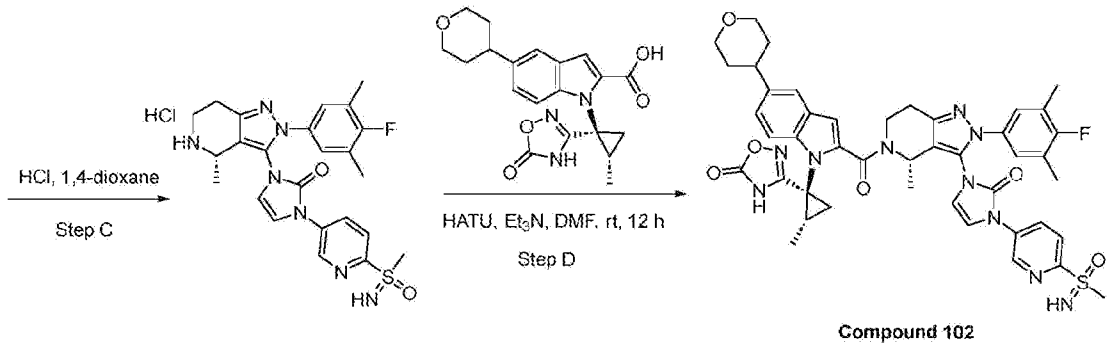
[1054] Example A2

[1055] 3- [(1S, 2S) -1- (2- { [(4S) -3- (3- {6- [azanylidene (methyl) (oxo) -λ^{6}-sulfanyl] pyridin-3-yl} -2-oxoimidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 102)



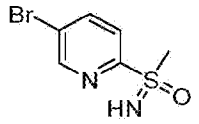
Compound 102





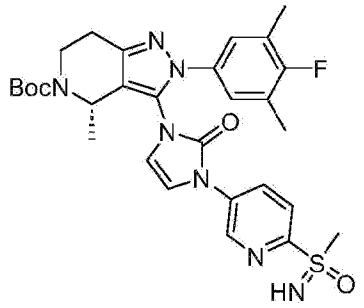
2-4

[1056] Step A (5-bromopyridin-2-yl) (imino) (methyl) -sulfanone



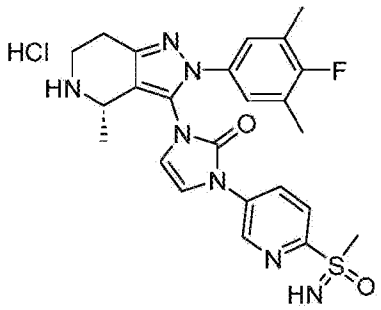
[1057] To a solution of 5-bromo-2- (methylthio) pyridine (1000 mg, 4.900 mmol) in MeO H (20 mL) was added PhI (OAc) $_2$ (3.96 g, 12.249 mmol) and $H_2NCO_2NH_4$ (765 mg, 9.800 mmol) . The reaction mixture was stirred at 65 ℃ for 24 h. After cool ing, the reaction mixture was concentrated. The residue was purified by flash silica gel chromatography (Silica Flash Column, Eluent of 0～50%EtOAc/PE gra dient) to give (5-bromopyridin-2-yl) (imino) (methyl) -sulfanone (723 mg , 62.8%yield) . LC-MS: m/z 235.0 $(M+H)^+$.

[1058] Step B tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (3- (6- (S-methylsulfonimidoyl) pyridin-3-yl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate



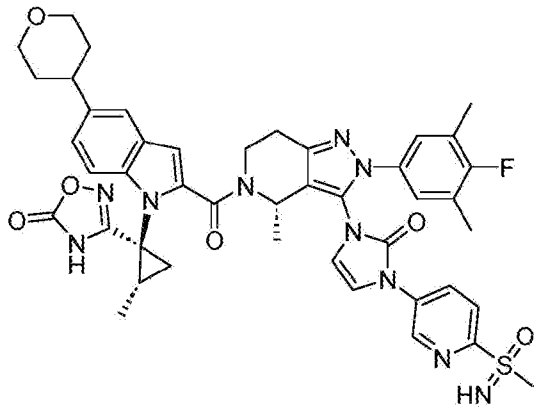
[1059] To a solution of (5-bromopyridin-2-yl) (imino) (methyl) -sulfanone (80 mg, 0.340 mmol) in NMP (5 mL) was added tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (150 mg, 0.340 mmol) , (1S, 2S) -N1, N2-dimethylcyclohexane-1, 2-diamine (19 mg, 0.136 mmol) , and K_2CO_3 (141 mg, 1.021 mmol) , CuI (13 mg, 0.068 mmol) . The reaction mixtu re was stirred at 130 ℃ for 3 h. After cooling and concentration, the residue was pur ified by flash silica gel chromatography (Silica Flash Column, Eluent of 0～ 25%EtOAc /PE gradient) to give tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (3- (6- (S-methylsulfonimidoyl) pyridin-3-yl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (150 mg, 74.0%yield) . LC-MS: m/z 596.3 $(M+H)^+$.

[1060] Step C 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (6- (S-methylsulfonimidoyl) pyridin-3-yl) -1, 3-dihydro-2H-imidazol-2-one HCl salt



[1061] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (3- (6- (S-methylsulfonimid oyl) pyridin-3-yl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (55 m g, 0.092 mmol) in DCM (10 mL) was added 4 M HCl (gas) in 1, 4-dioxane (0.23 mL) at 0 ℃. The reaction mixture was stirred at room temperature for 2 h. Then the react ion mixture was concentrated to give the crude 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (6- (S-methylsulfonimidoyl) pyridin-3-yl) -1, 3-dihydro-2H-imidazol-2-one HCl salt (45 mg, 98.4%yield) . LC-MS: m/z 496.3 $(M+H)^+$.

[1062] Step D 3- [(1S, 2S) -1- (2- { [(4S) -3- (3- {6- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] pyridin-3-yl} -2-oxoimidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 102)

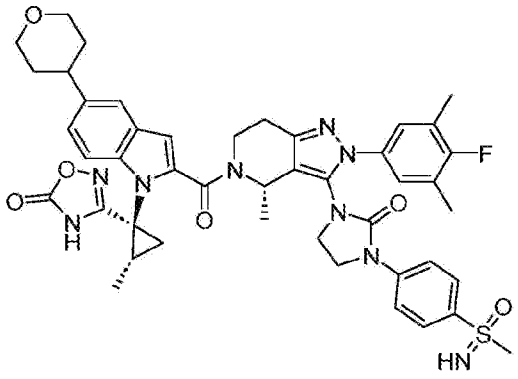


[1063] To a solution of 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (6- (S-methylsulfonimido yl) pyridin-3-yl) -1, 3-dihydro-2H-imidazol-2-one HCl salt (45 mg, 0.091 mmol) i n DMF (2 mL) was added Et_3N (0.025 mL, 0.182 mmol) , 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (34.8 mg, 0.091 mmol) , HATU (51.8 mg, 0.136 mmol) . The reaction mixture was stirred at room temperatu re for 12 h. The mixture was filtered and the residue was purified by prep. HPLC (Col

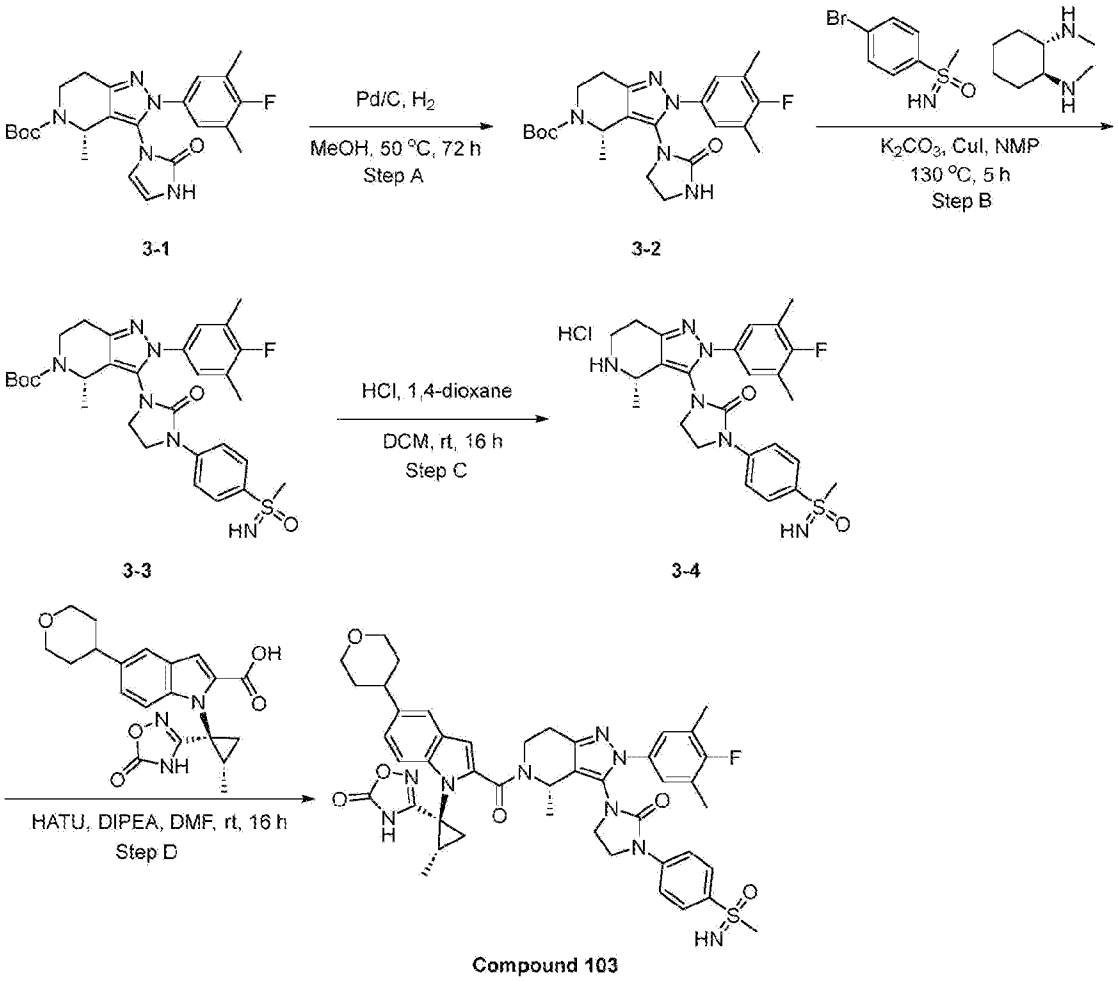
umn: XBridge C18 19*250mm*10μm; Mobile Phase A: Water (10 mM NH_4HCO_3) , B: CH_3CN; Flow rate: 20 mL/min; Gradient: 32%B to 42%B; Retention Time: 8.25 -9.2 min) to obtain 3- [(1S, 2S) -1- (2- { [(4S) -3- (3- {6- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] pyridin-3-yl} -2-oxoimidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (12.6 mg, 16.1%yield) . LC-MS: m/z 861.5 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.70 (s, 1H) , 9.08 (s, 1H) , 8.45 (d, J = 8.4 Hz, 1H) , 8.19 (d, J = 8.8 Hz, 1H) , 7.54 (d, J = 8.4 Hz, 2H) , 7.40 (d, J = 9.2 Hz, 1H) , 7.26 -7.23 (m, 1H) , 7.17 -7.13 (m, 3H) , 6.94 (s, 1 H) , 5.60 (s, 1H) , 4.46 -4.34 (m, 2H) , 3.98 -3.95 (m, 2H) , 3.51 -3.44 (m, 2H) , 3.24 (s, 3H) , 2.94 -2.81 (m, 3H) , 2.21 (s, 6H) , 1.72 -1.60 (m, 7H) , 1.40 -1.38 (m, 2H) , 1.32 -1.24 (m, 2H) , 1.14 -1.13 (m, 2H) .

[1064] Example A3

[1065] 3- [(1S, 2S) -1- (2- { [(4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxotetrahydro-1H-imidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 103)



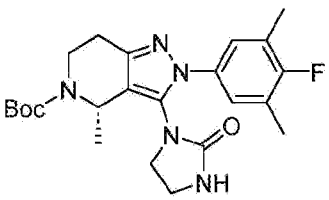
Compound 103



3-1 3-2 3-3 3-4

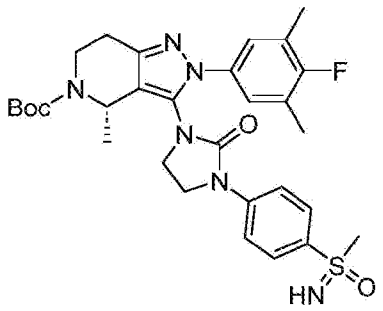
Compound 103

[1066] Step A tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxotetrahydro-1H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



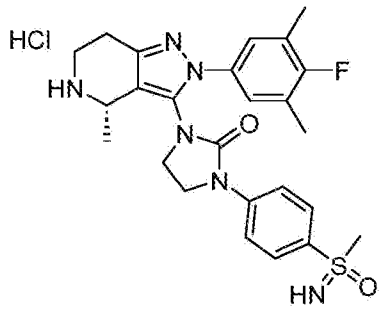
[1067] The mixture of tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-2, 3-dihydro-1H imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (100 mg, 0.226 mmol) and 10%Pd/C (24.1 mg) in MeOH (10 m L) was stirred at 50 ℃ under H_2 balloon for 72 h. After cooling and filtration, th e filtrate was concentrated. The residue was purified by reverse ISCO (water (0.1%formic acid) /CH_3CN) to obtain tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxotetrahydro-1H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (20 mg, 19.9%yield) . LC-MS: m/z 444.8 $(M+H)^+$.

[1068] Step B tert-butyl (4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxotetrahydro-1H-imidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



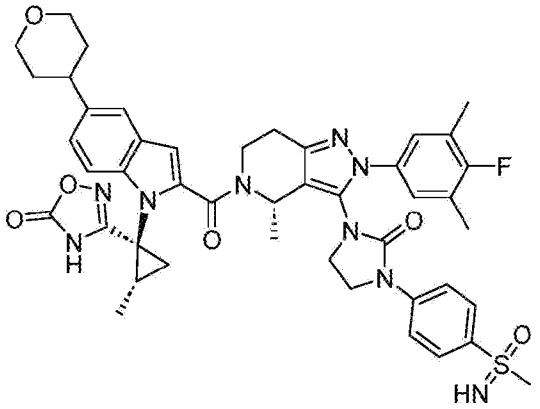
[1069] The mixture of 1-bromo-4- (S-methylsulfonimidoyl) benzene (105 mg, 0.449 mmol) , tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxotetrahydro-1H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (199 mg, 0.449 mmol) , CuI (17.1 mg, 0.090 mmol) , (1S, 2S) -N1, N2-dimethylcyclohexane-1, 2-diamine (25.5 mg, 0.179 mmol) and K_2CO_3 (186 mg, 1.346 mmol) in NMP (5 mL) was stirred at 130 ℃ for 5 h und er Biotage microwave. After cooling and filtration, the filtrate was purified by reve rse ISCO (water (0.1%formic acid) /CH3CN) to obtain tert-butyl (4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxotetrahydro-1H-imidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (50 mg, 18.7%yield) . LC-MS: m/z 597.4 $(M+H)^+$.

[1070] Step C (4- {1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxotetrahydro-1H-imidazol-3-yl} phenyl) (methyl) (oxo) -λ^6-sulfanimine HCl salt



[1071] The mixture of tert-butyl (4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxotetrahydro-1H-imidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (50 mg, 0.084 mmol) and 4 M HCl (gas) in 1, 4-dioxane (0.5 mL) in DCM (2 mL) was stirred at rt for 16 h. The reaction mixture was concentrated to ob tain (4- {1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxotetrahydro-1H-imidazol-3-yl} phenyl) (methyl) (oxo) -λ^6-sulfanimine hydrochloric acid salt (44 mg, 98.3%yie ld) . LC-MS: m/z 497.1 $(M+H)^+$.

[1072] Step D 3- [(1S, 2S) -1- (2- { [(4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxotetrahydro-1H-imidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 103)



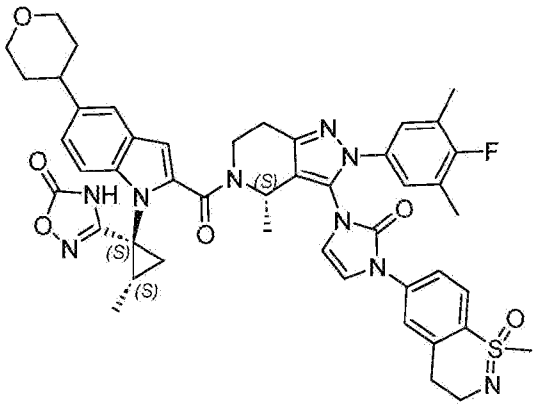
[1073] The mixture of (4- {1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxotetrahydro-1H-imidazol-3-yl} phenyl) (methyl) (oxo) -λ^6-sulfanimine hydrochloric acid salt (44 mg, 0.083 mm ol) , 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (31.7 mg, 0.083 mmol) , HATU (62.8 mg, 0.165 mmol) and DIPEA (31.9 mg , 0.248 mmol) in DMF (2 mL) was stirred at rt for 16 h. The mixture was filtrated and

purified by prep. HPLC (Column: XBridge C18, 19*250mm*10 μm; Mobile Phase A: Water (10 mM NH_4HCO_3) , B: CH_3CN; Flow rate: 20 mL/min; Gradient : 40%B to 45%B; Retention Time: 7.7 min) to obtain 3- [(1S, 2S) -1- (2- { [(4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxotetrahydro-1H-imidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (31.6 mg, 44.4%yield) . LC-MS: m/z 862.4 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.00 -7.64 (m, 4H) , 7.51 (s, 1H) , 7.46 -7.43 (m, 1H) , 7.32 -7.18 (m, 4H) , 6.81 (brs, 1H) , 5.79 -5.44 (m, 1H) , 4.40 (brs, 1H) , 4.03 -3.92 (m, 4H) , 3.72 -3.56 (m, 2H) , 3.55 -3.45 (m, 3H) , 2.95 -2.75 (m, 4H) , 2.26 (s, 6H) , 2.05 (d, J = 4.0 Hz, 3H) , 1.81 -1.59 (m, 7H) , 1.50 (s, 3H) , 1.17 (brs, 3H) .

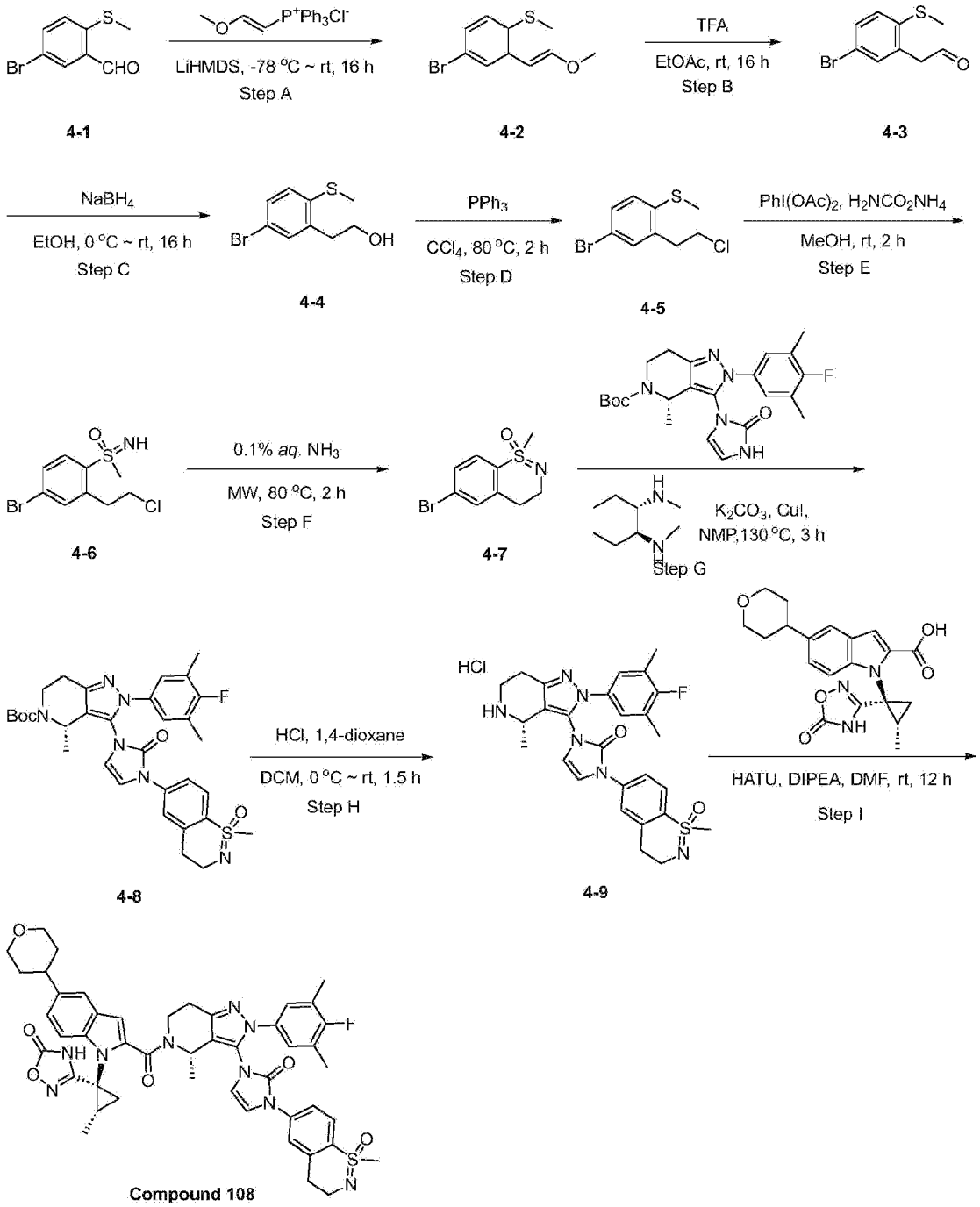
[1074] Example compound 166 and 167, 168 and 169, 173, 174 and 175, 176 and 177, 178, 179, 181, 183, 184, 189 and 190 were synthesized using a similar procedure described in the Example A3 above using the appropriate materials.

[1075] Example A4

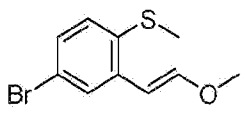
[1076] 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3, 4-dihydro-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 108)



Compound 108



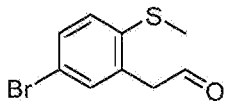
[1077] Step A (E) - (4-bromo-2- (2-methoxyvinyl) phenyl) (methyl) sulfane



[1078] To a solution of (methoxymethyl) triphenylphosphanium chloride (12.5 2 g, 36.519 mmol) in THF (100 mL) was added 1 M LiHMDS in THF (45.7 mL, 45.7 mmol) . After being stirred at -78 °C for 10 min and rt for 2 h, th e mixture was cooled to -78 °C again. Then 5-bromo-2- (methylsulfanyl) benzene-1-carbaldehyde (4.22 g, 18.260 mmol) was added. The reaction mixture w

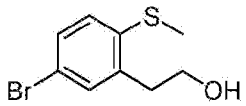
as warmed to rt and stirred for 16 h. The mixture was quenched with water (50 mL) , e xtracted with EtOAc (200 mL x 3) . The combined organic layer was wa shed with brine, dried with Na_2SO_4 and concentrated. The residue was purified by flas h silica gel chromatography (Silica Flash Column, Eluent of 100%PE) to afford (E) - (4-bromo-2- (2-methoxyvinyl) phenyl) (methyl) sulfane (3.13 g, 47.3%yield) . LC-MS: m/z 259.0 $(M+H)^+$.

[1079] Step B 2- (5-bromo-2- (methylthio) phenyl) acetaldehyde



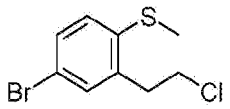
[1080] To a solution of (E) - (4-bromo-2- (2-methoxyvinyl) phenyl) (methyl) sul fane (3.13 g, 12.13 mmol) in EtOAc (30 mL) was added TFA (6.26 mL, 8 1.750 mmol) at 0 ℃. The reaction mixture was warmed to rt and stirre d for 16 h. The mixture was diluted with EtOAc (100 mL) and water (1 00 mL) . The organic layer was separated, washed with brine, and concentrated. The re sidue was purified by flash silica gel chromatography (Silica Flash Column, Eluent of 100%PE) to afford 2- (5-bromo-2- (methylthio) phenyl) acetaldehyde (2.96 g, 99%yield) . LC-MS: m/z 245.0 $(M+H)^+$.

[1081] Step C 2- (5-bromo-2- (methylthio) phenyl) ethan-1-ol



[1082] To a solution of 2- (5-bromo-2- (methylthio) phenyl) acetaldehyde (1.30 g, 5.303 m mol) in EtOH (15 mL) was added $NaBH_4$ (401.25 mg, 10.607 mmol) at 0 ℃. The reaction mixture was warmed to rt and stirred for 16 h. The mixture was diluted w ith EtOAc (100 mL) and water (100 mL) . The organic layer was separa ted, washed with brine, and concentrated. The residue was purified by flash silica ge l chromatography (Silica Flash Column, Eluent of 0-20%EtOAc/PE gradi ent) to afford 2- (5-bromo-2- (methylthio) phenyl) ethan-1-ol (289 mg, 22.0% yield) . ^1H NMR (400 MHz, CD_3OD-d4) δ 7.35 -7.34 (m, 2 H) , 7.07 (d, J = 8.8 H z, 1 H) , 3.87 (t, J = 6.4 Hz, 2 H) , 2.96 (t, J = 6.4 Hz, 2 H) , 2.45 (s, 3 H) .

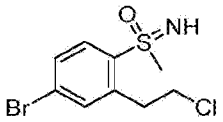
[1083] Step D (4-bromo-2- (2-chloroethyl) phenyl) (methyl) sulfane



[1084] To a solution of 2- (5-bromo-2- (methylthio) phenyl) ethan-1-ol (370 mg, 1.497 mmol) in CCl_4 (3.7 mL) was added PPh_3 (510 mg, 1.946 mmol) . The mixtur e was stirred at 80 ℃ for 2 h under N_2. The mixture was poured into wate

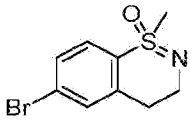
r (100 mL) and extracted with EtOAc (100 mL x 2) . The combined orga nic layer was washed with brine, dried over sodium sulfate, filtered and concentrated . The residue was purified by flash silica gel chromatography (Silica Flash Column, E luent of 0-10%EtOAc/PE gradient) to obtain (4-bromo-2- (2-chloroethyl) phen yl) (methyl) sulfane (80 mg, 20.1%yield) . ^{1}H NMR (400 MHz, DMSO-d6) δ 7.51 - 7.44 (m, 2 H) , 7.24 -7.19 (m, 1 H) , 3.84 (t, J = 7.2 Hz, 2 H) , 3.11 (t, J = 7.2 Hz, 2 H) , 2.51 (s, 3 H) .

[1085] Step E [4-bromo-2- (2-chloroethyl) phenyl] (methyl) (oxo) -λ^6-sulfanimine



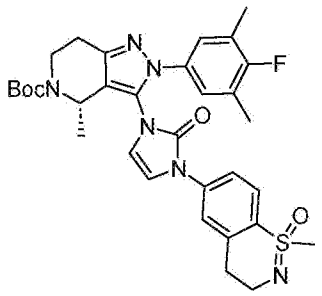
[1086] To a solution of (4-bromo-2- (2-chloroethyl) phenyl) (methyl) sulfane (80 mg, 0.301 mmol) in MeOH (5 mL) was added PhI (OAc) $_2$ (244 mg, 0.753 mmol) and $H_2NCO_2NH_4$ (59 mg, 0.753 mmol) . The mixture was stirred at rt for 2 h under N $_2$. The mixture was poured into water (100 mL) and extracted with DCM (100 mL x2) . The combined organic layer was washed with brine, drie d over sodium sulfate, filtered and concentrated. The residue was purified by flash s ilica gel chromatography (Silica Flash Column, Eluent of 0-5%MeOH/DCM gradie nt) to obtain [4-bromo-2- (2-chloroethyl) phenyl] (methyl) (oxo) -λ^6-sulfanimine (50 m g, 54.1%yield) . LC-MS: m/z 295.9 (M+H) $^+$.

[1087] Step F 6-bromo-1-methyl-3, 4-dihydro-1λ^4-benzo [e] [1, 2] thiazine 1-oxide



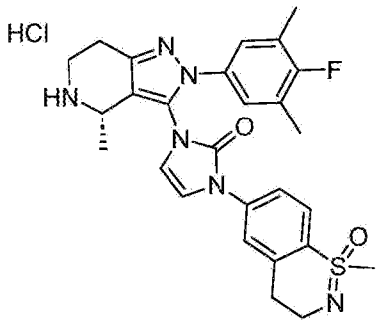
[1088] To a solution of [4-bromo-2- (2-chloroethyl) phenyl] (methyl) (oxo) -λ^6-sulfanimine (50 mg, 0.169 mmol) in dioxane (2 mL) was added 0.1%aq. $NH_3 . H_2O$ (1 mL) . The mixture was stirred at 80 °C for 2 h under N_2 in a sealed tube . After cooling, the mixture was poured into water (100 mL) and extr acted with DCM (100 mL x 2) . The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to obtain 6-bromo-1-methyl-3, 4-dihydro-1λ^4-benzo [e] [1, 2] thiazine 1-oxide (40 mg, 79.4%yield) . LC-MS: m/z 260.0 (M+H) $^+$.

[1089] Step G tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (1-methyl-1-oxo-3, 4-dihydro-1λ^6-benzo [2, 1-e] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1090] To a solution of 6-bromo-1-methyl-3, 4-dihydro-1λ^4-benzo [e] [1, 2] thiazine 1-oxide (40 mg, 0.154 mmol) and tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-3H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (27 mg, 0.062 mmol) in NMP (5 mL) was added methyl [(1S, 2S) -2- (methylamino) cyclohexyl] amine (22 mg, 0.154 mmol) , K_2CO_3 (64 mg, 0.461 mmol) , CuI (6 mg, 0.031 mmol) . The mixture was stirred at 130 ℃ for 5 h under N_2. After cooling, the mixture was poured into water (50 mL) and extracted with DCM (50 mL x2) . The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash silica gel chromatography (Silica Flash Column, Eluent of 0-5%MeOH/DCM gradient) to obtain tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (1-methyl-1-oxo-3, 4-dihydro-1λ^6-benzo [2, 1-e] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (100 mg, 72.0%yield) . LC-MS: m/z 621.4 $(M+H)^+$.

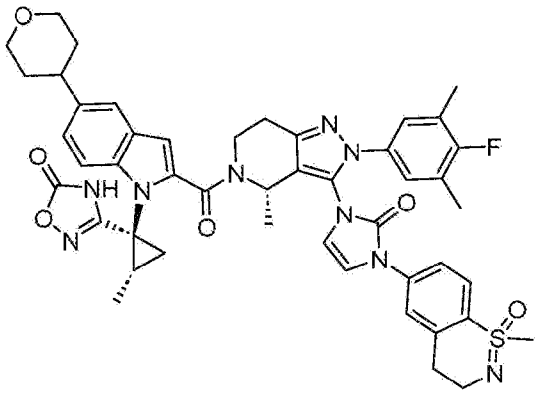
[1091] Step H 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3, 4-dihydro-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one hydrochloride salt



[1092] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (1-methyl-1-oxo-3, 4-dihydro-1λ^6-benzo [2, 1-e] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (100 mg, 0.111 mmol) in DCM (10 mL) was added 4 M HCl (gas) /dioxane (0.4 mL) at 0 ℃. The mixture was stirred at rt for 1.5 h under N_2. The mixture was concentrated to afford 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-

4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3, 4-dihydro-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one hydrochloride salt (100 mg, crude) . LC-MS: m/z 521.3 (M+H) $^+$.

[1093] Step I 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3, 4-dihydro-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 108)



[1094] To a solution of 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3, 4-dihydro-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one hydrochloride salt (100 mg, 0.180 mmol) in DMF (2 mL) was added 1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indole-2-carboxylic acid (69 mg, 0.180 mmol) , HATU (102 mg, 0.269 mmol) , DIPEA (116 mg, 0.898 mmol) . The mixture was stirred at rt for 3 h under N_2. The mixture was filtrated and purified by prep. HPLC (Column: Sunfire C18 19*250mm*10μm; Mobile Phase A: Water (0.1%formic acid) , B: CH_3CN; Flow rate: 20 mL/min; Gradient: 57%B to 67%B; Retention Time: 9.0 min) to obtain 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3, 4-dihydro-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (15.4 mg, 9.5%yield) . LC-MS: m/z 886.4 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.05 -7.95 (m, 1 H) , 7.88 -7.78 (m, 1 H) , 7.73 -7.64 (m, 1 H) , 7.56 (s, 1 H) , 7.47 (d, J = 8.8 Hz, 1 H) , 7.37 -7.28 (m, 2 H) , 7.18 (d, J = 6.0 Hz, 2 H) , 7.01 -6.85 (m, 2 H) , 6.97 -6.85 (m, 2 H) , 5.70 -5.50 (m, 1 H) , 4.57 -4.38 (m, 1 H) , 4.01 (d, J = 10.8 Hz, 2 H) , 3.68 -3.43 (m, 5 H) , 3

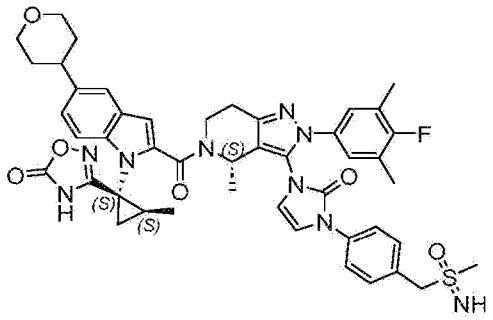
.25 (s, 1 H) , 2.97 -2.84 (m, 4 H) , 2.80 -2.69 (m, 1 H) , 2.25 (s, 6 H) , 1.82 -1.66 (m, 7 H) , 1.51 -1.42 (m, 3 H) , 1.25 -1.12 (m, 3 H) .

[1095] Example compound 185 and 186, 187 and 188, , 197 and 198, 199 and 200, 212 and 213 were synthesized using a similar procedure described in the Example A4 above using the appropriate materials.

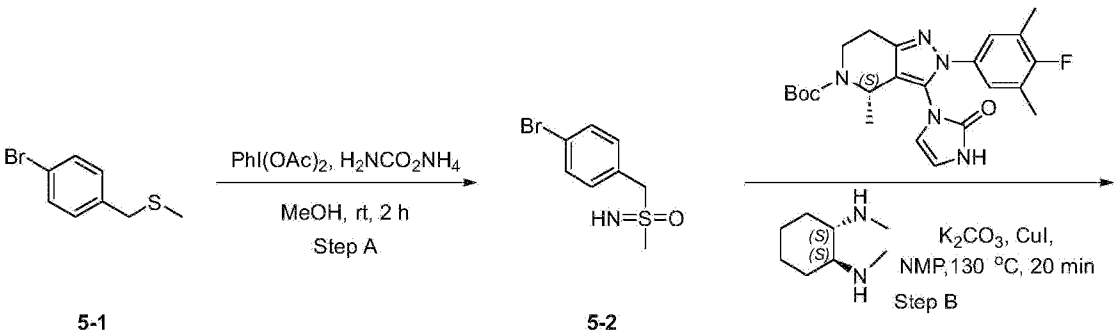
[1096] Example A5

[1097] 3- [(1S, 2S) -1- (2- { [(4S) -3- [3- (4- { [azanylidene (methyl) (oxo) -λ^6-sulfanyl] methyl} phenyl) -2-

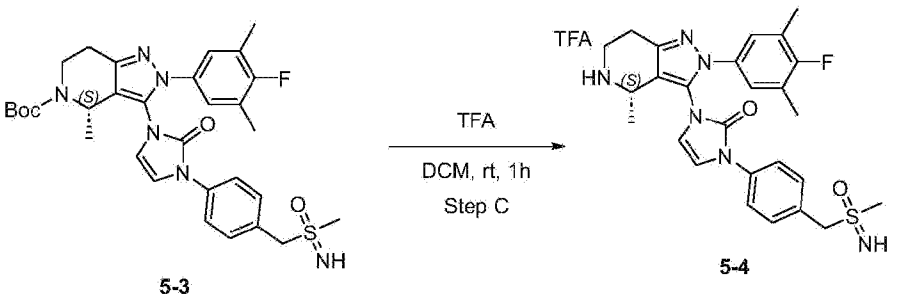
[1098] oxoimidazol-1-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 111)



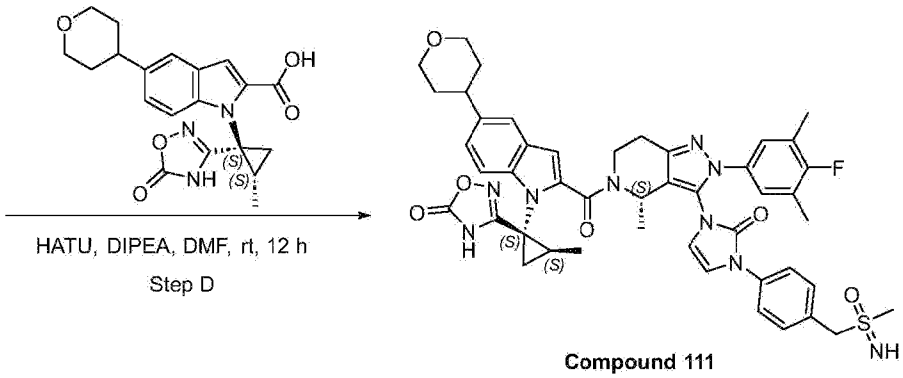
Compound 111



5-1 5-2

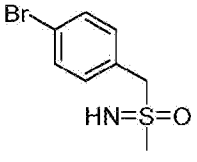


5-3 5-4



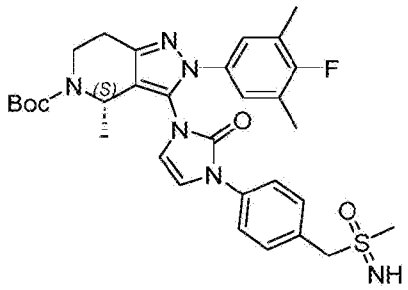
Compound 111

[1099] Step A (4-bromobenzyl) (imino) (methyl) -λ^6-sulfanone



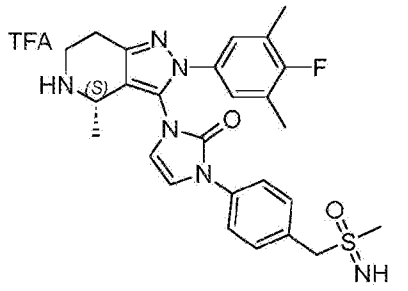
[1100] To a solution of [(4-bromophenyl) methyl] (methyl) sulfane (500 mg, 2.30 3 mmol) in EtOH (50 mL) was added PhI (OAc) $_2$ (2239 mg, 6.909 mmol) and $H_2NCO_2NH_4$ (719 mg, 9.211 mmol) . The reaction mixture was stirred at rt for 2 h under N_2 . The reaction mixture was concentrated, the residue was purified by reverse ISCO (water (0.1%formic acid) /CH_3CN system) to afford the (4-bromobenzyl) (imino) (methyl) -λ^6-sulfanone (134 mg, 23.5%yield) . LC-MS: m/z 248.1 $(M+H)^+$.

[1101] Step B tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (3- (4- ((S-methylsulfonimidoyl) methyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate



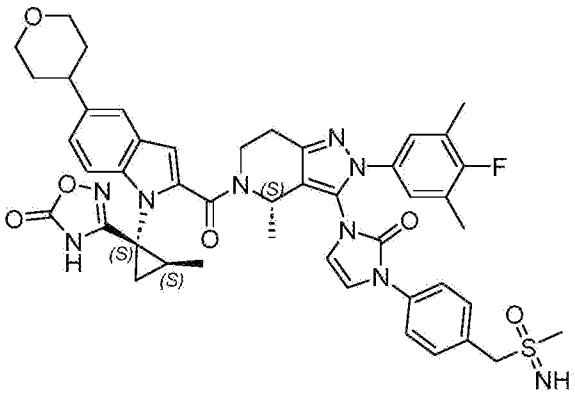
[1102] To a solution of [(4-bromophenyl) methyl] (methyl) (oxo) -λ^6-sulfanimine (90 mg, 0.363 mmol) in NMP (3 mL) was added tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-3H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (144 mg, 0.326 mmol) , methyl [(1S, 2S) -2- (methylamino) cyclohexyl] amine (20.6 mg, 0.145 mmol) , K_2CO_3 (150 mg, 1.088 mmol) , CuI (13.8 mg, 0.073 mmol) . The reaction mixture was stirred at 130 ℃ for 20 min under N_2. After cooling and filtration, the solution was purified by reverse ISCO (water (0.1%formic acid) / CH_3CN system) to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (3- (4- ((S-methylsulfonimidoyl) methyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (53 mg, 9.5%yield) . LC-MS: m/z 609.6 $(M+H)^+$.

[1103] Step C 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- ((S-methylsulfonimidoyl) methyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one TFA salt



[1104] To a solution of tert-butyl (4S) -3- [3- (4- { [azanylidene (methyl) (oxo) -λ^6-sulfanyl] methyl} phenyl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (40 m g, 0.066 mmol) in DCM (3 mL) was added TFA (0.38 mL, 4.897 mmol) . T he reaction mixture was stirred at rt for 1 h under N_2. The solvent was removed to affor d 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- ((S-methylsulfonimidoyl) methyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one TFA salt (40 mg, 96.9%yield) . LC-MS: m/z 509.6 (M+ H) $^+$.

[1105] Step D 3- [(1S, 2S) -1- (2- { [(4S) -3- [3- (4- { [azanylidene (methyl) (oxo) -λ^6-sulfanyl] methyl} phenyl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 111)

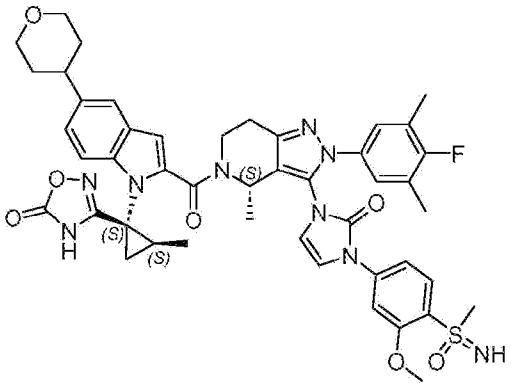


[1106] To a solution of 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- ((S-methylsulfonimido yl) methyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one TFA salt (40 mg, 0.066 mmol) i n DMF (1 mL) was added DIPEA (11.5 mg, 0.089 mmol) , 1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indole-2-carboxylic acid (11.4 mg, 0.030 mmol) , HATU (17 mg, 0.045 mmol) . T he reaction mixture was stirred at rt for 12 h under N_2. After filtration, the solution w as purified using prep. HPLC (Column: Sunfire C18 19*250mm*10μm; Mob ile Phase A: Water (0.05%TFA) , B: CH_3CN; Flow rate: 20 mL/min; Gradient : 57%B to 67%B; Retention Time: 9.0 min) to afford 3- [(1S, 2S) -1- (2- { [(4S) -3- [3- (4- { [azanylidene (methyl) (oxo) -λ^6-sulfanyl] methyl} phenyl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3, 5- dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (13.9 mg, 52.6%yield) . LC-

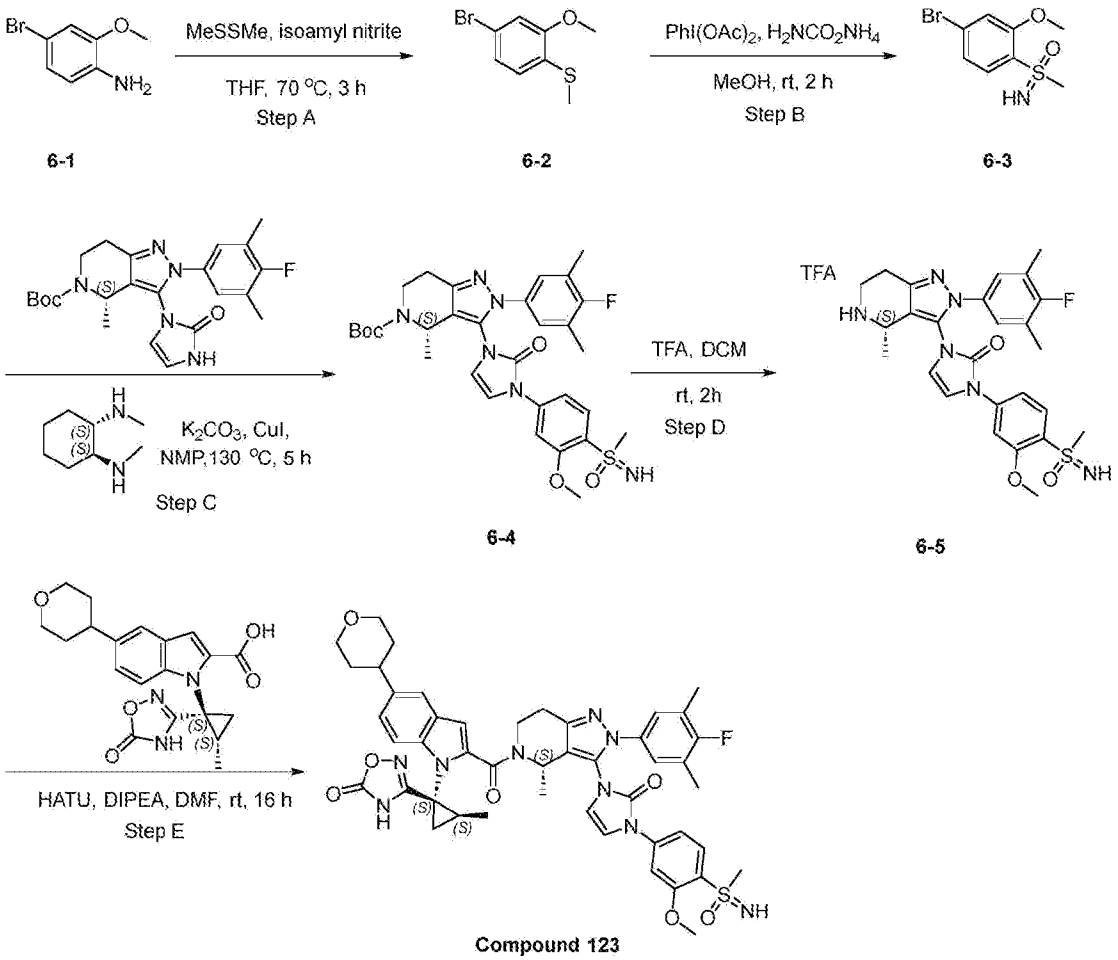
MS: m/z 874.5 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.78 -7.64 (m, 2H) , 7. 59 -7.50 (m, 3H) , 7.43 (d, J = 8.4 Hz, 1H) , 7.30 -7.21 (m, 2H) , 7.15 (d, J = 6.0 Hz , 2H) , 6.97 -6.83 (m, 2H) , 5.72 -5.42 (m, 1H) , 4.66 (s, 2H) , 4.45 (brs, 1H) , 3.98 (d, J = 10.8 Hz, 2H) , 3.53 -3.46 (m, 2H) , 3.06 (s, 2H) , 2.95 -2.81 (m, 3H) , 2. 22 (s, 6H) , 2.05 (s, 3H) , 1.81 -1.60 (m, 7H) , 1.44 (d, J = 3.6 Hz, 3H) , 1.18 (d, J = 6.0 Hz, 3H) .

[1107] Example A6

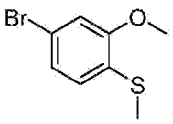
[1108] 3- [(1S, 2S) -1- (2- { [(S) -2- (4-fluoro-3, 5-xylyl) -3- {3- [4- (iminomethyloxot hio) -3-methoxyphenyl] -2-oxo-1, 3-dihydro-1-imidazolyl} -4-methyl-4, 5, 6, 7-tetrahydro-2H-1, 2, 5-triazainden-5-yl] carbonyl} -5- (tetrahydro-2H-pyran-4-yl) -1-indolyl) -2-methylcyclopropyl] -1, 2, 4-oxadiazol-5 (4H) -one (Compound 123)



Compound 123

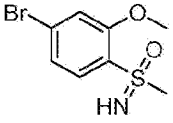


[1109] Step A (4-bromo-2-methoxyphenyl) (methyl) sulfane



[1110] To a solution of dimethylsulfane (0.11 mL, 1.485 mmol) and isoamyl n itrite (0.30 mL, 1.980 mmol) in THF (5 mL) was added 4-bromo-2-methoxyaniline (2 00 mg, 0.990 mmol) . The reaction mixture was stirred at 70 °C for 3 h. After cooling and concentration, the residue was purified by flash silica gel chromatography (Silic a Flash Column, Eluent of 0～10 %EtOAc/PE gradient) to obtain (4-bromo-2-methoxyphenyl) (methyl) sulfane (210 mg, 91.0%yield) . LC-MS: m/z 234.1 $(M+H)^+$.

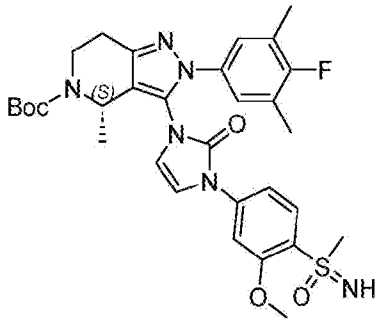
[1111] Step B (4-bromo-2-methoxyphenyl) (imino) (methyl) -sulfanone



[1112] To a solution of (4-bromo-2-methoxyphenyl) (methyl) sulfane (210 mg, 0.901 mmol) in MeOH (10 mL) was added PhI $(OAc)_2$ (1022 mg, 3.153 mmol) and $H_2NCO_2NH_4$ (246 mg, 3.153 mmol) . The reaction mixture was stirred at room tem

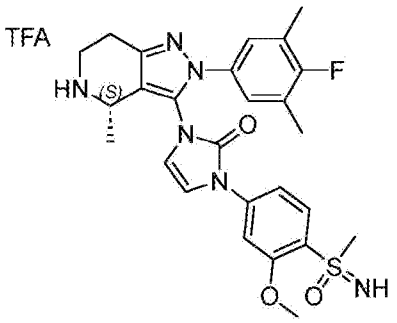
perature 2 h under N_2. The reaction mixture was diluted with EtOAc (50 m L) and water (50 mL) . The organic layer was separated, washed with brine, dried with Na_2SO_4 and concentrated. The residue was purified by flash silica gel chro matography (Silica Flash Column, Eluent of 0～50%EtOAc/PE gradient) to obtain (4-bromo-2-methoxyphenyl) (imino) (methyl) -sulfanone (200 mg, 84.0%yield) . LC-MS: m/z 264.0 $(M+H)^+$.

[1113] Step C tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (3-methoxy-4- (S-methylsulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate



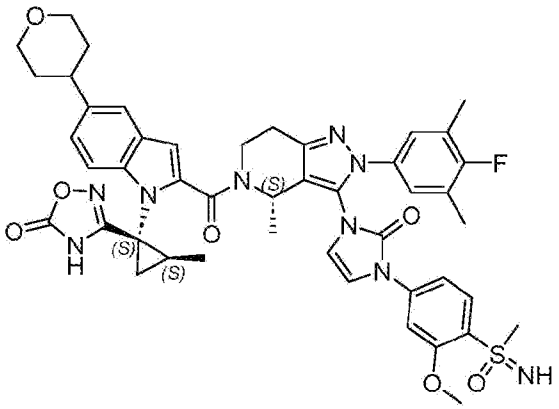
[1114] To a solution of (4-bromo-2-methoxyphenyl) (imino) (methyl) -sulfanone (200 mg , 0.757 mmol) in NMP (3 mL) was added methyl [(1R, 2R) -2- (methylamino) cy clohexyl] amine (43 mg, 0.303 mmol) , tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-3H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazol o [4, 3-c] pyridine-5-carboxylate (368 mg, 0.833 mmol) , K_2CO_3 (314 mg, 2.272 m mol) , CuI (28.8 mg, 0.151 mmol) . The reaction mixture was stirred at 130 ℃ for 5 h under N_2. After cooling, the reaction mixture was diluted with EtOAc (50 mL) and water (50 mL) . The organic layer was separated, washed with brine, dried with N a_2SO_4 and concentrated. The residue was purified by flash silica gel chro matography (Silica Flash Column, Eluent of 0～5%MeOH/DCM gradient) to obtain tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (3-methoxy-4- (S-methylsulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (400 mg, 84.6%yield) . LC-MS: m/z 625.4 $(M+H)^+$.

[1115] Step D 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (3-methoxy-4- (S-methylsulfonimido yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one TFA salt



[1116] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (3-methoxy-4- (S-methylsulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (120 mg, 0.192 mmol) in DCM (5 mL) was added TFA (0.5 mL) at 0 ℃. The res ulting mixture was stirred at rt for 2 h under N_2. The reaction mixture was concent rated to obtain 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (3-methoxy-4- (S-methylsulfonimido yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one TFA salt (120 mg, 95.3%yield) . LC-MS: m/z 525.3 $(M+H)^+$.

[1117] Step E 3- [(1S, 2S) -1- (2- { [(4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] -3-methoxyphenyl} -2-oxoimidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 123)



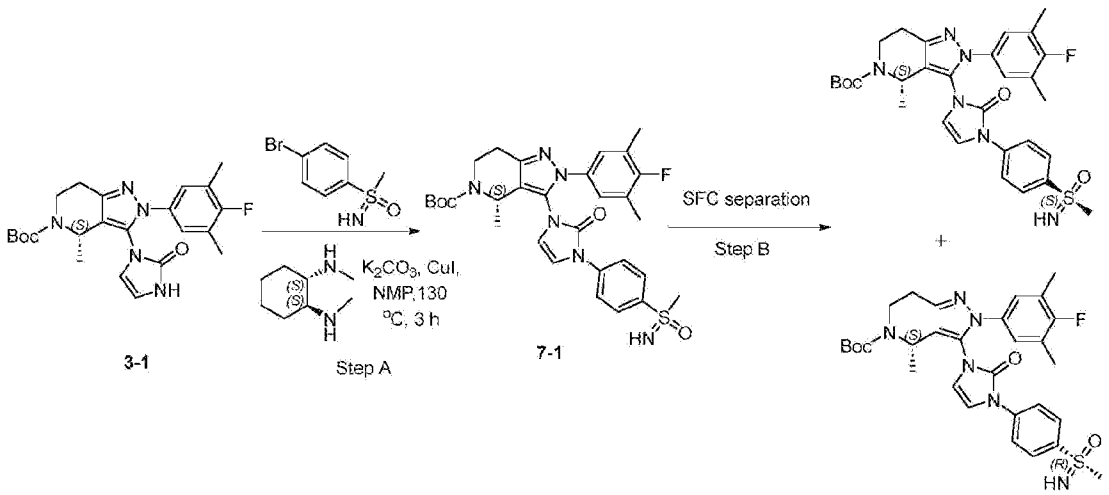
[1118] To a solution of 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (3-methoxy-4- (S-methylsulfonimido yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one TFA salt (120 mg, 0.183 mmol) in DMF (2 mL) was added 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (88 mg, 0.229 mmol) , DIPEA (88 mg, 0.686 mmol) and HATU (131 mg, 0.343 mmol) . The reaction mixture was stirred at rt f

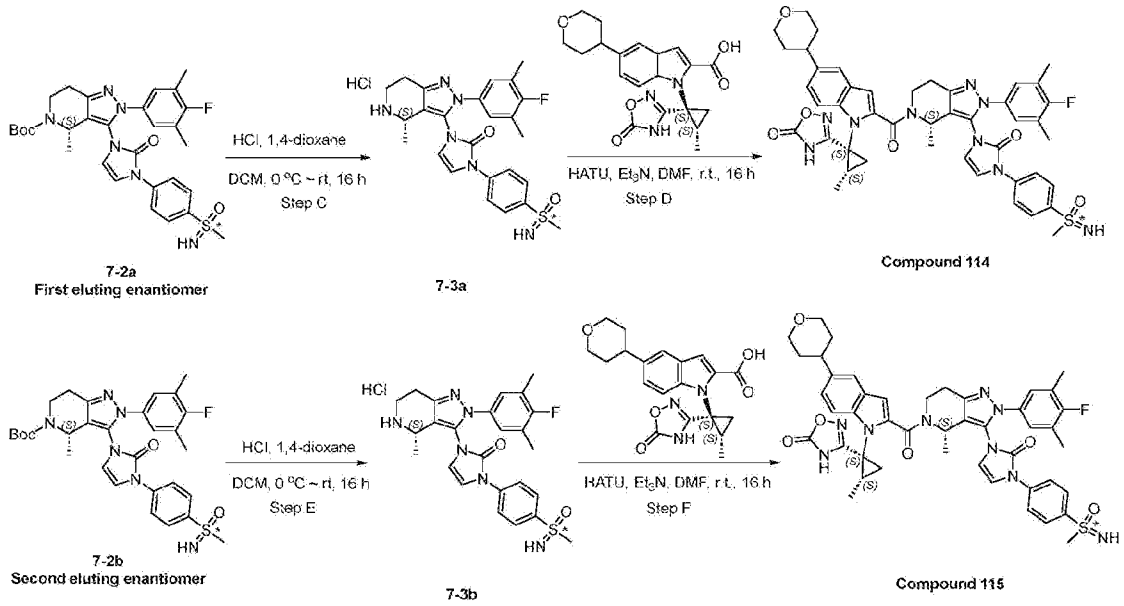
or 2 h under N_2. The mixture was filtered and the residue was purified by prep. HPLC (Column: Sunfire C18 19*250mm*10μm; Mobile Phase A: Water (0.05%TFA) , B: CH_3CN; Flow rate: 20 mL/min; Gradient: 50%B to 60%B; Retention Time: 8.0 min) to obtain 3- [(1S, 2S) -1- (2- { [(4S) - 3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] -3-methoxyphenyl} -2-oxoimidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (10.8 mg, 5.3%yield) . LC-MS: m/z 890.4 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.59 (s, 1 H) , 7.91 (d, J = 8.0 Hz, 1 H) , 7.70 -7.40 (m, 5 H) , 7.27 (d, J = 9.2 Hz, 1 H) , 7.16 -7.14 (m, 2 H) , 7.01 -6.84 (m, 2 H) , 5.69 -5.44 (m, 1 H) , 4.58 -4.39 (m, 1 H) , 4.04 -3.87 (m, 5 H) , 3.64 -3.43 (m, 4 H) , 3.32 (s, 3 H) , 2.95 -2.84 (m, 3 H) , 2.23 (s, 6 H) , 1.81 -1.61 (m, 7 H) , 1.44 (s, 3 H) , 1.17 (s, 3 H) .

[1119] Example compound 124 was synthesized using a similar procedure described in the Example A6 above using the appropriate materials.

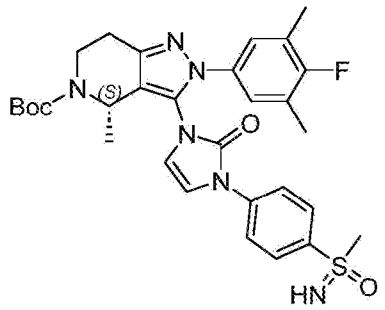
[1120] Example A7

[1121] 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [(S) -azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one and 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [(R) -azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compounds 114) and 115)





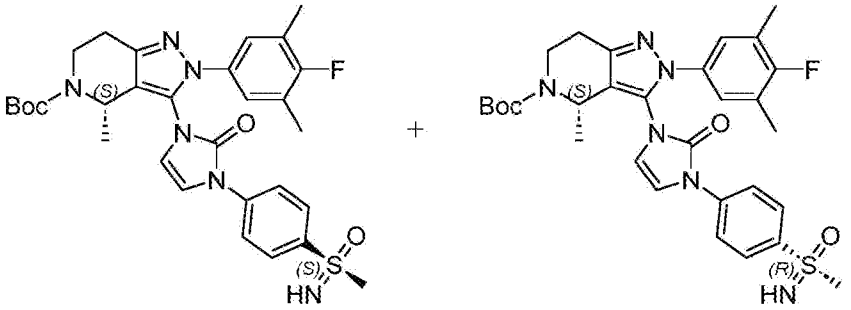
[1122] Step A tert-butyl (4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1123] To a solution of 1-bromo-4- (S-methylsulfonimidoyl) benzene (400 mg, 1.709 mmol) in NMP (30 mL) was added tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-2, 3-dihydro-1H -imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (754 mg, 1.709 mmol) , (1S, 2S) -N1, N2-dimethylcyclohexane-1, 2-diamine (97 mg, 0.683 mmol) and K_2CO_3 (708 mg, 5.126 mmol) , CuI (65 mg, 0.342 mmol) . The reaction mixture was stirred at 130 ℃ for 3 h. After cooling and concentration, the residue was purified by flash silica gel chromatography (Silica Flash Column, Eluent of 0～50%EtOAc/PE gradient) to give tert-butyl (4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (1000 mg, 98.4%yield) . LC-MS: m/z 595.3 $(M+H)^+$.

[1124] Step B tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-

tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 7-2a (first eluting enantiomer) and tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [azanylidene (me thyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 7-2b (second eluting enantiomer)

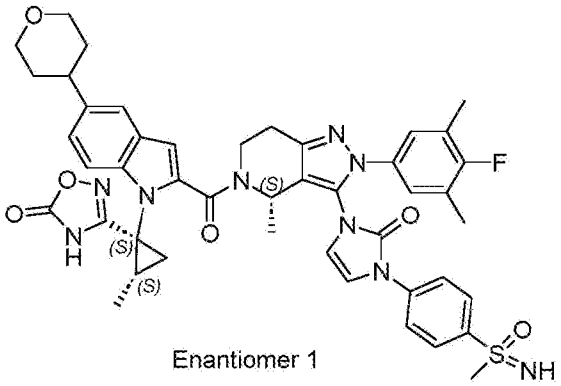


[1125] The compound mixture tert-butyl (4S) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (1.20 g, 2.02 mmol) wa s separated by SFC (Column: DAICELCHIRALCEL®IC 250*25 mm 10 μ m, Mobile phase A (Supercritical CO2) , Mobile phase B (MeOH (0.1%7. 0 M ammonia in MeOH)) , Gradient: A/B = 45/55, Flow rate: 70 mL/min) to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [(S) -azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 7-2a (307 mg, 25.6% yield) as the fast eluent (Rt = 6.03 min) , LC-MS: m/z 595.3 (M+H) $^+$. And tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [(R) -azanylidene (meth yl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 7-2b (260 mg, 6.8%y ield) as the slow eluent (Rt = 7.85 min) , LC-MS: m/z 595.3 (M+H) $^+$.

[1126] Step C 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 7-3a

[1127] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4-azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 7-2a (60 mg, 0.101 mmol) in DCM (10 mL) was added 4.0 M HCl (gas) in 1, 4-dioxane HCl (0.25 mL) at 0 ℃. The reaction mixture was stirred at room temperature for 16 h. Then it w as concentrated to afford 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [azanylidene (me thyl) (oxo) -λ^6-sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 7-3a (50 mg, 99%yield) . LC-MS: m/z 495.3 (M+H) $^+$.

[1128] Step D 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 114)

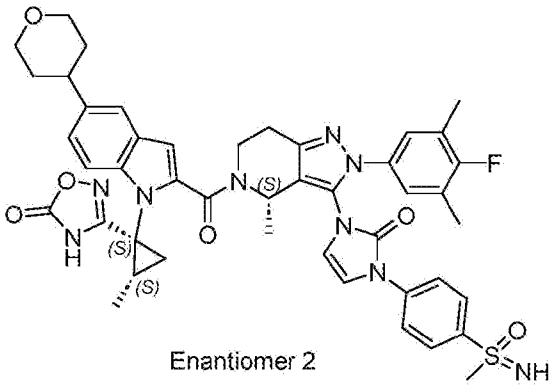


[1129] To a solution of 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (38.8 mg, 0.101 mmol) and 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 7-3a (50 mg, 0.101 mmol) in DMF (2 mL) , was added Et$_3$N (0.028 mL, 0.202 mmol) and HATU (58 mg, 0.152 mmol) . The reaction mixture was stirred at room temperature for 16 h. After filtration, the solution was purified by prep. HPLC (Column: Sunfire C18 19*250mm*10μm; Mobile P hase A: Water (0.1%formic acid) , B: CH_3CN; Flow rate: 20 mL/min; Gradient : 58%B to 68%B; Retention Time: 8.7 min) to obtain 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazol o [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (enantiomer 1) (33.3 mg, 38.3%yield) . LC-MS: m/z 860.4 $(M+H)^+$. ^{1}H NMR (400 MHz, D MSO-d6) δ 8.00 -7.87 (m, 4H) , 7.53 (s, 1 H) , 7.44 (d, J = 8.4 Hz, 1H) , 7.34 -7.27 (m, 3H) , 7.15 (d, J = 6.0 Hz, 2H) , 6.93 -6.87 (m, 2H) , 5.62 -5.45 (m, 1H) , 4. 63 -4.51 (m, 1H) , 3.99 -3.97 (m, 2H) , 3.63 -3.60 (m, 4H) , 3.11 (s, 3H) , 2.91 -2.86 (m, 3H) , 2.21 (s, 6H) , 1.78 -1.62 (m, 7H) , 1.44 (brs, 3H) , 1.18 (brs, 3H) .

[1130] Step E 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [-azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 7-3b

[1131] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 7-3a (60 mg, 0.101 mmol) in DCM (10 mL) was added 4.0 M HCl (gas) in 1, 4-dioxane HCl (0.25 mL) at 0 ℃. The reaction mixture was stirred at room temperature for 16 h. Then it w as concentrated to afford 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4- methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [azanylidene (me thyl) (oxo) -λ^6-sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 7-3b (55 mg, 100%yield) . LC-MS: m/z 495.3 (M+H) $^+$.

[1132] Step F 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 115)



Enantiomer 2

[1133] To a solution of 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (42.64 mg, 0.111 mmol) and 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [azanylidene (me thyl) (oxo) -λ^6-sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 7-3b (55 mg, 0.111 mmol) in DMF (2 mL) , were added HATU (63 mg, 0.167 mmol) and Et_3N (0.03 mL, 0.222 mmol) . The reaction mixture was stirred at room t emperature for 16 h. After filtration, the solution was purified by prep. HPLC (Colum n: Sunfire C18 19*250mm*10μm; Mobile Phase A: Water (0.1%formic acid) , B: CH_3CN; Flow rate: 20 mL/min; Gradient: 62%B to 62%B; Retention Time: 8. 1 min) to obtain 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (enantiomer 2) (15.3 mg, 16.0%yield) . LC-MS: m/z 860.4 (M+

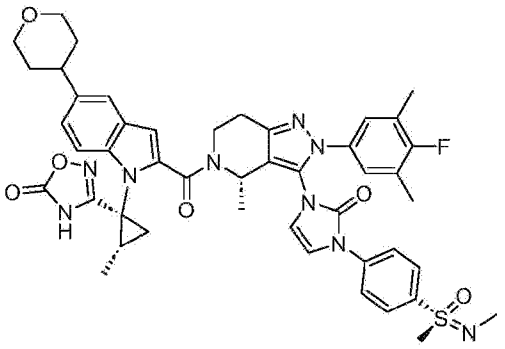
H) $^{+}$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.73 (brs, 1H) , 8.00 -7.80 (m, 4H) , 7. 53 (s, 1H) , 7.44 (d, J = 8.4 Hz, 1H) , 7.33 -7.27 (m, 3H) , 7.15 (d, J = 6.4 Hz , 2H) , 6.92 -6.88 (m, 2H) , 5.62 -5.45 (m, 1H) , 4.63 -4.51 (m, 1H) , 3.99 - 3.97 (m, 2H) , 3.63 -3.60 (m, 4 H) , 3.11 (s, 3H) , 2.91 -2.86 (m, 3H) , 2. 21 (s, 6H) , 1.78 -1.62 (m, 7H) , 1.44 (brs, 3H) , 1.18 (brs, 3H) .

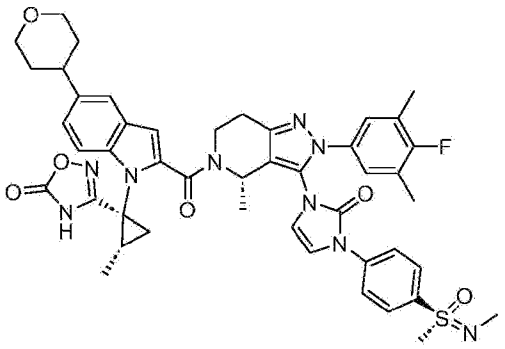
[1134] Example compounds 116 and 117, 132 and 133, 134 and 135, 136 and 137 , 138 and 139, 140 and 141 were synthesized using a similar procedure described in th e Example A7 above using the appropriate materials.

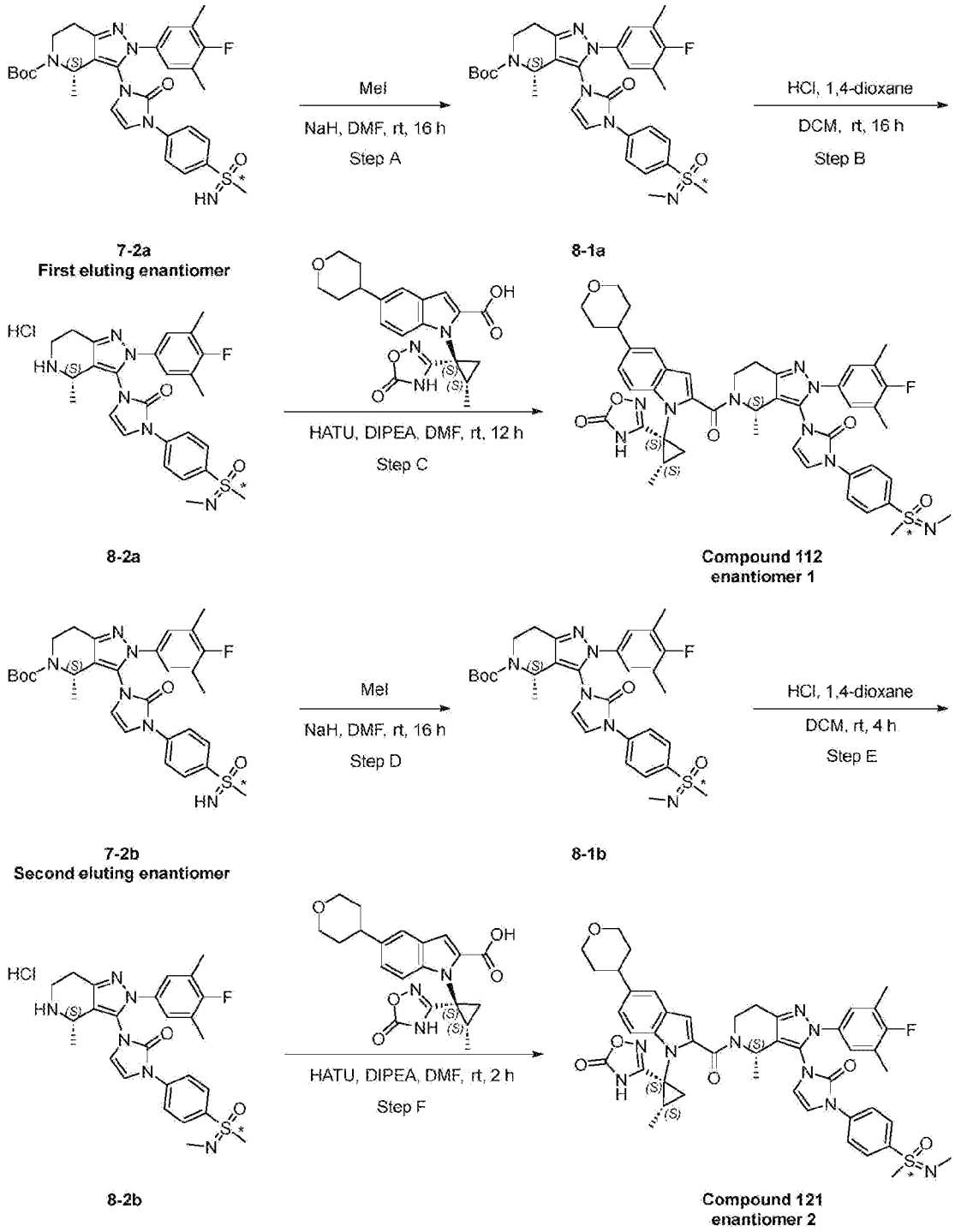
[1135] Example A8

[1136] 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [(S) - methyl (methylazanylidene) (oxo) -λ^{6}-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4- methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6- tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4- oxadiazol-5-one and

[1137] 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [(R) - methyl (methylazanylidene) (oxo) -λ^{6}-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4- methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6- tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4- oxadiazol-5-one (Compounds 112 and 121)







[1138] Step A tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 8-1a

[1139] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 7-2a (80 mg, 0.135 mmol) in DMF (5 mL) was added NaH (10.8 mg, 0.269 m

mol, 60%in oil) at rt. After being stirred at rt for 0.5 h, then iodomethane (0.025 m L, 0.404 mmol) was added. The resulting mixture was stirred at rt for another 16 h. T he mixture was poured into water (50 mL) , extracted with EtOAc (50 mL x 2) . The combined organic layer was washed with brine, dried over Na_2SO_4 , filtered and the residue was concentrated to obtain tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 8-1a (80 mg, 97.7%yield) . LC-MS: m/z 609.3 $(M+H)^+$.

[1140] Step B 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [methyl (methylazanylidene) (oxo) -λ^6 -sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 8-2a

[1141] The mixture of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 8-1a (40 mg, 0.066 mmol) and 4 M HCl (gas) in 1, 4-dioxane solution (0.2 mL) in DCM (1 mL) was stirred at rt for 16 h. The mixture was concentrated to ob tain 1- (4- (N, dimethylsulfonimidoyl) phenyl) -3- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -1, 3-dihydro-2H-imidazol-2-one hydrochloride salt 8-2a (35 mg, 97.7%yield) . LC-MS: m/z 509.2 $(M+H)^+$.

[1142] Step C 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (enantiomer 1) (Compound 112)

[1143] The mixture of 1- (4- (N, dimethylsulfonimidoyl) phenyl) -3- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -1, 3-dihydro-2H-imidazol-2-one hydrochloride salt 8-2a (70 mg, 0.128 mmol) , 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (49.2 mg, 0.128 mmol) , HATU (97.6 mg, 0.257 mmol) and DIPEA (49.7 mg , 0.385 mmol) in DMF (2 mL) was stirred at rt for 12 h. The mixture was purified by p rep. HPLC (Column: XBridge C18 19*250mm*10μm; Mobile Phase A: Water (0.05%NH_3. H_2O) , B: CH_3CN; Flow rate: 20 mL/min; Gradient: 27%B to 34%B; R etention Time: 8.85 -10.03 min) to obtain 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [-methyl (methylazanylidene) (oxo) -λ^6 -sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazol

o [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (enantiomer 1) (51.5 mg, 45.9%yield) . LC-MS: m/z 874.4 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.02 -7.92 (m, 3H) , 7.85 (s, 1H) , 7.56 -7.35 (m, 3H) , 7.28 -7.06 (m, 4H) , 6.98 -6.79 (m, 1H) , 6.59 -6.50 (m, 1H) , 5.71 -5.56 (m, 1H) , 4.44 -4.32 (m, 1H) , 4.02 -3.92 (m, 2H) , 3.65 -3.50 (m, 1H) , 3.47 -3.39 (m, 3H) , 3.14 (s, 3H) , 3.10 -3.08 (m, 1H) , 2.91 -2.79 (m, 2H) , 2.48 (s, 3H) , 2.19 (s, 6H) , 1.83 -1.70 (m, 4H) , 1.65 -1.56 (m, 1H) , 1.40 -1.32 (m, 1H) , 1.25 -1.05 (m, 7H) .

[1144] Step D tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4-[methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate

[1145] The mixture of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [-azanylidene (methyl) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 7-2b (50 mg, 0.084 mmol) in DMF (4 mL) was added NaH (4.0 mg, 0.101 mmol, 60 %in oil) a nd MeI (11.93 mg, 0.084 mmol) . The reaction mixture was stirred at rt for 16 h under N_2. Then reaction was quenched with water (50 ml) , extracted with EtO Ac (50 ml) . The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 8-1b (67 mg, crude) . LC-MS: m/z 609.0 (M+H) $^+$.

[1146] Step E 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [methyl (methylazanylidene) (oxo) -λ^6 -sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 8-2b

[1147] The mixture of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4-[methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 8-1b (67 mg, 0.110 mmol) in DCM (4 mL) was added 4 M HCl (gas) in diox ane (0.27 mL) . The reaction mixture was stirred rt for 4 h under N_2. The reaction mi xture was concentrated to afford 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [methyl (methyla zanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 8-2b (67 mg, crude) . LC-MS: m/z 509.0 (M+H) $^+$.

[1148] Step F 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4-[methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-

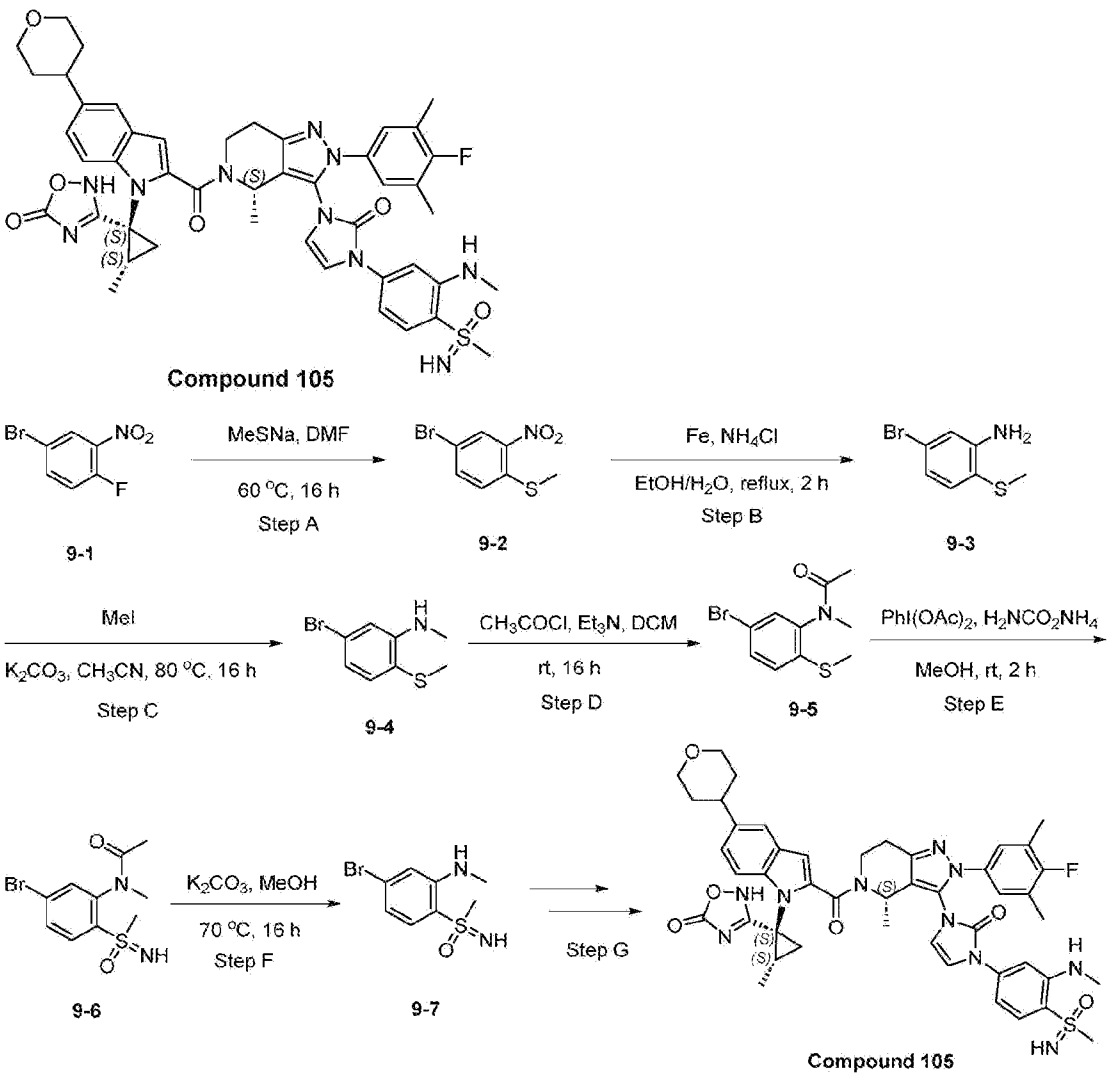
tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (enantiomer 2) (Compound 121)

[1149] To a solution of 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2, 3-dihydro-1H-imidazol-2-one hydrochloride salt 8-2b (67 mg, 0.132 mmol) in DMF (2 mL) was added 1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4- yl) indole-2-carboxylic acid (76 mg, 0.198 mmol) , DIPEA (85 mg, 0.659 mmol) , HATU (75 mg, 0.198 mmol) . The reaction mixture was stirred at rt for 2 h under N_2. The reaction mixture was purified using prep. HPLC (Column: Sunfire C18 19*250mm*10μm; Mobile Phase A: Water (0.1%formic acid) , B: CH_3CN; Flow rate: 20 mL/min; Gradient: 31%B to 41%B; Retention Time: 8.0 - 9.5 min) to afford 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [(R) -methyl (methylazanylidene) (oxo) -λ^6-sulfanyl] phenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (enantiomer 2) (11.3 mg, 9.8%yield) . LC-MS: m/z 874.5 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.01 -7.91 (m, 3 H) , 7.85 -7.76 (m, 1 H) , 7.51 -7.40 (m, 2 H) , 7.41 (d, J = 8.0 Hz, 1 H) , 7.29 -7.23 (m, 1 H) , 7.17 -7.09 (m, 3 H) , 6.98 -6.82 (m, 1 H) , 5.63 -5.56 (m, 1 H) , 4.46 -4.32 (m, 1 H) , 3.97 (d, J = 8.0 Hz, 2 H) , 3.71 -3.53 (m, 1 H) , 3.50 -3.36 (m, 3 H) , 3.13 -3.09 (m, 3 H) , 2.94 -2.84 (m, 2 H) , 2.12 (s, 6 H) , 1.80 -1.65 (m, 7 H) , 1.65 -1.56 (m, 1 H) , 1.41 -1.37 (m, 2 H) , 1.31 -1.27 (m, 1 H) , 1.17 -1.01 (m, 3 H) .

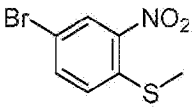
[1150] Example compounds 113 and 122, 144, 148, 149 and 150, 151 and 152 were synthesized using a similar procedure described in the Example A8 above using the appropriate materials, e.g., in step D.

[1151] Example A9

[1152] 3- [(1S, 2S) -1- (2- { [(S) -2- (4-fluoro-3, 5-xylyl) -3- {3- [4- (iminomethyloxothio) -3- (methylamino) phenyl] -2-oxo-1, 3-dihydro-1-imidazolyl} -4-methyl-4, 5, 6, 7-tetrahydro-2H-1, 2, 5-triazainden-5-yl] carbonyl} -5- (tetrahydro-2H-pyran-4-yl) -1-indolyl) -2-methylcyclopropyl] -1, 2, 4-oxadiazol-5 (4H) -one (Compound 105)

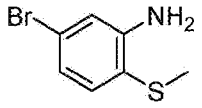


[1153] Step A (4-bromo-2-nitrophenyl) (methyl) sulfane



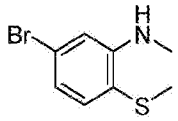
[1154] To the solution of 4-bromo-1-fluoro-2-nitrobenzene (5.0 g, 22.045 mmol) in DMF (50 mL) was added sodium methanethiolate (1994 mg, 26.455 mmo l) . The mixture was vigorously stirred at 60 ℃ for 16 h under argon protection. The resulting solution was diluted with water (60 mL) and extracted by dichloromethane (6 0 mL×3) . The combined organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash silica gel chromatogra phy (Silica Flash Column, Eluent of 100%PE) to (4-bromo-2-nitrophenyl) (met hyl) sulfane (2.7 g, 49.6%yield) . ^{1}H NMR (400 MHz, DMSO-d6) δ 8.37 (d, J = 2.0 Hz, 1 H) , 7.93 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1 H) , 7.54 (d, J = 8.4 Hz, 1 H) , 2.82 (s, 3 H) .

[1155] Step B 5-bromo-2- (methylthio) aniline



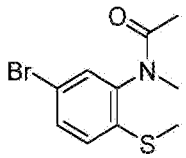
[1156] To a solution of (4-bromo-2-nitrophenyl) (methyl) sulfane (2.33 g, 9.392 mmol) in EtOH/H_2O (50 mL/7 mL) was added Fe powder (2.62 g, 55.84 mmol) and NH_4 Cl (5.02 g, 93.92 mmol) . The mixture was stirred at 75 ℃ for 2 h. After cooling, the mixture was diluted with EtOAc (100 mL) and water (50 mL) . The o rganic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated to afford 5-bromo-2- (methylthio) aniline (2.16 g, crude) . LC-MS: m/z 218.0 $(M+H)^+$.

[1157] Step C 5-bromo-N-methyl-2- (methylthio) aniline



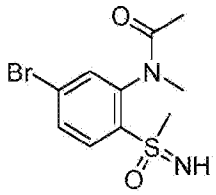
[1158] To a solution of 5-bromo-2- (methylthio) aniline (380 mg, 1.742 mmol) in CH_3CN (15 mL) was added iodomethane (0.21 mL, 2.613 mmol) and K_2CO_3 (482 mg, 3.484 mmol) . The reaction mixture was stirred at 80 ℃ for 16 h. After cool ing, the mixture was diluted with EtOAc (100 mL) and water (50 mL) . The organic layer was separated, washed with brine, dried with Na_2SO_4 and concentrated. The residue was purified by flash silica gel chromatography (Silic a Flash Column, Eluent of 0-15% EtOAc/PE gradient) to afford the title compound 5-bromo-N-methyl-2- (methylthio) aniline (230 mg, 56.9%yield) . LC-MS: m/z 232.0 $(M+H)^+$.

[1159] Step D N- (5-bromo-2- (methylthio) phenyl) -N-methylacetamide



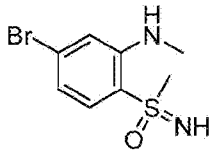
[1160] To the mixture of 5-bromo-2- (methylsulfanyl) phenyl] (methyl) amine (1.20 g, 5 .062 mmol) and TEA (2.11 mL, 15.185 mmol) in DCM (10.0 mL) at 0 ℃, w as added CH_3COCl (0.72 mL, 10.12 mmol) . After addition, the reaction mixture wa s warmed to room temperature and stirred for 16 h. The reaction was quenched with water (50 mL) , extracted with EtOAc (50 mL x2) . The organic layer was washed with brine, dried over Na_2SO_4 and concentrated . The residue was purified by flash silica gel chromatography (Silica Flash Column, E luent of 0-10%EtOAc/PE gradient) to afford N- (5-bromo-2- (methylthio) phenyl) -N-methylacetamide (1.0 g, 72.3%yield) . LC-MS: m/z 274.0 $(M+H)^+$.

[1161] Step E N- (5-bromo-2- (S-methylsulfonimidoyl) phenyl) -N-methylacetamide



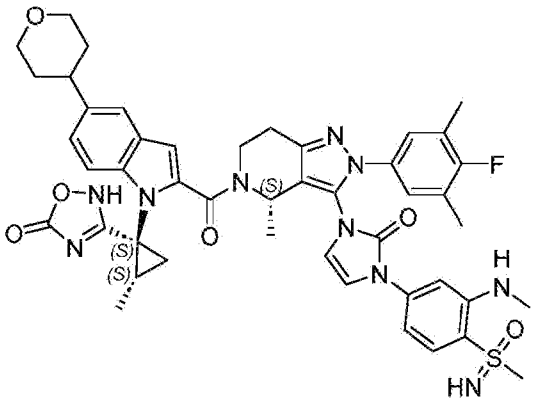
[1162] To a solution of N- (5-bromo-2- (methylthio) phenyl) -N-methylacetamide (1.0 g, 3.66 mmol) in MeOH (10 mL) was added PhI (OAc) $_2$ (2.36 g, 7.29 mm ol) and $H_2NCO_2NH_4$ (570 mg, 7.29 mmol) . The reaction mixture was sti rred at rt for 2 h under N_2. The mixture was poured into water (100 mL) , extracted with DCM (100 mL x 2) . The combined organic layer was washed with br ine, dried over Na_2SO_4, filtered and concentrated. The residue was purifi ed by flash silica gel chromatography (Silica Flash Column, Eluent of 0-5%MeOH/ DCM gradient) to afford N- (5-bromo-2- (S-methylsulfonimidoyl) phenyl) -N- methylacetamide (300 mg, 26.9%yield) . LC-MS: m/z 305.1 $(M+H)^+$.

[1163] Step F N- (5-bromo-2- (S-methylsulfonimidoyl) phenyl) -N-methylacetamide



[1164] To a solution of N- (5-bromo-2- (S-methylsulfonimidoyl) phenyl) -N- methylacetamide (220 mg, 0.721 mmol) in MeOH (5 mL) was added K_2CO $_3$ (399 mg, 2.883 mmol) . The mixture was stirred at 70 ℃ for 16 h under N_2 in a sealed tube. After cooling, the mixture was poured into water (100 mL) , extrac ted with DCM (100 mL x 2) . The combined organic layer was washed wi th brine, dried over sodium sulfate, filtered and concentrated to obtain N- (5-bromo- 2- (S-methylsulfonimidoyl) phenyl) -N-methylacetamide (134 mg, 70.6%yield) . LC- MS: m/z 263.0 $(M+H)^+$.

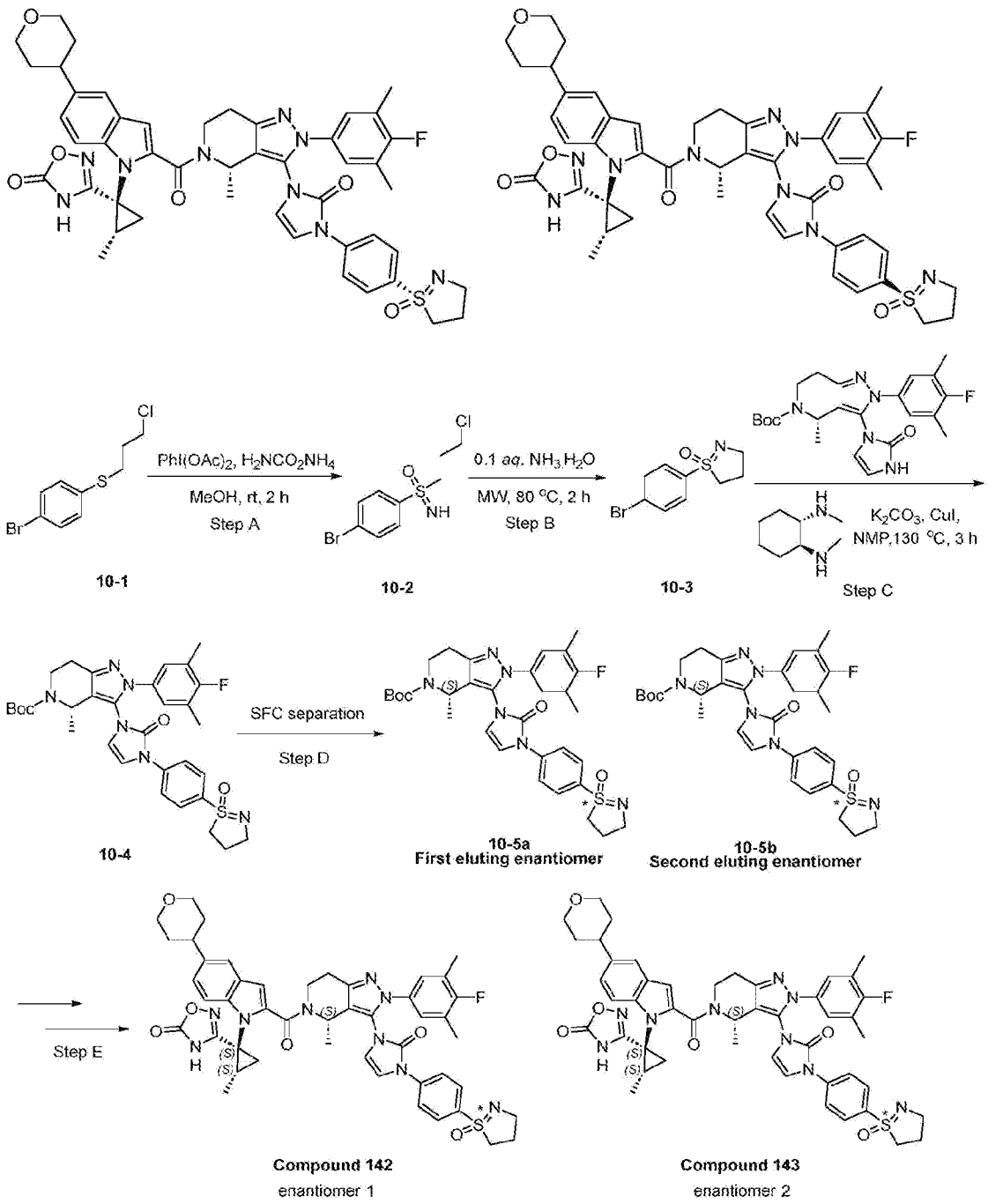
[1165] Step G 3- [(1S, 2S) -1- (2- { [(S) -2- (4-fluoro-3, 5-xylyl) -3- {3- [4- (iminomethyloxothio) -3- (methylamino) phenyl] -2-oxo-1, 3-dihydro-1-imidazolyl} - 4-methyl-4, 5, 6, 7-tetrahydro-2H-1, 2, 5-triazainden-5-yl] carbonyl} -5- (tetrahydro- 2H-pyran-4-yl) -1-indolyl) -2-methylcyclopropyl] -1, 2, 4-oxadiazol-5 (4H) - one (Compound 105)



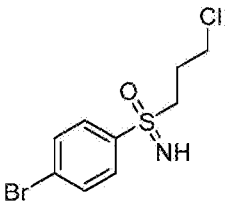
[1166] 3- [(1S, 2S) -1- (2- { [(S) -2- (4-fluoro-3, 5-xylyl) -3- {3- [4- (iminomethyloxothio) -3- (methylamino) phenyl] -2-oxo-1, 3-dihydro-1-imidazolyl} -4-methyl-4, 5, 6, 7-tetrahydro-2H-1, 2, 5-triazainden-5-yl] carbonyl} -5- (tetrahydro-2H-pyran-4-yl) -1-indolyl) -2-methylcyclopropyl] -1, 2, 4-oxadiazol-5 (4H) -one (Compound 105) was synthesized according to the procedures described for the preparation of Example A2 (step B to D) by using N- (5-bromo-2- (S-methylsulfonimidoyl) phenyl) -N-methylacetamide in step B. LC-MS: m/z 889.4 $(M+H)^+$. (400 MHz, DMSO-d6) δ 7.74 (s, 1H) , 7.52 (s, 1H) , 7.44 (d, J = 8.4 Hz, 1H) , 7.28 -7.26 (m, 2H) , 7.15 (d, J = 6.0 Hz, 2H) , 7.06 (s, 1H) , 6.87 (s, 1H) , 5.67 -5.39 (m, 1H) , 4.50 (brs, 1H) , 3.52 -3.43 (m, 4H) , 3.01 (s, 3H) , 2.91 -2.75 (m, 3H) , 2.22 (s, 6H) , 1.78 -1.68 (m, 7H) , 1.43 (s, 3H) , 1.17 (brs, 3H) .

[1167] Example A10

[1168] (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-2-yl} carbonyl) -3- (3- {4- [(1S) -1-oxo-1λ^6-4H,3H, 5H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine and (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [(1R) -1-oxo-1λ^6-4H, 3H, 5H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -5- ({1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine (Compounds 142 and 143)



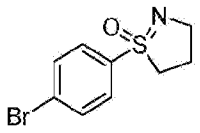
[1169] Step A (4-bromophenyl) (3-chloropropyl) (oxo) -λ^6-sulfanimine



[1170] To a solution of (4-bromophenyl) (3-chloropropyl) sulfane (3.78 g, 14.214 mmol) in MeOH (45 mL) was added PhI (OAc) $_2$ (13.73 g, 42.641 mmol) and H $_2$NCO$_2$NH$_4$ (4.43 g, 56.855 mmol) . The reaction mixture was stirred at 25 ℃ fo

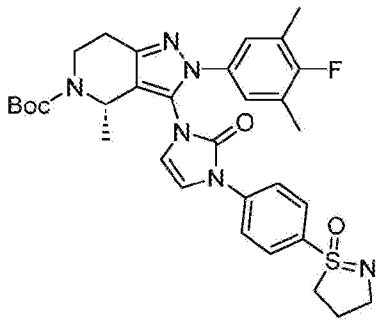
r 2 h under N_2. The reaction mixture was poured into sat. aq. sodium bicarbonate s olution (20 mL) , extracted with EtOAc (20 mL x 3) . The residue was purified by flas h silica gel chromatography (Silica Flash Column, Eluent of 0-50%EtOAc/PE gradi ent) to afford (4-bromophenyl) (3-chloropropyl) (oxo) -λ^6-sulfanimine (3.50 g, 83.1%yield) . LC-MS: m/z 296.0 $(M+H)^+$.

[1171] Step B 1- (4-bromophenyl) -1λ^6-5H, 4H, 3H-1, 2-thiazol-1-one



[1172] A mixture of (4-bromophenyl) (3-chloropropyl) (oxo) -λ^6-sulfanimine (3.50 3 g, 11.877 mmol) in 0.1%aq. $NH_3{\cdot}H_2O$ (72 mL) was stirred at 80 ℃ for 2 h under N_2 in a sealed tube. After cooling, the mixture was poured into water (100 mL) and extr acted with DCM (100 mL x 2) . The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was pur ified by flash silica gel chromatography (Silica Flash Column, Eluent of 0-50%EtOAc/PE gradient) to afford1- (4-bromophenyl) -1λ^6-5H, 4H, 3H-1, 2-thiazol-1-one (1.43 g, 46.2%yield) . LC-MS: m/z 260.1 $(M+H)^+$.

[1173] Step C tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- {2-oxo-3- [4- (1-oxo-1λ^6-4H, 5H, 3H-1, 2-thiazol-1-yl) phenyl] imidazol-1-yl} -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



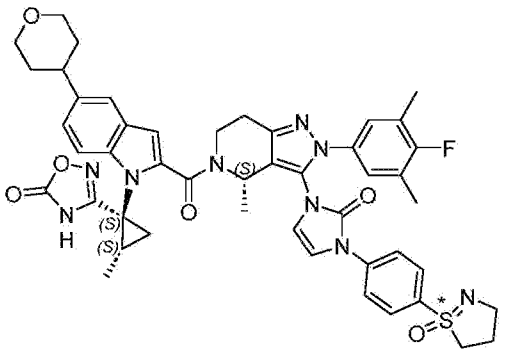
[1174] To a solution of 1- (4-bromophenyl) -1λ^6-5H, 4H, 3H-1, 2-thiazol-1-one (1.43 g, 5.48 5 mmol) and tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-3H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (2.20 g, 4.987 mmol) in NMP (30 mL) was added methyl [(1S, 2S) -2- (methylamino) cy clohexyl] amine (1.06 g, 7.480 mmol) , potassium carbonate (1.38 g, 9.973 mmol) , and CuI (1.14 g, 5.984 mmol) . The reaction mixture was stirred at 120 ℃ for 4 h under N_2. After cooling, the mixture was poured into water (20 mL) , extract ed with EtOAc (20 mL × 3) . The combined organic layers were washed with brine (20 mL × 3) , dried over anhydrous sodium sulfate, filtered and concentrat ed. The resulting residue was purified by flash silica gel chromatography (Silica Fla

sh Column, Eluent of 0-50%EtOAc/PE gradient) to afford the tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- {2-oxo-3- [4- (1-oxo-1λ^6-4H, 5H, 3H-1, 2-thiazol-1-yl) phenyl] imidazol-1-yl} -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (3.12 g, 91.7%yield) . LC-MS: m/z 621.4 (M+H) $^+$.

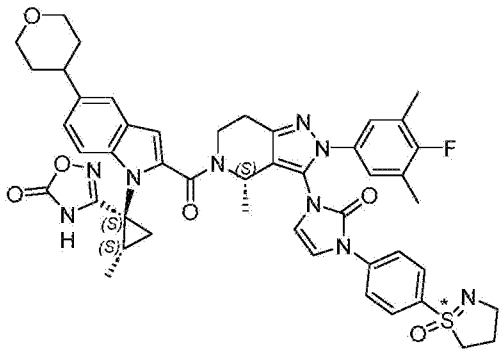
[1175] Step D tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [1-oxo-1λ^6 -4H, 5H, 3H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 10-5a (first eluting enantiomer) and tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [1-oxo-1λ^6-4H, 5H, 3H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 10-5b (second eluting enantiomer)

[1176] The compound mixture tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- {2-oxo-3- [4- (1-oxo-1λ^6-4H, 5H, 3H-1, 2-thiazol-1-yl) phenyl] imidazol-1-yl} -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (4.20 g, 6.774 mmol) was separated by SFC (Column: REGIS (S, S) WHELK-O1 250*25 mm 10 μm, Mobile phase A (Supercritical CO_2) , Mobile phase B (MeOH (0.1%7.0 M ammonia in MeOH)) , Gradient: A/B = 65/35, Flow rate: 70 mL/min) to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [-1-oxo-1λ^6-4H, 5H, 3H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 10-5a (first eluting enantiomer) (2.00 g, 47.6%yield) as the fast eluent (Rt = 1.95 min) , LC-MS: m/z 621.4 (M+H) $^+$. And tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [-1-oxo-1λ^6-4H, 5H, 3H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 10-5b (second eluting enantiomer) (2.20 g, 52.4%yield) as the slow eluent (Rt = 2.74 min) , LC-MS: m/z 621.4 (M+H) $^+$.

[1177] Step E (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-2-yl} carbonyl) -3- (3- {4- [1-oxo-1λ^6-4H, 3H, 5H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine and (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [1-oxo-1λ^6-4H, 3H, 5H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -5- ({1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine (Compounds 142 and 143) .



Compound 142
enantiomer 1



Compound 143
enantiomer 2

[1178] (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-2-yl} carbonyl) -3- (3- {4- [1-oxo-1λ^6-4H, 3H, 5H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine (Compound 142) (enantiomer 1) and (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [1-oxo-1λ^6-4H, 3H, 5H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -5- ({1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-2-yl} carbonyl) -4-methyl- 4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine (Compound 143) (enantiomer 2) were synthesized according to the procedures described for the preparation of Example A7 (step C to F) by using tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [1-oxo-1λ^6-4H, 5H, 3H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 10-5a (first eluting enantiomer) in step C and tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [1-oxo-1λ^6-4H, 5H, 3H-1, 2-thiazol-1-yl] phenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate 10-5b (second eluting enantiomer) in step E.

[1179] Compound 142: LC-MS: m/z 886.4 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.95 -7.88 (m, 4H) , 7.49 (s, 1H) , 7.43 (d, J= 8.4 Hz, 1H) , 7.32 (m, 1H) , 7.23 (d, J= 8.4 Hz, 1H) , 7.17 -7.15 (m, 2H) , 6.98 (m, 1H) , 6.77 (m, 1H) , 5.55 (m, 1H) , 4.39 (m, 1H) , 4.00 -3.97 (m, 2H) , 3.86 -3.81 (m, 1H) , 3.72 -3.69 (m, 1H) , 3.52 -3.46 (m, 2H) , 3.40 -3.32 (m, 2H) , 2.90 -2.83 (m, 3H) , 2.33 -2.26 (m, 3H) , 2.22 (s, 6H) , 1.76 -1.69 (m, 5H) , 1.65 (m, 2H) , 1.39 (s, 3H) , 1.20 (s, 3H) .

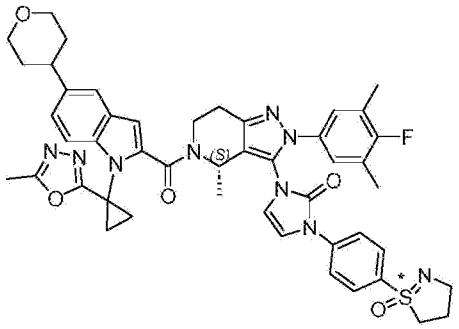
[1180] Compound 143: LC-MS: m/z 886.4 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.59 (brs, 1H) , 7.95 -7.91 (m, 4 H) , 7.53 (s, 1H) , 7.44 (d, J= 8.4 Hz, 1H) , 7.37 (m, 1 H) , 7.28 (d, J=8.4 Hz, 1H) , 7.16 -7.14 (m, 2H) , 6.96 (m, 1H) , 6.88 (m, 1H) , 5.57 (m, 1H) , 4.50 (m, 1H) , 4.00 -3.97 (m, 2H) , 3.89 -3.84 (m, 1H) , 3.

77 -3.72 (m, 1H) , 3.53 -3.46 (m, 4H) , 2.92 -2.86 (m, 2H) , 2.36 -2.28 (m, 3H) , 2. 22 (s, 6H) , 2.05 -2.02 (m, 1H) , 1.78 -1.73 (m, 6H) , 1.66 (m, 1H) , 1.43 (s, 3H) , 1.17 (s, 3H) .

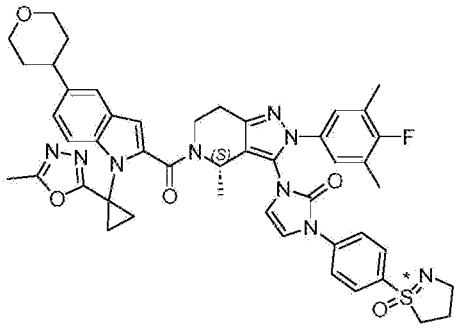
[1181] Example compound 130 and 131 was synthesized using a similar procedu re described in the Example A10 above using the appropriate materials in step D.

[1182] Example A11

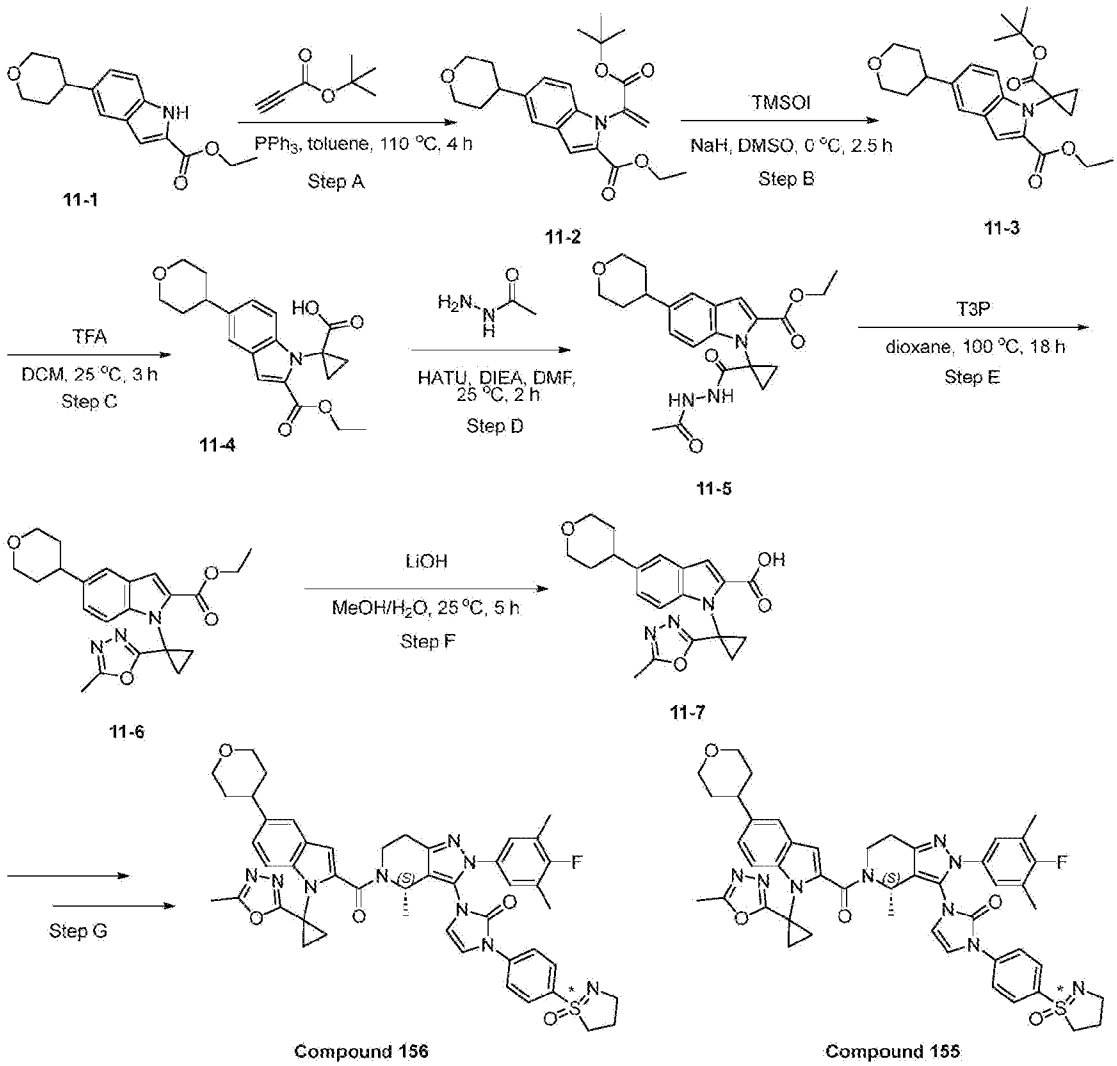
[1183] 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-5- (1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carbonyl) -4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- (1-oxido-4, 5-dihydro-3H-1λ^6-isothiazol-1-yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one (Compound 156) and 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-5- (1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carbonyl) -4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- (1-oxido-4, 5-dihydro-3H-1λ^6-isothiazol-1-yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one (Compound 155)



Compound 156



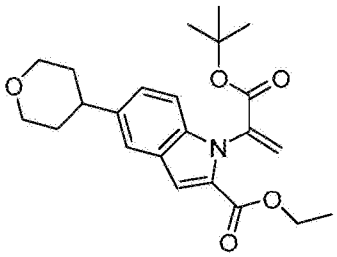
Compound 155



11-1 11-2 11-3 11-4 11-5 11-6 11-7

Compound 156 Compound 155

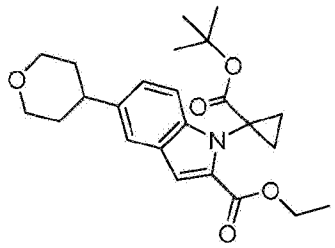
[1184] Step A ethyl 1- (3- (tert-butoxy) -3-oxoprop-1-en-2-yl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate



[1185] To a solution of ethyl 5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate (4.00 g, 14.63 mmol) in toluene (40 mL) were added triphenylphosphane (2. 69 g, 10.24 mmol) and tert-butyl propiolate (2.77 g, 21.95 mmol) . After addit ion, the reaction mixture was stirred at 110 ℃ for 4 h under N2 atmosphere. After coo ling, the reaction mixture was diluted with H_2O (40 mL) , extracted with ethyl a cetate (40 mL × 3) . The combined organic layers were washed with br ine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by

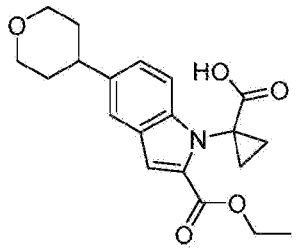
silica gel column chromatography eluting with 0-50%EtOAc/PE to give ethyl 1- (3- (tert-butoxy) -3-oxoprop-1-en-2-yl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate (3.00 g, 51.3%yield) . LC-MS: m/z 400.4 $(M+H)^+$.

[1186] Step B ethyl 1- (1- (tert-butoxycarbonyl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate



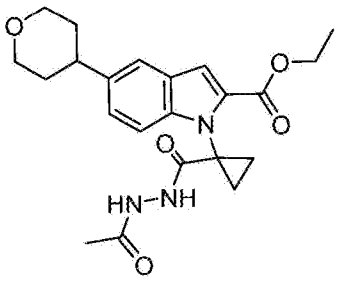
[1187] To a solution of NaH (0.27 g, 11.26 mmol, 60%purity) in DMSO (40 mL) was added trimethylsulfoxonium iodide (2.48 g, 11.26 mmol) in portions for 30 min, f ollowed by ethyl 1- (3- (tert-butoxy) -3-oxoprop-1-en-2-yl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate (3.00 g, 7.51 mmol) at 0 ℃. After addition, the reaction mixture was stirred at 25 ℃ for 2 h under N2 atmosphere. The resulting mixture was d iluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL × 3) . The combine d organic layers were washed with brine, dried over Na_2SO_4, filtered and co ncentrated. The residue was purified by silica gel column chromatography eluting with 0-50%EtOAc/PE to give ethyl 1- (1- (tert-butoxycarbonyl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate (2.00 g, 64.5%yield) . LC-MS: m/z 414.4 $(M+H)^+$.

[1188] Step C 1- (2- (ethoxycarbonyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indol-1-yl) cyclopropane-1-carboxylic acid



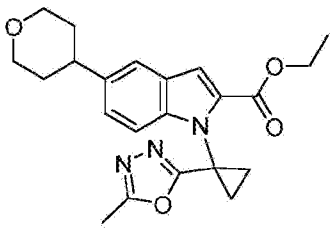
[1189] To a solution of ethyl 1- (1- (tert-butoxycarbonyl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate (0.70 g, 1.693 mmol) in DCM (10 mL) was added TFA (10 mL, 152 mmol) . After addition, the reaction mixture was stirred at 25 ℃ for 3 h. The resulting mixture was concentrated to give 1- (2- (ethoxycarbonyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indol-1-yl) cyclopropane-1-carboxylic acid (0.60 g, crude) , which was used for the next step directly without further purificati on. LC-MS: m/z 358.3 $(M+H)^+$.

[1190] Step D ethyl 1- (1- (2-acetylhydrazine-1-carbonyl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate



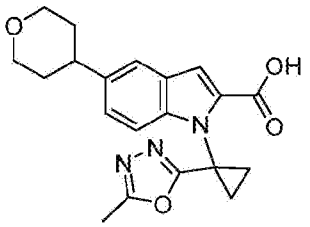
[1191] To a solution of 1- (2- (ethoxycarbonyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indol-1-yl) cyclopropane-1-carboxylic acid (600.0 mg, 3.02 mmol) in DMF (10 mL) were added acetohydrazide (185.0 mg, 2.52 mmol) , HATU (957.0 mg, 2.52 mmol) and DIEA (1.17 mL, 6.72 mmol) . After addition, the mixtu re was stirred at 25 ℃ for 2 h. The resulting mixture was diluted with H_2 O (20 mL) and extracted with ethyl acetate (20 mL × 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The r esidue was purified by silica gel column chromatography eluting with 5-10%MeOH/ DCM to afford ethyl 1- (1- (2-acetylhydrazine-1-carbonyl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate (0.40 g, 57.6%yield) . LC-MS: m/z 414.2 $(M+H)^+$.

[1192] Step E ethyl 1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate



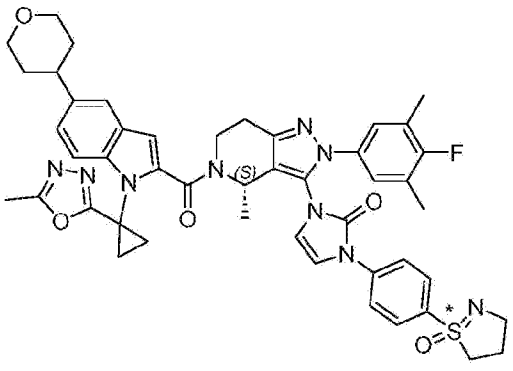
[1193] To a solution of ethyl 1- (1- (2-acetylhydrazine-1-carbonyl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate (700.0 mg, 1.81 mmol) in 1, 4-dioxane (10 mL) was added T3P (1.54 g, 4.84 mmol, 50%purity) . After addition, the mixture was degassed and purged with N2 for 3 times and stirred at 100 ℃ for 18 h under N2 atmosphere. The reaction mixture was diluted with H_2 O (20 mL) and extracted with ethyl acetate (20 mL × 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The r esidue was purified by silica gel column chromatography 10-30%EtOAc/PE to af ford ethyl 1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate (200.0 mg, 52.3%yield) . LC-MS: m/z 396.2 (M +H) $^+$.

[1194] Step F 1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid

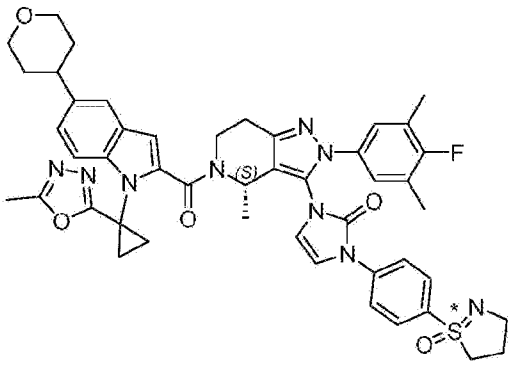


[1195] To a solution of ethyl 1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylate (200.0 mg, 0.51 mmol) in THF (0.95 mL) , MeOH (0.95 mL) and H_2O (0.95 mL) was added lithium hydr oxide (24.23 mg, 1.01 mmol) . The mixture was stirred at 25 ℃for 5 h. The resulting m ixture was concentrated under reduced pressure to remove solvent. The residue was dil uted with water (5 mL) and adjusted pH to ~4 with 1 M HCl, extracted with EtOAc (20 mL × 3) . The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give 1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (150.0 mg, 80.6%yield) . LC-MS: m/z 368.2 $(M+H)^+$.

[1196] 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-5- (1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carbonyl) -4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- (1-oxido-4, 5-dihydro-3H-1λ^6-isothiazol-1-yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one (Compound 156) and 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-5- (1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carbonyl) -4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- (1-oxido-4, 5-dihydro-3H-1λ^6-isothiazol-1-yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one (Compound 155) .



Compound 156



Compound 155

[1197] 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-5- (1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carbonyl) -4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- (1-oxido-4, 5-dihydro-

3H-1λ^6-isothiazol-1-yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one (Compound 156) (enantiomer 1) and 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-5- (1- (1- (5-methyl-1, 3, 4-oxadiazol-2-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carbonyl) -4, 5, 6, 7- tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- (1-oxido-4, 5-dihydro-3H-1λ^6-isothiazol-1-yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one (Compound 155) (enantiomer 2) were synthesized according to the procedures described for the preparation of Example A10 (step E) .

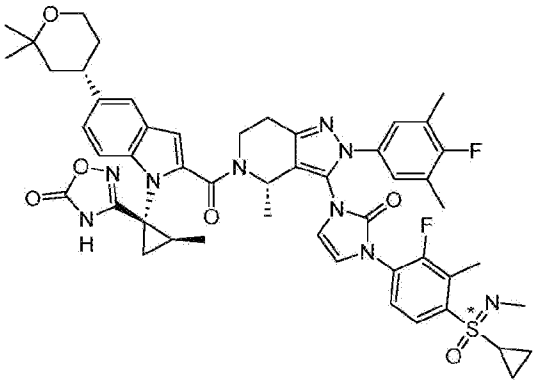
[1198] Compound 156: LC-MS: m/z 870.2 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.95 (m, 4H) , 7.55 -7.52 (m, 2H) , 7.40 -7.38 (m, 1H) , 7.26 (d, J = 8.0 Hz , 1H) , 7.17 (d, J = 4.0 Hz, 2H) , 7.04 -7.02 (m, 1H) , 6.80 (s, 1H) , 5.55 -5.53 (m, 1H) , 4.03 -4.00 (m, 2H) , 3.89 -3.83 (m, 1H) , 3.75 -3.70 (m, 1H) , 3. 55 -3.49 (m, 2H) , 3.47 -3.36 (m, 3H) , 2.86 (s, 3H) , 2.39 -2.36 (m, 3H) , 2.35 -2.29 (m, 2H) , 2.25 -2.23 (s, 6H) , 1.89 -1.76 (m, 8H) , 1.37 -1.34 (m, 4H) .

[1199] Compound 155: LC-MS: m/z 870.2 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.94 (m, 4H) , 7.55 -7.52 (m, 2H) , 7.40 -7.38 (m, 1H) , 7.26 (d, J = 8.0 Hz , 1H) , 7.16 (d, J = 4.0 Hz, 2H) , 7.04 -7.02 (m, 1H) , 6.80 (s, 1H) , 5.55 -5.50 (m, 1H) , 4.03 -4.01 (m, 2H) , 3.87 -3.83 (m, 1H) , 3.76 -3.71 (m, 1H) , 3. 56 -3.49 (m, 2H) , 3.47 -3.37 (m, 3H) , 2.95 -2.82 (m, 3H) , 2.40 (s, 3H) , 2.34 -2.27 (m, 2H) , 2.24 -2.23 (s, 6H) , 1.90 -1.73 (m, 8H) , 1.37 -1.30 (m, 4H) .

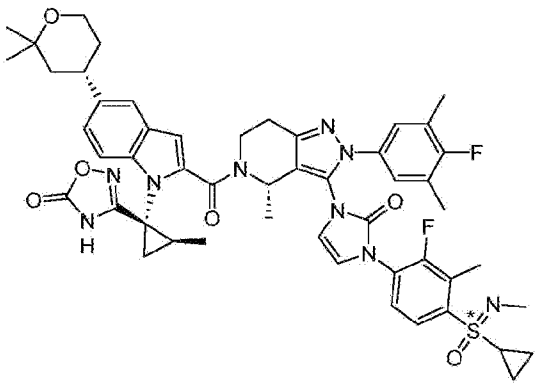
[1200] Example compounds 153, 157 and 158, 159 to 163, 165, 170 and 171 wer e synthesized using a similar procedure described in the Example A11 above using the appropriate materials.

[1201] Example A12

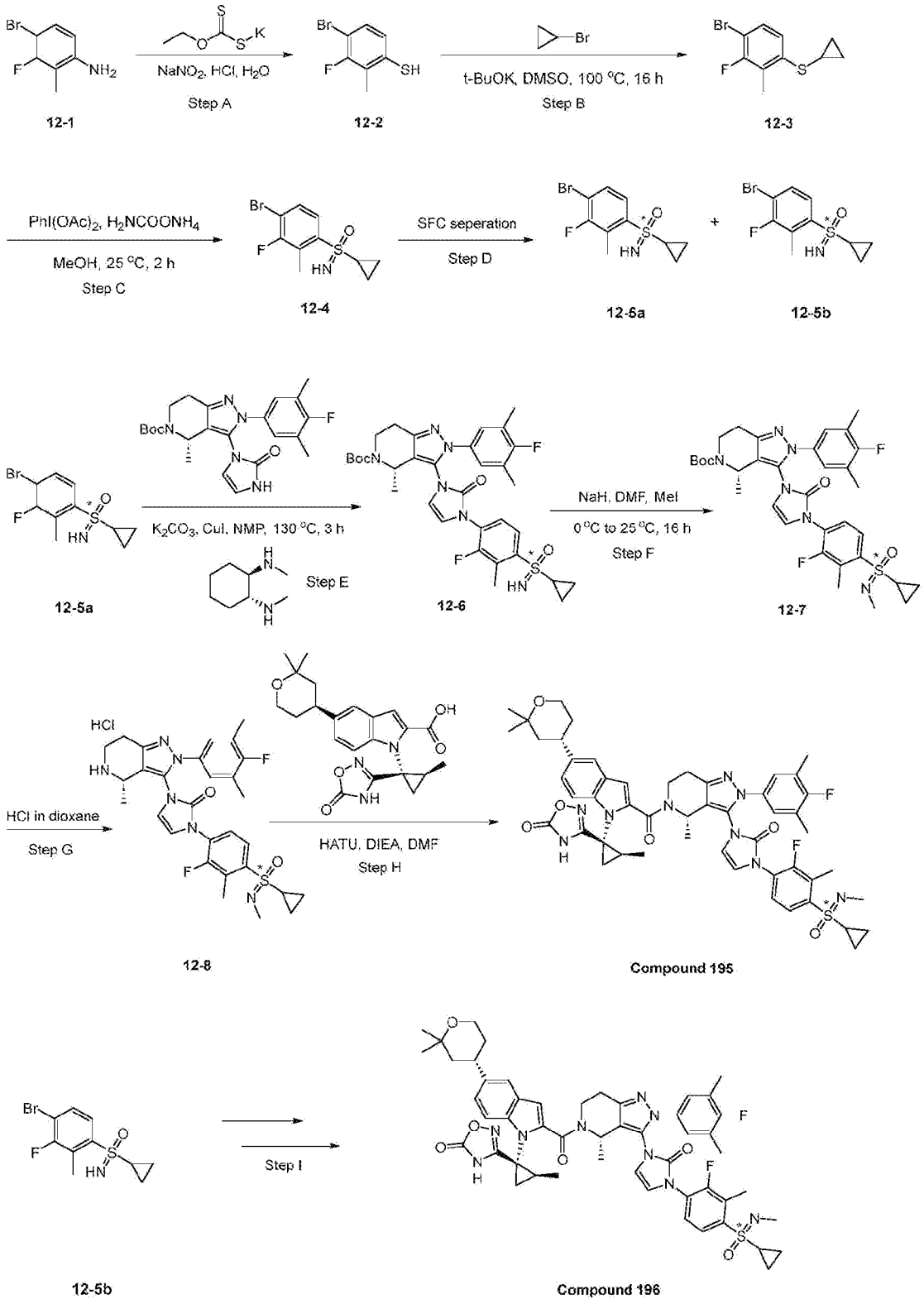
[1202] 3- [(1S, 2S) -1- {5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (me thylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} indol-1-yl} -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 195) (enantiomer 1) and 3- [(1S, 2S) -1- {5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (me thylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} indol-1-yl} -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 196) (enantiomer 2)



Compound 195

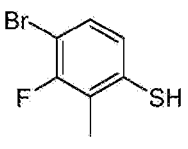


Compound 196



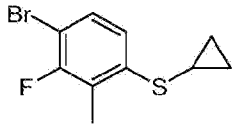
12-1 12-2 12-3 12-4 12-5a 12-5b 12-6 12-7 12-8 Compound 195 12-5b Compound 196

[1203] Step A 4-bromo-3-fluoro-2-methylbenzene-1-thiol



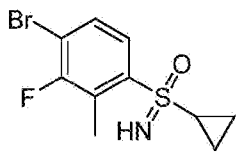
[1204] To a mixture of 4-bromo-3-fluoro-2-methylaniline (2.7 g, 13.233 mmol) in H2O (10 mL) was added conc. HCl (2.205 mL, 26.465 mmol) . The reaction mixture was cooled in an ice/NaCl bath (approximately -5 to -10 ℃) , a solution of sodium nitrite (958.6 mg, 13.894 mmol) in H_2O (10 mL) was added slowly over 10 minutes. The mixture was stirred for an additional 30 minutes with cooling. Separately, a solution of [(ethoxythioxomethyl) sulfanyl] potassium (2545.3 mg, 15.879 mmol) in H2O (30 mL) was prepared and heated to 65 ℃. The cold solution of diazonium salt was then added slowly over 20 minutes to the warmed solution of potassium ethyl xanthogenate. The reaction mixture was stirred for an additional 30 minutes at 65 ℃ and then cooled to ambient temperature. A solution of NaOH (2646.6 mg, 66.165 mmol) in H_2O (10 mL) was added, the reaction was stirred at 70 ℃ for 18 h. After the reaction was completed, monitored by TLC, the mixture was cooled to rt, the mixture was poured into ice (200 g) , acidified with concentrated HCl to pH=1, the mixture was extracted with EtOAc (50 mL x 3) . The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to afford 4-bromo-3-fluoro-2-methylbenzene-1-thiol (3.7 g, crude) , used for the next step without purification.

[1205] Step B (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) sulfane



[1206] To a solution of 4-bromo-3-fluoro-2-methylbenzene-1-thiol (3.7 g, 16.735 mmol) in DMSO (60 mL) were added potassium tert-butoxide (3.76 g, 33.471 mmol) and bromocyclopropane (10.12 g, 83.676 mmol) , the reaction was stirred at 100 ℃ for 18 h under N_2. TLC showed the reaction was completed. The mixture was poured into water (100 mL) , extracted with EtOAc (200 mL x 2) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel chromatography (eluting PE 100%) to afford (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) sulfane (2.23 g, 50.3%yield) .

[1207] Step C (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine



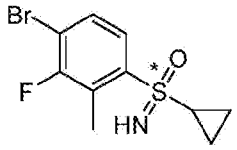
[1208] To a solution of (4-bromo-2-fluorophenyl) (cyclopropyl) sulfane (2.2 g, 8.524 mmol) in MeOH (30 mL) was added (diacetoxyiodo) benzene (8.29 g, 25.572 mmol) and ammonium carbaminate (2.66 g, 34.095 mmol) . The reacti

on was stirred at room temperature for 1 h. After the reaction was completed, water (50 mL) was added. The mixture was extracted with EtOAc (30 mL x 3) .

The combined organic layers were washed with brine, dried over sodium sulfate, filte red and concentrated. The resulting residue was purified by silica gel chromatography (eluting 0-50%EtOAc/PE) to afford (4-bromo-3-fluoro-2-methylphenyl) (cy clopropyl) (oxo) -λ^6-sulfanimine (1.17 g, 47.5%yield) . LC-MS: m/z 294.0 $(M+H)^+$.

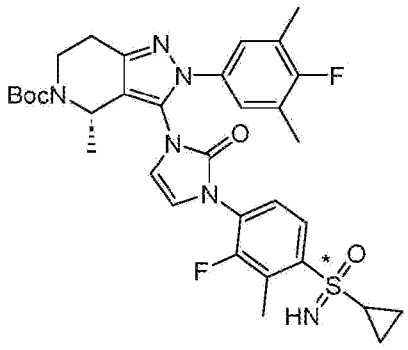
[1209] Step D (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (enantiomer 1)

[1210] 12-5a



[1211] The compound mixture (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (1.17 g, 4.00 mmol) was separated by SFC (Column: DAICELCHIRALCEL®AS250 mm*25 mm, 10 μm, Mobile phase A (Supercritical CO_2) , Mobile phase B (MeOH (0.1%7.0 M Ammonia in MeOH)) , Gradient: B = 20%, Flow rate: 100 mL/min, Column temp.: 25 °C.) to afford (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (enantiomer 1) (517 mg , 44.2%yield) as the fast eluent, LC-MS: m/z 294.0 $(M+H)^+$. And (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (enantiomer 2) (460 mg , 39.3%yield) as the slow eluent, LC-MS: m/z 294.0 $(M+H)^+$.

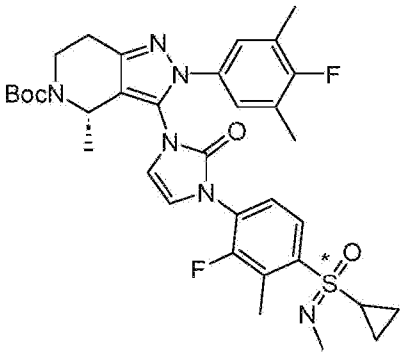
[1212] Step E 2-methylpropan-2-yl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [azanylidene (cyclopropyl) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1213] To a solution of 2-methylpropan-2-yl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-3H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (2.35 g, 5.320 mmol) in NMP (10 mL) were added (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (520 mg, 1.780 mmol) ,

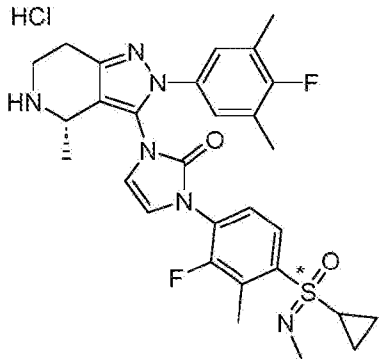
methyl [(1R, 2R) -2- (methylamino) cyclohexyl] amine (379.8 mg, 2.670 m mol) , CuI (406.8 mg, 2.136 mmol) and K_2CO_3 (491.9 mg, 3.560 mmol) . The reac tion mixture was stirred at 130 ℃for 2 h under N2. After cooling, the mixture was pou red into water (30 mL) , extracted with EtOAc (30 mL x 2) . The comb ined organic layers were washed with brine, dried over Na_2SO_4, filtered and co ncentrated under vacuum. The resulting residue was purified by silica gel chromatogra phy (eluting DCM/MeOH=30/1) to afford 2-methylpropan-2-yl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [azanylidene (cyclopropyl) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (1.10 g, 90%yield) . LC-MS: m/z 653.7 $(M+H)^+$.

[1214] Step F 2-methylpropan-2-yl (4S) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



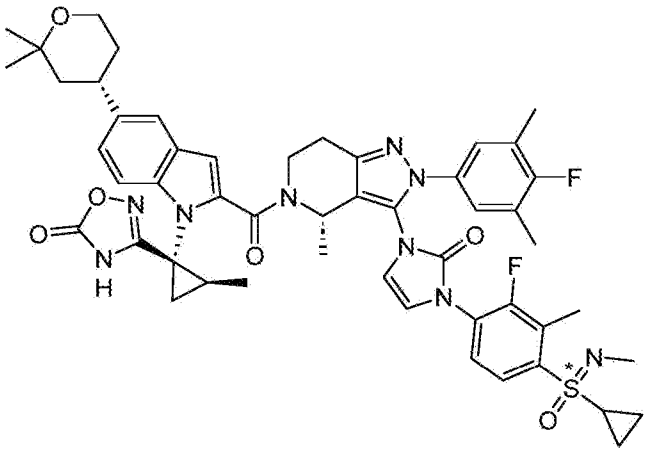
[1215] To a solution of 2-methylpropan-2-yl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- {4- [azanylidene (cyclopropyl) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (1.1 g, 1.685 mmol) in DMF (10 mL) were added NaH (0.17 g, 4.213 mmol) at 0 ℃ under N2. The mixture was stirred at 0 ℃ for 1 0 min, then iodomethane (0.164 mL, 2.022 mmol) was added, the reacti on was stirred at 25 ℃ for 18 h under N2. The reaction mixture was poured into water (20 mL) , extracted with EA (20 mL x 2) . The combined organic layer s were washed with brine, dried over Na_2SO_4, filtered and concentrated. The r esulting residue was purified by silica gel chromatography (eluting DCM/ MeOH=50/1) to afford 2-methylpropan-2-yl (4S) -3- (1- {4- [cyclopropyl (me thylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (830 mg, 73.9%yield) . LC-MS: m/z 667.5 $(M+H)^+$.

[1216] Step G 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2, 3-dihydro-1H-imidazol-2-one HCl salt



[1217] To a solution of 2-methylpropan-2-yl (4S) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (50 mg, 0.075 mmol) in dioxane (2 mL) was added HCl-dioxane (4M, 2 mL) . The reaction was stirred at 25 ℃ for 1 h. LCMS showed the reaction was completed. The reaction was concentrated to give 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2, 3-dihydro-1H-imidazol-2-one HCl salt (45 mg, 84.7%yield) . LC-MS: m/z 567.5 $(M+H)^+$.

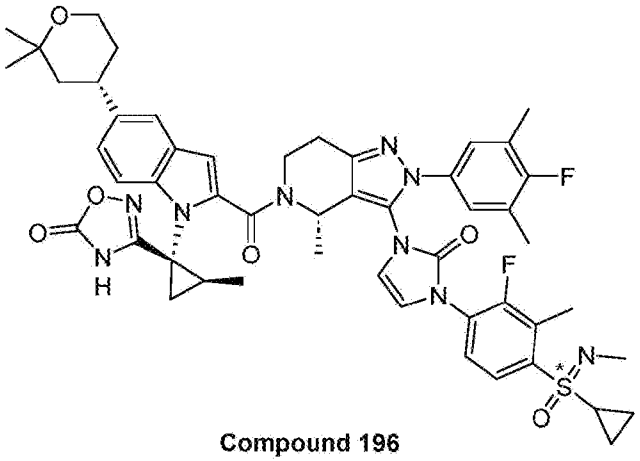
[1218] Step H 3- [(1S, 2S) -1- {5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} indol-1-yl} -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 195) (enantiomer 1) .



Compound 195

[1219] To a solution of 5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (30.5 mg, 0.074 mmol) and HATU (28.2 mg, 0.074 mmol) in DMF (5 mL) was added 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2, 3-dihydro-1H-imidazol-2-one HCl salt (42 mg, 0.074 mmol) and DIEA (9.56 mg, 0.074 mmol) in DMF (5 mL) , the reaction was stirred at rt for 18 h. After the reaction was completed , water (20 mL) was added into the reaction mixture. The mixture was extracted with EtOAc (20 mL x 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by prep. TLC (DCM/CH_3OH=10/1) and further by prep. HPLC (Waters 3767/Qda Column: SunFire Sunfire C18, 19*250mm*10 um; Mobile Phase A: 0.1%FA/H_2O, B: CH_3CN; Flow rate: 20 ml/min; Gradient: 64%-74%; Retention Time: 7.6-8.7 min of 17 min) to afford 3- [(1S, 2S) -1- {5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} indol-1-yl} -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (19.8 mg, 27.4%yield) . LC-MS: m/z 960.8 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.58 (brs, 1 H) , 7.77 -7.74 (m, 1 H) , 7.65 -7.52 (m, 2 H) , 7.42 (d, J= 8.8 Hz , 1 H) , 7.27-7.24 (dd, J_1= 8.8 Hz, J_2= 1.6 Hz, 1 H) , 7.16 (d, J= 6.0 Hz, 2 H) , 7.02 (m , 1 H) , 6.87 (m, 2 H) , 5.62 5.54 (m, 1 H) , 4.44 (m, 1 H) , 3.74 (d, J= 9.2 Hz, 2 H) , 3.57 (m, 1 H) , 3.03 (m, 2 H) , 2.90 -2.86 (m, 2 H) , 2.63 (s, 3 H) , 2.56 (s, 3 H) , 2.25 (s, 6 H) , 1.72 -1.54 (m, 7 H) , 1.51-1.45 (m, 3 H) , 1.29 (m, 4 H) , 1.20 -1.12 (m, 7 H) , 0.94 -0.83 (m, 2 H) .

[1220] Step I 3- [(1S, 2S) -1- {5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} indol-1-yl} -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 196) (enantiomer 2)



Compound 196

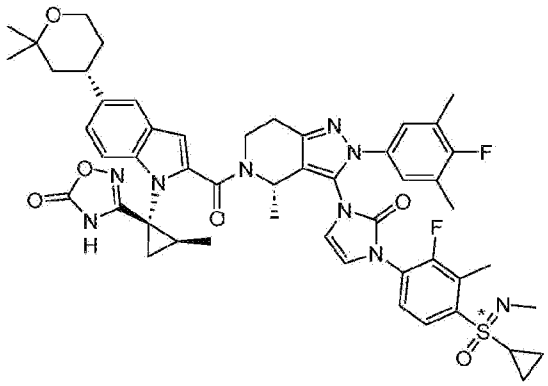
[1221] 3- [(1S, 2S) -1- {5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} indol-1-yl} -2- methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 196) (enantiomer 2) were synthesized according to the procedures described for the preparation of Compound 195) (enantiomer 1) (step E to step H) . LC-MS: m/z 960.8 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.58 (brs, 1 H) , 7.75 (m, 1 H) , 7.64 -7.53 (m, 2 H) , 7.41 (d, J= 8.4 Hz, 1 H) , 7.26 (d, J= 8.8 Hz, 1 H) , 7.16 (d, J= 6.0 Hz, 2 H) , 7.01 (m, 1 H) , 6.87 (m, 2 H) , 5.57 (m, 1 H) , 4.43 (m, 1 H) , 3.74 (d, J= 8.8 Hz, 2 H) , 3.58 (m, 1 H) , 3.04 -3.01 (m, 2 H) , 2.90 -2.86 (m, 2 H) , 2.63 (s, 3 H) , 2.56 (s, 3 H) , 2.24 (s, 6 H) , 1.72-1.63 (m, 4 H) , 1.62 -1.46 (m, 6 H) , 1.29 (m, 4 H) , 1.20 -1.12 (m, 7 H) , 0.94 -0.81 (m, 2 H) .

[1222] Example compounds 193 and 194, 214 and 215, 216, 217, 219 and 220 were synthesized using a similar procedure described in the Example A12 above using the appropriate materials.

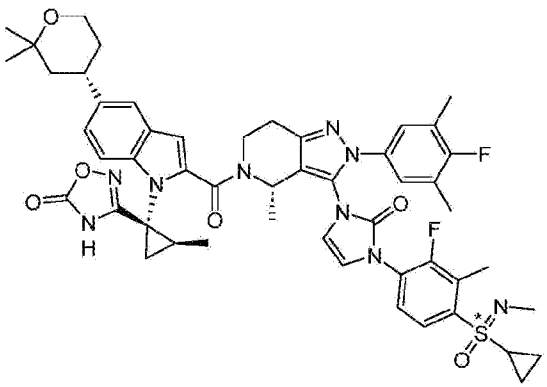
[1223] Example A12-a

[1224] 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5- dimethylphenyl) -3- (3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 1) (Compound 195)

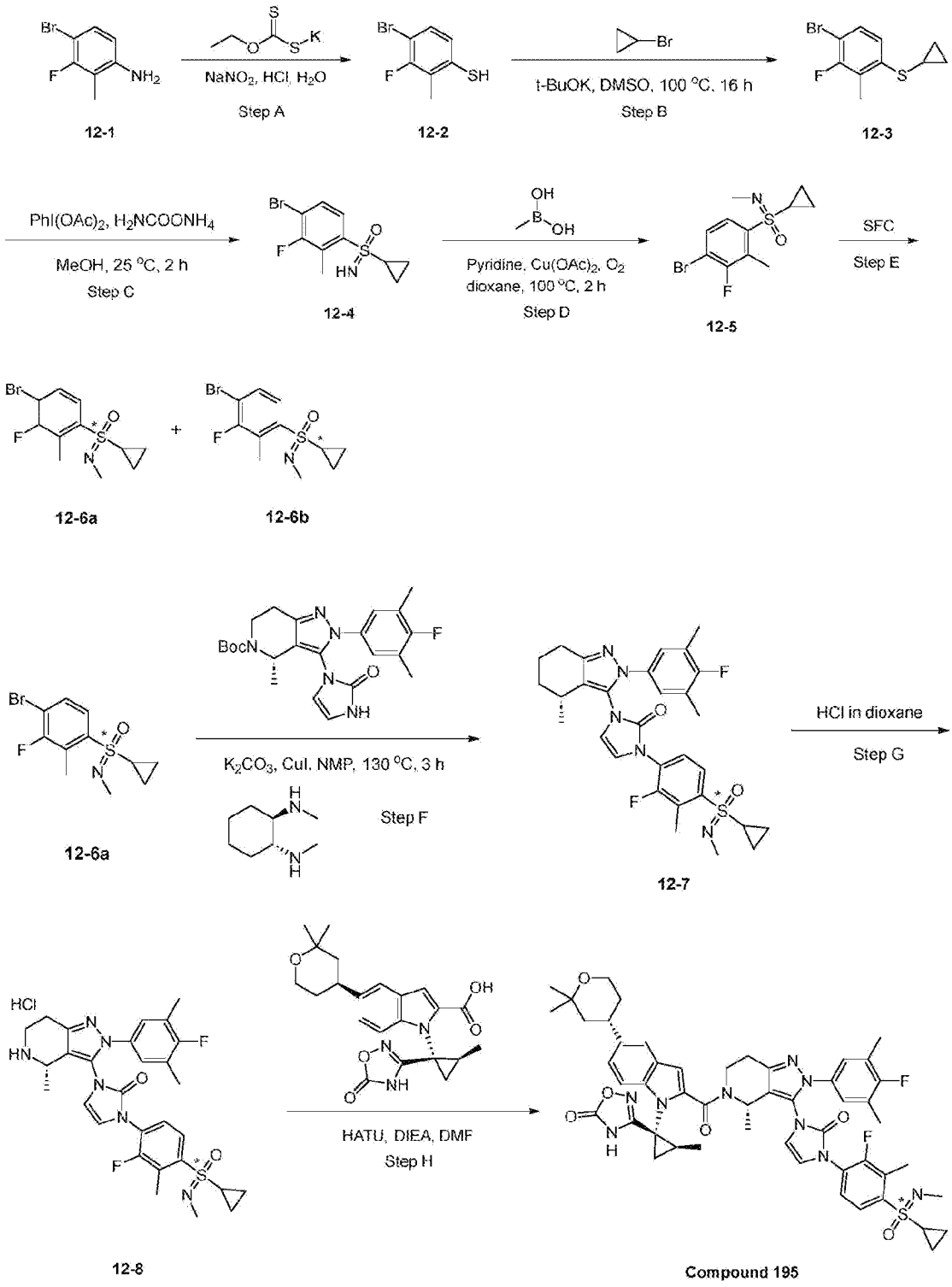
and 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 2) (Compound 196)



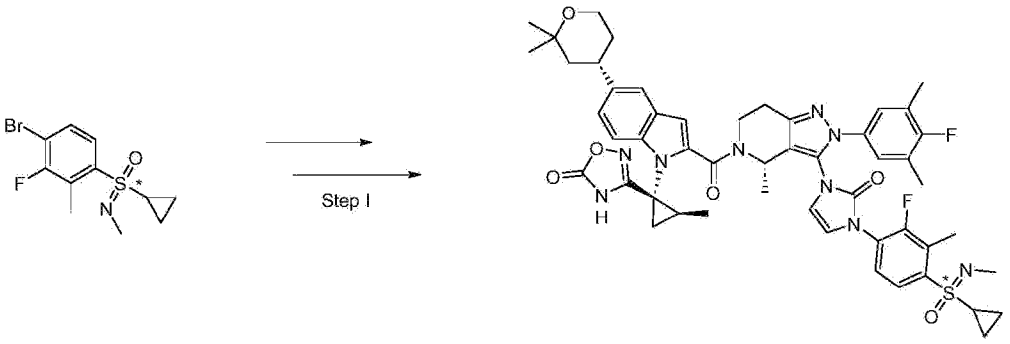
Compound 195



Compound 196

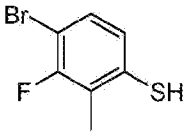


12-1 12-2 12-3 12-4 12-5 12-6a 12-6b 12-6a 12-7 12-8 Compound 195



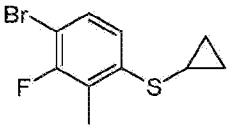
12-6b Compound 196

[1225] Step A 4-bromo-3-fluoro-2-methylbenzene-1-thiol



[1226] To a mixture of 4-bromo-3-fluoro-2-methylaniline (2.7 g, 13.233 mmol) in H_2O (10 mL) was added conc. HCl (2.205 mL, 26.465 mmol) . The reaction mixture was cooled in an ice/NaCl bath (approximately -5 to -10 ℃) , a solution of sodium nitrite (958.6 mg, 13.894 mmol) in H_2O (10 mL) was added slowly over 10 minutes. The mixture was stirred for an additional 30 minutes with cooling. Separately, a solution of [(ethoxythioxomethyl) sulfanyl] potassium (2545.3 mg, 15.879 mmol) in H_2O (30 mL) was prepared and heated to 65 ℃. The cold solution of diazonium salt was then added slowly over 20 minutes to the warmed solution of potassium ethyl xanthogenate. The reaction mixture was stirred for an additional 30 minutes at 65 ℃ and then cooled to ambient temperature. A solution of NaOH (2646.6 mg, 66.165 mmol) in H_2O (10 mL) was added, the reaction was stirred at 70 ℃ for 18 h. After the reaction was completed, monitored by TLC, the mixture was cooled to rt, the mixture was poured into ice (200 g) , acidified with concentrated HCl to pH=1, the mixture was extracted with EtOAc (50 mL x 3) . The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated to afford 4-bromo-3-fluoro-2-methylbenzene-1-thiol (3.7 g, crude) , used for the next step without purification.

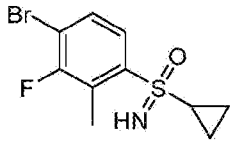
[1227] Step B (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) sulfane



[1228] To a solution of 4-bromo-3-fluoro-2-methylbenzene-1-thiol (3.7 g, 16.735 mmol) in DMSO (60 mL) were added potassium tert-butoxide (3.76 g, 33.471 mmol) and bromocyclopropane (10.12 g, 83.676 mmol) , the reaction was stirred at 100 ℃ for 18 h under N_2. TLC showed the reaction was comp

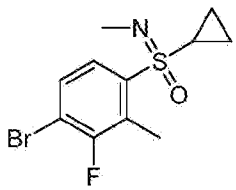
leted. The mixture was poured into water (100 mL) , extracted with E tOAc (200 mL x 2) . The combined organic layers were washed with bri ne, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purifi ed by silica gel chromatography (eluting PE 100%) to afford (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) sulfane (2.23 g, 50.3%yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.28 (m, 1 H) , 7.10-7.12 (m, 1 H) , 2 .13 (s, 3 H) , 2.01-2.05 (m, 1 H) , 1.02-1.07 (m, 2 H) , 0.60-0.64 (m, 2 H) .

[1229] Step C (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine



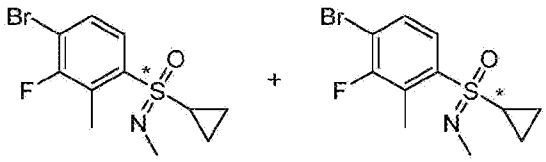
[1230] To a solution of (4-bromo-2-fluorophenyl) (cyclopropyl) sulfane (2.2 g, 8.524 m mol) in MeOH (30 mL) was added (diacetoxyiodo) benzene (8.29 g, 25.5 72 mmol) and ammonium carbaminate (2.66 g, 34.095 mmol) . The reacti on was stirred at room temperature for 1 h. After the reaction was completed, water (50 mL) was added. The mixture was extracted with EtOAc (30 mL x 3) . The combined organic layers were washed with brine, dried over sodium sulfate, filte red and concentrated. The resulting residue was purified by silica gel chromatography (eluting 0-50%EtOAc/PE) to afford (4-bromo-3-fluoro-2-methylphenyl) (cy clopropyl) (oxo) -λ^6-sulfanimine (1.17 g, 69.2%yield) . LC-MS: m/z 292.0 $(M+H)^+$.

[1231] Step D 1- (4-bromo-3-fluoro-2-methylphenyl) -1-cyclopropyl-N-methyl-1-oxo-λ^6-sulfanimine



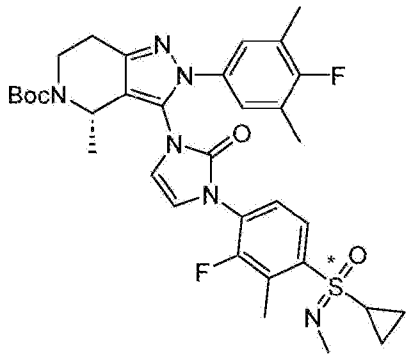
[1232] To a solution of (4-bromo-3-fluoro-2-methylphenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (3200 mg, 10.953 mmol) in dioxane (50 mL) were added cup ric bis (acetate) (5967.92 mg, 32.858 mmol) , Pyridine (3.543 mL, 43 .810 mmol) and methylboranediol (2622.47 mg, 43.810 mmol) . The reac tion was stirred at 100 °C for 2 h under O_2. The mixture was concentrated und er vacuum. The resulting residue was purified by silica gel chromatography (eluting P E/EA=10/1) to afford 1- (4-bromo-3-fluoro-2-methylphenyl) -1-cyclopropyl-N-methyl-1-oxo-λ^6-sulfanimine (2616 mg, 78.01%) as a yellow oil. LC-MS: m/ z 306.2 $(M+H)^+$.

[1233] Step E 1- (4-bromo-3-fluoro-2-methylphenyl) -1-cyclopropyl-N-methyl-1-oxo-λ^6-sulfanimine (enantiomer 1) and 1- (4-bromo-3-fluoro-2-methylphenyl) -1-cyclopropyl-N-methyl-1-oxo-λ^6-sulfanimine (enantiomer 2)



[1234] The compound mixture 1- (4-bromo-3-fluoro-2-methylphenyl) -1-cyclopropyl-N-methyl-1-oxo-λ^6-sulfanimine (2616 mg, 8.544 mmol) was separated by SFC (system: Waters SFC 150; Column name: DAICELCHIRALPAK®IG; Column size: 250*25 mm 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: IPA (+0.1%7.0 mol/L Ammonia in MeOH) ; Gradient: A/B = 80/20; Flow rate: 100 mL/min) to afford 1- (4-bromo-3-fluoro-2-methylphenyl) -1-cyclopropyl-N-methyl-1-oxo-λ^6-sulfanimine (enantiomer 1) (1.25 g, 37.42%) as the fast eluent, R. T =1.28 min, LC-MS: m/z 306.2 $(M+H)^+$. And 1- (4-bromo-3-fluoro-2-methylphenyl) -1-cyclopropyl-N-methyl-1-oxo-λ^6-sulfanimine (enantiomer 2) (1.16 g, 34.72%) as the slow eluent, R. T=1.97 min. LC-MS: m/z 306.2 $(M+H)^+$.

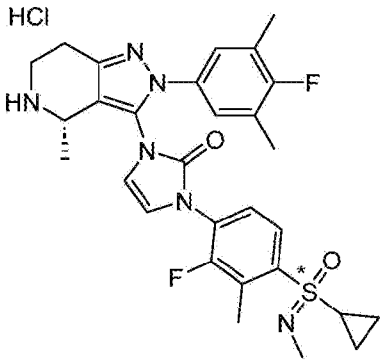
[1235] Step F tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enan tiomer 1)



[1236] To a solution of 1- (4-bromo-3-fluoro-2-methylphenyl) -1-cyclopropyl-N-methyl-1-oxo-λ^6-sulfanimine (enantiomer 1) (775 mg, 2.531 mmol) in NMP (15 mL) were added 2-methylpropan-2-yl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-3H-imidazol-1-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (1117.51 mg, 2.531 mmol) , CuI (578.46 mg, 3.037 mmol) , K_2CO_3 (699.60 mg, 5.062 mmol) and methyl [(1R, 2R) -2- (methylamino) cyclohexyl] amine (540.08 mg, 3.797 mmol) , the reaction was stirred at 130 ℃ for 3 h under N_2. The mixture was added to water (50 mL) , extracted with EA (30 mL

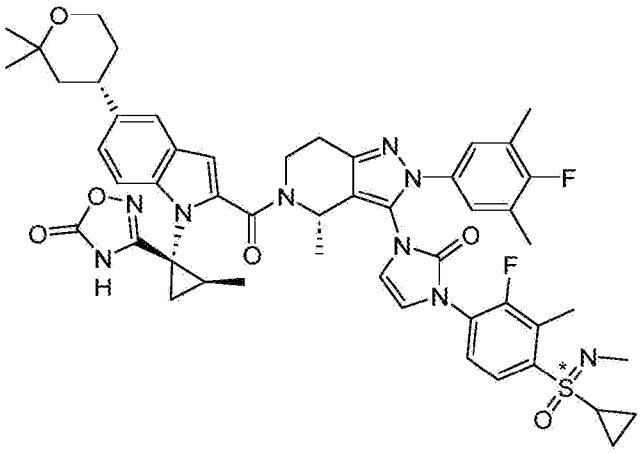
X 2) , the combined organic layers were washed with brine (30 mL X 3) , dried over so dium sodium sulfate, filtered and concentrated under vacuum. The resulting residue wa s purified by flash column chromatography (eluting PE/EA=1/2) , then purified by C18 column chromatography (eluting 50%of ACN in water, 0.1%FA) to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enantiomer 1) (1100 mg, 65.18%) as a yellow solid. LC-MS: m/z 667.7 $(M+H)^+$.

[1237] Step G 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one, HCl salt (enantiomer 1)



[1238] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enantiomer 1) (1050 mg, 1.575 mmol) in DCM (10 mL) were added HCl (3.937 mL, 15.747 mmol) , the mixture was stirred at rt for 16 h under N_2 protection. The mixture was concentrated under vacuum to afford 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one, HCl salt (enantiomer 1) (893 mg, 100.0%) , used for the next step with no purification. LC-MS: m/z 567.1 (M+H-HCl) $^+$.

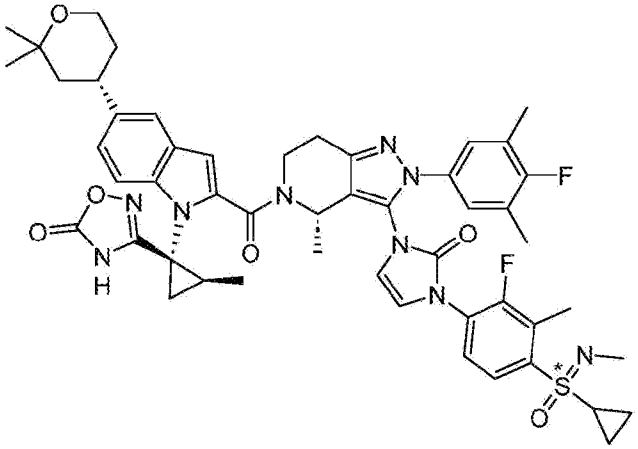
[1239] Step H 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 1) (Compound 195) .



Compound 195

[1240] To a solution of 5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (778.15 mg, 1.891 mmol) and HATU (898.25 mg, 2.364 m mol) in DMF (20 mL) was added a solution of 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one, HCl salt (enantiomer 1) (893 mg, 1.576 mmol) a nd DIPEA (1.370 mL, 7.879 mmol) in DMF (5 mL) , the mixture was stir red at rt for 18 h under Ar. After the reaction was completed, water (50 mL) was adde d. The mixture was extracted with EA (50 mL X 3) . The combined orga nic layers were washed with brine (50 mL X 3) , dried over sodium sodium sulfate, fil tered and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (DCM/MeOH=50/1) , then purified by C18 column chroma tography (48%of MeCN in water, 0.1%FA) and C18 column chromatography (50%of MeCN in water, 0.1% NH_4HCO_3) to afford 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 1) (791 mg, 51.38%) . LC-MS: m/z 960.9 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.60 (brs, 1 H) , 7.76-7.74 (m, 1 H) , 7.59-7.53 (m, 2 H) , 7.42 (d, J=8.4 Hz, 1 H) , 7.27-7.24 (dd, J_1=8.4 Hz, J_2=1.6 Hz, 1 H) , 7 .16 (d, J=6.4 Hz, 2 H) , 7.01 (m, 1 H) , 6.86 (m, 2 H) , 5.56-5.54 (m, 1 H) , 4.48-4.42 (m, 1 H) , 3.75-3.72 (m, 2 H) , 3.61-3.51 (m, 1 H) , 2.90-2.86 (m, 2 H) , 2 .63 (s, 3 H) , 2.57 (s, 3 H) , 2.25 (s, 6 H) , 1.78-1.45 (m, 11 H) , 1.31-1.26 (m, 5 H) , 1 .20-1.12 (m, 7 H) , 0.96-0.91 (m, 1 H) , 0.87-0.82 (m, 1 H) .

[1241] Step I 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 2) (Compound 196)



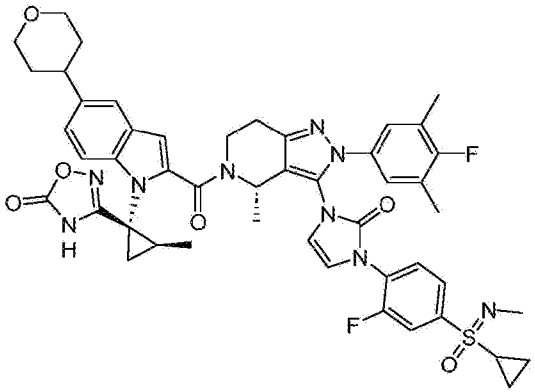
Compound 196

[1242] 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3-methyl-4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 2) (Compound 196) were synthesized according to the procedures described for the preparation of Compound 195) (enantiomer 1) (step F to step H) . LC-MS: m/z 960.8 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.58 (brs, 1 H) , 7.75 (m, 1 H) , 7.64 -7.53 (m, 2 H) , 7.41 (d, J= 8.4 Hz, 1 H) , 7.26 (d, J= 8.8 Hz, 1 H) , 7.16 (d, J= 6.0 Hz, 2 H) , 7.01 (m, 1 H) , 6.87 (m, 2 H) , 5.57 (m, 1 H) , 4.43 (m, 1 H) , 3.74 (d, J= 8.8 Hz, 2 H) , 3.58 (m, 1 H) , 3.04 -3.01 (m, 2 H) , 2.90 -2.86 (m, 2 H) , 2.63 (s, 3 H) , 2.56 (s, 3 H) , 2.24 (s, 6 H) , 1.72-1.63 (m, 4 H) , 1.62 -1.46 (m, 6 H) , 1.29 (m, 4 H) , 1.20 -1.12 (m, 7 H) , 0.94 -0.81 (m, 2 H) .

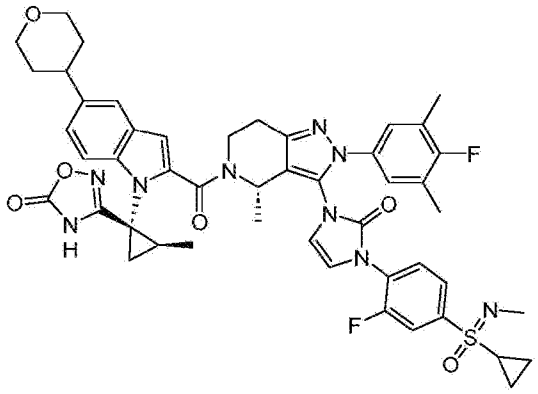
[1243] Example A13

[1244] 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -5H, 4H-1, 2, 4-oxadiazol-5-one (Compound 221) (enantiomer 1) and 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-

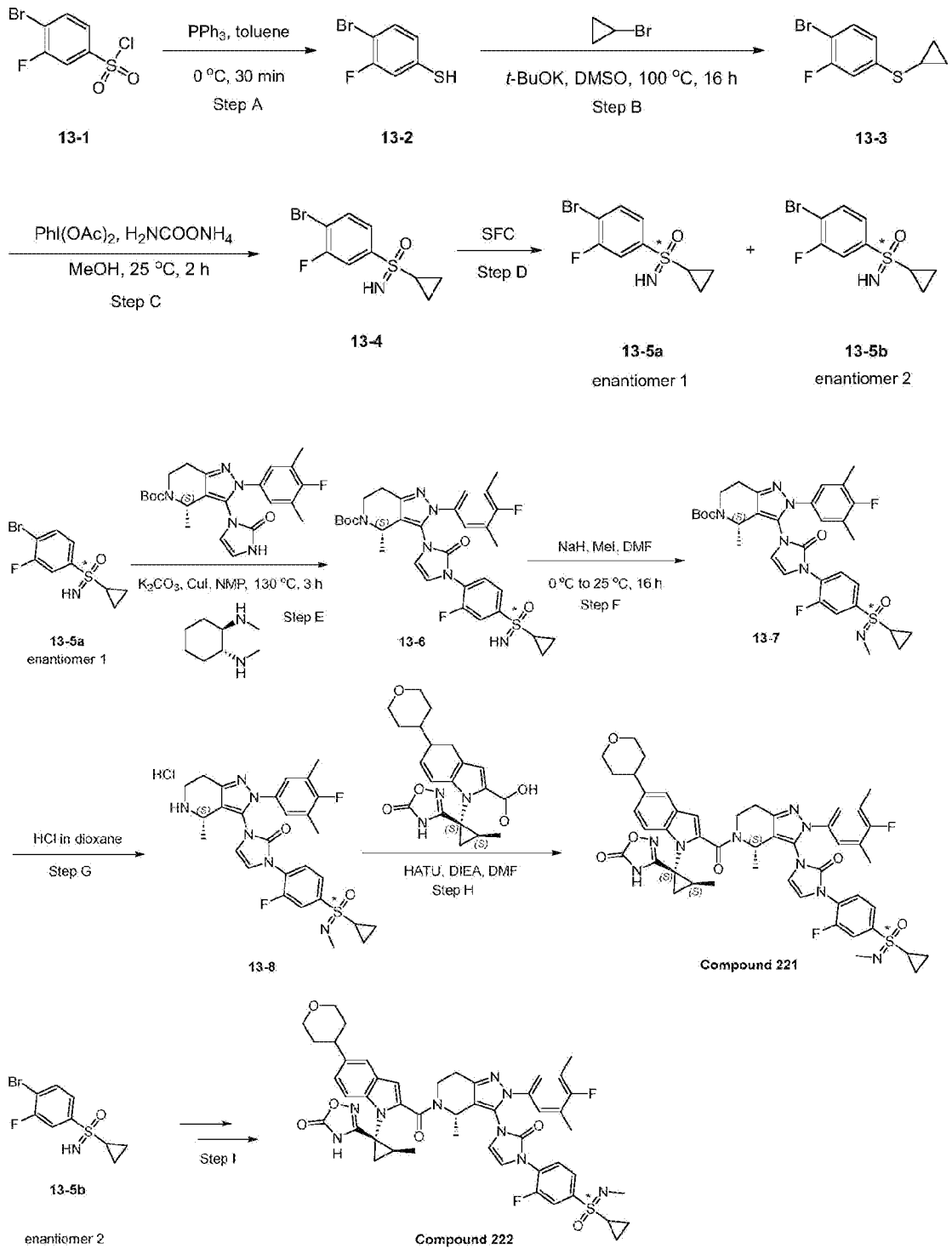
5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -5H, 4H-1, 2, 4-oxadiazol-5-one (Compound 222) (enantiomer 2)



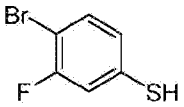
Compound 221



Compound 222



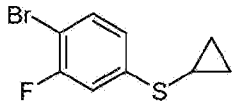
[1245] Step A 4-bromo-3-fluorobenzene-1-thiol



[1246] To a stirred solution 4-bromo-3-fluorobenzenesulfonyl chloride (3 g, 10.969 mmol) i n toluene (30 mL) was added triphenylphosphane (11.51 g, 43.876 mmol) . The reaction mixture was stirred at room temperature for 40 minutes. TLC indicate

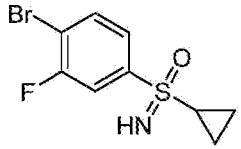
d completion of reaction. The reaction was diluted with water (15 mL) and stirred for 10 minutes. The two phases were separated, and the organic phase was washed with 10%sodium hydroxide solution (25 mL x 2) . The combined sodium hydroxide solution phase was washed with toluene (50 mL) , acidified with dilute HC1 to pH 4～5, and extracted with CH_2CI_2 (40 mL x 2) . The organic phases were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel (eluting with ethyl acetate in petroleum ether from 0 to 3%) to afford 4-bromo-3-fluorobenzene-1-thiol (1.8 g, 79.3%yield) .

[1247] Step B (4-bromo-3-fluorophenyl) (cyclopropyl) sulfane



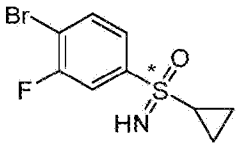
[1248] To a solution of 4-bromo-3-fluoro-2-methylbenzene-1-thiol (1.0 g, 4.830 mmol) in DMSO (10 mL) were added potassium 2-methylpropan-2-olate (1.62 g, 14.489 mmol) and bromocyclopropane (3.095 mL, 38.636 mmol) , the reaction was stirred at 100 ℃ for 18 h under N2. TLC showed the reaction was completed. The mixture was added to water (100 mL) , extracted with EA (100 mL x 2) . The combined organic layers were washed with brine (100 mL x 3) , dried over sodium sulfate, filtered and concentrated under vacuum . The resulting residue was purified by silica gel chromatography (eluting 100%PE) to afford (4-bromo-3-fluorophenyl) (cyclopropyl) sulfane (1.4 g, 52.9%yield) .

[1249] Step C (4-bromo-3-fluorophenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine



[1250] To a solution of (4-bromo-3-fluorophenyl) (cyclopropyl) sulfane (6.4 g, 25.897 mmol) in MeOH (60 mL) was added (diacetoxyiodo) benzene (25.18 g, 77.692 mmol) and ammonium carbamate (8.09 g, 103.589 mmol) . The reaction was stirred at room temperature for 1 h. After the reaction was completed, water (100 mL) was added. The mixture was extracted with EA (50 mL x 3) . The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (PE/EA=4/1) to afford (4-bromo-3-fluorophenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (3.0 g, 41.6%yield) . LC-MS: m/z 280.0 $(M+H)^+$.

[1251] Step D (4-bromo-3-fluorophenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (enantiomer 1) 13-5a

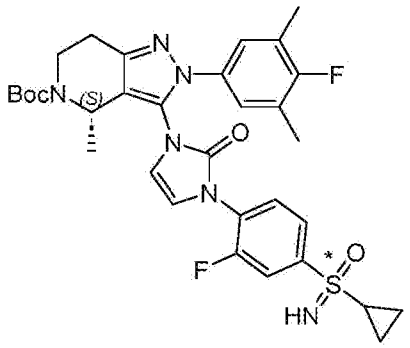


13-5a

enantiomer 1

[1252] The compound mixture (4-bromo-3-fluorophenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (3.0 g, 4.00 mmol) was separated by SFC (Column: DAICELCHIRALCEL®AS250 mm*25 mm, 10 μm, Mobile phase A (Supercritical CO_2) , Mobile phase B (MeOH (0.1%7.0 M Ammonia in MeOH)) , Gradient: B =20%, Flow rate: 100 mL/min, Column temp.: 25 ℃.) to afford (4-bromo-3-fluorophenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (enantiomer 1) (1.34 g , 44.6%yield) as the fast eluent, LC-MS: m/z 280.0 $(M+H)^+$ and (4-bromo-3-fluorophenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (enantiomer 2) (1.36 g , 45.3%yield) as the slow eluent, LC-MS: m/z 280.0 $(M+H)^+$.

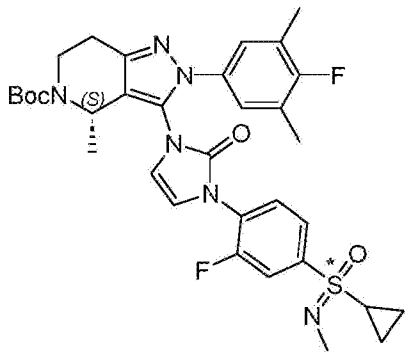
[1253] Step E 2-methylpropan-2-yl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4-[azanylidene (cyclopropyl) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1254] To a solution of 2-methylpropan-2-yl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (67 mg, 0.152 mmol) in NMP (10 mL) was added (4-bromo-3-fluorophenyl) (cyclopropyl) (oxo) -λ^6-sulfanimine (50.65 mg, 0.182 mmol) , (1R, 2R) -N1, N2-dimethylcyclohexane-1, 2-diamine (32.32 mg, 0.228 mmol) , CuI (57.80 mg, 0.304 mmol) and K_2CO_3 (41.94 mg, 0.304 mmol) , the mixture was stirred at 130 ℃ for 3 h. After the reaction was completed, water (20 mL) was added. The mixture was extracted with EA (20 mL X 3) . The combined organic layers were washed with brine (15 mL) , dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting residue was purified by prep-TLC (PE/EA=1/1) to afford 2-methylpropan-2-yl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [azanylidene (cyclopropyl) (oxo) -λ^6- sulfanyl] -2-

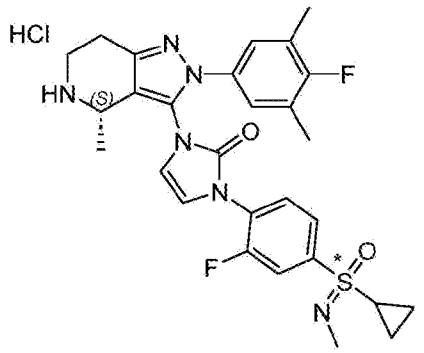
fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (100 mg, 0.119 mmol, 78.4%) (1.10 g, 90%yield) . LC-MS: m/z 639.5 $(M+H)^+$.

[1255] Step F 2-methylpropan-2-yl (4S) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



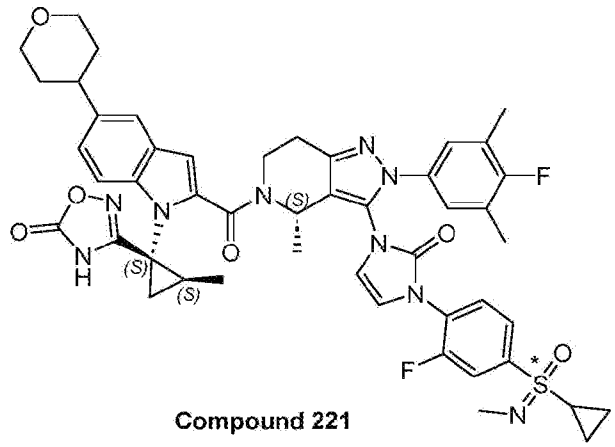
[1256] To a solution of 2-methylpropan-2-yl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [azanylidene (cyclopropyl) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (50 mg, 0.078 mmol) in DMF (6 mL) was added NaH (3.76 mg , 0.157 mmol) at 0 ℃, and the reaction was stirred at 0 ℃ for 1 h. CH_3 I (0.019 mL, 0.235 mmol) was added, the reaction was stirred at rt for 18 h. After th e reaction was completed, water (10 mL) was added. The mixture was e xtracted with EtOAc (10 mL x 3) . The combined organic layers were w ashed with brine (15 mL) , dried over anhydrous sodium sulfate, filtered and concentr ated under vacuum. The resulting residue was purified by prep. TLC (MeOH/ DCM=1/20) to afford 2-methylpropan-2-yl (4S) -3- (1- {4- [cyclopropyl (me thylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (35 mg, 68.5%yield) . LC-MS: m/z 653.4 $(M+H)^+$.

[1257] Step G 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2, 3-dihydro-1H-imidazol-2-one HCl salt



[1258] To a solution of 2-methylpropan-2-yl (4S) -3- (1- {4- [cyclopropyl (me thylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluoro-3-methylphenyl} -2-oxoimidazol-3-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (50 mg, 0.077 mmol) in dioxane (2 mL) was added HCl in d ioxane (4 mL) . The reaction was stirred at 25 ℃ for 18 h. LCMS show ed the reaction was completed. The reaction was concentrated under vacuum to give 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazol o [4, 3-c] pyridin-3-yl] -3- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2, 3-dihydro-1H-imidazol-2-one HCl salt (50 mg, 88.9%) as a y ellow solid. LC-MS: m/z 553.2 (M+H) $^+$.

[1259] Step H 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -5H, 4H-1, 2, 4-oxadiazol-5-one (Compound 221) (enantiomer 1) .

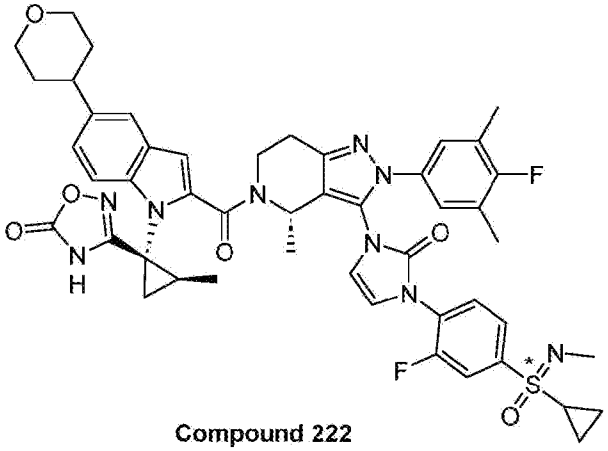


Compound 221

[1260] To a solution of 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2, 3-dihydro-1H-imidazol-2-one HCl salt (42 mg, 0.076 mmol) and HATU (57.76 mg, 0.152 mmol) in N, N-dimethylmethanami de (8 mL) was added 1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-

yl) cyclopropyl] -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indole-2-carboxylic acid (29.14 mg, 0.076 mmol) and DIEA (49.02 mg, 0.380 mmol) , the reaction was stirred at rt for 2 h. After the reaction was completed, water (20 mL) was added . The mixture was extracted with EA (20 mL x 3) . The combined organ ic layers were washed with brine (15 mL) , dried over sulfate, filtered and concentra ted under vacuum. The resulting residue was purified by prep. HPLC (Waters 2767/ Qda, Column: SunFire Sunfire C18, 19*250mm, 10 μm; Mobile Phase A: 0.1%FA/ H_2O, B: CH_3CN ; flow rate: 20 mL/min; gradient: 72%～77%; Retention Time: 7.1-7.9 min of 17 min) to afford 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -5H, 4H-1, 2, 4-oxadiazol-5-one (11.4 mg, 16.2%yield) . LC-MS: m/z 918.3 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.60 (brs, 1 H) , 7.77 - 7.71 (m, 3 H) , 7.53 (s, 1 H) , 7.44 (d, J= 8.4 Hz, 1 H) , 7.28 (d, J= 9.2 Hz, 1 H) , 7.16 (d, J= 6.0 Hz, 2 H) , 7.05 (s, 1 H) , 6.88 (s, 2 H) , 5.58 (m, 1 H) , 4.46 (m, 1 H) , 4.00 -3.97 (d, J= 10.8 Hz, 2 H) , 3.58 -3.46 (m, 3 H) , 2.91 -2.87 (m, 3 H) , 2.80 - 2.77 (m, 1 H) , 2.59 (s, 3 H) , 2.25 (s, 6 H) , 1.76 -1.62 (m, 7 H) , 1.46 (m, 3 H) , 1.27 - 1.12 (m, 4 H) , 1.10 -1.08 (m, 1 H) , 1.01 -0.91 (m, 2 H) ..

[1261] Step I 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -5H, 4H-1, 2, 4-oxadiazol-5-one (Compound 222) (enantiomer 2)



Compound 222

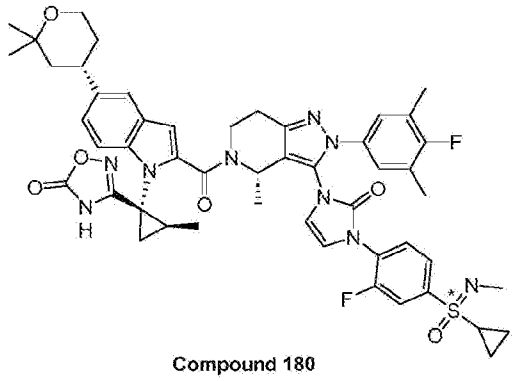
[1262] 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-

5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -5H, 4H-1, 2, 4-oxadiazol-5-one (Compound 222) (enantiomer 2) were synthesized according to the procedures described for the prepa ration of Compound 221) (enantiomer 1) (step E to step H) . LC-MS: m/z 918.3 (M +H) $^{+}$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.59 (brs, 1 H) , 7.78 -7.75 (m, 3 H) , 7 .53 (s, 1 H) , 7.44 (d, J= 8.4 Hz, 1 H) , 7.28 (d, J= 8.8 Hz, 1 H) , 7.16 (d, J= 6.4 Hz, 2 H) , 7.05 (s, 1 H) , 6.88 (s, 2 H) , 5.58 (m, 1 H) , 4.48 (m, 1 H) , 4.00 - 3.97 (m, 2 H) , 3.59 -3.46 (m, 3 H) , 2.91 -2.87 (m, 2 H) , 2.80 -2.77 (m, 1 H) , 2 .60 (s, 3 H) , 2.25 (s, 6 H) , 1.76 -1.72 (m, 6 H) , 1.64 (m, 1 H) , 1.46 (m, 3 H) , 1.27 - 1.08 (m, 6 H) , 1.01 -0.91 (m, 2 H) .

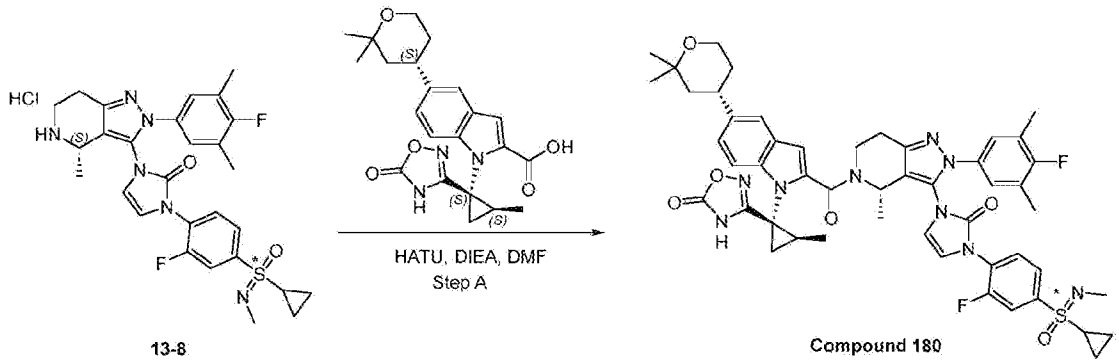
[1263] Example compounds 164, 203, 204 and 205, 208 and 209 were synthesize d using a similar procedure described in the Example A13 above using the appropriate materials.

[1264] Example A14

[1265] 3- [(1S, 2S) -1- {5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (me thylazanylidene) (oxo) -λ^{6}-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} indol-1-yl} -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 180)



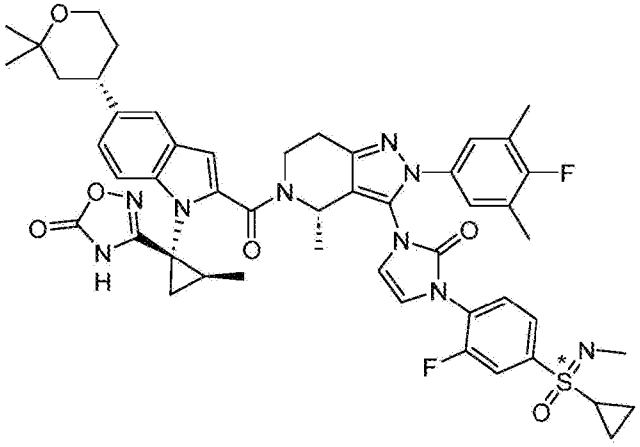
Compound 180



13-8 Compound 180

[1266] Step A 3- [(1S, 2S) -1- {5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (me

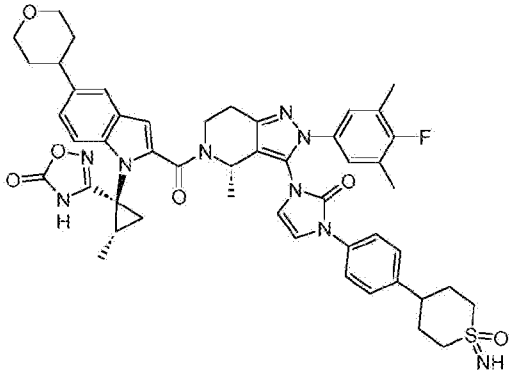
thylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} indol-1-yl} -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 180)



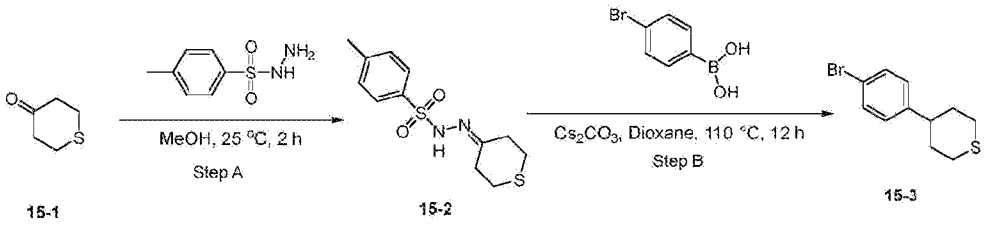
[1267] To a solution of 5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (37.23 mg, 0.090 mmol) and HATU (68.76 mg, 0.181 mmol) in N, N-dimethylmethanamide (8 mL) was added 3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -1- {4- [cyclopropyl (me thylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2, 3-dihydro-1H-imidazol-2-one (50 mg, 0.090 mmol) and DIEA (58.36 mg, 0.452 mmol) . The mixtur e was stirred at rt for 2 h. After the reaction was completed, water (20 mL) was adde d into the mixture. The solution was extracted with EtOAc (20 mL x 3) . The combined organic layers were washed with brine, dried over sulfate, filtered and concentrated under vacuum. The resulting residue was purified by prep. HPLC (Waters 2767/Qda, Column: SunFire Sunfire C18, 19*250mm, 10 μm; Mobile Phase A: 0.1%FA/H2O, B: CH_3CN ; flow rate: 20 mL/min; gradien t: 76%-81%; Retention Time: 7.9-8.7min of 17 min) to afford 3- [(1S, 2S) -1- {5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (1- {4- [cyclopropyl (methylazanylidene) (oxo) -λ^6-sulfanyl] -2-fluorophenyl} -2-oxoimidazol-3-yl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} indol-1-yl} -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (39.9 mg, 46.7%yield) . LC-MS: m/z 946.7 (M +H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ11.55 (brs, 1 H) , 7.78 -7.75 (m, 3 H) , 7 .51 (s, 1 H) , 7.42 (d, J= 8.4 Hz, 1 H) , 7.24 (d, J= 8.0 Hz, 1 H) , 7.16 (d, J= 6.4 Hz, 2 H) , 7.04 (s, 1 H) , 6.89 -6.76 (m, 2 H) , 5.54 (m, 1 H) , 4.40 (m, 1 H) , 3.7 4 (d, J= 9.2 Hz, 2 H) , 3.51 (m, 1 H) , 2.83 (m, 1 H) , 2.79 (m, 1 H) , 2.59 (s, 3 H) , 2.24 (s, 6 H) , 1.73 -1.55 (m, 8 H) , 1.44 (s, 3 H) , 1.30 -1.21 (m, 11 H) , 1.10 (m, 1 H) , 0.98 -0.90 (m, 2 H) .

[1268] Example A15

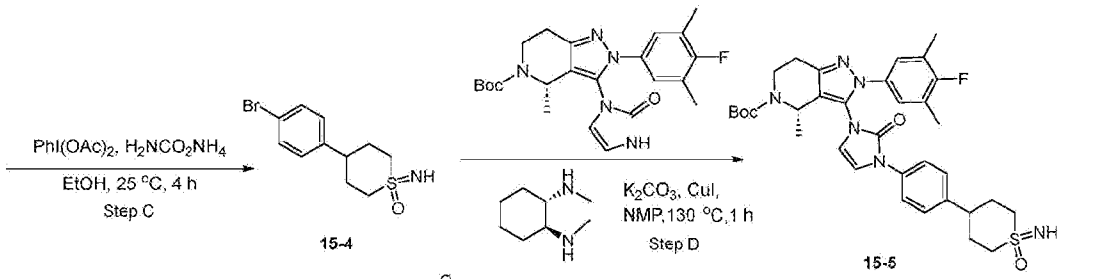
[1269] 3- [(1S, 2S) -1- (2- { [(4S) -3- {1- [4- (1-azanylidene-1-oxo-1λ^6-thian-4-yl) phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -5H, 4H-1, 2, 4-oxadiazol-5-one (Compound 182)



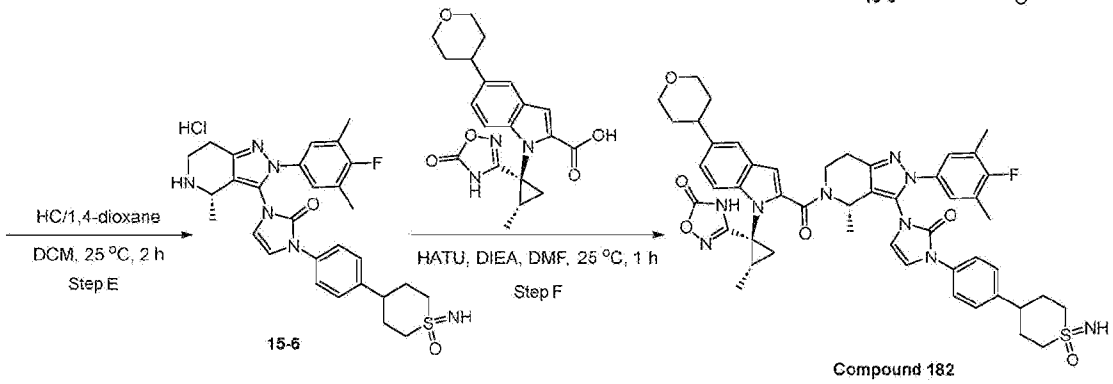
Compound 182



15-1 15-2 15-3

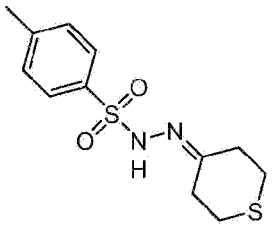


15-4 15-5



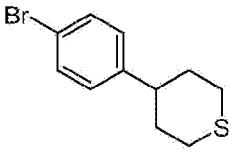
15-6 Compound 182

[1270] Step A 4-methyl-N'- (tetrahydro-4H-thiopyran-4-ylidene) benzenesulfonohydrazide



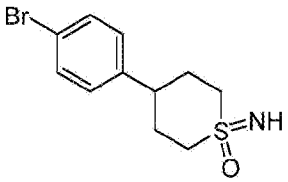
[1271] To a solution of tetrahydro-4H-thiopyran-4-one (5.00 g, 43.00 mmol) in MeOH (50 mL) was added 4-methylbenzenesulfonohydrazide (8.01 g, 43.00 mmol) . The mixture was stirred at 25 ℃ for 2 h. The reaction mixture was filtered and the cake was washed with cold ethanol (3 mL) . The filter cake was dried under reduced pr essure to afford 4-methyl-N'- (tetrahydro-4H-thiopyran-4-ylidene) benzenes ulfonohydrazide (11.20 g, 91.6%yield) . LC-MS: m/z: 285.3 $(M+H)^+$.

[1272] Step B 4- (4-bromophenyl) tetrahydro-2H-thiopyran



[1273] To a solution of (4-bromophenyl) boronic acid (1.00 g, 4.98 mmol) in di oxane (10 mL) were added 4-methyl-N'- (tetrahydro-4H-thiopyran-4-ylidene) benzenes ulfonohydrazide (1.70 g, 5.98 mmol) and cesium carbonate (2.43 g, 7. 47 mmol) . The mixture was degassed and purged with N2 for 3 times a nd was stirred at 110 ℃ for 12 h under N2 atmosphere. After cooling, the resulting mi xture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3) . Th e combined organic layers were washed with brine, dried over Na_2SO_4, filtered and co ncentrated. The residue was purified by silica gel column chromatography eluting with 0-3%EtOAc/PE to afford 4- (4-bromophenyl) tetrahydro-2H-thiopyran (0.39 g , 30.1%yield) . ^1H NMR (400 MHz, DMSO-d6) δ 7.46 (d, J = 8.0 Hz, 2H) , 7 .19 (d, J = 8.0 Hz, 2H) , 2.80 -2.62 (m, 2H) , 2.59 -2.58 (m, 2H) , 2.55 - 2.56 (m, 1H) , 2.03 -1.99 (m, 2H) , 1.98 -1.63 (m, 2H) .

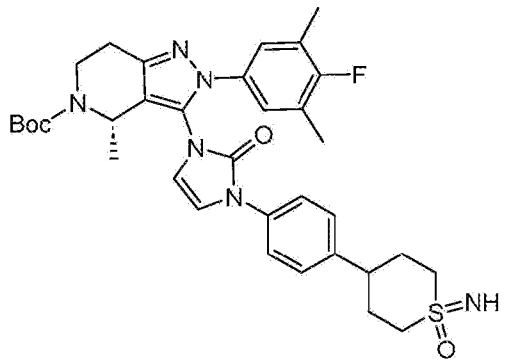
[1274] Step C 4- (4-bromophenyl) -1-iminohexahydro-1λ^6-thiopyran 1-oxide



[1275] To a solution of 4- (4-bromophenyl) tetrahydro-2H-thiopyran (386.0 mg, 1.50 mmol) in EtOH (4.0 mL) were added iodobenzene diacetate (14 50.0 mg, 4.50 mmol) and ammonium acetate (463.0 mg, 6.00 mmol) . The mixture was stirred at 25 ℃ for 4 h. The resulting mixture was diluted with H

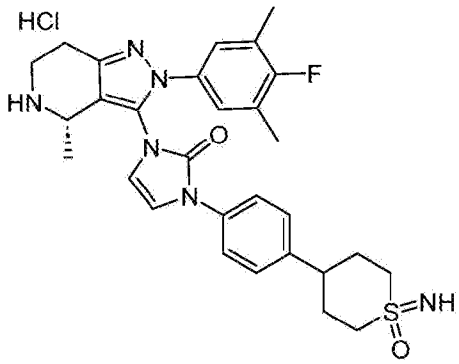
$_2$O (2 mL) and extracted with EtOAc (2 mL × 3) . The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue wa s purified by prep. TLC (SiO_2, DCM: MeOH = 20: 1) to afford 4- (4-bromophenyl) -1-iminohexahydro-1λ^6-thiopyran 1-oxide (227.0 mg, 52.5%yield) . LC-MS: m/z: 287.8 (M+H) $^+$.

[1276] Step D tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (4- (1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate



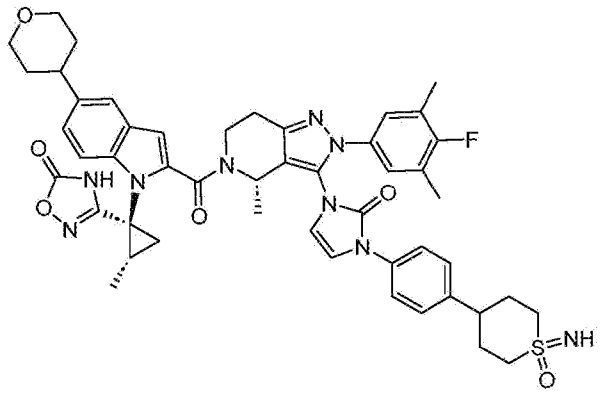
[1277] To a solution of 4- (4-bromophenyl) -1-iminohexahydro-1λ^6-thiopyran 1-oxide (100.0 mg, 0.35 mmol) in NMP (1 mL) were added tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (230.0 mg, 0.52 mmol) , (1S, 2S) -N1, N2-dimethylcyclohexane-1, 2-diamine (24.7 mg, 0.17 mmol) , cop per (I) iodide (132.0 mg, 0.69 mmol) and K_2CO_3 (96.0 mg, 0.69 mmol) . The mixtur e was degassed and purged with N2 for 3 times and stirred at 130 ℃ for 1 h under N2 a tmosphere. After cooling, the resulting mixture was diluted with H_2O (5mL) and extra cted with EtOAc (5 mL x 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purifi ed by prep. TLC (SiO2, DCM: MeOH = 15: 1) to afford tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (4- (1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (85.0 mg, 37.8%yield) . LC-MS: m/z 649.9 (M+H) $^+$.

[1278] Step E (S) -1- (2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- (1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one HCl salt



[1279] To a solution of tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (4- (1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (85.0 mg, 0.13 mmol) in DCM (2 mL) was added HCl (0.85 m L, 4 mol/L in dioxane) . After addition, the mixture was stirred at 25 ℃ for 2 h. The resulting mixture was concentrated to give (S) -1- (2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- (1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one HCl salt (86.0 mg, crude) , which was used in next step directly without further purification. LC-MS: m/z 549.4 $(M+H)^+$.

[1280] Step F 3- [(1S, 2S) -1- (2- { [(4S) -3- {1- [4- (1-azanylidene-1-oxo-1λ^6-thian-4-yl) phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -5H, 4H-1, 2, 4-oxadiazol-5-one (Compound 182)

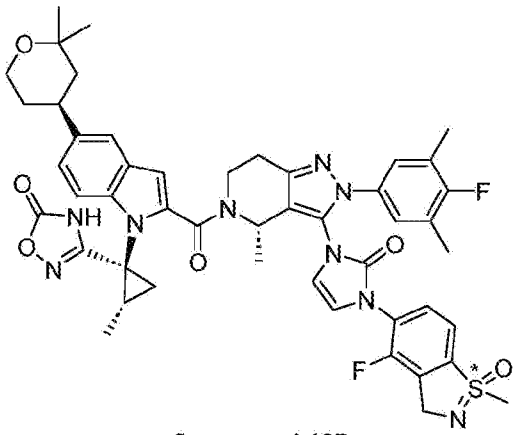


[1281] To a solution of (S) -1- (2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- (1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) phenyl) -1, 3-dihydro-2H-imidazol-2-one HCl salt (30. 0 mg, 0.050 mmol) in DMF (0.9 mL) were added 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (19.7 mg, 0.050 mmol) , HATU (21.4 mg, 0.060 mmol) a

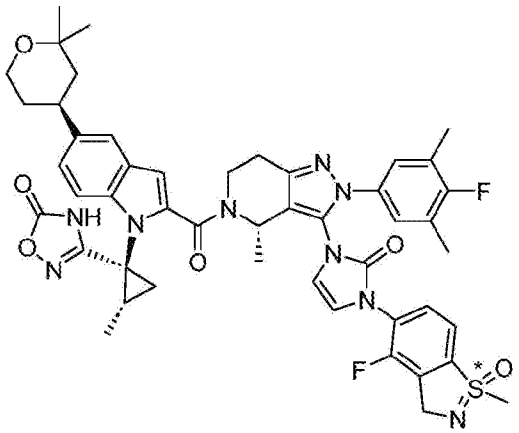
nd DIEA (0.036 mL, 0.21 mmol) . After addition, the mixture was stirred at 25 ℃ for 1 h. The resulting mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3) . The combined organic layers were dried over dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep. TLC (SiO_2 , DCM: MeOH = 20: 1) , then further purified by prep. HPLC (SHIMADZU LC-20AP, Column: YMC Triart C18, 20*250 mm, 5 μm; Mobile Phase A: 0.1%F A, B: CH_3CN; gradient: 70-90%B, flow rate: 15 mL/min; Retention Time: 17-20 min of 30min) to give 3- [(1S, 2S) -1- (2- { [(4S) -3- {1- [4- (1-azanylidene-1-oxo-1λ^6-thian-4-yl) phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -5H, 4H-1, 2, 4-oxadiazol-5-one (8.2 mg, 17.9%yield) . LC-MS: m/z 914.8 (M+H) +. 1H NMR (400 MHz, DMSO-d6) δ 7.60 -7.45 (m, 3H) , 7.43 -7.30 (m, 3H) , 7.26 -7.20 (m, 2H) , 7.13 (d, J = 8.0 Hz, 2H) , 6.92 -6.80 (m, 2H) , 5.62 -5.55 (m, 1H) , 4.50 -4.35 (m, 1H) , 4.00 -3.93 (m, 2H) , 3.55 -3.40 (m, 4H) , 3.05 -2.99 (m, 3H) , 2.95 -2.80 (m, 3H) , 2.21 -2.19 (m, 6H) , 2.18 -2.00 (m, 5H) , 1.85 -1.55 (m, 7H) , 1.45 -1.30 (m, 4H) , 1.20 -1.05 (m, 3H) .

[1282] Example A16

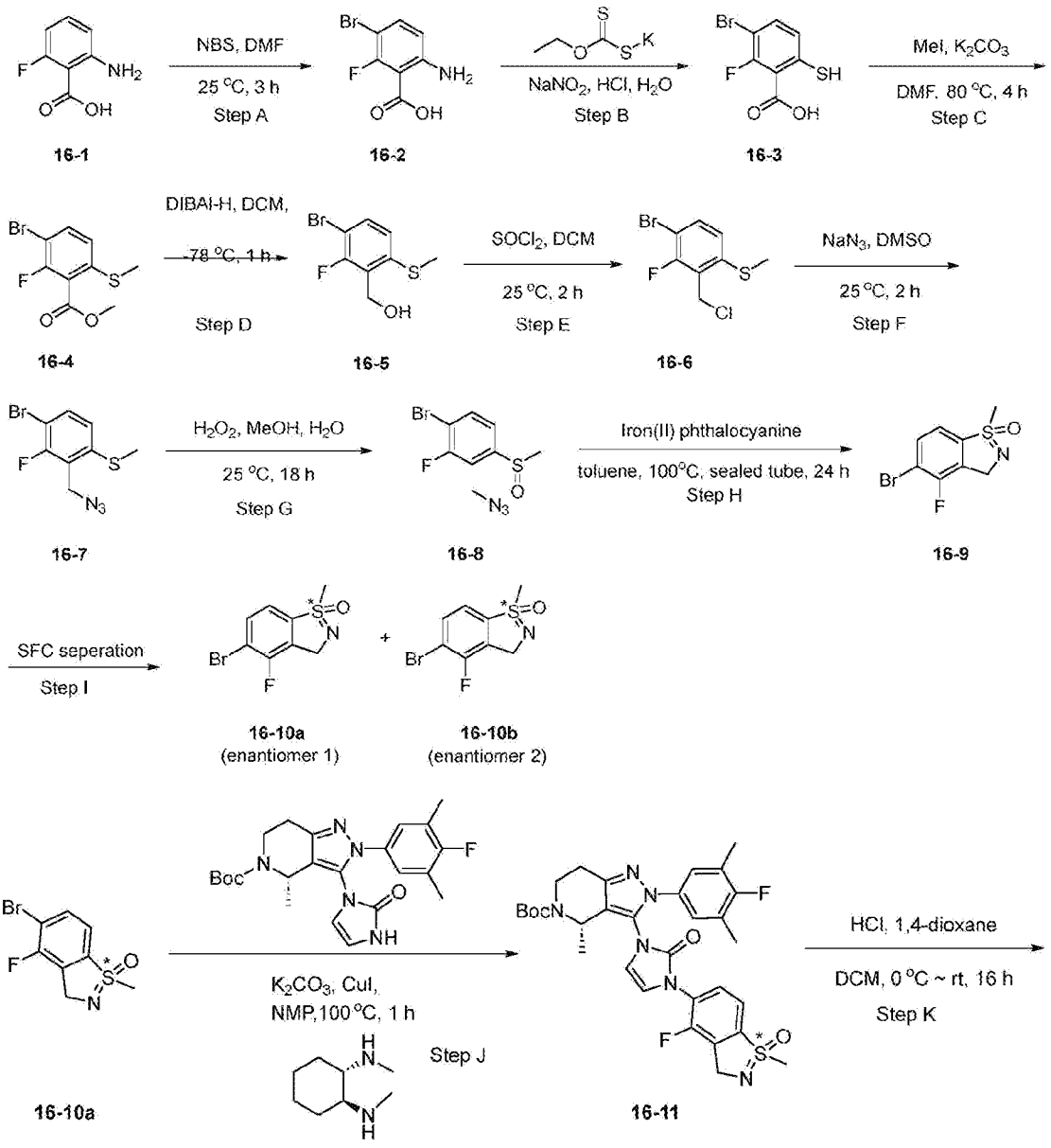
[1283] 4-fluoro-5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-1-one (Compound 187) and 4-fluoro-5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-1-one (Compound 188)

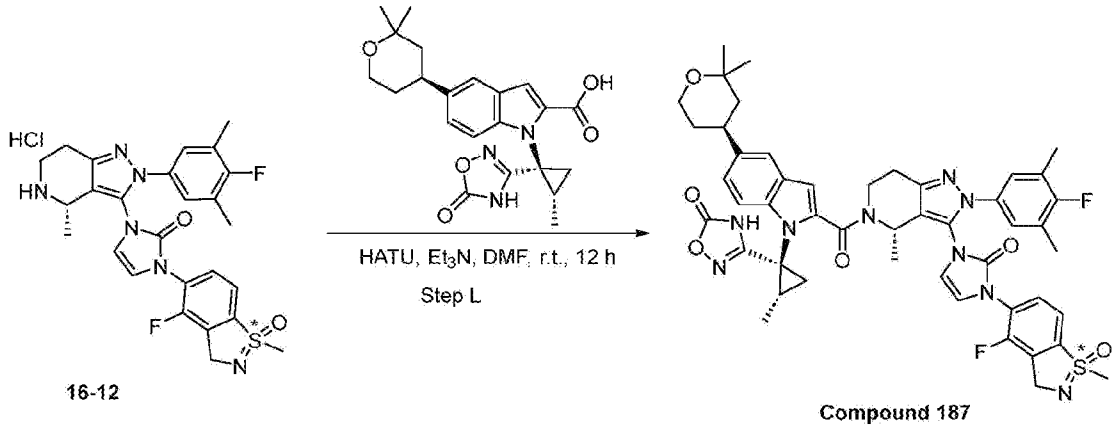


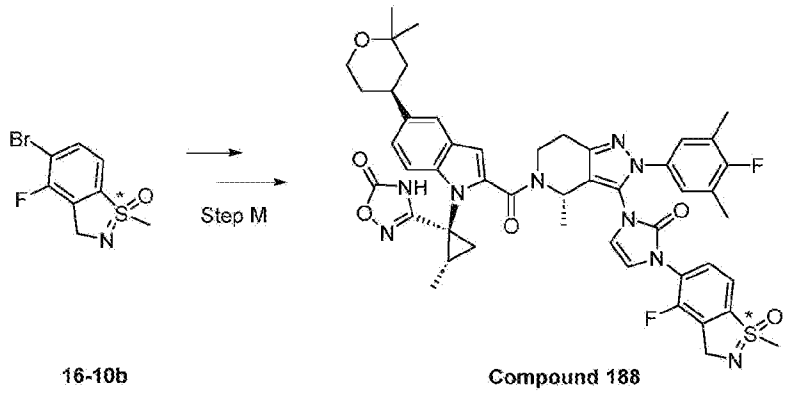
Compound 187



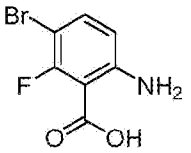
Compound 188





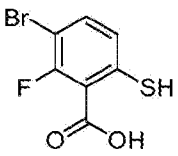


[1284] Step A 2-amino-5-bromo-4-fluorobenzoic acid



[1285] To a mixture of 2-amino-4-fluorobenzoic acid (10 g, 64.462 mmol) in DMF (100 ml) was added NBS (11.24 g, 63.173 mmol) in DMF (50 ml) at -10 ℃. The reactio n mixture was stirred for 2 h at -10 ℃. The reaction mixture was poured into ice (500 mL) , quenched with aq. $Na_2S_2O_3$ (100 mL) . After being stirred for 30 min. The mix ture was filtered, and the cake was washed with water, dried under vacuum to afford 2 -amino-5-bromo-4-fluorobenzoic acid (12.7 g, 84.2%yield) . LC-MS: m/z 234.0 $(M+H)^+$.

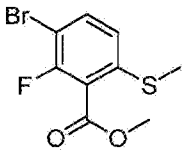
[1286] Step B 3-bromo-2-fluoro-6-sulfanylbenzoic acid



[1287] A mixture of concentrated HCl (0.7 mL) and chilled water (1 mL) was added dropwise to a stirred solution of 6-amino-3-bromo-2-fluorobenzoic aci d (4.5 g, 19.229 mmol) , NaOH (0.77 g, 19.229 mmol) and sodium nitri

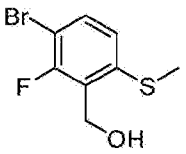
te (1.33 g, 19.229 mmol) in water (10 mL) by maintaining the internal temperature 3-6 ℃. The reaction mixture was stirred at 0 ° C for 30 min, and then neutralized with KOAc (6.23 g, 63.456 mmol) . This solution was added to a solution o f potassium ethoxymethanedithioate (9.25 g, 57.687 mmol) in water (6 mL) which had preheated to 90 ℃. The mixture was stirred at the sam e temperature for 30 min, cooled to 0 ℃, and acidified with conc. HCl (2.5 mL) . The reaction mixture was basified with 10 %aq. NaOH, and then stirred at 85 ℃ for 2 h. Th e mixture was filtered, cooled to 0 ℃, and acidified with conc. HCl until pH=1. The p recipitate was collected by filtration and washed with H_2O to obtain 3-bromo-2-fluoro-6-sulfanylbenzoic acid (4.4 g, 91.1%yield) . ^{1}H NMR (400 MHz, DMSO-d6) δ 7.86 (t, J = 8.4 Hz, 1H) , 7.86 (d, J = 8.8 Hz, 1H) .

[1288] Step C methyl 3-bromo-2-fluoro-6- (methylsulfanyl) benzoate



[1289] To a solution of 3-bromo-2-fluoro-6-sulfanylbenzoic acid (4.4 g, 17.52 5 mmol) in DMF (10 mL) were added iodomethane (7.111 mL, 87.625 mmol) , and K_2CO_3 (12.11 g, 87.625 mmol) . The reaction mixture was stirred at 80 ℃ f or 3 h. After cooling, the reaction mixture was poured into H_2O (10 mL) and ext racted with EA (10 mL x 3) . The combined organics was washed brine and dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel column chromatography eluting with 10%EtOAc/ PE to afford methyl 3-bromo-2-fluoro-6- (methylsulfanyl) benzoate (2.5 g, 51.1%yield) . ^{1}H NMR (400 MHz, DMSO-d6) δ 7.54 (t, J = 8.4 Hz, 1H) , 6 .97 (d, J = 8.4 Hz, 1H) , 3.96 (s, 3H) , 2.46 (s, 3H) .

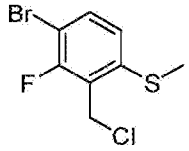
[1290] Step D [3-bromo-2-fluoro-6- (methylsulfanyl) phenyl] methanol



[1291] To a solution of methyl 3-bromo-2-fluoro-6- (methylsulfanyl) benzoate (2.5 g, 8.957 mmol) in DCM (25 mL) was added bis (2-methylpropyl) aluminum hydride (17 .914 mL, 26.871 mmol) . The reaction mixture was stirred at -78 ℃ for 3 h unde r Ar. TLC showed the reaction was completed. The reaction mixture wa s poured into water (50 mL) and extracted with DCM (50 mL x 2) . The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and co ncentrated. The residue was purified by silica gel column chromatography eluting with

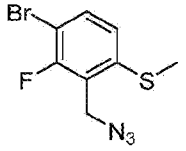
30%EtOAc/PE to obtain [3-bromo-2-fluoro- 6- (methylsulfanyl) phenyl] methanol (2 g, 88.9%yield) . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, J = 7.2 Hz, 1H) , 6.96 (d, J = 8.4 Hz, 1H) , 4.86 (d, J = 2.0 Hz, 1H) , 2.50 (s, 3H) .

[1292] Step E [4-bromo-2- (chloromethyl) -3-fluorophenyl] (methyl) sulfane



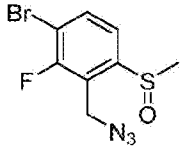
[1293] To a solution of [3-bromo-2-fluoro-6- (methylsulfanyl) phenyl] methanol (500 mg, 1.991 mmol) in DCM (10 mL) were added thionyl chloride (1421.2 mg, 11.947 mmol) . The reaction mixture was stirred at room temperature for 2 h. TLC showed the reaction was completed. The reaction mixture was concentrated to give [4-bromo-2- (chloromethyl) -3-fluorophenyl] (methyl) sulfane (500 mg, crude) .

[1294] Step F [2- (azidomethyl) -4-bromo-3-fluorophenyl] (methyl) sulfane



[1295] To a solution of [4-bromo-2- (chloromethyl) -3-fluorophenyl] (methyl) sulfane (0.51 g, 1.892 mmol) in DMSO (5 mL) was added NaN_3 (0.14 g, 2.081 mmol) . The reaction mixture was stirred at room temperature for 2 h. TLC showed the reaction was completed. The reaction mixture was quenched with water (20 mL) , extracted with EA (20 mL x 3) . The combined organic layers were washed with brine , dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by prep. TLC (SiO_2, PE 100%) to afford [2- (azidomethyl) -4-bromo-3-fluorophenyl] (methyl) sulfane (490 mg, 93.8%yield) .

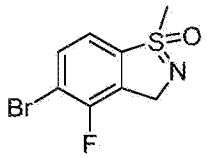
[1296] Step G [2- (azidomethyl) -4-bromo-3-fluorophenyl] (methyl) (oxo) -λ^4-sulfane



[1297] To a solution of [2- (azidomethyl) -4-bromo-3-fluorophenyl] (methyl) sulfane (950 mg, 3.440 mmol) in MeOH (5 mL) and H_2O (1 mL) , was added H_2O_2 (1.147 mL, 34.404 mmol) . The reaction mixture was stirred at room temperature for 18 h. After the reaction was completed, water (5 mL) was added. The mixture was extracted with EtOAc (10 mL x 3) . The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated un

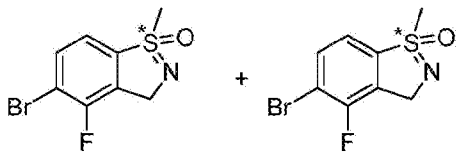
der vacuum. The residue was purified by prep. TLC (SiO_2, PE/EA=1/1) to afford [2- (azidomethyl) -4-bromo-3-fluorophenyl] (methyl) (oxo) -λ^4-sulfane (730 mg, 72.6%yield) . LC-MS: m/z 292.1 $(M+H)^+$.

[1298] Step H 5-bromo-4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazole



[1299] To a solution of [2- (azidomethyl) -4-bromo-3-fluorophenyl] (methyl) (oxo) -λ^4-sulfane (430 mg, 1.472 mmol) in toluene (5 mL) was added iron (II) p hthalocyanine (84.00 mg, 0.148 mmol) . The reaction was stirred at 100 ℃ for 18 h in a sealed tube. After cooling, the mixture poured into water, extracted with EtOAc (10 mL x 3) . The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The resulting residue was purified b y prep. TLC (SiO_2, EA/PE=5/1) to afford 5-bromo-4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazole (388 mg, 99.7%yield) . LC-MS: m/z 264.1 $(M+H)^+$.

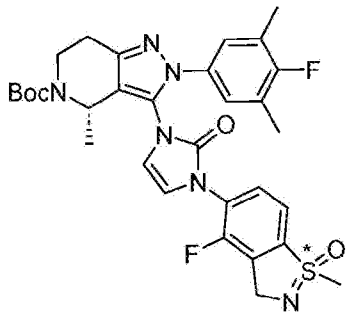
[1300] Step I 5-bromo-4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazole 16-10a (enantiomer 1) and 5-bromo-4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazole 16-10b (enantiomer 2)



enantiomer 1 **enantiomer 2**

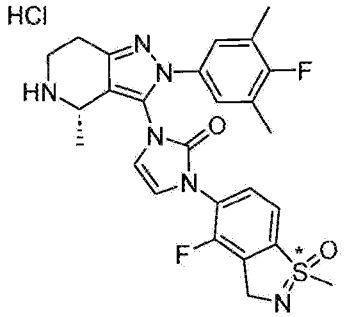
[1301] 5-bromo-4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazole (388 mg, 1.14 mmol) was separated by SFC (Column: DAICELCHIRALPAK®IG; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B =20%) . Flow rate: 70 mL/min, Column temp.: 25 ℃) to afford 5-bromo-4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazole 16-10a (enantiomer 1) (103 mg, 26.5%yield) Rt=1.392 min, LC-MS: m/z 264.1 $(M+H)^+$ and 5-bromo-4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazole 16-10b (enantiomer 2) (80 mg, 20.6%yield) . Rt=2.273 min, LC-MS: m/z 264.1 $(M+H)^+$.

[1302] Step J tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [1- (4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-5-yl) -2-oxoimidazol-3-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1303] To a solution of 5-bromo-4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazole 16-10a (enantiomer 1) (50 mg, 0.189 mmol) and tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (83.58 mg, 0.189 mmol) in NMP (8mL) was added methyl [(1R, 2R) -2- (methylamino) cyclohexyl] amine (40.40 mg, 0.284 mmol) , copper iodide (43.27 mg, 0.227 mmol) and pot assium carbonate (52.33 mg, 0.379 mmol) . The reaction was stirred at 100 ℃ for 1 h. After the reaction was completed, water (20 mL) was added. The mixtu re was extracted with EtOAc (20 mL x 3) . The combined organic layer s were washed with brine, dried over sodium sulfate, filtered and concentrated. The r esulting residue was purified by prep. TLC (SiO_2, MeOH/DCM=1/10) to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [1- (4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-5-yl) -2-oxoimidazol-3-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (100 mg, 84.6%yield) . LC-MS: m/z 625.5 $(M+H)^+$.

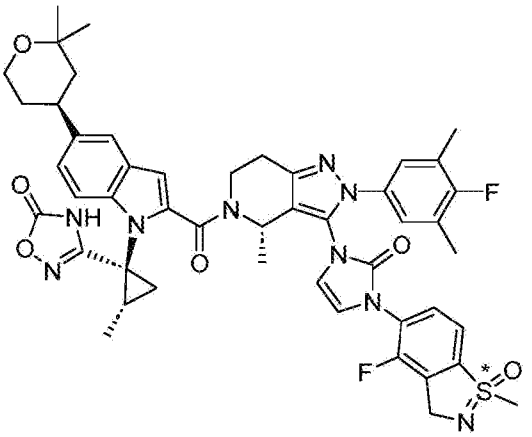
[1304] Step K 4-fluoro-5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-1-one HCl salt



[1305] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [1- (4-fluoro-1-methyl-1-oxo-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-5-yl) -2-oxoimidazol-3-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (80 m g, 0.128 mmol) in dioxane (2 mL) was added HCl in dioxane (2 mL) . T he reaction was stirred at 25 ℃ for 1 h. LCMS showed the reaction wa

s completed. The reaction was concentrated under vacuum to give 4-fluoro-5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-1-one HCl salt (70 mg, 88.6%yield) . LC-MS: m/z 525.4 (M+H) $^+$.

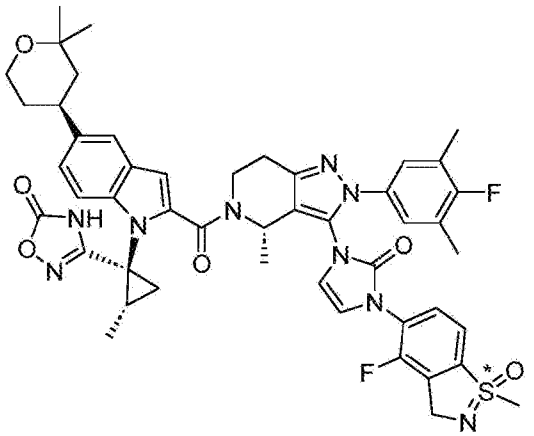
[1306] Step L 4-fluoro-5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-1-one (Compound 187)



[1307] To a solution of 5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (35.30 mg, 0.086 mmol) and HATU (35.95 mg, 0.095 mmo l) in DMF (8 mL) was added 4-fluoro-5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-1-one HCl salt (45 mg, 0.086 mmol) a nd DIEA (55.47 mg, 0.430 mmol) , the mixture was stirred at rt for 18 h. After the re action was completed, water (20 mL) was added. The mixture was extra cted with EtOAc (20 mL x 3) . The combined organic layers were washe d with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The resulting residue was purified by prep. HPLC (Waters 3767/Qda Column : SunFire Sunfire C18, 19*250mm*10 μm; Mobile Phase A: 0.1%FA/H_2O, B: CH $_3$CN ; Flow rate: 20 mL/min; Gradient: 54-59%B; Retention Time: 8.5 of 16 mi n) to afford 4-fluoro-5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-1-one (17.8 mg, 22.2%yield) . LC-MS: m/z 918.8 (M +H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.60 (brs, 1 H) , 7.97 (m, 1 H) , 7.79 -

7.70 (m, 1 H) , 7.51 (s, 1 H) , 7.41 (d, J= 8.0 Hz, 1 H) , 7.25 (d, J= 8.4 Hz, 1 H) , 7.15 (d, J= 6.4 Hz, 2 H) , 7.02 (m, 1 H) , 6.90 -6.79 (m, 2 H) , 5.69 -5.55 (m, 1 H) , 4 .82 (d, J= 17.2 Hz, 1 H) , 4.68 (d, J= 18.0 Hz, 1 H) , 4.48 -4.33 (m, 1 H) , 3 .74 (d, J= 8.8 Hz, 2 H) , 3.46 (s, 3 H) , 2.89 -2.84 (m, 1 H) , 2.24 (s, 6 H) , 1.78 - 1.69 (m, 4 H) , 1.61 -1.54 (m, 4 H) , 1.40 (m, 3 H) , 1.29 (m, 4 H) , 1.20 (m, 7 H) .

[1308] Step M 4-fluoro-5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2- yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3H-1λ^6-benzo [2, 1-d] [1, 2] thiazol-1-one (Compound 188)

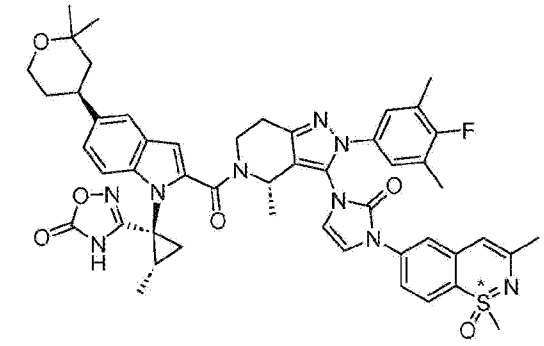


[1309] 4-fluoro-5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1-methyl-3H-1λ6-benzo [2, 1-d] [1, 2] thiazol-1-one (Compound 188) was synthesized according to the procedures described for the preparation of Compound 187) (enantiomer 1) (step J to step L) . LC-MS: m/z 918.8 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.57 (brs, 1 H) , 7.99 (m, 1 H) , 7.77 (m, 1 H) , 7.51 (s, 1 H) , 7.41 (d, J= 8.8 Hz, 1 H) , 7. 25 (d, J= 8.4 Hz, 1 H) , 7.16 (d, J= 6.4 Hz, 2 H) , 7.02 (m, 1 H) , 6.89 -6.84 (m, 2 H) , 5 .68 (m, 1 H) , 4.82 (d, J= 17.6 Hz, 1 H) , 4.68 (d, J= 17.6 Hz, 1 H) , 4.43 - 4.39 (m, 1 H) , 3.74 (d, J= 9.2 Hz, 2 H) , 3.46 (s, 3 H) , 2.88 -2.85 (m, 1 H) , 2 .24 (s, 6 H) , 1.72 -1.70 (m, 4 H) , 1.61 -1.54 (m, 4 H) , 1.44 (m, 3 H) , 1. 29 (m, 4 H) , 1.20 (m, 7 H) .

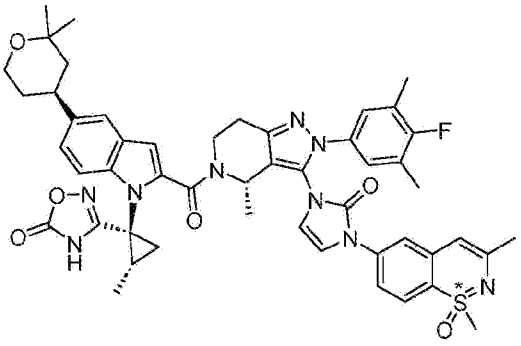
[1310] Example compounds 191 and 192, 201 and 202 were synthesized using a similar procedure described in the Example A16 above using the appropriate materials.

[1311] Example A17

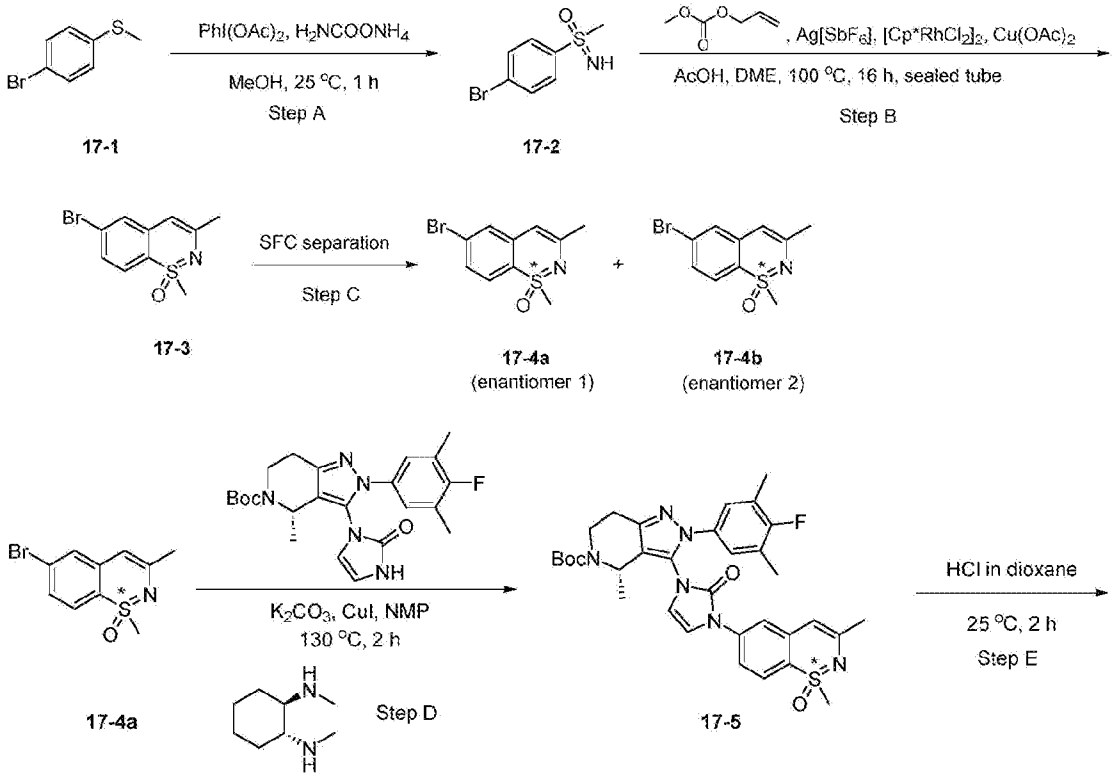
[1312] 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 206) and 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 207)

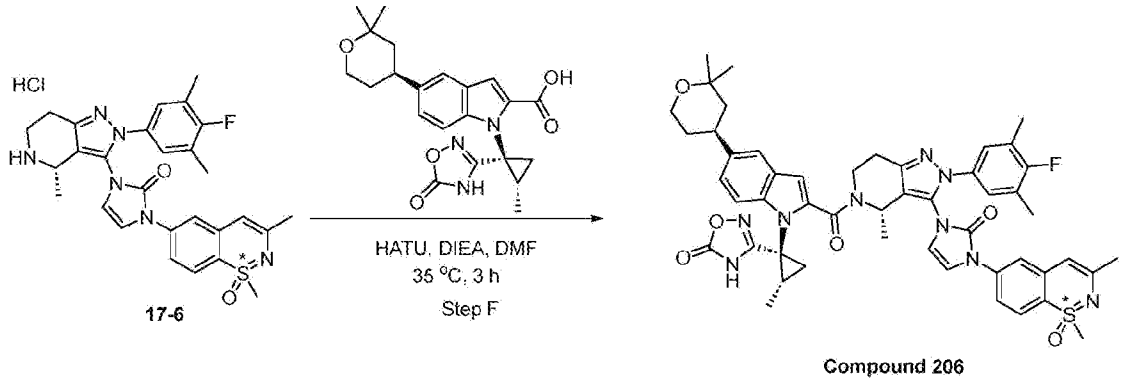


Compound 206

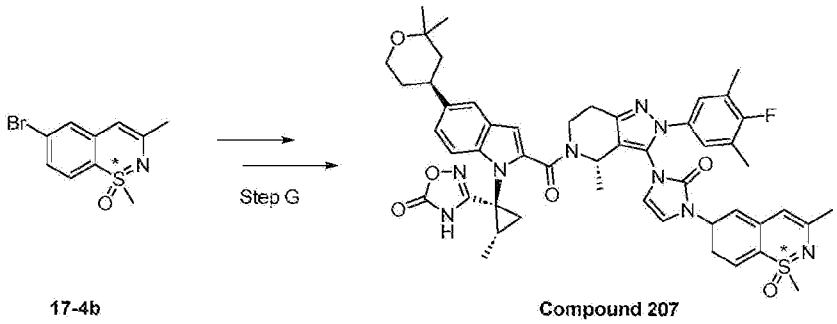


Compound 207



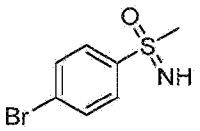


17-6 Compound 206



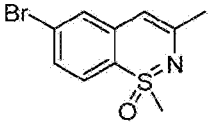
17-4b Compound 207

[1313] Step A (4-bromophenyl) (methyl) (oxo) -λ^6-sulfanimine



[1314] To a solution of (4-bromophenyl) (methyl) sulfane (2.0 g, 9.847 mmol) i n MeOH (60 mL) were added PhI (OAc) $_2$ (11.10 g, 34.466 mmol) and H_2 NCOONH$_4$ (2.69 g, 34.466 mmol) . The reaction was stirred at rt for 1 h. Aft er the reaction was completed, the mixture was poured into water (50 mL) , extracted with EtOAc (50 mL X3) , the combined organic layers were washed with brine (20 mL X3) , dried over anhydrous sodium sulfate, filtered and concentrated un der vacuum. The resulting residue was purified by silica gel chromatography eluting w ith 10%MeOH/DCM to afford (4-bromophenyl) (methyl) (oxo) -λ^6-sulfanimine (2.1 g, 91.1%yield) . LC-MS: m/z 236.1 $(M+H)^+$.

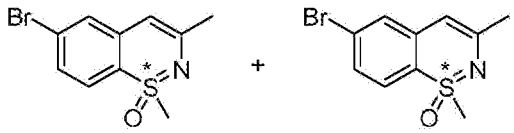
[1315] Step B 6-bromo-1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one



[1316] To a solution of (4-bromophenyl) (methyl) (oxo) -λ^6-sulfanimine (400 mg, 1.709 mmol) in DME (10 mL) were added methyl (prop-2-enyloxy) methanoa te (595.21 mg, 5.126 mmol) and silver hexafluoroantimonate (93.94 mg

, 0.273 mmol) , bis (1, 2, 3, 4, 5-pentamethylcyclopentane) bis [dichlororhodium (II)] (42.93 mg, 0.068 mmol) and copper (II) acetate monohydrate (716.36 mg, 3.588 mmol) . The reaction was stirred at 100 ℃ for 18 h under Ar in a sealed tu be. LC-MS showed the reaction was completed. The mixture was cooled, poured into water (30 mL) , extracted with EtOAc (50 mL x3) . The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by prep. TLC (SiO_2, PE/ EtOAc=1/1) to afford 6-bromo-1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (95 mg, 20.2%yield) . LC-MS: m/z 274.1 $(M+H)^+$.

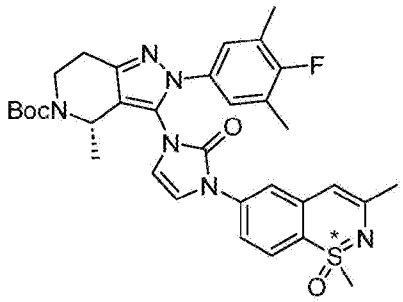
[1317] Step C 6-bromo-1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (enantiomer 1) and 6-bromo-1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (enantiomer 2)



enantiomer 1 **enantiomer 2**

[1318] 6-bromo-1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (95 mg, 0.349 mmol) was separated by SFC (Column: DAICELCHIRALPAK®AD; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 30%) . Flow rate: 120 mL/ min, Column temp.: 25 ℃.) to afford 6-bromo-1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one 17-4a (enantiomer 1) (30 mg, 31.6%yield) Rt=1.142 min, LC-MS: m/z 274.1 $(M+H)^+$ and 6-bromo-1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one 17-4b (enantiomer 2) (55 mg, 57.9%yield) . Rt=2.208 min, LC-MS: m/z 274.1 (M +H) $^+$.

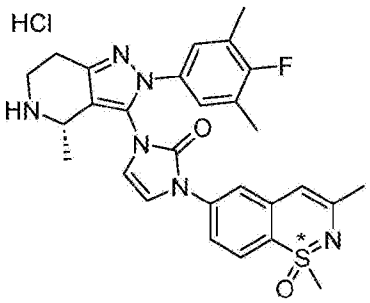
[1319] Step D tert-butyl (4S) -3- [1- (1, 3-dimethyl-1-oxo-1λ^6-benzo [2, 1-e] [1, 2] thiazin -6-yl) -2-oxoimidazol-3-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1320] To a solution of 6-bromo-1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one 17-4a (enantiomer 1) (30 mg, 0.110 mmol) in NMP (5 mL) were added tert-butyl (4S) -

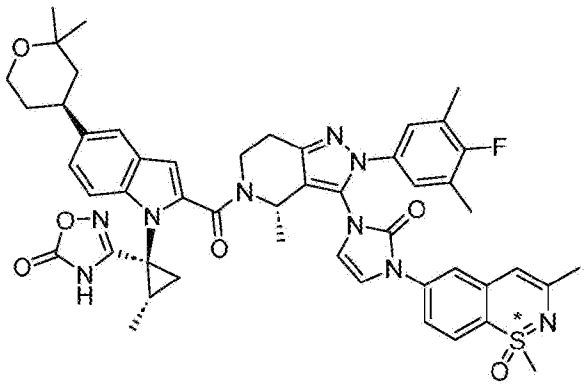
2- (4-fluoro-3, 5-dimethylphenyl) -4- methyl-3- (2-oxo-1H-imidazol-3-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (48.7 mg, 0.110 mmol) , methyl [(1R, 2R) -2- (methylamino) cyclohexyl] amine (23.5 mg, 0.165 mm ol) , CuI (25.2 mg, 0.132 mmol) and K_2CO_3 (30.5 mg, 0.220 mmol) . The react ion was stirred at 130 ℃ for 3 h under Ar. After cooling, the mixture was poured into water (10 mL) , extracted with EtOAc (10 mL x 3) . The combined org anic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by prep. TLC (SiO_2, PE/ EtOAc=1/1) to afford tert-butyl (4S) -3- [1- (1, 3-dimethyl-1-oxo-1λ^6-benzo [2, 1-e] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (45 m g, 64.5%yield) . LC-MS: m/z 633.4 $(M+H)^+$.

[1321] Step E 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one HCl salt



[1322] To a solution of tert-butyl (4S) -3- [1- (1, 3-dimethyl-1-oxo-1λ^6-benzo [2, 1-e] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (45 m g, 0.071 mmol) in dioxane (2 mL) was added 4 M HCl (gas) in dioxane (5 mL) . The mixture was stirred at 25 ℃ for 1 h. The reaction mixture was concentrat ed under vacuum to afford 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one HCl salt (30 mg, 79.2%yield) , which used for the next step without purification. LC-MS: m/z 533.1 $(M+H)^+$.

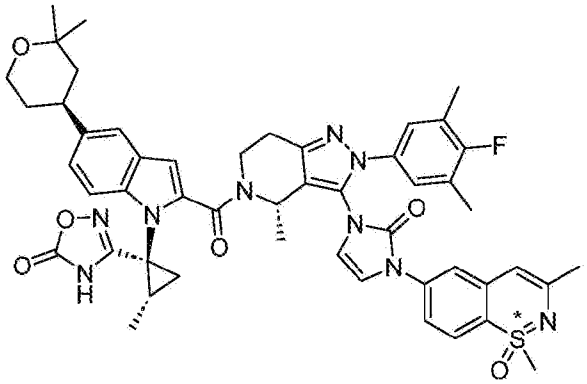
[1323] Step F 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 206)



[1324] To a solution of 5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (30.90 mg, 0.075 mmol) and HATU (31.41 mg, 0.083 mmol) in DMF (5 mL) was added a solution of 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one HCl salt (40 mg, 0.075 mmol) and DIEA (48.53 mg, 0.375 mmol) in DMF (2 mL) . The reaction was stirred at rt for 18 h. After the reaction was completed, the mixture was poured into water (10 mL) , extracted with EtOAc (10 mL x 3) . The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by prep. TLC (SiO2, PE/EA=1/1) and then further purified by prep. HPLC (Waters 3767/Qda Column: XBridge XBridge C18, 19*250mm*10 μm; Mobile Phase A: 10 mmol/L $NaHCO_3/H_2O$, B: CH_3CN; Flow rate: 20 mL/min; Gradient: 25%-30%B; Retention Time: 8.02 -9.75 min of 17 min) to afford 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 206) (27 mg, 38.9%yield) . LC-MS: m/z 926.2 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.62 (brs, 1 H) , 8.09 -8.06 (m, 1 H) , 7.69 -7.58 (m, 2 H) , 7.51 (s, 1 H) , 7.42 (d, J= 8.8 Hz, 1 H) , 7.31 -7.25 (m, 2 H) , 7.15 (d, J= 6.0 Hz, 2 H) , 6.91 -6.85 (m, 2 H) , 6.00 (m, 1 H) , 5.56 (m, 1 H) , 4.45 (m, 1 H) , 3.73 (d, J= 7.6 Hz, 2 H) , 3.66 (s, 3 H) , 2.90 -2.86 (m, 1 H) , 2.21 (s, 6 H) , 2.13 (s, 3 H) , 1.78 -1.58 (m, 7 H) , 1.53 -1.42 (m, 5 H) , 1.28 (s, 3 H) , 1.19 -1.15 (m, 7 H) .

[1325] Step G 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-

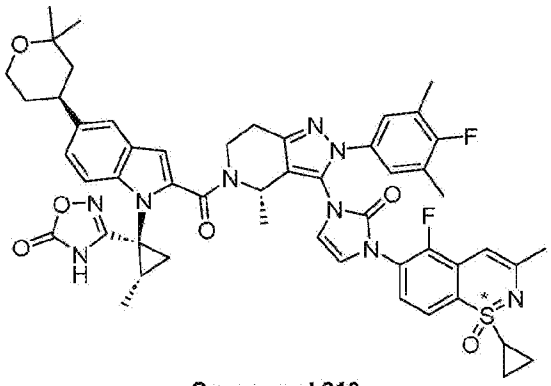
tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 207)



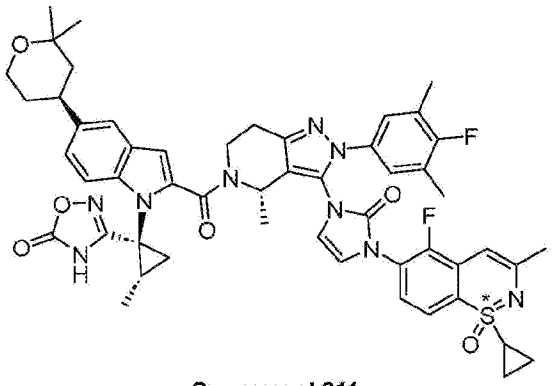
[1326] 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 207) was synthesized according to the procedures described for the preparation of Compound 206 (enantiomer 1) (step D to s tep F) . LC-MS: m/z 926.2 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.47 (brs, 1 H) , 8.06 (m, 1 H) , 7.67 -7.57 (m, 2 H) , 7.51 (s, 1 H) , 7.42 (d, J= 8.4 Hz, 1 H) , 7.31 -7.24 (m, 2 H) , 7.15 (d, J= 6.4 Hz, 2 H) , 6.92 -6.85 (m, 2 H) , 6 .01 (m, 1 H) , 5.58 (m, 1 H) , 4.42 (m, 1 H) , 3.73 (d, J= 7.6 Hz, 2 H) , 3.66 (s, 3 H) , 2.90 -2.84 (m, 1 H) , 2.21 (s, 6 H) , 2.12 (s, 3 H) , 1.78 -1.57 (m, 7 H) , 1.53-1.43 (m, 5 H) , 1.29 (s, 3 H) , 1.22 -1.19 (m, 7 H) .

[1327] Example A18

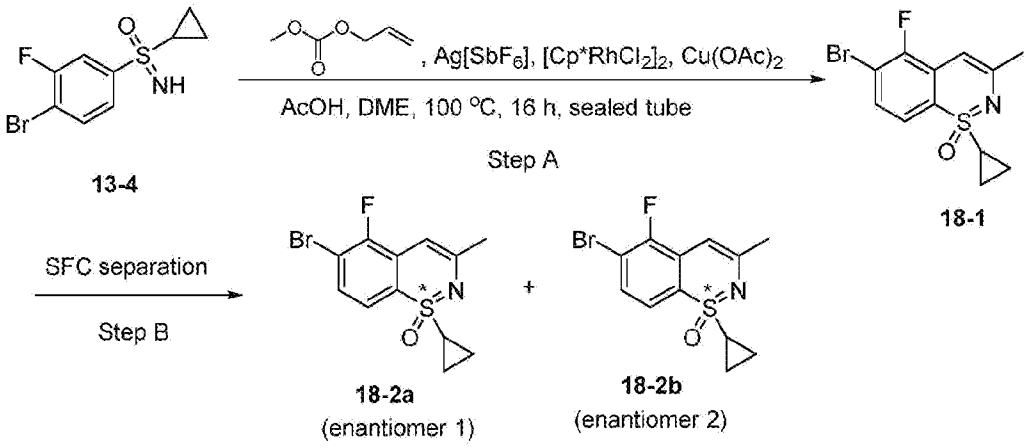
[1328] 1-cyclopropyl-5-fluoro-6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 210) and 1-cyclopropyl-5-fluoro-6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 211)

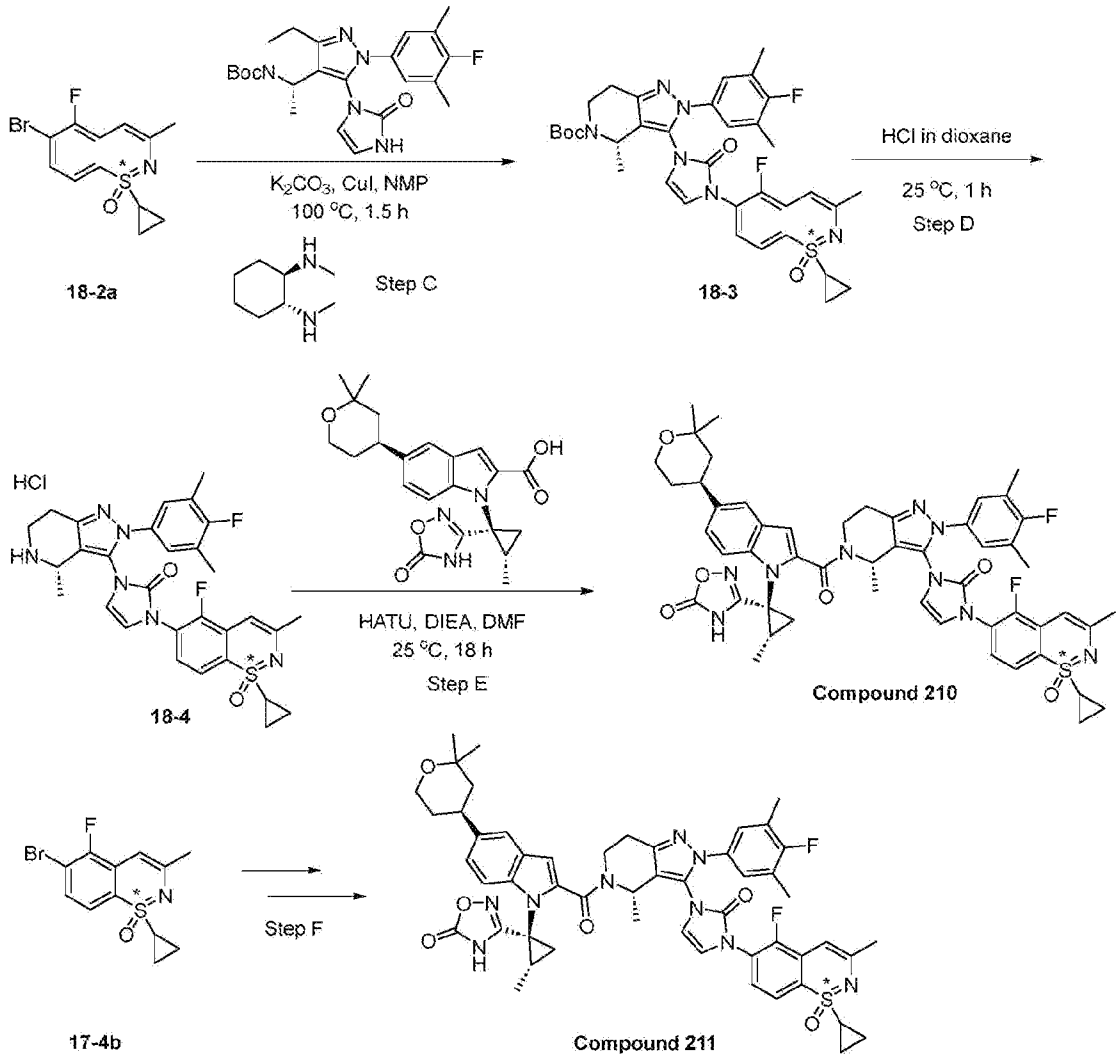


Compound 210

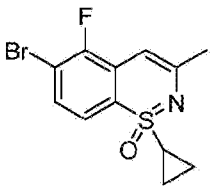


Compound 211





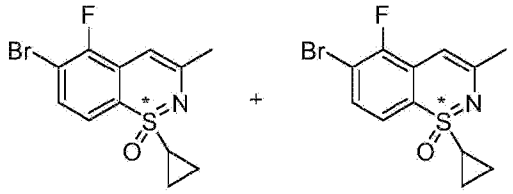
[1329] Step A 6-bromo-1-cyclopropyl-5-fluoro-3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one



[1330] To a solution of (4-bromo-3-fluorophenyl) (methyl) (oxo) -λ^6-sulfanimine (400 mg, 1.587 mmol) in DME (15 mL) were added methyl (prop-2-enyloxy) methanoate (500.9 mg, 4.314 mmol) , silver hexafluoroantimonate (78.7 mg, 0.230 mmol) , bis (1, 2, 3, 4, 5-pentamethylcyclopentane) bis [dichlororhodium (II)] (40 mg, 0.064 mmol) and Copper (II) acetate monohydrate (600.9 mg, 3.020 mmol) , AcOH (86.34 mg, 1.438 mmol) . The reaction mixture was stirred at 120 ℃ for 34 h under N2 in a sealed tube. The mixture was cooled, poured into water (30 mL) , extracted with EtOAc (50 mL x 3) . The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and

concentrated. The resulting residue was purified by prep. TLC (SiO_2, PE/EtOAc=1/1) to afford 6-bromo-1, 3-dimethyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (150 mg, 30%yield) . LC-MS: m/z 318.1 (M+H) $^+$.

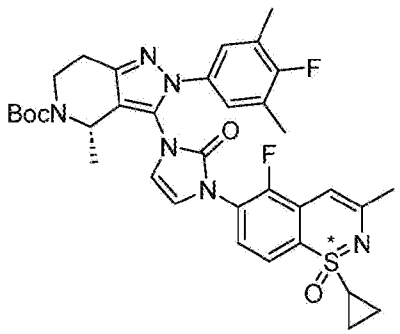
[1331] Step B 6-bromo-1-cyclopropyl-5-fluoro-3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (enantiomer 1) and 6-bromo-1-cyclopropyl-5-fluoro-3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (enantiomer 2)



18-2a (enantiomer 1) **18-2b** (enantiomer 2)

[1332] 6-bromo-1-cyclopropyl-5-fluoro-3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (150 mg, 0.475 mmol) was separated by SFC (Column: DAICELCHIRALCEL®AD; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 16%) . Flow rate: 120 mL/min, Column temp.: 25 ℃) to afford 6-bromo-1-cyclopropyl-5-fluoro-3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one 18-2a (enantiomer 1) (55 mg, 36.7%yield) , Rt=1.292 min, LC-MS: m/z 318.1 (M+H) $^+$ and 6-bromo-1-cyclopropyl-5-fluoro-3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one 18-2b (enantiomer 2) (50 mg, 33.3%yield) , Rt=2.358 min, LC-MS: m/z 318.1 (M+H) $^+$.

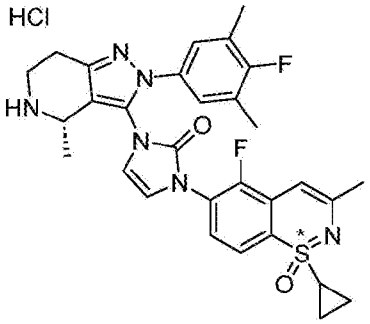
[1333] Step C tert-butyl (4S) -3- [1- (1-cyclopropyl-5-fluoro-3-methyl-1-oxo-1λ^6-benzo [2, 1-e] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1334] To a solution of 6-bromo-1-cyclopropyl-5-fluoro-3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one 18-2a (enantiomer 1) (55 mg, 0.174 mmol) and tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -4, 5, 6, 7-

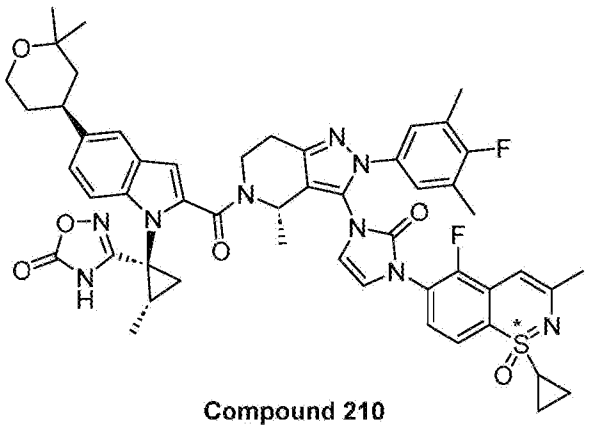
tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (76.8 mg, 0.174 mmol) in NMP (5 mL) , was added methyl [(1R, 2R) -2- (methylamino) cyclohexyl] amine (37.1 mg, 0.261 mmol) , copper iodide (39.8 mg, 0.209 mmol) and potas sium carbonate (48.08 mg, 0.348 mmol) . The mixture was stirred at 1 00 ℃ for 1.5 h. After cooling, the mixture was poured into water (20 mL) . The mixtur e was extracted with EtOAc (20 mL x 3) . The combined organic layers were washed with brine, dried over sulfate, filtered and concentrated. The resulting residue was purified by prep. TLC (SiO_2, MeOH/DCM=1/10) to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- {1- [(1R) -1-cyclopropyl-5-fluoro-3-methyl-1-oxo-1λ^6-benzo [2, 1-e] [1, 2] thiazin-6-yl] -2-oxoimidazol-3-yl} -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (77 mg, 65.4%yield) . LC-MS: m/z 677.7 $(M+H)^+$.

[1335] Step D 1-cyclopropyl-5-fluoro-6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one HCl salt



[1336] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- {1- [(1R) -1-cyclopropyl-5-fluoro-3-methyl-1-oxo-1λ^6-benzo [2, 1-e] [1, 2] thiazin-6-yl] -2-oxoimidazol-3-yl} -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (77 mg, 0.114 mmol) in dioxane (2 mL) was added 4 M HCl (gas) in dioxane (2 mL) . The reaction was stirred at 25 ℃ for 1 h. LCMS showed the r eaction was completed. The reaction was concentrated under vacuum to give 1-cyclopropyl-5-fluoro-6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one HCl salt (65 mg, crude) . LC-MS: m/z 577.6 $(M+H)^+$.

[1337] Step E 1-cyclopropyl-5-fluoro-6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 210)

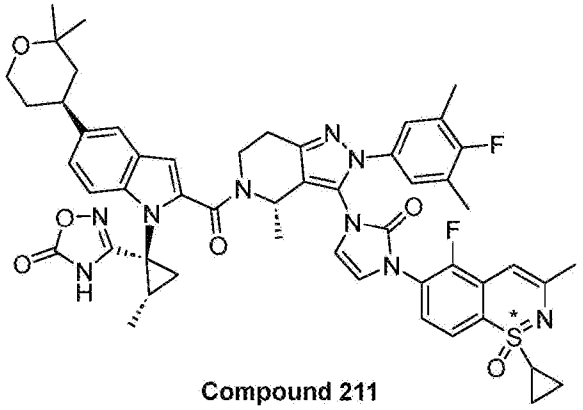


Compound 210

[1338] To a solution of 5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (46.4 mg, 0.113 mmol) and HATU (47.15 mg, 0.124 mmol) in N, N-dimethylmethanamide (5 mL) was added 1-cyclopropyl-5-fluoro-6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin -1-one HCl salt (65 mg, 0.113 mmol) and DIEA (72.84 mg, 0.564 mmol) . T he mixture was stirred at rt for 18 h. The reaction mixture was poured into water (20 mL) , extracted with EtOAc (20 mL x 3) . The combined organic layer s were washed with brine, dried over sulfate, filtered and concentrated. The resultin g residue was purified by prep. HPLC (Waters 3767/Qda Column: XBridg e XBridge C18, 19*250mm*10 μm; Mobile Phase A: 10 mmol/L $NaHCO_3$/ H_2O, B: CH_3CN; Flow rate: 20 mL/min; Gradient: 35%-40%B; Retention T ime: 9.12 -10.50 min of 17 min) to afford 1-cyclopropyl-5-fluoro-6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin -1-one (Compound 210) (37.5 mg, 34.3%yield) . LC-MS: m/z 970.3 (M+ H) +. 1H NMR (400 MHz, DMSO-d6) δ 11.64 (brs, 1 H) , 7.92 (d, J = 8.4 Hz, 1 H) , 7.52 -7.48 (m, 2 H) , 7.43 (d, J = 8.0 Hz, 1 H) , 7.27 (d, J = 8.0 Hz, 1 H) , 7.16 (d, J = 6.0 Hz, 2 H) , 7.03 (s, 1 H) , 6.88 (m, 2 H) , 6.14 (s, 1 H) , 5.72 -5.60 (m, 1 H) , 4.45 -4.30 (m, 1 H) , 3.74 (d, J= 7.6 Hz, 2 H) , 3.60 -3.56 (m, 1 H) , 3.32 -3.29 (m, 1 H) , 2 .90 -2.87 (m, 1 H) , 2.25 (s, 6 H) , 2.20 (s, 3 H) , 1.85 -1.80 (m, 4 H) , 1.74 -1.70 (m, 3 H) , 1.63 -1.62 (m, 2 H) , 1.51 -1.35 (m, 4 H) , 1.29 (m, 4 H) , 1.25 -1.10 (m, 7 H) , 1.03 -1.00 (m, 1 H) .

[1339] Step F 1-cyclopropyl-5-fluoro-6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-

methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 211)

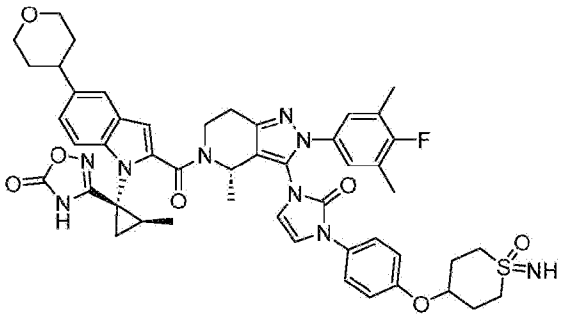


Compound 211

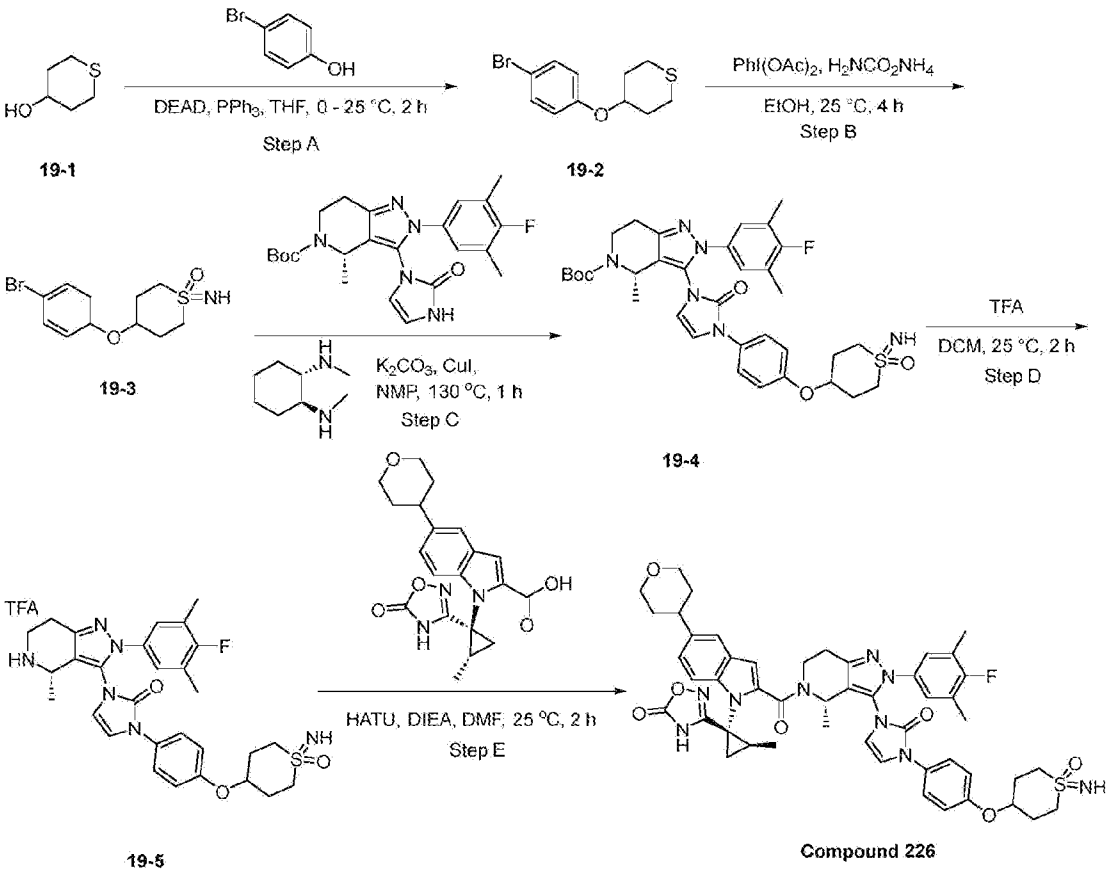
[1340] 1-cyclopropyl-5-fluoro-6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -3-methyl-1λ^6-benzo [2, 1-e] [1, 2] thiazin-1-one (Compound 211) was synthesized according to the procedures described for the preparation of Compound 210 (enantiomer 1) (step C to s tep E) . LC-MS: m/z 970.3 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.63 (brs, 1 H) , 7.90 (m, 1 H) , 7.52 -7.48 (m, 2 H) , 7.43 (d, J = 8.4 Hz, 1 H) , 7.27 (d , J = 8.0 Hz, 1 H) , 7.16 (d, J = 6.0 Hz, 2 H) , 7.04 (s, 1 H) , 6.88 (m, 2 H) , 6.14 (s, 1 H) , 5.72 -5.60 (m, 1 H) , 4.45 -4.30 (m, 1 H) , 3.74 (d, J= 7.6 Hz, 2 H) , 3.60 -3.56 (m, 1 H) , 3.32 -3.29 (m, 1 H) , 2.90 -2.87 (m, 1 H) , 2.25 (s, 6 H) , 2. 20 (s, 3 H) , 1.85 -1.80 (m, 4 H) , 1.75 -1.72 (m, 4 H) , 1.63 -1.62 (m, 3 H) , 1.51 -1.35 (m, 4 H) , 1.29 (m, 4 H) , 1.25 -1.10 (m, 7 H) , 1.04 -1.01 (m, 1 H) .

[1341] Example A19

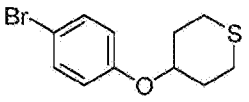
[1342] 3- ((1S, 2S) -1- (2- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (4- ((1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) oxy) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (Compound 226)



Compound 226



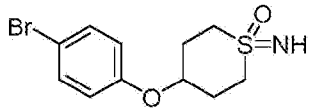
[1343] Step A 4- (4-bromophenoxy) tetrahydro-2H-thiopyran



[1344] To a solution of tetrahydro-2H-thiopyran-4-ol (1.00 g, 8.46 mmol) in THF (10 mL) were added 4-bromophenol (1.24 g, 7.19 mmol) and triphenylphosph ine (2.66 g, 10.15 mmol) . After addition, the reaction mixture was stirred at 25 ℃ f or 0.5 h under N2 atmosphere. Then, to the mixture was added diethyl azodicarboxylate (1.77 g, 10.15 mmol) at 0 ℃. After addition, the reaction mixture w as stirred at 25 ℃ for 1.5 h under N2 atmosphere. The mixture was poured into ice wat er (20 mL) and extracted with EtOAc (20 mL x 3) . The combined organ

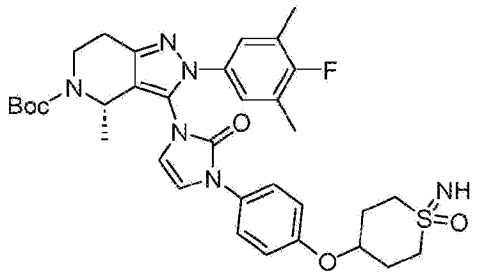
ic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The r esidue was purified by silica gel column chromatography (3%-10%EtOAc/PE) to a fford 4- (4-bromophenoxy) tetrahydro-2H-thiopyran (0.60 g, 26.0%yield) .

[1345] Step B 4- (4-bromophenoxy) -1-iminohexahydro-1λ^6-thiopyran 1-oxide



[1346] To a solution of 4- (4-bromophenoxy) tetrahydro-2H-thiopyran (0.25 g , 0.92 mmol) in EtOH (0.3 mL) were added ammonium acetate (0.28 g, 3 .66 mmol) and iodobenzene diacetate (0.88 g, 2.75 mmol) . The mixture was stirred at 25 ℃ for 4 h. The resulting mixture was diluted with H_2O (10 mL) and ext racted with EtOAc (10 mL × 3) . The combined organic layers were was hed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purifi ed by prep. TLC (SiO_2, DCM: MeOH = 20: 1) to give 4- (4-bromophenoxy) -1-iminohexahydro-1λ^6-thiopyran 1-oxide (0.15 g, 53.9%yield) . LC-MS: m/z: 303.8 (M +H) $^+$.

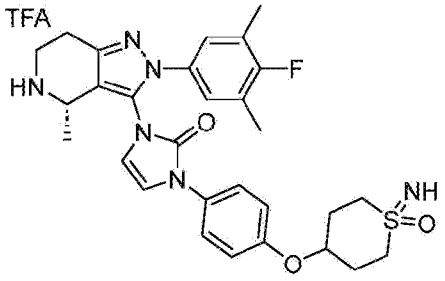
[1347] Step C tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (4- ((1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) oxy) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate



[1348] A mixture of tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (50.0 mg, 0.11 mmol) , (1S, 2S) -N1, N2-dimethylcyclohexane-1, 2-diamine (8.05 mg, 0.057 mmol) , 4- (4-bromophenoxy) -1-iminohexahydro-1λ^6-thiopyran 1-oxide (51.7 mg, 0.17 mmol) , copper (I) iodide (43.1 mg, 0.23 mmol) and K_2CO_3 (31.3 mg, 0.23 mmol) in NMP (0.5 mL) was degassed and purged with N 2 for 3 times. The mixture was stirred at 130 ℃ for 1 h under N2 atmosphere. The resu lting mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL × 3) . The combined organic layers were washed with brine, dried over Na $_2SO_4$, filtered and concentrated. The residue was purified by prep. TLC (SiO_2 , DCM: MeOH = 20: 1) to give tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (4- ((1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) oxy) phenyl) -2-oxo-

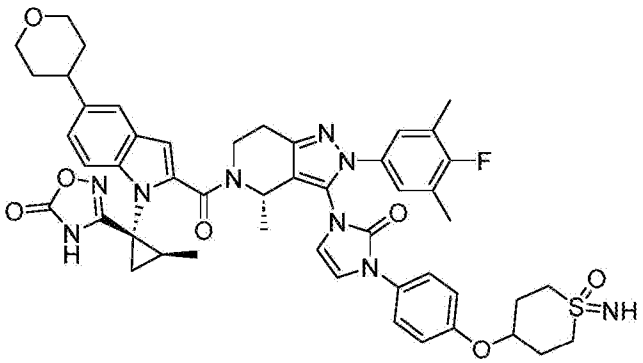
2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (70.0 mg, 93.2%yield) . LC-MS: m/z: 665.5 $(M+H)^+$.

[1349] Step D (S) -1- (2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- ((1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) oxy) phenyl) -1, 3-dihydro-2H-imidazol-2-one TFA salt



[1350] To a solution of tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (4- ((1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) oxy) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (50.0 mg, 0.075 mmol) in DCM (1 mL) was added TFA (0.4 m L, 5.19 mmol) . The mixture was stirred at 25 ℃ for 2 h. The resulting mixture was co ncentrated to give (S) -1- (2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- ((1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) oxy) phenyl) -1, 3-dihydro-2H-imidazol-2-one TFA salt (40. 0 mg, crude) , which was used for the next step directly without further purification . LC-MS: m/z 565.1 $(M+H)^+$.

[1351] Step E 3- ((1S, 2S) -1- (2- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (4- ((1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) oxy) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (Compound 226)



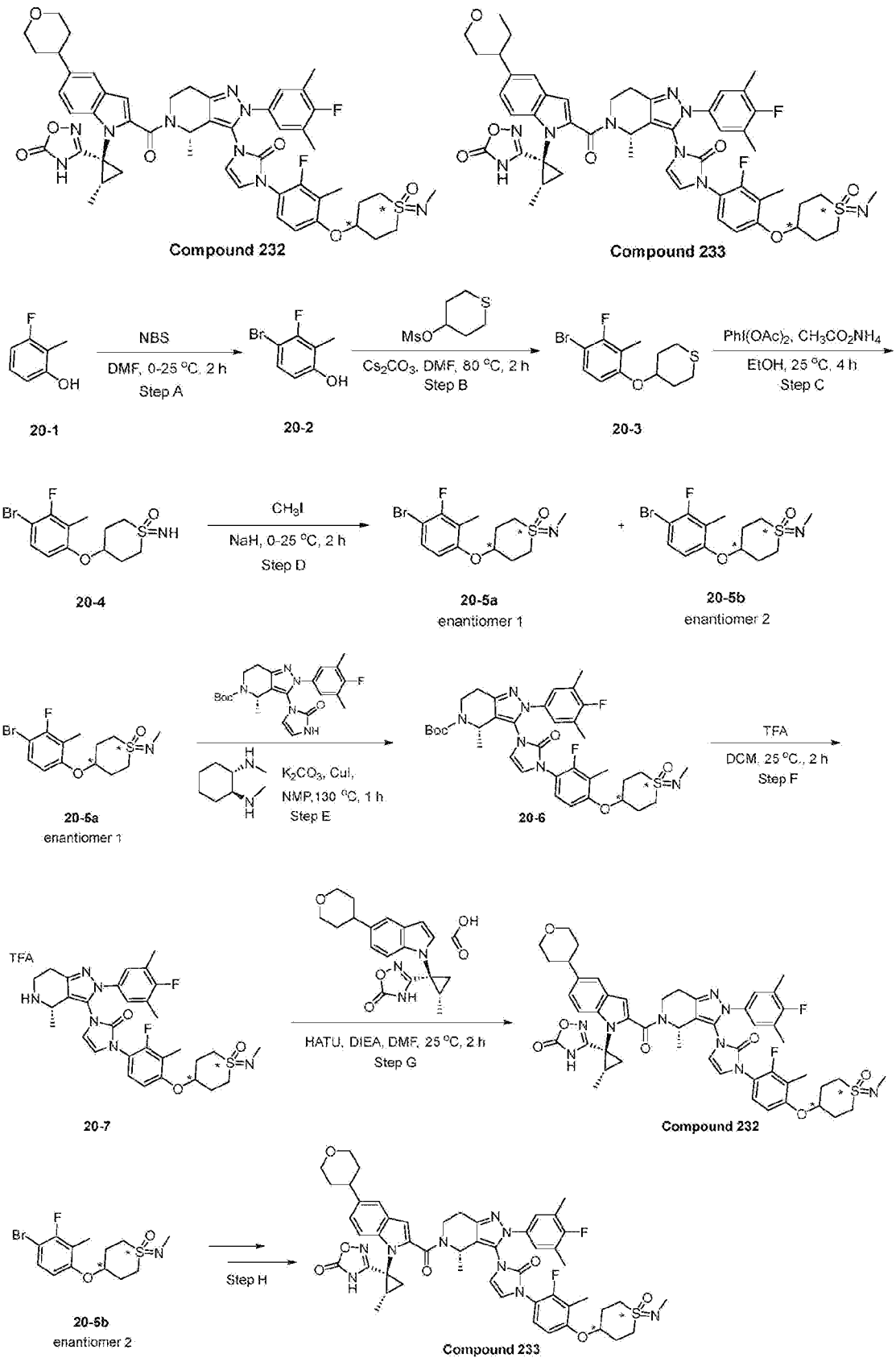
[1352] To a solution of (S) -1- (2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (4- ((1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) oxy) phenyl) -1, 3-dihydro-2H-imidazol-2-one TFA salt (26.

0 mg, 0.046 mmol) in DMF (0.5 ml) were added DIEA (0.032 ml, 0.18 mmol) , 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (17.7 mg, 0.046 mm ol) and HATU (21.01 mg, 0.055 mmol) . The mixture was stirred at 25 ℃ for 2 h. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL × 3) . The combined organic layers were dried over dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep. TLC (SiO_2 , DCM: MeOH = 20: 1) and then purified by prep. HPLC (SHIMADZU LC-20AP, Column: YMC Triart C18, 20*250 mm, 5 μm; Mobile Phase A: 0. 1%FA, B: CH_3CN; flow rate: 15 mL/min; gradient: 70-90%B; Retention T ime: 17-20 min of 30 min) to give 3- ((1S, 2S) -1- (2- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (4- ((1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-yl) oxy) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (6.4 mg, 15.0 %yield) . LC-MS: m/z 930.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.60 - 7.40 (m, 4H) , 7.28 (d, J = 8.0 Hz, 1H) , 7.20 -7.10 (m, 5H) , 6.95 -6.80 (m, 2H) , 5. 62 -5.55 (m, 1H) , 4.70 (s, 1H) , 4.40 -4.35 (m, 1H) , 4.00 -3.96 (m, 2H) , 3.75 - 3.73 (m, 1H) , 3.67 -3.60 (m, 1H) , 3.52 -3.45 (m, 2H) , 3.11 -3.08 (m, 3H) , 2.91 - 2.85 (m, 2H) , 2.24 -2.17 (m, 9H) , 1.78 -1.64 (m, 6H) , 1.45 -1.40 (m, 2H) , 1.32 - 1.24 (m, 6H) , 1.22 -1.15 (m, 2H) .

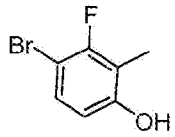
[1353] Example A20

[1354] 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [1- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl) -2-oxoimidazol-3-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 232) and

[1355] 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [1- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl) -2-oxoimidazol-3-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 233)

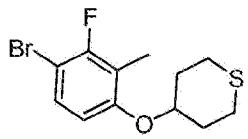


[1356] Step A 4-bromo-3-fluoro-2-methylphenol



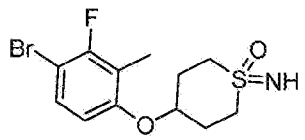
[1357] To a solution of 3-fluoro-2-methylphenol (1.00 g, 7.93 mmol) in DMF (10 mL) was added NBS (1.40 g, 7.93 mmol) at 0 ℃. After addition, the reaction mixture was stirred at 25 ℃ for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography eluting with 10%-20%EtOAc/PE to give 4-bromo-3-fluoro-2-methylphenol (0.90 g, 55.4%yield) . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, J = 8.0 Hz, 1H) , 6.51 (dd, J_1 = 8.0 Hz, J_2 = 0.4 Hz, 1H) , 5.61 (s, 1H) , 2.19 (s, 3H) .

[1358] Step B 1- (4- (azetidin-3-yl) -1- (4-fluoro-3, 5-dimethylphenyl) -1H-pyrazol-5-yl) -3- (1-methyl-1H-indazol-5-yl) -1, 3-dihydro-2H-imidazol-2-one TFA salt



[1359] To a solution of 4-bromo-3-fluoro-2-methylphenol (400.0 mg, 1.95 mmol) in DMF (4 mL) was added tetrahydro-2H-thiopyran-4-yl methanesulfonate (383.0 mg, 1.95 mmol) . After addition, the reaction mixture was stirred at 80 ℃ for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL × 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography eluting with 0 %to 10 %EtOAc/PE to give 1- (4- (azetidin-3-yl) -1- (4-fluoro-3, 5-dimethylphenyl) -1H-pyrazol-5-yl) -3- (1-methyl-1H-indazol-5-yl) -1, 3-dihydro-2H-imidazol-2-one TFA salt (380.0 mg, 63.8%yield) . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 8.0 Hz, 1H) , 6.52 (dd, J_1 = 8.0 Hz, J_2 = 0.4 Hz, 1H) , 4.43 -4.34 (m, 1H) , 2.97 -2.88 (m, 2H) , 2.58 -2.51 (m, 2H) , 2.20 (s, 3H) , 2.17 -2.12 (m, 2H) , 2.09 -2.01 (m, 2H) .

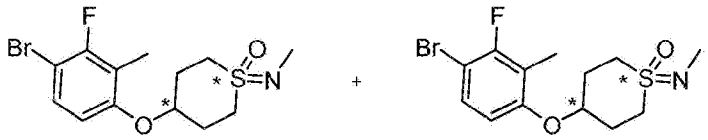
[1360] Step C 4- (4-bromo-3-fluoro-2-methylphenoxy) -1-iminohexahydro-1λ^6-thiopyran 1-oxide



[1361] To a solution of 4- (4-bromo-3-fluoro-2-methylphenoxy) tetrahydro-2H-thiopyran (380.0 mg, 1.25 mmol) in EtOH (4 mL) was added (diacetoxyi

odo) benzene (1.20 g, 3.72 mmol) and ammonium acetate (384.0 mg, 5.0 mmol) in one portion at 25 ℃. After addition, the reaction mixture was stirred at 25 ℃for 4 h. The reaction mixture was concentrated, the residue was diluted with water (10 mL) , extracted with EtOAc (15 mL x 3) . The combined organic la yers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The r esidue was purified by silica gel column chromatography eluting with 30%to 50%EtOAc/PE to give 4- (4-bromo-3-fluoro-2-methylphenoxy) -1-iminohexahydro-1λ⁶-thiopyran 1-oxide (300.0 mg, 71.6%yield) . LC-MS: m/z 335.9 $(M+H)^+$.

[1362] Step D 4- [(4-bromo-3-fluoro-2-methylphenyl) oxy] -1- (methylazanylidene) -1λ⁶-thian-1-one 20-5a (enantiomer 1) and 4- [(4-bromo-3-fluoro-2-methylphenyl) oxy] -1-(methylazanylidene) -1λ⁶-thian-1-one 20-5b (enantiomer 2)

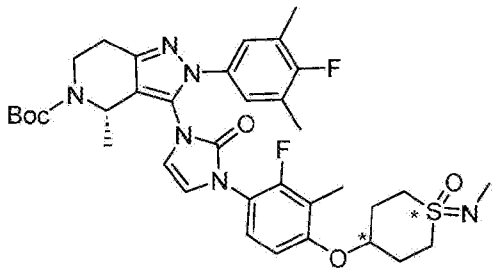


20-5a
enantiomer 1

20-5b
enantiomer 2

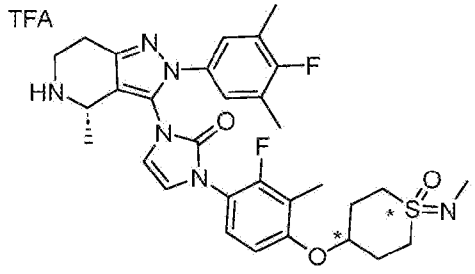
[1363] To a solution of 4- (4-bromo-3-fluoro-2-methylphenoxy) -1-iminohexahydro-1λ⁶-thiopyran 1-oxide (300.0 mg, 0.90 mmol) in DMF (3.0 mL) was added 60%NaH (43.0 mg, 1.2 mmol) at 0 ℃ and stirred at 0 ℃ for 0.5 h under N2 atmosphere. Then, to the mixture was added iodomethane (190.0 mg, 1.34 mmol) . After addition, the reaction mixture was stirred at 25 ℃ for 1.5 h under N2 atmosphere. The mixture was poured into ice water (10 mL) and extracted with EtOAc (10 mL × 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep. TLC (SiO_2, DCM: MeOH = 20: 1) to give 4- [(4-bromo-3-fluoro-2-methylphenyl) oxy] -1- (methylazanylidene) -1λ⁶-thian-1-one 20-5a (enantiomer 1) (50.0 mg, 16.0%yield) , LC-MS: m/z 349.9 $(M+H)^+$. And 4- [(4-bromo-3-fluoro-2-methylphenyl) oxy] -1- (methylazanylidene) -1λ⁶-thian-1-one 20-5b (enantiomer 2) (50.0 mg, 16.0%yield) , LC-MS: m/z 349.9 $(M+H)^+$.

[1364] Step E tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [3- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ⁶-thian-4-yl] oxy} phenyl) -2-oxoimidazol-1-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1365] To a solution of 4- [(4-bromo-3-fluoro-2-methylphenyl) oxy] -1- (methylazanylide ne) -1λ^6-thian-1-one 20-5a (enantiomer 1) (50.0 mg, 0.14 mmol) in NMP (0.5 mL) were added tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (40.0 mg, 0.14 mmol) , K_2CO_3 (31.0 mg, 0.28 mmol) , copper (I) iodide (43.0 mg, 0.28 mmol) and (1S, 2S) -N1, N2-dimethylcyclohexane-1, 2-diamine (8.1 mg, 0.07 mmol) at 25 ℃. After addition, the mixture was purged with N2 for 3 times and stirred at 130 ℃ for 1 h under N2 atmosphere. After c ooling to room temperature, the resulting mixture was added water (5 mL) and extracte d with ethyl acetate (5 mL x 3) . The combined organic layers were washed with brine. dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography eluting with 50%to 100%EtOAc/PE to give tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [3- (2-fluoro-3-methyl-4- { [1- (methylazanylide ne) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl) -2-oxoimidazol-1-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (50.0 mg, 50.2%yield) . LC-MS: m/z 711.2 $(M+H)^+$.

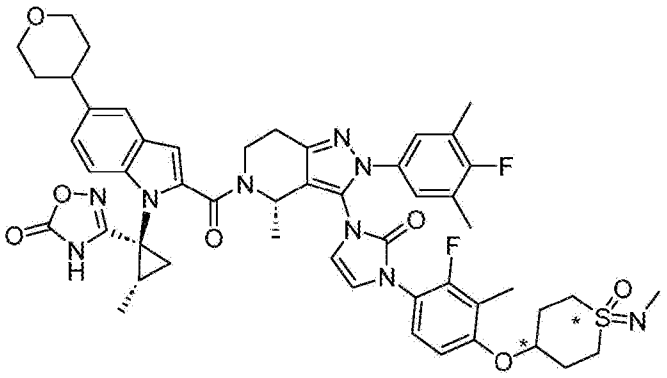
[1366] Step F 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl) -2, 3-dihydro-1H-imidazol-2-one TFA salt



[1367] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [3- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl) -2-oxoimidazol-1-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (40.0 mg, 0.06 mmol) in DCM (1 mL) was added TFA (0.5 mL , 6.5 mmol) at 25 ℃. After addition, the reaction mixture was stirred at 25 ℃ for 1 h

. The resulting mixture was concentrated to give 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl) -2, 3-dihydro-1H-imidazol-2-one TFA salt (40.0 mg, crude) , which was used for the next step directly without further purification. LC-MS: m/z 611.2 (M+H) $^+$.

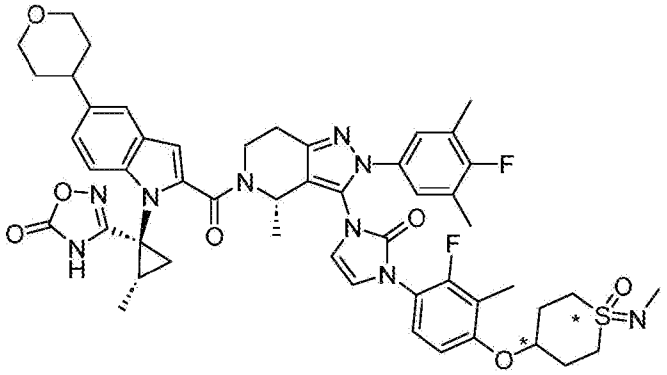
[1368] Step G 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [1- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl) -2-oxoimidazol-3-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 232)



[1369] To a solution of 1- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -3- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl) -2, 3-dihydro-1H-imidazol-2-one TFA salt (40.0 mg, 0.07 mmol) and 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (25.0 mg, 0.07 mmol) in DMF (0.5 mL) were added HATU (30.0 mg, 0.08 mmol) and DIEA (0.043 mL, 0.28 mmol) at 25 ℃. After addition, the reaction mixture was stirred at 25 ℃ for 2 h. The reac tion mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL x 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and co ncentrated. The residue was purified by prep. TLC (SiO_2, DCM: MeOH = 20: 1) and then purified by prep. HPLC (SHIMADZU LC- 20AP, Colum n: YMC Triart C18, 20*250 mm, 5 μm, Mobile Phase A: 0.1%FA, B: CH_3 CN, flow rate: 15 mL/min; gradient: 55-75%B, Retention time: 12 min of 20 min) to give 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [1- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl) -2-oxoimidazol-3-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 232) (5.0 mg, 7.3%yi

eld) . LC-MS: m/z 976.4 (M+H) $^{+}$. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.49 (s, 1H) , 7.42 -7.38 (m, 1H) , 7.33 -7.19 (m, 2H) , 7.14 (d, J = 8.0 Hz, 2H) , 7.02 - 6.95 (m, 1H) , 6.89 -6.75 (m, 3H) , 5.65 -5.55 (m, 1H) , 4.85 -4.74 (m, 1H) , 4. 01 -3.97 (m, 2H) , 3.55 -3.40 (m, 3H) , 2.97 -2.80 (m, 3H) , 2.66 (s, 3H) , 2.24 - 2.10 (m, 14H) , 1.85 -1.55 (m, 8H) , 1.48 -1.32 (m, 4H) , 1.26 -1.05 (m, 5H) .

[1370] Step H 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) - 3- [1- (2-fluoro-3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^{6}-thian-4- yl] oxy} phenyl) -2-oxoimidazol-3-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3- c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2- methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 233)

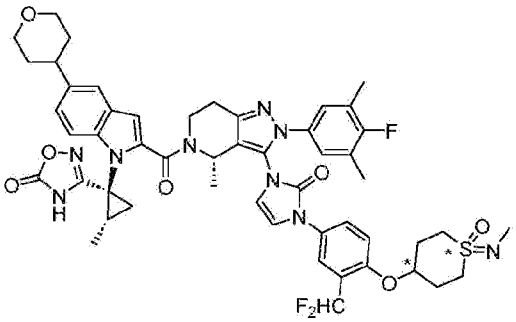


[1371] 3- [(1S, 2S) -1- (2- { [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- [1- (2-fluoro- 3-methyl-4- { [1- (methylazanylidene) -1-oxo-1λ^{6}-thian-4-yl] oxy} phenyl) - 2-oxoimidazol-3-yl] -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin- 5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2- methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 233) (enantiomer 2) was synthesized according to the procedures described for the prepar ation of Compound 232 (enantiomer 1) (step E to step G) . LC-MS: m/z 976.4 (M +H) $^{+}$. 1H NMR (400 MHz, DMSO-d6) δ 7.49 (s, 1H) , 7.42 -7.35 (m, 1H) , 7.33 - 7.19 (m, 2H) , 7.14 (d, J = 8.0 Hz, 2H) , 7.02 -6.95 (m, 1H) , 6.89 -6.75 (m, 3H) , 5. 65 -5.55 (m, 1H) , 4.85 -4.74 (m, 1H) , 4.01 -3.90 (m, 2H) , 3.65 -3.40 (m, 3H) , 2. 97 -2.80 (m, 3H) , 2.64 (s, 3H) , 2.24 -2.10 (m, 14H) , 1.85 -1.55 (m, 8H) , 1.48 - 1.32 (m, 4H) , 1.26 -1.05 (m, 5H) .

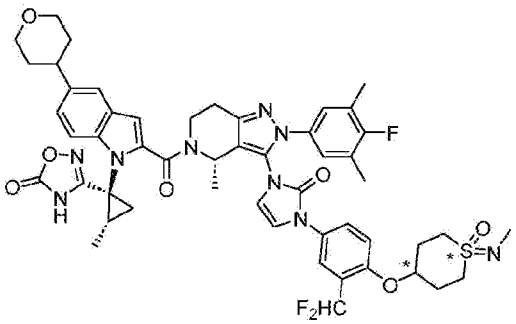
[1372] Example A21

[1373] 3- [(1S, 2S) -1- (2- { [(4S) -3- {1- [3- (difluoromethyl) -4- { [1- (methylazanylide ne) -1-oxo-1λ^{6}-thian-4-yl] oxy} phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro- 3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin- 5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2- methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 234) and 3- [(1S, 2S) -1- (2- { [(4S) -3- {1- [3- (difluoromethyl) -4- { [1- (methylazanylide

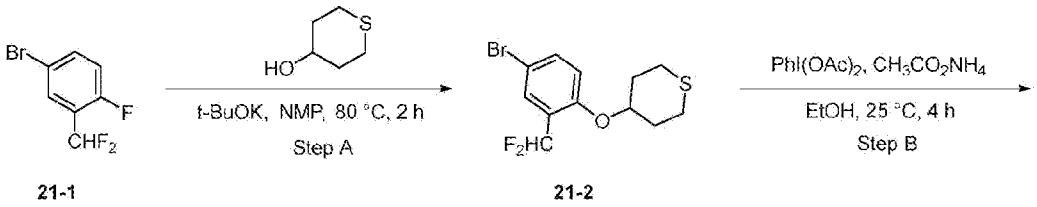
ne) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 235)



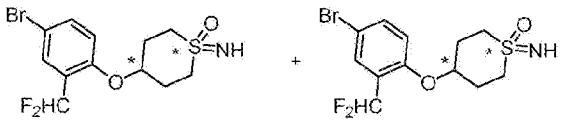
Compound 234



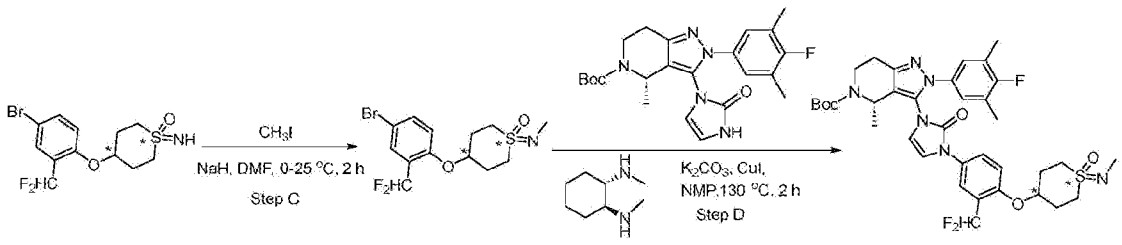
Compound 235



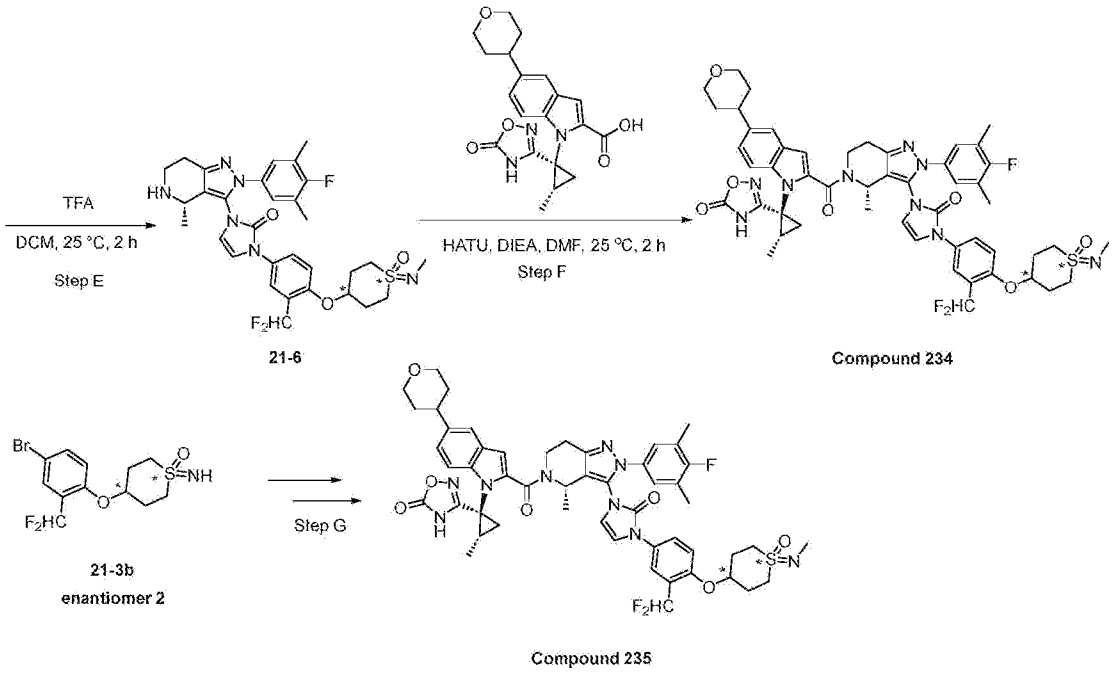
21-1 21-2



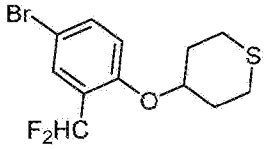
21-3a enantiomer 1 21-3b enantiomer 2



21-3a enantiomer 1 21-4 21-5

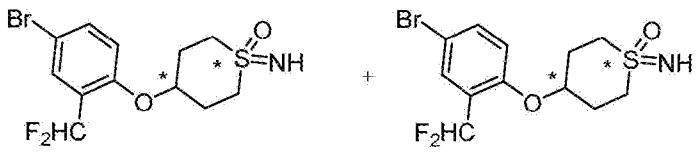


[1374] Step A 4- (4-bromo-3- (difluoromethyl) phenoxy) tetrahydro-2H-thiopyran



[1375] To a solution of 4-bromo-2- (difluoromethyl) -1-fluorobenzene (1.00 g, 4.44 mmol) in NMP (10 mL) were added tetrahydro-2H-thiopyran-4-ol (0.53 g, 4.44 mmol) and potassium tert-butoxide (1.00 g, 8.91 mmol) . The reaction mixture was stirred at 80 ℃ for 2 h. After cooling, the mixture was diluted with H $_2$O (10 mL) , extracted with EtOAc (10 mL x 3) . The combined organic layers were washed with brine (10 mL x 3) , dried over Na_2SO_4, filtered and co ncentrated. The residue was purified by silica gel column chromatography eluting with 10%-30%EtOAc/PE to afford 4- (4-bromo-3- (difluoromethyl) phenoxy) tetrahydro-2H-thiopyran (0.75 g, 2.32 mmol, 52.3 %yield) .

[1376] Step B 1-azanylidene-4- { [4-bromo-2- (difluoromethyl) phenyl] oxy} -1λ^6-thian-1-one 21-3a (enantiomer 1) and 1-azanylidene-4- { [4-bromo-2- (difluoromethyl) phenyl] oxy} -1λ^6-thian-1-one 21-3b (enantiomer 2)

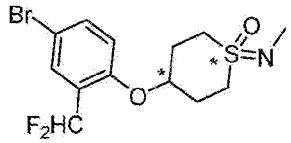


21-3a
enantiomer 1

21-3b
enantiomer 2

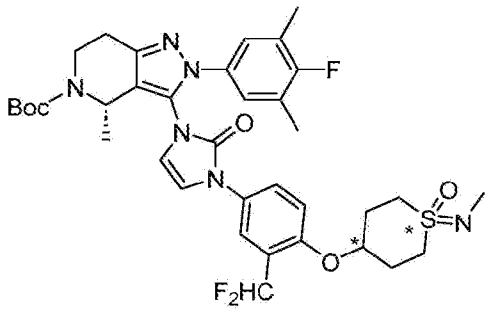
[1377] To a solution of 4- (4-bromo-3- (difluoromethyl) phenoxy) tetrahydro-2H-thiopyran (0.75 g, 2.32 mmol) in EtOH (7.5 ml) were added ammonium a cetate (0.72 g, 9.29 mmol) and iodobenzene diacetate (2.24 g, 6.95 mmol) . The mixtur e was stirred at 25 ℃ for 4 h. The resulting mixture was diluted with H_2 O (10 mL) and extracted with ethyl acetate (10 mL x 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The r esidue was purified by prep. TLC (SiO_2, DCM: MeOH = 20: 1) to give 1-azanylidene-4- { [4-bromo-2- (difluoromethyl) phenyl] oxy} -1λ^6-thian-1-one 21-3a (enantiomer 1) (0.25 g, 30.6%yield) , LC-MS: m/z 355.9 (M+H) $^+$. And 1-azanylidene-4- { [4-bromo-2- (difluoromethyl) phenyl] oxy} -1λ^6-thian-1-one 21-3b (enantiomer 2) (0.24 g, 0.68 mmol, 29.3%yield) , LC-MS: m/z 355.9 (M+H) $^+$.

[1378] Step C 4- { [4-bromo-2- (difluoromethyl) phenyl] oxy} -1- (methylazanylidene) -1λ^6 -thian-1-one



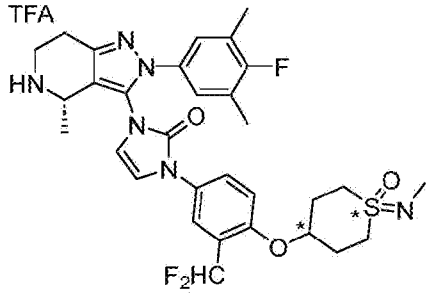
[1379] To a solution of 1-azanylidene-4- { [4-bromo-2- (difluoromethyl) phenyl] oxy} -1λ^6-thian-1-one 21-3a (enantiomer 1) (200 mg, 0.56 mmol) in DMF (2 ml) was added 60%NaH (20.3 mg, 0.85 mmol) . After addition, the mixture was stirred at 0 ℃ for 30 min. Then, to the reaction mixture was added iodomethane (42 μL, 0.68 mmol) . The resulting mixture was stirred at 25 ℃ for 1.5 h. The mixture was diluted with H_2O (1 mL) and extracted with ethyl acetate (1 mL x 3) . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep. TLC (SiO_2 , DCM: MeOH = 20: 1) to give 4- { [4-bromo-2- (difluoromethyl) phenyl] oxy} -1- (methylazanylidene) -1λ^6-thian-1-one (40.0 mg, 19.4%yield) . LC-MS: m/z 369.9 (M+H) $^+$.

[1380] Step D tert-butyl (4S) -3- {1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1381] A mixture of tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (50.0 mg, 0.11 mmol) , 4- { [4-bromo-2- (difluoromethyl) phenyl] oxy} -1- (methylazanylidene) -1λ^6-thian-1-one (40.0 mg, 0.10 mmol) , copper (I) iodide (1 2.3 mg, 0.05 mmol) , K_2CO_3 (30.1 mg, 0.22 mmol) and (1S, 2S) -N1, N2-dimethylcyclohexane-1, 2-diamine (8 mg, 0.05 mmol) in NMP (1 ml) was degasse d and purged with N2 for 3 times. The mixture was stirred at 130 ℃ for 2 h under N2 a tmosphere. The resulting mixture was diluted with H_2O (20 mL) and ext racted with EtOAc (20 mL x 3) . The combined organic layers were was hed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purifi ed by prep. TLC (SiO_2, DCM: MeOH = 20: 1) to give tert-butyl (4S) -3- {1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (70.0 mg, 96.0%yield) . LC-MS: m/z 729.2 $(M+H)^+$.

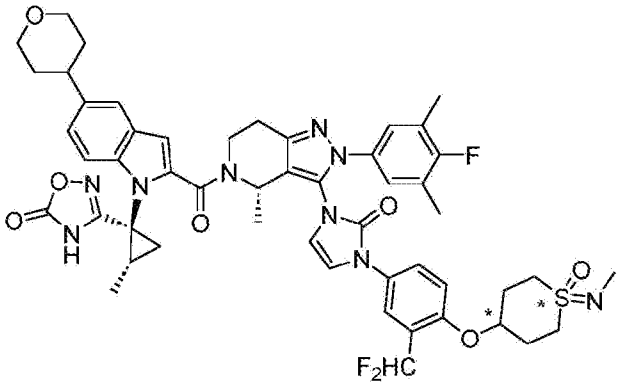
[1382] Step E 1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl] -3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2, 3-dihydro-1H-imidazol-2-one TFA salt



[1383] To a solution of tert-butyl (4S) -3- {1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (70.0 mg, 0.096 mmol) in DCM (1 mL) was added TFA (500 μL, 6.49 mmol) . The mixture was stirred at 25 ℃ for 2 h. The resulting mixture was co ncentrated to give 1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ

^{6}-thian-4-yl] oxy} phenyl] -3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2, 3-dihydro-1H-imidazol-2-one TFA salt (60.0 mg, crude) , which was used for the next step directly without fur ther purification. LC-MS: m/z 629.1 (M+H) $^{+}$.

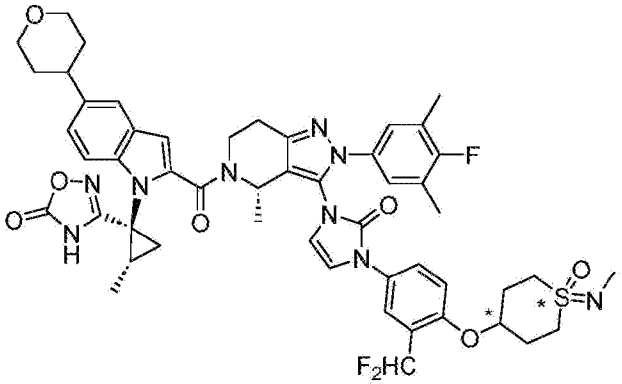
[1384] Step F 3- [(1S, 2S) -1- (2- { [(4S) -3- {1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ^{6}-thian-4-yl] oxy} phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 234)



[1385] To a solution of 1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ^{6}-thian-4-yl] oxy} phenyl] -3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2, 3-dihydro-1H-imidazol-2-one TFA salt (50.0 mg, 0.08 mmol) in DMF (1 ml) were added DIEA (0.056 ml, 0.32 mmol) , 1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -5- (tetrahydro-2H-pyran-4-yl) -1H-indole-2-carboxylic acid (36.6 mg, 0.95 mmol) and HATU (36.3 mg, 0.10 mmol) . The mixture was stirred at 25 ℃ for 2 h. The resulting mixture was diluted with H$_{2}$O (10 mL) and extracted with EtOAc (10 mL x 3) . The combined organic layers were dried over dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep. TLC (SiO_2, DCM: MeOH = 20: 1) and then purified by prep. HPLC (SHIMADZU LC-20AP, Column: YMC Triart C18, 20*250 mm, 5 μm; Mobile Phase A: 0.1%FA, B: CH_3CN; flow rate: 15 mL/min; gradient: 50-70%B; Retention Time: 15 min of 20 min) to give 3- [(1S, 2S) -1- (2- { [(4S) -3- {1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ^{6}-thian-4-yl] oxy} phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 234) (10.8 mg, 13.6%yield) . LC-MS: m/z 994.2 (M+H) $^{+}$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.68 (s, 1H) , 7.80 -7.65 (m, 2H) , 7.

49 (s, 1H) , 7.42 -7.38 (m, 1H) , 7.37 -7.19 (m, 3H) , 7.15 -7.10 (m, 3H) , 7.02 -6.80 (m, 2H) , 5.65 -5.55 (m, 1H) , 4.90 -4.80 (m, 1H) , 4.50 -4.20 (m, 1H) , 4.01 -3.90 (m, 2H) , 3.65 -3.40 (m, 3H) , 2.92 -2.80 (m, 3H) , 2.66 (s, 3H) , 2.24 -2.10 (m, 11H) , 1.90 -1.55 (m, 8H) , 1.50 -1.10 (m, 8H) .

[1386] Step G 3- [(1S, 2S) -1- (2- { [(4S) -3- {1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 235)

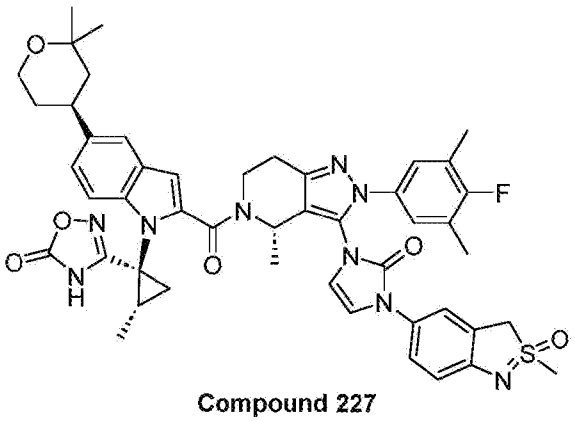


[1387] 3- [(1S, 2S) -1- (2- { [(4S) -3- {1- [3- (difluoromethyl) -4- { [1- (methylazanylidene) -1-oxo-1λ^6-thian-4-yl] oxy} phenyl] -2-oxoimidazol-3-yl} -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-5-yl] carbonyl} -5- (3, 4, 5, 6-tetrahydro-2H-pyran-4-yl) indol-1-yl) -2-methylcyclopropyl] -4H, 5H-1, 2, 4-oxadiazol-5-one (Compound 235) (enantiomer 2) was synthesized according to the procedures described for the preparation of Compound 234 (enantiomer 1) (step C to step F) . LC-MS: m/z 994.2 (M+H)$^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.68 (s, 1H) , 7.80 -7.60 (m, 2H) , 7.49 (s, 1H) , 7.45 -7.30 (m, 3H) , 7.26 -7.19 (m, 2H) , 7.13 (d, J = 8.0 Hz, 2H) , 6.95 -6.75 (m, 2H) , 5.70 -5.55 (m, 1H) , 4.90 -4.85 (m, 1H) , 4.50 -4.25 (m, 1H) , 4.00 -3.90 (m, 2H) , 3.65 -3.40 (m, 3H) , 2.95 -2.80 (m, 3H) , 2.64 (s, 3H) , 2.30 -2.10 (m, 11H) , 1.90 -1.55 (m, 8H) , 1.50 -1.00 (m, 8H) .

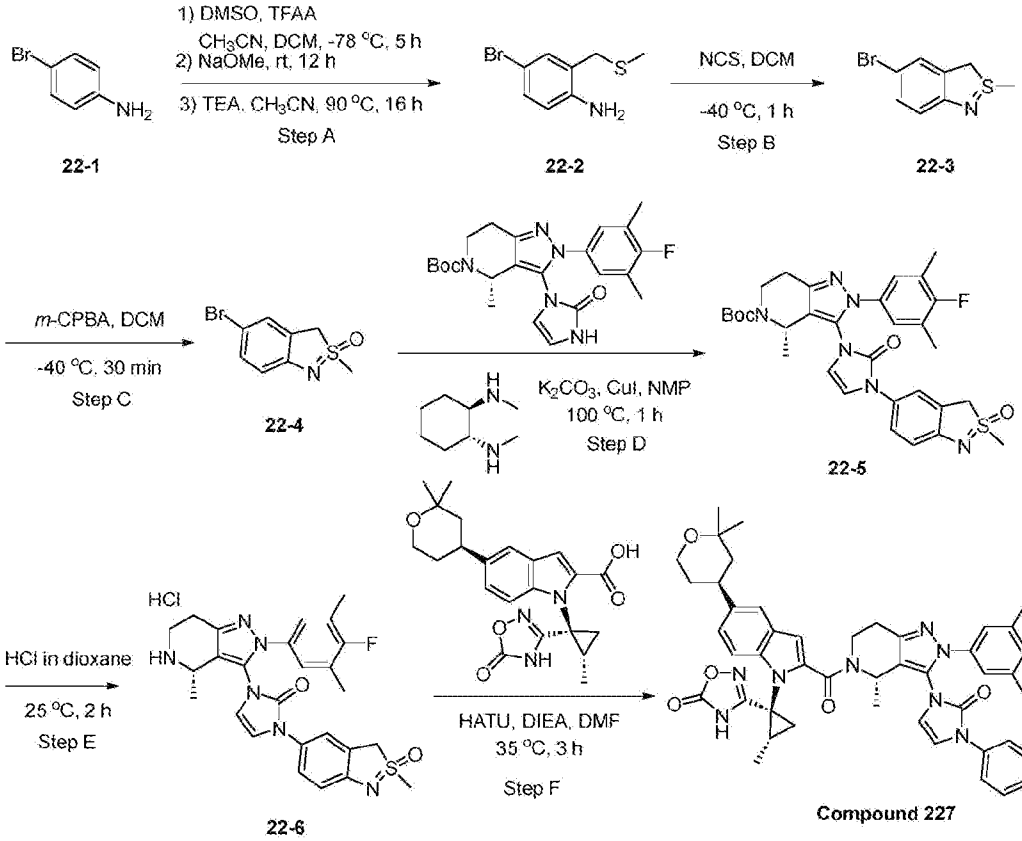
[1388] Example compounds 236 and 237 were synthesized using a similar procedure described in the Example A21 above using the appropriate materials.

[1389] Example A22

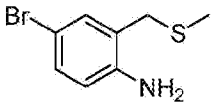
[1390] 5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3H-2λ^6-benzo [c] [1, 2] thiazol-2-one (Compound 227)



Compound 227



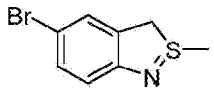
[1391] Step A 4-bromo-2- [(methylsulfanyl) methyl] aniline



[1392] To a solution of DMSO (3.849 mL, 53.991 mmol) in CH_3CN (10 mL) and DC M (10 mL) were added TFAA (6.30 g, 29.995 mmol) at -78 ℃ under Ar. Then 4-bromoaniline (5.16 g, 29.995 mmol) in CH_3CN (10 mL) was added. After being stirred at -78 ℃ for 5 h, a solution of MeONa (2.07 g, 89.984 mmol) in MeOH (16. 6 mL) were added. The reaction was stirred at 25 ℃ for 18 h. The mix ture was quenched with 2.8 M aq. NaOH (60 mL) , extracted with DCM (50 mL x 3) . The combined organic layers were washed with brine, dri

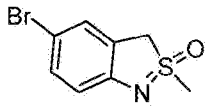
ed over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolve d in the mixture of TEA (10 mL) and CH_3CN (100 mL) . After being stirred at 90 ℃ for 18 h under Ar. The mixture was concentrated, the residue was purified by silica gel column chromatography eluting with 10%EtOAc/PE to give 4-bromo-2- [(methylsulfanyl) methyl] aniline (4.2 g, 63.6%yield) . LC-MS: m/z 232.1 $(M+H)^+$.

[1393] Step B 5-bromo-2-methyl-3H-2λ^4-benzo [c] [1, 2] thiazole



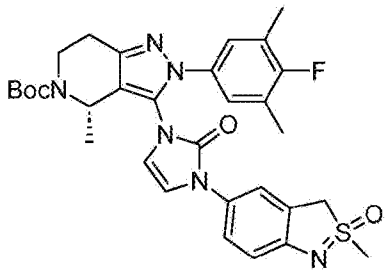
[1394] To a solution of 4-bromo-2- [(methylsulfanyl) methyl] aniline (3.4 g, 14.646 mmol) in DCM (50 mL) was added NCS (1.96 g, 14.646 mmol) in DCM (50 mL) dropwise at -40 ℃ under Ar. The mixture was stirred at -40 ℃ for 1 h unde r Ar. LCMS showed the reaction was completed. The mixture was quench ed by 10%aq. NaOH (10 mL) and allowed to warm to 25 ℃. The mixture w as poured into water (100 mL) , extracted with DCM (100 mL) . The or ganic layer was dried over Na_2SO_4, filtrated and then used in the next step directly. LC-MS: m/z 230.1 $(M+H)^+$.

[1395] Step C 5-bromo-2-methyl-3H-2λ^6-benzo [c] [1, 2] thiazol-2-one



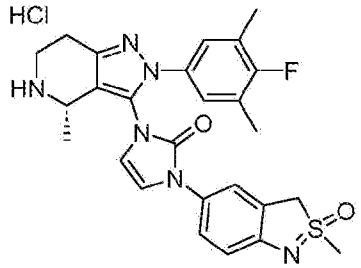
[1396] The above solution was cooled to -40 ℃, a solution of m-CPBA (3.046 g, 15 .004 mmol) in DCM (15 mL) was added. The resulting mixture was stirred at -40 ℃ for 0.5 h and warmed to 25 ℃. LCMS showed the reaction was comp leted. The mixture was washed with aq. $NaHSO_3$ (100 mL x 2) and then aq.$NaHCO_3$ (100 mL x 2) . The organic layers was dried over sodium sulfate, filtered and concen trated. The resulting residue was purified by silica gel column chromatography elutin g with 2%MeOH/DCM to give 5-bromo-2-methyl-3H-2λ^6-benzo [c] [1, 2] thiazol-2- one (2.28 g, 63.3%yield) . LC-MS: m/z 248.1 $(M+H)^+$.

[1397] Step D tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (2- methyl-2-oxo-3H-2λ^6-benzo [c] [1, 2] thiazol-5-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7- tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



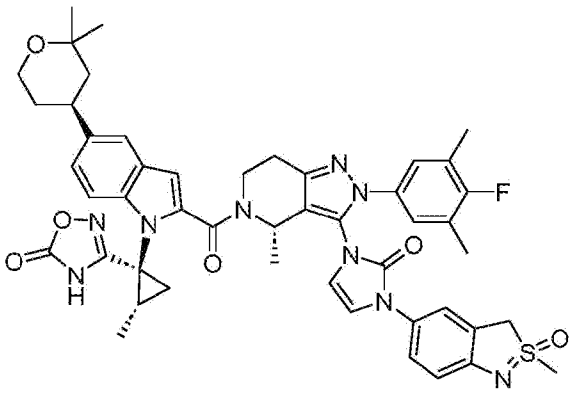
[1398] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (164 mg, 0.371 mmol) in NMP (5 mL) were added copper (1 $^{+}$) iodide (84.89 mg, 0.446 mmol) , potassium carbonate (154.0 mg, 1.1 14 mmol) , 5-bromo-2-methyl-3H-2λ^{6}-benzo [c] [1, 2] thiazol-2-one (100.6 mg, 0. 409 mmol) and methyl [(1S, 2S) -2- (methylamino) cyclohexyl] amine (79.3 mg, 0.557 mmol) . The reaction mixture was stirred at 100 ℃ for 1 h. After cooli ng, the mixture was diluted with water (15mL) , extracted with EtOAc (20mL x 3) . The combined organic layers were washed with brine, dr ied over sodium sulfate and concentrated. The residue was purified by pre p. TLC (SiO_2, DCM/MeOH=10/1) to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (2-methyl-2-oxo-3H-2λ^{6}-benzo [c] [1, 2] thiazol-5-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (243 mg, 98.1%yield) . LC-MS: m/z 607.5 (M+H) $^{+}$.

[1399] Step E 5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3H-2λ^{6}-benzo [c] [1, 2] thiazol-2-one HCl salt



[1400] The mixture of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (2-methyl-2-oxo-3H-2λ^{6}-benzo [c] [1, 2] thiazol-5-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (223 mg, 0.368 mmol) i n 4 M HCl (gas) /dioxane (5 mL) was stirred at 25 ℃ for 1 h. The reaction mixture was concentrated under vacuum to give 5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3H-2λ^{6}-benzo [c] [1, 2] thiazol-2-one HCl salt (183 mg, 98.3%yield) . LC-MS: m/z 507.3 (M+H) $^{+}$.

[1401] Step F 5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3H-2λ^{6}-benzo [c] [1, 2] thiazol-2-one (Compound 227)

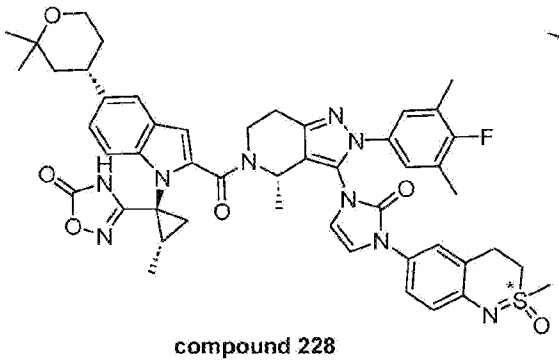


[1402] To a solution of 5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3H-2λ^6-benzo [c] [1, 2] thiazol-2-one HCl salt (91 mg, 0.180 mmol) a nd 5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (74.1 mg, 0.180 mmol) in DMF (5 mL) was added HATU (75.1 mg, 0.198 mmol) and DIEA (116.1 mg, 0.898 mmol) under Ar. The reaction was sti rred at 25 ℃ for 18 h. the reaction mixture was diluted with water (20 mL) , extracte d with EtOAc (20 mL x 3) . The combined organic layers were washed w ith brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residu e was purified by purified by prep. TLC (SiO_2, DCM/CH_3OH=10/1) and then by prep. HPLC (Waters 3767/Qda Column: SunFire Sunfire C18, 19*250 mm, 10 μm; Mobile Phase A: 10 M NH_4HCO_3/H_2O, B: CH_3CN ; Flow rate: 20 mL/ min; Gradient: 37%-47%B; Retention Time: 9.3-9.95 min of 16 min) to afford 5- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3H-2λ^6-benzo [c] [1, 2] thiazol-2-one (5.91 mg, 3.5%yield) . LC-MS: m/z 900.6 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.72 (brs, 1 H) , 7.52 (s, 1 H) , 7.43 -7.40 (m, 2 H) , 7.27 -7.25 (m, 2 H) , 7 .14 (d, J= 6.4 Hz, 2 H) , 6.98 (m, 1 H) , 6.86 (m, 1 H) , 6.81 -6.74 (m, 2 H) , 5 .63 (m, 1 H) , 4.98 (d, J= 17.6 Hz, 1 H) , 4.52 (d, J= 17.6 Hz, 1 H) , 4.41 (m, 1 H) , 3.74 -3.72 (m, 2 H) , 3.47 (s, 3 H) , 2.89 -2.83 (m, 1 H) , 2.23 (s, 6 H) , 1. 77 -1.70 (m, 4 H) , 1.65 -1.50 (m, 4 H) , 1.43 (m, 3 H) , 1.29 (m, 4 H) , 1.20 - 1.14 (m, 7 H) .

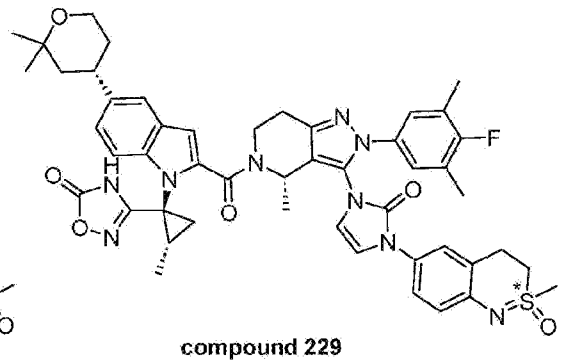
[1403] Example compounds 225 were synthesized using a similar procedure des cribed in the Example A22 above using the appropriate materials.

[1404] Example A23

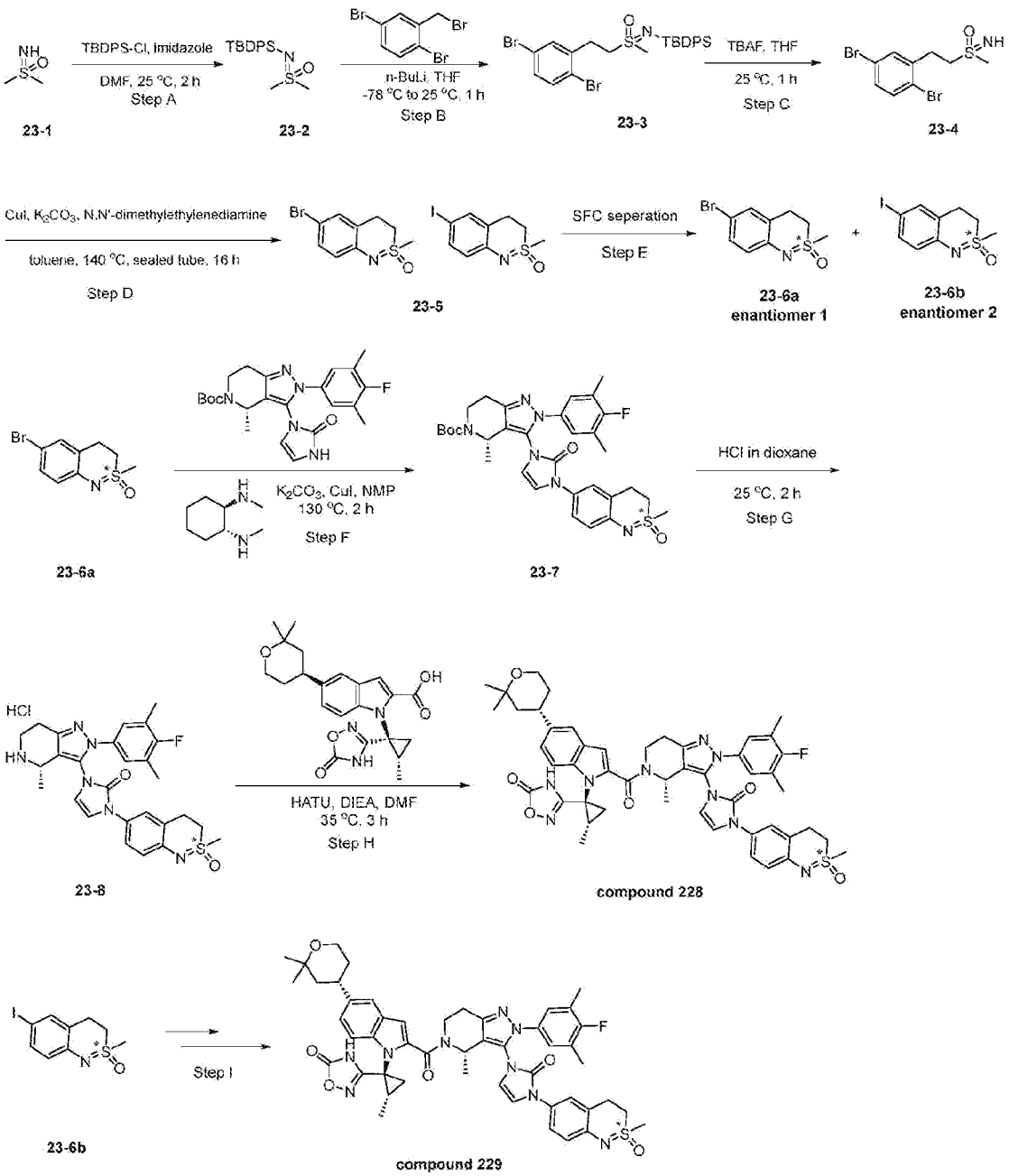
[1405] 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 228) and 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 229)



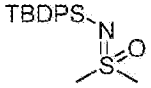
compound 228



compound 229



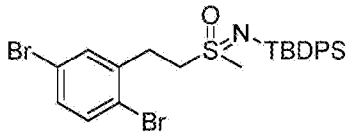
[1406] Step A 1, 1-dimethyl-N- [(2-methylprop-2-yl) diphenylsilyl] -1-oxo-λ^6-sulfanimine



[1407] To a solution of dimethyl (oxo) -λ^6-sulfanimine (500 mg, 5.368 mmol) i n DMF (10 mL) was added imidazole (1.09 g, 16.105 mmol) and TBDPS-Cl (1.77 g, 6.442 mmol) . The reaction mixture was stirred at 25 °C for 2 h unde r N2. The reaction mixture was poured into water (100 mL) and extrac ted with EtOAc (100 mL x 2) . The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by s ilica gel chromatography eluting with 0-20%EtOAc/PE to obtain 1, 1-dimethyl-N-

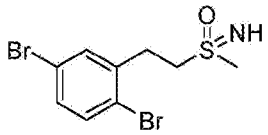
[(2-methylprop-2-yl) diphenylsilyl] -1-oxo-λ^6-sulfanimine (1.25 g, 70.2%yield) . LC-MS: m/z 332.3 (M+H) $^+$.

[1408] Step B 1- [2- (2, 5-dibromophenyl) ethyl] -1-methyl-N- [(2-methylprop-2-yl) diphenylsilyl] -1-oxo-λ^6-sulfanimine



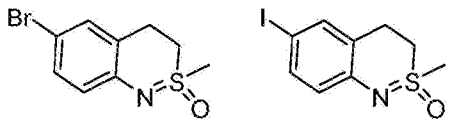
[1409] To a solution of 1, 1-dimethyl-N- [(2-methylprop-2-yl) diphenylsilyl] -1-oxo-λ^6-sulfanimine (1.25 g, 3.468 mmol) in THF (100 mL) was added n-BuLi (1.6 mol/L, 2.4 mL, 3.82 mmol) at -78 ℃ dropwise. The solution was st irred at -78 ℃ for 0.5 h, then a solution of 1, 4-dibromo-2- (bromomethyl) be nzene (1.37 g, 4.17 mmol) in THF (10 mL) was added slowly. After addition, the reacti on mixture was warmed to rt and stirred for 16 h under Ar. The reaction mixture was p oured into water (100 mL) and extracted with EtOAc (100 mL x 2) . Th e combined organic layer was washed with brine, dried over sodium sulfate, filtered a nd concentrated. The residue was purified by silica gel chromatography eluting with 0 -25%EtOAc/PE to obtain 1- [2- (2, 5-dibromophenyl) ethyl] -1-methyl-N- [(2-methylprop-2-yl) diphenylsilyl] -1-oxo-λ^6-sulfanimine (570 mg, 28.4 %yield) . LC-MS: m/z 580.4 (M+H) $^+$.

[1410] Step C [2- (2, 5-dibromophenyl) ethyl] (methyl) (oxo) -λ^6-sulfanimine



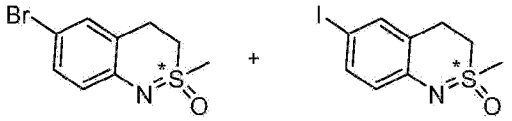
[1411] To a solution of 1- [2- (2, 5-dibromophenyl) ethyl] -1-methyl-N- [(2-methylprop-2-yl) diphenylsilyl] -1-oxo-λ^6-sulfanimine (570 mg, 0.984 mmol) in THF (20 mL) was added TBAF (1M in THF, 3.604 mL, 3.604 mmol) at rt. After being stirred at rt for 2 h, H_2O (20 ml) was added to the mixture. It was extracted with EtOAc (20 mL x 2) . The combined organic layers were dried over sodium sulfate, filtered and co ncentrated. The residue was purified by silica gel chromatography eluting with 100%Et OAc to afford [2- (2, 5-dibromophenyl) ethyl] (methyl) (oxo) -λ^6-sulfanimine (330 mg, 98.3 %yield) . LC-MS: m/z 340.1 (M+H) $^+$.

[1412] Step D 6-bromo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one and 6-iodo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one



[1413] To a solution of [2- (2, 5-dibromophenyl) ethyl] (methyl) (oxo) -λ^6-sulfanimine (330 mg, 0.967 mmol) in toluene (50 mL) was added K_2CO_3 (533.8mg, 3.87 m mol) , CuI (18.5 mg, 0.097 mmol) and N, N'-dimethylethylenediamine (16.7 mg, 0.19 mmol) . The reaction mixture was stirred at 140 ℃ for 18 h unde r N2 in a sealed tube. The reaction mixture was poured into water (50 mL) and extract ed with EtOAc (50 mL x 2) . The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was pur ified by silica gel chromatography eluting with 100%EtOAc 100%to aff ord a mixture of 6-bromo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one and 6-iodo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (120 mg) .

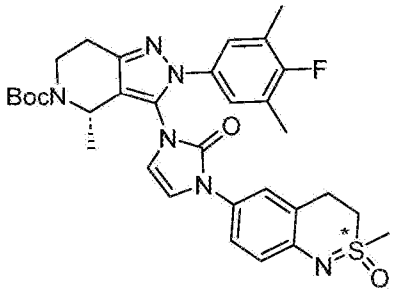
[1414] Step E 6-bromo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one and 6-iodo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one



23-6a enantiomer 1 **23-6b enantiomer 2**

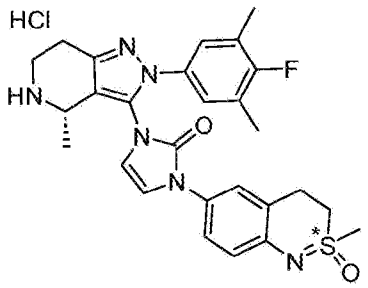
[1415] The mixture of 6-bromo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one and 6-iodo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (120 mg) was purified by SFC (system: Waters SFC 150; Column nam e: DAICELCHIRALCEL®AD; Column size: 250*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+0.1%7.0 M ammonia in MeOH) ; Gradient: A/B = 75/25; Flow rate: 100 mL/min, Column temp: RT) to give 6-bromo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (18 mg) (the 1st eluting fraction, enantiomer 1) , LC-MS: m/z 260.1 $(M+H)^+$. And 6-iodo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (20 mg) (the 4th eluting fraction , enantiomer 2) , LC-MS: m/z 308.0 $(M+H)^+$.

[1416] Step F tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (2-methyl-2-oxo-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



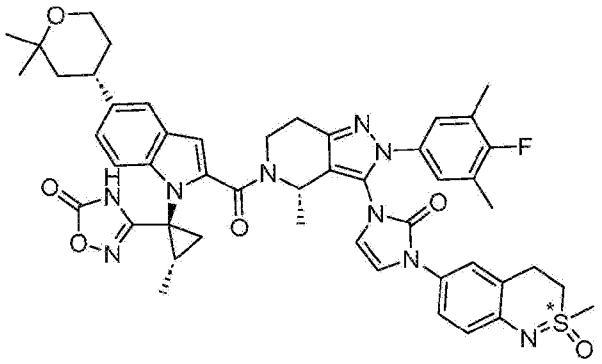
[1417] To a solution of 6-bromo-2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (18.21 mg, 0.070 mmol) in NMP (5 mL) were added tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (31 mg, 0.070 mmol) , methyl [(1R, 2R) -2- (methylamino) cyclohexyl] amine (14.98 mg, 0.105 m mol) , CuI (16.01 mg, 0.084 mmol) and K_2CO_3 (19.41 mg, 0.140 mmol) . The reac tion was stirred at 130 ℃ for 3 h under N2. After cooling, the mixture was diluted wi th water (30 mL) , extracted with EtOAc (30 mL x 2) . The combined o rganic layers were washed with brine, dried over sodium sulfate, filtered and concent rated. The residue was purified by silica gel chromatography eluting with 0-3%MeOH、 DCM to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (2-methyl-2-oxo-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (20 m g, 46.0%yield) . LC-MS: m/z 621.1 (M+H) $^+$.

[1418] Step G 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one HCl salt



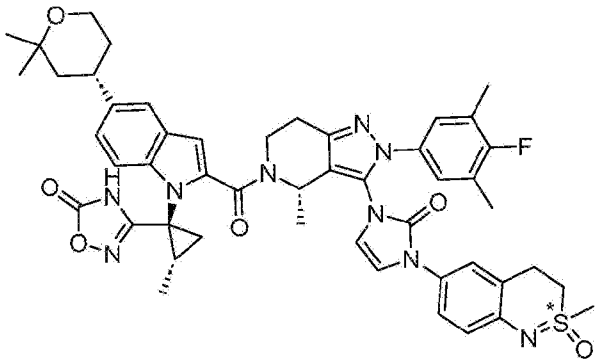
[1419] To a solution of tert-butyl -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (3- ((R) -2-methyl-2-oxido-3, 4-dihydro-2l4-benzo [c] [1, 2] thiazin-6-yl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (20 mg, 0.032 mmol) in dioxane (3 mL) were added 4 M HCl (gas) in dioxane (0.5 mL) . The mixture was stirred at rt for 1 h under N2. The reac tion mixture was concentrated under reduced pressure to afford 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one HCl salt (17 mg crude) . LC-MS: m/z 521.1 (M+H) $^+$.

[1420] Step H 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 228)



[1421] To a solution of 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one HCl salt (17 mg, 0.033 mmol) i n DMF (5 mL) , was added 5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (13.44 mg, 0.033 mmol) , HATU (13.6 6 mg, 0.036 mmol) and DIEA (21.10 mg, 0.163 mmol) . The reaction mix ture was stirred at 35 ℃ for 18 h under N2. After the reaction was completed, water (20 mL) was added, the mixture was extracted with EtOAc (20 mL x 3) . The combined organic layers were washed with brine, dried over anhy drous sodium sulfate, filtered and concentrated. The resulting residue was purified b y purified by prep. TLC (SiO_2, DCM/CH_3OH=15/1) and then prep. HPLC (Wate rs 3767/Qda Column: XBridge XBridge C18, 19*250 mm, 10 μm; Mobile Ph ase A: 0.05%NH_3H2O/H_2O, B: CH_3CN ; Flow rate: 20 mL/min; Gradient: 29%-39%B; Retention Time: 9-10 min of 17 min) to afford 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 228) (enantiomer 1) (1.0 mg, 3.4%yield) . LC-MS: m/z 914.5 (M +H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.41 (m, 2 H) , 7.25 -7.14 (m, 5 H) , 6 .92 -6.72 (m, 3 H) , 6.51 (m, 1 H) , 5.35 (m, 1 H) , 3.75 -3.73 (m, 2 H) , 3.41 -3.38 (m, 3 H) , 3.25 (m, 5 H) , 2.67 (m, 3 H) , 2.21 (s, 6 H) , 1.76 -1.72 (m, 4 H) , 1 .65 -1.47 (m, 6 H) , 1.33 -1.16 (m, 11 H) .

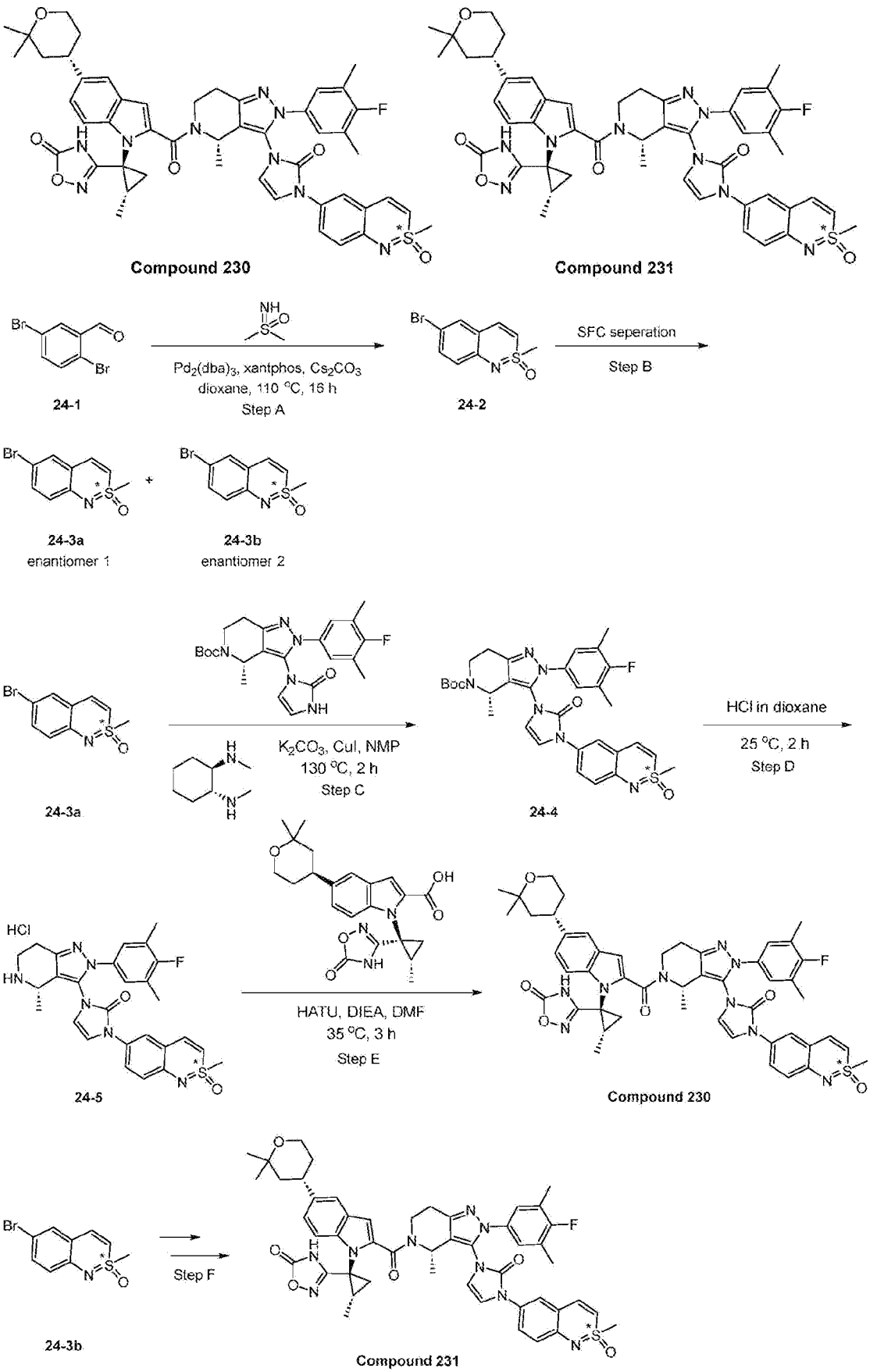
[1422] Step I 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 229)



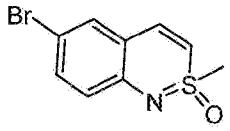
[1423] 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-3, 4-dihydro-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 229) (enantiomer 2) was synthesized according to the procedures described for the preparation of Compound 228 (enantiomer 1) (step F to step H) . LC-MS: m/z 914.5 (M+H) $^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.50 (s, 1 H) , 7.42 (d, J= 8.4 Hz, 1 H) , 7.25 -7.23 (m, 3 H) , 7.14 (d, J= 6.4 Hz, 2 H) , 6.99 (m, 1 H) , 6.67 (m , 3 H) , 5.55 (m, 1 H) , 4.44 (m, 1 H) , 3.75 -3.73 (m, 2 H) , 3.39 (m, 1 H) , 3.38 (m, 2 H) , 3.25 (m, 4 H) , 3.01 (m, 1 H) , 2.90-2.80 (m, 2 H) , 2.22 (d, J= 1.2 Hz, 6 H) , 1.77 -1.70 (m, 4 H) , 1.64 -1.41 (m, 6 H) , 1.29 (m, 4 H) , 1.20 (m, 7 H) .

[1424] Example A24

[1425] 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 230) and 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 231)

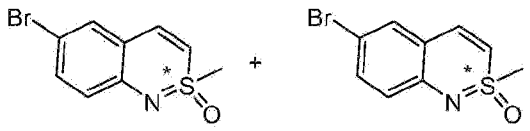


[1426] Step A 6-bromo-2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one



[1427] Pd_2 (dba) $_3$ (173 mg, 0.189 mmol) and Cs_2CO_3 (1.851 g, 5.684 mmol) were added to 2, 5-dibromobenzene-1-carbaldehyde (1.0 g, 3.789 mmol) and dimethylsulfox imine (352 mg, 3.789 mmol) in 1, 4-dioxane (20 mL) at rt, and the rea ction mixture was heated at reflux for 3 h. The mixture was allowed to cool to rt, fi ltered, and the filtrate was evaporated. The residue was purified by silica gel chrom atography eluting with 15%-50%EtOAc/PE to afford 6-bromo-2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one (435 mg, 44.5%) . LC-MS: m/z 260.0 (M+H) $^+$.

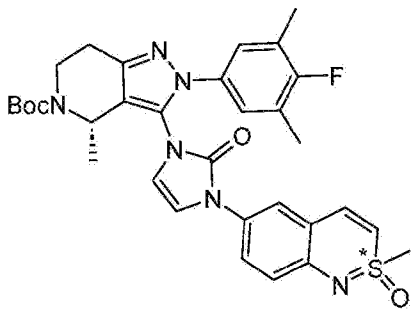
[1428] Step B 6-bromo-2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one 24-3a (enantiomer 1) and 6-bromo-2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one 24-3b (enantiomer 2)



24-3a enantiomer 1 **24-3b** enantiomer 2

[1429] The 6-bromo-2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one (435 mg) was purified by SFC (system: Waters SFC 150; Column name : DAICELCHIRALCEL®AD; Column size: 250*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+0.1%7.0 M ammonia in MeOH) ; Gradient: A/B = 70/30; Flow rate: 100 mL/min, Column temp: RT) to give 6-bromo-2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one 24-3a (enantiomer 1) (210 mg, 48.3%yi eld) , LC-MS: m/z 260.0 (M+H) $^+$. And 6-bromo-2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one 24-3b (enantiomer 2) (200 mg, 45.9 yield) , LC-MS: m/z 260.0 (M+H) $^+$.

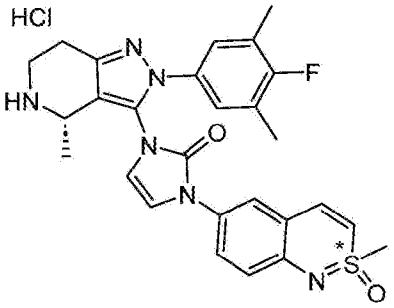
[1430] Step C tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (2-methyl-2-oxo-2λ^6-benzo [c] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate



[1431] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-

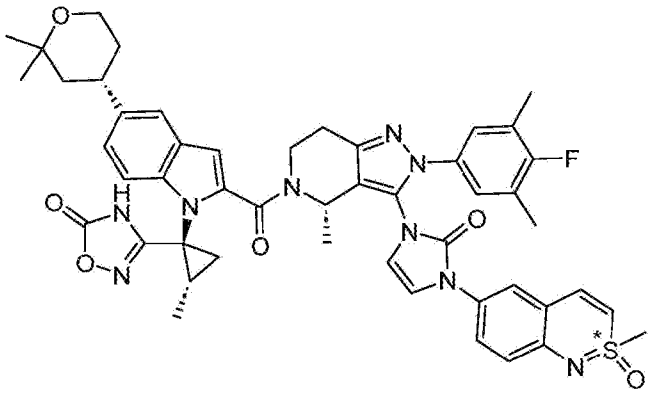
carboxylate (72 mg, 0.163 mmol) in NMP (5 mL) were added 6-bromo-2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one 24-3a (enantiomer 1) (50.5 mg, 0.196 mmol) , methyl [(1R, 2R) -2- (methylamino) cyclohexyl] amine (34.8 mg, 0.245 mmol) , CuI (37.27 mg, 0.196 mmol) and K_2CO_3 (45.1 mg, 0.326 mmol) . The reaction mixture was s tirred at 100 ℃ for 2 h under Ar. After the reaction was completed, the mixture was p oured into to water (30 mL) , extracted with EtOAc (30 mL x 2) . The comb ined organic layers were washed with brine, dried over sodium sulfate, filtered and c oncentrated. The residue was purified by silica gel chromatography eluting 0-3% MeOH/DCM to afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (2-methyl-2-oxo-2λ^6-benzo [c] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (170 mg, crude) . LC-MS: m/z 619.4 (M+H) $^+$.

[1432] Step D 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one HCl salt



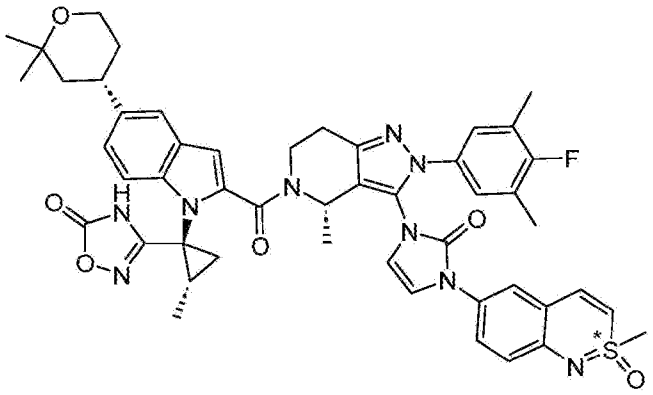
[1433] To a solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [1- (2-methyl-2-oxo-2λ^6-benzo [c] [1, 2] thiazin-6-yl) -2-oxoimidazol-3-yl] -4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridine-5-carboxylate (170 mg, 0.275 mmol) i n dioxane (4 mL) were added 4M HCl (gas) in dioxane (2 mL) . The mix ture was stirred at rt for 1 h under Ar. The reaction mixture was concentrated to get 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazol o [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one HCl salt (112 mg, 78.3%yield) . LC-MS: m/z 519.3 (M+H) $^+$.

[1434] Step E 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 230)



[1435] To a solution of 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one HCl salt (112 mg, 0.216 mmol) in DMF (5 mL) was added 5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (88.9 mg, 0.216 mmol) , HATU (90.3 mg, 0.238 mmol) and DIEA (139.6 mg , 1.080 mmol) . The reaction was stirred at 30 ℃ for 18 h under N2. The reaction mixture was poured into water (30 mL) , extracted with EtOAc (30 mL x 3) . The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The resulting residue was purified by prep. TLC (SiO_2, DCM/MeOH=15/1) to afford a crude product (80 mg) , and then further purified by prep. HPLC (Waters 3767/Qda Column: SunFire Sunfire C18, 19*250 mm, 10 μm; Mobile Phase A: 0.05%NH_3H_2O/H_2O, B: CH_3CN ; Flow rate: 20 mL/min; Gradient: 26%-36%B; Retention Time: 11-12 min of 18 min) to afford 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 230) (12.9 mg, 10.1%yield) . LC-MS: m/z 912.6 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.80 -7.51 (m, 4 H) , 7 .42 (d, J= 8.4 Hz, 1 H) , 7.25 (d, J= 8.4 Hz, 1 H) , 7.15 -7.07 (m, 5 H) , 6.83 -6.80 (m, 2 H) , 5.55 (m, 1 H) , 4.45 (m, 1 H) , 3.74 -3.72 (m, 2 H) , 3.57 (m, 1 H) , 3. 49 (s, 3 H) , 3.01 -2.84 (m, 2 H) , 2.22 (d, J= 2.0 Hz, 6 H) , 1.72 -1.69 (m, 4 H) , 1.63 -1.54 (m, 3 H) , 1.51 -1.44 (m, 3 H) , 1.29 (m, 4 H) , 1.20 -1.13 (m, 6 H) .

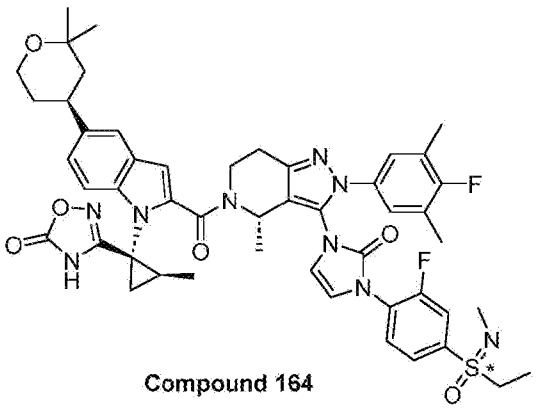
[1436] Step F 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 231)



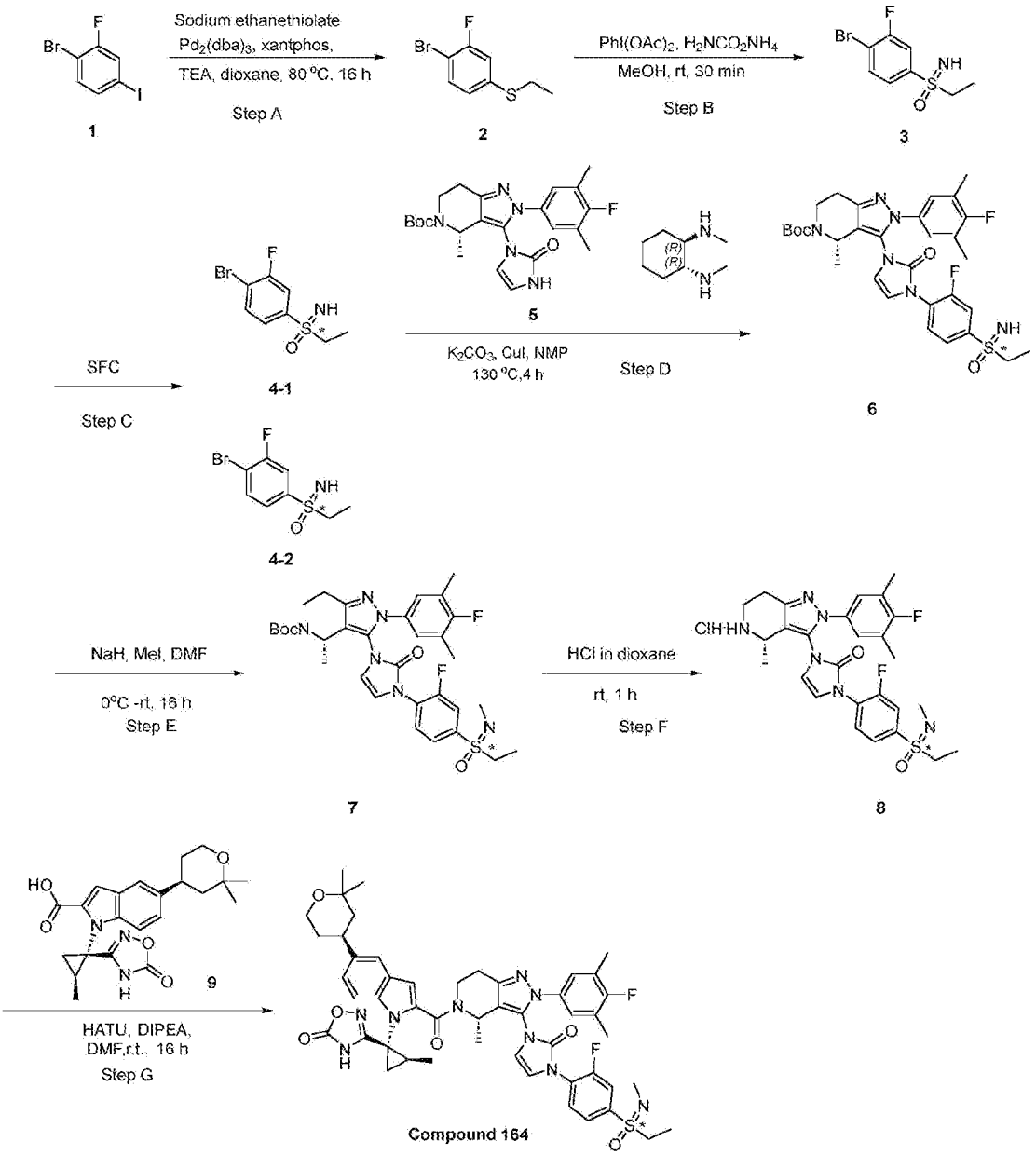
[1437] 6- {3- [(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -5- ({5- [(4S) -2, 2-dimethyl-3, 4, 5, 6-tetrahydro-2H-pyran-4-yl] -1- [(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2, 4-oxadiazol-3-yl) cyclopropyl] indol-2-yl} carbonyl) -4-methyl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridin-3-yl] -2-oxoimidazol-1-yl} -2-methyl-2λ^6-benzo [c] [1, 2] thiazin-2-one (Compound 231) (enantiomer 2) was synthesized a ccording to the procedures described for the preparation of Compound 230 (enan tiomer 1) (step C to step E) . LC-MS: m/z 912.6 (M+H) $^+$. ^{1}H NMR (400 MHz, D MSO-d6) δ 7.80 -7.51 (m, 4 H) , 7.42 (d, J= 8.4 Hz, 1 H) , 7.25 (d, J= 8.4 Hz, 1 H) , 7.15 -7.07 (m, 5 H) , 6.83 -6.80 (m, 2 H) , 5.55 (m, 1 H) , 4.45 (m, 1 H) , 3.74 -3.72 (m, 2 H) , 3.57 (m, 1 H) , 3.49 (s, 3 H) , 3.01 -2.84 (m, 2 H) , 2.22 (d, J= 2.0 Hz , 6 H) , 1.72 -1.69 (m, 4 H) , 1.63 -1.54 (m, 3 H) , 1.51 -1.44 (m, 3 H) , 1 .29 (m, 4 H) , 1.20 -1.13 (m, 6 H) .

[1438] Example A25

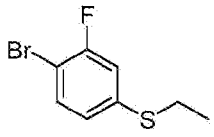
[1439] 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-4- (N-methylethylsulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 1) (Compound 164)



Compound 164



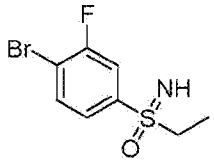
[1440] Step A (4-bromo-3-fluorophenyl) (ethyl) sulfane



[1441] A mixture of 1-bromo-2-fluoro-4-iodobenzene (10 g, 33.234 mmol) , (ethylsulfanyl) sodium (3.35 g, 39.880 mmol) , Pd_2 (dba) $_3$ (1.52 g, 1.662 m mol) and xantphos (1.92 g, 3.323 mmol) in dry dioxane (200 mL) was s tirred at 80℃ for 16 hrs. The reaction mixture was poured into water (500 mL) , extra cted with EA (3 X 200 mL) . The organic layers were dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by silica gel c olumn chromatography eluting with PE (100%) to afford (4-bromo-3-fluorophenyl) (et

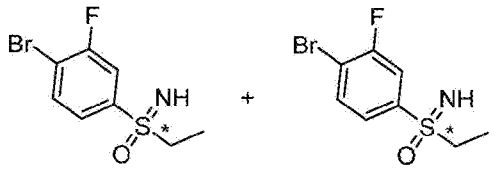
hyl) sulfane (6.3 g, 80.63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 1H) , 7.05 (dd, J = 9.2, 2.0 Hz, 1H) , 6.95 (dd, J = 8.4, 2.0 Hz, 1H) , 2.94 (q, J = 7.2 Hz, 2H) , 1.33 (t, J = 7.2 Hz, 3H) .

[1442] Step B (4-bromo-3-fluorophenyl) (ethyl) (imino) -λ^6-sulfanone



[1443] To a solution of (4-bromo-3-fluorophenyl) (ethyl) sulfane (4.00 g, 17.013 mmol) in MeOH (100 mL) were added (diacetoxyiodo) benzene (16.54 g, 51.039 mmol) , ammonium aminomethanoate (5.31 g, 68.052 mmol) , and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water (500 mL) , extracted with EA (3 X 200 mL) . The organic layers were washed with saturated NaCl solution, dried over Na_2SO_4 , and concentrated in vacuum. The residue was purified by using silica gel column chromatography eluting with EA in PE (1/1) to afford both isomers.

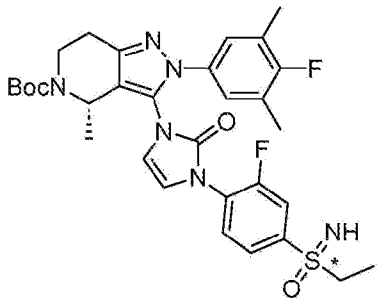
[1444] Step C (4-bromo-3-fluorophenyl) (ethyl) (imino) -λ^6-sulfanone (enantiomer 1) and (4-bromo-3-fluorophenyl) (ethyl) (imino) -λ^6-sulfanone (enantiomer 2)



4-1 4-2

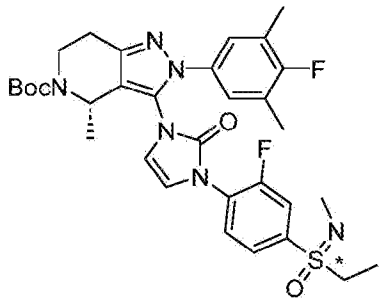
[1445] (4-bromo-3-fluorophenyl) (ethyl) (imino) -λ^6-sulfanone obtained above was separated by SFC (Column: DAICELCHIRALPAK®AS; Column size: 250 mm*40 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 10%) . Flow rate: 140 mL/min, Column temp.: 25 °C) to afford (4-bromo-3-fluorophenyl) (ethyl) (imino) -λ^6-sulfanone (enantiomer 1) (1500 mg, 33.13%) as a colorless oil as the fast eluent, R. T=1.16 min. LC-MS: m/z 266.0 (M+H) $^+$. And (4-bromo-3-fluorophenyl) (ethyl) (imino) -λ^6-sulfanone (enantiomer 2) (1500 mg, 33.13%) as the slow eluent, R. T= 1.47 min. LC-MS: m/z 266.0 (M+H) $^+$.

[1446] Step D tert-butyl (4S) -3- (3- (4- (ethylsulfonimidoyl) -2-fluorophenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enantiomer 1)



[1447] To a solution of tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (2 g, 4.530 mmol) in NMP (24 mL) were added copper $^{(1+)}$ iodide (1.04 g, 5.436 mmol) , potassium carbonate (1.25 g, 9.060 mmol) , (4-bromo-3-fluorophenyl) (ethyl) (imino) -λ^6-sulfanone (enantiomer 1) (1.57 g, 5.889 mmol) and (1R, 2R) -N^1, N^2-dimethylcyclohexane-1, 2-diamine (0.64 g, 4.530 mmol) , and the reaction mixture was stirred at 130 ℃ for 4 hrs under N_2. The mixture was poured into water (50 mL) , extracted with EA ((3 X 30 mL) , washed with brine ((3 X 20 mL) . The organic layer was dried and concentrated in vacuum.
The residue was purified by silica gel column chromatography eluting with (eluting PE /EA=1/1) to afford tert-butyl (4S) -3- (3- (4- (ethylsulfonimidoyl) -2-fluorophenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enan tiomer 1) (1.75 g, 61.64%) . LC-MS: m/z 627.8 $(M+H)^+$.

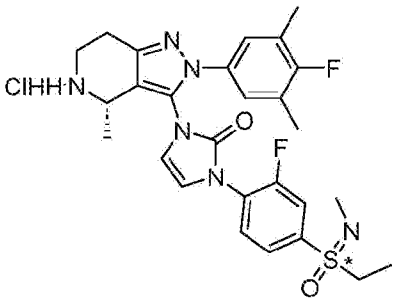
[1448] Step E tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-4- (N-methylethylsulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enantiomer 1)



[1449] To a solution of tert-butyl (4S) -3- (3- (4- (ethylsulfonimidoyl) -2-fluorophenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enan tiomer 1) (500 mg, 0.798 mmol) in DMF (10 mL) was added sodium hydri de (19.15 mg, 0.798 mmol) at 0 ℃ under N_2 . The reaction mixture was stirre d at 0 ℃ for 1 hr and iodomethane (0.078 mL, 0.957 mmol) was added.
The reaction mixture was stirred at room temperature for another 16 hrs. The mixture

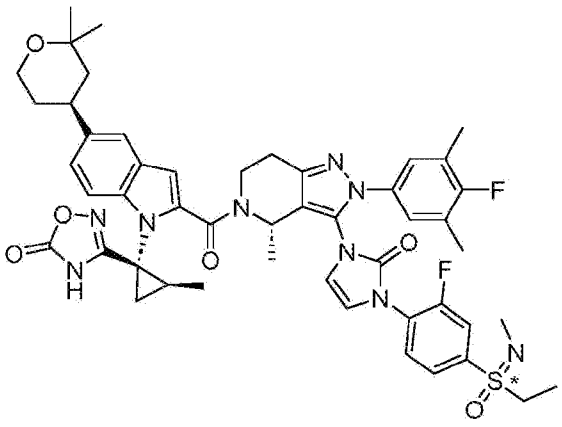
was poured into water (50 mL) , extracted with EA (20 mL X 3) . The combined organic layers were washed with brine (50 mL) , dried over Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by silica gel colu mn chromatography eluting with (eluting PE/EA=1/1) to give tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-4- (N-methylethylsulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enantiomer 1) (200 mg, 97.81%) . LC-MS: m/z 641.4 $(M+H)^+$.

[1450] Step F 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (2-fluoro-4- (N-methylethylsulfonimidoyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one, hydrochloride salt (enantiomer 1)



[1451] A solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-4- (N-methylethylsulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enantiomer 1) (215 mg, 0.312 mmol) in HCl/dioxane (3 mL) was stirred at room temperature for 1 hr. The reaction mixture was concentrated in vacuum to afford 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (2-fluoro-4- (N-methylethylsulfon imidoyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one, hydrochloride salt (enantiome r 1) (168 mg, 99.77%) which was used in the next step without further purification. L C-MS: m/z 541.2 $(M+H-HCl)^+$.

[1452] Step G 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-4- (N-methylethylsulfon imidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 1) (Compound 164)



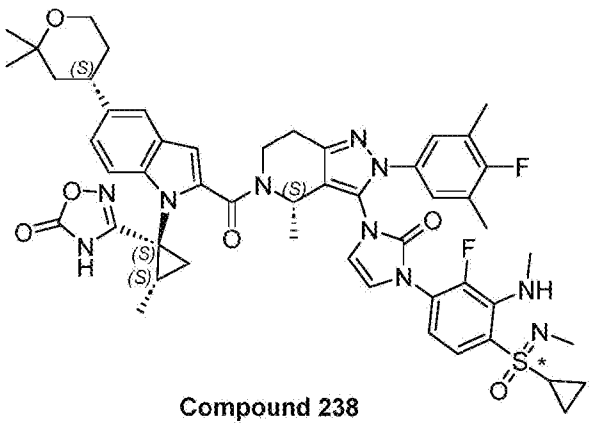
[1453] To a solution of 5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -1H-indole-2-carboxylic acid (114.16 mg, 0.277 mmol) in DMF (3 mL) were added HATU (158.25 mg, 0.416 mmol) , DIPEA (143.44 mg, 1.110 mmol) , and 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (2-fluoro-4- (N-methylethylsulfonimidoyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one, hydrochloride salt (enantiomer 1) (150 mg, 0.277 mmol) , and the reaction mixture was stirred at room temperature for 16 hrs. The mixture was poured into water (50 mL) , extracted with EA (20 mL X 3) . The combined organic layers were washed with brine (50 mL) , dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with 3%MeOH in DCM and then prep-HPLC (NH_4HCO_3) to afford 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-4- (N-methylethylsulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 1) (63.60 mg, 24.24%) .

[1454] LC-MS: m/z 934.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1H) , 7.75-7.73 (m, 3H) , 7.53 (s, 1H) , 7.42 (d, J = 8.4 Hz, 1H) , 7.30-7.21 (m, 1H) , 7.16 (d, J = 6.4 Hz, 2H) , 7.04 (s, 1H) , 6.90-6.88 (m, 2H) , 5.60 (s, 1H) , 4.47 (s, 1H) , 3.75-3.72 (m, 2H) , 3.60 (s, 1H) , 3.31-3.25 (m, 2H) , 2.90-2.86 (m, 1H) , 2.57 (s, 3H) , 2.25 (d, J =1.6 Hz, 6H) , 1.76-1.71 (m, 4H) , 1.66-1.63 (m, 2H) , 1.62-1.58 (m, 2H) , 1.45 (s, 3H) , 1.30-1.29 (m, 4H) , 1.20-1.13 (m, 9H) . ^{19}F NMR (376 MHz, DMSO-d_6) δ -118.55, -122.06.

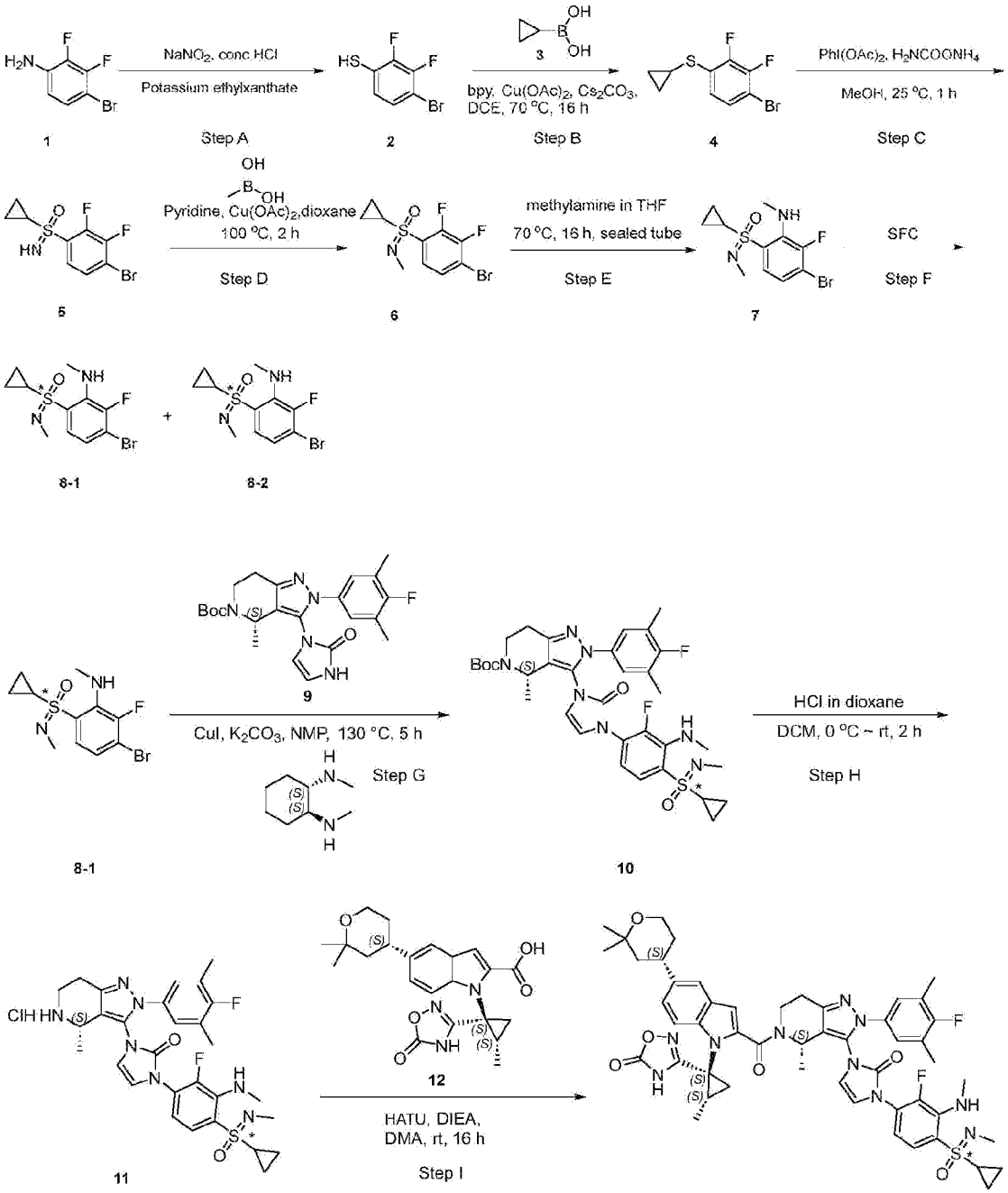
[1455] Example A26

[1456] 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3- (methylamino) -4- (N-

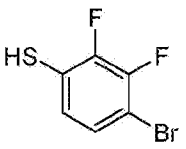
methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 1) (Compound 238)



Compound 238



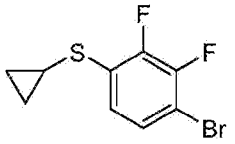
[1457] Step A 4-bromo-2, 3-difluorobenzenethiol



[1458] To a solution of 4-bromo-2, 3-difluoroaniline (1000 mg, 4.807 mmol) in con. HCl (25 mL) was added sodium nitrite (398. mg, 5.769 mmol) at 0 ℃. The mi xture was stirred at room temperature for 5 min. To the mixture was adde d potassium ethylxanthate (1926.47 mg, 12.019 mmol) at 0 ℃. The mixt ure was stirred for 20 min at 0 ℃. The mixture was diluted with water (30 mL) , extra

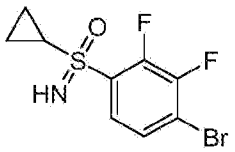
cted with EA (3×30 mL) . The combined EA layers were washed with bri ne (3×10 mL) , dried over Na_2SO_4, filtered and concentrated. The residue was purifi ed by flash column chromatography, eluting with PE/EA (100: 1) to af ford the intermediate. The intermediate was dissolved with EtOH (10 mL) . To the solu tion was added KOH (1348.73 mg, 24.037 mmol) . The mixture was stirr ed for another 10 min at 75 ℃. The mixture was concentrated. The residue was diluted with water (20 mL) , extracted with DCM (3×10 mL) . The aqueous laye r was adjusted to pH 1-2 with HCl (aq.) , extracted with EA (3×20 mL) . T he combined organic layers were washed with brine (3×10 mL) , dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography, eluting with DCM/MeOH (20/1) to afford 4-bromo-2, 3-difluorobenzeneth iol (500 mg, 46.21%) . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.18 (m, 1H) , 6.97- 6.93 (m, 1H) , 3.68 (s, 1H) .

[1459] Step B (4-bromo-2, 3-difluorophenyl) (cyclopropyl) sulfane



[1460] To a solution of 4-bromo-2, 3-difluorobenzenethiol (500 mg, 2.222 mmol) and cyclo propylboranediol (286.27 mg, 3.333 mmol) in DCE (10 mL) were added 2- (pyridin-2-yl) pyridine (347.01 mg, 2.222 mmol) , cupric bis (acetate) (403.53 mg, 2.222 mmol) and Cs_2CO_3 (723.88 mg, 2.222 mmol) . The reaction mixture was sealed up and stirred at 70 ℃ for 16 hrs under O_2. The reaction mixture was filtere d and the filtrate was concentrated. The residue was purified by flash column chromat ography, eluting with PE/EA (100/1) to afford (4-bromo-2, 3-difluorophenyl) (cyclopropyl) sulfane (150 mg, 25.47%) . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31- 7.24 (m, 1H) , 7.17-7.13 (m, 1H) , 2.20-2.15 (m, 1H) , 1.11-1.06 (m, 2H) , 0.73- 0.69 (m, 2H) .

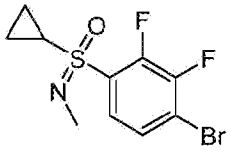
[1461] Step C (4-bromo-2, 3-difluorophenyl) (cyclopropyl) (imino) -λ^6-sulfanone



[1462] To a solution of (4-bromo-2, 3-difluorophenyl) (cyclopropyl) sulfane (400 mg, 1.50 9 mmol) in methanol (500 mL) were added ammonium aminomethanoate (23 5.58 mg, 3.018 mmol) and 1- [(acetoxyphenyl-λ3-iodanyl) oxy] ethan- 1-one (1222.50 mg, 3.772 mmol) . The reaction mixture was stirred for 1 hr at room temperature. The mixture was concentrated and the residue was purified b

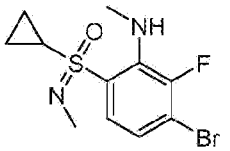
y flash column chromatography, eluting with PE/EA (2/1) to afford (4-bromo-2, 3-difluorophenyl) (cyclopropyl) (imino) -λ^6-sulfanone (300 mg, 67.15%) . LC-MS: m/z 296.0 (M+H) $^+$.

[1463] Step D (4-bromo-2, 3-difluorophenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone



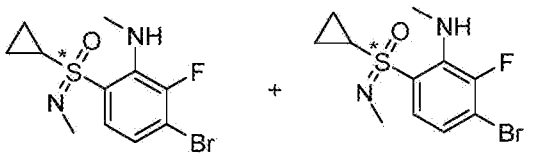
[1464] To a solution of (4-bromo-2, 3-difluorophenyl) (cyclopropyl) (imino) -λ^6-sulfanone (280 mg, 0.946 mmol) in dry dioxane (3 mL) were added cupric bis (acetate) (515.21 mg, 2.837 mmol) , pyridine (0.306 mL, 3.782 mmol) and methylboronic acid (808.56 mg, 13.508 mmol) . The reaction mixture was sealed up and stirred at 100 ℃ for 2 hrs under O_2. The mixture was filtered and the filtrate was concentrated in vacuum. The resulting residue was purified by silica gel chromatography (eluting PE/EA=1/1) to afford (4-bromo-2, 3-difluorophenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone (200 mg, 68.20%) . LC-MS: m/z 309.9 (M+H) $^+$.

[1465] Step E (4-bromo-3-fluoro-2- (methylamino) phenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone



[1466] To a solution of (4-bromo-2, 3-difluorophenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone (200 mg, 0.645 mmol) in THF (3 mL) was added methylamine in THF (2 mol/L, 5 mL) . The reaction mixture was sealed up and stirred at 70 ℃ for 16 hrs under N_2. To the mixture was added water (30 mL) , extracted with EA (30 mL x 3) . The combined organic layers were washed with brine (30 mL x 3) , dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting residue was purified by silica gel chromatography, eluting with PE/EA (3/1) to afford (4-bromo-3-fluoro-2- (methylamino) phenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone (200 mg, 96.56%) . LC-MS: m/z 320.7 (M+H) $^+$.

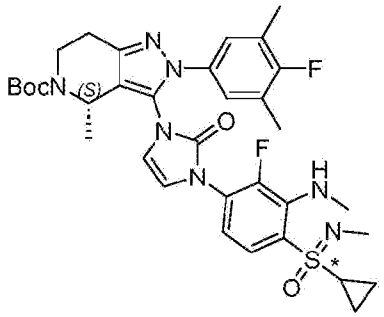
[1467] Step F (4-bromo-3-fluoro-2- (methylamino) phenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone (enantiomer 1) and (4-bromo-3-fluoro-2- (methylamino) phenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone (enantiomer 2)



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[1468] (4-bromo-3-fluoro-2- (methylamino) phenyl) (cyclopropy l) (methylimino) -λ^6-sulfanone (200 mg) was separated by SFC (Column: DAICELCHIRALPAK®AY; Column size: 250 mm*40 mm, 10 μm; Mobile Phas e A: Supercritical CO_2; Mobile Phase B: EtOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 15%) . Flow rate: 140 mL/min, Column temp.: 25 ℃) to afford (4-bromo-3-fluoro-2- (methylamino) phenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone (enantiomer 1) (100 mg, 99%ee, 50%) as a colorless oil as the fast eluent, R. T=2.19 min. LC-MS: m/z 320.7 $(M+H)^+$. And (4-bromo-3-fluoro-2- (methylamino) phenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone (enanti omer 2) (90 mg, 45%) as the slow eluent, R. T=3.23 min. LC-MS: m/z 320.7 $(M+H)^+$.

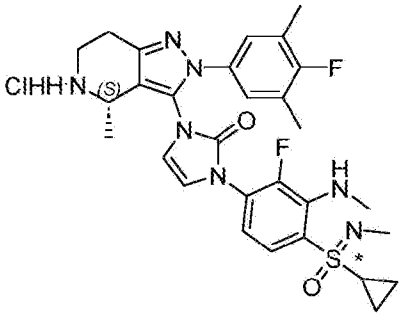
[1469] Step G tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3- (methylamino) -4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enantiomer 1)



[1470] To a solution of tert-butyl (S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- (2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (106 mg, 0.240 mmol) in NMP (2.4 mL) were added copper $^{(1+)}$ iodide (54.87 mg, 0.288 mmol) , potassium carbonate (66.36 mg, 0.480 mmol) , (4-bromo-3-fluoro-2- (methylamino) phenyl) (cyclopropyl) (methylimino) -λ^6-sulfanone (enantiomer 1) (100 mg, 0.310 mmol) and methyl [(1R, 2R) -2- (methylamino) cyclohexyl] amine (34.15 mg, 0.240 mmol) , and the re action mixture was stirred at 130 ℃ for 4 hrs under N_2. The mixture was poured into water (15 mL) , extracted with EA (20 mL x 3) , washed with brine (20 mL x 3) . The organic layer was dried and concentrated in vacuum. The residue was purified by silica gel column chromatography, eluting with PE/EA (1/1) to

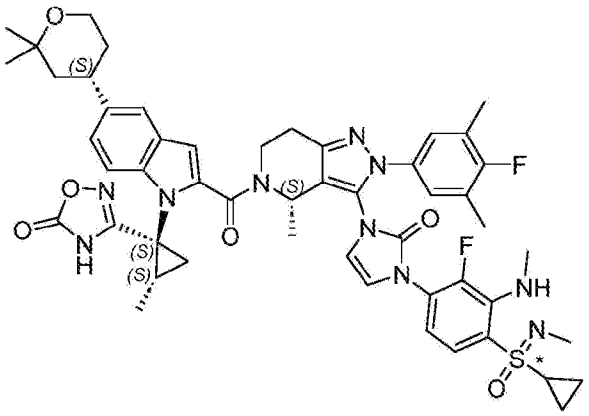
afford tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3- (methylamino) -4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enantiomer 1) (155 mg, 85.2%) . LC-MS: m/z 682.4 (M+H) $^{+}$.

[1471] Step H 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (2-fluoro-3- (methylamino) -4- (N-methylcyclopropanesulfonimidoyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one, hydrochloride salt (enantiomer 1)



[1472] A solution of tert-butyl (4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3- (methylamino) -4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-2, 4, 6, 7-tetrahydro-5H-pyrazolo [4, 3-c] pyridine-5-carboxylate (enantiomer 1) (155 mg, 0.227 mmol) in HCl/dioxane (4 mol/L, 10 mL) was stirred at rt for 2 hrs. The residue was concentrated in vacuum to afford 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (2-fluoro-3- (methylamino) -4- (N-methylcyclopropanesulfonimidoyl) phenyl) -1, 3-dihydro-2H-imidazol-2-one, hydrochloride salt (enantiomer 1) (130 mg, 88.48%) which was used in the next step without further purification. LC-MS: m/z 582.4 (M+H-HCl) $^{+}$.

[1473] Step I 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3- (methylamino) -4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 1) (Compound 238)



[1474] To a solution of 5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -1- ((1S, 2S) -2-methyl-1- (5-oxo-4, 5-dihydro-1, 2, 4-oxadiazol-3-yl) cyclopropyl) -1H-indole-2-carboxylic acid (30 mg, 0.073 mmol) in DMA (2 mL) were added DIPEA (56.54 mg, 0.437 mmol) , HATU (33.27 mg, 0.087 mmol) and the mixture was stirred at room temperature for 30 min. 1- ((S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridin-3-yl) -3- (2-fluoro-3- (methylamino) -4- (N-methylcyclopropanesulfonimidoyl) p henyl) -1, 3-dihydro-2H-imidazol-2-one, hydrochloride salt (enantiomer 1) (42.41 mg, 0.073 mmol) was added and the reaction mixture was fu rther stirred at room temperature for 16 hrs. The reaction mixture was diluted with E A (50 mL) and washed with saturated NaCl solution (20 mL x 3) . The organic layer was concentrated in vacuum and the crude was purified by prep-HPLC (FA) to afford 3- ((1S, 2S) -1- (5- ((S) -2, 2-dimethyltetrahydro-2H-pyran-4-yl) -2- ((4S) -2- (4-fluoro-3, 5-dimethylphenyl) -3- (3- (2-fluoro-3- (methylamino) -4- (N-methylcyclopropanesulfonimidoyl) phenyl) -2-oxo-2, 3-dihydro-1H-imidazol-1-yl) -4-methyl-4, 5, 6, 7-tetrahydro-2H-pyrazolo [4, 3-c] pyridine-5-carbonyl) -1H-indol-1-yl) -2-methylcyclopropyl) -1, 2, 4-oxadiazol-5 (4H) -one (enantiomer 1) (40 mg, 56.26%) .

[1475] LC-MS: m/z 488.4 (1/2M+H) $^{+}$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H) , 7.52 (s, 1H) , 7.48-7.37 (m, 2H) , 7.25 (d, J = 7.2 Hz, 1H) , 7.29-7.21 (m, 2H) , 7. 03-6.66 (m, 5H) , 5.54 (s, 1H) , 4.44 (s, 1H) , 3.79-3.68 (d, J = 7.2 Hz, 2H) , 3.56 (s , 1H) , 3.18-3.05 (m, 5H) , 2.93-2.77 (m, 2H) , 2.64 (s, 3H) , 2.30-2.20 (d, J = 1.6 Hz, 6H) , 1.90-1.38 (m, 10H) , 1.33-1.05 (m, 11H) , 0.98-0.81 (m, 2H) . ^{19} F NMR (376 MHz, DMSO-d_6) δ -122.13, -136.34.

[1476] The following molecules were synthesized using a similar procedure d escribed in the Examples above using the appropriate starting material. SFC Separatio n conditions for certain intermediates is as follows.

[1477] For compounds 116 and 117, 132 and 133, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALCEL®AS (250 mm*25 mm, 10 μm) ; mobile phase: A for CO_2, B for [0.1%7.0 M Ammonia in MeOH] ; B%: 15%) . Flow rate: 90 mL/min, Column temp.: 25 ℃.

[1478] For compounds 134 and 135, the sulfoximine intermediate were separated as follows: SFC separation (Column: ChiralCel OX (250 mm*30 mm, 10 μm) ; mobile phase: A for CO_2, B for [0.1%7.0 M Ammonia in MeOH] ; B%: 30%) . Flow rate: 150 mL/min, Column temp.: 38 ℃.

[1479] For compounds 136 and 137, the sulfoximine intermediate were separated as follows: SFC separation (Column: ChiralPak IC (250 mm*30 mm, 10 μm) ; mobile phase: A for CO_2, B for [0.1%7.0 M Ammonia in MeOH] ; B%: 30%) . Flow rate: 150 mL/min, Column temp.: 38 ℃.

[1480] For compounds 138 and 139, the sulfoximine intermediate were separated as follows: SFC separation (Column: ChiralPak IC (250 mm*30 mm, 10 μm) ; mobile phase: A for CO_2, B for [0.1%7.0 M Ammonia in MeOH] ; B%: 30%) . Flow rate: 80 mL/min, Column temp.: 38 ℃.

[1481] For compounds 140 and 141, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALCEL®AS (250 mm*25 mm, 10 μm) ; mobile phase: A for CO_2, B for [0.1%7.0 M Ammonia in MeOH] ; B%: 10%) . Flow rate: 100 mL/min, Column temp.: 25 ℃.

[1482] For compounds 174 and 175, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALPAK®AY; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 10%) . Flow rate: 100 mL/min, Column temp.: 25 ℃.

[1483] For compounds 176 and 177, the sulfoximine intermediate were separated as follows: SFC separation (Column: REGIS (S, S) WHELK-O1 250 mm*25 mm, 10 μm, Mobile phase A (Supercritical CO_2) , Mobile phase B (MeOH (0.1%7.0 M Ammonia in MeOH)) , Gradient: B = 35%) . Flow rate: 70 mL/min, Column temp.: 25 ℃.

[1484] For compounds 187 and 188, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALPAK®IG; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 20%) . Flow rate: 70 mL/min, Column temp.: 25 ℃.

[1485] For compounds 189 and 190, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALPAK®IG; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 35%) . Flow rate: 70 mL/min, Column temp.: 25 ℃.

[1486] For compounds 191 and 192, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALCEL®AS; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 35%) . Flow rate: 70 mL/min, Column temp.: 25 ℃.

[1487] For compounds 197 and 198, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALCEL®AS; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 12%) . Flow rate: 120 mL/min, Column temp.: 25 ℃.

[1488] For compounds 199 and 200, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALPAK®IC; Column size: 250*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 50%) . Flow rate: 70 mL/min, Column temp.: 25 ℃.

[1489] For compounds 201 and 202, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALPAK®AS; Column size: 250*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 17%) . Flow rate: 120 mL/min, Column temp.: 25 ℃.

[1490] For compounds 206 and 207, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALPAK®AD; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 30%) . Flow rate: 120 mL/min, Column temp.: 25 ℃.

[1491] For compounds 210 and 211, the sulfoximine intermediate were separated as follows: SFC separation (Column: DAICELCHIRALCEL®AD; Column size: 250 mm*25 mm, 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 16%) . Flow rate: 120 mL/min, Column temp.: 25 ℃.

[1492] For compounds 212 and 213, the sulfoximine intermediate were separated as follows: SFC separation (DAICELCHIRALPAK®AD; Column size: 250*25 mm, 10 μm;

Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (0.1%7.0 M Ammonia in MeOH) ; Gradient: B = 30%) . Flow rate: 120 mL/min, Colum n temp.: 25 ℃.

[1493] For compounds 204 and 205, the sulfoximine intermediate were separat ed as follows: SFC separation (Column: ChiralPak AD 150 mm*4.6 mm, 1 0 μm, Mobile phase A (Supercritical CO_2) , Mobile phase B (EtOH (0.05%DEA in EtOH)) , Gradient: B = 30%) . Flow rate: 50 mL/min, Column temp.: 25 ℃.

[1494] For compounds 214 and 215, the sulfoximine intermediate were separat ed as follows: SFC separation (Column: Chiral Whelk -O1 (S, S) 250 mm* 30 mm, 5 μm, Mobile phase A (Supercritical CO_2) , Mobile phase B (EtOH (0.1%NH_3 H_2O in EtOH)) , Gradient: B = 40%) . Flow rate: 50 mL/min, Column temp.: 25 ℃.

[1495] For compounds 219 and 220, the sulfoximine intermediate were separat ed as follows: SFC separation (Column: Chiral Pak IG-H 250 mm*30 mm, 5 μm, Mobile phase A (Supercritical CO_2) , Mobile phase B (EtOH)) , Grad ient: B = 10%) . Flow rate: 50 mL/min, Column temp.: 25 ℃.

Compound No.	LC-MS: m/z	^{1}H NMR
101	872.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 7.74 - 7.65 (m, 3H), 7.52 (s, 1H), 7.50 - 7.42 (m, 1H), 7.28 - 7.25 (m, 2H), 7.14 (d, *J* = 6.0 Hz, 2H), 6.91 - 6.81 (m, 2H), 5.69 - 5.44 (m, 1H), 4.55 - 4.27 (m, 1H), 3.99 - 3.94 (m, 2H), 3.50 - 3.47 (m, 4H), 3.32 - 3.28 (m, 2H), 2.92 - 2.86 (m, 5H), 2.22 (s, 6H), 1.76 - 1.70 (m, 7H), 1.43 (s, 3H), 1.18 (s, 3H).
102	861.5 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.70 (brs, 1H), 9.08 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 9.2 Hz, 1H), 7.26 - 7.23 (m, 1H), 7.17 - 7.13 (m, 3H), 6.94 (s, 1H), 5.60 (s, 1H), 4.46 - 4.34 (m, 2H), 3.98 - 3.95 (m, 2H), 3.51 - 3.44 (m, 2H), 3.24 (s, 3H), 2.94 - 2.81 (m, 3H), 2.21 (s, 6H), 1.72 - 1.60 (m, 7H), 1.40 - 1.38 (m, 2H), 1.32 - 1.24 (m, 2H), 1.14 - 1.13 (m, 2H).

Compound No.	LC-MS: m/z	^{1}H NMR
103	862.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 8.00 - 7.64 (m, 4H), 7.51 (s, 1H), 7.46 - 7.43 (m, 1H), 7.32 - 7.18 (m, 4H), 6.81 (brs, 1H), 5.79 - 5.44 (m, 1H), 4.40 (brs, 1H), 4.03 - 3.92 (m, 4H), 3.72 - 3.56 (m, 2H), 3.55 - 3.45 (m, 3H), 2.95 - 2.75 (m, 4H), 2.26 (s, 6H), 2.05 (d, *J* = 4.0 Hz, 3H), 1.81 - 1.59 (m, 7H), 1.50 (s, 3 H), 1.17 (brs, 3H).
105	889.5 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 7.74 (s, 1H), 7.52 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.28 - 7.26 (m, 2H), 7.15 (d, *J* = 6.0 Hz, 2H), 7.06 (s, 1H), 6.87 (s, 1H), 5.67 - 5.39 (m, 1H), 4.50 (brs, 1H), 3.52 - 3.43 (m, 4H), 3.01 (s, 3H), 2.91 - 2.75 (m, 3H), 2.22 (s, 6H), 1.78 - 1.68 (m, 7H), 1.43 (s, 3H), 1.17 (brs, 3H).
106	847.3 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 7.99 - 7.94 (m, 2H), 7.86 - 7.81 (m, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.25 - 7.23 (m, 1H), 7.08 - 7.03 (m, 4 H), 6.85 (s, 1H), 6.65 (s, 1H), 5.65 - 5.40 (m, 1H), 4.41 (brs, 1H), 3.73 - 3.71 (m, 4H), 3.34 - 3.32 (m, 2H), 3.12 (s, 3H), 3.04 - 3.02 (m, 4H), 2.90 - 2.80 (m, 2H), 2.13 (s, 6H), 1.76 - 1.58 (m, 3H), 1.76 - 1.58 (m, 3H), 1.48 1.47 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H).
107	846.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 8.34 - 8.32 (m, 2H), 8.03 - 7.96 (m, 4H), 7.89 - 7.87 (m, 1H), 7.19 (s, 1H), 7.13 - 7.12 (m, 3H), 7.03 (s, 1H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.24 (s, 1H), 5.73 - 5.48 (m, 1H), 4.01 - 3.92 (m, 4H), 3.51 - 3.43 (m, 4H), 2.76 - 2.70 (m, 1H), 2.18 (s, 6H), 1.81 - 1.61 (m, 7H), 1.46 - 1.41 (m, 2H), 1.29 - 1.23 (m, 3H).
108	886.5 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 8.07 - 8.01 (m, 1H), 7.85 - 7.73 (m, 2H), 7.57 - 7.53 (m, 2H), 7.43 - 7.41 (m, 2H), 7.34 - 7.32 (m, 1H), 7.27 - 7.25 (m, 2H), 7.14 - 7.13 (m, 3H), 6.93 (s, 1H), 6.86 (s, 1H), 6.24 (s, 1H), 5.59 - 5.48 (m, 1H), 4.50 – 4.45 (m, 1H), 4.01 - 3.92 (m, 4H), 3.52 - 3.38 (m, 5H), 2.91 - 2.82 (m, 5H), 2.21 (s, 6H), 1.76 - 1.71 (m, 7H), 1.46 - 1.41 (m, 4H), 1.29 - 1.23 (m, 2H).
109	846.3 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 8.58 - 8.39 (m, 3H), 8.12 - 8.09 (m, 1H), 8.02 - 7.96 (m, 1H), 7.51 (s, 1H), 7.41 - 7.39 (m, 1H), 7.23 - 7.21 (m, 2H), 6.81 - 677 (m, 1H), 6.72 (s, 1H), 5.73 - 5.61 (m, 1H), 5.43 - 5.40 (m, 1H), 4.37 - 4.31 (m, 3H), 3.17 (s, 3H), 2.76 - 2.70 (m, 1H), 2.22 (s, 6H), 2.17 - 2.01 (m, 4H), 1.79 - 1.75 (m, 2H), 1.53 - 1.47 (m, 5H).

Compound No.	LC-MS: m/z	^{1}H NMR
110	860.4 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 11.71 (brs, 1H), 8.03 - 7.95 (m, 3H), 7.54 - 7.40 (m, 3H), 7.28 (d, J = 8.8 Hz, 1H), 7.16 - 7.08 (m, 3H), 6.96 - 6.86 (m, 1H), 5.60 - 5.58 (m, 1H), 4.40 - 4.38 (m, 1H), 4.60 - 4.25 (m, 1H), 3.97 - 3.96 (m, 2H), 3.64 - 3.62 (m, 1H), 3.46 - 3.44 (m, 2H), 3.27 - 3.20 (m, 1H), 3.18 (s, 3H), 2.91 - 2.82 (m, 2H), 2.22 (s, 6H), 1.73 (s, 5H), 1.64 - 1.59 (m, 1H), 1.54 - 1.52 (m, 2H), 1.43 - 1.38 (m, 2H), 1.32 - 1.24 (m, 2H), 1.19 - 1.04 (m, 1H).
111	874.5 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 7.78 - 7.64 (m, 2H), 7.59 - 7.50 (m, 3H), 7.43 (d, J = 8.4 Hz, 1H), 7.30 - 7.21 (m, 2H), 7.15 (d, J = 6.0 Hz, 2H), 6.97 - 6.83 (m, 2H), 5.72 - 5.42 (m, 1H), 4.66 (s, 2H), 4.45 (brs, 1H), 3.98 (d, J = 10.8 Hz, 2H), 3.53 - 3.46 (m, 2H), 3.06 (s, 2H), 2.95 - 2.81 (m, 3H), 2.22 (s, 6H), 2.05 (s, 3H), 1.81 - 1.60 (m, 7H), 1.44 (d, J = 3.6 Hz, 3H), 1.18 (d, J = 6.0 Hz, 3H).
112	874.4 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 8.02 - 7.92 (m, 3H), 7.85 (s, 1H), 7.56 - 7.35 (m, 3H), 7.28 - 7.06 (m, 4H), 6.98 - 6.79 (m, 1H), 6.59 - 6.50 (m, 1H), 5.71 - 5.56 (m, 1H), 4.44 - 4.32 (m, 1H), 4.02 - 3.92 (m, 2H), 3.65 - 3.50 (m, 1H), 3.47 - 3.39 (m, 3H), 3.14 (s, 3H), 3.10 - 3.08 (m, 1H), 2.91 - 2.79 (m, 2H), 2.48 (s, 3H), 2.19 (s, 6H), 1.83 - 1.70 (m, 4H), 1.65 - 1.56 (m, 1H), 1.40 - 1.32 (m, 1H), 1.25 - 1.05 (m, 7H).
113	885.4 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 8.17 - 8.15 (m, 3H), 8.11 - 7.78 (m, 1H), 7.60 - 7.47 (m, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.20 - 7.07 (m, 3H), 6.97 (s, 1H), 5.76 - 5.50 (m, 1H), 4.44 - 4.32 (m, 1 H), 3.97 (d, J = 10.4 Hz, 2 H), 3.73 - 3.71 (m, 3 H), 3.67 - 3.58 (m, 1H), 3.50 - 3.44 (m, 2H), 3.27 - 3.19 (m, 1H), 2.92 - 2.84 (m, 2H), 2.22 (s, 6H), 1.82 - 1.62 (m, 7H), 1.40 (brs, 3H), (brs, 3H).
114	860.4 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 8.00 - 7.87 (m, 4H), 7.53 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.34 - 7.27 (m, 3 H), 7.15 (d, J = 6.0 Hz, 2H), 6.93 - 6.87 (m, 2H), 5.62 - 5.45 (m, 1H), 4.63 - 4.51 (m, 1H), 3.99 - 3.97 (m, 2H), 3.63 - 3.60 (m, 4H), 3.11 (s, 3H), 2.91 - 2.86 (m, 3H), 2.21 (s, 6 H), 1.78 - 1.62 (m, 7H), 1.44 (brs, 3H), 1.18 (brs, 3H).

Compound No.	LC-MS: m/z	^{1}H NMR
115	860.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.73 (brs, 1H), 8.00 - 7.80 (m, 4H), 7.53 (s, 1H), 7.44 (d, *J* = 8.4Hz, 1 H), 7.33 - 7.27 (m, 3H), 7.15 (d, *J* = 6.4 Hz, 2H), 6.92 - 6.88 (m, 2H), 5.62 - 5.45 (m, 1H), 4.63 - 4.51 (m, 1H), 3.99 - 3.97 (m, 2H), 3.63 - 3.60 (m, 4H), 3.11 (s, 3 H), 2.91 - 2.86 (m, 3 H), 2.21 (s, 6H), 1.78 - 1.62 (m, 7H), 1.44 (brs, 3H), 1.18 (brs, 3H).
116	874.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.72 (brs, 1H), 7.95 - 7.78 (s, 4H), 7.53 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.34 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.18 - 7.12 (m, 2H), 6.88 - 6.83 (m, 2H), 5.70 - 5.48 (m, 1H), 4.59 - 4.43 (m, 1H), 3.98 - 3.95 (m, 2H), 3.49 - 3.43 (m, 3H), 3.18 - 3.09 (m, 3H), 2.94 - 2.84 (m, 2H), 2.21 (s, 6H), 1.76 - 1.63 (m, 7H), 1.64 - 1.61 (m, 3H), 1.18 - 1.13 (m, 6H).
117	874.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.72 (brs, 1 H), 7.97 - 7.93 (m, 3 H), 7.93 - 7.73 (m, 1 H), 7.53 - 7.48 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.17 - 7.15 (m, 2H), 7.11 - 7.06 (s, 1H), 6.96 - 6.86 (m, 1H), 5.64 - 5.55 (m, 1H), 4.43 - 4.33 (m, 1H), 3.98 - 3.95 (m, 2H), 3.67 - 3.58 (m, 1H), 3.51 - 3.40 (m, 3H), 3.20 - 3.14 (m, 3H), 2.94 - 2.84 (m, 2H), 2.21 (s, 6H), 1.72 - 1.62 (s, 7H), 1.66 - 1.55 (m, 1H), 1.39 - 1.37 (m, 2H), 1.14 (d, *J* = 8.0 Hz, 2H), 1.09 - 1.02 (m, 4H).
118	872.5 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.59 (brs, 1H), 8.03 - 7.90 (m, 4H), 7.53 (s, 1H), 7.47 - 7.38 (m, 2H), 7.29 - 7.22 (m, 3H), 7.06 -6.80 (m, 3H), 5.71 - 5.44 (m, 1H), 4.65 - 4.31 (m, 1H), 3.98 (d, *J* = 10.4 Hz, 2H), 3.70 - 3.37 (m, 4H), 2.97 - 2.84 (m, 3H), 2.45 - 2.37 (m, 1H), 2.05 (s, 3H), 1.85 - 1.66 (m, 7H), 1.44 (s, 3H), 1.18 (s, 3H), 0.96 (d, *J* = 8.4 Hz, 2H), 0.68 - 0.44 (m, 2H).
119	955.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 8.50 (d, *J* = 4.8 Hz, 2H), 8.03 - 8.00 (m, 4H), 7.93 - 7.87 (m, 2H), 7.74 - 7.70 (m, 1H), 7.63 - 7.57 (m, 2H), 7.33 -7.32 (m, 1H), 7.24 - 7.16 (m, 4H), 7.05 -7.03 (m, 1H), 6.95 - 6.85 (m, 2H), 5.40 - 5.35 (m, 1H), 4.25 - 4.21 (m, 1H), 4.01 - 3.98 (m, 1H), 3.56 - 3.45 (m, 4H), 2.93 - 2.89 (m, 1H), 2.87 (s, 3H), 2.74 2.64 (m, 2H), 2.20 (s, 6H), 1.82 - 1.70 (m, 4H), 1.14 - 1.08 (m, 3H).

Compound No.	LC-MS: m/z	^{1}H NMR
121	874.5 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 8.01 - 7.91 (m, 3H), 7.85 - 7.76 (m, 1H), 7.51 - 7.40 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.29 - 7.23 (m, 1 H), 7.17 - 7.09 (m, 3H), 6.98 - 6.82 (m, 1H), 5.63 - 5.56 (m, 1H), 4.46 - 4.32 (m, 1H), 3.97 (d, *J* = 8.0 Hz, 2H), 3.71 - 3.53 (m, 1 H), 3.50 - 3.36 (m, 3H), 3.13 - 3.09 (m, 3H), 2.94 - 2.84 (m, 2H), 2.12 (s, 6H), 1.80 - 1.65 (m, 7H), 1.65 - 1.56 (m, 1H), 1.41 - 1.37 (m, 2H), 1.31 - 1.27 (m, 1H), 1.17 - 1.01 (m, 3H).
122	885.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 8.17 - 8.07 (m, 3H), 8.04 - 7.86 (m, 1H), 7.63 - 7.49 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.21 - 7.08 (m, 3H), 6.97 (s, 1H), 5.78 - 5.57 (m, 1H), 4.44 - 4.35 (m, 1H), 4.01 - 3.92 (m, 3H), 3.79 - 3.66 (m, 5H), 2.96 - 2.81 (m, 3H), 2.22 (s, 6H), 1.73 - 1.56 (m, 7 H), 1.39 - 1.14 (m, 3H), 1.11 - 0.96 (m, 3H).
123	890.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.59 (brs, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.70 - 7.40 (m, 5H), 7.27 (d, *J* = 9.2 Hz, 1H), 7.16 - 7.14 (m, 2H), 7.01 - 6.84 (m, 2H), 5.69 - 5.44 (m, 1H), 4.58 - 4.39 (m, 1H), 4.04 - 3.87 (m, 5H), 3.64 - 3.43 (m, 4H), 3.32 (s, 3H), 2.95 - 2.84 (m, 3H), 2.23 (s, 6H), 1.81 - 1.61 (m, 7H), 1.44 (s, 3H), 1.17 (s, 3H).
124	874.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 8.08 - 7.97 (m, 1H), 7.81 - 7.58 (m, 2H), 7.53 (s, 1H), 7.35 - 7.26 (m, 2H), 6.95 - 6.78 (m, 2H), 5.71 - 5.31 (m, 1H), 4.61 - 4.30 (m, 1H), 3.97 (d, *J* = 12.0 Hz, 2H), 3.51 - 3.44 (m, 3H), 2.94 (s, 3H), 2.71 (s, 3H), 2.21 (s, 6H), 1.75 - 1.72 (m, 5H), 1.66 - 1.58 (m, 2H), 1.45 (s, 2H), 1.32 - 1.23 (m, 3H).
125	924.3 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 8.50 - 8.41 (m, 3H), 8.06 - 8.00 (m, 2H), 7.96 - 7.92 (m, 2H), 7.37 (d, *J* = 3.2 Hz, 1H), 7.17 - 7.11 (m, 3 H), 7.04 - 7.00 (m, 1H), 6.72 (d, *J* = 6.8 Hz, 1H), 5.72 - 5.70 (m, 1H), 4.00 - 3.94 (m, 3H), 3.51 - 3.43 (m, 3H), 3.05 - 3.00 (m, 3H), 2.20 (s, 6H), 1.87 - 1.70 (m, 4H), 1.50 - 1.47 (m, 1H), 1.37 - 1.18 (m, 5H), 0.86 - 0.83 (m, 3H).
130	888.3 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 12.62 (brs, 1H), 8.00 - 7.93 (m, 4H), 7.50 - 7.44 (m, 3 H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.16 - 7.14 (m, 2H), 7.07 (s, 1H), 6.84 (s, 1H), 5.62 - 5.60 (m, 1H), 4.34 - 4.24 (m, 1H), 3.83 - 3.78 (m, 1H), 3.69 - 3.67 (m, 1H), 3.50 - 3.43 (m, 3H), 3.40 - 3.35 (m, 2H), 2.86 - 2.83 (m, 2H), 2.29 - 2.26 (m, 3H), 2.20 (s, 6H), 1.90 - 1.85 (m, 1H), 1.80 - 1.65 (m, 5H), 1.57 - 1.48 (m, 2H), 1.30 - 1.24 (m, 4H).

Compound No.	LC-MS: m/z	^{1}H NMR
131	888.4 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 12.60 (brs, 1H), 8.00 - 7.93 (m, 4H), 7.48 - 7.42 (m, 3 H), 7.20 (s, 1H), 7.15 - 7.13 (m, 2H), 7.10 (s, 1H), 6.74 (s, 1H), 5.62 - 5.60 (m, 1H), 4.34 - 4.24 (m, 1 H), 3.98 - 3.96 (m, 2H), 3.83 - 3.77 (m, 1H), 3.71 - 3.65 (m, 1H), 3.48 - 3.41 (m, 3H), 3.38 - 3.35 (m, 2H), 2.86 - 2.83 (m, 2H), 2.33 - 2.24 (m, 3H), 2.20 (s, 6 H), 1.90 - 1.85 (m, 1 H), 1.80 - 1.65 (m, 5H), 1.57 - 1.48 (m, 2H), 1.32 - 1.24 (m, 4H).
132	877.2 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 8.26 (s, 1H), 8.14 - 8.09 (m, 2H), 7.88 (s, 1H), 7.80 - 7.78 (d, *J*=8.0 Hz, 1 H), 7.57 - 7.54 (m, 2H), 7.39 (d, *J*=6.8 Hz, 1H), 7.14 - 7.09 (m, 2H), 7.01 (s, 1H), 5.65 (q, *J*=4.8 Hz, 1H), 4.12 - 4.09 (m, 1H), 3.99 (d, *J*=10.4 Hz, 2H), 3.87 -3.84 (m, 1H), 3.50 - 3.42 (m, 3H), 2.93 - 2.89 (m, 1H), 2.67 - 2.64 (m, 2H), 2.33 - 2.16 (m, 7H), 1.75 (m, 4H), 1.51-1.47 (m, 3H), 1.23-1.20 (m, 7H).
134	886.2 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 11.60 (brs, 1H), 8.04 - 7.78 (m, 4H), 7.51 (s, 1H), 7.42 - 7.37 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 6.98 - 6.97 (m, 2H), 7.00 - 6.89 (m, 2H), 5.62 - 5.60 (m, 1H), 4.47 - 4.40 (m, 1H), 4.05 - 3.94 (m, 3H), 3.68 - 3.44 (m, 4H), 2.90 - 2.83 (m, 2H), 2.66 - 2.64 (m, 1H), 2.20 (s, 6H), 1.85 -1.69 (m, 7H), 1.53 - 1.38 (m, 3H), 1.20 - 1.11 (m, 4H), 1.01 - 0.88 (m, 3H).
135	886.3 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 11.65 (brs, 1H), 8.04 - 7.78 (m, 4H), 7.51 (s, 1H), 7.42 - 7.37 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 6.98 - 6.97 (m, 2H), 7.00 - 6.89 (m, 2H), 5.62 - 5.60 (m, 1H), 4.40 - 4.35 (m, 1H), 4.05 - 3.94 (m, 3H), 3.68 - 3.44 (m, 4H), 2.90 - 2.83 (m, 2H), 2.66 - 2.64 (m, 1H), 2.20 (s, 6H), 1.85 -1.69 (m, 7H), 1.53 - 1.38 (m, 3H), 1.20 - 1.11 (m, 4H), 1.01 - 0.88 (m, 3H).
136	908.2 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 11.69 (brs, 1H), 8.06 - 7.96 (m, 2H), 7.74 (s, 1H), 7.52 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.18 - 7.17 (m, 2H), 7.05 - 6.89 (m, 3H), 5.72 - 5.63 (m, 1H), 4.40 - 4.35 (m, 2H), 4.01 - 3.96 (m, 2H), 3.60 - 3.47 (m, 3H), 3.27 - 3.21 (m, 2H), 2.92 - 2.85 (m, 2H), 2.25 (s, 6H), 1.85 -1.69 (m, 7H), 1.52 - 1.35 (m, 3H), 1.26 - 1.12 (m, 6H).

Compound No.	LC-MS: m/z	^{1}H NMR
137	908.2 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.65 (brs, 1H), 8.07 - 7.96 (m, 2H), 7.74 (s, 1H), 7.52 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.18 - 7.17 (m, 2H), 7.05 - 6.86 (m, 3H), 5.72 - 5.60 (m, 1H), 4.40 - 4.35 (m, 2H), 4.00 - 3.96 (m, 2H), 3.60 - 3.46 (m, 3H), 3.27 - 3.21 (m, 2H), 2.92 - 2.85 (m, 2H), 2.25 (s, 6H), 1.80 -1.69 (m, 7H), 1.52 - 1.35 (m, 3H), 1.26 - 1.12 (m, 6H).
138	892.0 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.66 (brs, 1H), 7.96 - 7.75 (m, 3H), 7.53 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.16 - 7.08 (m, 3H), 7.00 - 6.90 (m, 2H), 5.65 - 5.61 (m, 1H), 4.40 - 4.35 (m, 2H), 4.00 - 3.96 (m, 2H), 3.60 - 3.45 (m, 3H), 3.25 - 3.19 (m, 2H), 2.92 - 2.84 (m, 2H), 2.24 (s, 6H), 1.78 -1.71 (m, 7H), 1.52 - 1.34 (m, 3H), 1.21 - 1.12 (m, 6H).
139	892.3 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.54 (brs, 1H), 7.78 - 7.71 (m, 3H), 7.45 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.11 - 6.99 (m, 3H), 6.93 - 6.83 (m, 2H), 5.65 - 5.61 (m, 1H), 4.37 - 4.31 (m, 1H), 3.92 - 3.88 (m, 2H), 3.52 - 3.35 (m, 4H), 3.25 - 3.19 (m, 2H), 2.85 - 2.76 (m, 2H), 2.16 (s, 6H), 1.70 -1.61 (m, 7H), 1.50 - 1.30 (m, 3H), 1.11 - 1.10 (m, 6H).
140	875.6 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.59 (brs, 1H), 9.03 (s, 1H), 8.36 (s, 1H), 8.12 (s, 1H), 7.51 (s, 1H), 7.43 - 7.41 (m, 2H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.15 - 7.13 (m, 2H), 6.97 - 6.86 (m, 2H), 5.62 - 5.57 (m, 1H), 4.50 - 4.40 (m, 1H), 3.99 - 3.96 (m, 2H), 3.57 - 3.45 (m, 3H), 3.25 - 3.29 (m, 2H), 2.91 - 2.84 (m, 2H), 2.21 (s, 6H), 1.75 -1.72 (m, 6H), 1.68 -1.67 (m, 2H), 1.43 - 1.40 (m, 3H), 1.17 - 1.30 (m, 6H).
141	875.6 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.64 (brs, 1H), 9.02 (s, 1H), 8.36 (s, 1H), 8.13 (s, 1H), 7.48 (s, 1H), 7.43 - 7.41 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.15 - 7.13 (m, 2H), 6.81 - 6.71 (m, 2H), 5.60 - 5.54 (m, 1H), 4.12 - 4.04 (m, 1H), 3.98 - 3.96 (m, 2H), 3.51 - 3.45 (m, 3H), 3.35 - 3.29 (m, 2H), 2.87 - 2.82 (m, 2H), 2.20 (s, 6H), 1.77 -1.71 (m, 6H), 1.67 -1.64 (m, 2H), 1.43 - 1.40 (m, 3H), 1.17 - 1.30 (m, 6H).

Compound No.	LC-MS: m/z	^{1}H NMR
142	886.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 7.95 - 7.88 (m, 4H), 7.49 (s, 1H), 7.43 (d, *J*= 8.4 Hz, 1H), 7.32 (m, 1H), 7.23 (d, *J*= 8.4 Hz, 1H), 7.17 - 7.15 (m, 2H), 6.98 (m, 1H), 6.77 (m, 1H), 5.55 (m, 1H), 4.39 (m, 1H), 4.00 - 3.97 (m, 2H), 3.86 - 3.81 (m, 1H), 3.72 - 3.69 (m, 1H), 3.52 - 3.46 (m, 2H), 3.40 - 3.32 (m, 2H), 2.90 - 2.83 (m, 3H), 2.33 - 2.26 (m, 3H), 2.22 (s, 6H), 1.76 - 1.69 (m, 5H), 1.65 (m, 2H), 1.39 (s, 3H), 1.20 (s, 3H).
143	886.2 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.59 (brs, 1H), 7.95 - 7.91 (m, 4H), 7.53 (s, 1H), 7.44 (d, *J*= 8.4 Hz, 1H), 7.37 (m, 1 H), 7.28 (d, *J*=8.4 Hz, 1H), 7.16 - 7.14 (m, 2H), 6.96 (m, 1H), 6.88 (m, 1H), 5.57 (m, 1H), 4.50 (m, 1H), 4.00 - 3.97 (m, 2H), 3.89 - 3.84 (m, 1H), 3.77 - 3.72 (m, 1H), 3.53 - 3.46 (m, 4H), 2.92 - 2.86 (m, 2H), 2.36 - 2.28 (m, 3H), 2.22 (s, 6H), 2.05 - 2.02 (m, 1H), 1.78 - 1.73 (m, 6H), 1.66 (m, 1H), 1.43 (s, 3H), 1.17 (s, 3H).
144	888.3 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.62 (brs, 1H), 7.95 - 7.88 (m, 4H), 7.56 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.37 (s, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.20 - 7.18 (m, 2H), 6.97 (s, 1H), 6.90 (s, 1H), 5.63 - 5.58 (m, 1H), 4.53 - 4.48 (m, 1H), 4.03 - 4.00 (m, 2H), 3.56 - 3.50 (m, 3H), 3.27 - 3.22 (m, 2H), 2.94 - 2.91 (m, 2H), 2.58 (s, 3H), 2.25 (s, 6H), 1.81 -1.65 (m, 7H), 1.46 (s, 3H), 1.31 - 1.30 (m, 1H). 1.18 - 1.16 (m, 2H), 1.15 - 1.13 (m, 4H).
147	890.4 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 12.49 (brs, 1H), 7.98 (m, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.55 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.39 (s, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 6.0 Hz, 1H), 7.00 - 6.99 (m, 1H), 6.85 (s, 1H), 5.66 -5.63 (m, 1H), 4.52 (m, 1H), 3.99 - 3.92 (m, 5H), 3.56 - 3.50 (m, 3H), 3.35 (q, *J* = 7.2 Hz, 2H), 2.92 - 2.88 (m, 2H), 2.61 (s, 3H), 2.26 (d, *J* = 1.6 Hz, 6H), 1.96 - 1.95 (m, 1H), 1.82 -1.77 (m, 4H), 1.57 -1.56 (m, 1H), 1.43 - 1.41 (m, 2H), 1.17 (t, *J* = 8.8 Hz, 3H).
148	904.3 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 12.91 (brs, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.59 - 7.50 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.16 - 7.14 (m, 2H), 6.91 (s, 1H), 6.89 (s, 1H), 5.67 (q, *J* = 6.8 Hz, 1H), 4.37 - 4.34 (m, 1H), 3.98 - 3.95 (m, 2H), 3.70 - 3.64 (m, 1H), 3.49 - 3.43 (m, 2H), 3.24 - 3.17 (m, 3H), 2.92 - 2.82 (m, 2H), 2.22 (s, 6H), 1.89 - 1.86 (m, 1H), 1.76 -1.65 (m, 6H), 1.53 -1.50 (m, 2H), 1.42 - 1.40 (m, 2H), 1.06 (t, *J* = 6.0 Hz, 3H), 0.92 (d, *J* = 5.2 Hz, 3H).

Compound No.	LC-MS: m/z	^{1}H NMR
149	906.1 (M+H)$^+$	(400 MHz, DMSO-*d*6) δ 11.68 (s, 1H), 7.98 - 7.65 (m, 3H), 7.53 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.17 - 7.09 (m, 3H), 6.95 - 6.90 (m, 2H), 5.65 - 5.61 (m, 1H), 4.00 - 3.97 (m, 2H), 3.59 - 3.47 (m, 3H), 3.32 - 3.25 (m, 3H), 2.91 - 2.85 (m, 2H), 2.56 (s, 3H), 2.24 (s, 6H), 1.78 - 1.64 (m, 7H), 1.65 - 1.63 (m, 3H), 1.16 - 1.08 (m, 6H).
150	906.3 (M+H)$^+$	(400 MHz, DMSO-*d*6) δ 11.64 (brs, 1H), 7.98 - 7.65 (m, 3H), 7.53 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.17 - 7.09 (m, 3H), 6.95 - 6.90 (m, 2H), 5.70 - 5.62 (m, 1H), 4.40 - 4.35 (m, 1H), 4.00 - 3.96 (m, 2H), 3.62 - 3.48 (m, 3H), 3.32 - 3.25 (m, 3H), 2.91 - 2.85 (m, 2H), 2.56 (s, 3H), 2.24 (s, 6H), 1.78 - 1.64 (m, 7H), 1.65 - 1.63 (m, 3H), 1.16 - 1.08 (m, 6H).
151	922.2 (M+H)$^+$	(400 MHz, DMSO-*d*6) δ 11.67 (brs, 1H), 7.98 - 7.78 (m, 3H), 7.53 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.18 - 7.16 (m, 2H), 7.03 - 6.92 (m, 3H), 5.71 - 5.62 (m, 1H), 4.40 - 4.35 (m, 1H), 4.01 - 3.96 (m, 2H), 3.60 - 3.46 (m, 3H), 3.32 - 3.25 (m, 2H), 2.91 - 2.84 (m, 2H), 2.56 (s, 3H), 2.25 (s, 6H), 1.77 - 1.63 (m, 7H), 1.46 (s, 3H), 1.16 - 1.08 (m, 6H).
152	922.1 (M+H)$^+$	(400 MHz, DMSO-*d*6) δ 11.68 (brs, 1H), 7.97 - 7.78 (m, 3H), 7.54 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.18 - 7.16 (m, 2H), 7.02 - 6.92 (m, 3H), 5.71 - 5.62 (m, 1H), 4.40 - 4.35 (m, 1H), 4.01 - 3.96 (m, 2H), 3.60 - 3.46 (m, 3H), 3.32 - 3.25 (m, 2H), 2.92 - 2.84 (m, 2H), 2.56 (s, 3H), 2.23 (s, 6H), 1.78 - 1.63 (m, 7H), 1.46 (s, 3H), 1.17 - 1.08 (m, 6H).
153	830.5 (M+H)$^+$	(400 MHz, DMSO-*d*6) δ 8.00 - 7.98 (d, *J*= 8.8 Hz, 2 H), 7.95 - 7.93 (d, *J*=8.8 Hz, 2 H), 7.59 - 7.57 (d, *J*= 8.8, 1 H), 7.55 (s, 1 H), 7.35 - 7.34 (d, *J*= 3.2 Hz, 1 H), 7.25 - 7.23 (d, *J*= 8.4 Hz, 1 H), 7.17 - 7.16 (d, *J*= 6.4 Hz, 2 H), 7.14 (s, 1 H), 6.91 (s, 1 H), 6.85 (s, 1 H), 5.82 (s, 1 H), 5.62 (s, 2 H), 5.46 - 5.43 (m, 1 H), 4.43 - 4.41 (m, 1 H), 4.04 - 3.97 (m, 3 H), 3.71 (s, 3 H), 3.56 - 3.49 (m, 2 H), 3.40 - 3.33 (m, 1 H), 3.21 - 3.15 (m, 2 H), 2.94 - 2.87 (m, 1 H), 2.84 - 2.78 (m, 2 H), 2.24 (s, 6 H), 1.81 - 1.76 (m, 4 H) , 1.31 - 1.30 (d, *J*=6.4 Hz, 3 H), 1.15 (t, *J*= 7.4 Hz, 3 H).

Compound No.	LC-MS: m/z	^{1}H NMR
155	870.2 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 7.94 (m, 4H), 7.55 - 7.52 (m, 2H), 7.40 - 7.38 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 4.0 Hz, 2H), 7.04 - 7.02 (m, 1H), 6.80 (s, 1H), 5.55 - 5.50 (m, 1H), 4.03 - 4.01 (m, 2H), 3.87 - 3.83 (m, 1H), 3.76 - 3.71 (m, 1H), 3.56 - 3.49 (m, 2H), 3.47 - 3.37 (m, 3H), 2.95 - 2.82 (m, 3H), 2.40 (s, 3H), 2.34 - 2.27 (m, 2H), 2.24 - 2.23 (s, 6H), 1.90 - 1.73 (m, 8H), 1.37 - 1.30 (m, 4H)
156	870.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.95 (m, 4H), 7.55 - 7.52 (m, 2H), 7.40 - 7.38 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.17 (d, J = 4.0 Hz, 2H), 7.04 - 7.02 (m, 1H), 6.80 (s, 1H), 5.55 - 5.53 (m, 1H), 4.03 - 4.00 (m, 2H), 3.89 - 3.83 (m, 1H), 3.75 - 3.70 (m, 1H), 3.55 - 3.49 (m, 2H), 3.47 - 3.36 (m, 3H), 2.86 (s, 3H), 2.39 - 2.36 (m, 3H), 2.35 - 2.29 (m, 2H), 2.25 - 2.23 (s, 6H), 1.89 - 1.76 (m, 8H), 1.37 - 1.34 (m, 4H).
157	844.2 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.96 (m, 4H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.43 - 7.36 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 4.0 Hz, 2H), 7.05 - 7.00 (m, 1H), 6.91 (s, 1H), 5.86 - 5.75 (m, 2H), 5.60 - 5.55 (m, 1H), 4.03 - 4.00 (m, 2H), 3.87 -3.83 (m, 1H), 3.76 - 3.70 (m, 1H), 3.55 - 3.49 (m, 2H), 3.44 - 3.35 (m, 3H), 2.93 - 2.83 (m, 3H), 2.40 (s, 3H), 2.34 - 2.27 (m, 2H), 2.24 - 2.23 (s, 6H), 1.81-1.74 (m, 4H), 1.39 - 1.30 (m, 3H).
158	844.0 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.96 (m, 4H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.41 - 7.39 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 4.0 Hz, 2H), 7.02 - 7.00 (m, 1H), 6.91 (s, 1H), 5.86 - 5.75 (m, 2H), 5.60 - 5.55 (m, 1H), 4.55 - 4.40 (m, 1H), 4.03 - 4.00 (m, 2H), 3.89 - 3.83 (m, 1H), 3.75 - 3.70 (m, 1H), 3.55 - 3.34 (m, 5H), 2.92 - 2.84 (m, 3H), 2.40 (s, 3H), 2.33 - 2.26 (m, 2H), 2.25 - 2.24 (s, 6H), 1.81 - 1.75 (m, 4H), 1.40 - 1.36 (m, 3H).
159	845.2 $(M+H)^+$	(400 MHz, DMSO-d6) δ 8.97 (s, 1 H), 7.92 (m, 4 H), 7.48 (s, 1 H), 7.37 (s, 1 H), 7.14 - 7.12 (d, *J*= 6.0 Hz, 2 H), 6.94 (s, 1 H), 6.89 (s, 1 H), 5.92 - 5.88 (m, 1 H), 5.82 - 5.77 (m, 1 H), 5.51 - 5.49 (m, 1 H), 4.38 (m, 1 H), 4.00 - 3.98 (m, 2 H), 3.85 - 3.81 (m, 1 H), 3.73 - 3.69 (m, 1 H), 3.54 - 3.47 (m, 2 H), 3.43 - 3.33 (m, 3 H), 3.02 - 3.00 (m, 2 H), 2.91 - 2.83 (m, 2 H), 2.39 (s, 3 H), 2.25 - 2.24 (m, 1 H), 2.21 (m, 6 H), 1.86 - 1.82 (m, 4 H), 1.34 (d, *J*= 6.8 Hz, 3 H).

Compound No.	LC-MS: m/z	^{1}H NMR
160	871.5 $(M+H)^+$	(400 MHz, DMSO-d6) δ 8.90 (s, 1 H), 8.45 (s, 1 H), 7.91 (m, 3 H), 7.49 (s, 1 H), 7.33 (s, 1 H), 7.14-7.12 (d, *J*= 6.4 Hz, 2 H), 6.96 (s, 1 H), 6.80 (s, 1 H), 5.56 - 5.54 (m, 1 H), 4.01 - 3.98 (m, 2 H), 3.84 - 3.83 (m, 1 H), 3.73 - 3.68 (m, 1 H), 3.51 - 3.49 (m, 2 H), 3.38 - 3.02 (m, 3 H), 3.05 - 3.36 (m, 1 H), 2.85 - 2.80 (m, 2 H), 2.36 - 2.27 (m, 5 H), 2.21 (m, 7 H), 1.99 - 1.95 (m, 1 H), 1.89 - 1.86 (m, 7 H), 1.34 - 1.33 (d, *J*= 6.8 Hz, 3 H).
161	842.4 $(M+H)^+$	(400 MHz, DMSO-d6) δ 8.03 (s, 1 H), 7.5 (t, *J*= 8.8, 2 H), 7.39 (d, *J*= 2.8 Hz, 1 H), 7.25 - 7.23 (d, *J*= 8.8 Hz, 1 H), 7.17 - 7.15 (d, *J*= 6.0 Hz, 3 H), 6.95 (s, 1 H), 6.85 (s, 1 H), 5.82 (d, *J*= 1.2 Hz, 1 H), 5.61 (s, 2 H), 5.44 (s, 1 H), 4.42 (s, 1 H), 4.04 - 4.00 (m, 2 H), 3.95 - 3.90 (m, 1 H), 3.82 - 3.76 (m, 1 H), 3.71 (s, 3 H), 3.67 - 3.61 (m, 2 H), 3.55 - 3.49 (m, 2 H), 2.94 (s, 1 H), 2.90 - 2.87 (m, 1 H), 2.82 - 2.78 (m, 2 H), 2.48 - 2.35 (m, 2 H), 2.24 (d, *J*= 1.2 Hz, 6 H), 1.81 - 1.76 (m, 4 H) , 1.31 - 1.29 (d, *J*= 6.4 Hz, 3 H).
162	820.5 $(M+H)^+$	(400 MHz, DMSO-d6) δ 8.34 (s, 1 H), 7.96 - 7.93 (d, *J*= 8.4 Hz, 2 H), 7.87 - 7.85 (d, *J*= 8.8 Hz, 2 H), 7.53 - 7.51 (d, *J*= 8.4 Hz, 1 H), 7.47 (s, 1 H), 7.33 (s, 1 H), 7.18 - 7.16 (d, J= 8.4 Hz, 1 H), 7.14 - 7.13 (d, *J*= 6.0 Hz, 2 H), 6.86 (m, 1 H), 6.72 (s, 1 H), 5.50 (m, 1 H), 4.87 - 4.81 (m, 1 H), 4.70 - 4.64 (m, 1 H), 4.47 -4.43 (m, 2 H), 4.35 - 4.20 (m, 2 H), 4.00 - 3.97 (m, 2 H), 3.53 - 3.41 (m, 3 H), 3.24 - 3.19 (m, 3 H), 2.94 - 2.81 (m, 2 H), 2.67 - 2.62 (m, 1 H), 2.55 (s, 3 H), 2.33 - 2.29 (m, 1 H), 2.21 (s, 6 H), 1.79 - 1.77 (m, 4 H), 1.39 - 1.38 (d, *J*= 6.8 Hz, 3 H), 1.12 (t, *J*= 7.4 Hz, 3 H).
163	834.2 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.99 - 7.95 (m, 2 H), 7.89 -7.87 (d, *J*= 8.8 Hz, 2 H), 7.51 - 7.47 (m, 2 H), 7.37 - 7.35 (m, 1 H), 7.18 - 7.14 (m, 3 H), 6.94 - 6.92 (m, 1 H), 6.72 - 6.71 (d, *J*= 3.2 Hz, 1 H), 5.61 - 5.48 (m, 1 H), 4.49 - 4.31 (m, 3 H), 4.00 - 3.97 (m, 3 H), 3.53 - 3.46 (m, 4 H), 3.31 - 3.25 (m, 3 H), 2.86 (m, 3 H), 2.57 (s, 3 H), 2.21 (s, 6 H), 1.92 (m, 1 H), 1.79 - 1.73 (m, 6 H), 1.55 (m, 1 H), 1.41 - 1.37 (m, 3 H), 1.13 (t, *J*= 7.2 Hz, 3 H).
164	934.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.71 (brs, 1 H), 7.79 - 7.73 (m, 3 H), 7.54 (s, 1 H), 7.46 - 7.44 (d, *J*= 8.4 Hz, 1 H), 7.28 - 7.26 (d, *J*= 8.4 Hz, 1 H), 7.20 - 7.19 (d, *J*= 6.0 Hz, 2 H), 7.06 (m, 1 H), 6.95 (m, 1 H), 6.84 (m, 1 H), 5.62 (m, 1 H), 4.49 (m, 1 H), 3.78 - 3.77 (d, *J*= 7.6 Hz, 2 H), 3.56 (m, 1 H), 3.35 - 3.29 (m, 2 H), 2.89 (m, 1 H), 2.60 (s, 3 H), 2.28 (s, 6 H), 1.77 - 1.55 (m, 8 H), 1.47 (m, 3 H), 1.33 - 1.28 (m, 4 H), 1.24 - 1.16 (m, 9 H).

Compound No.	LC-MS: m/z	^{1}H NMR
165	820.5 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.97 (d, J= 8.8 Hz, 2 H), 7.87 (d, J= 8.8 Hz, 2 H), 7.54 (d, J= 8.8 Hz, 1 H), 7.50 (s, 1 H), 7.35 (d, J= 3.2 Hz, 1 H), 7.19 (d, J= 8.4 Hz, 1 H), 7.16 (d, J= 6.4 Hz, 2 H), 6.93 (s, 1 H), 6.77 (s, 1 H), 5.59 - 5.57 (m, 1 H), 4.96 - 4.94 (m, 1 H), 4.64 - 4.59 (m, 1 H), 4.55 - 4.48 (m, 2 H), 4.38 - 4.37 (m, 1 H), 4.15 - 4.10 (m, 1 H), 4.00 - 3.98 (m, 2 H), 3.53 - 3.44 (m, 3 H), 3.24 - 3.18 (m, 3 H), 2.98 - 2.75 (m, 4 H), 2.56 (s, 3 H), 2.22 (s, 6 H), 1.80 - 1.74 (m, 4 H), 1.38 - 1.36 (d, J= 6.4 Hz, 3 H), 1.13 (t, J= 7.2 Hz, 3 H).
166	904.1 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.75 - 7.70 (m, 3 H), 7.51 (s, 1 H), 7.43 (d, J= 9.6 Hz, 1 H), 7.26 - 7.24 (m, 3 H), 7.06 - 6.99 (m, 2 H), 6.93 - 6.83 (m, 2 H), 5.56 (s, 1 H), 4.44 (s, 1 H), 3.99 (d, J= 10.8 Hz, 2 H), 3.58 - 3.42 (m, 2 H), 3.31 - 3.26 (m, 2 H), 2.89 - 2.84 (m, 2 H), 2.57 (s, 3 H), 2.08 - 2.05 (m, 1 H), 1.76 - 1.64 (m, 7 H), 1.43 (s, 3 H), 1.20 - 1.13 (m, 6 H), 1.00 (d, J= 7.6 Hz, 2 H), 0.67 - 0.64 (m, 2 H).
167	904.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.82 - 7.66 (m, 3 H), 7.45 -7.40 (m, 2 H), 7.29 - 7.17 (m, 3 H), 7.01 - 6.98 (m, 3 H), 6.61 (m, 1 H), 4.19 (m, 1 H), 3.99 - 3.97 (m, 2 H), 3.52 - 3.46 (m, 2 H), 3.24 - 3.18 (m, 3 H), 2.90 - 2.83 (m, 3 H), 2.74 - 2.72 (m, 1 H), 2.05 (m, 1 H), 1.77 - 1.73 (m, 5 H), 1.61 (m, 2 H), 1.35 (m, 3 H), 1.27 - 1.23 (m, 3 H), 1.14 (t, J= 7.2 Hz, 3 H), 0.98 - 0.96 (d, J= 8.8 Hz, 2 H), 0.68 - 0.65 (m, 2 H).
168	918.4 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.61 (brs, 1 H), 7.81 - 7.78 (m, 2 H), 7.52 (s, 1 H), 7.44 (d, J= 8.8 Hz, 1 H), 7.27 (d, J= 8.0 Hz, 1 H), 7.16 (d, J= 6.4 Hz, 2 H), 7.02 (s, 1 H), 6.88 (s, 2 H), 5.57 (m, 1 H), 4.44 (m, 1 H), 4.16 (m, 1 H), 4.04 - 3.97 (m, 3 H), 3.52 - 3.46 (m, 3 H), 2.90 - 2.86 (m, 2 H), 2.41 - 2.36 (m, 2 H), 2.24 (s, 6 H), 2.19 - 2.04 (m, 2 H), 1.94 - 1.84 (m, 2 H), 1.78 - 1.70 (m, 7 H), 1.63 (m, 1 H), 1.45 (s, 3 H) , 1.19 (s, 3 H).
169	918.4 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.61 (brs, 1 H), 7.78 (m, 3 H), 7.52 (s, 1 H), 7.44 (d, J= 8.4 Hz, 1 H), 7.27 (d, J= 8.4 Hz, 1 H), 7.16 (d, J= 6.0 Hz, 2 H), 7.02 (s, 1 H), 6.89 (m, 2 H), 5.55 (m, 1 H), 4.43 (m, 1 H), 4.17 (m, 1 H), 4.01 - 3.97 (m, 3 H), 3.52 - 3.46 (m, 3 H), 2.89 - 2.87 (m, 2 H), 2.41 - 2.36 (m, 2 H), 2.24 (s, 6 H), 2.17 - 2.06 (m, 2 H), 1.91 - 1.85 (m, 2 H), 1.76 - 1.72 (m, 6 H), 1.64 (m, 1 H), 1.44 (s, 3 H) , 1.19 (s, 3 H).

Compound No.	LC-MS: m/z	^{1}H NMR
170	874.2 $(M+H)^+$	(400 MHz, DMSO-d6) δ 8.40 - 8.25 (m, 2H), 7.85 - 7.68 (m, 3H), 7.63 - 7.55 (m, 1H), 7.50 (s, 1H), 7.19 - 7.14 (m, 3H), 7.10 - 7.05 (m, 1H), 6.90 - 6.86 (m, 1H), 6.82 (s, 1H), 5.66 - 5.56 (m, 2H), 5.54 - 5.40 (m, 1H), 4.50 - 4.35 (m, 1H), 4.25 - 4.24 (m, 1H), 3.99 - 3.96 (m, 1H), 3.88 - 3.85 (m, 1H), 3.51 - 3.45 (m, 2H), 3.32 - 3.26 (m, 3H), 2.86 - 2.76 (m, 3H), 2.55 (s, 3H), 2.36 - 2.34 (m, 3H), 2.25 - 2.24 (m, 6H), 1.77 - 1.71 (m, 3H), 1.31 - 1.26 (m, 3H), 1.13 (t, J = 8.0 Hz, 3H).
171	873.0 $(M+H)^+$	(400 MHz, DMSO-d6) δ 8.42 (s, 1H), 7.83 - 7.69 (m, 4H), 7.57 - 7.55 (m, 2H), 7.41 - 7.39 (m, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.11 - 7.09 (m, 1H), 6.90 (s, 2H), 5.64 - 5.53 (m, 2H), 5.45 - 5.40 (m, 1H), 4.44 - 4.40 (m, 1H), 4.04 - 4.39 (m, 2H), 3.55 - 3.48 (m, 3H), 3.40 - 3.33 (m, 3H), 2.94 - 2.87 (m, 1H), 2.80 - 2.76 (m, 1H), 2.59 (s, 3H), 2.50 - 2.48 (m, 3H), 2.29 - 2.27 (m, 6H), 1.81 - 1.75 (m, 4H), 1.36 - 1.34 (m, 3H), 1.18 (t, J = 4.0 Hz, 3H).
172	856.2 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.90 (m, 4H), 7.52 (s, 1H), 7.39 - 7.35 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.01 - 7.00 (m, 1H), 6.80 (s, 1H), 5.56 - 5.45 (m, 1H), 4.45 - 4.40 (m, 1H), 4.03 - 4.00 (m, 2H), 3.89 - 3.83 (m, 1H), 3.75 - 3.70 (m, 1H), 3.50 - 3.44 (m, 3H), 3.31 - 3.29 (m, 3H), 2.90 - 2.78 (m, 3H), 2.31 - 2.28 (m, 2H), 2.26 (s, 6H), 1.86 - 1.60 (m, 8H), 1.40 - 1.36 (m, 3H).
173	906.1 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.61 (brs, 1H), 7.85 - 7.80 (m, 3H), 7.52 (s, 1H), 7.47 - 7.38 (m, 1H), 7.28 - 7.24 (m, 1H), 7.20 - 7.05 (m, 3H), 6.99 - 6.80 (m, 2H), 5.65 - 5.60 (m, 1H), 4.40 - 4.35 (m, 1H), 4.02 - 3.89 (m, 2H), 3.69 - 3.40 (m, 4H), 3.17 - 3.10 (m, 2H), 2.95 - 2.80 (m, 3H), 2.24 - 2.21 (m, 6H), 1.82 - 1.64 (m, 7H), 1.61 - 1.35 (m, 4H), 1.20 - 0.88 (m, 7H).
174	892.5 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.54 (brs, 1 H), 7.53 (m, 2 H), 7.49 - 7.46 (m, 1 H), 7.43 (d, J= 8.4 Hz, 1 H), 7.39 - 7.37 (m, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.16 (d, J = 6.4 Hz, 2 H), 6.93 (s, 1 H), 6.88 (s, 1 H), 6.82 (s, 1 H), 5.57 (m, 1 H), 4.49 - 4.42 (m, 3 H), 4.00 - 3.97 (m, 2 H), 3.58 - 3.46 (m, 3 H), 3.00 - 2.88 (m, 2 H), 2.86 (s, 3 H), 2.25 (d, J = 0.8 Hz, 6 H), 1.78 - 1.65 (m, 8 H), 1.46 (s, 3 H), 1.19 (s, 3 H).

Compound No.	LC-MS: m/z	^{1}H NMR
175	892.5 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.56 (brs, 1 H), 7.53 - 7.46 (m, 3 H), 7.43 (d, *J*= 8.4 Hz, 1 H), 7.39 - 7.37 (m, 1 H), 7.27 (d, *J* = 8.4 Hz, 1 H), 7.16 (d, *J* = 6.4 Hz, 2 H), 6.94 (s, 1 H), 6.87 - 6.82 (m, 2 H), 5.57 (m, 1 H), 4.48 - 4.41 (m, 3 H), 4.00 - 3.97 (m, 2 H), 3.59 - 3.46 (m, 3 H), 2.91 - 2.88 (m, 2 H), 2.85 (s, 3 H), 2.25 (s, 6 H), 1.77 - 1.63 (m, 8 H), 1.46 (m, 3 H), 1.20 (s, 3 H).
176	$(M+H)^+$	(400 MHz, DMSO-d6) δ 7.63 (m, 4 H), 7.51 (s, 1 H), 7.43 (d, *J*= 8.4 Hz, 1 H), 7.26 (d, *J*= 8.4 Hz, 1 H), 7.23 - 7.20 (m, 1 H), 7.15 (d, *J*= 6.0 Hz, 2 H), 6.88 - 6.81 (m, 2 H), 5.56 (m, 1 H), 4.44 (m, 1 H), 4.00 - 3.97 (m, 2 H), 3.52 - 3.46 (m, 3 H), 2.91 - 2.84 (m, 2 H), 2.74 (s, 3 H), 2.22 (s, 6 H), 1.78 - 1.64 (m, 8 H), 1.58 - 1.53 (m, 1 H), 1.41 - 1.37 (m, 3 H), 1.27 - 1.16 (m, 6 H).
177	450.9 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.64 (m, 4 H), 7.48 (s, 1 H), 7.42 (d, *J*= 8.4 Hz, 1 H), 7.23 - 7.14 (m, 4 H), 6.89 (m, 1 H), 6.75 (m, 1 H), 5.56 (m, 1 H), 4.42 (m, 1 H), 4.00 - 3.97 (m, 2 H), 3.52 - 3.46 (m, 2 H), 3.37 (m, 1 H), 2.88 - 2.84 (m, 2 H), 2.74 (s, 3 H), 2.21 (s, 6 H), 1.76 - 1.70 (m, 6 H), 1.65 (m, 2 H), 1.57 - 1.53 (m, 1 H), 1.37 (m, 3 H), 1.27 - 1.14 (m, 6 H).
178	918.4 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.60 (brs, 1 H), 7.84 - 7.71 (m, 3 H), 7.52 (s, 1 H), 7.44 - 7.41 (d, *J*= 8.4 Hz, 1 H), 7.27 - 7.25 (d, *J*= 8.4 Hz, 1 H), 7.16 - 7.15 (d, *J*= 6.4 Hz, 2 H), 7.02 (s, 1 H), 6.88 - 6.84 (m, 2 H), 5.56 (m, 1 H), 4.44 (m, 1 H), 4.17 (m, 1 H), 3.99 - 3.97 (m, 2 H), 3.52 - 3.46 (m, 2 H), 3.19 - 3.17 (m, 2 H), 2.92-2.84 (m, 2 H), 2.24 (s, 6 H), 1.76 - 1.72 (m, 7 H), 1.64 - 1.63 (m, 1 H), 1.45 (s, 3 H), 1.19 (s, 3 H), 0.96 - 0.93 (m, 1 H) , 0.48 - 0.46 (m, 2 H), 0.15 (m, 2 H).
179	923.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 13.5 (brs, 1H), 7.95 - 7.85 (m, 4H), 7.54 (s, 1H), 7.42 - 7.36 (m, 2H), 7.23 - 7.20 (m, 1H), 7.14 (d, *J* = 4.0 Hz, 2H), 7.00 - 6.95 (m, 1H), 6.82 (s, 1H), 5.56 - 5.54 (m, 1H), 4.47 - 4.45 (m, 1H), 4.06 (s, 1H), 4.00 - 3.97 (m, 2H), 3.53 - 3.46 (m, 3H), 2.92 - 2.79 (m, 3H), 2.69 - 2.62 (m, 1H), 2.23 - 2.21 (m, 6H), 1.86 - 1.55 (m, 8H), 1.35 - 1.26 (m, 3H), 1.14 - 1.09 (m, 1H), 1.03 - 0.86 (m, 3H).

Compound No.	LC-MS: m/z	^{1}H NMR
180	946.7 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.55 (brs, 1 H), 7.78 - 7.75 (m, 3 H), 7.51 (s, 1 H), 7.42 (d, *J*= 8.4 Hz, 1 H), 7.24 (d, J= 8.0 Hz, 1 H), 7.16 (d, J= 6.4 Hz, 2 H), 7.04 (s, 1 H), 6.89 - 6.76 (m, 2 H), 5.54 (m, 1 H), 4.40 (m, 1 H), 3.74 (d, *J*= 9.2 Hz, 2 H), 3.51 (m, 1 H), 2.83 (m, 1 H), 2.79 (m, 1 H), 2.59 (s, 3 H), 2.24 (s, 6 H), 1.73 - 1.55 (m, 8 H), 1.44 (s, 3 H), 1.30 - 1.21 (m, 11 H), 1.10 (m, 1 H), 0.98 - 0.90 (m, 2 H).
181	932.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.61 (brs, 1 H), 7.84 - 7.72 (m, 3 H), 7.54 (s, 1 H), 7.42 (d, *J*= 8.4 Hz, 1 H), 7.26 (d, *J*= 8.4 Hz, 1 H), 7.16 (d, *J*= 6.4 Hz, 2 H), 7.04 (s, 1 H), 6.87 (m, 2 H), 5.59 (m, 1 H), 4.42 (m, 1 H), 4.22 (m, 1 H), 3.74 (d, *J*= 8.8 Hz, 2 H), 3.55 (m, 1 H), 2.90 - 2.86 (m, 1 H), 2.76 (m, 1 H), 2.25 (s, 6 H), 1.73 - 1.45 (m, 11 H), 1.30 - 1.21 (m, 4 H), 1.19 - 1.17 (m, 7 H), 1.06 - 0.97 (m, 3 H).
182	914.8 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.60 - 7.45 (m, 3H), 7.43 - 7.30 (m, 3H), 7.26 - 7.20 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.92 - 6.80 (m, 2H), 5.62 - 5.55 (m, 1H), 4.50 - 4.35 (m, 1H), 4.00 - 3.93 (m, 2H), 3.55 - 3.40 (m, 4H), 3.05 - 2.99 (m, 3H), 2.95 - 2.80 (m, 3H), 2.21 - 2.19 (m, 6H), 2.18 - 2.00 (m, 5H), 1.85 - 1.55 (m, 7H), 1.45 - 1.30 (m, 4H), 1.20 - 1.05 (m, 3H).
183	946.1 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.61 (brs, 1 H), 7.81 - 7.68 (m, 3 H), 7.53 (s, 1 H), 7.42 (d, *J*= 8.4 Hz, 1 H), 7.26 (d, *J*= 8.4 Hz, 1 H), 7.15 (d, *J*= 6.4 Hz, 2 H), 7.03 (s, 1 H), 6.87 (m, 2 H), 5.57 (m, 1 H), 4.45 (m, 1 H), 4.16 (m, 1 H), 4.06 - 3.97 (m, 1 H), 3.75 - 3.73 (m, 2 H), 3.58 - 3.55 (m, 1 H), 3.02 - 2.87 (m, 2 H), 2.41 - 2.34 (m, 2 H), 2.24 (s, 6 H), 2.19 - 2.03 (m, 2 H), 1.91 - 1.71 (m, 6 H), 1.64 - 1.51 (m, 3 H), 1.45 (m, 3 H), 1.30 (s, 3 H), 1.21 - 1.18 (m, 6 H).
184	946.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.87 - 7.75 (m, 3 H), 7.49 (s, 1 H), 7.41 (d, *J*= 8.4 Hz, 1 H), 7.22 (d, *J*= 8.4 Hz, 1 H), 7.16 (d, *J*= 6.4 Hz, 2 H), 7.01 - 6.78 (m, 3 H), 5.69 (s, 1 H), 4.41 (m, 1 H), 4.17 (s, 1 H), 3.75 - 3.73 (m, 2 H), 3.52 - 3.48 (m, 1 H), 3.18 (d, *J*= 7.2 Hz, 2 H), 2.89 - 2.80 (m, 1 H), 2.24 (s, 6 H), 1.76 - 1.58 (m, 6 H), 1.55 - 1.52 (m, 1 H), 1.44 - 1.42 (m, 3 H), 1.30 - 1.27 (m, 4 H), 1.21 (s, 6 H), 0.98 - 0.90 (m, 1 H), 0.49 - 0.46 (m, 2 H), 0.16 - 0.15 (m, 2 H).

Compound No.	LC-MS: m/z	^{1}H NMR
185	932.8 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.64 (brs, 1 H), 7.89 (m, 1 H), 7.61 (m, 1 H), 7.51 (s, 1 H), 7.42 (d, *J*= 8.8 Hz, 1 H), 7.25 (d, *J*= 8.8 Hz, 1 H), 7.16 (d, *J*= 6.4 Hz, 2 H), 6.99 (s, 1 H), 6.88 - 6.74 (m, 2 H), 5.56 (m, 1 H), 4.41 (m, 1 H), 3.74 (d, *J*= 9.2 Hz, 2 H), 3.48 - 3.45 (m, 2 H), 3.25 (s, 3 H), 2.88 - 2.79 (m, 2 H), 2.69 - 2.60 (m, 1 H), 2.24 (s, 6 H), 1.73 - 1.55 (m, 8 H), 1.45 - 1.39 (m, 3 H), 1.30 (s, 4 H), 1.21 - 1.15 (m, 7 H).
186	932.8 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.62 (brs, 1 H), 7.88 (m, 1 H), 7.60 (m, 1 H), 7.50 (s, 1 H), 7.42 (d, *J*= 8.8 Hz, 1 H), 7.23 (d, *J*= 8.4 Hz, 1 H), 7.16 (d, *J*= 6.4 Hz, 2 H), 6.97 (s, 1 H), 6.89 - 6.71 (m, 2 H), 5.56 (m, 1 H), 4.40 (m, 1 H), 3.74 (d, *J*= 8.0 Hz, 2 H), 3.48 - 3.45 (m, 2 H), 3.25 (s, 3 H), 2.85 - 2.77 (m, 2 H), 2.68 - 2.60 (m, 1 H), 2.24 (s, 6 H), 1.73 - 1.55 (m, 8 H), 1.43 (m, 3 H), 1.30 (s, 4 H), 1.21 (m, 7 H).
187	918.8 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.60 (brs, 1 H), 7.97 (m, 1 H), 7.79 - 7.70 (m, 1 H), 7.51 (s, 1 H), 7.41 (d, *J*= 8.0 Hz, 1 H), 7.25 (d, *J*= 8.4 Hz, 1 H), 7.15 (d, *J*= 6.4 Hz, 2 H), 7.02 (m, 1 H), 6.90 - 6.79 (m, 2 H), 5.69 - 5.55 (m, 1 H), 4.82 (d, *J*= 17.2 Hz, 1 H), 4.68 (d, *J*= 18.0 Hz, 1 H), 4.48 - 4.33 (m, 1 H), 3.74 (d, J= 8.8 Hz, 2 H), 3.46 (s, 3 H), 2.89 - 2.84 (m, 1 H), 2.24 (s, 6 H), 1.78 - 1.69 (m, 4 H), 1.61 - 1.54 (m, 4 H), 1.40 (m, 3 H), 1.29 (m, 4 H), 1.20 (m, 7 H).
188	918.8 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.57 (brs, 1 H), 7.99 (m, 1 H), 7.77 (m, 1 H), 7.51 (s, 1 H), 7.41 (d, *J*= 8.8 Hz, 1 H), 7.25 (d, *J*= 8.4 Hz, 1 H), 7.16 (d, *J*= 6.4 Hz, 2 H), 7.02 (m, 1 H), 6.89 - 6.84 (m, 2 H), 5.68 (m, 1 H), 4.82 (d, *J*= 17.6 Hz, 1 H), 4.68 (d, *J*= 17.6 Hz, 1 H), 4.43 - 4.39 (m, 1 H), 3.74 (d, *J*= 9.2 Hz, 2 H), 3.46 (s, 3 H), 2.88 - 2.85 (m, 1 H), 2.24 (s, 6 H), 1.72 - 1.70 (m, 4 H), 1.61 - 1.54 (m, 4 H), 1.44 (m, 3 H), 1.29 (m, 4 H), 1.20 (m, 7 H).
189	946.7 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.60 (brs, 1 H), 7.83 (d, *J*= 9.6 Hz, 1 H), 7.57 - 7.53 (m, 2 H), 7.42 (d, *J*= 8.8 Hz, 1 H), 7.27 (dd, J_1= 8.4 Hz, J_2= 1.2 Hz, 1 H), 7.15 (d, *J*= 6.4 Hz, 2 H), 7.00 (s, 1 H), 6.86 (s, 2 H), 5.57 (m, 1 H), 4.45 (m, 1 H), 3.75 - 3.73 (m, 2 H), 3.56 (m, 1 H), 2.91 - 2.86 (m, 3 H), 2.72 (s, 3 H), 2.25 (s, 6 H), 1.75 - 1.70 (m, 4 H), 1.62 - 1.58 (m, 2 H), 1.54 - 1.51 (m, 2 H), 1.47 - 1.38 (m, 3 H), 1.29 - 1.25 (m, 4 H), 1.21 (m, 6 H), 1.09 - 1.01 (m, 4 H).

Compound No.	LC-MS: m/z	^{1}H NMR
190	946.7 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.63 (brs, 1 H), 7.83 (d, J= 9.6 Hz, 1 H), 7.57 - 7.52 (m, 2 H), 7.41 (d, J= 8.4 Hz, 1 H), 7.26 (dd, J_1= 8.4 Hz, J_2= 0.8 Hz, 1 H), 7.15 (d, J= 6.0 Hz, 2 H), 7.00 (s, 1 H), 6.86 (s, 2 H), 5.58 (m, 1 H), 4.43 (m, 1 H), 3.74 - 3.72 (m, 2 H), 3.55 (m, 1 H), 2.91 - 2.85 (m, 3 H), 2.71 (s, 3 H), 2.24 (s, 6 H), 1.84 - 1.71 (m, 4 H), 1.63 - 1.54 (m, 4 H) , 1.45 (m, 3 H), 1.29 (m, 4 H), 1.18 (m, 6 H), 1.10 - 1.02 (m, 4 H).
191	944.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.60 (brs, 1 H), 7.90 (m, 1 H), 7.75 (m, 1 H), 7.52 (s, 1 H), 7.41 (d, J= 8.4 Hz, 1 H), 7.26 (d, J= 8.0 Hz, 1 H), 7.16 (d, J= 6.4 Hz, 2 H), 7.03 (m, 1 H), 6.85 (m, 2 H), 5.57 (m, 1 H), 4.79 (d, J= 18.4 Hz, 1 H), 4.63 (d, J= 18.0 Hz, 1 H), 4.44 (m, 1 H), 3.74 - 3.72 (m, 2 H), 3.58 (m, 1 H), 3.01 - 2.85 (m, 3 H), 2.24 (s, 6 H), 1.72 - 1.70 (m, 4 H), 1.64 - 1.45 (m, 8 H), 1.29 (s, 3 H), 1.20 - 1.16 (m, 7 H), 1.01 (m, 1 H), 0.71 (m, 1 H).
192	944.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.61 (brs, 1 H), 7.90 (m, 1 H), 7.77 (m, 1 H), 7.52 (s, 1 H), 7.41 (d, J= 8.8 Hz, 1 H), 7.26 (d, J= 8.8 Hz, 1 H), 7.16 (d, J= 6.4 Hz, 2 H), 7.03 (m, 1 H), 6.86 (m, 2 H), 5.57 (m, 1 H), 4.80 (d, J= 18.0 Hz, 1 H), 4.63 (d, J= 17.6 Hz, 1 H), 4.47 (m, 1 H), 3.74 - 3.72 (m, 2 H), 3.56 (m, 1 H), 2.98 - 2.85 (m, 3 H), 2.24 (s, 6 H), 1.72 - 1.70 (m, 4 H), 1.64 - 1.45 (m, 8 H), 1.29 (s, 3 H), 1.20 - 1.16 (m, 7 H), 1.00 (m, 1 H), 0.71 (m, 1 H).
193	960.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.61 (brs, 1 H), 7.73 (m, 1 H), 7.61 (s, 1 H), 7.53 (s, 1 H), 7.43 (d, J= 8.4 Hz, 1 H), 7.27 (d, J= 8.4 Hz, 1 H), 7.16 (d, J= 6.0 Hz,2 H), 7.03 (s, 2 H), 6.87 (m, 2 H), 5.56 (m, 1 H), 4.45 (m, 2 H), 3.75 (d, J= 9.2 Hz, 2 H), 3.56 (s, 1 H), 2.91 - 2.86 (m, 2 H), 2.67 (s, 3 H), 2.56 (s, 3 H), 2.25 (s, 6 H), 1.74 - 1.70 (m, 4 H), 1.64 - 1.54 (m, 4 H), 1.47 - 1.46 (m, 3 H), 1.30 (s, 4 H), 1.21 (s, 4 H), 1.15 - 1.13 (m, 2 H), 0.94 - 0.84 (m, 3 H).
194	960.7 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.60 (brs, 1 H), 7.73 - 7.70 (m, 1 H), 7.60 (m, 1 H), 7.52 (s, 1 H), 7.41 (d, J= 8.8 Hz, 1 H), 7.25 (d, J= 8.4 Hz, 1 H), 7.15 (d, J= 6.4 Hz, 2 H), 7.02 (s, 1 H), 6.87 (s, 2 H), 5.57 (m, 1 H), 4.45 (m, 2 H), 3.74 - 3.72 (m, 2 H), 3.57 (m, 1 H), 2.90 - 2.87 (m, 2 H), 2.65 (s, 3 H), 2.55 (s, 3 H), 2.24 (s, 6 H), 1.73 - 1.69 (m, 4 H), 1.63 - 1.46 (m, 6 H), 1.29 - 1.26 (m, 6 H), 1.20 - 1.10 (m, 7 H), 0.95 - 0.82 (m, 2 H).

Compound No.	LC-MS: m/z	^{1}H NMR
195	960.8 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.58 (brs, 1 H), 7.77 - 7.74 (m, 1 H), 7.65 - 7.52 (m, 2 H), 7.42 (d, J= 8.8 Hz, 1 H), 7.27-7.24 (dd, J_1= 8.8 Hz, J_2= 1.6 Hz, 1 H), 7.16 (d, J= 6.0 Hz, 2 H), 7.02 (m, 1 H), 6.87 (m, 2 H), 5.62 5.54 (m, 1 H), 4.44 (m, 1 H), 3.74 (d, J= 9.2 Hz, 2 H), 3.57 (m, 1 H), 3.03 (m, 2 H), 2.90 - 2.86 (m, 2 H), 2.63 (s, 3 H), 2.56 (s, 3 H), 2.25 (s, 6 H), 1.72 - 1.54 (m, 7 H), 1.51-1.45 (m, 3 H), 1.29 (m, 4 H), 1.20 - 1.12 (m, 7 H), 0.94 - 0.83 (m, 2 H).
196	960.8 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.58 (brs, 1 H), 7.75 (m, 1 H), 7.64 - 7.53 (m, 2 H), 7.41 (d, J= 8.4 Hz, 1 H), 7.26 (d, J= 8.8 Hz, 1 H), 7.16 (d, J= 6.0 Hz, 2 H), 7.01 (m, 1 H), 6.87 (m, 2 H), 5.57 (m, 1 H), 4.43 (m, 1 H), 3.74 (d, J= 8.8 Hz, 2 H), 3.58 (m, 1 H), 3.04 - 3.01 (m, 2 H), 2.90 - 2.86 (m, 2 H), 2.63 (s, 3 H), 2.56 (s, 3 H), 2.24 (s, 6 H), 1.72-1.63 (m, 4 H), 1.62 - 1.46 (m, 6 H), 1.29 (m, 4 H), 1.20 - 1.12 (m, 7 H), 0.94 - 0.81 (m, 2 H).
197	958.8 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.73 (brs, 1 H), 7.95 (d, J= 8.0 Hz, 1 H), 7.69 (t, J= 7.6 Hz, 1 H), 7.53 (s, 1H), 7.41 (d, J= 8.4 Hz, 1 H), 7.27 (d, J= 8.8 Hz, 1 H), 7.16 -7.14 (m, 3 H), 7.01 (m, 1 H), 6.94 (m, 1 H), 5.57 (m, 1 H), 4.39 - 4.37 (m, 1 H), 3.72 - 3.70 (m, 3 H), 3.44 - 3.42 (m, 2 H), 3.06 - 3.03 (m, 1 H), 2.90 - 2.85 (m, 2 H), 2.67 - 2.65 (m, 1 H), 2.24 (s, 6 H), 1.72 - 1.52 (m, 8 H), 1.42 - 1.40 (m, 4 H), 1.32 -1.27 (m, 4 H), 1.23 - 1.10 (m, 7 H), 0.94 - 0.82 (m, 2 H).
198	958.8 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.74 (brs, 1 H), 7.95 (d, J= 8.0 Hz, 1 H), 7.69 (t, J= 7.6 Hz, 1 H), 7.53 (s, 1H), 7.41 (d, J= 8.4 Hz, 1 H), 7.27 (d, J= 8.8 Hz, 1 H), 7.16 -7.14 (m, 3 H), 7.00 (m, 1 H), 6.94 (m, 1 H), 5.57 (m, 1 H), 4.39 - 4.37 (m, 1 H), 3.72 - 3.70 (m, 3 H), 3.44 - 3.42 (m, 2 H), 3.06 - 3.03 (m, 1 H), 2.90 - 2.85 (m, 3 H), 2.67 - 2.65 (m, 1 H), 2.24 (s, 6 H), 1.72 - 1.52 (m, 8 H), 1.42 - 1.40 (m, 4 H), 1.32 -1.27 (m, 4 H), 1.23 - 1.09 (m, 7 H), 0.90 - 0.81 (m, 2 H).

Compound No.	LC-MS: m/z	^{1}H NMR
199	918.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.63 (brs, 1 H), 8.19 (m, 1 H), 7.79 (m, 1 H), 7.52 (s, 1 H), 7.41 (d, *J*= 8.4 Hz, 1 H), 7.26 (d, *J*= 8.8 Hz, 1 H), 7.16 (d, *J*= 6.4 Hz, 2 H), 7.02 (s, 1 H), 6.87 (m, 2 H), 5.58 (m, 1 H), 4.73 (d, *J*= 17.2 Hz, 1 H), 4.58 (d, *J*= 19.2 Hz, 1 H), 4.42 (m, 1 H), 3.74 - 3.72 (m, 2 H), 3.57 (m, 1 H), 3.44 (s, 3 H), 2.91 - 2.84 (m, 1 H), 2.25 (s, 6 H), 1.73 - 1.69 (m, 4 H), 1.63 - 1.54 (m, 4 H), 1.46 (m, 3 H), 1.29 (m, 4 H), 1.20 (m, 6 H).
200	918.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.62 (brs, 1 H), 8.19 (m, 1 H), 7.80 (m, 1 H), 7.52 (s, 1 H), 7.41 (d, *J*= 8.4 Hz, 1 H), 7.26 (d, *J*= 8.8 Hz, 1 H), 7.15 (d, *J*= 6.4 Hz, 2 H), 7.02 (s, 1 H), 6.87 (m, 2 H), 5.56 (m, 1 H), 4.73 (d, *J*= 16.8 Hz, 1 H), 4.58 (d, *J*= 16.0 Hz, 1 H), 4.45 (m, 1 H), 3.74 (d, *J*= 8.8 Hz, 2 H), 3.58 (m, 1 H), 3.44 (s, 3 H), 2.89 - 2.85 (m, 1 H), 2.25 (s, 6 H), 1.75 - 1.69 (m, 4 H), 1.63 - 1.51 (m, 4 H), 1.46 (m, 3 H), 1.29 (m, 4 H), 1.20 (m, 6 H).
201	934.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 8.11 (m, 1 H), 7.71 (m, 1 H), 7.50 (s, 1 H), 7.41 (d, *J*= 8.0 Hz, 1 H), 7.24 (d, *J*= 8.8 Hz, 1 H), 7.17 (d, *J*= 6.4 Hz, 2 H), 6.90 (m, 2 H), 6.81 (m, 1 H), 5.57 (m, 1 H), 4.69 - 4.55 (m, 2 H), 4.41 (m, 1 H), 3.73 (d, *J*= 8.8 Hz, 2 H), 3.47 (m, 3 H), 2.85 (m, 1 H), 2.25 (s, 6 H), 1.73 - 1.55 (m, 8 H), 1.45 (m, 3 H), 1.38 - 1.34 (m, 1 H), 1.29 (m, 3 H), 1.20 (m, 6 H), 0.92 - 0.88 (m, 1 H).
202	934.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 8.15 - 8.13 (m, 1 H), 7.72 (m, 1 H), 7.51 (s, 1 H), 7.41 (d, *J*= 8.8 Hz, 1 H), 7.24 (d, *J*= 8.0 Hz, 1 H), 7.18 (d, *J*= 6.4 Hz, 2 H), 6.95 - 6.90 (m, 2 H), 6.81 (m, 1 H), 5.62 - 5.48 (m, 1 H), 4.69 - 4.57 (m, 2 H), 4.41 (m, 1 H), 3.73 (d, *J*= 8.8 Hz, 2 H), 3.47 (s, 3 H), 2.88 - 2.82 (m, 1 H), 2.25 (s, 6 H), 1.73 - 1.52 (m, 8 H), 1.45 (m, 3 H), 1.38 - 1.34 (m, 1 H), 1.29 (m, 3 H), 1.20 (m, 6 H), 0.92 - 0.87 (m, 1 H).
203	962.2 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.68 (brs, 1 H), 7.90 - 7.70 (m, 3 H), 7.53 (s, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.30 - 7.24 (m, 3 H), 7.15 - 7.10 (m, 1 H), 7.00 - 6.85 (m, 2 H), 5.65 - 5.60 (m, 1 H), 4.45 - 4.35 (m, 1 H), 3.75 (d, *J*= 8.8 Hz, 2 H), 3.65 - 3.55 (m, 1 H), 3.05 - 3.02 (m, 1 H), 3.00 - 2.75 (m, 2 H), 2.58 (s, 3 H), 2.40 - 2.36 (m, 6 H), 1.80 - 1.69 (m, 4 H), 1.66 - 1.40 (m, 7 H), 1.29 (s, 3 H), 1.28 - 1.22(m, 3 H), 1.20 (s, 3 H), 1.15 - 1.04 (m, 2 H), 1.00 - 0.85 (m, 2 H).

Compound No.	LC-MS: m/z	^{1}H NMR
204	962.0 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.62 (brs, 1 H), 8.00 - 7.70 (m, 3 H), 7.52 (s, 1 H), 7.41 - 7.37 (m, 1 H), 7.28 - 7.20 (m, 1 H), 7.15 (d, *J* = 4.0 Hz, 2 H), 7.05 - 6.80 (m, 3 H), 5.65 - 5.58 (m, 1 H), 4.45 - 4.30 (m, 1 H), 3.73 (d, *J*= 8.8 Hz, 2 H), 3.64 - 3.50 (m, 1 H), 3.06 - 2.99 (m, 1 H), 2.90 - 2.80 (m, 2 H), 2.56 (s, 3 H), 2.25 - 2.23 (m, 6 H), 1.75 - 1.68 (m, 4 H), 1.65 - 1.37 (m, 7 H), 1.28 (s, 3 H), 1.26 - 1.21 (m, 2 H), 1.19 (s, 3 H), 1.18 - 1.15 (m, 1 H), 1.14 - 1.05 (m, 2 H), 0.98 - 0.84 (m, 2 H).
205	961.9 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.65 (brs, 1 H), 8.05 - 7.70 (m, 3 H), 7.51 (s, 1 H), 7.41 - 7.37 (m, 1 H), 7.24 (d, J = 8.0 Hz, 1 H), 7.15 (d, *J* = 4.0 Hz, 2 H), 7.05 - 6.80 (m, 3 H), 5.65 - 5.58 (m, 1 H), 4.45 - 4.30 (m, 1 H), 3.73 (d, *J*= 8.8 Hz, 2 H), 3.64 - 3.50 (m, 1 H), 3.06 - 2.99 (m, 1 H), 2.90 - 2.80 (m, 2 H), 2.57 (s, 3 H), 2.25 - 2.23 (m, 6 H), 1.75 - 1.68 (m, 4 H), 1.65 - 1.37 (m, 7 H), 1.28 (s, 3 H), 1.26 - 1.21 (m, 2 H), 1.19 (s, 3 H), 1.16 - 1.14 (m, 1 H), 1.13 - 1.05 (m, 2 H), 0.99 - 0.84 (m, 2 H).
206	926.2 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.62 (brs, 1 H), 8.09 - 8.06 (m, 1 H), 7.69 - 7.58 (m, 2 H), 7.51 (s, 1 H), 7.42 (d, *J*= 8.8 Hz, 1 H), 7.31 - 7.25 (m, 2 H), 7.15 (d, *J*= 6.0 Hz, 2 H), 6.91 - 6.85 (m, 2 H), 6.00 (m, 1 H), 5.56 (m, 1 H), 4.45 (m, 1 H), 3.73 (d, *J*= 7.6 Hz, 2 H), 3.66 (s, 3 H), 2.90 - 2.86 (m, 1 H), 2.21 (s, 6 H), 2.13 (s, 3 H), 1.78 - 1.58 (m, 7 H), 1.53 - 1.42 (m, 5 H), 1.28 (s, 3 H), 1.19 - 1.15 (m, 7 H).
207	926.2 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.47 (brs, 1 H), 8.06 (m, 1 H), 7.67-7.57 (m, 2 H), 7.51 (s, 1 H), 7.42 (d, *J*= 8.4 Hz, 1 H), 7.31 - 7.24 (m, 2 H), 7.15 (d, *J*= 6.4 Hz, 2 H), 6.92 - 6.85 (m, 2 H), 6.01 (m, 1 H), 5.58 (m, 1 H), 4.42 (m, 1 H), 3.73 (d, *J*= 7.6 Hz, 2 H), 3.66 (s, 3 H), 2.90 - 2.84 (m, 1 H), 2.21 (s, 6 H), 2.12 (s, 3 H), 1.78-1.57 (m, 7 H), 1.53-1.43 (m, 5 H), 1.29 (s, 3 H), 1.22-1.19 (m, 7 H).
208	960.0 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.60 (brs, 1 H), 7.90 - 7.72 (m, 3 H), 7.51 (s, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 7.20 - 7.08 (m, 3 H), 7.00 - 6.85 (m, 2 H), 5.75 - 5.60 (m, 1 H), 4.50 - 4.47 (m, 1 H), 3.80 - 3.70 (m, 3 H), 3.08 - 2.81 (m, 6 H), 2.24 - 2.20 (m, 6 H), 1.90 - 1.51 (m, 8 H), 1.47 - 1.38 (m, 2 H), 1.30 - 1.20 (m, 10 H), 1.12 - 1.05 (m, 4 H), 0.95 - 0.85 (m, 2 H).

Compound No.	LC-MS: m/z	^{1}H NMR
209	972.5 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.68 (brs, 1 H), 7.88 - 7.78 (m, 3 H), 7.53 (s, 1 H), 7.41 (d, J = 8.0 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 1 H), 7.20 - 7.10 (m, 3 H), 7.00 - 6.85 (m, 2 H), 5.75 - 5.60 (m, 1 H), 4.45 - 4.30 (m, 1 H), 3.82 - 3.46 (m, 3 H), 3.08 - 2.99 (m, 2 H), 2.90 - 2.80 (m, 2 H), 2.42 - 2.33 (m, 1 H), 2.25 - 2.23 (m, 6 H), 1.85 - 1.38 (m, 10 H), 1.31 - 1.20 (m, 10 H), 1.14 - 1.08 (m, 1H), 0.95 - 0.85 (m, 2 H), 0.48 - 0.35 (m, 3 H), 0.30 - 0.25 (m, 1 H).
210	970.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.64 (brs, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.52 - 7.48 (m, 2 H), 7.43 (d, J = 8.0 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.16 (d, J = 6.0 Hz, 2 H), 7.03 (s, 1 H), 6.88 (m, 2 H), 6.14 (s, 1 H), 5.72 - 5.60 (m, 1 H), 4.45 - 4.30 (m, 1 H), 3.74 (d, J= 7.6 Hz, 2 H), 3.60 - 3.56 (m, 1 H), 3.32 - 3.29 (m, 1 H), 2.90 - 2.87 (m, 1 H), 2.25 (s, 6 H), 2.20 (s, 3 H), 1.85 - 1.80 (m, 4 H), 1.74 - 1.70 (m, 3 H), 1.63 - 1.62 (m, 2 H), 1.51 - 1.35 (m, 4 H), 1.29 (m, 4 H), 1.25 - 1.10 (m, 7 H), 1.03 - 1.00 (m, 1 H).
211	970.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.63 (brs, 1 H), 7.90 (m, 1 H), 7.52 - 7.48 (m, 2 H), 7.43 (d, J = 8.4 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.16 (d, J = 6.0 Hz, 2 H), 7.04 (s, 1 H), 6.88 (m, 2 H), 6.14 (s, 1 H), 5.72 - 5.60 (m, 1 H), 4.45 - 4.30 (m, 1 H), 3.74 (d, J= 7.6 Hz, 2 H), 3.60 - 3.56 (m, 1 H), 3.32 - 3.29 (m, 1 H), 2.90 - 2.87 (m, 1 H), 2.25 (s, 6 H), 2.20 (s, 3 H), 1.85 - 1.80 (m, 4 H), 1.75 - 1.72 (m, 4 H), 1.63 - 1.62 (m, 3 H), 1.51 - 1.35 (m, 4 H), 1.29 (m, 4 H), 1.25 - 1.10 (m, 7 H), 1.04 - 1.01 (m, 1 H).
212	954.9 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.59 (brs, 1 H), 7.78 (m, 2 H), 7.68 (m, 1 H), 7.52 (s, 1H), 7.43 (d, J = 8.4 Hz, 1 H), 7.32 (s, 1H), 7.26 (d, J = 7.2 Hz, 1 H), 7.16 (d, J = 6.0 Hz, 2 H), 6.92 (m, 1 H), 6.86 (m, 2 H), 5.72 - 5.60 (m, 1 H), 4.45 - 4.30 (m, 1 H), 3.75 (d, J= 7.6 Hz, 2 H), 3.60 - 3.54 (m, 1 H), 3.26 - 3.19 (m, 2 H), 2.91 - 2.76 (m, 3 H), 2.22 (s, 6 H), 2.04 (m, 1 H), 1.75 - 1.67 (m, 5 H), 1.66 - 1.62 (m, 2 H), 1.57 - 1.51 (m, 2H), 1.42 (m, 3 H), 1.29 - 1.27 (m, 4 H), 1.20 - 1.15 (m, 8 H), 1.04 - 1.01 (m, 2 H), 0.94 - 0.90 (m, 1 H).

Compound No.	LC-MS: m/z	^{1}H NMR
213	954.9 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.61 (brs, 1 H), 7.79 (m, 2 H), 7.68 (m, 1 H), 7.52 (s, 1H), 7.43 (d, J = 8.4 Hz, 1 H), 7.32 (s, 1H), 7.26 (d, J = 7.2 Hz, 1 H), 7.16 (d, J = 6.0 Hz, 2 H), 6.91 (m, 1 H), 6.86 (m, 2 H), 5.72 - 5.60 (m, 1 H), 4.45 - 4.30 (m, 1 H), 3.74 (d, J= 7.6 Hz, 2 H), 3.60 - 3.54 (m, 1 H), 3.26 - 3.17 (m, 2 H), 2.89 - 2.79 (m, 3 H), 2.22 (s, 6 H), 2.04 (m, 1 H), 1.75 - 1.67 (m, 5 H), 1.65 - 1.61 (m, 2 H), 1.57 - 1.51 (m, 2H), 1.42 (m, 3 H), 1.29 - 1.27 (m, 4 H), 1.20 - 1.15 (m, 8 H), 1.05 - 1.03 (m, 2 H), 0.93 - 0.90 (m, 1 H).
214	980.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.64 (brs, 1 H), 7.89 - 7.81 (m, 2 H), 7.53 (s, 1H), 7.42 (d, J = 8.0 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.16 - 7.15 (m, 3 H), 6.97 - 6.92 (m, 2 H), 5.70 - 5.60 (m, 1 H), 4.40 - 4.30 (m, 1 H), 3.73 (d, J= 7.6 Hz, 2 H), 3.60 - 3.54 (m, 1 H), 3.26 - 3.10 (m, 3 H), 2.89 - 2.81 (m, 1 H), 2.54 (s, 3 H), 2.25 (s, 6 H), 1.75 - 1.65 (m, 4 H), 1.65 - 1.47 (m, 6 H), 1.37 - 1.33 (m, 2 H), 1.30 (m, 3 H), 1.29 - 1.27 (m, 6 H), 1.00 - 0.96 (m, 1 H), 0.86 - 0.84 (m, 1 H).
215	980.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.63 (brs, 1 H), 7.87 - 7.79 (m, 2 H), 7.51 (s, 1H), 7.41 (d, J = 8.0 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.14 - 7.13 (m, 3 H), 6.96 - 6.89 (m, 2 H), 5.70 - 5.60 (m, 1 H), 4.40 - 4.30 (m, 1 H), 3.73 (d, J= 7.6 Hz, 2 H), 3.60 - 3.54 (m, 1 H), 3.26 - 3.10 (m, 3 H), 2.89 - 2.81 (m, 1 H), 2.54 (s, 3 H), 2.25 (s, 6 H), 1.73 - 1.63 (m, 4 H), 1.61 - 1.45 (m, 6 H), 1.37 - 1.33 (m, 2 H), 1.31 (m, 3 H), 1.29 - 1.27 (m, 6 H), 1.00 - 0.95 (m, 1 H), 0.86 - 0.84 (m, 1 H).
216	948.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.64 (brs, 1 H), 7.81 - 7.77 (m, 1 H), 7.60 - 7.52 (m, 1H), 7.42 (d, J = 8.4 Hz, 1 H), 7.26 (d, J = 8.8 Hz, 1 H), 7.17 (d, J = 6.0 Hz, 2 H), 7.00 (m, 1 H), 6.86 - 6.80 (m, 2 H), 5.70 - 5.60 (m, 1 H), 4.40 - 4.30 (m, 1 H), 3.73 (d, J= 7.6 Hz, 2 H), 3.60 - 3.54 (m, 1 H), 3.31 - 3.25 (m, 2 H), 3.10 - 3.05 (m, 1H), 2.89 - 2.81 (m, 1 H), 2.85 (m, 1 H), 2.58 (s, 3 H), 2.56 (s, 3 H), 2.25 (d, J = 1.6 Hz, 6 H), 1.75 - 1.70 (m, 4 H), 1.64 - 1.61 (m, 3 H), 1.45 (m, 3 H), 1.30 (s, 3 H), 1.20 – 1.13 (m, 9 H).

Compound No.	LC-MS: m/z	^{1}H NMR
217	972.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.76 (m, 2 H), 7.55 - 7.50 (m, 1H), 7.42 (d, J = 8.0 Hz, 1 H), 7.28 - 7.22 (m, 3 H), 7.01 - 7.00 (m, 2 H), 6.92 (m, 1 H), 6.79 (m, 1 H), 5.70 - 5.60 (m, 1 H), 4.40 - 4.30 (m, 1 H), 3.73 (d, J= 7.6 Hz, 2 H), 3.54 - 3.44 (m, 1 H), 2.85 - 2.83 (m, 2 H), 2.63 (s, 3 H), 2.57 (s, 3 H), 1.74 - 1.69 (m, 4 H), 1.64 - 1.55 (m, 4 H), 1.40 (m, 3 H), 1.31 - 1.30 (m, 5 H), 1.27 - 1.15 (m, 7 H), 1.00 - 0.98 (m, 2 H), 0.92 - 0.90 (m, 1 H), 0.85 - 0.80 (m, 1 H), 0.68 - 0.65 (m, 2 H).
218	957.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.57 (brs, 1 H), 7.57 - 7.47 (m, 2 H), 7.42 (d, J = 8.4 Hz, 1 H), 7.28 (s, 1H), 7.25 (d, J = 8.8 Hz, 1 H), 7.16 (d, J = 6.0 Hz, 2 H), 7.06 - 7.02 (m, 2 H), 6.90 (m, 1 H) 6.82 (m, 1 H), 5.70 - 5.60 (m, 1 H), 4.40 - 4.30 (m, 1 H), 3.75 (d, J= 8.0 Hz, 2 H), 2.89 - 2.76 (m, 5 H), 2.61 (s, 3 H), 2.22 (s, 6 H), 1.72 - 1.51 (m, 8 H), 1.41 (m, 3 H), 1.30 - 1.27 (m, 6 H), 1.22 - 1.17 (m, 7 H), 1.06 – 1.01 (m, 1 H), 0.82 - 0.80 (m, 1 H).
219	988.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.61 (brs, 1 H), 7.79 (m, 1 H), 7.61 (m, 1 H), 7.52 (s, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.14 (s, 2 H), 7.06 (m, 1 H), 6.92 - 6.88 (m, 2 H), 5.70 - 5.60 (m, 1 H), 4.38 - 4.28 (m, 2 H), 3.72 (d, J= 7.6 Hz, 2 H), 3.58 - 3.54 (m, 1 H), 3.05 - 3.00 (m, 1H), 2.89 - 2.80 (m, 2 H), 2.58 (s, 3 H), 2.24 (d, J = 1.6 Hz, 6 H), 1.72 - 1.67 (m, 4 H), 1.63 - 1.50 (m, 6 H), 1.45 - 1.20 (m, 11 H), 1.27 - 1.18 (m, 7 H), 0.98 - 0. 96 (m, 1 H), 0.85 - 0.79 (m, 1 H).
220	988.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.62 (brs, 1 H), 7.79 (m, 1 H), 7.61 (m, 1 H), 7.51 (s, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.14 (s, 2 H), 7.07 (m, 1 H), 6.92 - 6.88 (m, 2 H), 5.70 - 5.60 (m, 1 H), 4.38 - 4.28 (m, 2 H), 3.72 (d, J= 7.6 Hz, 2 H), 3.58 - 3.54 (m, 1 H), 3.05 - 3.00 (m, 1H), 2.89 - 2.80 (m, 2 H), 2.58 (s, 3 H), 2.24 (d, J = 1.6 Hz, 6 H), 1.72 - 1.67 (m, 4 H), 1.63 - 1.50 (m, 6 H), 1.45 - 1.20 (m, 11 H), 1.27 - 1.18 (m, 7 H), 0.98 - 0. 96 (m, 1 H), 0.85 - 0.79 (m, 1 H).
221	918.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.60 (brs, 1 H), 7.77 - 7.71 (m, 3 H), 7.53 (s, 1 H), 7.44 (d, J= 8.4 Hz, 1 H), 7.28 (d, J=9.2 Hz, 1 H), 7.16 (d, J= 6.0 Hz, 2 H), 7.05 (s, 1 H), 6.88 (s, 2 H), 5.58 (m, 1 H), 4.46 (m, 1 H), 4.00 - 3.97 (d, J= 10.8 Hz, 2 H), 3.58 - 3.46 (m, 3 H), 2.91 - 2.87 (m, 3 H), 2.80 - 2.77 (m, 1 H), 2.59 (s, 3 H), 2.25 (s, 6 H), 1.76 - 1.62 (m, 7 H), 1.46 (m, 3 H), 1.27 - 1.12 (m, 4 H), 1.10 - 1.08 (m, 1 H), 1.01 - 0.91 (m, 2 H).

Compound No.	LC-MS: m/z	^{1}H NMR
222	918.3 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.59 (brs, 1 H), 7.78 - 7.75 (m, 3 H), 7.53 (s, 1 H), 7.44 (d, *J*= 8.4 Hz, 1 H), 7.28 (d, *J*= 8.8 Hz, 1 H), 7.16 (d, *J*= 6.4 Hz, 2 H), 7.05 (s, 1 H), 6.88 (s, 2 H), 5.58 (m, 1 H), 4.48 (m, 1 H), 4.00 - 3.97 (m, 2 H), 3.59 - 3.46 (m, 3 H), 2.91 - 2.87 (m, 2 H), 2.80 - 2.77 (m, 1 H), 2.60 (s, 3 H), 2.25 (s, 6 H), 1.76 - 1.72 (m, 6 H), 1.64 (m, 1 H), 1.46 (m, 3 H), 1.27 - 1.08 (m, 6 H), 1.01 - 0.91 (m, 2 H).
225	872.5 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 11.77 (brs, 1 H), 7.52 (s, 1 H), 7.43 - 7.41 (m, 2 H), 7.28 - 7.25 (m, 2 H), 7.14 (d, *J*= 6.0 Hz, 2 H), 6.98 (m, 1 H), 6.87 (m, 1 H), 6.80 - 6.74 (m, 2 H), 5.64 (m, 1 H), 4.98 (d, *J*= 17.6 Hz, 1 H), 4.52 (d, *J*= 17.2 Hz, 1 H), 4.48 - 4.36 (m, 1 H), 3.99 - 3.96 (m, 2 H), 3.55 - 3.45 (m, 6 H), 2.89 - 2.86 (m, 2 H), 2.23 (s, 6 H), 1.77 - 1.61 (m, 8 H), 1.43 (m, 3 H), 1.17 (m, 3 H).
226	930.2 $(M+H)^+$	(400 MHz, DMSO-*d*6) δ 7.60 - 7.40 (m, 4H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.20 - 7.10 (m, 5H), 6.95 - 6.80 (m, 2H), 5.62 - 5.55 (m, 1H), 4.70 (s, 1H), 4.40 - 4.35 (m, 1H), 4.00 - 3.96 (m, 2H), 3.75 - 3.73 (m, 1H), 3.67 - 3.60 (m, 1H), 3.52 - 3.45 (m, 2H), 3.11 - 3.08 (m, 3H), 2.91 - 2.85 (m, 2H), 2.24 - 2.17 (m, 9H), 1.78 - 1.64 (m, 6H), 1.45 - 1.40 (m, 2H), 1.32 - 1.24 (m, 6H), 1.22 - 1.15 (m, 2H).
227	900.6 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.72 (brs, 1 H), 7.52 (s, 1 H), 7.43 - 7.40 (m, 2 H), 7.27 - 7.25 (m, 2 H), 7.14 (d, *J*= 6.4 Hz, 2 H), 6.98 (m, 1 H), 6.86 (m, 1 H), 6.81 - 6.74 (m, 2 H), 5.63 (m, 1 H), 4.98 (d, *J*= 17.6 Hz, 1 H), 4.52 (d, *J*= 17.6 Hz, 1 H), 4.41 (m, 1 H), 3.74 - 3.72 (m, 2 H), 3.47 (s, 3 H), 2.89 - 2.83 (m, 1 H), 2.23 (s, 6 H), 1.77 - 1.70 (m, 4 H), 1.65 - 1.50 (m, 4 H), 1.43 (m, 3 H), 1.29 (m, 4 H), 1.20 - 1.14 (m, 7 H).
228	914.5 $(M+H)^+$	(400 MHz, DMSO-d6) δ 7.41 (m, 2 H), 7.25 - 7.14 (m, 5 H), 6.92 - 6.72 (m, 3 H), 6.51 (m, 1 H), 5.35 (m, 1 H), 3.75 - 3.73 (m, 2 H), 3.41 - 3.38 (m, 3 H), 3.25 (m, 5 H), 2.67 (m, 3 H), 2.21 (s, 6 H), 1.76 - 1.72 (m, 4 H), 1.65 - 1.47 (m, 6 H), 1.33 - 1.16 (m, 11 H).

Compound No.	LC-MS: m/z	^{1}H NMR
229	914.5 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 7.50 (s, 1 H), 7.42 (d, *J*= 8.4 Hz, 1 H), 7.25 - 7.23 (m, 3 H), 7.14 (d, *J*= 6.4 Hz, 2 H), 6.99 (m, 1 H), 6.67 (m ,3 H), 5.55 (m, 1 H), 4.44 (m, 1 H), 3.75 - 3.73 (m, 2 H), 3.39 (m, 1 H), 3.38 (m, 2 H), 3.25 (m, 4 H), 3.01 (m, 1 H), 2.90-2.80 (m, 2 H), 2.22 (d, *J*= 1.2 Hz, 6 H), 1.77 - 1.70 (m, 4 H), 1.64 - 1.41 (m, 6 H), 1.29 (m, 4 H), 1.20 (m, 7 H)
230	912.6 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 7.80 - 7.51 (m, 4 H), 7.42 (d, *J*= 8.4 Hz, 1 H), 7.25 (d, *J*= 8.4 Hz, 1 H), 7.15 - 7.07 (m, 5 H), 6.83 - 6.80 (m, 2 H), 5.55 (m, 1 H), 4.45 (m, 1 H), 3.74 - 3.72 (m, 2 H), 3.57 (m, 1 H), 3.49 (s, 3 H), 3.01 - 2.84 (m, 2 H), 2.22 (d, *J*= 2.0 Hz, 6 H), 1.72 - 1.69 (m, 4 H), 1.63 - 1.54 (m, 3 H), 1.51 - 1.44 (m, 3 H), 1.29 (m, 4 H), 1.20 - 1.13 (m, 6 H).
231	912.6 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 7.80 - 7.51 (m, 4 H), 7.42 (d, *J*= 8.4 Hz, 1 H), 7.25 (d, *J*= 8.4 Hz, 1 H), 7.15 - 7.07 (m, 5 H), 6.83 - 6.80 (m, 2 H), 5.55 (m, 1 H), 4.45 (m, 1 H), 3.74 - 3.72 (m, 2 H), 3.57 (m, 1 H), 3.49 (s, 3 H), 3.01 - 2.84 (m, 2 H), 2.22 (d, *J*= 2.0 Hz, 6 H), 1.72 - 1.69 (m, 4 H), 1.63 - 1.54 (m, 3 H), 1.51 - 1.44 (m, 3 H), 1.29 (m, 4 H), 1.20 - 1.13 (m, 6 H).
232	976.4 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 7.49 (s, 1H), 7.42 - 7.38 (m, 1H), 7.33 - 7.19 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.02 - 6.95 (m, 1H), 6.89 - 6.75 (m, 3H), 5.65 - 5.55 (m, 1H), 4.85 - 4.74 (m, 1H), 4.01 - 3.97 (m, 2H), 3.55 - 3.40 (m, 3H), 2.97 - 2.80 (m, 3H), 2.66 (s, 3H), 2.24 - 2.10 (m, 14H), 1.85 - 1.55 (m, 8H), 1.48 - 1.32 (m, 4H), 1.26 - 1.05 (m, 5H)
233	976.4 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 7.49 (s, 1H), 7.42 - 7.35 (m, 1H), 7.33 - 7.19 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.02 - 6.95 (m, 1H), 6.89 - 6.75 (m, 3H), 5.65 - 5.55 (m, 1H), 4.85 - 4.74 (m, 1H), 4.01 - 3.90 (m, 2H), 3.65 - 3.40 (m, 3H), 2.97 - 2.80 (m, 3H), 2.64 (s, 3H), 2.24 - 2.10 (m, 14H), 1.85 - 1.55 (m, 8H), 1.48 - 1.32 (m, 4H), 1.26 - 1.05 (m, 5H).
234	994.2 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 11.68 (s, 1H), 7.80 - 7.65 (m, 2H), 7.49 (s, 1H), 7.42 - 7.38 (m, 1H), 7.37 - 7.19 (m, 3H), 7.15 - 7.10 (m, 3H), 7.02 - 6.80 (m, 2H), 5.65 - 5.55 (m, 1H), 4.90 - 4.80 (m, 1H), 4.50 - 4.20 (m, 1H), 4.01 - 3.90 (m, 2H), 3.65 - 3.40 (m, 3H), 2.92 - 2.80 (m, 3H), 2.66 (s, 3H), 2.24 - 2.10 (m, 11H), 1.90 - 1.55 (m, 8H), 1.50 - 1.10 (m, 8H).

Compound No.	LC-MS: m/z	^{1}H NMR
235	994.2 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 11.68 (s, 1H), 7.80 - 7.60 (m, 2H), 7.49 (s, 1H), 7.45 - 7.30 (m, 3H), 7.26 - 7.19 (m, 2H), 7.13 (d, J =8.0 Hz, 2H), 6.95 - 6.75 (m, 2H), 5.70 - 5.55 (m, 1H), 4.90 - 4.85 (m, 1H), 4.50 - 4.25 (m, 1H), 4.00 - 3.90 (m, 2H), 3.65 - 3.40 (m, 3H), 2.95 - 2.80 (m, 3H), 2.64 (s, 3H), 2.30 - 2.10 (m, 11H), 1.90 - 1.55 (m, 8H), 1.50 - 1.00 (m, 8H).
236	1012.4 $(M+H)^+$	(400 MHz, DMSO-*d6*) δ 11.61 (s, 1H), 7.51 (s, 1H), 7.45 - 7.30 (m, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.20 - 7.07 (m, 4H), 7.05 - 6.75 (m, 3H), 5.65 - 5.50 (m, 1H), 4.80 - 4.65 (m, 1H), 4.45 - 4.30 (m, 1H), 3.75 - 3.70 (m, 2H), 3.65 - 3.45 (m, 1H), 3.30 - 3.20 (m, 3H), 3.05 - 2.99 (m, 1H), 2.96 - 2.83 (m, 1H), 2.66 (s, 3H), 2.30 - 2.10 (m, 12H), 1.85 - 1.65 (m, 4H),1.64 - 1.50 (m, 3H), 1.45 - 1.33 (m, 3H), 1.30 - 1.25 (m, 4H), 1.20 - 1.10 (m, 6H), 0.98 - 0.90 (m, 2H), 0.70 - 0.55 (m, 2H).
237	1012.4 $(M+H)^+$	(400 MHz, DMSO-d6) δ 11.63 (s, 1H), 7.51 (s, 1H), 7.45 - 7.30 (m, 2H), 7.25 (dd, J_1 = 8.0, J_2= 2.0 Hz, 1H), 7.20 - 7.00 (m, 5H), 6.95 - 6.75 (m, 2H), 5.65 - 5.50 (m, 1H), 4.80 - 4.70 (m, 1H), 4.45 - 4.30 (m, 1H), 3.75 - 3.70 (m, 2H), 3.65 - 3.45 (m, 1H), 3.30 - 3.20 (m, 3H), 3.05 - 2.99 (m, 1H), 2.96 - 2.83 (m, 1H), 2.64 (s, 3H), 2.30 - 2.10 (m, 12H), 1.85 - 1.65 (m, 4H),1.64 - 1.50 (m, 3H), 1.45 - 1.33 (m, 3H), 1.30 - 1.25 (m, 4H), 1.20 - 1.10 (m, 6H), 0.98 - 0.90 (m, 2H), 0.70 - 0.55 (m, 2H).
238	488.4 $(1/2M+H)^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H), 7.52 (s, 1H), 7.48-7.37 (m, 2H), 7.25 (d, J = 7.2 Hz, 1H), 7.29-7.21 (m, 2H), 7.03-6.66 (m, 5H), 5.54 (s, 1H), 4.44 (s, 1H), 3.79-3.68 (d, J = 7.2 Hz, 2H), 3.56 (s, 1H), 3.18-3.05 (m, 5H), 2.93-2.77 (m, 2H), 2.64 (s, 3H), 2.30-2.20 (d, J = 1.6 Hz, 6H), 1.90-1.38 (m, 10H), 1.33-1.05 (m, 11H), 0.98- 0.81 (m, 2H).

[1496] BIOLOGICAL EXAMPLES

[1497] cAMP Assays

[1498] Activation of GLP-1 receptor is known to stimulate cyclic AMP (cAMP) production in cells which indicates primary coupling to the G αs subunit of the G pro tein heterotrimeric complex. Evidence suggests signaling through G α s induced cAMP stimulation elicits the desired pharmacological response regarding ins ulin release from pancreatic β-cells.

[1499] To optimize functional activity directed toward G αs coupling, a HEK293/CRE-Luc cell line developed by HDB stably expressing the GLP-1 Receptor was us ed. 200× concentration of compound working solutions were prepared (Agilent Tech nologies Bravo) with 1/2 log serial dilution in 384-well Echo LDV pla te (Labcyte, Cat#LP-0200) . 50 nL/well 200× concentration of compound w

orking solutions were moved to 384-well white low volume plate (Grein er, Cat#784075) using Labcyte ECHO550.1×10 5 cells/mL HEK293/GLP1R/ CRE-LUC (HD Biosciences) cell suspensions prepared with assay buffer (DP BS containing 0.5 mM IBMX (Sigma, Cat#I5879) and 0.1%BSA (GENVIEW, C at#FA016-100g)) , 10 uL cell suspensions were added to each well of previous generated assay plate which already contains 50 nl compound at 200× concentration using ThermoFisher Multidrop Combi (1000 cells/well) . Seal the plate a nd incubate at 37 ℃ with 5%CO_2 for 30 min.

[1500] After incubation the cAMP assay signal was generated using cAMP dyna mic 2 Kit (Cisbio) . 5μL cAMP-d2 working solution was added to each well, followe d with 5μL Anti-cAMP antibody-cryptate working solution added to each well using ThermoFisher Multidrop Combi. Incubate at room temperature for 1 hou r protected from light. Read the fluorescence at 665 and 615 nm with Reader PerkinElmer EnVision.

[1501] %Activity = 100%x (mean RLU of test sample –mean RLU of vehicle cont rol) / (mean RLU of MAX control -mean RLU of vehicle control)

[1502] Table 3 shows the biological activity of compounds in GLP-1R agonist cAMP s timulation assay (EC_{50}, nM) .

[1503] Table 3

Compound No.	EC_{50} (nM)
101	0.067
102	0.17
103	0.14
105	0.009
106	0.67
107	0.46
108	0.013
109	0.27
110	0.028
111	0.014
112	0.057
113	0.035
114	0.017
115	0.049
116	0.049

Compound No.	EC_{50} (nM)
117	0.011
118	0.04
119	1
121	0.019
122	0.046
123	0.071
124	0.01
130	0.23
131	0.05
132	0.98
134	0.0051
135	0.001
136	0.047
137	0.15
138	0.001

Compound No.	EC_{50} (nM)
139	0.062
140	0.099
141	0.022
142	0.045
143	0.019
144	0.017
147	0.12
148	0.12
149	0.023
150	0.11
151	0.072
152	0.6
155	0.99
156	1.5
157	1.5

Compound No.	EC_{50} (nM)
158	2.5
159	5.9
160	2.8
161	5.5
162	3.2
163	20
164	0.024
165	9.9
166	0.019
167	0.12
168	0.011
169	0.07
170	1.8
171	8.8
172	0.037
173	0.012
174	0.067
175	0.025
176	0.024
177	0.026
178	0.094
179	0.21
180	0.034
181	0.018
182	0.077
183	0.001
184	0.01
185	0.016

Compound No.	EC_{50} (nM)
186	0.0047
187	0.01
188	0.017
189	0.047
190	0.026
191	0.0096
192	0.02
193	0.1
194	0.046
195	0.018
196	0.039
197	0.018
198	0.023
199	0.01
200	0.01
201	0.011
202	0.018
203	0.032
204	0.039
205	0.072
206	0.02
207	0.02
208	0.11
209	0.22
210	0.067
211	0.041
212	0.038
213	0.12

Compound No.	EC_{50} (nM)
214	0.033
215	0.074
216	0.065
217	0.2
218	0.083
219	0.193
220	0.134
221	0.030
222	0.084
225	0.028
226	0.025
227	0.015
228	0.34
229	0.042
230	0.048
231	0.014
232	0.037
233	0.028
234	0.058
235	0.057
236	0.053
237	0.07
238	0.11

[1504] Certain compounds were tested in the assays as described below. As shown by the data presented below, certain compounds of the present disclsoure exhibit one or more improved properties, such as increased half-life (t1/2) , enhanced potency, improved permeability/reduced efflux ratio, increased exposure, and/or improved solubility (Tables 4, 5A and 5B) . Compounds C-1, C-2, C-3, C-4, C-5, and C-6 were synthesized according to literature procedures (see, e.g., WO 2022/048665, WO2022/017388, and WO2018/056453) .

[1505] Caco-2 study protocol:

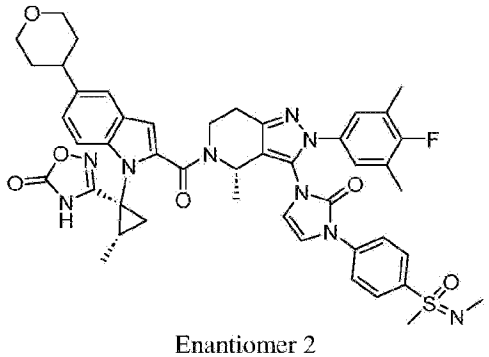
[1506] Incubations with Caco-2 cell monolayers were performed in duplicate in a 96-well Transwell plate. Transport buffer solution (HBSS, 10 mM HEPES, pH 7.4, with 0.5%BSA) containing test article (10 μM) , and either the control compou nds metoprolol (10 μM) , cimetidine (10 μM) and erythromycin (10 μM) , was added to appropriate donor wells of the apical or basolateral plate. The trans port buffer with DMSO was added to appropriate wells of receiver wel ls. Following incubation at 37°C for 2 hours, the cell plates were removed and 50 μL s amples from both apical and basolateral sides were transferred into new 96-well plates. Subsequently, 200 μL of acetonitrile containing internal standard was ad ded to all samples to precipitate protein prior to analysis by UPLC-MS/MS. Lucifer ye llow was used as a marker to confirm the integrity of the cell monolayers after 2 hou rs incubation.

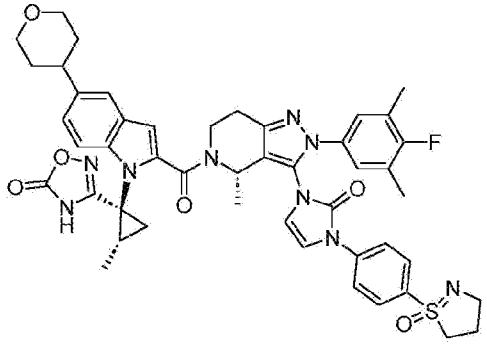
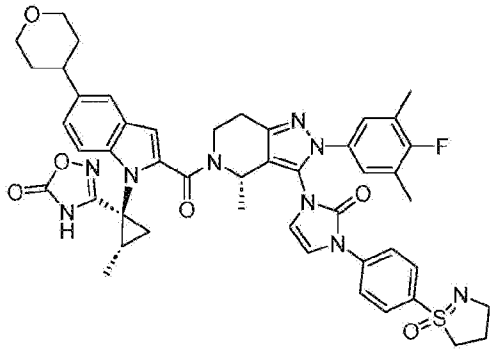
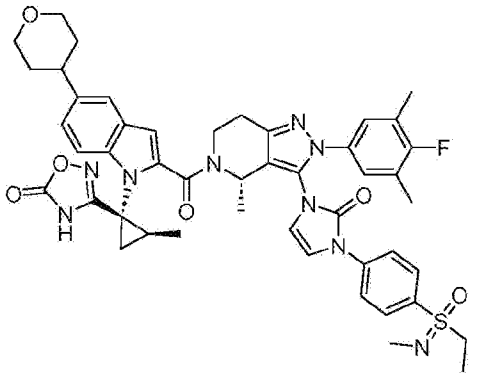
[1507] FaSSIF solubility protocol:

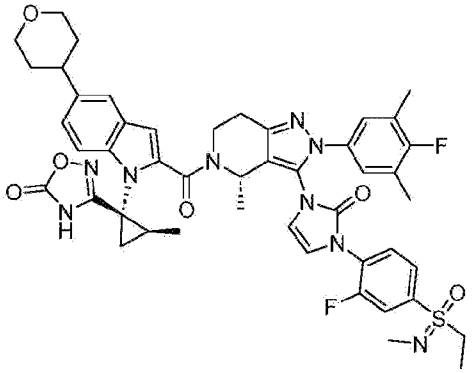
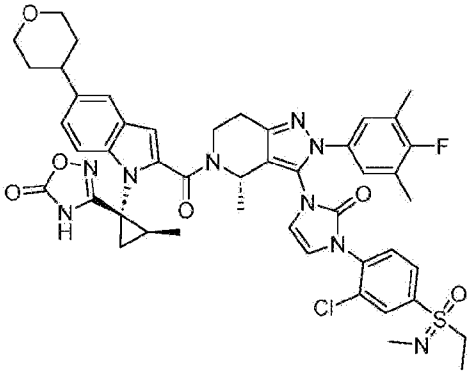
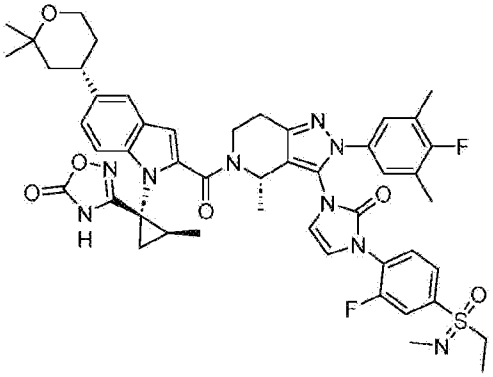
[1508] Stock solution of test article and control compound (chlorpromazine, astemizole, and phenytoin) were prepared in DMSO at 10 mM. 50 μL ea ch of stock solutions were dried down, followed by reconstitution to 1 mM with FaSSIF buffer in the well. The incubation plate was shake d at 25°C, 1, 100 rpm for 4 hours. And then, the samples were filtered by using the va cuum manifold. 10 μL aliquots from each well was transferred to a new 96-well plate and adjust the volume to 80 μLwith blank buffer. Using a mixture of H $_2$O and acetonitrile containing internal standard (1: 1) to dilute the sample 100-fold, 500-fold and 2, 500-fold. The samples are evaluated by LC/MS/MS analysi s. All compounds were tested in singlet.

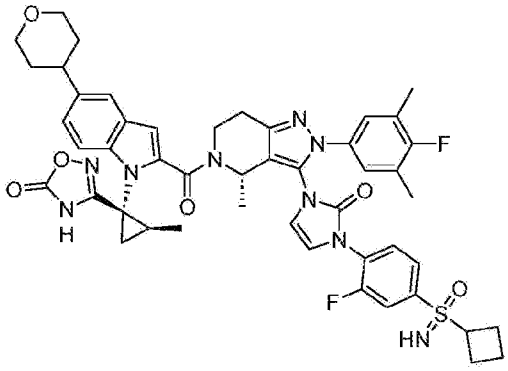
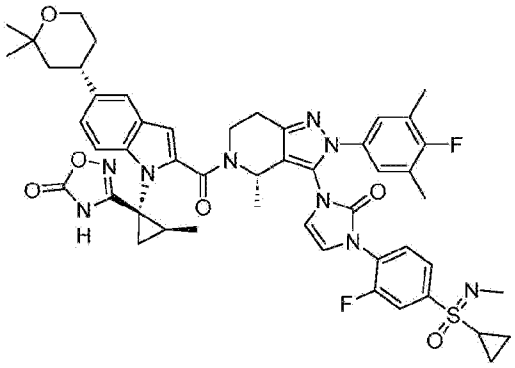
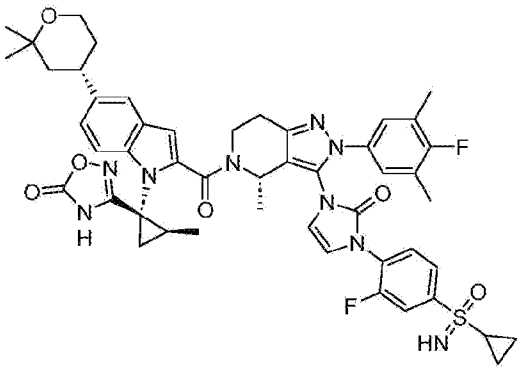
[1509] Data for select compounds are shown in Table 4.

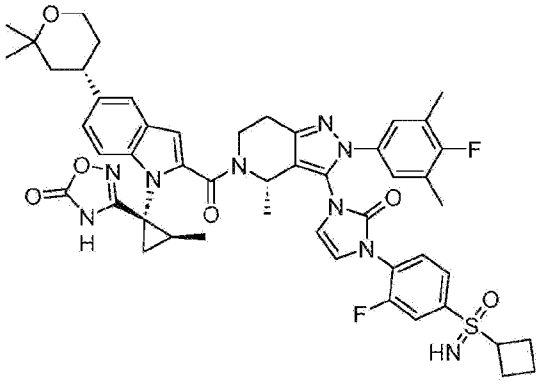
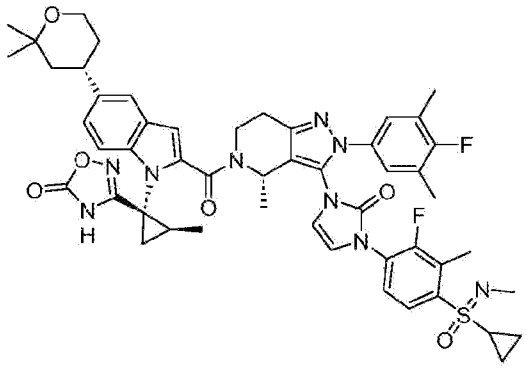
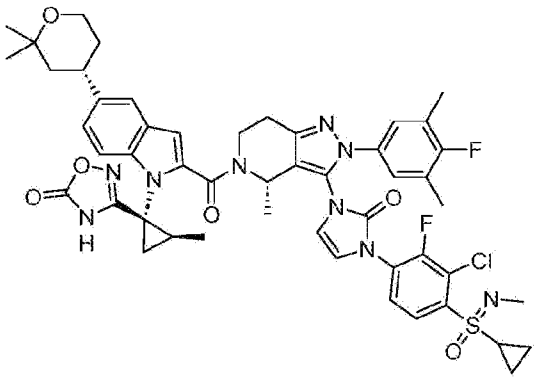
[1510] Table 4

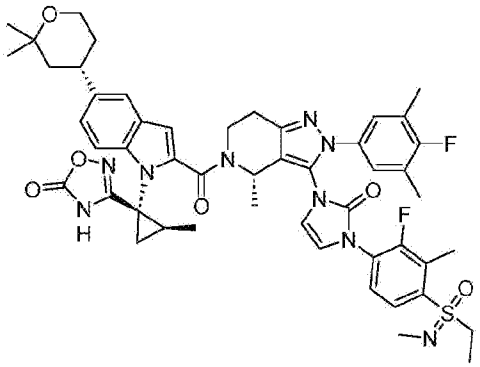
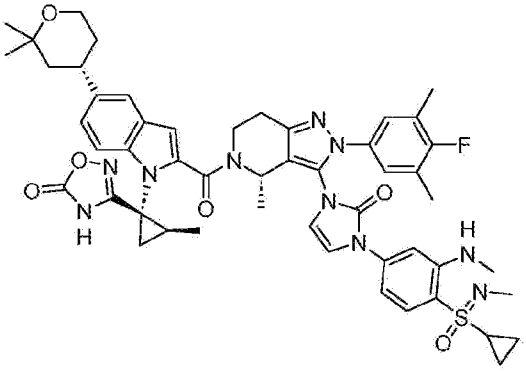
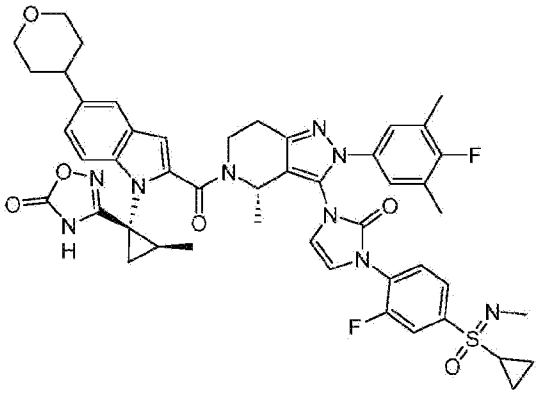
Compound No.	Structure	Data
121	 Enantiomer 2	EC_{50}: 15 pM Caco-2 Perm (nm/s): 1.0 Efflux: 90.8 Solubility (FaSSIF, μM): 7.3

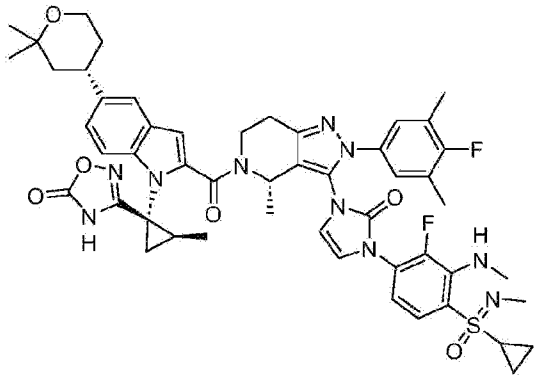
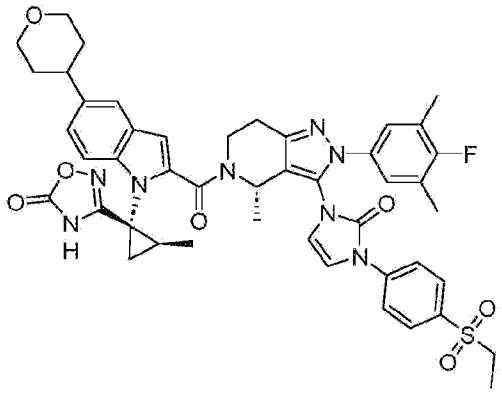
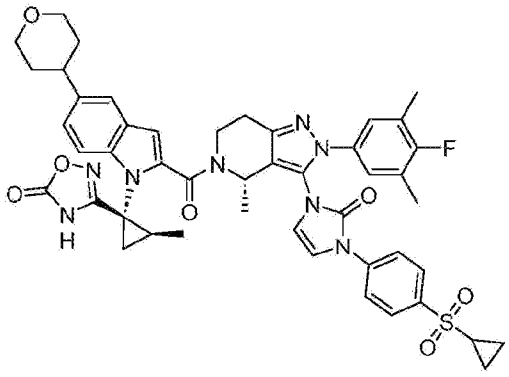
Compound No.	Structure	Data
142	 Enantiomer 1	EC_{50}: 63 pM Caco-2 Perm (nm/s): <0.5 Efflux: >156.2 Solubility (FaSSIF, μM): 8.07
143	 Enantiomer 2	EC_{50}: 19 pM Caco-2 Perm (nm/s): 1.2 Efflux: 99.3 Solubility (FaSSIF, μM): 4.98
144	 Single unknown enantiomer	EC_{50}: 17 pM Caco-2 Perm (nm/s): 3.6 Efflux: 24.1 Solubility (FaSSIF, μM): 2.56

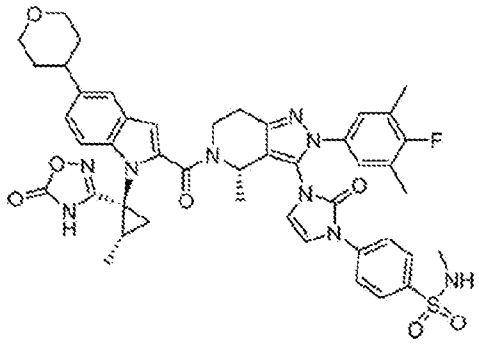
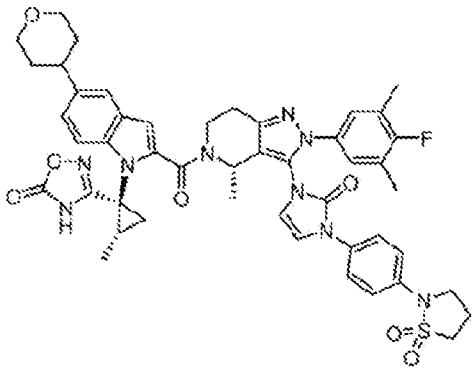
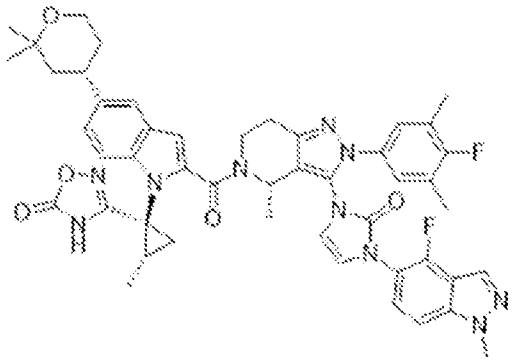
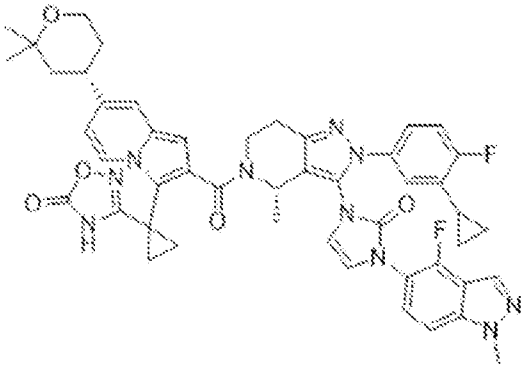
Compound No.	Structure	Data
149	 Enantiomer 1	EC_{50}: 23 pM Caco-2 Perm (nm/s): 3.3 Efflux: 26 Solubility (FaSSIF, μM): 2.04
151	 Enantiomer 1	EC_{50}: 72 pM Caco-2 Perm (nm/s): 3.0 Efflux: 36.8
164	 Single unknown enantiomer	EC_{50}: 24 pM Caco-2 Perm (nm/s): 6.2 Efflux: 5.5 Solubility (FaSSIF, μM): 8.9

Compound No.	Structure	Data
168	 Enantiomer 1	EC_{50}: 11 pM Caco-2 Perm (nm/s): 2.1 Efflux: 50
180	 Single unknown enantiomer	EC_{50}: 30 pM Caco-2 Perm (nm/s): 6.1 Efflux: 5.4 Solubility (FaSSIF, μM): 30
181	 Single unknown enantiomer	EC_{50}: 14 pM Caco-2 Perm (nm/s): 2.4 Efflux: 38

Compound No.	Structure	Data
183	 Single unknown enantiomer	EC_{50}: 11 pM Caco-2 Perm (nm/s): 1.9 Efflux: 45
195	 Enantiomer 1	EC_{50}: 18 pM Caco-2 Perm (nm/s): 2.2 Efflux: 12 Solubility (FaSSIF, μM): 7.2
214	 Enantiomer 1	EC_{50}: 33 pM Caco-2 Perm (nm/s): 3.4 Efflux: 11.4 Solubility (FaSSIF, μM): 9.9

Compound No.	Structure	Data
216	 Single unknown enantiomer	EC_{50}: 68 pM Caco-2 Perm (nm/s): 3.2 Efflux: 15.7 Solubility (FaSSIF, μM): 7.9
218	 Single unknown enantiomer	EC_{50}: 59 pM Caco-2 Perm (nm/s): 0.9 Efflux: 20.7
221	 Enantiomer 1	EC_{50}: 31 pM Caco-2 Perm (nm/s): 3.4 Efflux: 38.5 Solubility (FaSSIF, μM): 4.05

Compound No.	Structure	Data
238	 Single unknown enantiomer	EC_{50} 110 pM Caco-2 Perm (nm/s): 1.9 Efflux: 9.8 Solubility (FaSSIF, μM): 26
C-1		EC_{50}: 22 pM Caco-2 Perm (nm/s): 1.26 Efflux: 51.7 Solubility (FaSSIF, μM): 4.0
C-2		EC_{50}: 43 pM Caco-2 Perm (nm/s): <0.5 Efflux: >62.6 Solubility (FaSSIF, μM): 9.3

Compound No.	Structure	Data
C-3		EC_{50}: 81 pM Caco-2 Perm (nm/s): 0.5 Efflux: 78.1 Solubility (FaSSIF, μM): 6.45
C-4		EC_{50}: 140 pM Caco-2 Perm (nm/s): 1.8 Efflux: 16.7 Solubility (FaSSIF, μM): 5.38
C-5		EC_{50}: 33 pM (n=12) Caco-2 Perm (nm/s): 2.1 Efflux: 7.4 Solubility (FaSSIF, μM): 0.4
C-6		EC_{50}: 67.5 pM (n=6) Caco-2 Perm (nm/s): 1.6 Efflux: 26 Solubility (FaSSIF, μM): 4.5

[1511] Rat IV/PO PK study protocol, Method A:

[1512] Pharmacokinetics (PK) study was conducted on male Sprague Dawley (SD) rats by two delivery routes intravenous (IV) and/or oral gavage (PO) . Rats in IV r oute (n=3) were free access to food and water. Rats in PO route (n=3) were fasted ove rnight and fed at 4 hrs post dosing. Test article was formulated in solution (10%solu tol HS 15 in saline) for IV route and solution or suspension (10%solutol HS 15 in sal ine/water) for PO route, respectively. On the day of experiment, test article was adm inistered via vein (e.g. foot dorsal vein) injection (commonly at 1 mg/kg and 5 mL/ kg) for IV route or via oral gavage (commonly at 2 or 5 mg/kg and 5 mL/ kg) for PO route, respectively. Blood samples were collected via serial bleeding at ~8 time points from 0.083 to 24 hrs post dose. Approximate 150 μL of blood/time point was collected into K_2EDTA tube via tail vein or jugular vein. Blood samples were put on wet ice and centrifuged to obtain plasma samples and plasma samples were submitted to LC-MS/MS for sample analysis. Pharmac okinetics parameters, including elimination half life ($t_{1/2}$) (IV) , area und er the curve (AUC) and oral bioavailability (F%) , etc. were calculated by non-compartmental model using WinNonlin.

[1513] Data for select compounds are shown in Table 5A.

[1514] Table 5A

Compound No.	Bioavailablility (%F)	$t_{1/2}$ (hr)	AUC (ng.h/mL)_free form/dose
C-5	36%	8.1	4,398/2 mpk
C-6	47%	3.1	4,276/5 mpk
149	32%	1.6	4,276/5 mpk
180	28%	3.0	4,954/5 mpk
181	30%	1.66	6,097/5 mpk
164	29.4%	2.4	6,094/5 mpk
195	14%	4.3	9,545/5 mpk
238	25.5%	4.78	4,997/5 mpk

[1515] Rat PO PK study protocol, Method B:

[1516] Pharmacokinetics (PK) study was conducted on male Sprague Dawley (SD) rats by oral gavage (PO) . Rats in PO route (n=3) were free access to food and wate r. Test article was formulated in solution or suspension (10%solutol HS 15 in saline/ water) . On the day of experiment, test article was administered via oral gavage

(commonly at 10, 30, or 100 mg/kg, with dose volume as 10 mL/kg) .

Blood samples were collected via serial bleeding at ~8 time points from 0.25 to 24 hrs post dose. Approximate 150 μL of blood/time point was collected into K_2 EDTA tube via tail vein or jugular vein. Blood samples were put on wet ice and centrifuged to obtain plasma samples and plasma samples were submitted to LC-MS/MS for sample analysis. Pharmacokinetics parameters, including C_{max}, and area under the curve (AUC) , etc. were calculated by non-compartmental model using WinNonlin.

[1517] Data for select compounds are shown in Table 5B.

[1518] Table 5B

Compound No.	Dose (mg/kg)	Cmax (ng/mL)	AUC (ng.h/mL)
C-5	2*	573	4,398
	10	1,250	14,491
	30	1,012	13,023
C-6	5*	744	4,276
	30	7,543	58,799
	100	7,480	86,039
164	5*	1,880	9,545
	30#	5,403	66,166
	100#	11,200	172,912
180	5*	1,793	6,097
	30	8,340	97,026
	100	13,267	166,937
195	5*	774	4,997
	30	3,907	51,065
	100	7,690	102,420

Compound No.	Dose (mg/kg)	Cmax (ng/mL)	AUC (ng.h/mL)
238	5*	1,065	7,426
	30#	4,713	67,518
	100#	8,677	124,394

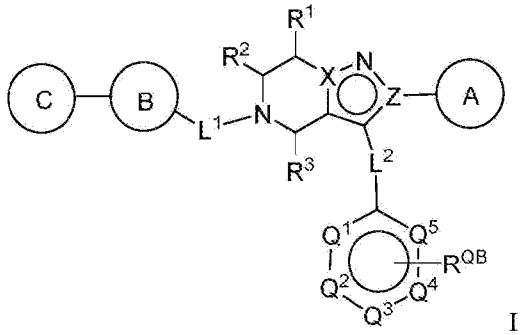
*obtained under method 3A

#used 20%solutol HS 15 in water

[1519] Under the same formulation using free form of the compounds, the rat PK exposure of C-5 is plateaued at 10 mg/kg, while C-7 is less proportional to dose from 30 to 100 mg/kg. In contrast, compounds 164, 180, 195 and 238 demonstrate good rat PK dose proportionality from 5 to 100 mg/kg and achieve higher exposure than C-5 and C-6.

Claims

[Claim 1] A compound of Formula I:



I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

X is C and Z is N, or X is N and Z is C;

Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2, Q^3, and Q^4 are each independently N, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, and Q^4 is CR^{QB}; or

Q^1 is a bond; and Q^2, Q^3, Q^4, and Q^5 are each independently O, S, N, NH, NR^c, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, Q^4, and Q^5 is CR^{QB};

provided that the ring including Q^1-Q^5 is aromatic;

R^{QB} is –S (O) (=NR^a) R^b, – (CR^iR^j) $_n$–S (O) (=NR^a) R^b, –N=S (O) (R^{1a}) R^b, or –O– (CR^iR^j) $_n$–S (O) (=NR^a) R^b;

R^{1a} is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C

$_{3-6}$ cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

or R^a and R^b taken together with the atoms to which each is att ached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

n is 1, 2, 3, 4, 5, or 6;

each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

or R^a and R^i, or R^b and R^i, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein s aid heterocyclyl is optionally substituted with 1-3 independently s elected C_{1-6} alkyl;

each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

or one R^i and one R^j, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

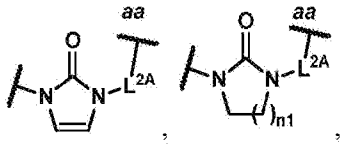
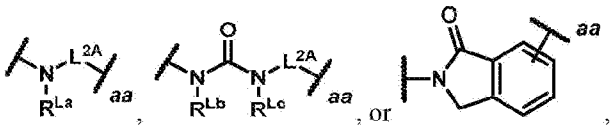
or one R^i and one R^j on adjacent carbon atoms taken together with the a tom (s) to which each is attached form an alkene, wherein said alken e is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heter ocyclyl optionally substituted with one or more substituents each in dependently selected from the group consisting of C_{1-6} alkyl and $-C(O)(C_{1-6}$ alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected $-C(O)(C_{1-6}$ alkyl) , and 5-10 membered heter oaryl optionally substituted with 1-6 independently selected R^g;

or two R^{QA} on adjacent carbon atoms, taken together with the atom to which each is attached form a 5-8 membered hetero cyclyl, wherein said ring is optionally substituted with 1-2 independently selected R^h;

or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered hetero

cyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

L^2 is C_{6-10} aryl optionally substituted with 1-2 independently s elected R^h, 5-10 membered heteroaryl optionally substituted with 1-2 independently selected R^h,   wherein aa repres ents the point of attachment to the ring containing Q^1-Q^5;

n1 is 1, 2, or 3;

L^{2A} is a bond or C_{1-10} alkylene;

R^{La} is hydrogen, C_{1-6} alkyl, or -C (O) (C_{1-6} alkyl) ;

each of R^{Lb} and R^{Lc} is independently hydrogen or C_{1-6} alkyl;

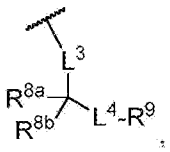
Ring A is C_{6-10} aryl, C_{5-7} cycloalkyl, 5-7 membered heterocyclyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-5 independently selected R^A;

each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

R^1, R^2, and R^3 are each independently hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the grou p consisting of halo, hydroxy, and C_{1-6} alkoxy;

L^1 is -C (O) -, -CH_2-, -CH (C_{1-6} alkyl) -, or -S (O) $_2$-;

Ring B is a 5, 6-fused heteroaryl having from 5 to 8 carbon atoms an d from 1 to 3 heteroatoms independently selected from O, S, and N, w herein Ring B is substituted with R^8 and optionally substituted with 1 to 4 substituents independently selected from halo, oxo, and C_{1-6} alkyl;

R^8 is phenyl, 5-6 membered heteroaryl, or  wherein the phenyl or 5-6 membered hetero aryl are substituted with R^{8c}, and are optionally further subst ituted with 1-3 independently selected R^h;

L^3 is a bond or C_{1-3} alkylene;

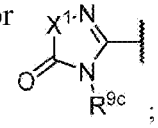
L^4 is a bond or C_{1-5} alkylene;

R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected fr om the group consisting of halo and C_{3-15} cycloalkyl; or

R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optional ly substituted with 1-3 independently selected C_{1-6} alkyl, wherein the C $_{1-6}$ alkyl is optionally substituted with 1-6 independently selected R^f;

each R^{8c} is independently -C (O) OH, -S (O) $_2$OH, -S (O) $_2$$NH_2$, -$L^5$-C $_{1-6}$ alkyl, -L^5-C_{3-6} cycloalkyl, -L^5-C_{6-10} aryl, -L^5-5-6 membered hetero cyclyl, -L^5- (5-6 membered heteroaryl) , wherein each is optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

each L^5 is independently -C (O) -, -C (O) O-, -OC (O) -, -S (O) $_{1-2}$-, -S (O) $_2$O-, -S (O) $_2$NH-, or -NHS (O) $_2$-;

R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered hetero aryl optionally substituted with 1-3 independently selected R ^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

X^1 is O or S;

R^{9a} is hydrogen or C_{1-6} alkyl;

R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

Ring C is 3-12 membered heterocyclyl, C_{3-15} cycloalkyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-3 R^{Ca};

each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

or a pair of R^{Ca} on the same or different ring atoms, taken togethe r with the ring atom (s) to which each is attached, forms a carbocyc lic ring including 3-8 ring atoms;

each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

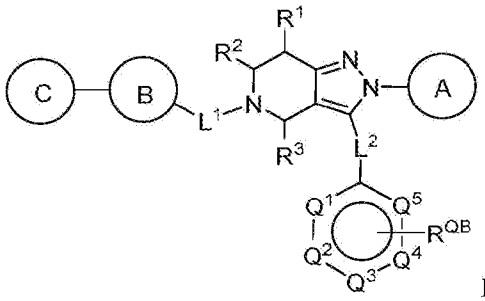
R^e is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

each R^f is independently halo, hydroxy, -NR^cR^d, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3-12 membered heterocyclyl which is optionally substituted with 1-4 substituents each independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, -NR^cR^d , or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

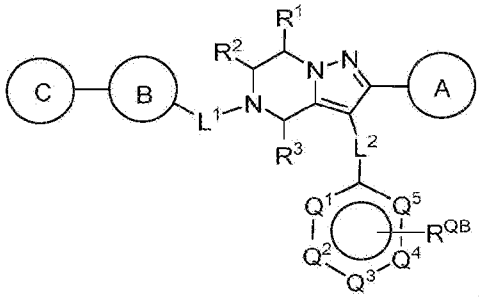
each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, -NH_2, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[Claim 2] The compound of claim 1, wherein the compound is represented by Formula II;



II.

[Claim 3] The compound of claim 1, wherein the compound is represented by Formula III;



III.

[Claim 4] The compound of any preceding claim, wherein Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2, Q^3, and Q^4 are each independently N, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, and Q^4 is CR^{QB}.

[Claim 5] The compound of any preceding claim, wherein each R^{QA} is independently hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or $-NR^cR^d$.

[Claim 6] The compound of any preceding claim, wherein Q^1 and Q^5 are each independently CR^{QA}; where each R^{QA} is independently hydrogen or halo.

[Claim 7] The compound of any preceding claim, wherein one of Q^2, Q^3, and Q^4 is N.

[Claim 8] The compound of any preceding claim, wherein R^{QB} is $-S(O)(=NR^a)R^b$ or $-CH_2-S(O)(=NR^a)R^b$.

[Claim 9] The compound of any one of claims 1-7, wherein R^{QB} is $-O-(CR^iR^j)_n-S(O)(=NR^a)R^b$.

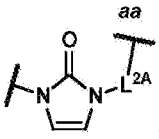
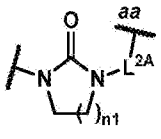
[Claim 10] The compound of any preceding claim, wherein R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl.

[Claim 11] The compound of any preceding claim, wherein R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, or C_{3-6} cycloalkyl.

[Claim 12] The compound of any one of claims 1-9, wherein R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl.

[Claim 13] The compound of any one of claims 1-9, wherein R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h.

[Claim 14] The compound of any preceding claim, wherein L^2 is C_{6-10} aryl optionally substituted with 1-2 independently selected R^h,



wherein aa represents the point of attachment to the ring containing Q^1-Q^5.

[Claim 15] The compound of any preceding claim, wherein L^{2A} is a bond.

[Claim 16] The compound of any preceding claim, wherein R^1 and R^2 are each hydrogen.

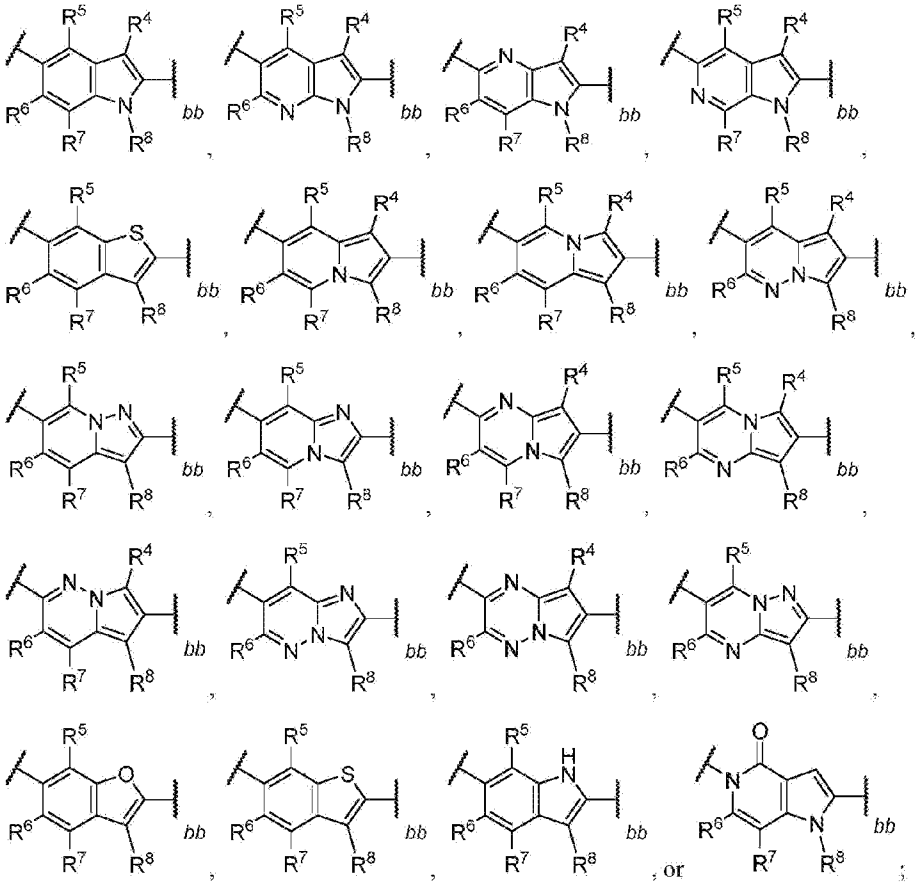
[Claim 17] The compound of any preceding claim, wherein R^3 is C_{1-6} alkyl.

[Claim 18] The compound of any preceding claim, wherein L^1 is -C (O) -,

[Claim 19] The compound of any preceding claim, wherein Ring A is C_{6-10} aryl which is optionally substituted with 1-5 substituents in dependently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl.

[Claim 20] The compound of any preceding claim, wherein Ring A is phenyl substituted with 2-3 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, and C_{3-6} cycloalkyl.

[Claim 21] The compound of any preceding claim, wherein Ring B is:

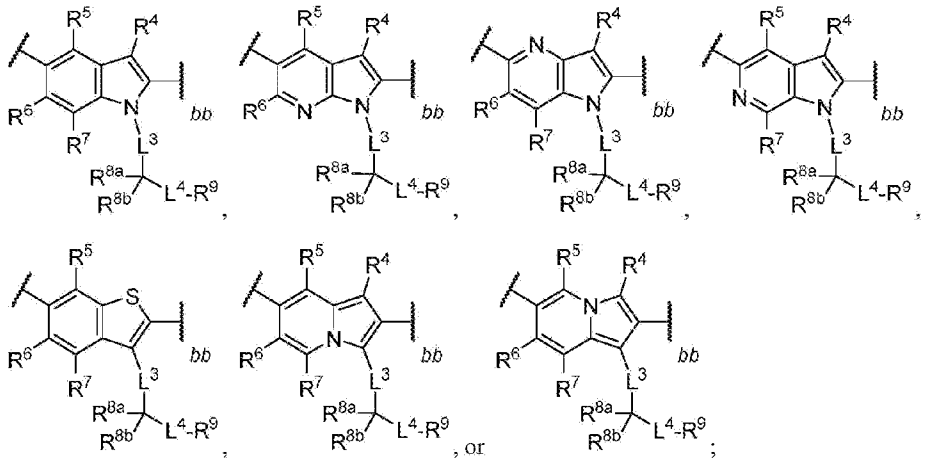


wherein bb represents point of attachment to L^1.

[Claim 22] The compound of any preceding claim, wherein R^8 is phenyl substituted with R^{8c}.

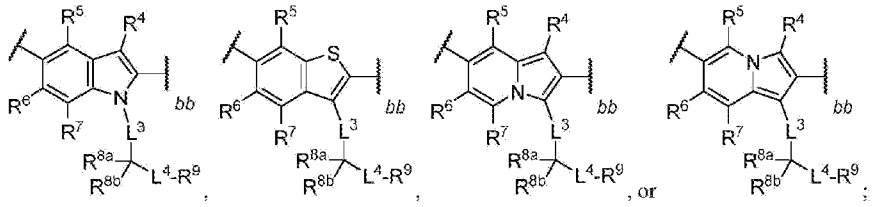
[Claim 23] The compound of any preceding claim, wherein R^8 is a 5-6 membered heteroaryl substituted with R^{8c}.

[Claim 24] The compound of any preceding claim, wherein Ring B is:



wherein bb represents point of attachment to L^1.

[Claim 25] The compound of any preceding claim, wherein Ring B is:

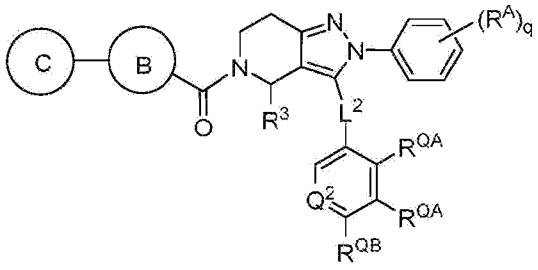


wherein bb represents point of attachment to L^1.

[Claim 26] The compound of any one of claims 1-21 or 24-25, wherein L^3 is a bond.

[Claim 27] The compound of any one of claims 1-21 or 24-25, wherein L^4 is a bond.

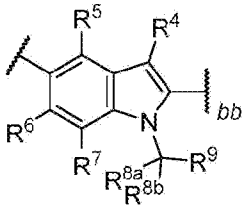
[Claim 28] The compound of claim 1, represented by Formula IIA:



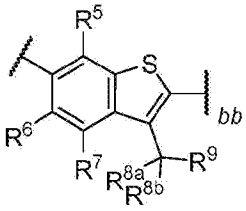
IIA

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, 4, or 5.

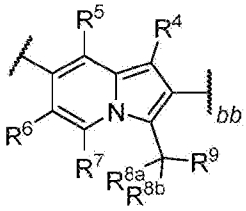
[Claim 29] The compound of any preceding claim, wherein Ring B is



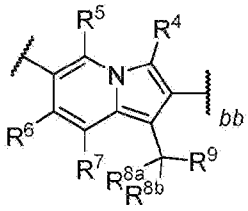
,



,



, or



; wherein bb represents point of attachment to L^1.

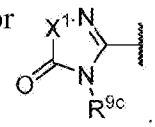
[Claim 30] The compound of any preceding claim, wherein R^4 is hydrogen or halo.

[Claim 31] The compound of any preceding claim, wherein R^5, R^6, and R^7 are each hydrogen.

[Claim 32] The compound of any preceding claim, wherein R^{8a} and R^{8b} are each independently hydrogen.

[Claim 33] The compound of any preceding claim, wherein R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted C_{1-6} alkyl.

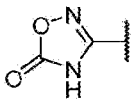
[Claim 34] The compound of any preceding claim, wherein R^9 is a 5-6 membered heteroaryl optionally substituted with 1-3 independently selected R^{9c}, or



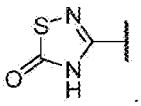
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[Claim 35] The compound of any preceding claim, wherein R^9 is a 6 membered heteroaryl.

[Claim 36] The compound of any preceding claim, wherein R^9 is



or

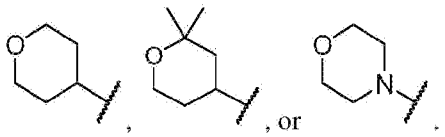


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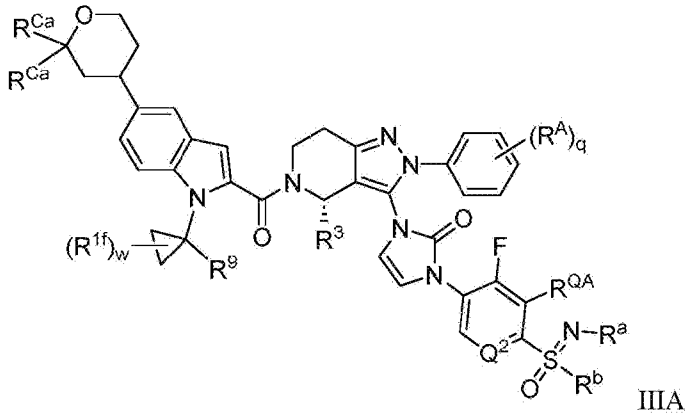
[Claim 37] The compound of any preceding claim, wherein Ring C is 3-12 membered heterocyclyl which is optionally substituted with 1-3 R^{Ca}.

[Claim 38] The compound of any preceding claim, wherein each R^{Ca} is C_{1-6} alkyl.

[Claim 39] The compound of any preceding claim, wherein Ring C is:



[Claim 40] The compoud of claim 1, wherein the compound is of Formula IIIA:



IIIA

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

Q^2 is N or CR^{QA};

R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

or R^a and R^b taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1-6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1-

6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) (C_{1-6} alkyl) , C_{6-10} aryl optionally substituted with 1-3 independently selected -C (O) (C_{1-6} alkyl) , and 5-10 membered heteroaryl optionally substituted with 1-6 independently selected R^g;

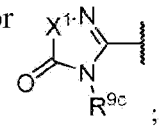
or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

each R^{Ca} is independently C_{1-6} alkyl;

q is 0, 1, 2, 3, 4, or 5;

each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

R^3 is hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered heteroaryl optionally substituted with 1-3 independently selected R^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

X^1 is O or S;

R^{9a} is hydrogen or C_{1-6} alkyl;

R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally s

ubstituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

each R^e is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

w is 0, 1, 2, or 3;

each R^{1f} is independently C_{1-6} alkyl, wherein each C_{1-6} alkyl is indepen dently optionally substituted with 1-6 independently selected R^f;

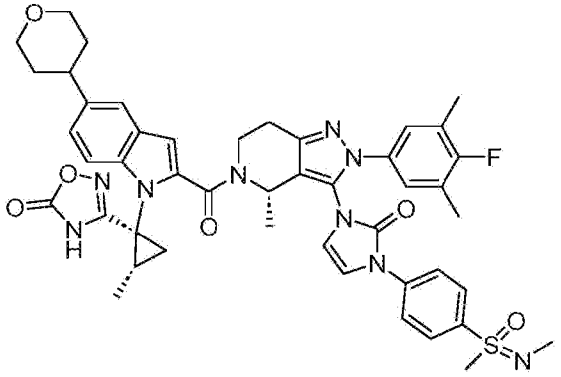
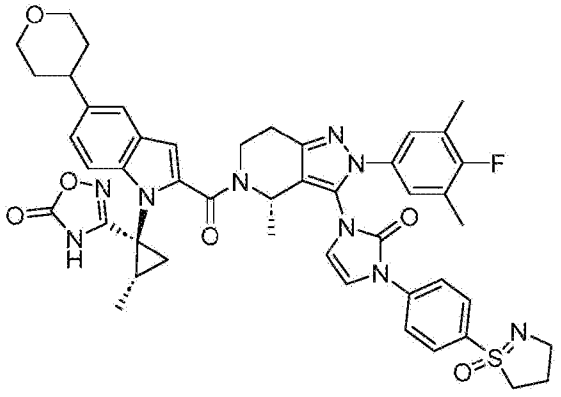
each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3-12 membered heterocyclyl which is optionally substi tuted with 1-4 substituents each independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heter ocyclyl;

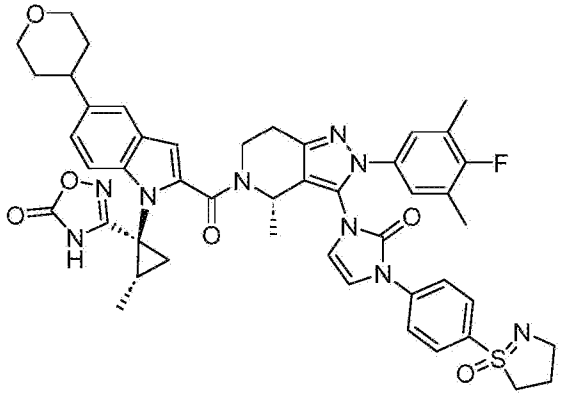
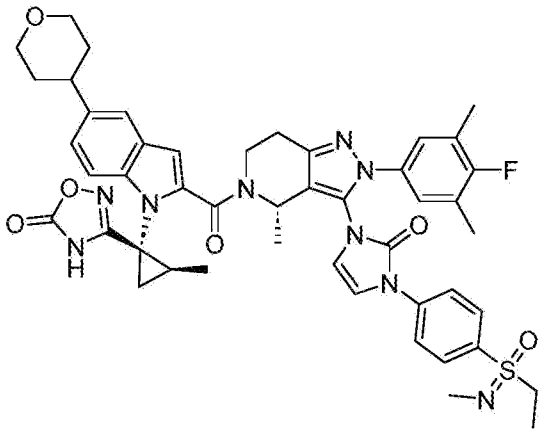
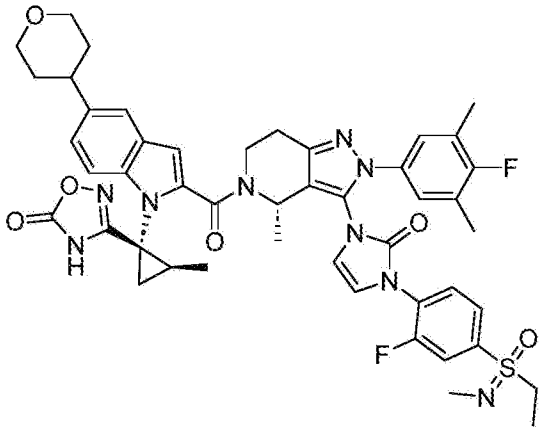
each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 membered heterocyclyl optionally substituted with one o r more substituents each independently selected from the group consi sting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

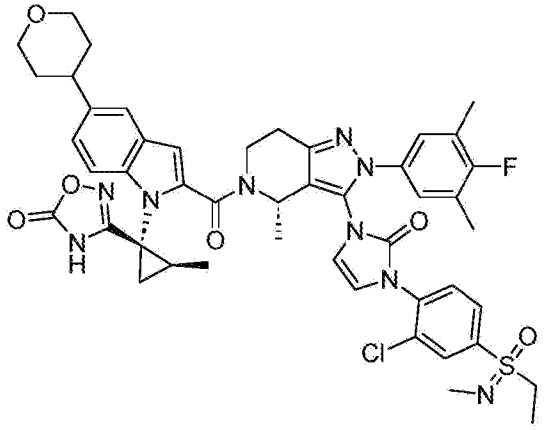
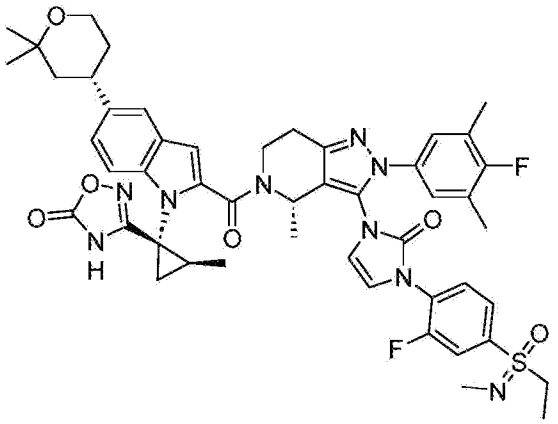
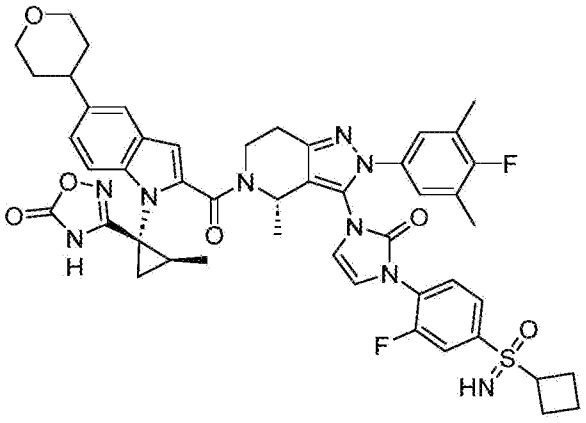
each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

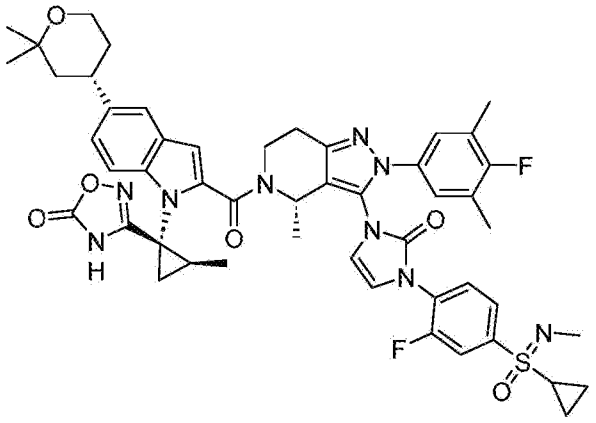
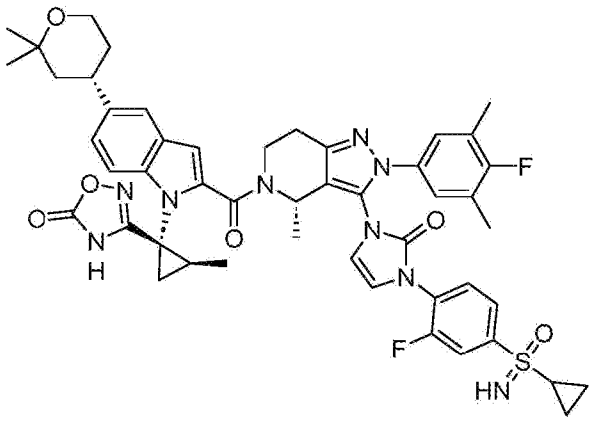
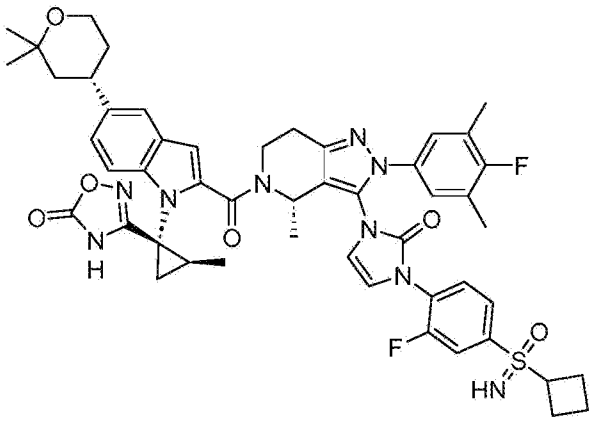
[Claim 41] A compound selected from Table 1 or Table 2, or a pharmaceutically a cceptable salt, stereoisomer, mixture of stereoisomers, or prodrug t hereof.

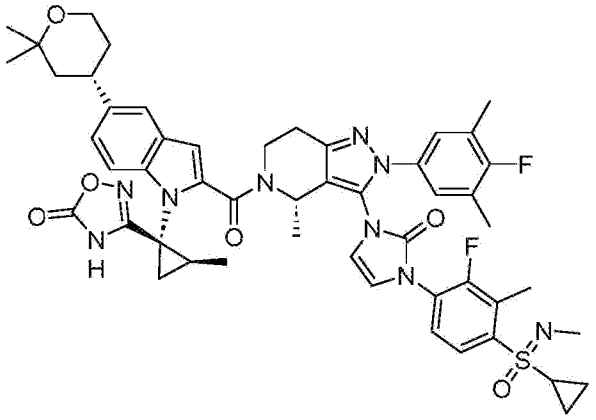
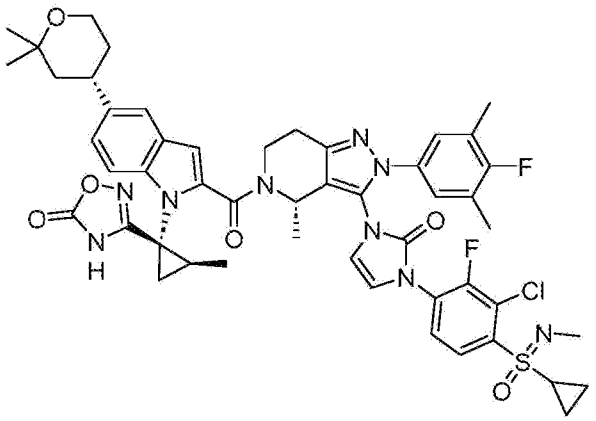
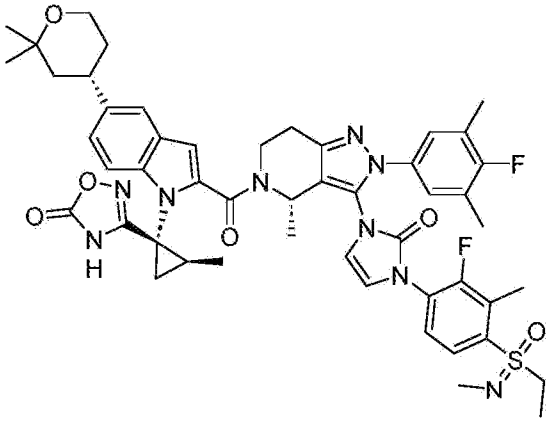
[Claim 42] A compound selected from:

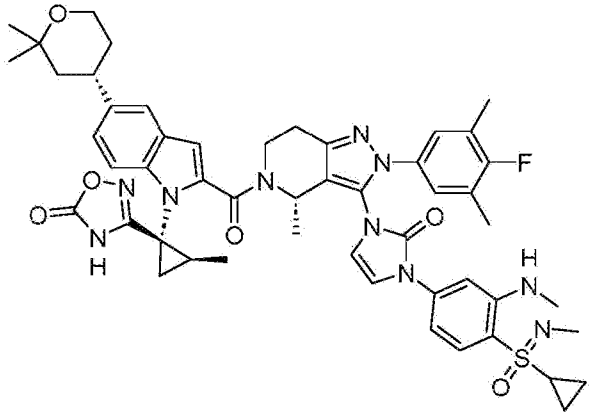
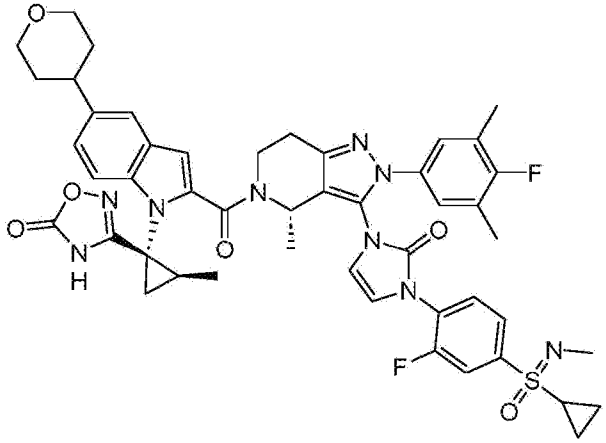
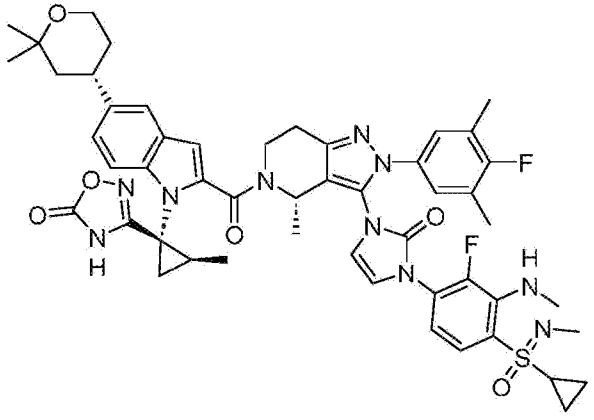
121	 Enantiomer 2
142	 Enantiomer 1

143	 Enantiomer 2
144	 Single unknown enantiomer
149	 Enantiomer 1

151	 Enantiomer 1
164	 Single unknown enantiomer
168	 Enantiomer 1

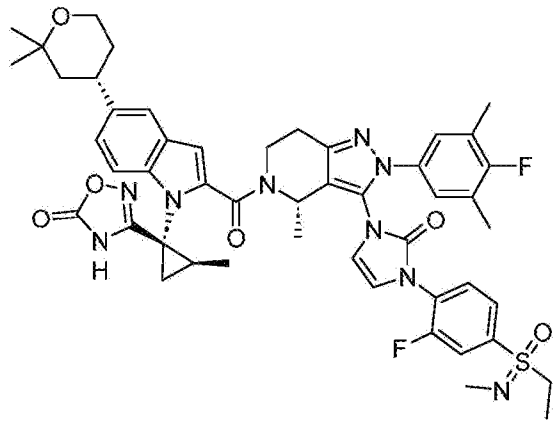
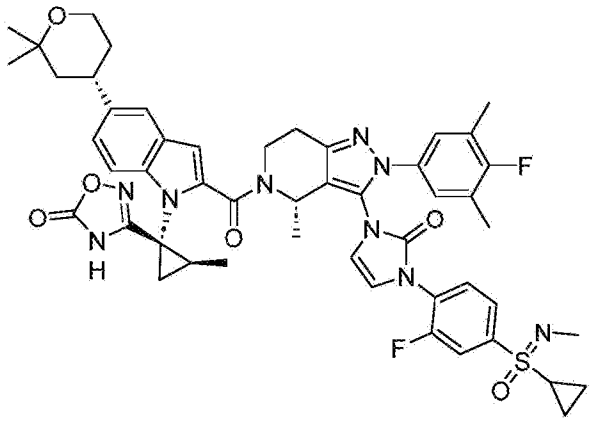
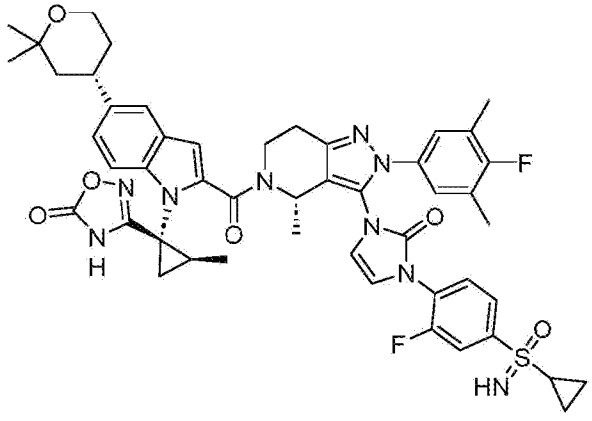
180	 Single unknown enantiomer
181	 Single unknown enantiomer
183	 Single unknown enantiomer

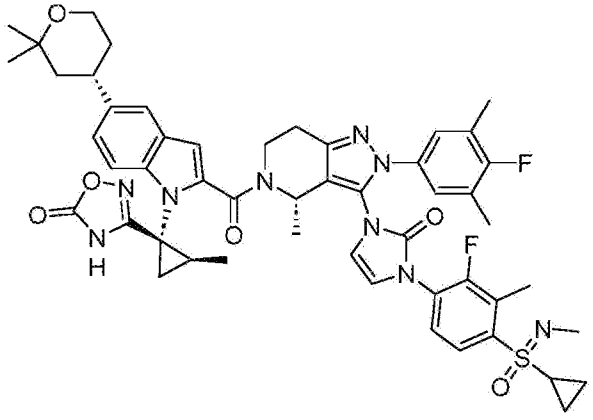
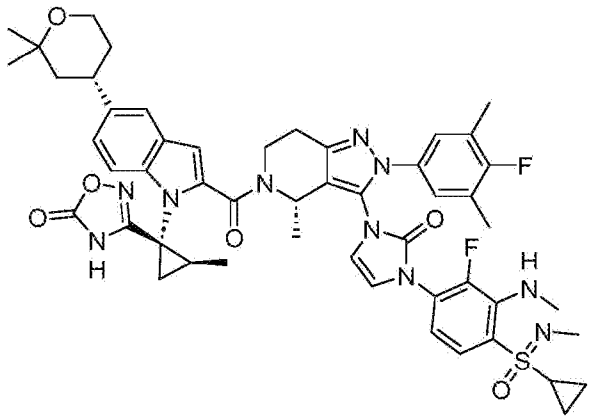
195	 Enantiomer 1
214	 Enantiomer 1
216	 Single unknown enantiomer

218	 Single unknown enantiomer
221	 Enantiomer 1
and	
238	 Single unknown enantiomer

or a pharmaceutically acceptable salt, stereoisomer, mixture of ster eoisomers, or prodrug thereof.

[Claim 43] A compound selected from:

164	 Single unknown enantiomer
180	 Single unknown enantiomer
181	 Single unknown enantiomer

195	 Enantiomer 1
and	
238	 Single unknown enantiomer

or a pharmaceutically acceptable salt, stereoisomer, mixture of ster eoisomers, or prodrug thereof.

[Claim 44] A pharmaceutical composition comprising a compound of any preceding claim, or a pharmaceutically acceptable salt, stere oisomer, mixture of stereoisomers, or prodrug thereof, and a pharmac eutically acceptable excipient.

[Claim 45] A method for treating a GLP-1 associated disease, disorder, or condition, the method comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1–43, or a pharmaceutically acceptable salt, stereoisomer, mixture of st ereoisomers, or prodrug thereof, or the pharmaceutical composition a ccording to claim 44.

[Claim 46] The method of claim 45, wherein the disease, disorder, or condition is selected from the group consisting of type 1 diabetes mellitus, type

Rule 26, 24.04.2024

2 diabetes mellitus, early onset type 2 diabetes mellitus, idiopathic type 1 diabetes mellitus (Type 1b) , youth-onset atypical diabetes (YOAD) , maturity onset diabetes of the young (MODY) , latent autoimmune diabetes in adults (LADA) , obesity, weight gain from use of other agents, gout, excessive sugar craving, hypertriglyceridemia, dyslipidemia, malnutrition-related diabetes, gestational diabetes, kidney disease, adipocyte dysfunction, sleep apnea, visceral adipose deposition, eating disorders, cardiovascular disease, congestive heart failure, myocardial infarction, left ventricular hypertrophy, peripheral arterial disease, stroke, hemorrhagic stroke, ischemic stroke, transient ischemic attacks, atherosclerotic cardiovascular disease, traumatic brain injury, peripheral vascular disease, endothelial dysfunction, impaired vascular compliance, vascular restenosis, thrombosis, hypertension, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis, hyperinsulinemia, impaired glucose metabolism, insulin resistance, hepatic insulin resistance, alcohol use disorder, chronic renal failure, metabolic syndrome, syndrome X, smoking cessation, premenstrual syndrome, angina pectoris, diabetic nephropathy, impaired glucose tolerance, diabetic neuropathy, diabetic retinopathy, macular degeneration, cataract, glomerulosclerosis, arthritis, osteoporosis, treatment of addiction, cocaine dependence, bipolar disorder/major depressive disorder, skin and connective tissue disorders, foot ulcerations, psoriasis, primary polydipsia, non-alcoholic steatohepatitis (NASH) , non-alcoholic fatty liver disease (NAFLD) , ulcerative colitis, inflammatory bowel disease, colitis, irritable bowel syndrome, Crohn's disease, short bowel syndrome, Parkinson's, Alzheimer's disease, impaired cognition, schizophrenia, Polycystic Ovary Syndrome (PCOS) , or any combination thereof.

[Claim 47] A method of treating type 2 diabetes mellitus in a patient in need t hereof, the method comprising administering to a patient in need the reof an effective amount of a compound of any one of claims 1–43, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereo isomers, or prodrug thereof, or the pharmaceutical composition accor ding to claim 44. **Rule 26, 24.04.2024**

[Claim 48] A method for modulating insulin levels in a patient in need of such modulating, the method comprising administering to a patient in need **Rule 26, 24.04.2024**

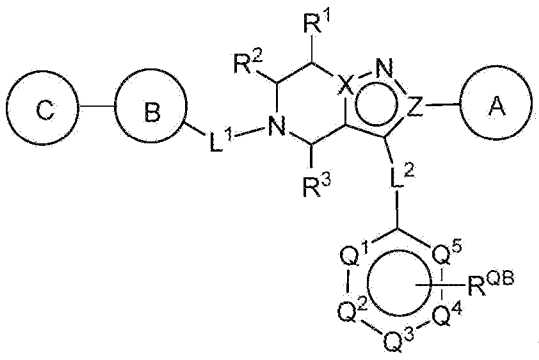
thereof an effective amount of a compound of any one of claims 1–40, or a pharmaceutically acceptable salt, stereoisomer, mixture of st ereoisomers, or prodrug thereof, or the pharmaceutical composition a ccording to claim 44.

[Claim 49] A method for modulating glucose levels in a patient in need of such modulating, the method comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1–43, or a pharmaceutically acceptable salt, stereoisomer, mixture of st ereoisomers, or prodrug thereof, or the pharmaceutical composition a ccording to claim 44. Rule 26, 24.04.2024

[Claim 50] The method of any one of claims 45-49, further comprising administeri ng an additional therapy or therapeutic agent to the patient. Rule 26, 24.04.2024

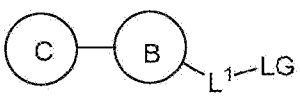
[Claim 51] The method of claim 50, wherein the additional therapy or therapeuti c agent is selected from the group consisting of an antidiabetic age nt, an anti-obesity agent, a GLP-1 receptor agonist, an anti-emetic agent, an agent to treat non-alcoholic steatohepatitis (NASH) , gastric electrical stimulation, dietary monitoring, physical activi ty, or a combination thereof. Rule 26, 24.04.2024

[Claim 52] A process for preparing a compound of Formula I: Rule 26, 24.04.2024



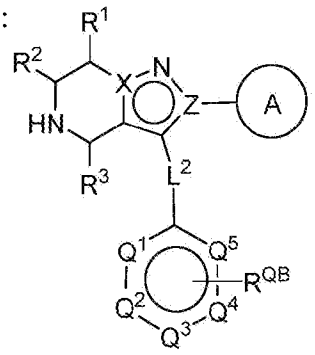
I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, compris ing contacting a compound of Formula I-1:



I-1

with a compound of Formula I-2:



I-2

under conditions sufficient to provide the compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, s tereoisomer, mixture of stereoisomers, or prodrug thereof; wherein:

LG is a leaving group;

X is C and Z is N, or X is N and Z is C;

Q^1 and Q^5 are each independently N or CR^{QA}; and Q^2, Q^3, and Q^4 are each independently N, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, and Q^4 is CR^{QB}; or

Q^1 is a bond; and Q^2, Q^3, Q^4, and Q^5 are each independently O, S, N, NH, NR^c, CR^{QA}, or CR^{QB}, provided that at least one of Q^2, Q^3, Q^4, and Q^5 is CR^{QB};

provided that the ring including Q^1-Q^5 is aromatic;

R^{QB} is –S (O) (=NR^a) R^b, – (CR^iR^j) $_n$–S (O) (=NR^a) R^b, –N=S (O) (R^{1a}) R^b, or –O– (CR^iR^j) $_n$–S (O) (=NR^a) R^b;

R^{1a} is C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

R^a is hydrogen, cyano, C_{1-6} alkyl which is optionally substituted with 1-6 substituents each independently selected from the group consisting of halo, oxo, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and heteroaryl, C_{3-6} cycloalkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1-3 independently selected C_{1-3} alkyl;

R^b is C_{1-6} alkyl which is optionally substituted with 1-6 substituents ea ch independently selected from the group consisting of C_{1-6} alkoxy, C $_{3-6}$ cycloalkyl, and halo, C_{3-6} cycloalkyl optionally substituted with 1- 3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo, or C_{6-10} aryl optionally substituted with 1- 3 independently selected C_{1-3} alkyl;

or R^a and R^b taken together with the atoms to which each is att ached form a 5-8 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

n is 1, 2, 3, 4, 5, or 6;

each R^i is independently hydrogen, halo, or C_{1-6} alkyl;

or R^a and R^i, or R^b and R^i, taken together with the atoms to which each is attached form a 5-8 membered heterocyclyl, wherein s aid heterocyclyl is optionally substituted with 1-3 independently s elected C_{1-6} alkyl;

each R^j is independently hydrogen, halo, or C_{1-6} alkyl;

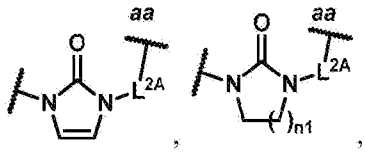
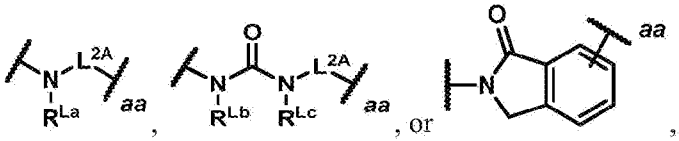
or one R^i and one R^j, taken together with the atom (s) to which each is attached, form a C_{3-6} cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

or one R^i and one R^j on adjacent carbon atoms taken together with the a tom (s) to which each is attached form an alkene, wherein said alken e is optionally substituted with 1-3 independently selected C_{1-6} alkyl;

each R^{QA} is independently hydrogen, halo, cyano, hydroxy, $-NR^cR^d$, $-C(O)NR^cR^d$, $-S(O)_{0-2}R^e$, C_{1-6} alkyl optionally substituted with 1- 6 independently selected R^f, C_{1-6} alkoxy optionally substituted with 1- 6 substituents each independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy, 3-12 membered heter ocyclyl optionally substituted with one or more substituents each in dependently selected from the group consisting of C_{1-6} alkyl and - $C(O)(C_{1-6}$ alkyl) , C_{6-10} aryl optionally substituted with 1- 3 independently selected $-C(O)(C_{1-6}$ alkyl) , and 5-10 membered heter oaryl optionally substituted with 1-6 independently selected R^g;

or two R^{QA} on adjacent carbon atoms, taken together with the atom to which each is attached form a 5-8 membered hetero cyclyl, wherein said ring is optionally substituted with 1- 2 independently selected R^h;

or R^a or R^b and an adjacent R^{QA} are taken together with the atom to which each is attached to form a 5-8 membered hetero cyclyl, wherein said heterocyclyl is optionally substituted with 1-2 independently selected R^h;

L^2 is C_{6-10} aryl optionally substituted with 1-2 independently s elected R^h, 5-10 membered heteroaryl optionally substituted with 1-2 independently selected R^h,  , wherein aa repres  , or ,

ents the point of attachment to the ring containing Q^1-Q^5;

n1 is 1, 2, or 3;

L^{2A} is a bond or C_{1-10} alkylene;

R^{La} is hydrogen, C_{1-6} alkyl, or -C (O) (C_{1-6} alkyl) ;

each of R^{Lb} and R^{Lc} is independently hydrogen or C_{1-6} alkyl;

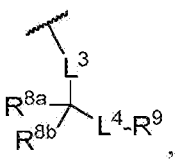
Ring A is C_{6-10} aryl, C_{5-7} cycloalkyl, 5-7 membered heterocyclyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-5 independently selected R^A;

each R^A is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-6} cycloalkyl;

R^1, R^2, and R^3 are each independently hydrogen or C_{1-6} alkyl optionally substituted with 1-6 substituents independently selected from the grou p consisting of halo, hydroxy, and C_{1-6} alkoxy;

L^1 is -C (O) -, -CH_2-, -CH (C_{1-6} alkyl) -, or -S (O) $_2$-;

Ring B is a 5, 6-fused heteroaryl having from 5 to 8 carbon atoms an d from 1 to 3 heteroatoms independently selected from O, S, and N, w herein Ring B is substituted with R^8 and optionally substituted with 1 to 4 substituents independently selected from halo, oxo, and C_{1-6} alkyl;

R^8 is phenyl, 5-6 membered heteroaryl, or  , wherein the phenyl or 5-6 membered hetero

aryl are substituted with R^{8c}, and are optionally further subst ituted with 1-3 independently selected R^h;

L^3 is a bond or C_{1-3} alkylene;

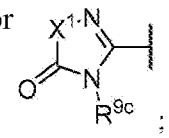
L^4 is a bond or C_{1-5} alkylene;

R^{8a} and R^{8b} are each independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents independently selected fr om the group consisting of halo and C_{3-15} cycloalkyl; or

R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optional ly substituted with 1-3 independently selected C_{1-6} alkyl, wherein the C $_{1-6}$ alkyl is optionally substituted with 1-6 independently selected R^f;

each R^{8c} is independently -C (O) OH, -S (O) $_2$OH, -S (O) $_2$$NH_2$, -$L^5$-C $_{1-6}$ alkyl, -L^5-C_{3-6} cycloalkyl, -L^5-C_{6-10} aryl, -L^5-5-6 membered hetero cyclyl, -L^5- (5-6 membered heteroaryl) , wherein each is optionally substituted with 1-6 substituents independently selected from the grou p consisting of hydroxy, halo, and C_{1-6} alkoxy;

each L^5 is independently -C (O) -, -C (O) O-, -OC (O) -, -S (O) $_{1-2}$-, -S (O) $_2$O-, -S (O) $_2$NH-, or -NHS (O) $_2$-;

R^9 is -C (O) OR^{9a}, -C (O) $NR^{9a}R^{9b}$, 5-6 membered hetero aryl optionally substituted with 1-3 independently selected R ^{9c}, 4-6 membered heterocyclyl optionally substituted with 1-3 independently selected R^{9c}, or  ;

X^1 is O or S;

R^{9a} is hydrogen or C_{1-6} alkyl;

R^{9b} is hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -S (O) $_{0-2}$ (C_{1-6} alkyl) , or cyano;

each R^{9c} is independently hydrogen, oxo, C_{1-6} alkyl optionally substituted with 1-6 independently selected halo and C_{1-6} alkoxy, or -C (O) (C_{1-6} alkyl) ;

Ring C is 3-12 membered heterocyclyl, C_{3-15} cycloalkyl, or 5-10 membered heteroaryl, each of which is optionally substituted with 1-3 R^{Ca};

each R^{Ca} is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or NR^cR^d;

or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring atom (s) to which each is attached, forms a carbocyclic ring including 3-8 ring atoms;

each R^c and R^d are each independently hydrogen, C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , or -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) , wherein the C_{1-6} alkyl, -C (O) (C_{1-6} alkyl) , -C (O) (C_{3-6} cycloalkyl) , -C (O) O (C_{1-6} alkyl) , -S (O) $_{1-2}$ (C_{1-6} alkyl) , and -S (O) $_{1-2}$ (C_{3-6} cycloalkyl) are each optionally substituted with 1-6 substituents independently selected from the group consisting of hydroxy, halo, and C_{1-6} alkoxy;

R^e is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

each R^f is independently halo, hydroxy, $-NR^cR^d$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or 3-12 membered heterocyclyl which is optionally substituted with 1-4 substituents each independently selected from the group consisting of hydroxy, C_{1-6} alkyl, and 3-12 membered heterocyclyl;

each R^g is independently C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^cR^d$, or 3 to 12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6} alkyl and -C (O) C_{1-6} alkyl; and

each R^h is independently halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NH_2$, -NH (C_{1-3} alkyl) , -N (C_{1-3} alkyl) $_2$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[Claim 53] The process of claim 52, wherein the process further comprises a hydrolysis or transesterification step prior to or after the contacting. **Rule 26, 24.04.2024**

[Claim 54] The process of claim 52 or 53, wherein the process comprises a base, and optionally elevated temperature. **Rule 26, 24.04.2024**

INTERNATIONAL SEARCH REPORT

International application No
PCT/CN2024/077096

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 C07D519/00 A61K31/437 A61P3/10
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)
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.
Y	WO 2022/048665 A1 (GASHERBRUM BIO INC [US]; MENG QINGHUA [CN]) 10 March 2022 (2022-03-10) cited in the application pages 102-103; claim 1	1-39, 44-55
Y	WO 2018/056453 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]) 29 March 2018 (2018-03-29) cited in the application pages 137-138; claim 1	1-39, 44-55

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

[x] See patent family annex.

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

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2024	27/05/2024

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	Grassi, Damian

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INTERNATIONAL SEARCH REPORT

International application No
PCT/CN2024/077096

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Ulrich Luecking: "Sulfoximines in Medicinal Chemistry: Emerging Trends and Opportunities from the Drug Designer's Perspective", , 18 May 2022 (2022-05-18), pages 1-11, XP093160026, DOI: 10.26434/chemrxiv-2022-g58r5 Retrieved from the Internet: URL:https://chemrxiv.org/engage/api-gateway/chemrxiv/assets/orp/resource/item/6284b5a844bdd53592675638/original/sulfoximines-in-medicinal-chemistry-emerging-trends-and-opportunities-from-the-drug-designer-s-perspective.pdf -----	1-39, 44-55
Y	YU HAN: "Application of sulfoximines in medicinal chemistry from 2013 to 2020", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 209, 1 January 2021 (2021-01-01), page 112885, XP093160045, AMSTERDAM, NL ISSN: 0223-5234, DOI: 10.1016/j.ejmech.2020.112885 Paragraphs 1 and 3 -----	1-39, 44-55

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CN2024/077096

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022048665 A1	10-03-2022	CN 116615430 A	18-08-2023
		EP 4211133 A1	19-07-2023
		JP 2023540558 A	25-09-2023
		US 2023322771 A1	12-10-2023
		WO 2022048665 A1	10-03-2022
WO 2018056453 A1	29-03-2018	AU 2017330733 A1	14-03-2019
		AU 2020223687 A1	10-09-2020
		AU 2022205222 A1	04-08-2022
		AU 2024201884 A1	11-04-2024
		BR 112019005322 A2	02-07-2019
		CA 3038479 A1	29-03-2018
		CL 2019000663 A1	26-07-2019
		CN 109790161 A	21-05-2019
		CO 2019002595 A2	29-03-2019
		CR 20190149 A	27-08-2019
		DK 3517538 T3	25-03-2024
		DO P2019000074 A	31-05-2019
		EA 201990518 A1	30-12-2019
		EA 202190802 A2	30-07-2021
		EC SP19020228 A	30-06-2019
		EP 3517538 A1	31-07-2019
		EP 4134367 A1	15-02-2023
		EP 4349840 A2	10-04-2024
		IL 264945 A	30-05-2019
		IL 287166 A	01-12-2021
		JP 6567778 B2	28-08-2019
		JP 6957564 B2	02-11-2021
		JP 7280929 B2	24-05-2023
		JP 2019203015 A	28-11-2019
		JP 2022003087 A	11-01-2022
		JP 2023100963 A	19-07-2023
		JP WO2018056453 A1	11-07-2019
		KR 20190039591 A	12-04-2019
		MA 46286 A	31-07-2019
		NZ 751725 A	26-03-2021
		PE 20190709 A1	17-05-2019
		PH 12019500659 A1	16-12-2019
		PT 3517538 T	09-04-2024
		SA 519401409 B1	07-04-2022
		SG 11201901565V A	28-03-2019
		TN 2019000054 A1	15-07-2020
		TW 201827426 A	01-08-2018
		UA 125586 C2	27-04-2022
		US 2019225604 A1	25-07-2019
		US 2021017176 A1	21-01-2021
		US 2023382912 A1	30-11-2023
		WO 2018056453 A1	29-03-2018
		ZA 201901070 B	30-06-2021