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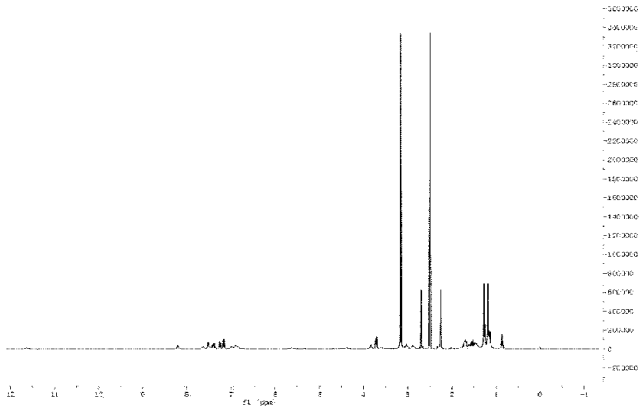
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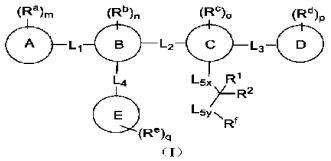
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(54) Title: A CLASS OF POLYCYCLIC COMPOUNDS AND USES THEREOF

(54) Title of the Invention: A Class of Polycyclic Compounds and Their Uses





(I)

Figure 1

(57) Abstract: Provided in the present invention are a class of compounds as shown in formula (I), stereoisomers, tautomers or pharmaceutically acceptable salts thereof. The compounds of the present invention are used as GLP-1R agonists, and the compounds and pharmaceutical compositions thereof can be used in the preparation of drugs for treating and/or preventing disorders mediated by GLP-1R.

(57) Abstract: The present invention provides a compound represented by Formula (I), its stereoisomers, tautomers, or pharmaceutically acceptable salts thereof. The compounds of the present invention act as GLP-1R agonists. Such compounds and pharmaceutical compositions thereof can be used for the preparation of drugs for treating and/or preventing disorders mediated by GLP-1R.

[See continuation page]

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Declaration under Rule 4.17:
- Regarding the applicant's right to claim priority right of earlier application (Rule 4.17(iii))

This International Publication:
- Includes International Search Report (Article 21(3) of the Treaty).

A Class of Polycyclic Compounds and Their Uses

This application claims the priority right of the applicant:

To the earlier application with patent application number 202311782864.9, titled "A Class of Polycyclic Compounds and Their Uses", filed with the China National Intellectual Property Administration on December 22, 2023;

To the earlier application with patent application number 202410173188.3, titled "A Class of Polycyclic Compounds and Their Uses", filed with the China National Intellectual Property Administration on February 7, 2024;

The entire content of the aforementioned earlier applications is incorporated herein by reference.

Technical Field

This application relates to the field of pharmaceutical technology, and more specifically, to a class of polycyclic compounds, pharmaceutical compositions comprising the same, and their use as GLP-1R agonists. The said polycyclic compounds can be used to prevent and/or treat diseases, disorders, and conditions mediated by GLP-1R.

Background Art

Overweight and obesity have become global health issues. They are major causes of several chronic diseases including diabetes, cardiovascular diseases, liver diseases, and cancer. Currently, about 50% of type 2 diabetes cases, 30% of ischemic cardiovascular and cerebrovascular diseases, and 10%-40% of cancers are caused by obesity or overweight. China already has the highest number of overweight and obese individuals worldwide, with a huge unmet clinical need for obesity treatment.

Diabetes is a common metabolic endocrine disease characterized mainly by disorders of glucose and lipid metabolism and elevated plasma glucose levels. Wherein, type 2 diabetes is the most common, accounting for more than 90% of diabetic patients. The pathogenesis of type 2 diabetes is not fully understood, but it is currently believed to be related to unhealthy lifestyles, genetic factors, environmental factors, and the toxic effects of lipotoxicity and glucotoxicity on pancreatic β-cells. Moreover, poor long-term blood glucose control in patients can lead to various complications, such as: Vascular complications (macrovascular disease (atherosclerosis) and microvascular disease (retinopathy and neuropathy)), renal complications (renal insufficiency and proteinuria), cardiac complications (myocarditis, heart failure), urinary tract infections, etc.

GLP-1 (glucagon-like peptide-1) is mainly synthesized and secreted by L-cells located in the ileum and colon. Its receptor GLP-1R (Glucagon-like peptide-1 receptor) is mainly distributed in pancreatic β-cells and α-cells, gastrointestinal tract, central nervous system, and cardiovascular system. GLP-1R belongs to the glucagon receptor subfamily of the B cluster of G protein-coupled receptors, characterized by a seven-transmembrane core domain and a relatively large extracellular domain. In the pancreas, GLP-1 induces glucose-dependent insulin secretion.

In the pancreas, GLP-1 induces glucose-dependent insulin secretion. It increases insulin secretion and decreases glucagon. In the central nervous system, activation of GLP-1R increases satiety, reduces food intake, nausea, and promotes neuronal survival. In other tissue systems, activation of GLP-1R also lowers blood pressure, improves microvascular function, reduces inflammation; lowers gastric emptying, lowers blood glucose, increases insulin sensitivity, and reduces gluconeogenesis. Therefore, activation of GLP-1R can reduce blood glucose and/or cause weight loss, thereby preventing and/or treating diabetes and/or obesity, and activation of GLP-1R can cause weight loss through multiple biological mechanisms.

Moreover, there is evidence that activation of GLP-1R is a promising strategy for preventing and/or treating Alzheimer's disease (AD), non-alcoholic fatty liver disease (NAFLD), and others.

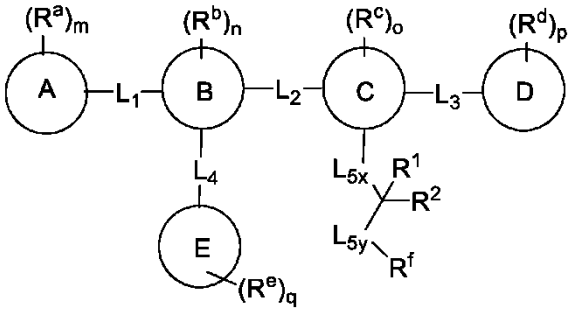
Alzheimer's disease is the most common neurodegenerative disease, characterized by incurable cognitive dysfunction. The basic mechanism of AD onset and progression has not been fully elucidated. Recent experimental and clinical studies show that AD can be considered a metabolic disorder corresponding to type 2 diabetes mellitus (T2DM), and in some cases is called type 3 diabetes. Insulin resistance is also present in the brains of deceased AD patients, and with disease progression, insulin receptor expression is significantly reduced, indicating that insulin signal transduction defects are related to AD pathogenesis. Additionally, studies show that in AD, when glucose metabolism is impaired and mitochondrial function is damaged, lactate shuttling in glial glycolysis becomes increasingly important for neuronal survival and serves as an energy substitute. GLP-1 can partially restore astrocyte glycolytic function and increase lactate flux, helping to relieve the neuronal energy crisis. The neuroprotective mechanism of GLP-1 is closely related to its promotion of aerobic glycolysis, mitigation of oxidative phosphorylation activation, and activation of the PI3K/Akt pathway. Therefore, GLP-1 agonists are

promising strategies for the prevention and treatment of AD.

Non-alcoholic fatty liver disease is divided into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), with excess metabolic substrate supply causing excess fat accumulation in hepatocytes, accompanied by gradual production of potentially toxic lipid species and progressive increase of NAFLD de novo lipogenesis (DNL). NASH, characterized by cell damage and inflammatory cell infiltration, is considered a more aggressive form of NAFLD, which may progress to cirrhosis and hepatocellular carcinoma, with limited treatment options. Obesity and type 2 diabetes are two main risk factors for NASH; people with NASH history have a greatly increased risk of liver and cardiovascular diseases. Moreover, insulin resistance in liver and adipose tissue is considered a key driver of NASH incidence and mortality, and GLP-1 analogs can improve blood glucose control, reduce weight, and activate liver enzymes in T2DM patients. Some evidence shows that liraglutide acts directly on human hepatocytes in vitro to reduce steatosis by lowering DNL levels and increasing fatty acid oxidation. Notably, after liraglutide treatment, most patients' steatosis and hepatocyte ballooning improved. Exciting experimental evidence in NASH patients shows that liraglutide has the potential to reduce lipotoxicity by improving insulin sensitivity in adipose tissue. Only a small portion of NASH patients progressed after liraglutide treatment. It is also reported that semaglutide, similar to liraglutide, can reduce alanine aminotransferase and inflammatory marker levels, with significant reductions in inflammatory biomarkers after treatment. Given the lack of hepatic GLP-1R expression, the potential mechanisms of GLP-1R agonists in NASH may relate to indirect benefits on weight and reducing metabolic dysfunction, lipotoxicity, and inflammation.

Summary of the Invention

In a first aspect, the invention provides a compound represented by formula (I), or its tautomer, stereoisomer, or pharmaceutically acceptable salt thereof, having the following structure:



(I) ,

Wherein,

Ring A is selected from C3-15 carbocyclic groups, 3-12 membered heterocyclic groups, C6-14 aryl groups, 5-12 membered heteroaryl groups;

Ring B is selected from 3-12 membered heterocyclic groups, C6-14 aryl groups, 5-12 membered heteroaryl groups;

Ring C is selected from a 9-membered bicyclic heteroaryl;

Ring D is selected from a C3-15 carbocyclyl, a 3-12-membered heterocyclyl, a C6-14 aryl, or a 5-12-membered heteroaryl;

Ring E is selected from C3-15 carbocyclic groups, 3-12 membered heterocyclic groups, C6-14 aryl groups, 5-12 membered heteroaryl groups;

Ra is independently selected each time from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -ORa1, -S(O)Ra1, -SO2(Ra1), -C(O)Ra1, -C(O)ORa1, -OC(O)Ra1, -N(Ra1)(Ra2), -C(O)N(Ra1)(Ra2), -N(Ra1)C(O)Ra2, -S(O)N(Ra1)(Ra2), -SO2N(Ra1)(Ra2), -N(Ra1)S(O)Ra2, -N(Ra1)S(O)2Ra2, and optionally substituted by one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) Ra3 of the following groups: C1-6 alkyl, C1-6 alkoxy, C1-6 alkanamine, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclic groups, C6-14 aryl groups, 5-12 membered heteroaryl groups;

Or two Ra together with the atoms to which they are attached form an optionally substituted 3-10 membered heterocyclic group or optionally substituted 5-12 membered heteroaryl group, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclic groups, C6-14 aryl and 5-12 membered heteroaryl groups.

Ra1, Ra2 are independently selected each time from hydrogen, deuterium, optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclic

groups, C6-14 aryl groups, 5-12 membered heteroaryl groups; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclic groups, phenyl, 5-6 membered heteroaryl substituents;

Ra3 is independently selected each time from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -Ra4, -ORa4, -SRa4, -S(O)Ra4, -S(O)2Ra4, -C(O)Ra4, -C(O)ORa4, -OC(O)Ra4, -N(Ra4)(Ra5), -C(O)N(Ra4)(Ra5), -N(Ra4)C(O)Ra5, -S(O)N(Ra4)(Ra5), -S(O)2N(Ra4)(Ra5), -N(Ra4)S(O)Ra5, -N(Ra4)S(O)2Ra5;

Ra4, Ra5 are independently selected each time from hydrogen, deuterium, optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, or 5-12 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, 3-7 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl.

Rb is independently selected each time from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, C3-10 The term "optionally substituted" refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the substituted group independently substituted with Rb1.

Alternatively, two Rb together with the atoms to which they are attached form an optionally substituted 3-10 membered heterocyclyl or an optionally substituted 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl.

Rb1 is independently selected each time from deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, -Rb2, -ORb2, -SRb2, -S(O)Rb2, -S(O)2Rb2, -C(O)Rb2, -C(O)ORb2, -OC(O)Rb2, -N(Rb2)(Rb3), -C(O)N(Rb2)(Rb3), -N(Rb2)C(O)Rb3, -S(O)N(Rb2)(Rb3), -S(O)2N(Rb2)(Rb3), -N(Rb2)S(O)Rb3, -N(Rb2)S(O)2Rb3;

Rb2 and Rb3 are independently selected each time from hydrogen, deuterium, and optionally substituted with the following groups: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) groups selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl.

Rc is independently selected each time from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, or optionally substituted with the following groups: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of an unsubstituted or substituted group are independently substituted with Rc1.

or two Rc together with the atoms to which they are attached form an optionally substituted 3-10 membered heterocyclyl or an optionally substituted 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl.

Rc1 is independently selected each time from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -Rc2, -ORc2, -SRc2, -S(O)Rc2, -S(O)2Rc2, -C(O)Rc2, -C(O)ORc2, -OC(O)Rc2, -N(Rc2)(Rc3), -C(O)N(Rc2)(Rc3), -N(Rc2)C(O)Rc3, -S(O)N(Rc2)(Rc3), -S(O)2N(Rc2)(Rc3), -N(Rc2)S(O)Rc3, -N(Rc2)S(O)2Rc3;

Rc2, Rc3 are independently selected each time from hydrogen, deuterium, optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclic groups, C6-14 aryl groups, 5-12 membered heteroaryl groups; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclic groups, C6-14 aryl groups, 5-12 membered heteroaryl groups.

Rd is independently selected each time from hydrogen, deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, -ORd1, -S(O)Rd1, -S(O)2Rd1, -C(O)Rd1, -C(O)ORd1, -OC(O)Rd1, -N(Rd1)(Rd2), -C(O)N(Rd1)(Rd2), -N(Rd1)C(O)Rd2, -S(O)N(Rd1)(Rd2), -S(O)2N(Rd1)(Rd2), -N(Rd1)S(O)Rd2, -N(Rd1)S(O)2Rd2, and the following groups optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) Rd3:

C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl.

Alternatively, two Rd's, taken together with the atoms to which they are attached, form an optionally substituted 3-10 membered heterocyclyl, an optionally substituted 3-7 membered cycloalkyl, or an optionally substituted 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl.

Rd1 and Rd2 are each independently selected from hydrogen, deuterium, optionally substituted 5-12 membered heteroaryl. C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl. The term optionally substituted refers to being unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, and 5-6 membered heteroaryl.

Rd3 is independently selected from hydrogen, deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, and 5-6 membered heteroaryl. group, cyano group, oxo group, -Rd4, -ORd4, -SRd4, -S(O)Rd4, -S(O)2Rd4, -C(O)Rd4, -C(O)ORd4, -OC(O)Rd4, -N(Rd4)(Rd5), -C(O) N(Rd4)(Rd5), -N(Rd4)C(O)Rd5, -S(O)N(Rd4)(Rd5), -S(O)2N(Rd4)(Rd5), -N(Rd4)S(O)Rd5, -N(Rd4)S(O)2Rd5;

Rd4 and Rd5 are independently selected each time from hydrogen, deuterium, or optionally substituted groups. C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, or 5-12 membered heteroaryl; optionally substituted groups are unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, 3-7 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl.

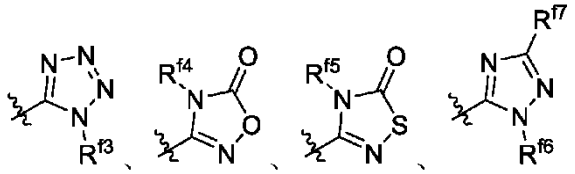
Re is independently selected each time from hydrogen, deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, -ORe1, -SRe1, -S(O)Re1, -S(O)2Re1, -C(O)Re1, -C(O)ORe1, -OC(O)Re1, -N(Re1)(Re2), -C(O)N(Re1)(Re2), -N(Re1)C(O)Re2, -S(O)N(Re1)(Re2), -S(O)2N(Re1)(Re2), -N(Re1)S(O)Re2, -N(Re1)S(O)2Re2, -C(O)N(Re1)S(O)2N(Re1)(Re2), -C(O)N(Re1)S(O)2Re2, -P(O)(Re1)Re2, and the following groups optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) Re3. C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl;

or two Re, together with the atoms to which they are attached, form an optionally substituted 3-10 membered heterocyclyl or an optionally substituted 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl.

Re1 and Re2 are independently selected each time from hydrogen, deuterium, or optionally substituted with the following groups: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from hydrogen, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl.

Re3 is independently selected each time from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -Re4, -ORe4, -SRe4, -S(O)Re4, -S(O)2Re4, -C(O)Re4, -C(O)ORe4, -OC(O)Re4, -N(Re4)(Re5), -C(O)N(Re4)(Re5), -N(Re4)C(O)Re5, -S(O)N(Re4)(Re5), -S(O)2N(Re4)(Re5), -N(Re4)S(O)Re5, -N(Re4)S(O)2Re5, -C(O)N(Re4)S(O)2N(Re4)(Re5), -C(O)N(Re4)S(O)2Re5, -P(O)(Re4)Re5;

Re4, Re5 are independently selected each time from hydrogen, deuterium, optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, 3-7 membered heterocyclyl, phenyl, 5-6 membered heteroaryl.

Rf is selected from -C(O)ORf1, -C(O)N(Rf1)(Rf2); 

Rf1, Rf2, Rf3, Rf4, Rf5, Rf6, and Rf7 are each independently selected from hydrogen, deuterium, optionally

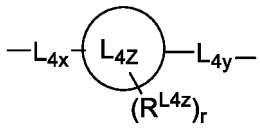
substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl.

R1 and R2, together with the atoms to which they are attached, form a C3-15 carbocyclyl; the C3-15 carbocyclyl is optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) R3. R3 is independently selected from hydrogen, deuterium, halogen, hydroxyl, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C3-10 cycloalkyl, 3-10 membered heterocyclyl; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) substitutable positions of the unsubstituted or substituted group are independently substituted by deuterium, halogen, hydroxyl, amino, cyano, oxo, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

L1 is selected from a bond, -C(RL1)2-, -O-, -C(RL1)2O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -N(RL1)C(O)-, -C(O)N(RL1)-, or -N(RL1)-; RL1 is independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 substituted with an alkynyl, C3-10 cycloalkyl, or 3-10 membered heterocyclyl.

L2 is independently selected from a bond, -C(RL2)2-, -O-, -C(RL2)2O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -N(RL2)C(O)-, -C(O)N(RL2)-, or -N(RL2)-; RL2 is independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, C1-6 alkyl, C1-6 alkoxy, C1-6 alkanamine, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

L3 is independently selected from bond, -C(RL3)2-, -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -N(RL3)C(O)-, -C(O)N(RL3)- or -N(RL3)-; RL3 is independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, C1-6 alkyl, C1-6 alkoxy, C1-6 alkanamine, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

L4 is independently selected from bond, -L4x-C(RL4a)(RL4b)-L4y-, -L4x-O-L4y-, -L4x-S-L4y-, -L4x-C(O)-L4y-, -L4x-C(O)O-L4y-, -L4x-OC(O)-L4y-, -L4x-N(RL4a)C(O)-L4y-, -L4x-C(O)N(RL4a)-L4y-, -L4x-N(RL4a)-L4y-, -L4x-N(RL4a)C(O)N(RL4b)-L4y-, -L4x-N(RL4a)C(S)N(RL4b)-L4y- or 

;

L4x, L4y are each independently selected from bond or optionally substituted C1-10 alkylene; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions independently selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C1-6 alkanamine, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl;

RL4a, RL4b are each independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) substitutable positions of the unsubstituted or substituted group are independently substituted by deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

Ring L4Z is selected from a C3-15 carbocyclyl, a 3-12 membered heterocyclyl, a C6-14 aryl, or a 5-12 membered heteroaryl.

RL4z is independently selected from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl; optionally substituted refers to that one or more substitutable positions of the unsubstituted or substituted group are independently substituted by deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

L5x and L5y are each independently selected from a bond or an optionally substituted C1-10 alkylene group; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the unsubstituted or substituted group are independently substituted with deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, or a 3-10 membered heterocyclyl.

m, n, o, p, q, r are each independently 0, 1, 2, or 3;

Unless otherwise specified, the heteroatoms in the above heterocyclyl and heteroaryl are independently selected from O, N, or S, with 1, 2, 3 or 4 heteroatoms;

Provided that the combination of the above variable definitions forms a stable chemical structure.

In some embodiments, Rd is independently selected each time from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo group, -ORd1, -S(O)Rd1, -S(O)2Rd1, -C(O)Rd1, -C(O)ORd1, -OC(O)Rd1, -N(Rd1)(Rd2), -C(O)N(Rd1)(Rd2), -N(Rd1)C(O)Rd2, -S(O)N(Rd1)(Rd2), -S(O)2N(Rd1)(Rd2), -N(Rd1)S(O)Rd2, -N(Rd1)S(O)2Rd2, and optionally substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) Rd3 groups selected from: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl;

Or two Rd together with the atoms they are attached to form an optionally substituted 3-10 membered heterocyclyl or 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) groups independently selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo group, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl and 5-12 membered heteroaryl.

In some embodiments, wherein, ring A is selected from C3-10 carbocyclyl, 3-10 membered heterocyclyl, C6-10 aryl, 5-10 membered heteroaryl;

Alternatively, ring A is selected from C3-8 carbocyclyl, 3-8 membered heterocyclyl, C6-8 aryl, 5-8 membered heteroaryl;

Alternatively, ring A is selected from C3-6 carbocyclyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl;

Wherein, the heteroatoms in the heterocyclyl and heteroaryl are selected from N, O or S, with 1 or 2 heteroatoms.

In some embodiments, wherein, ring A is C3-10 carbocyclyl; alternatively, ring A is C3-6 carbocyclyl;

Alternatively, ring A is C3-6 carbocyclyl, provided that Ring A is not  or cyclohexyl.

In some embodiments, wherein, ring A is 3-10 membered heterocyclyl; alternatively, ring A is 3-6 membered heterocyclyl; preferably, the heteroatoms in the heterocyclyl are selected from N, O or S, with 1 or 2 heteroatoms.

In some embodiments, ring A is 5-10 membered heteroaryl; alternatively, ring A is 5-8 membered heteroaryl, the heteroatoms in the heteroaryl are selected from N, O or S, with 1, 2 or 3 heteroatoms; alternatively, ring A is selected from 5-membered heteroaryl, 6-membered heteroaryl, the heteroatoms in the heteroaryl are selected from N, O or S, with 1 or 2 heteroatoms; alternatively, ring A is selected from pyridyl, pyrrolyl, furanyl, thienyl; alternatively, ring A is pyrrolyl, furanyl, thienyl.

In some embodiments, ring A is pyridyl.

In some embodiments, wherein, ring A is selected from C6-10 aryl; alternatively, ring A is selected from C6-8 aryl; alternatively, ring A is selected from phenyl.

In some embodiments, wherein, Ra is independently selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo group, -C(O)Ra1, -C(O)ORa1, -OC(O)Ra1, -N(Ra1)(Ra2), -C(O)N(Ra1)(Ra2), -N(Ra1)C(O)(Ra2)), and optionally substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) Ra3 groups selected from: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-4 alkenyl, C2-4 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, C6-8 aryl, 5-6 membered heteroaryl; alternatively, Ra is independently selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo group, -C(O)N(Ra1)(Ra2), -N(Ra1)C(O)(Ra2), and optionally substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) Ra3 groups selected from: C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl; the heteroatoms in the heterocyclyl are O or N, with 1 or 2 heteroatoms;

Alternatively, Ra is independently selected from halogen, hydroxyl, amino, cyano, and optionally substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) Ra3 groups selected from: C1-4 alkyl, C1-4 alkoxy, C3-4 cycloalkyl, 4-5 membered heterocyclyl; the heteroatoms in the heterocyclyl are O or N, with 1 or 2 heteroatoms;

Alternatively, Ra is independently selected from halogen, hydroxyl, amino, cyano, and optionally substituted by one or more (e.g., 2, 3) substituents substituted: C1-4 alkyl, C1-4 alkoxy, C3-4 cycloalkyl, 4-5 membered heterocyclyl; the substituents are selected from halogen, hydroxyl, and amino; the heteroatom in the heterocyclyl is 0, and there is 1 heteroatom.

In some embodiments, wherein, Ra is independently selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -C(O)N(Ra1)(Ra2), -N(Ra1)C(O)(Ra2), C1-6 alkyl, C1-6 alkoxy; the C1-6 alkyl, C1-6 alkoxy are optionally substituted by one or more Ra3 substituents;

Alternatively, Ra is independently selected from halogen, hydroxyl, amino, cyano, C1-4 alkyl, C1-4 alkoxy; the C1-4 alkyl, C1-4 alkoxy are optionally substituted by one or more Ra3 substituents.

In some embodiments, wherein, Ra is independently selected from halogen, hydroxyl, amino, cyano, optionally substituted groups as follows: Methyl, ethyl, n-propyl, isopropyl, n-butyl, methoxy or ethoxy; optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4) substituents selected from deuterium, halogen, hydroxyl, amino.

In some embodiments, wherein, Ra is independently selected from halogen, methyl, cyclopropyl; alternatively, Ra is independently selected from fluorine, methyl, cyclopropyl.

In some embodiments, wherein, Ra is independently selected from fluorine, methyl, deuteromethyl (-CD3), -CF3, methoxy, cyclopropyl, -OCF3.

In some embodiments, wherein, two Ra together with the atoms to which they are attached form an optionally substituted 3-10 membered heterocyclyl group or optionally substituted 5-12 membered heteroaryl group, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl, C6-8 aryl, 5-6 membered heteroaryl.

Alternatively, two Ra together with the atoms to which they are attached form an optionally substituted 3-6 membered heterocyclyl group or optionally substituted 5-6 membered heteroaryl group, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, or 4) groups selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, methyl, ethyl, n-propyl, isopropyl, n-butyl, methoxy, ethoxy.

In some embodiments, wherein, Ra1 and Ra2 are independently selected from hydrogen, deuterium, optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl.

Alternatively, Ra1 and Ra2 are independently selected from hydrogen, C1-6 alkyl (e.g., C1-3 alkyl; preferably methyl or ethyl); the C1-6 alkyl is optionally substituted with one or more substituents selected from hydrogen, halogen, hydroxyl, amino; alternatively, Ra1 and Ra2 are independently selected from hydrogen.

In some embodiments, wherein, Ra3 is independently selected from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -Ra4, -ORa4, -C(O)Ra4, -C(O)ORa4, -OC(O)Ra4, -N(Ra4)(Ra5), -C(O)N(Ra4)(Ra5), -N(Ra4)C(O)Ra5.

In some embodiments, wherein, Ra3 is independently selected from hydrogen, halogen, hydroxyl, amino, -Ra4; wherein, Ra4 is independently selected from C1-6 alkyl (e.g., C1-3 alkyl; preferably methyl or ethyl), C1-6 alkoxy (e.g., C1-3 alkoxy; preferably methoxy or ethoxy); the C1-6 alkyl is optionally substituted with one or more substituents selected from hydrogen, halogen.

In some embodiments, wherein, Ra3 is independently selected from hydrogen, halogen; alternatively, Ra3 is independently selected from hydrogen, fluorine, chlorine.

In some embodiments, wherein, Ra4 and Ra5 are independently selected from hydrogen and optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxyl, amino, cyano, methyl, ethyl, n-propyl, isopropyl, n-butyl, methoxy, ethoxy;

Alternatively, Ra4 and Ra5 are independently selected from hydrogen, C1-4 alkyl; the C1-4 alkyl is optionally substituted with one or more (e.g., 2, 3, or 4) substituents selected from hydrogen, halogen.

In some embodiments, wherein, Ra4 and Ra5 are independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, difluoromethyl, monofluoromethyl, trichloromethyl, dichloromethyl, monochloromethyl.

In some embodiments, wherein, m is selected from 0, 1, 2, 3; alternatively, m is selected from 2, 3.

In some embodiments, wherein, L1 is selected from a bond, -C(RL1)2-, -C(RL1)2O-, -O-, -C(O)-, -N(RL1)C(O)-, -C(O)N(RL1)-; RL1 is selected from hydrogen, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxyl, amino, cyano, C1-4 alkyl, C1-4 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl;

Alternatively, L1 is selected from a bond, -C(RL1)2-, -C(RL1)2O-; RL1 is selected from hydrogen, or optionally substituted C1-4 alkyl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3) groups selected from halogen, hydroxyl, amino, cyano;

Alternatively, L1 is selected from a bond, -C(RL1)2-, -C(RL1)2O-; RL1 is selected from hydrogen, optionally substituted methyl or optionally substituted ethyl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3) groups selected from fluorine, chlorine, bromine, hydroxyl, amino, cyano;

Alternatively, L1 is selected from a bond, -CH(CH3)-, -CH2-, -CH2O-; alternatively, L1 is selected from a

bond, -CH2-; alternatively, L1 is selected from a bond.

In some embodiments, L1 is not -CH(CH3)-.

In some embodiments, wherein, ring B is selected from 3-10 membered heterocyclyl, C6-10 aryl, 5-10 membered heteroaryl;

Alternatively, ring B is selected from 4-6 membered monocyclic heterocyclyl, 8-10 membered bicyclic heterocyclyl, phenyl, naphthyl, 5-6 membered monocyclic heteroaryl, 8-10 membered bicyclic heteroaryl;

Alternatively, ring B is selected from 8-10 membered bicyclic heterocyclyl, 8-10 membered bicyclic heteroaryl;

Alternatively, ring B is selected from 8-9 membered bicyclic heterocyclyl, 8-9 membered bicyclic heteroaryl; the heteroatoms in the 8-9 membered bicyclic heterocyclyl and 8-9 membered bicyclic heteroaryl are selected from N or S, with the number of heteroatoms being 1, 2, or 3;

In some embodiments, ring B is selected from 9-membered fused heterocyclyl, 9-membered bicyclic heteroaryl; wherein, the fused heterocyclyl is a heterocyclyl fused with a heteroaryl, the bicyclic heteroaryl is a heteroaryl fused with a heteroaryl or a heteroaryl fused with an aryl; the heteroatoms in the 9-membered fused heterocyclyl are N, with the number of heteroatoms being 3; the heteroatoms in the 9-membered bicyclic heteroaryl are N, with the number of heteroatoms being 1 or 2.

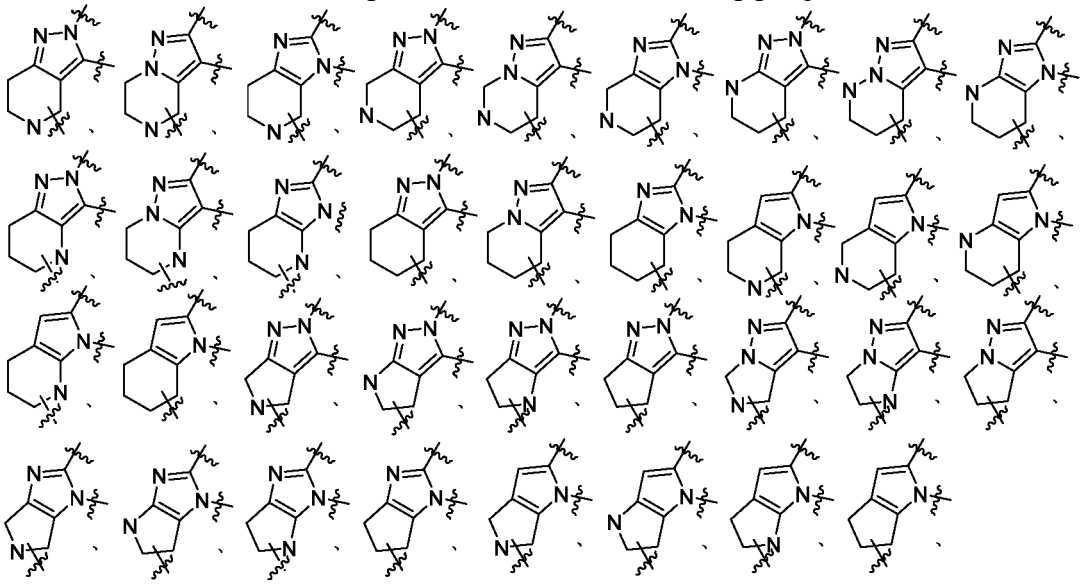
In some embodiments, wherein, ring B is selected from 4-6 membered heterocyclyl, 4-6 membered monocyclic heterocycloalkenyl, phenyl, naphthyl, 5-6 membered monocyclic heteroaryl, 3/5 membered fused heterocyclyl, 5/3 membered fused heterocyclyl, 4/4 membered fused heterocyclyl, 4/5 membered fused heterocyclyl, 5/4 membered fused heterocyclyl, 5/5 membered fused heterocyclyl, 4/6 membered fused heterocyclyl, 6/4 membered fused heterocyclyl, 5/6 membered fused heterocyclyl, 6/5 membered fused heterocyclyl, 6/6 membered fused heterocyclyl, 6/7 membered fused heterocyclyl, 7/6 membered fused heterocyclyl, 5/5 membered fused heteroaryl, 5/6 membered fused heteroaryl, 6/5 membered fused heteroaryl, 6/6 membered fused heteroaryl;

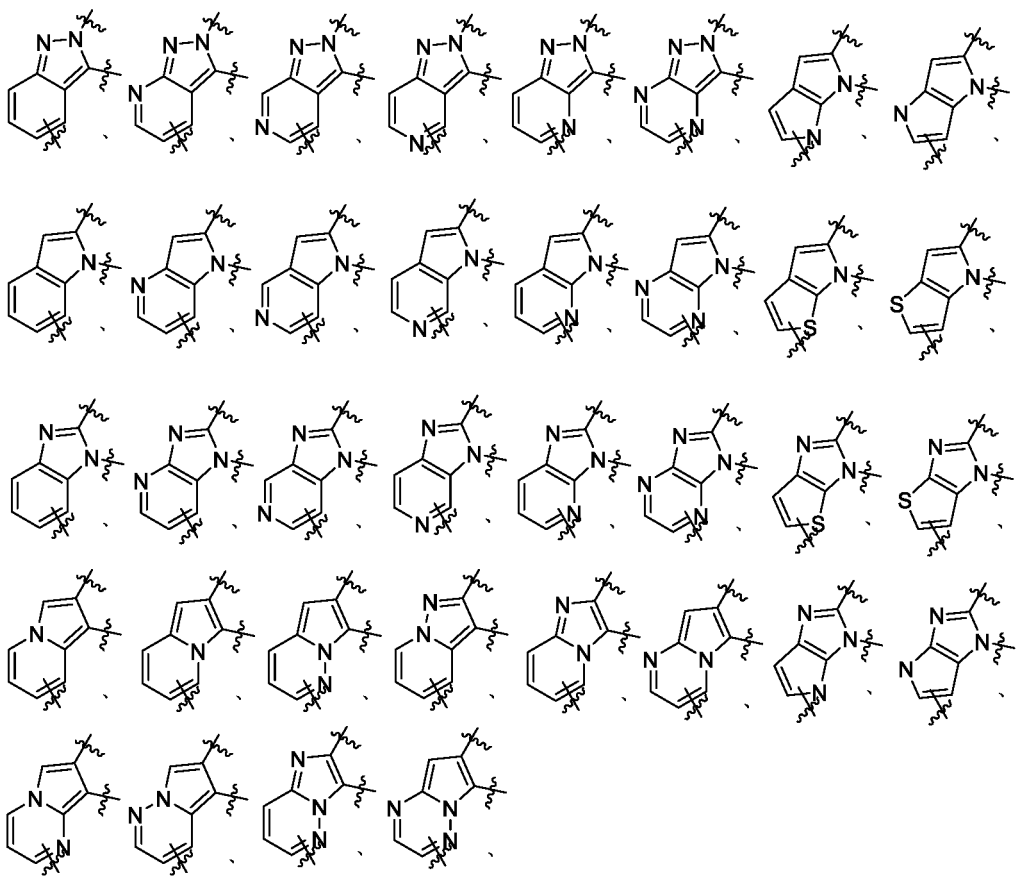
Alternatively, ring B is selected from 5/5 membered fused heterocyclyl, 5/6 membered fused heterocyclyl, 6/5 membered fused heterocyclyl, 5/5 membered fused heteroaryl, 5/6 membered fused heteroaryl, 6/5 membered fused heteroaryl;

Alternatively, ring B is selected from 5/5 membered fused heterocyclyl, 5/6 membered fused heterocyclyl, 6/5 membered fused heterocyclyl, the heteroatoms in the 5/5, 5/6, and 6/5 fused heterocyclyl are selected from N, with the number of heteroatoms being 1, 2, or 3;

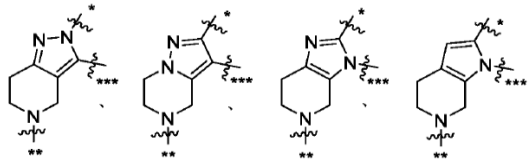
Alternatively, ring B is selected from 5/6 membered fused heterocyclyl, 6/5 membered fused heterocyclyl, the heteroatoms in the 5/6 and 6/5 fused heterocyclyl are selected from N, with the number of heteroatoms being 3.

In some embodiments, wherein, ring B is selected from the following groups:

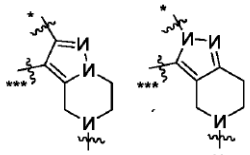


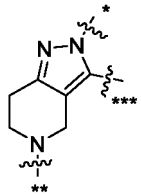


In some embodiments, wherein, ring B is selected from the following groups:



, wherein, the "*" end is the end connected to L1, the "**" end is the end connected to L2, the "***" end is the end connected to L4;

Alternatively, ring B is selected from the following groups: , wherein, the "*" end is the end connected to L1, the "**" end is the end connected to L2, the "***" end is the end connected to L4;



Alternatively, ring B is selected from , wherein, the "*" end is the end connected to L1, the "**" end is the end connected to L2, the "***" end is the end connected to L4.

In some embodiments, wherein, Rb is independently selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-4 alkenyl, C2-4 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, C6-8 aryl, 5-6 membered heteroaryl; optionally substituted refers to unsubstituted or at one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the substituent group each independently substituted with Rb1;

Alternatively, Rb is independently selected from halogen, hydroxyl, amino, mercapto, cyano, oxo, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy; optionally substituted refers to unsubstituted or at one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the substituent group each independently

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substituted with Rb1;

Alternatively, Rb is independently selected from halogen, hydroxyl, amino, cyano, or optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy; optionally substituted refers to unsubstituted or at one or more (e.g., 2, 3, 4, or 5) substitutable positions each independently substituted with Rb1;

Alternatively, Rb is independently selected from C1-4 alkyl (preferably C1-3 alkyl);

Alternatively, Rb is independently selected from methyl.

In some embodiments, wherein, two Rb together with the atoms to which they are attached form an optionally substituted 3-10 membered heterocyclyl or optionally substituted 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl, C6-8 aryl, 5-6 membered heteroaryl.

Alternatively, two Rb together with the atoms to which they are attached form an optionally substituted 3-7 membered heterocyclyl or optionally substituted 5-6 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, methyl, ethyl, methoxy, ethoxy.

In some embodiments, wherein, Rb1 is independently selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -Rb2, -ORb2, -C(O)Rb2, -C(O)ORb2, -OC(O)Rb2, -N(Rb2)(Rb3), -C(O)N(Rb2)(Rb3), -N(Rb2)C(O)(Rb3);

Alternatively, Rb1 is independently selected from halogen, hydroxyl, amino, -Rb2;

Alternatively, Rb1 is independently selected from halogen (e.g., fluorine, chlorine, bromine).

In some embodiments, wherein, Rb2 and Rb3 are each independently selected from hydrogen, optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl, C6-8 aryl, 5-6 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxyl, amino, cyano, C1-6 alkyl, C1-6 alkoxy;

Alternatively, Rb2 and Rb3 are each independently selected from hydrogen, optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5) groups selected from halogen, hydroxyl, amino, cyano;

Alternatively, Rb2 and Rb3 are each independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, methoxy, trifluoromethyl, difluoromethyl, monofluoromethyl, trichloromethyl, dichloromethyl, monochloromethyl.

In some embodiments, wherein, n is independently selected from 0, 1, 2; preferably, n is independently selected from 0, 1; more preferably, n is 1.

In some embodiments, wherein, L2 is independently selected from a bond, -C(RL2)2-, -O-, -C(RL2)2O-, -C(O)-, -N(RL2)C(O)-, -C(O)N(RL2)-; RL2 is selected from hydrogen, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxyl, amino, cyano, C1-4 alkyl, C1-4 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl;

Alternatively, L2 is independently selected from a bond, -C(RL2)2-, -C(RL2)2O-, -C(O)-; RL2 is selected from hydrogen, or C1-4 alkyl optionally substituted with one or more (e.g., 2, 3, 4) groups selected from halogen, hydroxyl, amino, cyano;

Alternatively, L2 is independently selected from a bond, -C(RL2)2-, -C(O)-; RL2 is selected from hydrogen, methyl or ethyl optionally substituted with one or more (e.g., 2, 3) groups selected from fluorine, chlorine, bromine, hydroxyl, amino, cyano;

In some embodiments, wherein, L2 is independently selected from a bond, -CH2-, -CH2O-, -O-, -C(O)-, -NHC(O)-, -C(O)NH-;

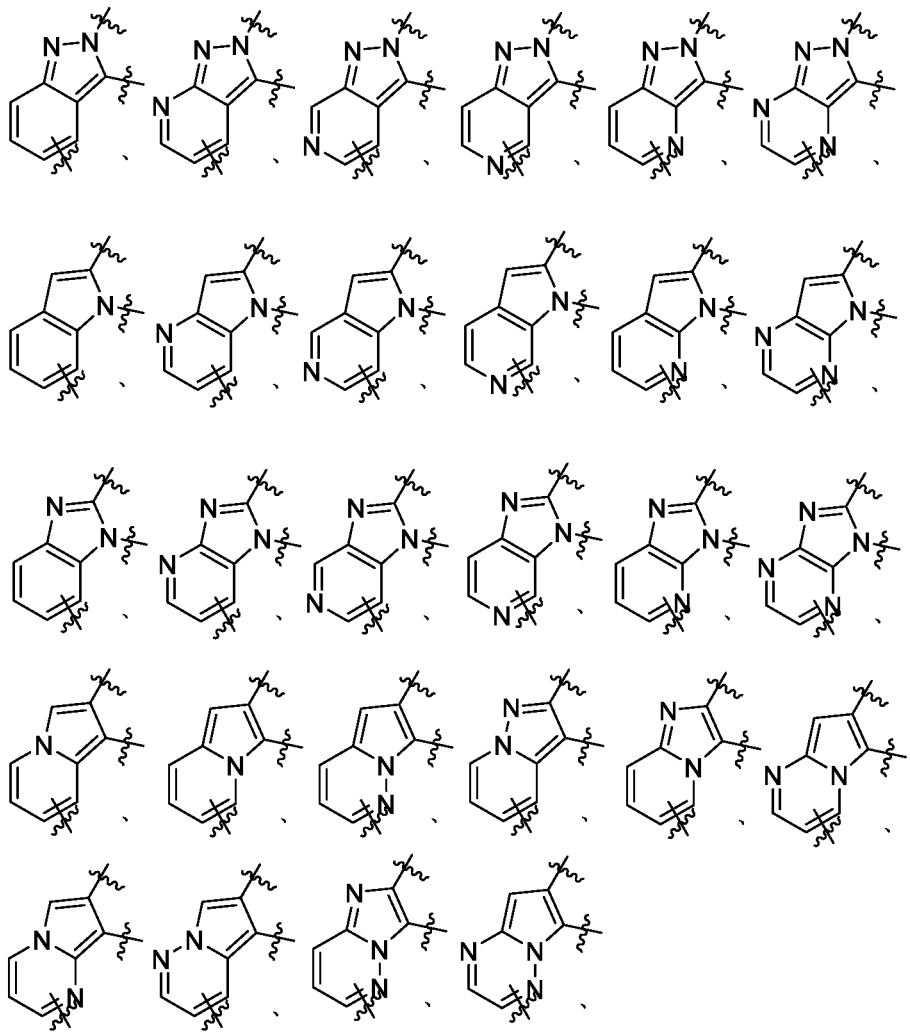
Alternatively, L2 is independently selected from a bond, -CH2-, -C(O)-;

Alternatively, L2 is -C(O)-.

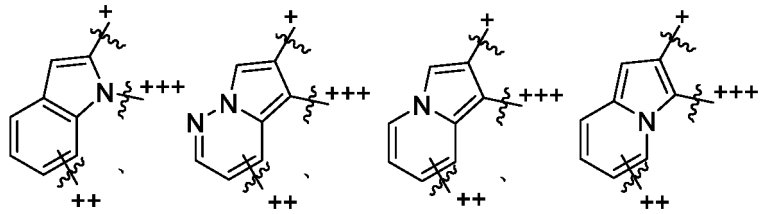
In some embodiments, wherein, ring C is independently selected from 9-membered fused bicyclic heteroaryl (e.g., a bicyclic system composed of heteroaryl fused with heteroaryl, or aryl fused with heteroaryl); the heteroatoms in the 9-membered fused heteroaryl are nitrogen, with the number of heteroatoms being 1, 2, or 3;

Alternatively, ring C is independently selected from 5/6 membered fused heteroaryl (e.g., a bicyclic system formed by fusion of heteroaryl with heteroaryl, or aryl with heteroaryl), the heteroatoms in the 5/6 fused heteroaryl are selected from nitrogen, with the number of heteroatoms being 1 or 2;

Alternatively, ring C is independently selected from the following groups:

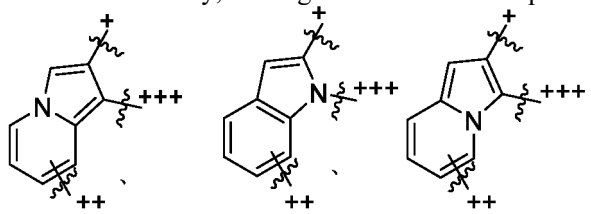


Alternatively, ring C is selected from the following groups:



, wherein, the "+" end is the end connected to L2, the "++" end is the end connected to L3, and the "+++" end is the end connected to L5x;

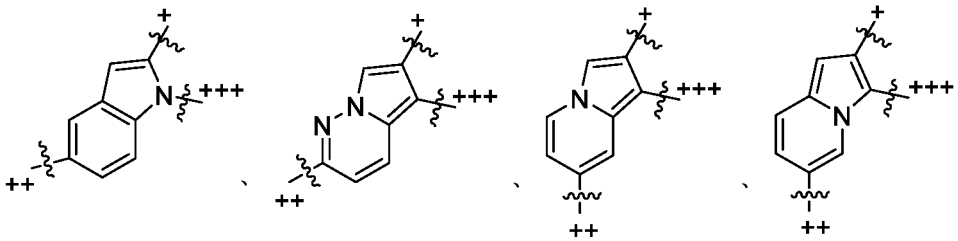
Alternatively, ring C is independently selected from the following groups: ,



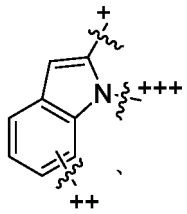
, wherein, the "+" end is the end connected to L2, the "++" end is the end connected to L3, and the "+++" end is the end connected to L5x.

Alternatively, ring C is selected from the following groups:

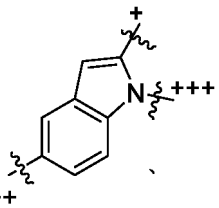
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, wherein, the "+" end is the end connected to L2, the "++" end is the end connected to L3, and the "+++" end is the end connected to L5x;



In some embodiments, ring C is independently selected from , wherein, the "+" end is the end connected to L2, the "++" end is the end connected to L3, and the "+++" end is the end connected to L5x.



In some embodiments, ring C is , wherein, the "+" end is the end connected to L2, the "++" end is the end connected to L3, and the "+++" end is the end connected to L5x.

In some embodiments, wherein, Rc is independently selected from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-4 alkenyl, C2-4 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl; optionally substituted refers to unsubstituted or substituted at one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions each independently substituted with Rc1;

Alternatively, Rc is independently selected from hydrogen, halogen, hydroxyl, amino, cyano, oxo, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy (preferably C1-3 alkoxy, e.g., methoxy, ethoxy); optionally substituted refers to unsubstituted or substituted at one or more (e.g., 2, 3, 4, 5, 6) substitutable positions each independently substituted with Rc1;

Alternatively, Rc is independently selected from hydrogen, halogen, hydroxyl, amino, cyano, oxo, or optionally substituted C1-4 alkyl; optionally substituted refers to unsubstituted or substituted at one or more (e.g., 2, 3) substitutable positions each independently substituted with Rc1;

Alternatively, Rc is independently selected from hydrogen, halogen, hydroxyl, amino, cyano, oxo, C1-4 alkyl (preferably C1-3 alkyl);

Alternatively, Rc is independently selected from hydrogen, fluorine, chlorine, oxo, methyl, ethyl, n-propyl, isopropyl, n-butyl;

Alternatively, Rc is independently selected from hydrogen, fluorine, chlorine;

Alternatively, Rc is independently selected from hydrogen.

In some embodiments, wherein, two Rc together with the atoms to which they are attached form an optionally substituted 3-6 membered heterocyclyl or optionally substituted 5-6 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl (preferably C1-3 alkyl), C1-6 alkoxy (preferably C1-3 alkoxy), C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl.

Alternatively, two Rc together with the atoms to which they are attached form an optionally substituted 3-6 membered heterocyclyl or optionally substituted 5-6 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxyl, amino, cyano, oxo, methyl, ethyl, methoxy, ethoxy.

In some embodiments, wherein, Rc1 is independently selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -Rc2, -ORc2, -C(O)Rc2, -C(O)ORc2, -OC(O)Rc2, -N(Rc2)(Rc3), -C(O)N(Rc2)(Rc3), -N(Rc2)C(O)Rc3;

Alternatively, Rc1 is independently selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -

Rc2, -ORc2;

Alternatively, Rc1 is independently selected from halogen (e.g., fluorine, chlorine, bromine).

In some embodiments, wherein, Rc2 and Rc3 are each independently selected from hydrogen, optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy, C2-4 alkenyl, C2-4 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, C6-8 aryl, 5-6 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxyl, amino, cyano, C1-6 alkyl, C1-6 alkoxy,

Alternatively, Rc2 and Rc3 are each independently selected from hydrogen, optionally substituted groups as follows: C1-4 alkyl (preferably C1-3 alkyl), C1-4 alkoxy (preferably C1-3 alkoxy); optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4) groups selected from halogen, hydroxyl, amino, cyano;

Alternatively, Rc2 and Rc3 are each independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, methoxy, trifluoromethyl, difluoromethyl, monofluoromethyl, trichloromethyl, dichloromethyl, monochloromethyl.

In some embodiments, wherein, o is independently selected from 0, 1, 2; preferably, o is independently selected from 0, 1; more preferably, o is 0.

In some embodiments, wherein, L3 is independently selected from a bond, -C(RL3)2-, -O-, -C(O)-, -N(RL3)C(O)-, -C(O)N(RL3)-; RL3 is selected from hydrogen, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxyl, amino, cyano, C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl;

Alternatively, L3 is independently selected from a bond, -C(RL3)2-, -C(O)-; RL3 is selected from hydrogen, or optionally substituted C1-4 alkyl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4) groups selected from halogen, hydroxyl, amino, cyano.

Alternatively, L3 is independently selected from a bond, -C(RL3)2-, or -C(O)-; RL3 is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, or n-butyl.

In some embodiments, wherein, L3 is independently selected from a bond, -CH2-, -CH(CH3)-, -O-, -C(O)-, -NHC(O)-, or -C(O)NH-;

Alternatively, L3 is independently selected from a bond, -CH2-, or -C(O)-;

Alternatively, L3 is independently selected from a bond.

In some embodiments, wherein, ring D is selected from a C3-10 carbocyclyl, a 3-10 membered heterocyclyl, a C6-10 aryl, or a 5-10 membered heteroaryl;

Alternatively, ring D is selected from a C3-8 carbocyclyl, a 3-8 membered heterocyclyl, a C6-8 aryl, or a 5-8 membered heteroaryl.

Alternatively, ring D is selected from a C3-6 carbocyclyl, a 3-6 membered heterocyclyl, a phenyl, or a 5-6 membered heteroaryl. The heteroatoms in the heterocyclyl or heteroaryl group are selected from N, O, or S, and the number of heteroatoms is 1, 2, or 3.

In some embodiments, wherein, ring D is independently selected from a C3-10 carbocyclyl.

Alternatively, ring D is independently selected from a C3-6 carbocyclyl.

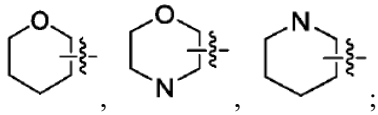
In some embodiments, ring D is independently selected from a 3-10 membered heterocyclyl;

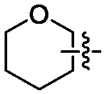
Alternatively, ring D is independently selected from a 3-6 membered heterocyclyl.

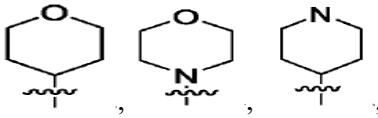
In some embodiments, wherein, ring D is independently selected from a 4- to 6-membered heterocyclyl; the heteroatom in the heterocyclyl is selected from N or O, and the number of heteroatoms is 1 or 2.

In some embodiments, wherein, ring D is selected from tetrahydropyranyl, morpholinyl, piperidinyl, pyrazinyl, tetrahydrofuranyl:

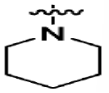
Alternatively, ring D is selected from tetrahydropyranyl.

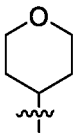
In some embodiments, wherein, ring D is independently selected from ;

Alternatively, ring D is independently selected from :

In some embodiments, wherein, ring D is independently selected from ,

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;



Alternatively, ring D is independently selected from .

In some embodiments, wherein, ring D is independently selected from a C6-10 aryl group or a 5-10 membered heteroaryl group;

Alternatively, ring D is independently selected from a C6-8 aryl group or a 5-8 membered heteroaryl group, the heteroatom in the heteroaryl group is selected from N, O, or S, and the number of heteroatoms is 1 or 2;

Alternatively, ring D is independently selected from a phenyl group, a 5-membered heteroaryl group, or a 6-membered heteroaryl group, the heteroatom in the heteroaryl group is selected from N, O, or S, and the number of heteroatoms is 1 or 2;

Alternatively, ring D is independently selected from a phenyl group, a pyridyl group, a pyrrolyl group, a furanyl group, or a thienyl group;

Alternatively, ring D is independently selected from a pyridyl group.

In some embodiments, wherein, Rd is independently selected from deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, -C(O)Rd1, -C(O)ORd1, -OC(O)Rd1, -N(Rd1)(Rd2), -C(O)N(Rd1)(Rd2), -N(Rd1)C(O)(Rd2), or the following groups optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) Rd3: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-4 alkenyl, C2-4 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, C6-8 aryl, 5-6 membered heteroaryl;

Alternatively, Rd is independently selected from halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, -N(Rd1)(Rd2), - C(O)N(Rd1)(Rd2), -N(Rd1)C(O)(Rd2), or the following groups optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) Rd3. C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, or a 3-6-membered heterocyclyl group; the heteroatom in the heterocyclyl group is O or N, and the number of heteroatoms is 1 or 2;

Alternatively, Rd is independently selected from halogen, hydroxy, amino, or cyano; or the following groups optionally substituted with one or more (e.g., 2 or 3) Rd3. C1-4 alkyl, C1-4 alkoxy, C3-4 cycloalkyl, 4-5 membered heterocyclyl; the heteroatom in the heterocyclyl is O or N, and the number of heteroatoms is 1 or 2;

Alternatively, Rd is independently selected from halogen, hydroxy, amino, cyano, and optionally substituted groups: C1-4 alkyl (preferably C1-3 alkyl), C1-4 alkoxy (preferably C1-3 alkoxy), C3-4 cycloalkyl, 4-5 membered heterocyclyl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2 or 3) substituents selected from halogen, hydroxy, and amino; the heteroatom in the heterocyclyl is O, and the number of heteroatoms is 1.

In some embodiments, wherein, Rd is independently selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, -N(Rd1)(Rd2), -C(O)N(Rd1)(Rd2), -N(Rd1)C(O)(Rd2)), optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) Rd3. C1-6 alkyl, C1-6 alkoxy;

Alternatively, Rd is independently selected from halogen, hydroxy, amino, cyano, or the following groups optionally substituted with one or more (e.g., 2, 3, or 4) Rd3: C1-4 alkyl, C1-4 alkoxy;

Alternatively, Rd is independently selected from halogen, hydroxyl, amino, cyano, and optionally substituted groups: C1-4 alkyl (preferably C1-3 alkyl), C1-4 alkoxy (preferably C1-3 alkoxy); the term "optionally substituted" refers to being unsubstituted or substituted with one or more (e.g., two or three) substituents selected from halogen, hydroxyl, and amino.

In some embodiments, wherein, Rd is independently selected from halogen, hydroxyl, amino, cyano, and optionally substituted groups: Methyl, ethyl, n-propyl, isopropyl, n-butyl, methoxy, and ethoxy; the term "optionally substituted" refers to being unsubstituted or substituted with one or more (e.g., two or three) substituents selected from halogen, hydroxyl, and amino.

Preferably, Rd is independently selected from methyl, methoxy, and ethoxy.

In some embodiments, wherein, two Rd, together with the atoms to which they are attached, form an optionally substituted: 3-10 membered heterocyclyl, 3-7 membered cycloalkyl, or 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl, C6-8 aryl, or 5-6 membered heteroaryl.

Alternatively, the two Rd together with the atoms to which they are attached are Forming an optionally substituted: 3-6 membered heterocyclyl (e.g., 3-, 4-, 5-, or 6-membered heterocyclyl), 3-6 membered cycloalkyl (e.g., 3-, 4-, 5-, or 6-membered cycloalkyl), or 5-6 membered heteroaryl, the optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxy,

amino, nitro, mercapto, cyano, oxo, methyl, ethyl, n-propyl, isopropyl, n-butyl, methoxy, or ethoxy.

In some embodiments, wherein, Rd1 and Rd2 are each independently selected from hydrogen, deuterium, and optionally substituted groups: C1-6 alkyl (preferably C1-3 alkyl), C1-6 alkoxy (preferably C1-3 alkoxy), C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, and 5-6 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, and 5-6 membered heteroaryl.

Alternatively, Rd1 and Rd2 are each independently selected from hydrogen, C1-6 alkyl (preferably C1-3 alkyl); the C1-6 alkyl (preferably C1-3 alkyl) is optionally substituted with one or more (e.g., two, three, or four) substituents selected from hydrogen, halogen, hydroxyl, and amino.

Alternatively, Rd1 and Rd2 are each independently selected from hydrogen.

In some embodiments, wherein, Rd3 is independently selected from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, -Rd4, -ORd4, -C(O)Rd4, -C(O)ORd4, -OC(O)Rd4, -N(Rd4)(Rd5), -C(O)N(Rd4)(Rd5), or -N(Rd4)C(O)Rd5.

In some embodiments, wherein, Rd3 is independently selected from hydrogen, halogen, hydroxy, amino, -Rd4; Rd4 is independently selected from C1-6 alkyl, C1-6 alkoxy; the C1-6 alkyl, C1-6 alkoxy group is optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from hydrogen and halogen.

Alternatively, Rd3 is independently selected from hydrogen, halogen, hydroxy, amino, or -Rd4; Rd4 is independently selected from C1-4 alkyl or C1-4 alkoxy; and the C1-4 alkyl or C1-4 alkoxy group is optionally substituted with one or more (e.g., 2, 3, 4, or 5) substituents selected from hydrogen or halogen.

Alternatively, Rd3 is independently selected from hydrogen, halogen, hydroxy, amino, or -Rd4; Rd4 is independently selected from C1-3 alkyl or C1-3 alkoxy; and the C1-3 alkyl or C1-3 alkoxy group is optionally substituted with one or more (e.g., 2 or 3) substituents selected from hydrogen or halogen.

In some embodiments, wherein, Rd3 is independently selected from hydrogen or halogen;

Alternatively, Rd3 is independently selected from hydrogen, fluorine, or chlorine.

In some embodiments, wherein, Rd4, Rd5 are independently selected from hydrogen, optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl; the term "optionally substituted" refers to being unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, cyano, methyl, ethyl, n-propyl, isopropyl, n-butyl, methoxy, or ethoxy.

Alternatively, Rd4 and Rd5 are each independently selected from hydrogen or C1-4 alkyl; the C1-4 alkyl is optionally substituted with one or more (e.g., 2, 3, or 4) substituents selected from hydrogen or halogen.

Preferably, Rd4 and Rd5 are each independently selected from hydrogen or C1-3 alkyl; the C1-3 alkyl is optionally substituted with one or more (e.g., 2 or 3) substituents selected from hydrogen or halogen.

In some embodiments, wherein, Rd4 and Rd5 are each independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, methoxy, trifluoromethyl, difluoromethyl, monofluoromethyl, trichloromethyl, dichloromethyl, and monochloromethyl.

In some embodiments, wherein, p is independently selected from 0, 1, or 2;

Alternatively, p is independently selected from 1 or 2;

Alternatively, p is 2.

In some embodiments, wherein, L4 is selected from a bond, -L4x-O-L4y-, -L4x-S-L4y-, -L4x-C(O)-L4y-, -L4x-N(RL4a)C(O)-L4y-, -L4x-C(O)N(RL4a)-L4y-, -L4x-N(RL4a)-L4y-, -L4x-N(RL4a)C(O)N(RL4b)-L4y-, -L4x-N(RL4a)C(S)N(RL4b)-L4y-; L4x, L4y is independently selected from a bond, or optionally substituted C1-6 alkylene (preferably C1-3 alkylene), optionally substituted refers to that one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) substitutable positions of the unsubstituted or substituted group are independently substituted by a substituent selected from deuterium, halogen, hydroxyl, amino, cyano, oxo, C1-4 alkyl, C1-4 alkoxy, C3-16 cycloalkyl, or 3-6 membered heterocyclyl. RL4a and RL4b are independently selected from hydrogen or optionally substituted groups as follows: C1-6 alkyl (preferably C1-3 alkyl), C1-6 alkoxy (preferably C1-3 alkoxy), C3-6 cycloalkyl; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the unsubstituted or substituted group are independently substituted with a substituent selected from deuterium, halogen, hydroxyl, amino, cyano, C1-4 alkyl, C1-4 alkoxy, C3-6 cycloalkyl, or 3-6 membered heterocyclyl.

In some embodiments, wherein, L4 is selected from -L4x-N(RL4a)-L4y-, -L4x-N(RL4a)C(O)N(RL4b)-L4y-, -L4x-N(RL4a)C(S) N(RL4b)-L4y-; L4x and L4y are each independently selected from a bond, or optionally substituted methylene or ethylene. Optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the unsubstituted or substituted group are independently substituted with substituents selected from fluorine, chlorine, bromine, hydroxyl, amino, cyano, or oxo. RL4a and RL4b are each independently selected from hydrogen, or optionally substituted: Methyl, ethyl, n-propyl, isopropyl, n-butyl, cyclopropane, cyclobutane, optionally substituted refers to unsubstituted or one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) substitutable

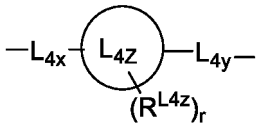
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sites of the substituted group are independently substituted by substituents selected from fluorine, chlorine, bromine, hydroxyl, amino, and cyano.

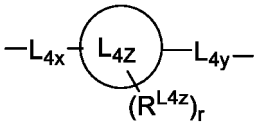
In some embodiments, wherein, L4 is selected from -NHC(O)NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-, -N(methyl)C(O)NH-, -N(methyl)C(O)N(methyl)-, -NHC(S)NH-, or -NH-;

Alternatively, L4 is selected from -NHC(O)NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-, or -N(methyl)C(O)NH-;

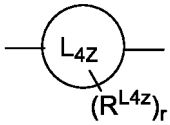
Alternatively, L4 is selected from -NHC(O)NH-.



In some embodiments, wherein, L4 is selected from ; ring L4z is independently selected from C3-10 carbocyclyl, 5-10 membered heterocyclyl, C6-8 aryl, 5-10 membered heteroaryl; L4x and L4y are independently selected from a bond, or optionally substituted C1-6 alkylene (preferably C1-3 alkylene, more preferably C1-2 alkylene); and optionally substituted refers to unsubstituted or substituted groups, one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions are independently substituted with a group selected from deuterium, halogen, hydroxy, amino, cyano, oxo, C1-4 alkyl, C1-4 alkoxy, C3-6 cycloalkyl, or 3-6 membered heterocyclyl. RL4z is independently selected from hydrogen, halogen, oxo, or the optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy; optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the unsubstituted or substituted group independently substituted by a group selected from deuterium, halogen, hydroxy, amino, cyano, C1-4 alkyl, C1-4 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl. r is independently selected from 0, 1, 2.

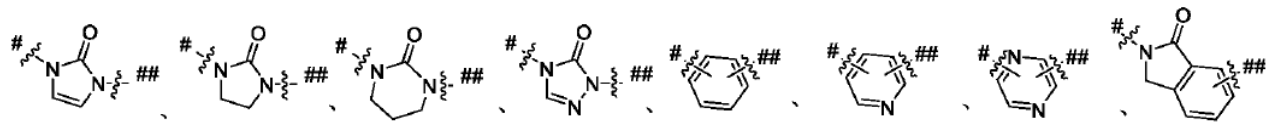


In some embodiments, wherein, L4 is selected from ; ring L4Z is selected from 5-10 membered heterocyclyl, phenyl, 6-8 membered monocyclic heteroaryl, 8-10 membered bicyclic heteroaryl; L4x, L4y are independently selected from a bond, or optionally substituted groups as follows: Methylene, ethylene, optionally substituted refers to one or more (e.g., 2, 3) substitutable positions of the unsubstituted or substituted group independently substituted by a group selected from fluoro, chloro, bromo, hydroxy, amino, cyano, oxo. RL4z is independently selected from hydrogen, halogen, oxo, or optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy, optionally substituted refers to one or more (e.g., 2, 3) substitutable positions of the unsubstituted or substituted group independently substituted by a group selected from halogen, hydroxy, amino, cyano. r is independently selected from 0, 1.



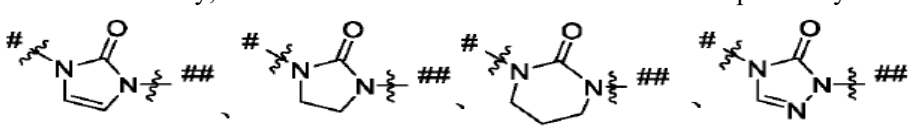
In some embodiments, wherein, L4 is selected from , ring L4Z is selected from 5-10 membered heterocyclyl (preferably 5-6 membered heterocyclyl), phenyl, 6-8 membered monocyclic heteroaryl; RL4z is independently selected from hydrogen, fluoro, chloro, bromo, oxo, methyl, ethyl, n-propyl, isopropyl, methoxy, trifluoromethyl, difluoromethyl, monofluoromethyl, trichloromethyl, dichloromethyl, monochloromethyl; r is independently selected from 1.

In some embodiments, wherein, L4 is selected from



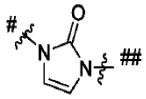
, wherein, the "#" end is connected to ring B and the "##" end is connected to ring E;

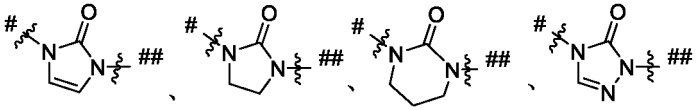
Alternatively, L4 is independently selected from

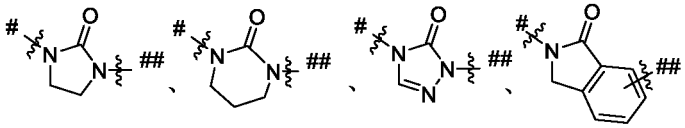


, wherein, the "#" end is connected to ring B and the "##" end is connected to ring E;

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Alternatively, L4 is independently selected from , wherein, the "#" end is connected to ring B and the "##" end is connected to ring E.

In some embodiments, L4 is -NHC(O)NH-, -N(methyl)C(O)NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-, , wherein, the "#" end is connected to ring B and the "##" end is connected to ring E.

In some embodiments, L4 is -NHC(O)NH-, , wherein, the "#" end is connected to ring B and the "##" end is connected to ring E.

In some embodiments, wherein, ring E is independently selected from C3-10 carbocyclyl, 3-10 membered heterocyclyl, C6-10 aryl, 5-10 membered heteroaryl;

Alternatively, ring E is independently selected from C3-8 carbocyclyl, 3-8 membered heterocyclyl, phenyl, naphthyl, 5-10 membered heteroaryl;

Alternatively, ring E is independently selected from C3-6 carbocyclyl, 3-6 membered heterocyclyl, phenyl, naphthyl, 5-10 membered heteroaryl; the heteroatoms in the heterocyclyl and heteroaryl are selected from N, O, or S, with the number of heteroatoms being 1, 2, or 3.

In some embodiments, wherein, ring E is independently selected from C3-10 carbocyclyl;

Alternatively, ring E is independently selected from C3-6 carbocyclyl.

In some embodiments, wherein, ring E is independently selected from 3-10 membered heterocyclyl;

Alternatively, ring E is independently selected from 3-6 membered heterocyclyl.

In some embodiments, wherein, ring E is independently selected from C6-10 aryl, 5-10 membered heteroaryl;

Alternatively, ring E is independently selected from phenyl, naphthyl, 5-10 membered heteroaryl, the heteroatoms in the heteroaryl are selected from N, O, or S, with the number of heteroatoms being 1, 2, or 3;

Alternatively, ring E is independently selected from phenyl, naphthyl, 8-9 membered bicyclic heteroaryl; the heteroatoms in the heteroaryl are selected from N, O, or S, with the number of heteroatoms being 1, 2, or 3;

Alternatively, ring E is independently selected from 9-membered bicyclic heteroaryl; the heteroatoms in the heteroaryl are selected from N, O, or S, with the number of heteroatoms being 1, 2, or 3.

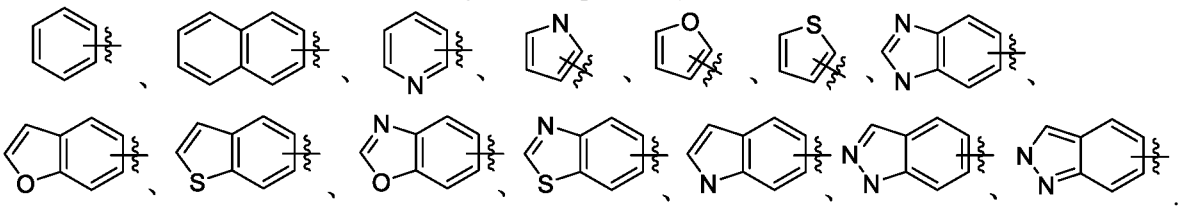
In some embodiments, wherein, ring E is independently selected from phenyl, naphthyl, 5-membered heteroaryl, 6-membered heteroaryl, 5/5 fused heteroaryl, 5/6 fused heteroaryl, 6/5 fused heteroaryl, 6/6 fused heteroaryl; the heteroatoms in the heteroaryl are selected from N, O, or S, with the number of heteroatoms being 1 or 2;

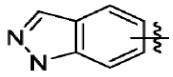
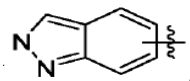
Alternatively, ring E is independently selected from 5/6 fused heteroaryl, 6/5 fused heteroaryl; the heteroatoms in the heteroaryl are selected from N, O, or S, with the number of heteroatoms being 1 or 2.

In some embodiments, wherein, ring E is independently selected from phenyl, naphthyl, pyridyl, pyrrolyl, furanyl, thienyl, benzimidazolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, indolyl, indazolyl;

Alternatively, ring E is independently selected from indazolyl.

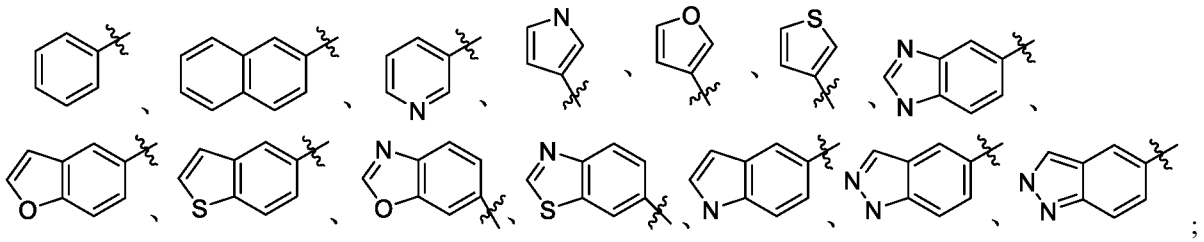
In some embodiments, wherein, ring E is independently selected from

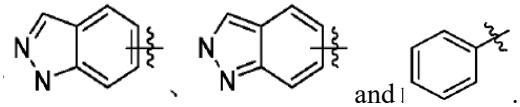
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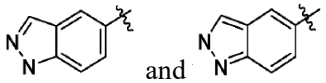
alternatively, ring E is independently selected from  and .

In some embodiments, wherein, ring E is independently selected from

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Alternatively, ring E is independently selected from .

Alternatively, ring E is independently selected from .

In some embodiments, wherein, Re is independently selected from deuterium, halogen, hydroxy, amino, nitro, cyano, -ORe1, -SO2(Re1), -C(O)Re1, -C(O)ORe1, -OC(O)Re1, -N(Re1)(Re2), -C(O)N(Re1)(Re2), -N(Re1)C(O)(Re2), -S(O)N(Re1)(Re2), -SO2N(Re1)(Re2), -N(Re1)SO2(Re2), -P(O)(Re1)(Re2), or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-4 alkenyl, C2-4 alkynyl, C3-6 cycloalkyl (preferably C3-5 cycloalkyl), 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl; optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the group independently substituted by Re3.

Alternatively, Re is independently selected from deuterium, halogen, hydroxy, amino, cyano, -ORe1, -N(Re1)(Re2), -SO2(Re1), -C(O)Re1, -SO2N(Re1)(Re2), -N(Re1)SO2(Re2), -P(O)(Re1)(Re2), or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl (preferably C3-5 cycloalkyl), 3-6 membered heterocyclyl; optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the group independently substituted by Re3. The heteroatoms in the heterocyclyl are O or N, with the number of heteroatoms being 1 or 2.

Alternatively, Re is independently selected from halogen, hydroxy, amino, cyano, -ORe1, -N(Re1)(Re2), -SO2(Re1), -P(O)(Re1)(Re2), or optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy, C3-4 cycloalkyl, 4-5 membered heterocyclyl; optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the group independently substituted by Re3. The heteroatoms in the heterocyclyl are O or N, with the number of heteroatoms being 1 or 2;

Alternatively, Re is independently selected from halogen, hydroxy, amino, cyano, -N(Re1)(Re2), -P(O)(Re1)(Re2), or optionally substituted groups as follows: C1-4 alkyl (preferably C1-3 alkyl), C1-4 alkoxy, C3-4 cycloalkyl, 4-5 membered heterocyclyl; optionally substituted refers to one or more (e.g., 2, 3, 4) substitutable positions of the group independently substituted by substituents selected from halogen, hydroxy, amino. The heteroatoms in the heterocyclyl are O, with the number of heteroatoms being 1.

In some embodiments, wherein, Re is independently selected from halogen, hydroxy, amino, cyano, -N(Re1)(Re2), -P(O)(Re1)(Re2), or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl; optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the group independently substituted by Re3.

Alternatively, Re is independently selected from halogen, hydroxy, amino, cyano, -N(Re1)(Re2), -P(O)(Re1)(Re2), or optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy, C3-4 cycloalkyl; optionally substituted refers to one or more (e.g., 2, 3) substitutable positions of the group independently substituted by Re3.

In some embodiments, wherein, Re is independently selected from halogen, hydroxy, amino, cyano, or optionally substituted groups as follows: Methyl, ethyl, n-propyl, isopropyl, n-butyl, methoxy, ethoxy, cyclopropyl, cyclobutyl, cyclopentyl, -N(C1-4 alkyl)2, -P(O)(C1-4 alkyl)2; optionally substituted refers to one or more (e.g., 2, 3, 4) substitutable positions of the group independently substituted by substituents selected from halogen, hydroxy, amino, cyclopropyl, methyl.

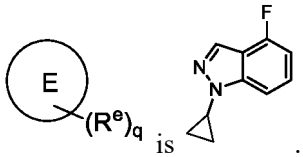
In some embodiments, wherein, Re is independently selected from halogen, methyl, cyclopropyl, -NH(CH3), -P(O)(C2H5)2; Alternatively, Re is independently selected from fluoro, methyl, cyclopropyl, -NH(CH3), -P(O)(C2H5)2.

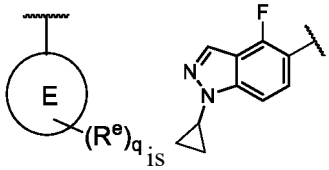
In some embodiments, wherein, Re is fluoro, methyl, cyclopropyl.

In some embodiments, wherein, Re is fluoro, cyclopropyl.

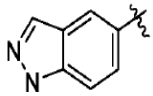
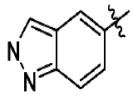
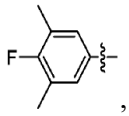
In some embodiments, wherein, q is 2, Re are respectively fluoro and cyclopropyl.

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In some embodiments, wherein,  is .

In some embodiments, wherein,  is .

In some embodiments, wherein, provided that Re is not methyl.

In some embodiments, wherein, provided that when ring E is  or  , ring A is  , and q is 2, both Re are not methyl and fluoro.

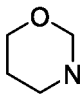
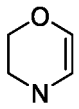
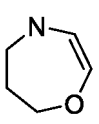
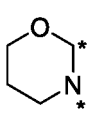
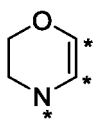
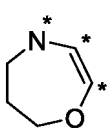
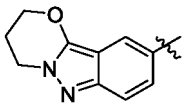
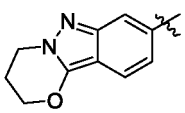
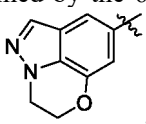
In some embodiments, wherein, the two Re together with the atoms to which they are attached form an optionally substituted 3-7 membered heterocyclic group or optionally substituted 5-6 membered heteroaryl group, optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions being independently substituted by a group selected from deuterium, halogen, hydroxyl, amino, oxo, cyano, C1-4 alkyl, C1-4 alkoxy.

Alternatively, the two Re together with the atoms to which they are attached form an optionally substituted 3-7 membered heterocyclic group or optionally substituted 5-6 membered heteroaryl group, optionally substituted refers to one or more (e.g., 2, 3, or 4) substitutable positions being independently substituted by a group selected from deuterium, fluoro, chloro, bromo, hydroxyl, amino, oxo, cyano, methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy.

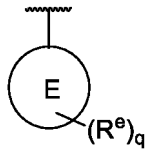
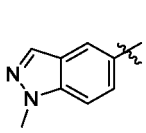
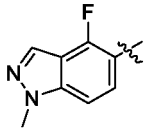
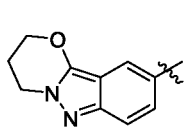
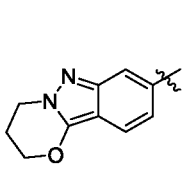
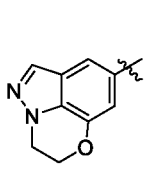
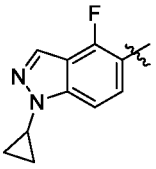
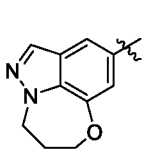
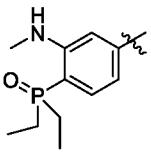
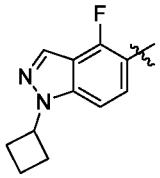
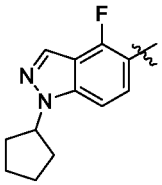
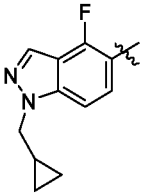
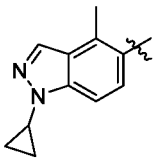
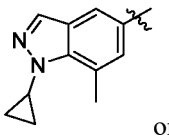
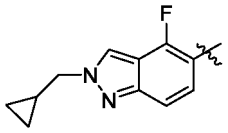
Alternatively, the two Re together with the atoms to which they are attached form an optionally substituted 5-7 membered heterocyclic group or optionally substituted 5-6 membered heteroaryl group, optionally substituted refers to one or more (e.g., 2, 3, or 4) substitutable positions being independently substituted by a group selected from deuterium, fluoro, chloro, bromo, hydroxyl, oxo, amino, cyano, methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy.

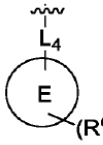
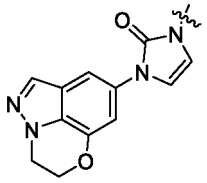
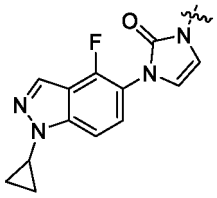
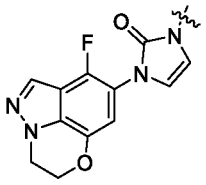
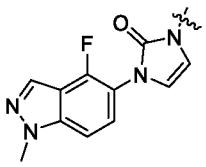
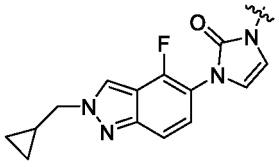
Alternatively, the two Re (preferably, two adjacent Re; more preferably, two Re located on different rings and adjacent) together with the atoms to which they are attached form an optionally substituted 6-7 membered heterocyclic group, optionally substituted refers to one or more (e.g., 2, 3, or 4) substitutable positions being independently substituted by a group selected from deuterium, fluoro, chloro, bromo, hydroxyl, oxo, amino, cyano, methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy.

Preferably, the heterocyclic group or heteroaryl group contains heteroatoms independently selected from N, O, or S, the number of heteroatoms being 1, 2, 3, or 4; more preferably, the heterocyclic group or heteroaryl group contains heteroatoms independently selected from N or O, the number of heteroatoms being 1 or 2;

Preferably, the 6-7 membered heterocyclic group forms a fused tricyclic ring with ring E (i.e., the heterocyclic group shares one chemical bond with ring E (i.e., shares 2 adjacent atoms) or two adjacent chemical bonds (i.e., shares 3 adjacent atoms)); preferably, the 6-7 membered heterocyclic group is selected from  、  and  ; preferably, the 6-7 membered heterocyclic group is selected from  、  or  , wherein * indicates atoms shared with ring E; preferably, the fused tricyclic ring formed by the 6-7 membered heterocyclic group and ring E is selected from  、  and  .

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In some embodiments, wherein,  is 、、、、、、、、、、、、、、or .

In some embodiments, wherein,  is selected from 、、、、and .

In some embodiments, wherein, Re1 and Re2 are independently selected from hydrogen, deuterium, optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclic group, phenyl, 5-6 membered heteroaryl group; the optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions being independently substituted by a substituent selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclic group, phenyl, 5-6 membered heteroaryl group.

Alternatively, Re1 and Re2 are independently selected from hydrogen, or optionally substituted C1-6 alkyl, C3-6 cycloalkyl; the optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions being independently substituted by a group selected from halogen, hydroxyl, amino, cyano.

Alternatively, Re1 and Re2 are independently selected from hydrogen, or optionally substituted C1-4 alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl), C3-4 cycloalkyl (e.g., cyclopropyl, cyclobutyl); the optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions being independently substituted by a group selected from fluoro, chloro, cyano.

In some embodiments, wherein, Re1 and Re2 are independently selected from hydrogen, hydroxyl, amino, trifluoromethyl, difluoromethyl, monofluoromethyl, trichloromethyl, dichloromethyl, monochloromethyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, methoxy, ethoxy, -CH2CN, -CH2CH2CN, cyclopropyl, cyclobutyl;

Alternatively, Re1 and Re2 are independently selected from hydrogen, methyl, ethyl.

In some embodiments, wherein, Re3 is independently selected from deuterium, halogen, hydroxyl, amino, nitro, cyano, -Re4, -ORe4, -S(O)2Re4, -C(O)Re4, -C(O)ORe4, -OC(O)Re4, -N(Re4)(Re5), -C(O)N(Re4)(Re5), -N(Re4)C(O)Re5, -S(O)N(Re4)(Re5), -SO2N(Re4)(Re5), -N(Re4)SO2Re5, -P(O)(Re4)Re5; Re4 and Re5 are independently selected from hydrogen, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-4 alkenyl, C2-4 alkynyl, C3-6 cycloalkyl (e.g., C3-5 cycloalkyl, C3-4 cycloalkyl), 3-6 membered heterocyclic group, phenyl, 5-6 membered heteroaryl group; the optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions being independently substituted by a substituent selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-4 alkyl, C1-4 alkoxy, C2-4 alkenyl, C2-4 alkynyl, C3-6 cycloalkyl, 3-6

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membered heterocyclic group, phenyl, 5-6 membered heteroaryl group.

Alternatively, Re3 is independently selected from deuterium, halogen, hydroxyl, amino, cyano, -Re4, ORe4, -SO2(Re4), -C(O)Re4, -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), -P(O)(Re4)Re5; Re4 and Re5 are independently selected from hydrogen, or substituted by one or more (e.g., 2, 3, 4, or 5) of the following: C1-6 alkyl (preferably C1-4 alkyl; more preferably C1-3 alkyl; e.g., methyl, ethyl, propyl, isopropyl) or C3-6 cycloalkyl (e.g., C3-5 cycloalkyl, C3-4 cycloalkyl).

In some embodiments, wherein, q is independently selected from 0, 1, 2, 3;

Alternatively, q is independently selected from 1, 2, or 3;

Alternatively, q is 2 or 3.

In some embodiments, wherein, L5x and L5y are independently selected from a bond or optionally substituted C1-6 alkylene; the optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions being independently substituted by a group selected from deuterium, halogen, hydroxyl, amino, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclic group.

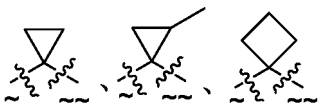
Alternatively, L5x and L5y are independently selected from a bond, hydrogen, optionally substituted methylene or optionally substituted ethylene, optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions being independently substituted by a group selected from fluoro, chloro, bromo, hydroxyl, amino, cyano, oxo.

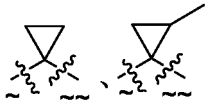
Alternatively, L5x and L5y are independently selected from a bond.

In some embodiments, wherein, R1 and R2 together with the atoms to which they are attached form a C3-10 carbocyclic ring; the C3-10 carbocyclic ring is optionally substituted by one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) R3; R3 is independently selected from hydrogen, halogen, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy; the optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions being independently substituted by a group selected from deuterium, halogen, hydroxyl, amino, cyano, oxo, C3-6 cycloalkyl, 3-6 membered heterocyclic group.

Alternatively, R1 and R2 together with the atoms to which they are attached form a C3-8 carbocyclic ring (preferably a C3-6 carbocyclic ring; more preferably a C3-5 carbocyclic ring, e.g., cyclopropyl, cyclobutyl, cyclopentyl); the C3-8 carbocyclic ring is optionally substituted by one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) R3; R3 is independently selected from hydrogen, halogen, or optionally substituted groups as follows: C1-5 alkyl, C1-5 alkoxy; the optionally substituted refers to one or more (e.g., 2, 3, 4, or 5) positions being substituted by a group selected from halogen, hydroxyl, amino, cyano.

Alternatively, R1 and R2 together with the atoms to which they are attached form the following groups optionally substituted by one or more (e.g., 2, 3, 4, or 5) R3. 3-membered carbocyclic ring, 4-membered carbocyclic ring, 3/3 spiro carbocyclic ring, 3/4 spiro carbocyclic ring, 3/5 spiro carbocyclic ring, 3/6 spiro carbocyclic ring; wherein, R3 is independently selected from hydrogen, fluoro, chloro, bromo, methyl, ethyl, n-propyl, isopropyl, methoxy, trifluoromethyl, difluoromethyl, monofluoromethyl, trichloromethyl, dichloromethyl, monochloromethyl;

Alternatively, the carbocyclic ring formed by R1 and R2 with the atoms to which they are attached is independently selected from , wherein, the "~" end is connected to L5x, and the "~~" end is connected to L5y;

Alternatively, the carbocyclic ring formed by R1 and R2 with the atoms to which they are attached is independently selected from , wherein, the "~" end is connected to L5x, and the "~~" end is connected to L5y;

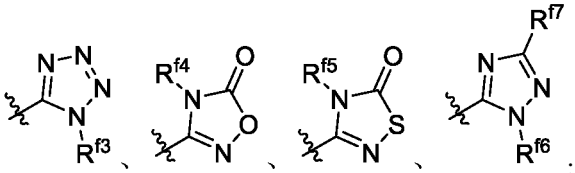
Alternatively, the carbocyclic ring formed by R1 and R2 with the atoms to which they are attached is , wherein, the "~" end is connected to L5x, and the "~~" end is connected to L5y.

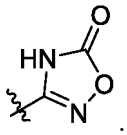
In some embodiments, wherein, Rf is independently selected from -C(O)ORf1, -C(O)N(Rf1)(Rf2);

Alternatively, Rf is independently selected from -C(O)ORf1;

Alternatively, Rf is independently selected from the following groups. -COOH.

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In some embodiments, wherein, Rf is independently selected from ;

Alternatively, Rf is independently selected from .

In some embodiments, wherein, Rf1, Rf2, Rf3, Rf4, Rf5, Rf6, Rf7 are independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-6 carbocyclic ring, 3-6 membered heterocyclic group, C6-8 aryl, 5-6 membered heteroaryl group; the optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions being independently substituted by a group selected from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-4 alkenyl, C2-4 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclic group, phenyl, 5-6 membered heteroaryl group.

Alternatively, Rf1, Rf2, Rf3, Rf4, Rf5, Rf6, Rf7 are independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-6 carbocyclic ring, 3-6 membered heterocyclic group, phenyl, 5-6 membered heteroaryl group; the optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) positions being substituted by a group selected from halogen, hydroxyl, amino, cyano, oxo, C1-4 alkyl, C1-4 alkoxy.

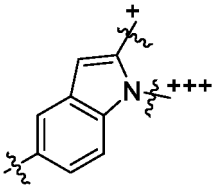
Alternatively, Rf1, Rf2, Rf3, Rf4, Rf5, Rf6, Rf7 are each independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy, C3-6 carbocyclic group, 3-6 membered heterocyclic group, phenyl, 5-6 membered heteroaryl group; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxyl, amino, cyano, oxo, C1-4 alkyl, C1-4 alkoxy.

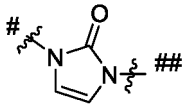
Alternatively, Rf1, Rf2, Rf3, Rf4, Rf5, Rf6, Rf7 are each independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-3 alkyl, C1-3 alkoxy, C3-6 carbocyclic group, 3-6 membered heterocyclic group, phenyl, 5-6 membered heteroaryl group; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxyl, amino, cyano, oxo, C1-3 alkyl, C1-3 alkoxy.

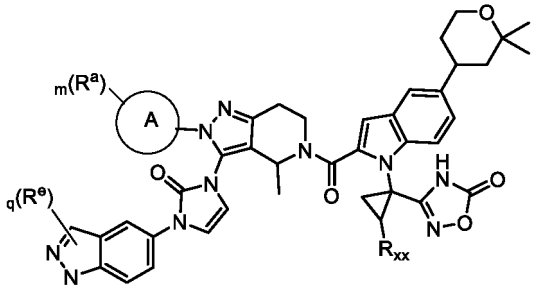
In some embodiments, wherein, Rf1, Rf2, Rf3, Rf4, Rf5, Rf6, Rf7 are each independently selected from hydrogen, deuterium, trifluoromethyl, difluoromethyl, monofluoromethyl, trichloromethyl, dichloromethyl, monochloromethyl, methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy.

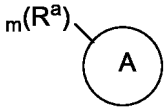
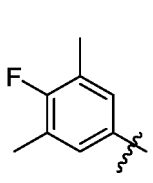
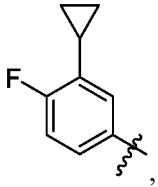
In some embodiments, wherein Rf1, Rf2, Rf3, Rf4, Rf5, Rf6, Rf7 are each independently selected from hydrogen.

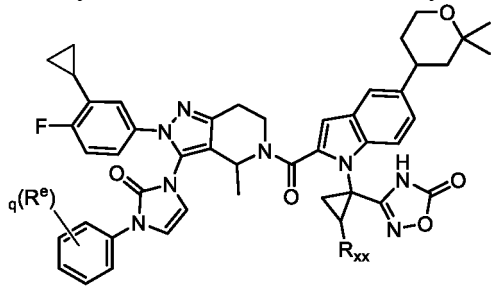
In some embodiments, the compound must satisfy the following conditions:

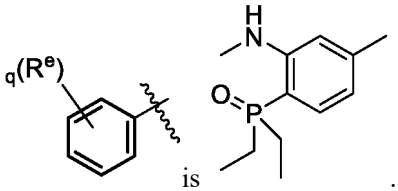
a) Ring C is not , wherein, "+" end is connected to one end of L2, "++" end is connected to one end of L3, "+++" end is connected to one end of L5x; and/or

b) L4 is not , wherein, "#" end is connected to one end of ring B, "##" end is connected to one end of ring E; and/or

c) When the compound structure of formula (I) is 

(wherein, Rxx is H or CH3, Re can be substituted on any ring of the bicyclic system), when  is  or , Re is selected from halogen, optionally substituted C3-6 cycloalkyl; q is 1 or 2; optionally substituted refers to unsubstituted or one or more (e.g., 2, 3, 4, 5) substitutable sites of the substituent independently substituted by Re3. Re3 is independently selected from deuterium, halogen, hydroxyl, amino, cyano, ORe4, -SO2(Re4), -C(O)Re4, -N(Re3)(Re4), -SO2N(Re4)(Re5), -N(Re4)S(O)2Re5, -P(O)(Re4)(Re5); Re4, Re5 are each independently selected from hydrogen or optionally substituted C1-6 alkyl, optionally substituted refers to unsubstituted or substituted with one or more substituents selected from hydrogen, halogen, hydroxyl, amino, cyano. Alternatively, two Res together with their connected atoms form an optionally substituted 3-10 membered heterocyclic group (preferably 3-10 membered heterocycloalkyl, more preferably 5-7 membered heterocycloalkyl), optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclic group, C6-14 aryl and 5-12 membered heteroaryl. And/or

d) When the compound structure of formula (I) is 

(wherein, Rxx is H or CH3), is .

In some embodiments, wherein, ring A is selected from phenyl, 3-6 membered heterocyclic group;

Ring B is selected from 8-9 membered bicyclic heterocyclic group, 8-9 membered bicyclic heteroaryl;

Ring C is selected from 9 membered bicyclic heteroaryl;

Ring D is selected from 6 membered heterocyclic group, 6 membered heteroaryl;

Ring E is selected from C6-8 aryl, 5-10 membered heteroaryl;

Ra is independently selected each time from halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, -C(O)N(Ra1)(Ra2), -N(Ra1)C(O)(Ra2), and optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, 3-6 membered heterocyclyl; optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from hydrogen, halogen, hydroxyl, amino.

Rb is independently selected each time from halogen, hydroxyl, amino, cyano, oxo, C1-6 alkyl;

Rc is independently selected each time from halogen, hydroxyl, amino, cyano, oxo, C1-6 alkyl;

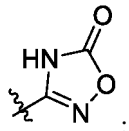
Rd is independently selected each time from halogen, hydroxyl, amino, cyano, oxo, or optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy; optionally substituted refers to unsubstituted or substituted by one or

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more (e.g., 2, 3, 4, 5) substituents selected from hydrogen, halogen, hydroxyl, amino.

Re is independently selected each time from deuterium, halogen, hydroxyl, amino, cyano, -ORe1, -SO2(Re1), -C(O)Re1, -N(Re1)(Re2), -SO2N(Re1)(Re2), -N(Re1)SO2(Re2), -P(O)(Re1)(Re2), optionally substituted C1-6 alkyl, or optionally substituted C3-6 cycloalkyl; Re1, Re2 each independently selected from hydrogen, methyl, ethyl; optionally substituted refers to unsubstituted or one or more (e.g., 2, 3, 4, 5) substitutable sites independently substituted by Re3; Re3 independently selected from deuterium, halogen, hydroxyl, amino, cyano, -Re4, ORe4, -SO2(Re4), -C(O)Re4, -N(Re4)(Re5), -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), -P(O)(Re4)(Re5); Re4, Re5 each independently selected from hydrogen, or optionally substituted by one or more (e.g., 2, 3, 4, 5) of hydrogen, halogen, hydroxyl, amino, cyano: C1-6 alkyl, C3-6 cycloalkyl (preferably C3-5 cycloalkyl, preferably C3-4 cycloalkyl, for example cyclopropyl, cyclobutyl);

R1 and R2 together with the atoms to which they are connected form a C3-8 carbocyclic group; the C3-8 carbocyclic group is optionally substituted by one or more R3. R3 independently selected from hydrogen, halogen, or optionally substituted groups as follows: C1-5 alkyl, C1-5 alkoxy; optionally substituted refers to unsubstituted or substituted by one or more groups selected from hydrogen, halogen, hydroxyl, amino, cyano (e.g., 2, 3, 4, 5).

Rf is selected from -COOH, ;

L1 is selected from bond, -CH2-;

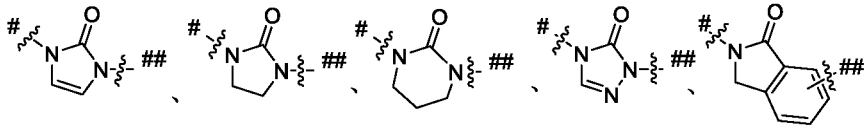
L2 is selected from bond, -CH2-, -C(O)-;

L3 is selected from bond, -CH2-, -C(O)-;

L5x, L5y are each independently selected from bond;

m, n, o, p, q, r each independently 0, 1, 2, 3;

L4 selected from -NHC(O)NH-, -NHC(S)NH-, -NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-, -N(methyl)C(O)NH-, -N(methyl)C(O)N(methyl)-, -NHC(S)NH-, -NH-



wherein "#" end is one end connected to ring B, "##" end is one end connected to ring E.

In some embodiments, wherein, ring A selected from phenyl, 3-6 membered heterocyclic group;

Ring B selected from 9-membered fused heterocyclic group, 9-membered bicyclic heteroaryl;

Ring C selected from 9-membered bicyclic heteroaryl;

Ring D selected from 6-membered heterocyclic group, 6-membered heteroaryl; the heteroatom in the 6-membered heterocyclic group is O, the number of heteroatoms is 1; the heteroatoms in the 6-membered heteroaryl are N, the number of heteroatoms is 1 or 2;

Ring E selected from phenyl, 5-membered/6-membered fused heteroaryl, 6-membered/5-membered fused heteroaryl; the heteroatoms contained in the 5-membered/6-membered fused heteroaryl or 6-membered/5-membered fused heteroaryl are N, the number of heteroatoms is 1, 2, or 3;

Ra is independently selected each time from halogen, hydroxyl, amino, cyano, and optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy, C3-4 cycloalkyl, 4-5 membered heterocyclic group; optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from hydrogen, halogen, hydroxyl, amino.

Rb is independently selected each time from halogen, hydroxyl, amino, cyano, oxo, C1-4 alkyl;

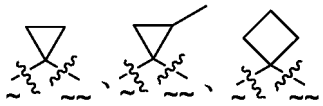
Rc is independently selected each time from halogen, hydroxyl, amino, cyano, oxo, C1-4 alkyl;

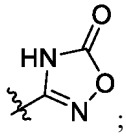
Rd is independently selected each time from halogen, hydroxyl, amino, cyano, or optionally substituted groups as follows: C1-4 alkyl, C1-4 alkoxy; optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, or 5) substituents selected from hydrogen, halogen, hydroxyl, amino.

Re is independently selected each time from halogen, -N(Re1)(Re2), -P(O)(Re1)(Re2), optionally substituted C1-6 alkyl, or optionally substituted C3-6 cycloalkyl; Re1 and Re2 are each independently selected from hydrogen, methyl, ethyl; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5) substitutable sites of the substituent are independently substituted by Re3. Re3 is independently selected from deuterium, halogen, hydroxyl, amino, cyano, -Re4, -ORe4, -SO2(Re4), -C(O)Re4, -N(Re4)(Re5), -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), -P(O)(Re4)Re5; Re4 and Re5 are each independently selected from hydrogen or optionally substituted: C1-6 alkyl, C3-6 cycloalkyl (preferably C3-5 cycloalkyl, more preferably C3-4 cycloalkyl, e.g., cyclopropyl, cyclobutyl); optionally substituted

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refers to unsubstituted or substituted by one or more substituents selected from hydrogen, halogen, hydroxyl, amino, cyano (e.g., 2, 3, 4, 5).

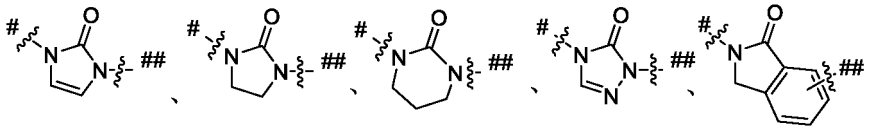
R1 and R2 together with the atoms to which they are connected independently form a carbocyclic ring selected from , wherein the "～" end is one end connected to L5x, and the "～～" end is one end connected to L5y;

Rf is selected from -COOH, ;

L1 is selected from bond, -CH2-;

L2 is selected from bond, -CH2-, -C(O)-;

L3 is selected from bond, -CH2-, -C(O)-;

L4 is selected from -NHC(O)NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-, -N(methyl)C(O)NH-, -N(methyl)C(O)N(methyl)-, -NHC(S)NH-, -NH- , wherein, "#" end is one end connected to ring B, "##" end is one end connected to ring E;

L5x, L5y are independently selected from bond;

m, n, o, p, q, r are each independently 0, 1, 2, 3.

In some embodiments, wherein, ring A is selected from phenyl, 3-6 membered heterocyclyl;

Ring B is selected from 9-membered fused heterocyclyl, 9-membered bicyclic heteroaryl; the heteroatoms in the 9-membered fused heterocyclyl, 9-membered bicyclic heteroaryl are selected from N, the number of heteroatoms is 1, 2 or 3;

Ring C is selected from 9-membered bicyclic heteroaryl; the heteroatoms in the 9-membered bicyclic heteroaryl are selected from N, the number of heteroatoms is 1 or 2;

Ring D is selected from tetrahydropyranyl, pyridyl;

Ring E is selected from phenyl, indazolyl;

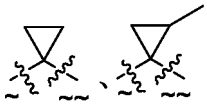
Ra is independently selected each time from halogen, methyl, cyclopropyl;

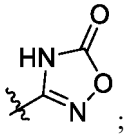
Rb is independently selected each time from fluoro, chloro, oxo, methyl;

Rc is independently selected each time from fluoro, chloro, oxo, methyl, ethyl, n-propyl, isopropyl, n-butyl;

Rd is independently selected each time from optionally substituted C1-4 alkyl and optionally substituted C1-4 alkoxy; the C1-4 alkyl or C1-4 alkoxy is optionally substituted by one or more (e.g., 2, 3, 4, 5) substituents selected from hydrogen, halogen, hydroxy, amino.

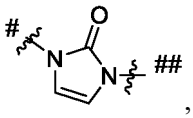
Re is independently selected from halogen, -N(Re1)(Re2), -P(O)(Re1)(Re2), optionally substituted C1-6 alkyl and optionally substituted C3-6 cycloalkyl; Re1, Re2 are each independently selected from hydrogen, methyl, ethyl; optionally substituted refers to one or more (e.g., 2, 3, 4, 5) substitutable positions of the substituent are independently substituted by Re3. Re3 is independently selected from deuterium, halogen, hydroxy, amino, cyano, -Re4, -ORe4, -SO2(Re4), -C(O)Re4, -N(Re3)(Re4), -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), -P(O)(Re4)(Re5); Re4, Re5 are each independently selected from hydrogen or optionally substituted: C1-6 alkyl (preferably C1-3 alkyl, e.g., methyl, ethyl), C3-6 cycloalkyl (preferably C3-5 cycloalkyl, preferably C3-4 cycloalkyl, for example cyclopropyl, cyclobutyl), optionally substituted refers to unsubstituted or substituted by one or more substituents selected from hydrogen, halogen, hydroxy, amino, cyano.

R1 and R2 together with the atoms they are attached to independently form a carbocycle selected from , wherein, "～" end is one end connected to L5x, "～～" end is one end connected to L5y;

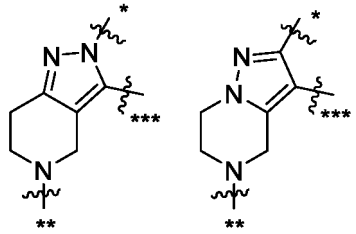
Rf is selected from -COOH, ;

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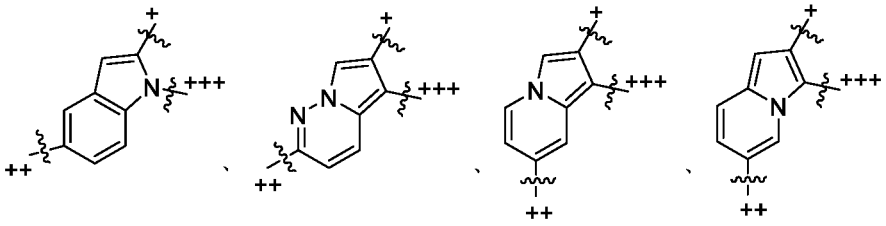
L1 is selected from bond, -CH2-;
L2 is selected from -C(O)-;
L3 is selected from bond;



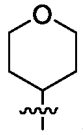
L4 is selected from -NHC(O)NH-, , wherein, "#" end is one end connected to ring B, "##" end is one end connected to ring E;
L5x, L5y are independently selected from bond;
m, n, o, p, q, r are each independently 0, 1, 2.
In some embodiments, wherein, ring A is selected from phenyl;



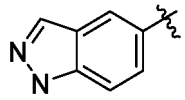
Ring B is selected from 、 , wherein, "*" end is one end connected to L1, "**" end is one end connected to L2, "***" end is one end connected to L4;
Ring C is selected from the following groups.



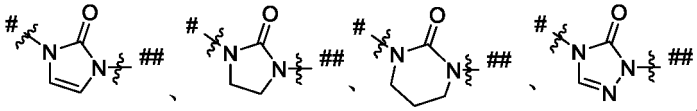
, wherein, "+" end is one end connected to L2, "++" end is one end connected to L3, "+++" end is one end connected to L5x;



Ring D is ;



Ring E is or ;
L1 is selected from a bond;
L2 is selected from -C(O)-;
L3 is selected from bond;
L4 is selected from -NHC(O)NH-, -N(methyl)C(O)NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-,

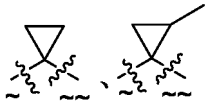


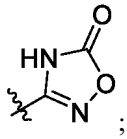
, wherein, "#" end is one end connected to ring B, "##" end is one end connected to ring E;
L5x, L5y are independently selected from bond;
Ra is independently selected each time from halogen, methyl, C3-5 cycloalkyl-(CH2)w-;
Rb is independently selected each time from fluoro, chloro, oxo, methyl;
Rc is independently selected each time from hydrogen, fluorine, chlorine, oxo, methyl, ethyl, n-propyl, isopropyl, and n-butyl;
Rd is independently selected each time from optionally substituted C1-3 alkyl and optionally substituted C1-3 alkoxy; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, or 5) substituents selected from hydrogen, deuterium, halogen, hydroxyl, and amino.
Re is independently selected each time from fluoro, or optionally substituted groups as follows: C1-3 alkyl (e.g., methyl, ethyl), C3-5 cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl), C3-5 cycloalkyl-(CH2)w-;
provided that when L4 is , at least one (e.g., 1 or 2) of the substituents on Ra or ring E (or Re) is C3-5

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cycloalkyl-(CH2)w-;

Alternatively, two Re (preferably two adjacent Re; more preferably two Re located on different rings and adjacent) together with the atoms they are attached to form optionally substituted 5-7 membered heterocyclyl (e.g., 5-membered, 6-membered or 7-membered heterocyclyl), the heterocyclyl contains 1-3 (for example 1, 2 or 3) heteroatoms independently selected from N, O or S; optionally substituted refers to the hydrogen on the substituent is unsubstituted or one or more substitutable positions of the substituent are independently substituted by Re3.

R1 and R2 together with the atoms they are attached to independently form a carbocycle selected from , wherein, "～" end is one end connected to L5x, "～～" end is one end connected to L5y;

Rf is selected from ;

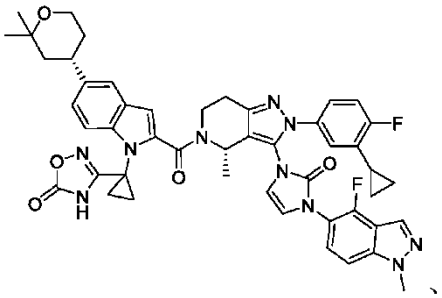
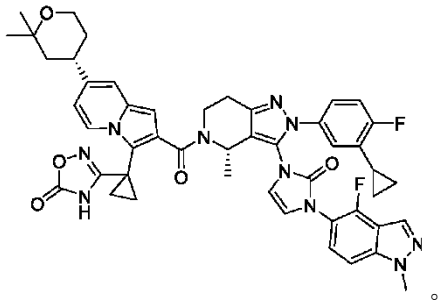
m is 2 or 3; q is 1, 2, or 3;

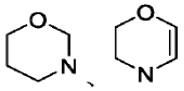
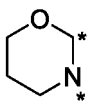
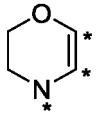
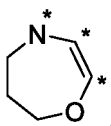
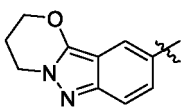
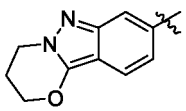
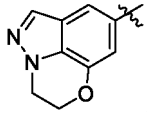
n, o, p are each independently 0, 1, 2;

w is 0, 1 or 2;

The Re3 is as defined in compound of formula (I);

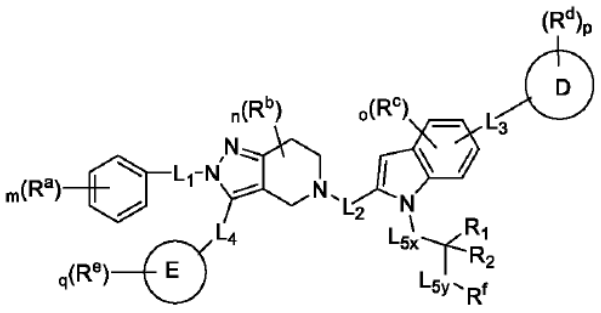
Provided that the following compounds are excluded:

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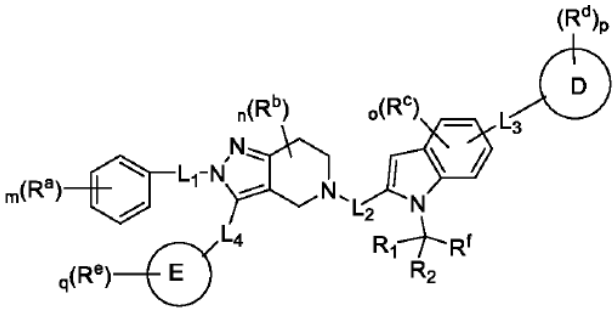
In some embodiments, two Re (preferably, two adjacent Re; more preferably, two Re located on different rings and adjacent) together with the atoms each connected thereto form an optionally substituted 6-7 membered heterocyclic group, the heterocyclic group (preferably a heterocycloalkyl) containing 1-3 (for example 1, 2 or 3) heteroatoms each independently selected from N, O or S; preferably, the 6-7 membered heterocyclic group and ring E form a fused three-membered ring (i.e., the heterocyclic group and ring E share one chemical bond (i.e., share 2 adjacent atoms) or 2 adjacent chemical bonds (i.e., share 3 adjacent atoms)); preferably, the 6-7 membered heterocyclic group is selected from 、 and ; preferably, the 6-7 membered heterocyclic group is selected from 、 or , where * indicates an atom shared with ring E; preferably, the fused three-membered ring formed by the 6-7 membered heterocyclic group and ring E is selected from 、 and .

In some embodiments, wherein, the compound represented by formula (I) is the compound represented by the following formula:

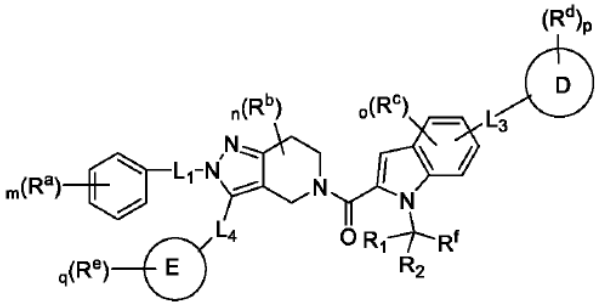
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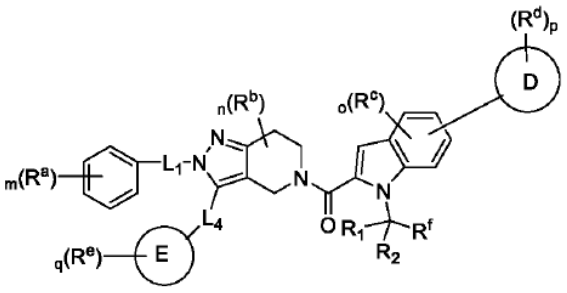
(I-1) ,



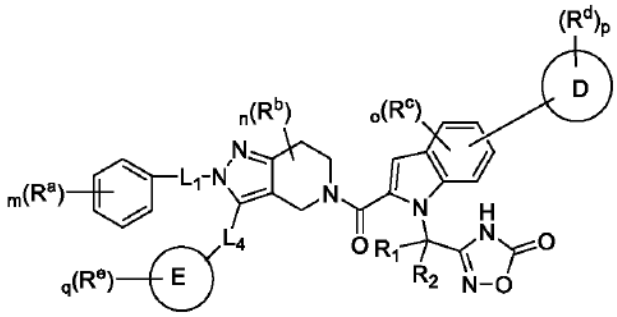
(I-2) ,



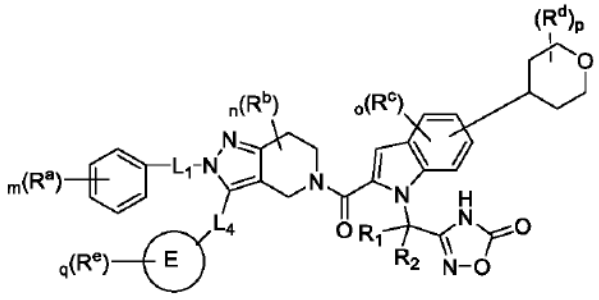
(I-3) ,



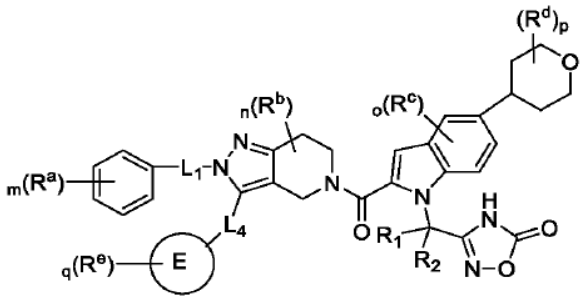
(I-4) ,



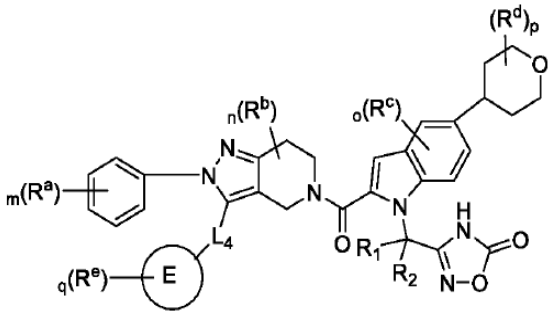
(I-5) ,



(I-6) ,



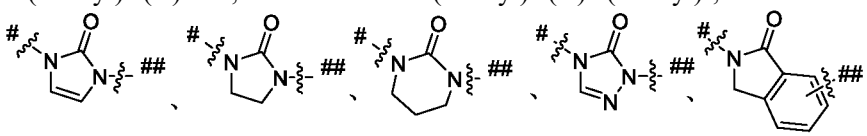
(I-7) or



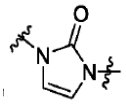
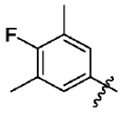
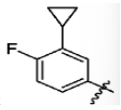
(I-8) ,

Ring D, ring E, Ra, Rb, Rc, Rd, Re, R1, R2, L1, L4, m, n, o, p, q are as defined for the compound of formula (I).

In some embodiments, L4 is -NHC(O)NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-, -N(methyl)C(O)NH-, -N(methyl)C(O)N(methyl)-, -NHC(S)NH-, -NH-,

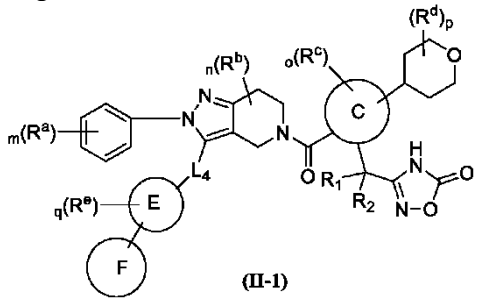


, wherein, the "#" end is the end

connected to ring B, and the "##" end is the end connected to ring E; when L4 is , and Ra substitution position on the phenyl ring is  or , Re is selected from halogen, optionally substituted C3-6 cycloalkyl; q is 1 or 2; optionally substituted refers to one or more (e.g., 2, 3, 4 or 5) substitution sites not substituted or substituted independently by Re3.

Re3 is independently selected from deuterium, halogen, hydroxyl, amino, cyano, ORe4, -SO2(Re4), -C(O)Re4, -N(Re3)(Re4), -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), -P(O)(Re4)(Re5); Re4 and Re5 are independently selected from hydrogen or optionally substituted C1-6 alkyl, optionally substituted refers to unsubstituted or substituted by one or more substituents selected from hydrogen, halogen, hydroxyl, amino, and cyano. Alternatively, two R together with the atoms to which they are attached form an optionally substituted 3-10 membered heterocyclyl (preferably a 3-10 membered heterocycloalkyl, more preferably a 5-7 membered heterocycloalkyl), optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl and 5-12 membered heteroaryl.

In some embodiments, wherein, the compound represented by Formula (I) is a compound represented by the following formula:



(II-1)

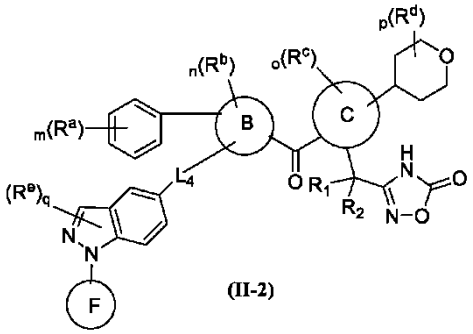
,

Ring C, ring E, Ra, Rb, Rc, Rd, Re, R1, R2, L1, L4, m, n, o, p, q are as defined for compounds of Formula (I), Formula (II), or Formulas (I-1) to (I-8);

Wherein, ring F is a C3-6 cycloalkyl group.

In some embodiments, ring F is a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl group; preferably, ring F is a cyclopropyl group.

In some embodiments, wherein, the compound represented by Formula (I) is a compound represented by the following formula:



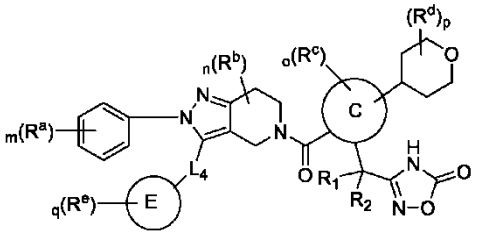
(II-2)

,

Ring C, ring B, Ra, Rb, Rc, Rd, Re, R1, R2, L1, L4, m, n, o, p, q are as defined for compounds of Formula (I), Formula (II), or Formulas (I-1) to (I-8); wherein, ring F is a C3-6 cycloalkyl group.

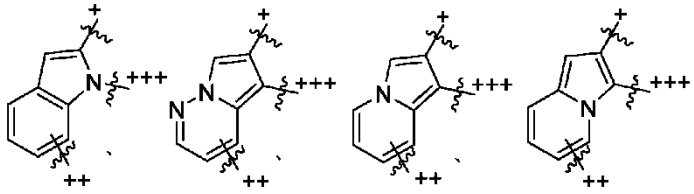
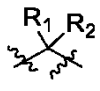
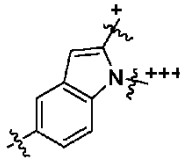
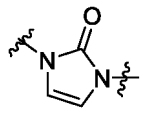
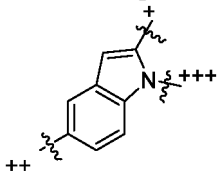
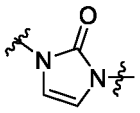
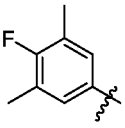
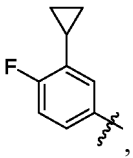
In some embodiments, ring F is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; preferably, ring F is cyclopropyl.

In some embodiments, wherein, the compound represented by Formula (I) is a compound represented by the following formula:



(II)

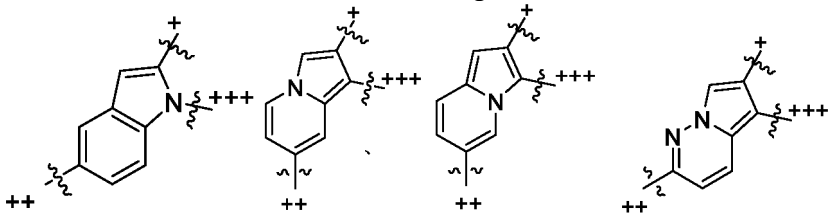
Ring C, ring E, Ra, Rb, Rc, Rd, Re, R1, R2, L1, L4, m, n, o, p, and q are as defined for compounds of Formula (I) and Formulas (I-1) to (I-8).

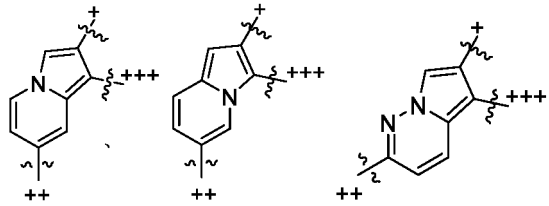
In some embodiments, the compound represented by Formula (II), wherein, Ring C selected from the following groups: , wherein, the "+" end is the end connected to -C(=O)-, the "++" end is the end connected to tetrahydropyran, and the "+++" end is the end connected to ; provided that, when ring C is , L4 is not ; alternatively, when ring C is , L4 is , the substitution position of Ra on the phenyl ring is  or , Re is selected from halogen, optionally substituted C3-6 cycloalkyl, substituted C1-3 alkyl, and q is 1 or 2; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5) substitutable positions of an unsubstituted or substituted group are independently replaced by Re3, and the substitution means that one or more (e.g., 2, 3, 4, 5) substitutable positions of an unsubstituted or substituted group are independently replaced by Re3.

Re3 is independently selected from deuterium, halogen, hydroxy, amino, cyano, -Re4, -ORe4, -SO2(Re4), -C(O)Re4, -N(Re3)(Re4), -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), or -P(O)(Re4)(Re5); Re4 and Re5 are independently selected from hydrogen or optionally substituted: C1-6 alkyl (preferably C1-3 alkyl, such as methyl or ethyl) or C3-6 cycloalkyl (preferably C3-5 cycloalkyl, such as cyclopropyl, cyclobutyl, or cyclopentyl), where optionally substituted refers to unsubstituted or substituted with one or more substituents selected from hydrogen, halogen, hydroxy, amino, or cyano.

Alternatively, two Res together with the atoms to which they are attached form an optionally substituted 3-10-membered heterocyclyl (preferably a 5-7-membered heterocyclyl, such as a 5-membered heterocyclyl, a 6-membered heterocyclyl, or a 7-membered heterocyclyl; more preferably a 5-7-membered heterocycloalkyl, such as a 5-membered heterocycloalkyl, a 6-membered heterocycloalkyl, or a 7-membered heterocycloalkyl), optionally substituted refers to being unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) atoms selected from deuterium, halogen, hydroxyl, the alkyl group is substituted by an amino group, a nitro group, a mercapto group, a cyano group, an oxo group, a C1-6 alkyl group (preferably a C1-3 alkyl group, for example, a methyl group, an ethyl group), a C1-6 alkoxy group (preferably a C1-3 alkoxy group, for example, a methoxy group, an ethoxy group), a C3-10 cycloalkyl group, a 3-10 membered heterocyclic group, a C6-14 aryl group and a 5-12 membered heteroaryl group. Preferably, the heteroatoms in the heterocyclic group or heterocycloalkyl group are independently selected from N, O or S, and the number of heteroatoms is 1, 2, 3 or 4.

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In some embodiments, ring C is selected from the following groups: , wherein, the "+" end is connected to L2, the "++" end is connected to L3, and the "+++" end is connected to L5x; alternatively,

Ring C is selected from the following groups: , wherein, the "+" end is connected to L2, the "++" end is connected to L3, and the "+++" end is connected to L5x.

In some embodiments, the compounds represented by Formula (I), (I-1) to (I-8), (II), (II-1), or (II-2) described above, wherein:

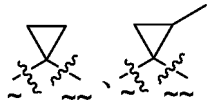
Ring E is selected from phenyl or indazolyl;

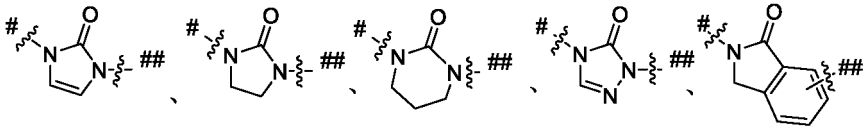
Ra is independently selected each time from halogen, methyl, or cyclopropyl;

Rb is independently selected each time from fluoro, chloro, oxo, or methyl;

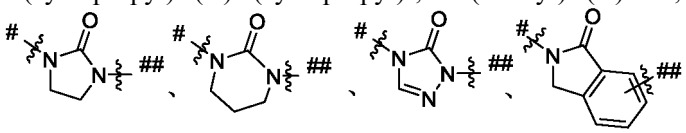
Rc is independently selected each time from fluoro, chloro, oxo, methyl, ethyl, n-propyl, isopropyl, or n-butyl;

Rd is independently selected each time from C1-4 alkyl and C1-4 alkoxy; and the C1-4 alkyl or C1-4 alkoxy is optionally substituted with one or more (e.g., 2, 3, 4, or 5) substituents selected from hydrogen, halogen, hydroxy, or amino.

R1 and R2, together with the atoms to which they are attached, form a carbon ring independently selected from , wherein, the "～" end is the end connected to L5x, and the "～～" end is the end connected to L5y;

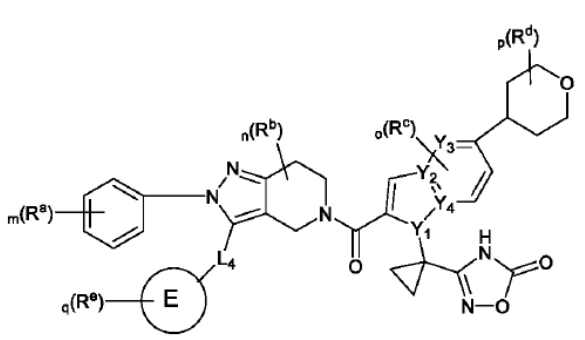
L4 is selected from the group consisting of -NHC(O)NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-, -N(methyl)C(O)NH-, -N(methyl)C(O)N(methyl)-, -NHC(S)NH-, and -NH-,  wherein, the "#" end is the end connected to Ring B, and the "##" end is the end connected to Ring E;

m, n, o, p, q, and r are each independently 0, 1, or 2.

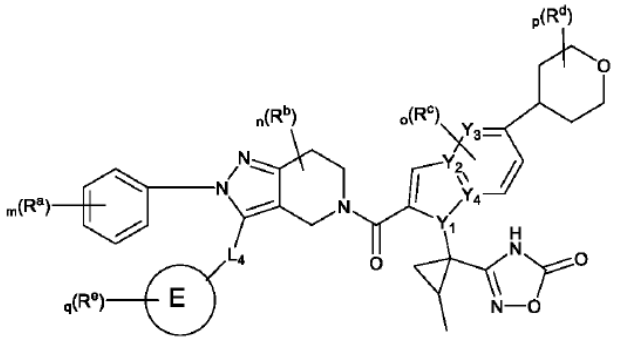
In some embodiments, the compound represented by formula (I), formula (I-1) to (I-8) or formula (II) as described above, wherein, L4 is selected from -NHC(O)NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-, -N(methyl)C(O)NH-, -N(methyl)C(O)N(methyl)-, -NHC(S)NH-, -NH-,  wherein, the "#" end is the end connected to ring B, and the "##" end is the end connected to ring E.

In some embodiments, the compound represented by Formula (I), Formula (I-1) to (I-8), or Formula (II) as described above is a compound represented by the following formula:

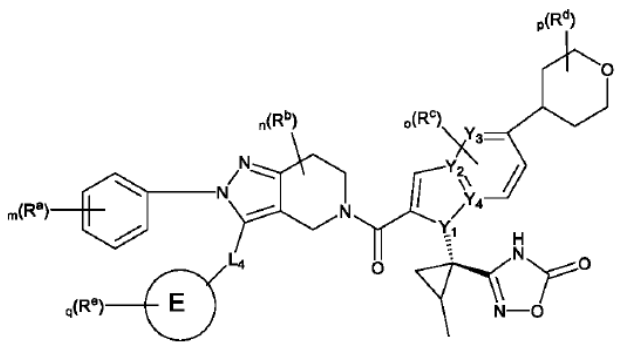
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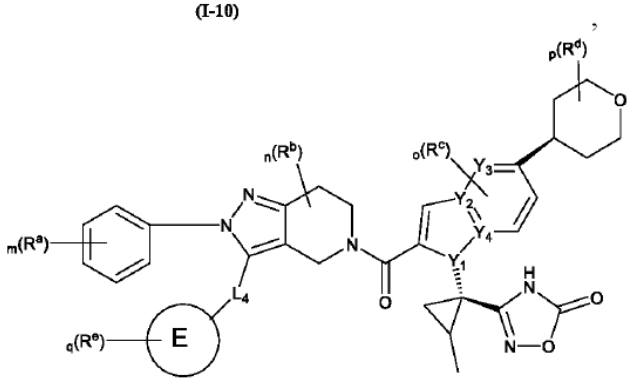
(I-9)



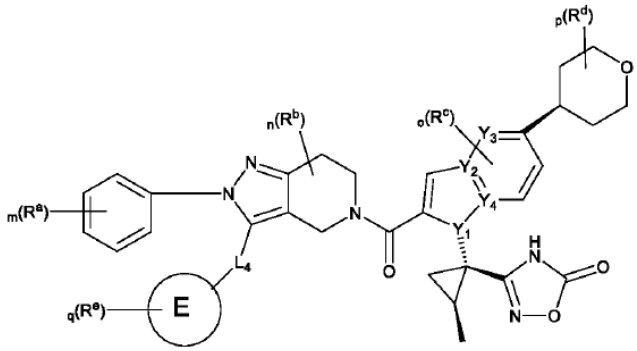
(I-10)



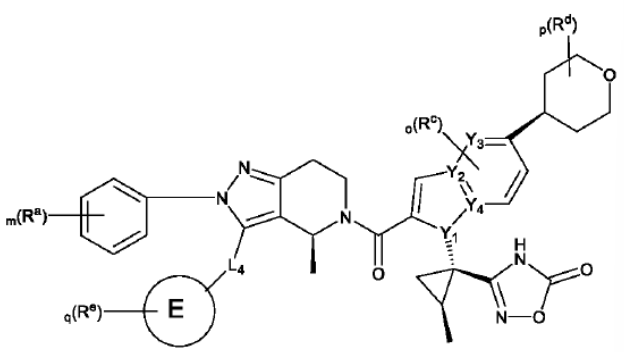
(I-11)



(I-12)



(I-13)



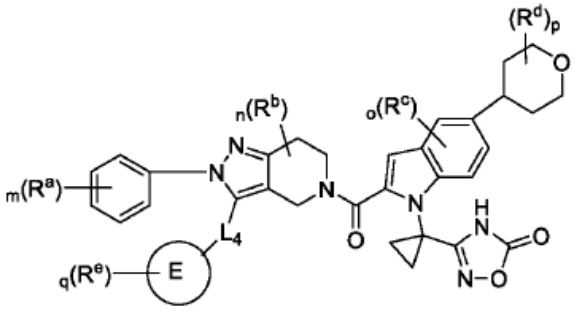
(I-14)

Alternatively,

Wherein, Y1 is N, Y2 and Y3 are both C, and Y4 is C or CH; alternatively, Y1 is C, Y2 is N, Y3 is C or CH, and Y4 is C; alternatively, Y1 is C, Y2 is C, Y3 is C or CH, and Y4 is N; alternatively, Y1 is C, Y2 is N, Y3 is N, and Y4 is C;

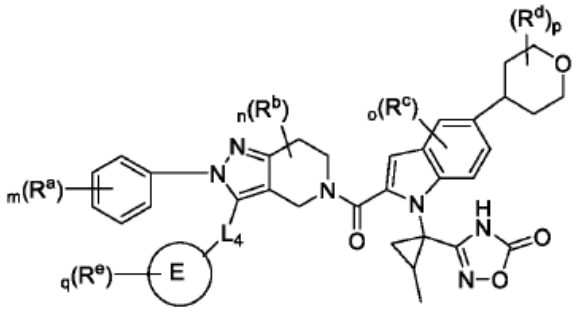
Ring E, Ra, Rb, Rc, Rd, Re, R1, R2, L1, L4, m, n, o, p, and q are as defined for the compound of Formula (I), Formulas (I-1) to (I-8), or Formula (II).

In some embodiments, wherein, the compound represented by Formula (I), Formula (I-1) to Formula (I-8), or Formula (II) is a compound represented by the following formula:

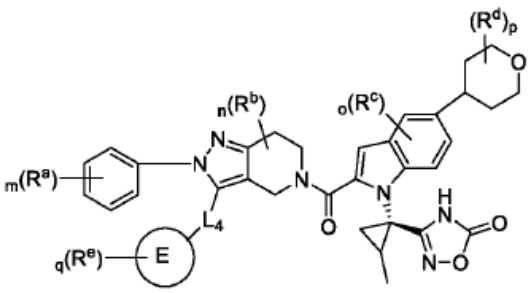


(I-15)

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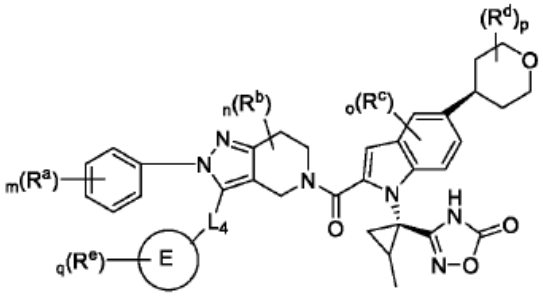


(I-16)

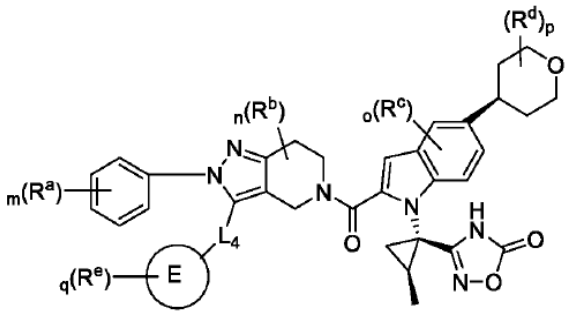


(I-17)

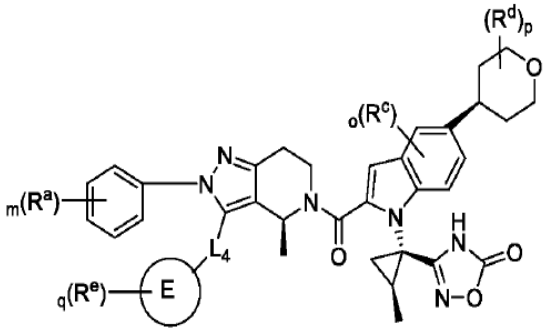
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(I-18)

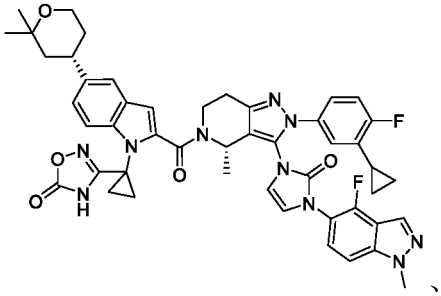


or

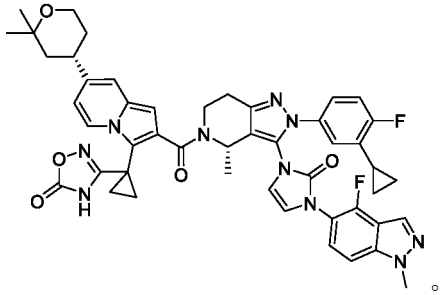


, wherein, ring E, Ra, Rb, Rc, Rd, Re, R1, R2, L1, L4, m, n, o, p, and q are as defined for the compound represented by Formula (I), Formula (I-1) to Formula (I-8), or Formula (II).

In some embodiments, provided that the following compounds are not included:

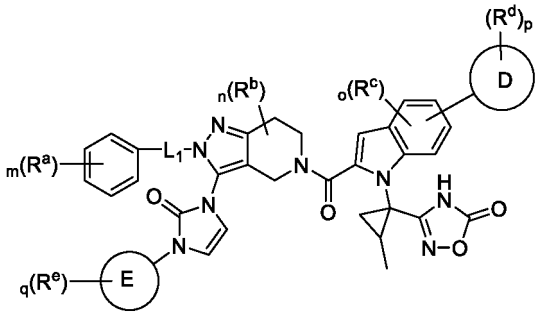


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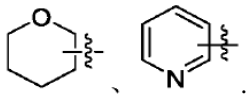


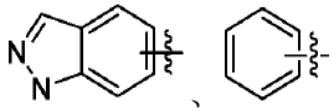
。

In some embodiments, wherein, the compound represented by Formula (I), Formula (II), or Formulas (I-1) to (I-8) is a compound represented by Formula (III):



(III)

Ring D is independently selected from ;

Ring E is selected from ;

Ra is selected from fluoro, methyl, and cyclopropyl;

Rb is selected from methyl;

Rc is selected from fluoro and chloro;

Rd is selected from methyl, methoxy, and ethoxy;

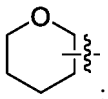
Re is selected from halogen, -N(Re1)(Re2), -P(O)(Re1)(Re2), or optionally substituted groups as follows: C1-6 alkyl (preferably C1-3 alkyl, e.g., methyl, ethyl), C3-6 cycloalkyl (preferably C3-5 cycloalkyl, e.g., cyclopropyl, cyclobutyl) are preferred; Re1 and Re2 are independently selected from hydrogen, methyl, and ethyl; optionally substituted refers to that the hydrogen on the substituted group is not substituted or one or more substitutable sites of the substituted group are independently replaced by Re3. Re3 is independently selected from deuterium, halogen, hydroxyl, amino, cyano, -Re4, -ORe4, -SO2(Re4), -C(O)Re4, -N(Re4)(Re5), -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), -P(O)(Re4)Re5; Re4 and Re5 are each independently selected from hydrogen or one or more of hydrogen, halogen, hydroxy, amino, and cyano, optionally substituted with: C1-6 alkyl or C3-6 cycloalkyl;

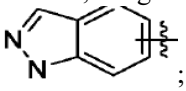
Alternatively, the two Res together with the atoms to which they are attached form an optionally substituted 5-7 membered heterocyclic group, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, or 4) groups selected from deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, methyl, ethyl, methoxy, and cyclopropyl.

L1 is independently selected from a bond;

m, n, o, p, q, and r are each independently 0, 1, 2, or 3.

In some embodiments, Re is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; preferably, Re is cyclopropyl.

In some embodiments, wherein, Ring D is independently selected from ;

Ring E is selected from ;

Ra is selected from fluoro, methyl, and cyclopropyl;

Rb is selected from methyl;

Rc is selected from H;

Rd is selected from methyl;

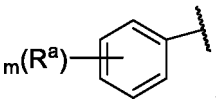
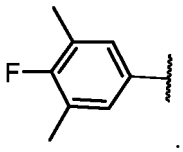
R is selected from halogen, or optionally substituted with the following groups: C1-6 alkyl (preferably C1-3 alkyl, e.g., methyl, ethyl), C3-6 cycloalkyl (preferably C3-5 cycloalkyl, e.g., cyclopropyl, cyclobutyl); optionally substituted refers to that a hydrogen atom on the substituted group is not replaced or one or more substitutable sites of the substituted group are independently replaced with R3. Re3 is independently selected from deuterium, halogen, hydroxyl, amino, cyano, -Re4, -ORe4, -SO2(Re4), -C(O)Re4, -N(Re4)(Re5), -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), -P(O)(Re4)Re5; Re4 and Re5 are independently selected from hydrogen or substituted by one or more of hydrogen, halogen, hydroxyl, amino and cyano: C1-6 alkyl or C3-6 cycloalkyl;

Alternatively, two Re, together with the atoms to which they are attached, form an optionally substituted 5-7

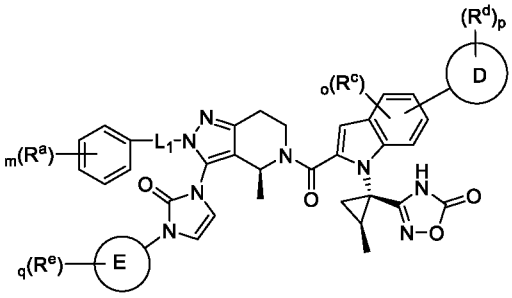
membered heterocyclic group, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, or 4) groups selected from deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, methyl, ethyl, methoxy, and cyclopropyl.

L1 is independently selected from a bond;

m, n, o, p, q, and r are each independently 0, 1, 2, or 3;

Provided that when q is 2, Re is F and methyl, and when m is 3,  is not .

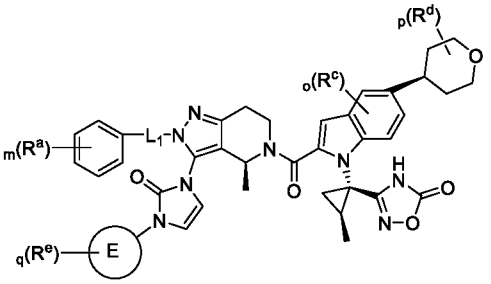
In some embodiments, the compound of formula (III) is a compound of formula (III-1):



(III-1)

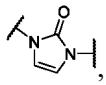
Wherein, ring E, ring D, Ra, Rc, Rd, Re, L1, m, o, p, and q are as defined for the compound of formula (III).

In some embodiments, the compound represented by formula (III) is a compound represented by formula (III-2):



(III-2)

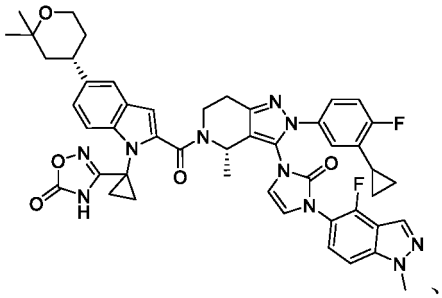
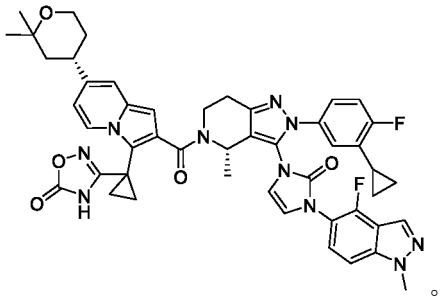
Wherein, ring E, Ra, Rc, Rd, Re, L1, m, o, p, and q are as defined for the compound of formula (III).

In some embodiments, in the aforementioned compounds (Formula I, I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, II, II-1, II-2, III, III-1, III-2), provided that when L4 is , at least one (e.g., one or two) of Ra or the substituents on ring E (or Re) is cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene, or cyclopentyl-ethylene: Alternatively, when both Re and the substituent on ring E (or Re) are not cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene or cyclopentyl-ethylene, two Re (preferably, two Re located on different rings) together with the atoms to which they are attached form an optionally substituted 5-7 membered heterocyclyl, said heterocyclyl (preferably heterocycloalkyl) containing 1-3 (e.g., 1, 2 or 3) groups each independently selected from N, O or S heteroatoms;

Optionally substituted refers to the hydrogen on the substituted group is unsubstituted or one or more substitutable sites of the substituted group are independently substituted with Re3. Re3 is as defined for the compound of formula (I);

Preferably, the C3-5 cycloalkyl group is selected from cyclopropyl, cyclobutyl, and cyclopentyl; more preferably, cyclopropyl;

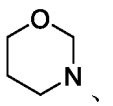
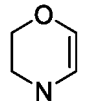
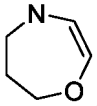
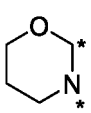
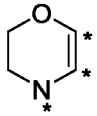
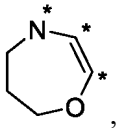
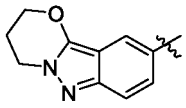
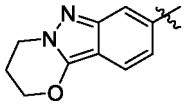
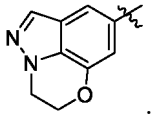
Provided that the following compounds are not included:


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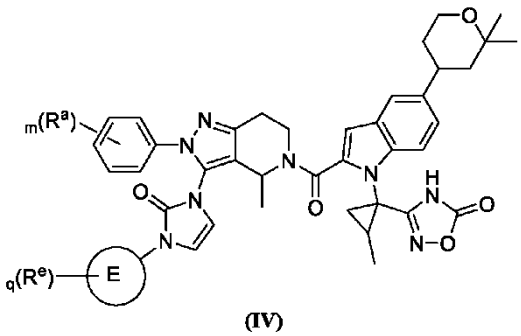
In some embodiments, in the aforementioned compounds (Formula I, Formula I-1, Formula I-2, Formula I-3, Formula I-4, Formula I-5, Formula I-6, Formula I-7, Formula I-8, Formula I-9, Formula I-10, Formula I-11, Formula I-12, Formula I-13, Formula I-14, Formula I-15, Formula I-16, Formula I-17, Formula I-18, Formula I-19, Formula I-20, Formula II, Formula II-1, Formula II-2, Formula II ... III, formula III-1, formula III-2), provided that at least one (e.g., one or two) of Ra or the substituents on ring E (or Re) is cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene or cyclopentyl-ethylene; alternatively, when neither Ra nor the substituents on ring E (or Re) are cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene or cyclopentyl-ethylene, two Re (preferably, two Re located on different rings) together with the atoms to which they are attached form an optionally substituted 5-7 membered heterocyclic group, said heterocyclic group (preferably heterocycloalkyl) containing 1-3 (e.g., 1, 2) or 3) heteroatoms independently selected from N, O, or S;

Optionally substituted refers to the hydrogen atoms on the substituted group are unsubstituted or that one or more substitutable sites of the substituted group are independently replaced by Re3. Re3 is as defined for the compound of formula (I);

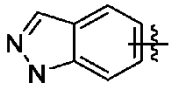
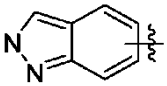
Preferably, the C3-5 cycloalkyl group is selected from cyclopropyl, cyclobutyl, and cyclopentyl; more preferably, cyclopropyl.

In some embodiments, two Re (preferably, two adjacent Re; more preferably, two adjacent Re located on different rings) together with the atoms to which they are attached form an optionally substituted 6-7 membered heterocyclyl, the heterocyclyl (preferably a heterocycloalkyl) contains 1-3 (e.g., 1, 2, or 3) heteroatoms independently selected from N, O, or S. Preferably, the 6-7 membered heterocyclyl forms a fused three-membered ring with Ring E (i.e., the heterocyclyl and Ring E share one chemical bond (i.e., two adjacent atoms) or two adjacent chemical bonds (i.e., three adjacent atoms)). Preferably, the 6-7 membered heterocyclyl is selected from 、 and ; preferably, the 6-7 membered heterocyclyl is selected from 、 or , wherein, * represents an atom shared with Ring E; preferably, the fused three-membered ring formed by the 6-7 membered heterocyclyl and Ring E is selected from 、 and .

In some embodiments, wherein, the compound represented by formula (I), formula (II), or formula (I-1) to formula (I-8) is a compound represented by formula (IV):



(IV)

Ring E is selected from  and ;

Ra is independently selected each time from fluorine, methyl, and C3-5 cycloalkyl;

m is 2 or 3;

q is 2 or 3;

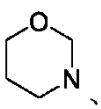
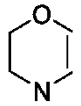
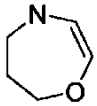
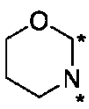
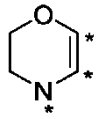
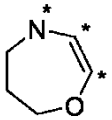
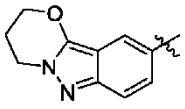
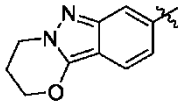
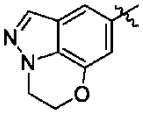
Re is independently selected each time from fluorine, or optionally substituted with the following groups: C1-3 alkyl (e.g., methyl, ethyl), C3-5 cycloalkyl; provided that at least one (e.g., one or two) of Ra or Re is cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene, or cyclopentyl-ethylene;

Alternatively, two Re (preferably, two adjacent Re; more preferably, two adjacent Re on different rings) together with the atoms to which they are attached form an optionally substituted 5-7 membered heterocyclic group containing 1-3 (e.g., 1, 2, or 3) heteroatoms independently selected from N, O, or S.

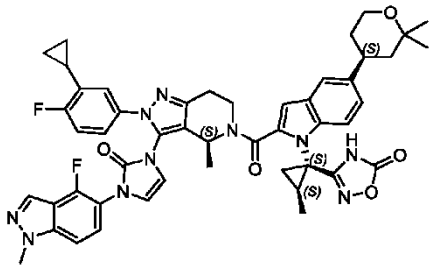
Optionally substituted refers to a hydrogen atom on the substituted group is unsubstituted or that one or more substitutable positions of the substituted group are independently replaced with Re3.

Re3 is independently selected from deuterium, halogen (e.g., Re4 and Re5 are independently selected from hydrogen or substituted by one or more (e.g., 2 or 3) of hydrogen, deuterium, halogen (e.g., fluorine or chlorine), hydroxyl, amino, oxo, cyano, -Re4, -ORe4, -S(O)2Re4, -C(O)Re4, -N(Re4)(Re5), -S(O)2N(Re4)(Re5), -N(Re4)S(O)2Re5, -P(O)(Re4)Re5: Re4 and Re5 are independently selected from hydrogen or substituted by one or more (e.g., 2 or 3) of hydrogen, deuterium, halogen (e.g., fluorine or chlorine), hydroxyl, amino, oxo, methoxy: C1-3 alkyl (e.g., methyl, ethyl, propyl) or C3-6 cycloalkyl (preferably 3-5 membered cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl);

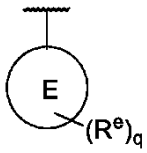
Preferably, the C3-5 cycloalkyl is selected from cyclopropyl, cyclobutyl, and cyclopentyl; more preferably, cyclopropyl.

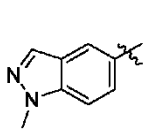
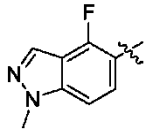
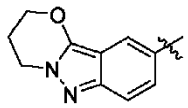
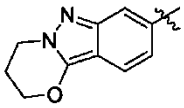
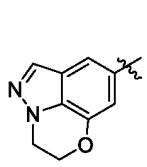
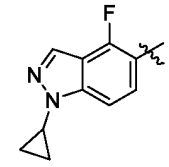
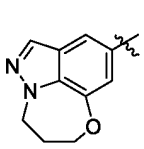
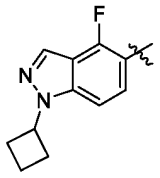
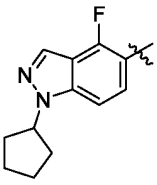
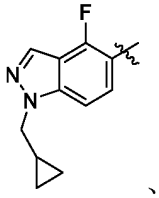
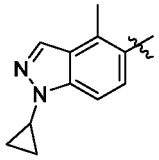
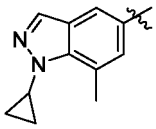
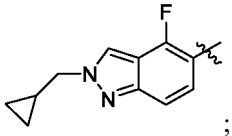
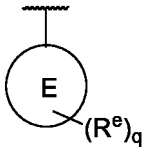
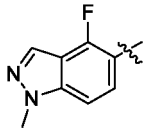
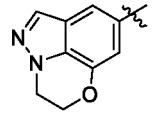
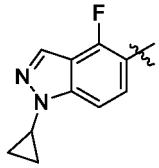
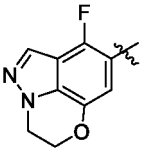
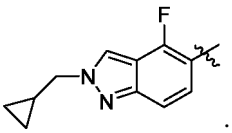
In some embodiments, two Re (preferably, two adjacent Re; further preferably, two adjacent Re located on different rings) together with the atoms to which they are attached form an optionally substituted 6-7 membered heterocyclyl, wherein, the heterocyclyl (preferably heterocycloalkyl) contains 1-3 (e.g., 1, 2 or 3) heteroatoms each independently selected from N, O or S; preferably, the 6-7 membered heterocyclyl forms a fused three-membered ring with ring E (i.e., the heterocyclyl shares 1 chemical bond (i.e., shares 2 adjacent atoms) or 2 adjacent chemical bonds (i.e., shares 3 adjacent atoms) with ring E); preferably, the 6-7 membered heterocyclyl is selected from 、 and ; preferably, the 6-7 membered heterocyclyl is selected from 、 or , wherein, * represents an atom shared with ring E; preferably, the fused three-membered ring formed by the 6-7 membered heterocyclyl and ring E is selected from 、 and .

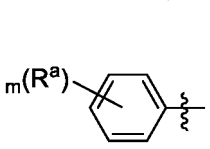
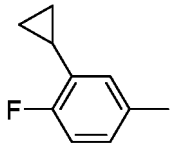
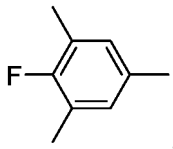
In some embodiments, provided that the following compounds are not included:

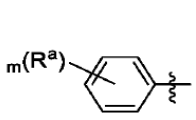
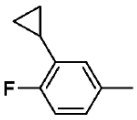
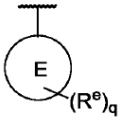
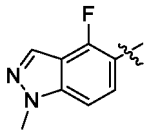


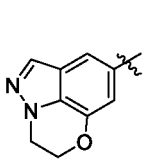
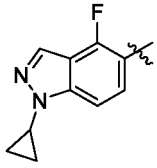
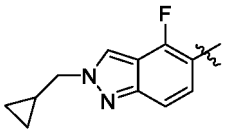
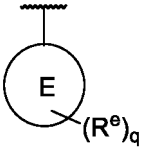
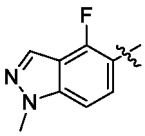
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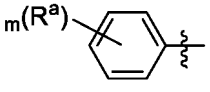
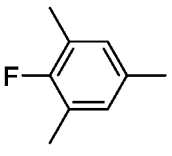
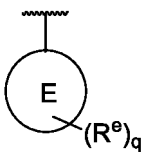
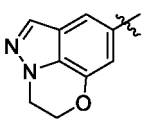
In some embodiments, wherein,  is

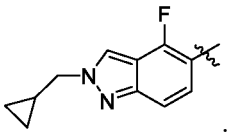
、、、、、、、、、、、、、or; preferably is 、、、, or ;

In some embodiments, wherein,  is  or .

In some embodiments, wherein, when  is ,  is 

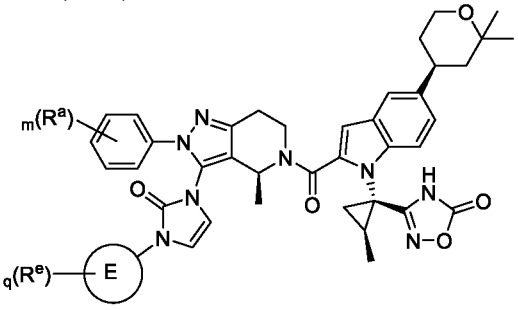
、、or; preferably,  is ;

when  is ,  is 、、or



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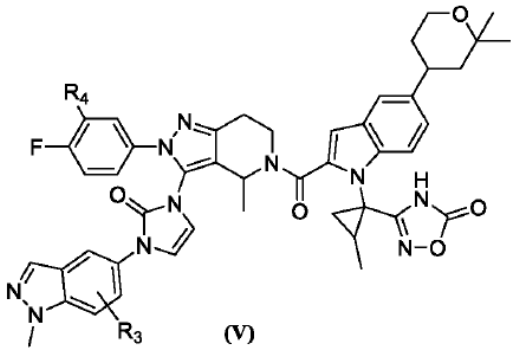
In some embodiments, wherein, the compound represented by formula (IV) is a compound represented by formula (IV-1):



(IV-1)

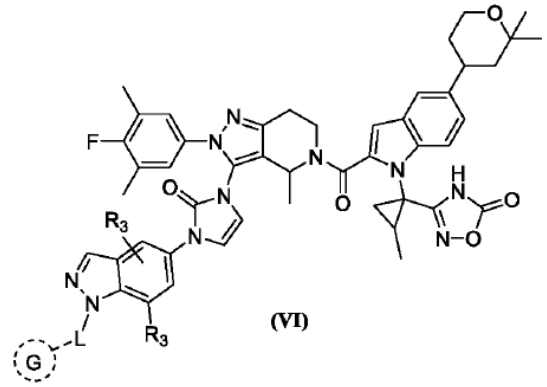
Wherein, ring E, m, q, Ra, and Re are defined as described for the compound represented by formula (IV).

In some embodiments, the compound represented by Formula (I), Formula (II), or Formula (I-1) to Formula (I-8) is a compound represented by Formula (V) to (VIII):



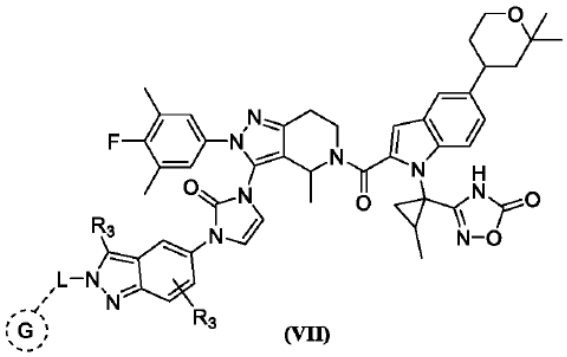
(V)

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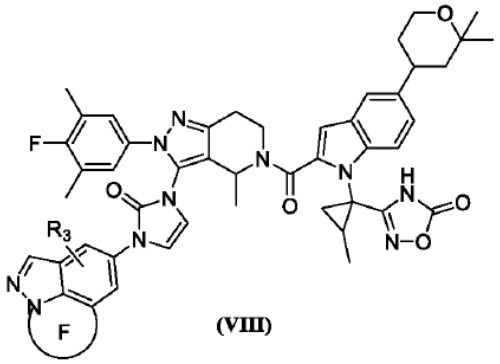
(VI)

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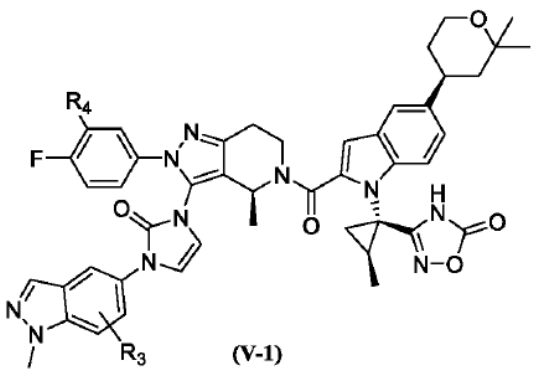
(VII)

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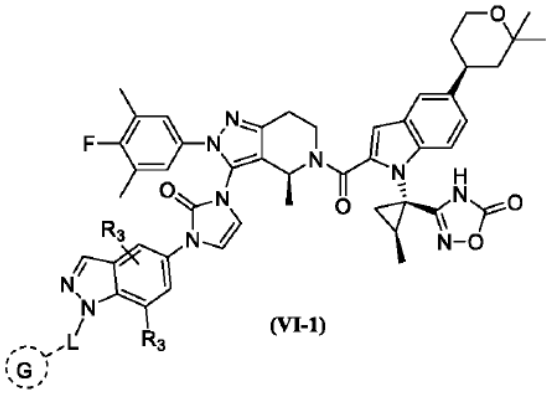
(VIII)

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(V-1)

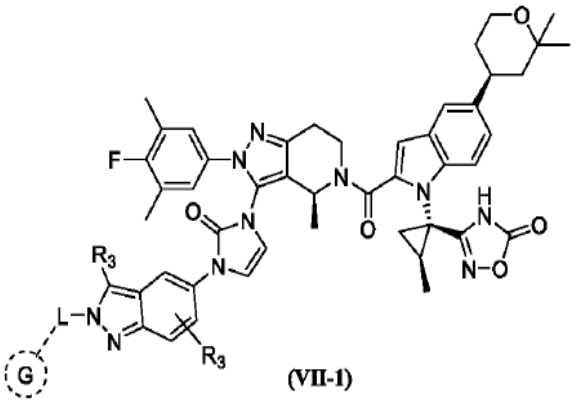
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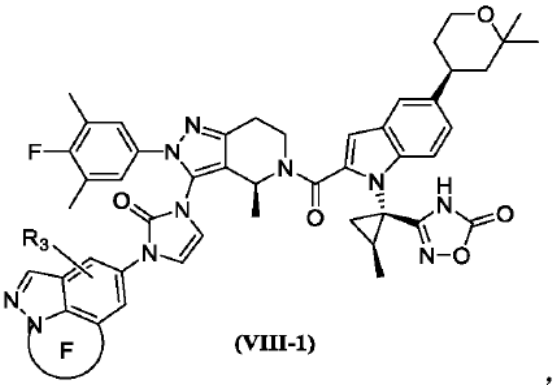
(VI-1)

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(VII-1)

or


(VIII-1)

,

Wherein, ---- represents the presence or absence of the bond;


represents the presence or absence of Ring G; when Ring G is present, ring G is a C3-5 cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl; preferably cyclopropyl);

L is a bond, a C1-3 alkylene group (e.g., methylene, ethylene, propylene; preferably methylene), or a C1-3 alkyl group (e.g., methyl, ethyl, propyl; preferably methyl);

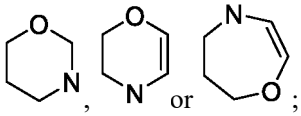
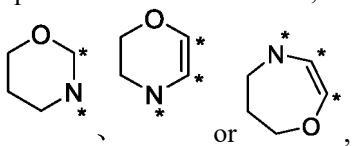
Alternatively, L and its adjacent R3 are cyclized to form an optionally substituted 5-7 membered heterocyclic group containing 1-3 (e.g., 1, 2, or 3) heteroatoms independently selected from N, O, or S, in which case Ring G is absent;

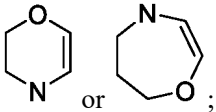
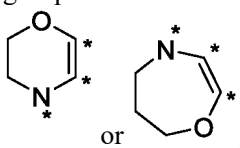
R3 is selected from H, F, or methyl;

R4 is selected from a C3-5 cycloalkyl group (e.g., cyclo =propyl, cyclobutyl, cyclopentyl; preferably cyclopropyl);

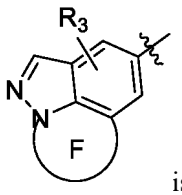
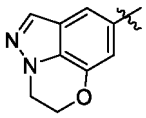
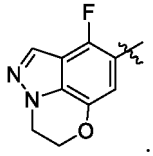
Ring F is an optionally substituted 5-7 membered heterocyclic group containing 1-3 (e.g., 1, 2, or 3) heteroatoms independently selected from N, O, or S;

Optionally substituted refers to the hydrogen atoms on the substituted group are not replaced or one or more substitutable positions of the substituted group are independently replaced by Re3. Re3 is independently selected from deuterium, halogen (e.g., fluorine, chlorine), oxo, hydroxy, amino, cyano, -Re4, -ORe4, -SO2(Re4), -C(O)Re4, -N(Re4)(Re5), -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), -P(O)(Re4)Re5; Re4 and Re5 are independently selected from hydrogen or substituted by one or more of hydrogen, halogen (e.g., fluorine or chlorine), hydroxy, amino, cyano, oxo, methoxy (e.g., 2 or 3) optionally substituted with: C1-3 alkyl (e.g., methyl, ethyl, propyl) or C3-6-membered cycloalkyl (preferably 3-5-membered cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl).

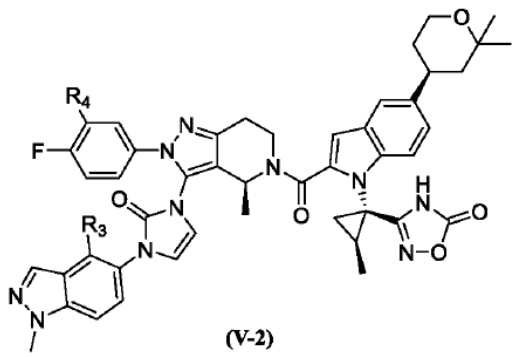
In some embodiments, L and its adjacent R3 form an optionally substituted 6-7-membered heterocyclic group containing 1-3 (e.g., 1, 2, or 3) heteroatoms independently selected from N, O, or S; preferably, the 6-7-membered heterocyclic group is selected from ; preferably, the 6-7-membered heterocyclic group is selected from , wherein, * represents a shared atom.

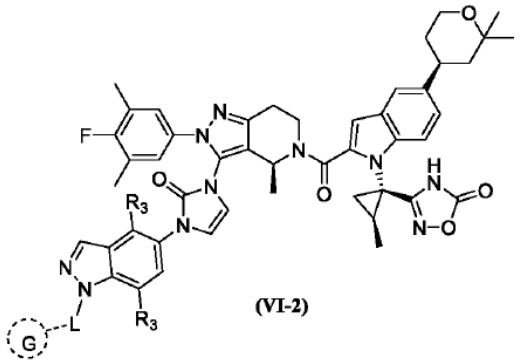
In some embodiments, ring F is an optionally substituted 6-7 membered heterocyclic group containing 1-3 (e.g., 1, 2, or 3) heteroatoms independently selected from N, O, or S: Preferably, the 6-7 membered heterocyclic group is selected from ; preferably, the 6-7 membered heterocyclic group is selected from , wherein, * represents a shared atom.

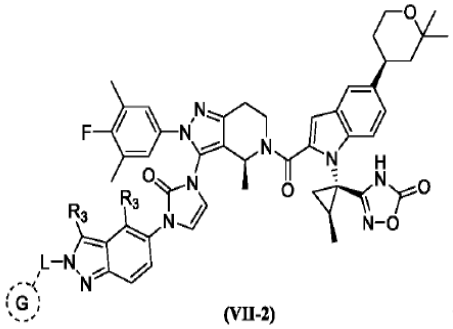
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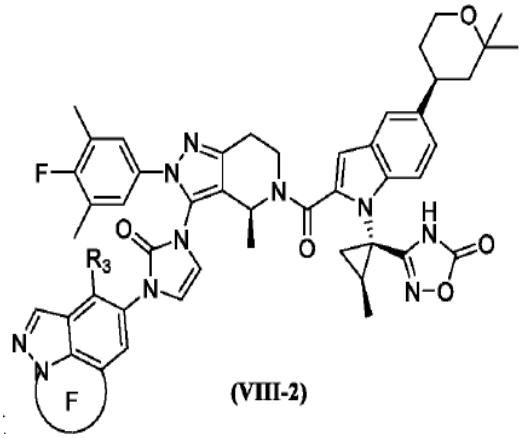
In some embodiments, in Formula (VIII) or Formula (VIII-1),  is  or .

In some embodiments, wherein, the compound represented by Formulas (V) to (VIII), (V-1) to (VIII-1) is a compound represented by Formulas (V-2) to (VIII-2):


(V-2)

, 
(VI-2)

, 
(VII-2)

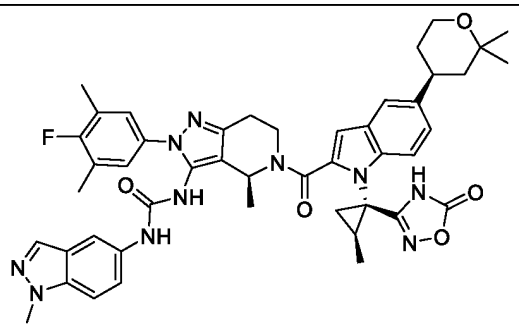
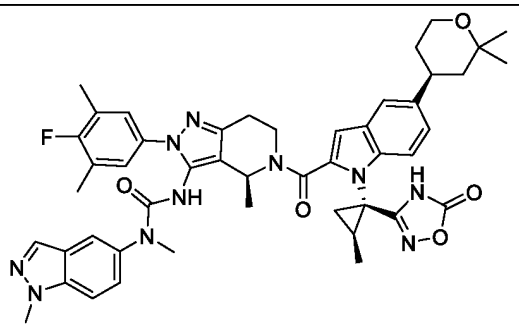
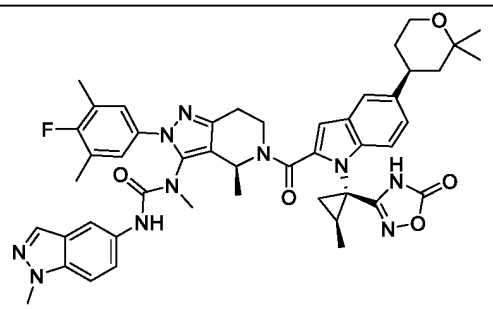
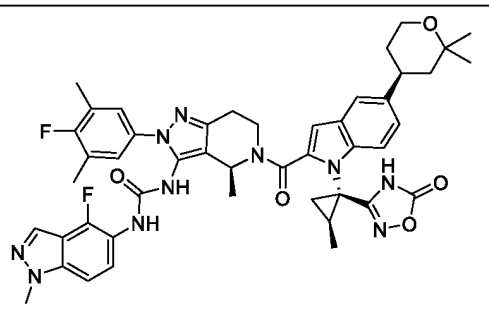
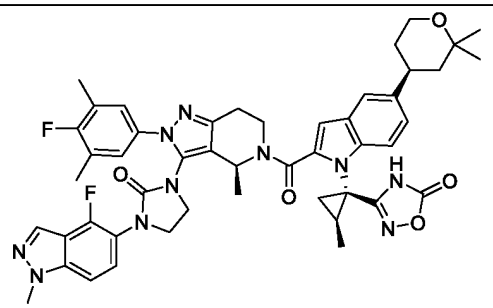
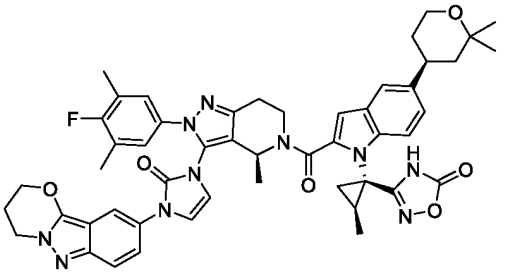
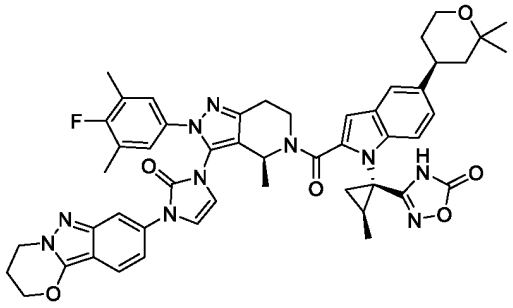
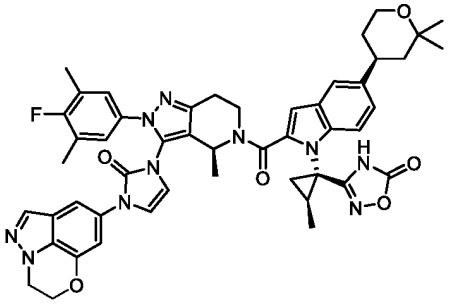
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(VIII-2)

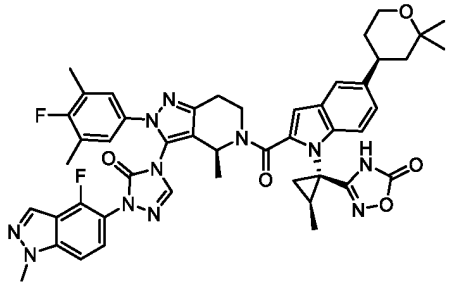
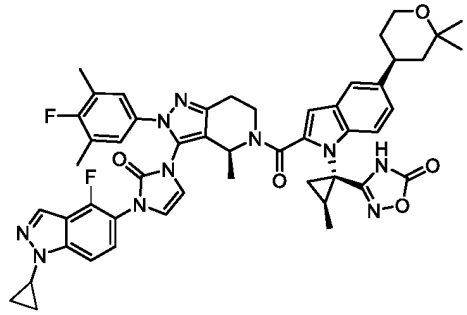
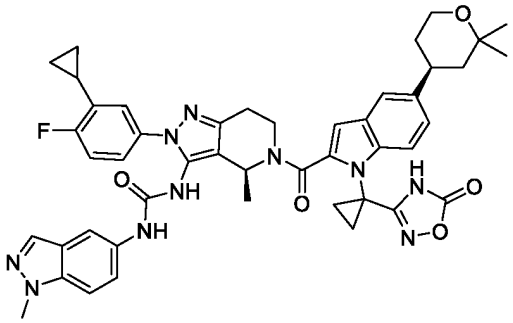
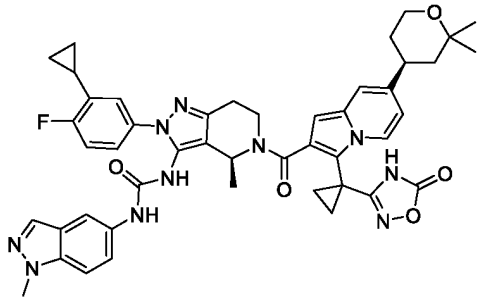
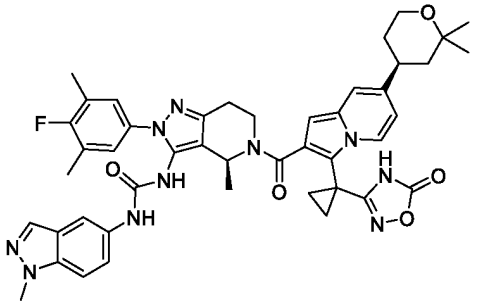
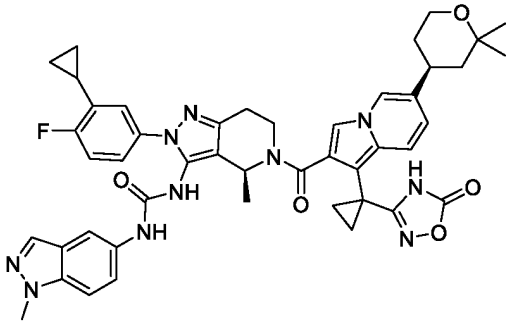
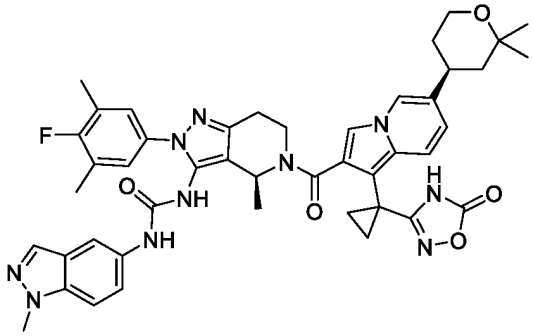
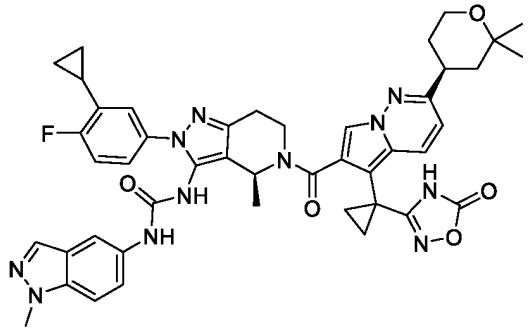
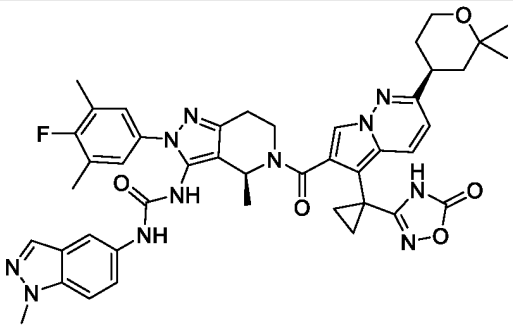
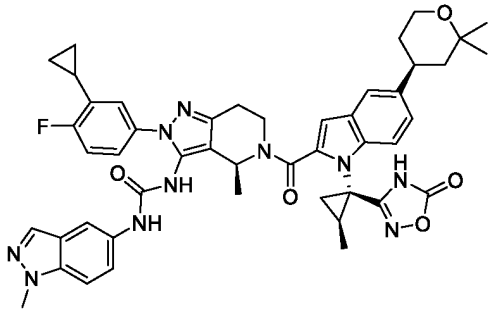
Wherein, R, R3, L, and Ring F are as defined for the compounds represented by Formulas (V) to (VIII), (V-1) to (VIII-1).

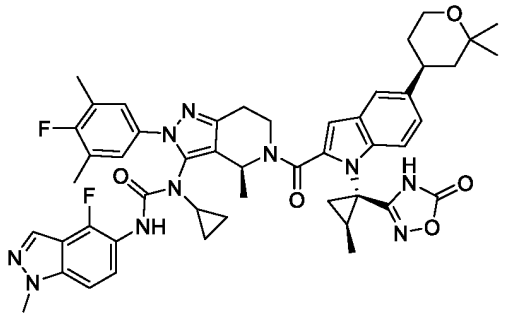
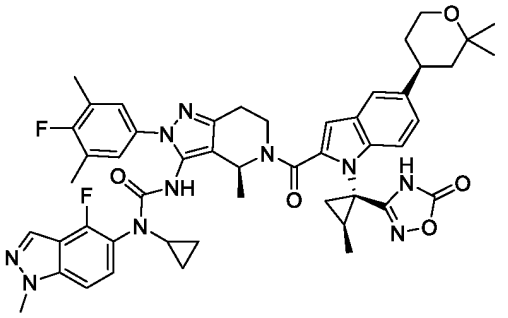
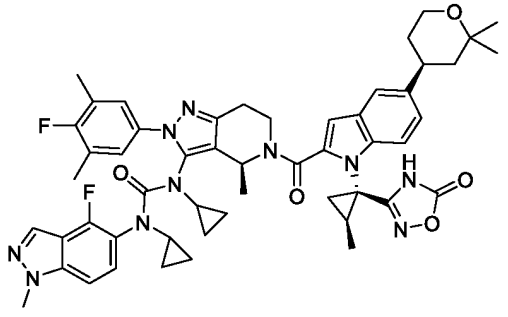
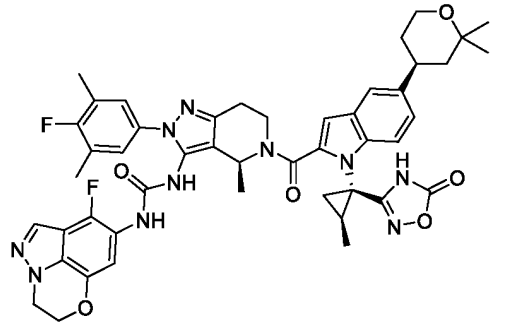
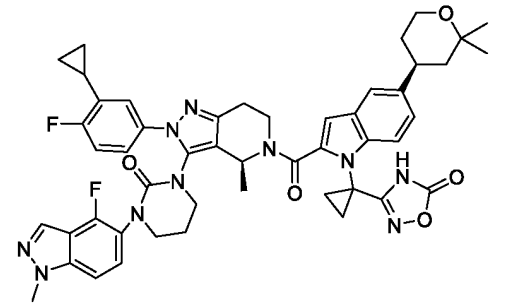
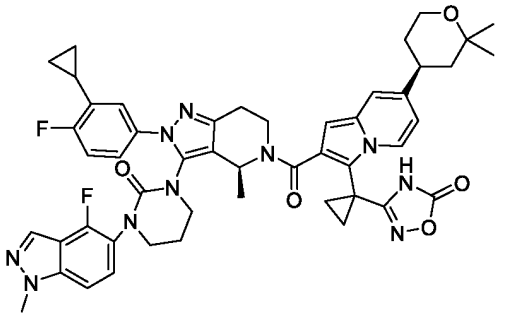
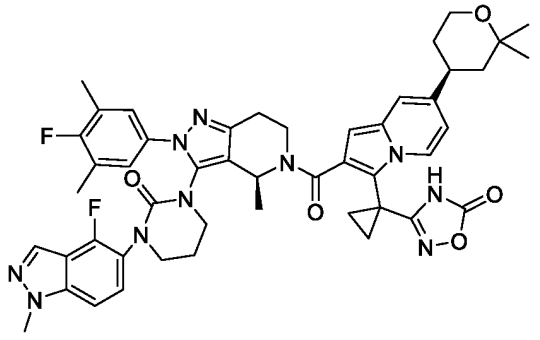
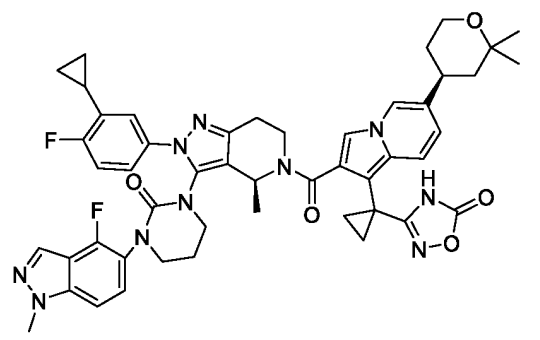
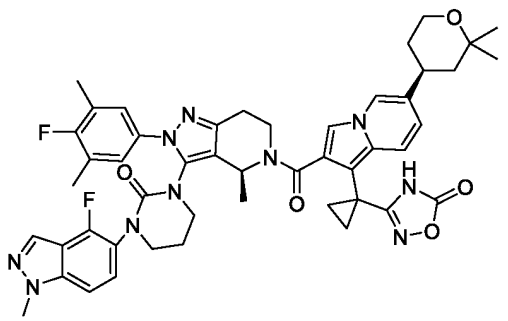
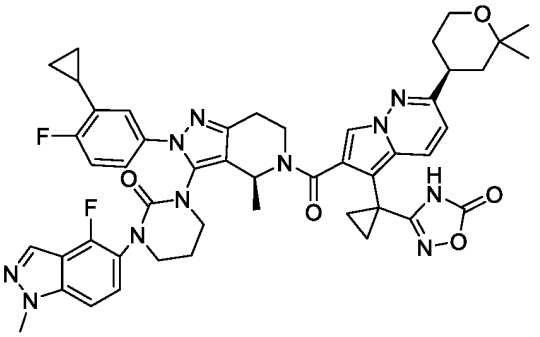
Based on common knowledge in the art, the above preferred conditions can be arbitrarily combined to obtain preferred embodiments of the present invention.

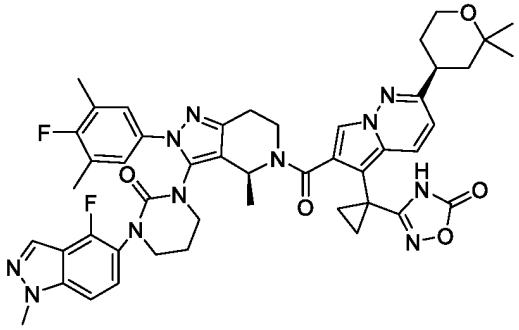
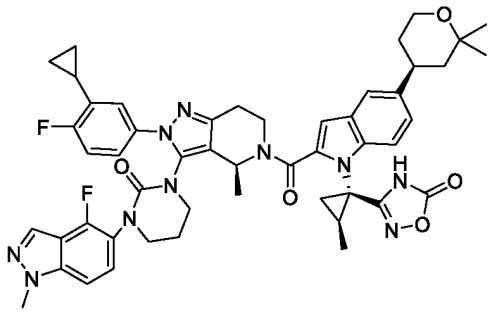
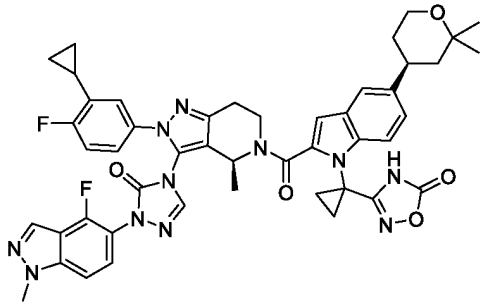
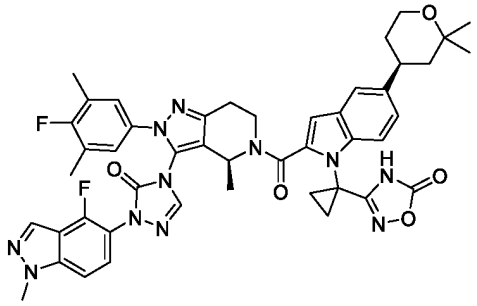
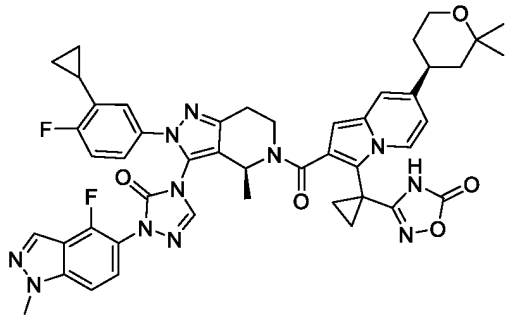
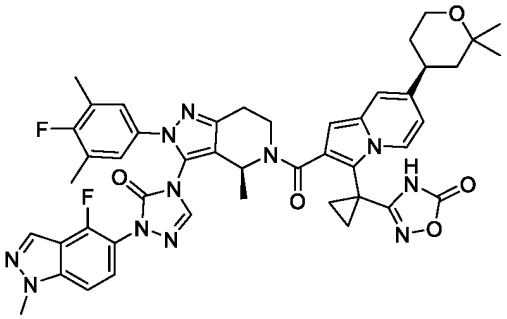
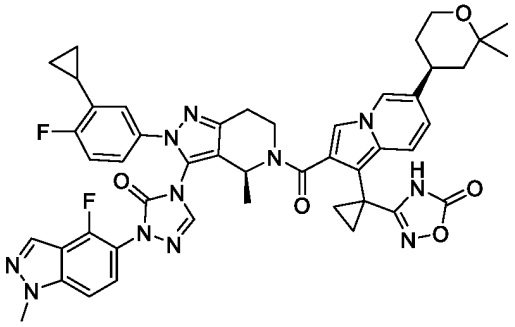
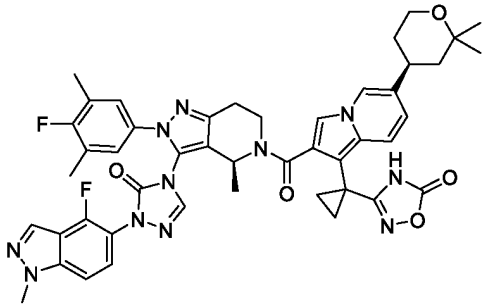
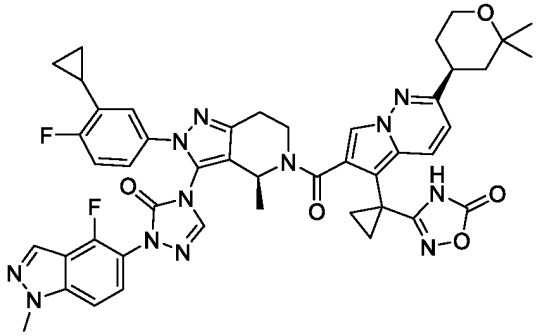
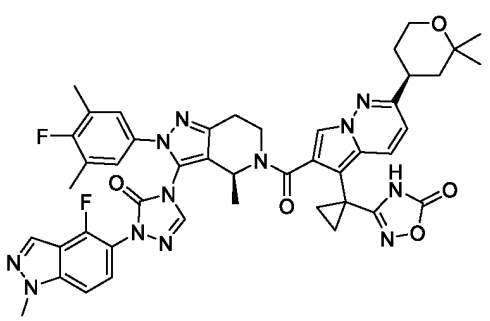
In some embodiments, the present invention provides the following compounds, or tautomers, stereoisomers, or pharmaceutically acceptable salts thereof, wherein, the compounds have the following structures:

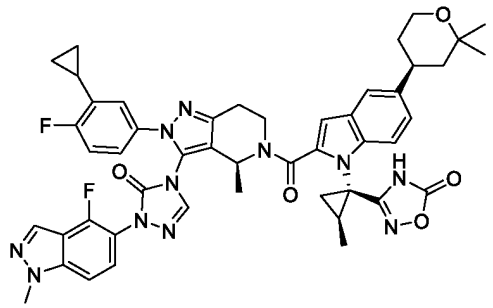
Ascletis EX2005
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Compound Structural Formula and Number	Compound Structural Formula and Number
 1	 2
 3	 4
 5	 6
 7	 8

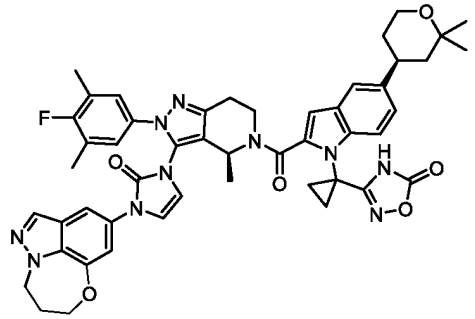
 9	 10
 11	 12
 13	 14
 15	 16
 17	 18

 19	 20
 21	 22
 23	 24
 25	 26
 27	 28

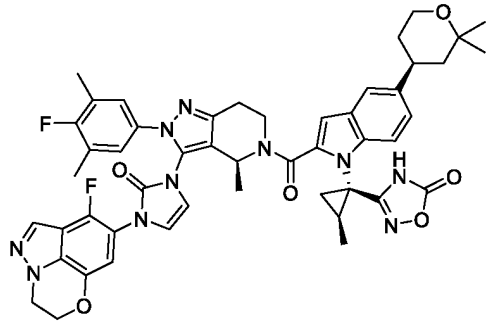
 29	 30
 31	 32
 33	 34
 35	 36
 37	 38



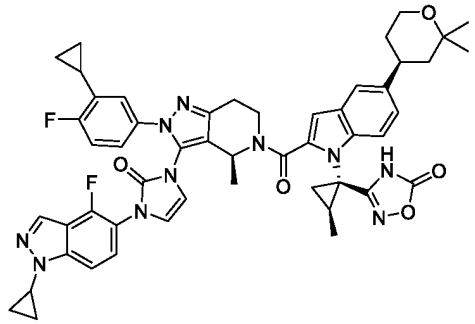
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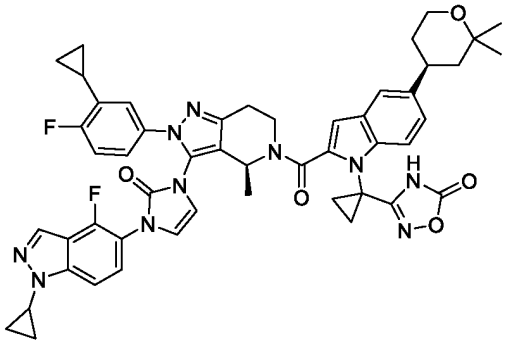
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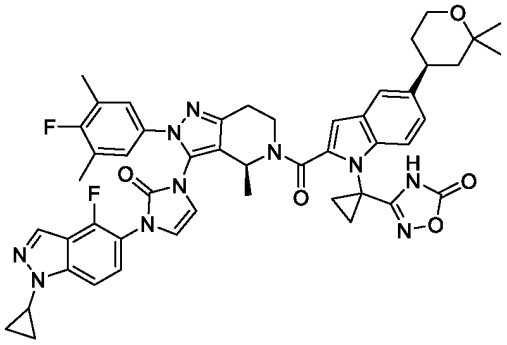
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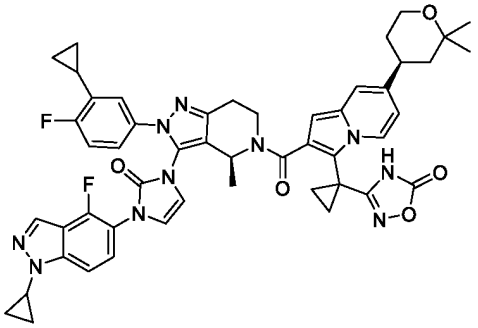
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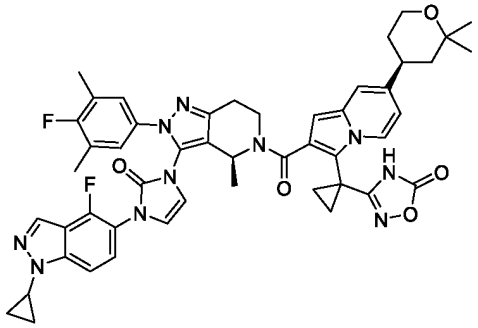
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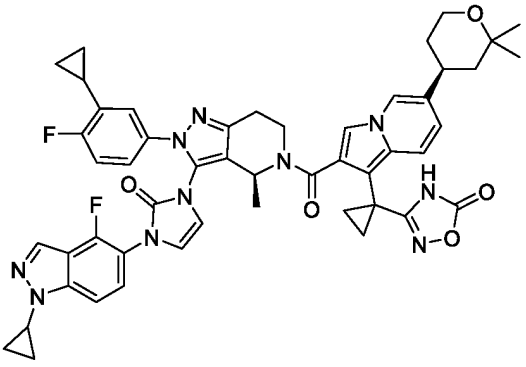
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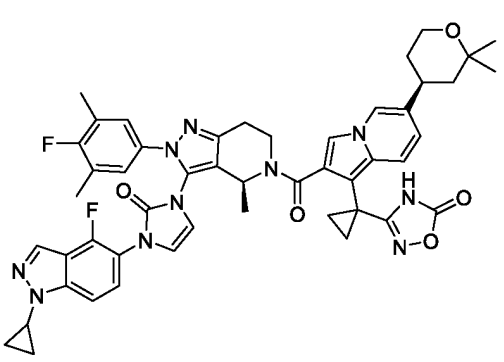
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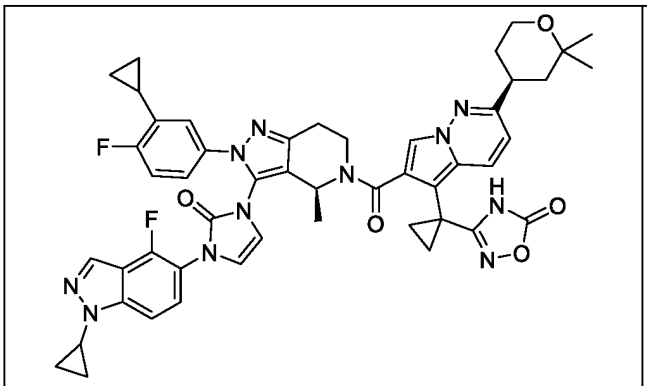
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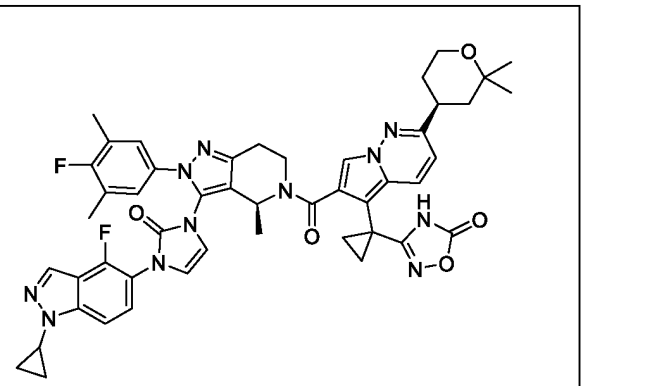
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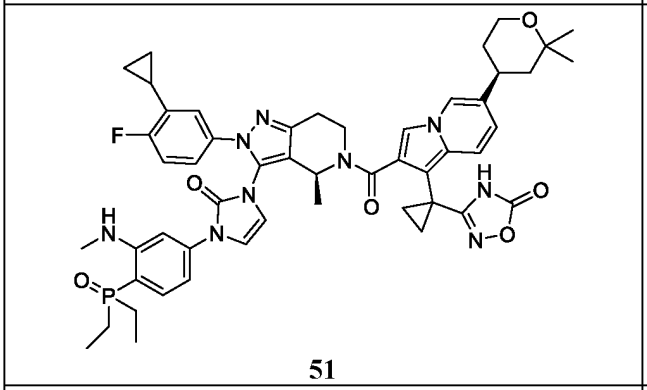
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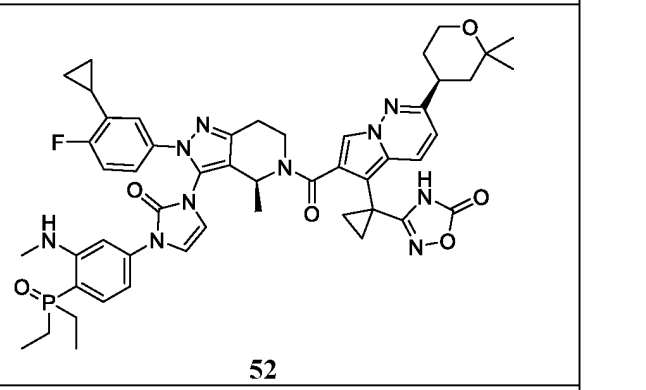
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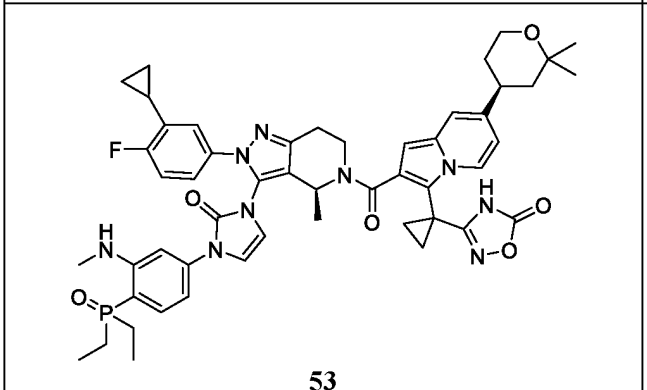
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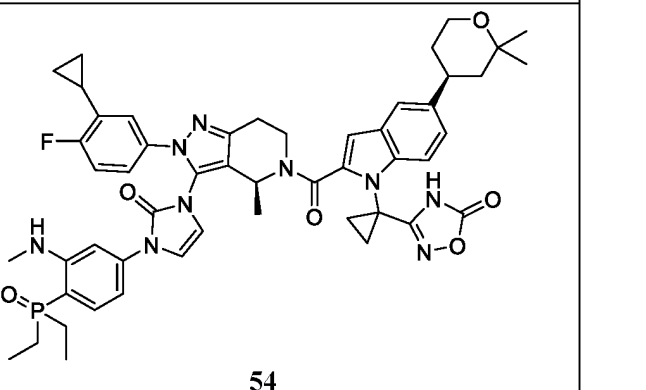
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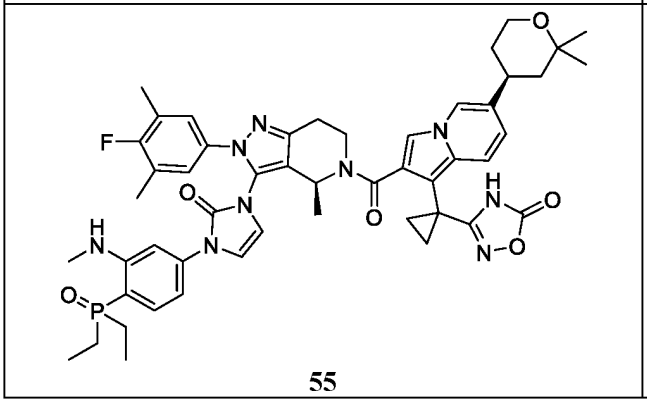
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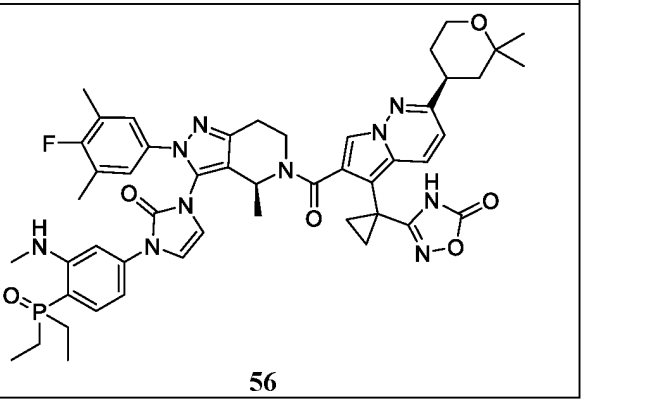
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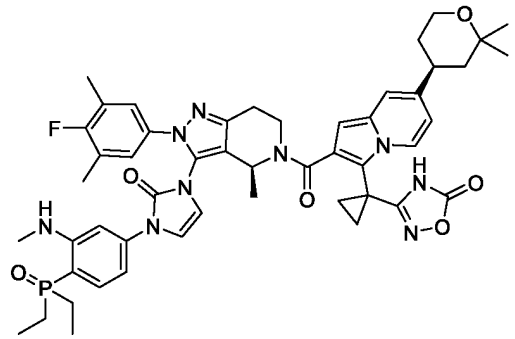
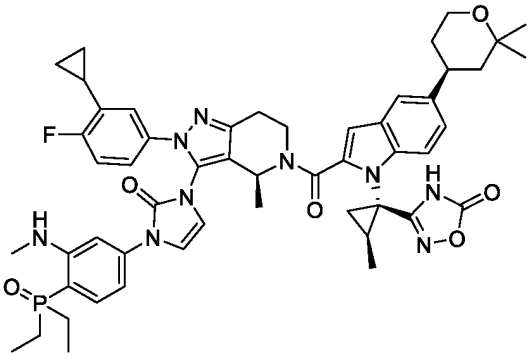
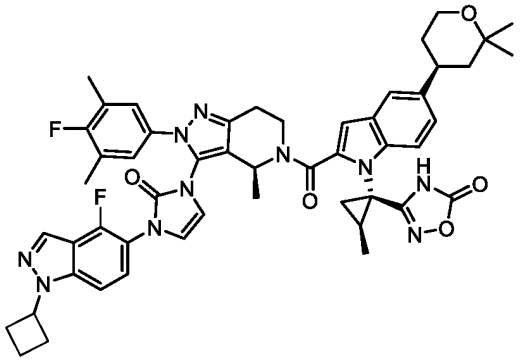
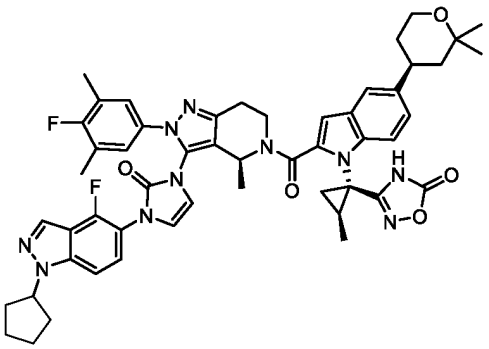
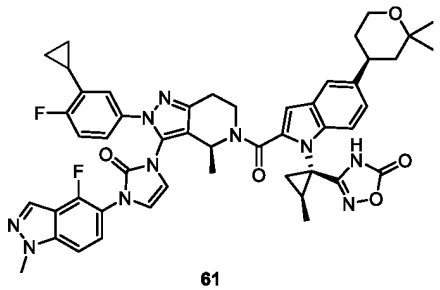
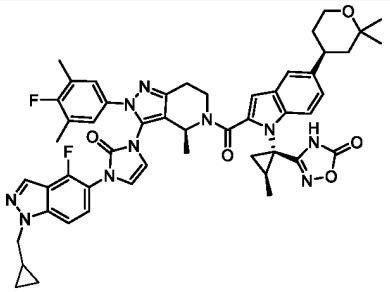
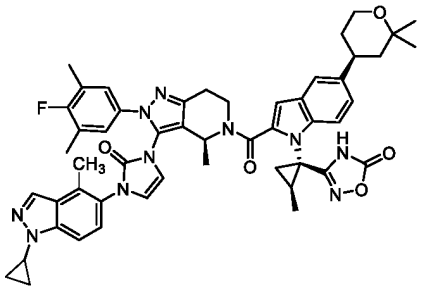
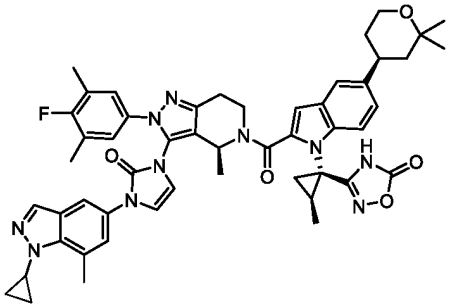
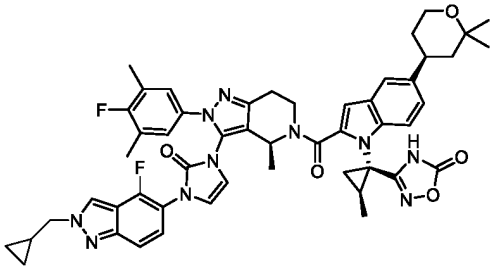
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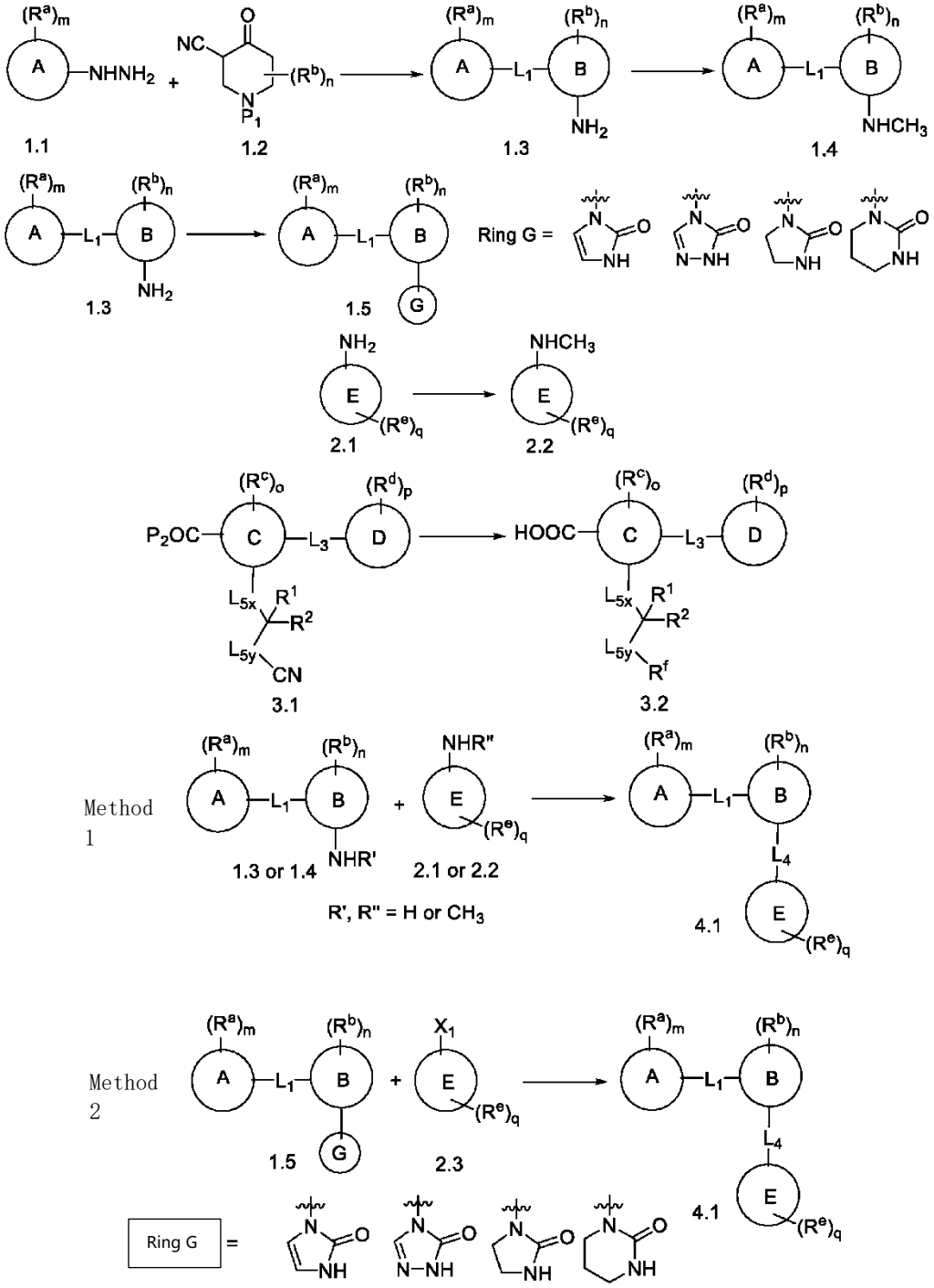
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In a second aspect, the present invention provides methods for preparing the compounds represented by

Formula (I) or their tautomers, stereoisomers, or pharmaceutically acceptable salts.

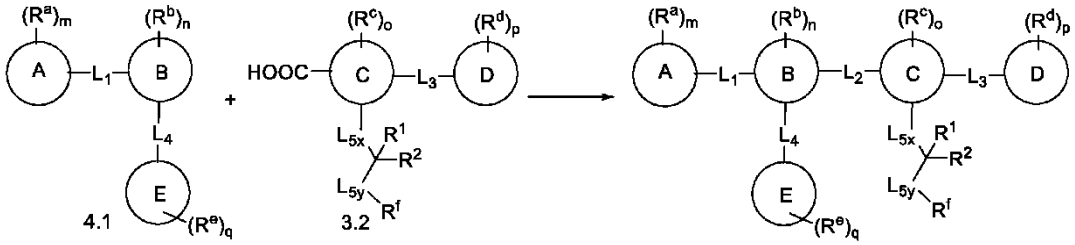
The methods can be prepared, e.g., using the methods shown in the following schemes:



The hydrazine group of intermediate 1.1 reacts with intermediate 1.2 to produce intermediate 1.3, which is then alkylated to produce intermediate 1.4; the amino group of intermediate 1.3 reacts to produce intermediate 1.5; intermediate 2.1 is alkylated to produce intermediate 2.2; the cyano group of intermediate 3.1 is converted to intermediate 3.2; and intermediate 4.1 can be synthesized by two methods:

Method 1: The amino group of intermediate 1.3 or 1.4 reacts with the amino group of intermediate 2.1 or 2.2 to produce intermediate 4.1;

Method 2: intermediate 1.5 and intermediate 2.3 are reacted via Ullmann reaction to give intermediate 4.1;



Intermediate 4.1 reacts with the carboxyl group of intermediate 3.2 to obtain the target compound;

Note: The partial protection and deprotection steps involved in this step have been omitted;

P1 is a protecting group (e.g., Boc, Bn, Cbz, etc.); X1 is a leaving group (e.g., I, Cl, Br, etc.);

Ring A, ring B, ring C, ring D, ring E, Ra, Rb, Rc, Rd, Re, R1, R2, L1, L2, L3, Rf, Re, L4, L5x, L5y, m, n, o, p, q, etc. are as defined for the compound of formula (I).

In a third aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention (Formula I, Formula I-1, Formula I-2, Formula I-3, Formula I-4, Formula I-5, Formula I-6, Formula I-7, Formula I-8, Formula I-9, Formula I-10, Formula I-11, Formula I-12, Formula I-13, Formula I-14, Formula I-15, Formula I-16, Formula I-17, Formula I-18, Formula I-19, Formula I-20, Formula II, Formula II-1, Formula II-2, Formula III, Formula IV, Formula IV-1, Formula V, Formula VI, Formula VII, Formula VIII, Formula V-1, Formula VI-1, Formula VII-1, Formula VIII-1, Formula V-2, Formula VI-2, Formula VII-2, Formula VIII-2, Compound 1-65) or a tautomer, stereoisomer or pharmaceutically acceptable salt thereof, optionally further comprising a pharmaceutically acceptable excipient.

Administration of the compounds of the present invention (Formula I, Formula I-1, Formula I-2, Formula I-3, Formula I-4, Formula I-5, Formula I-6, Formula I-7, Formula I-8, Formula I-9, Formula I-10, Formula I-11, Formula I-12, Formula I-13, Formula I-14, Formula I-15, Formula I-16, Formula I-17, Formula I-18, Formula I-19, Formula I-20, Formula II, Formula II-1, Formula II-2, Formula III, Formula IV, Formula IV-1, Formula V, Formula VI, Formula VII, Formula VIII, Formula V-1, Formula VI-1, Formula VII-1, Formula VIII-1, Formula V-2, Formula VI-2, Formula VII-2, Formula VIII-2, Compound 1-65) or their tautomers, stereoisomers or pharmaceutically acceptable salts thereof can be carried out in pure form or in the form of a suitable pharmaceutical composition by any acceptable mode of administration for providing drugs of similar use. The pharmaceutical compositions of the present invention can be prepared by combining the compounds of the present invention with suitable pharmaceutically acceptable excipients. The pharmaceutical compositions of the present invention can be formulated into solid, semisolid, liquid, or gaseous formulations. Generally, the pharmaceutical compositions can be prepared using conventional excipients in the pharmaceutical field using conventional preparation methods.

In a fourth aspect, the present invention provides the compounds as described above (Formula I, Formula I-1, Formula I-2, Formula I-3, Formula I-4, Formula I-5, Formula I-6, Formula I-7, Formula I-8, Formula I-9, Formula I-10, Formula I-11, Formula I-12, Formula I-13, Formula I-14, Formula I-15, Formula I-16, Formula I-17, Formula I-18, Formula I-19, Formula I-20, Formula II, Formula II-1, Formula II-2, Formula I II, Formula IV, Formula IV-1, Formula V, Formula VI, Formula VII, Formula VIII, Formula V-1, Formula VI-1, Formula VII-1, Formula VIII-1, Formula V-2, Formula VI-2, Formula VII-2, Formula VIII-2, Compound 1-65) and its tautomers, stereoisomers or pharmaceutically acceptable salts thereof or the pharmaceutical composition of the present invention as a drug or in the preparation of a drug; preferably, the drug is GLP-1R agonist; further preferably, the drug is a drug for treating and/or preventing GLP-1R-related disorders; further preferably, the drug is a drug for treating and/or preventing disorders mediated by GLP-1R; further preferably, the drug is a drug for treating and/or preventing disorders caused by or mediated by decreased GLP-IR activity; further preferably, the drug is a drug for preventing and/or treating disorders by stimulating GLP-1R-mediated cascade signals; further preferably, the disorders include diabetes, overweight or obesity, non-alcoholic fatty liver disease, Alzheimer's disease, etc.; further preferably, the diabetes is type 2 diabetes.

In some embodiments, wherein, the use is for treating and/or preventing diabetes, overweight or obesity, non-alcoholic fatty liver disease, or Alzheimer's disease; preferably, the drug is for treating and/or preventing diabetes, overweight or obesity; and further preferably, the diabetes is type 2 diabetes.

In a fifth aspect, the present invention provides the aforementioned compounds (Formula I, Formula I-1, Formula I-2, Formula I-3, Formula I-4, Formula I-5, Formula I-6, Formula I-7, Formula I-8, Formula I-9, Formula I-10, Formula I-11, Formula I-12, Formula I-13, Formula I-14, Formula I-15, Formula I-16, Formula I-17, Formula I-18, Formula I-19, Formula I-20, Formula II, Formula II-1, Formula II-2, Formula III, Formula IV, Formula IV-1, Formula V, Formula VI, Formula VII, Formula VIII, Formula V-1, Formula VI-1, Formula VII-1, Formula VIII-1, Formula V-2, Formula VI-2, Formula VII-2, Formula VIII-2, Compound 1-65) or its tautomers, stereoisomers or pharmaceutically acceptable salts or the pharmaceutical composition for treating and/or preventing a disease;

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preferably, the disease is a GLP-1R-related disease; further preferably, the disease is a GLP-1R-mediated disease; further preferably, the disease is a disease caused or mediated by decreased GLP-1R activity; further preferably, the disease includes diabetes, overweight or obesity, non-alcoholic fatty liver disease, Alzheimer's disease, etc.; further preferably, the disease includes diabetes, overweight or obesity; further preferably, the diabetes is type 2 diabetes.

In a sixth aspect, the present application provides a method for treating a disease, comprising: Administering a therapeutically effective amount of the aforementioned compound (Formula I, Formula I-1, Formula I-2, Formula I-3, Formula I-4, Formula I-5, Formula I-6, Formula I-7, Formula I-8, Formula I-9, Formula I-10, Formula I-11, Formula I-12, Formula I-13, Formula I-14, Formula I-15, Formula I-16, Formula I-17, Formula I-18, Formula I-19, Formula I-20, Formula II, Formula II-1, Formula II-2, Formula III, Formula IV, Formula IV-1, Formula V, Formula VI, Formula VII, Formula VIII, Formula V-1, Formula VI-1, Formula VII-1, Formula VIII-1, Formula V-2, Formula VI-2, Formula VII-2, Formula VIII-2, Compound I-65) or a tautomer, stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present invention is administered to a subject in need thereof; preferably, the condition is GLP-1R-related disorders; further preferably, the disorders are disorders mediated by GLP-1R; further preferably, the disorders are disorders caused by or mediated by decreased GLP-1R activity; further preferably, the disorders include diabetes, overweight or obesity, non-alcoholic fatty liver disease, Alzheimer's disease, etc.; further preferably, the disorders include diabetes, overweight or obesity; further preferably, the diabetes is type 2 diabetes.

In some embodiments, the present invention provides a use or method, wherein, the compound of the present invention (Formula I, Formula I-1, Formula I-2, Formula I-3, Formula I-4, Formula I-5, Formula I-6, Formula I-7, Formula I-8, Formula I-9, Formula I-10, Formula I-11, Formula I-12, Formula I-13, Formula I-14, Formula I-15, Formula I-16, Formula I-17, Formula I-18, Formula I-19, Formula I-20, Formula II, Formula II-1, Formula I I-2, Formula III, Formula IV, Formula IV-1, Formula V, Formula VI, Formula VII, Formula VIII, Formula V-1, Formula VI-1, Formula VII-1, Formula VIII-1, Formula V-2, Formula VI-2, Formula VII-2, Formula VIII-2, Compound 1-65) or its tautomers, stereoisomers or pharmaceutically acceptable salts or the pharmaceutical composition of the present invention is used in combination with another, two or more compounds or drugs with the same or similar indications.

The present invention also provides a composition comprising the compound of the present invention (Formula I, Formula I-1, Formula I-2, Formula I-3, Formula I-4, Formula I-5, Formula I-6, Formula I-7, Formula I-8, Formula I-9, Formula I-1 0, Formula I-11, Formula I-12, Formula I-13, Formula I-14, Formula I-15, Formula I-16, Formula I-17, Formula I-18, Formula I-19, Formula I-20, Formula II, Formula II-1, Formula II-2, Formula III, Formula IV, Formula IV-1, Formula V, Formula VI, Formula VII, Formula VIII, Formula V-1, Formula VI-1, Formula VII-1, Formula VIII-1, Formula V-2, Formula VI-2, Formula VII-2, Formula VIII-2, Compound 1-65) or its tautomers, stereoisomers or pharmaceutically acceptable salts thereof, or the pharmaceutical composition of the present invention, and another, two or more compounds with the same or similar indications.

Definitions

Unless otherwise specified, the following terms used herein have the following meanings. The absence of a specific definition for a particular term should not be construed as indefinite or unclear, but rather should be understood according to its ordinary meaning in the art. When a trade name appears herein, it is intended to refer to its corresponding commercial product or its active ingredient.

As used herein, Cm-n means that the moiety has an integer number of carbon atoms within a given range. For example, “C1-6" means that the group can have 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms.

When any variable (e.g., Ra) occurs more than once in a compound's composition or structure, its definition is independent at each occurrence. Thus, for example, if a group, site, or atom is substituted with two Ra , each Ra is independently defined.

As used herein, "multiple" means 2 to 10, for example, 2, 3, 4, 5, 6, 7, 8, 9, or 10, preferably 2, 3, 4, 5, 6, 7, 8, or 9; preferably 2, 3, 4, 5, 6, 7, or 8; preferably 2, 3, 4, 5, 6, 7, or 8; preferably 2, 3, 4, or 5; and preferably 2 or 3.

"Rb is independently selected each time from deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, or 5-12 membered heteroaryl" should be understood as meaning "Rb is independently selected each time from deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, optionally substituted C1-6 alkyl, optionally substituted C1-6 alkoxy, optionally substituted C1-6 alkylamino, optionally substituted C2-6 alkenyl, optionally substituted C2-6 alkynyl, optionally substituted C3-10 cycloalkyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C6-14 aryl, or optionally substituted 5-12 membered heteroaryl." Other similar expressions in the present invention should be understood in the same manner as above.

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The terms "optional," "arbitrary," “optionally," or "arbitrarily" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

The term "oxo" refers to the replacement of two hydrogen atoms at the same substitution position by a single oxygen atom to form a double bond.

Unless otherwise specified, the term "alkyl" refers to a monovalent saturated aliphatic hydrocarbon group, a straight or branched chain group containing 1-20 carbon atoms, preferably containing 1-10 carbon atoms (i.e., C1-10 alkyl), further preferably containing 1-8 carbon atoms (C1-8 alkyl), more preferably containing 1-6 carbon atoms (i.e., C1-6 alkyl), more preferably containing 1-4 carbon atoms (i.e., C1-4 alkyl), and more preferably containing 1-3 carbon atoms (i.e., C1-3 alkyl). E.g., "C1-6 alkyl" means that the group is an alkyl group and the number of carbon atoms in the carbon chain is between 1 and 6 (specifically 1, 2, 3, 4, 5 or 6). Embodiments include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, neopentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, n-heptyl, n-octyl, and the like.

Unless otherwise specified, the term "alkenyl" refers to a straight-chain or branched unsaturated aliphatic hydrocarbon group composed of carbon and hydrogen atoms and having at least one double bond. An alkenyl group may contain 2-20 carbon atoms, preferably 2-10 carbon atoms (i.e., C2-10 alkenyl), more preferably 2-8 carbon atoms (C2-8 alkenyl), and even more preferably 2-6 carbon atoms (i.e., C2-6 alkenyl), 2-5 carbon atoms (i.e., C2-5 alkenyl), 2-4 carbon atoms (i.e., C2-4 alkenyl), 2-3 carbon atoms (i.e., C2-3 alkenyl), or 2 carbon atoms (i.e., C2 alkenyl). E.g., "C2-6 alkenyl" means that the group is an alkenyl group and the number of carbon atoms in the carbon chain is between 2 and 6 (specifically, 2, 3, 4, 5, or 6). Non-limiting embodiments of alkenyl groups include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, isobutenyl, and 1,3-butadienyl.

Unless otherwise specified, the term "alkynyl" refers to a straight or branched, unsaturated aliphatic hydrocarbon group composed of carbon and hydrogen atoms, having at least one triple bond. Alkynyl groups may contain 2-20 carbon atoms, preferably 2-10 carbon atoms (i.e., C2-10 alkynyl), more preferably 2-8 carbon atoms (C2-8 alkynyl), and even more preferably 2-6 carbon atoms (i.e., C2-6 alkynyl), 2-5 carbon atoms (i.e., C2-5 alkynyl), 2-4 carbon atoms (i.e., C2-4 alkynyl), 2-3 carbon atoms (i.e., C2-3 alkynyl), or 2 carbon atoms (i.e., C2 alkynyl). E.g., "C2-6 alkynyl" means that the group is an alkynyl group and the number of carbon atoms in the carbon chain is between 2 and 6 (specifically, 2, 3, 4, 5, or 6). Non-limiting embodiments of alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, and 1-butynyl.

Unless otherwise specified, the term "alkoxy" refers to an -O-alkyl group, the alkyl group is as defined above, i.e., containing 1-20 carbon atoms, preferably 1-10 carbon atoms, more preferably 1-8 carbon atoms, more preferably 1-6 carbon atoms (specifically 1, 2, 3, 4, 5, or 6 carbon atoms), more preferably 1-4 carbon atoms, more preferably 1-3 carbon atoms, and even more preferably 1-2 carbon atoms. Representative embodiments include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, tert-butoxy, pentyloxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, 2,2-dimethylpropoxy, 1-ethylpropoxy, and the like.

Unless otherwise specified, the term "alkylamino" refers to -NR'R", where R' and R" are the same or different and may be H or an alkyl group as defined above, the alkyl group is as defined above, i.e., containing 1-20 carbon atoms, preferably 1-10 carbon atoms, more preferably 1-8 carbon atoms, more preferably 1-6 carbon atoms (specifically 1, 2, 3, 4, 5, or 6), more preferably 1-4 carbon atoms, more preferably 1-3 carbon atoms, and even more preferably 1-2 carbon atoms. Representative embodiments include, but are not limited to, -NH(CH3), -N(CH3)(CH3), -N(CH2CH3)(CH3), -N(CH2CH3)[CH(CH3)2], etc.

Unless otherwise specified, the term "halogen" or "halo" refers to F, Cl, Br, or I. The term "haloalkyl" refers to an alkyl group as defined above in which one, two, or more hydrogen atoms, or all of the hydrogen atoms, are replaced by halogen. Representative embodiments of haloalkyl include CCl3, CF3, CHCl2, CH2Cl, CH2Br, CH2I, CH2CF3, and CF2CF3.

Unless otherwise specified, the term "carbocyclyl" or "carbocycle" refers to a non-aromatic cyclic hydrocarbon group having from 3 to 15 ring carbon atoms ("C3-15 carbocyclyl") and no heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3-15 ring carbon atoms ("C3-15 carbocyclyl"), 3-14 ring carbon atoms ("C3-14 carbocyclyl"), 3-12 ring carbon atoms ("C3-12 carbocyclyl"), or 4-12 ring carbon atoms ("C4-12 carbocyclyl"), or 3 to 10 ring carbon atoms ("C3-10 carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C3-8 carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C3-7 carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C3-6 carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C4-6 carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C5-10 carbocyclyl"), or 5 to 7 ring carbon atoms ("C5-7 carbocyclyl"), or 3 to 5 ring carbon atoms ("C3-5 carbocyclyl"). Exemplary C3-6 carbocyclyl groups include, but are not limited to, cyclopropyl (C3), cyclopropenyl (C3),

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cyclobutyl (C4), cyclobutenyl (C4), cyclopentyl (C5), cyclopentenyl (C5), cyclohexyl (C6), cyclohexenyl (C6), cyclohexadienyl (C6), and the like. Exemplary C3-8 carbocyclyl groups include, but are not limited to, the aforementioned C3-6 carbocyclyl groups, as well as cycloheptyl (C7), cycloheptenyl (C7), cycloheptadienyl (C7), cycloheptatrienyl (C7), cyclooctyl (C8), cyclooctenyl (C8), bicyclo[2.2.1]heptyl (C7), bicyclo[2.2.2]octyl (C8), and the like. Exemplary C3-10 carbocyclyl groups include, but are not limited to, the aforementioned C3-8 carbocyclyl groups, as well as cyclononyl (C9), cyclononenyl (C9), cyclodecyl (C10), cyclodecenyl (C10), octahydro-1H-indenyl (C9), decahydronaphthyl (C10), spiro[4.5]decyl (C10), and the like. As illustrated in the above embodiments, in certain embodiments, the carbocyclyl group is monocyclic ("monocyclic carbocyclyl") or a fused (bicarbocyclyl), bridged (bridged carbocyclyl) or spiro-fused (spirocyclyl) ring system, such as a bicyclic ring system ("bicyclic carbocyclyl") and can be saturated or partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused to one or more aryl groups, wherein, the point of attachment is on the carbocyclyl or aryl ring, and in such cases, the number of members of the carbocyclyl ring system is the number of carbon atoms in the carbocyclyl ring system after fusion. In certain embodiments, each instance of a carbocyclyl group is independently optionally substituted, e.g., unsubstituted (an "unsubstituted carbocyclyl") or substituted with one or more substituents (a "substituted carbocyclyl"). In certain embodiments, the carbocyclyl group is an unsubstituted C3-10 carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C3-10 carbocyclyl.

Unless otherwise specified, the term "cycloalkyl" refers to a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms, preferably 3-12 carbon atoms (i.e., C3-12 cycloalkyl), more preferably 3-10 carbon atoms (C3-10 cycloalkyl), and even more preferably 3-7 carbon atoms (C3-7 cycloalkyl), 3-6 carbon atoms (C3-6 cycloalkyl), 3-5 carbon atoms (C3-5 cycloalkyl), 3-4 carbon atoms (C3-4 cycloalkyl), 4-6 carbon atoms (C4-6 cycloalkyl), or 5-6 carbon atoms (C5-6 cycloalkyl). Embodiments include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclopropyl, 2-ethylcyclopentyl, dimethylcyclobutyl, and the like.

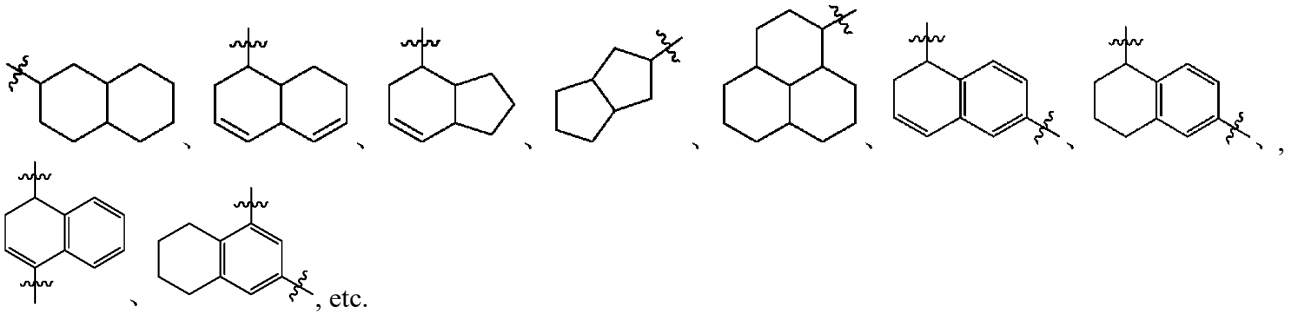
Unless otherwise specified, the term "heterocyclyl" or "heterocycle" refers to a saturated or partially unsaturated monocyclic or polycyclic non-aromatic substituent having ring carbon atoms and 1 to 4 ring heteroatoms, containing 320 ring atoms, wherein 1, 2, 3 or more ring atoms are selected from N, O or S, and the remaining ring atoms are C. It preferably contains 3 to 12 ring atoms (3-12 membered heterocyclyl), further preferably contains 3 to 10 ring atoms (3-10 membered heterocyclyl), or 3 to 8 ring atoms (3-8 membered heterocyclyl), or 3 to 6 ring atoms (3-6 membered heterocyclyl), or 4 to 6 ring atoms (4-6 membered heterocyclyl), or 4 to 5 ring atoms (4-5 membered heterocyclyl), or 3 to 5 ring atoms (3-5 membered heterocyclyl), or 5 to 7 ring atoms (5-7 membered heterocyclyl), or 5 to 6 ring atoms (5-6 membered heterocyclyl). The number of heteroatoms is preferably 1-4, more preferably 1-3 (i.e., 1, 2, or 3). Examples of monocyclic heterocyclic groups include pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, dihydropyrrolyl, piperidinyl, piperazinyl, pyranyl, and the like. Polycyclic heterocyclic groups include paracyclic, spirocyclic, and bridged heterocyclic groups. “Heterocyclic group” can be monocyclic (“monocyclic heterocyclic group”) or a fused (paracyclic heterocyclic group), bridged (“heterobridged heterocyclic group” or “bridged heterocyclic group”), or spirocyclic (“heterospirocyclic group”, “spiroheterocyclic group” or “spirocyclic heterocyclic group”) ring system, such as a bicyclic ring system (“bicyclic heterocyclic group”), and can be saturated or partially unsaturated. Heterocyclic bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring as defined above is fused or fused to one or more carbocyclyl groups, wherein, the point of attachment is on the carbocyclyl or heterocyclyl ring, or "heterocyclyl" also includes ring systems wherein the heterocyclyl ring as defined above is fused or fused to one or more aryl or heteroaryl groups, or cycloalkyl rings as defined above are fused or fused to one or more heteroaryl groups, wherein, the point of attachment is on the heterocyclyl or cycloalkyl or aryl or heteroaryl ring, and in such cases, the number of members of the heterocyclyl ring system is the number of ring system atoms after fusion. In certain embodiments, each instance of a heterocyclyl group is independently optionally substituted, e.g., unsubstituted (an “unsubstituted heterocyclyl”) or substituted with one or more substituents (a “substituted heterocyclyl”). Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include, but are not limited to, aziridine, oxiranyl, and thiorenyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include, but are not limited to, azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include, but are not limited to, tetrahydrofuranyl, dihydrofuranyl, tetrahydrophenylthio, dihydrophenylthio, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include, but are not limited to, dioxolanyl, oxathiolanyl, dithiolanyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include, but are not limited to, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, but are not limited to, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, but are not limited to,

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piperazinyl, morpholinyl, dithiolanyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include, but are not limited to, triazacyclohexanyl, oxadiazinyl, thiadiazinyl, oxathiazinyl, and dioxazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, but are not limited to, azepanyl, oxepanyl, and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, but are not limited to, azocanyl, oxepanyl, and thiepanyl. Exemplary 5-membered heterocyclyl groups fused to a C6 aryl ring (also referred to herein as a 5,6-bicyclic heterocycle) include, but are not limited to, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocycle) include, but are not limited to, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

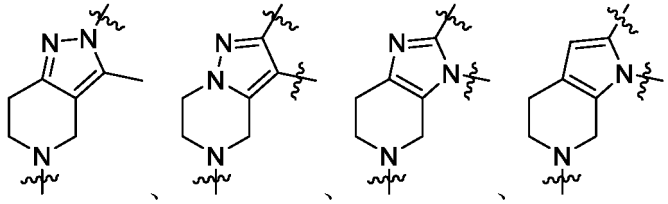
Unless otherwise specified, the term "carbocyclyl" refers to a non-aromatic, saturated or partially unsaturated ring system formed by two or more cyclic structures sharing two adjacent atoms, including carbocyclyl and heterocyclyl groups. "Non-aromatic" means that the entire ring system is non-aromatic.

A carbocyclyl group may contain 5-14 ring atoms, preferably 6-12 ring atoms, and more preferably 7-10 ring atoms (e.g., 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms). Carbocyclyl groups include bicyclic, tricyclic, tetracyclic, or polycyclic carbocyclyl groups, preferably bicyclic, tricyclic, or tetracyclic carbocyclyl groups, and more preferably bicyclic or tricyclic carbocyclyl groups. Illustrative embodiments of carbocyclyl groups include, but are not limited to



, etc.

The heterocyclyl group may contain 5-14 ring atoms, preferably 6-12 ring atoms, more preferably 7-10 ring atoms (e.g., 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms), wherein, the heterocyclyl group contains 1-4 ring heteroatoms, preferably 1-3 (i.e., 1, 2 or 3) ring heteroatoms, and the heteroatoms are independently selected from N, O and S. Heterocyclyl groups include bicyclic, tricyclic, tetracyclic, or polycyclic heterocyclyl groups, preferably bicyclic, tricyclic, or tetracyclic heterocyclyl groups, and more preferably bicyclic or tricyclic heterocyclyl groups. Illustrative embodiments of heterocyclyl groups include, but are not limited to



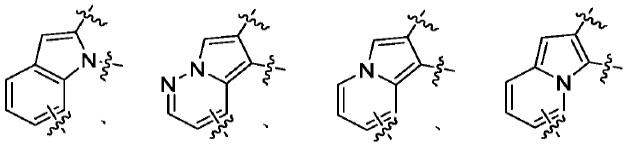
, etc.

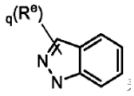
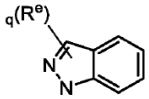
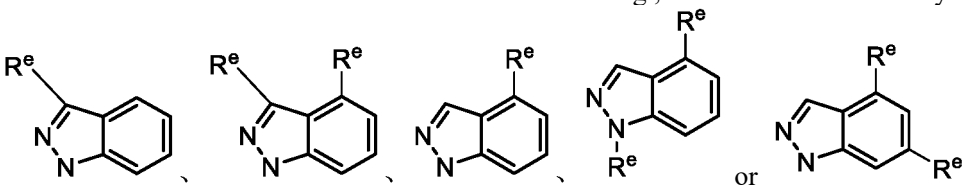
Unless otherwise specified, the term "aryl" or "aromatic ring group" refers to a monocyclic, bicyclic, or tricyclic aromatic carbocyclic ring system containing 6-16 carbon atoms, or 6-14 carbon atoms, or 6-12 carbon atoms, or 6-10 carbon atoms, or 6-8 carbon atoms, preferably 6-10 carbon atoms. The term "aryl" can be used interchangeably with the term "aromatic ring." Embodiments of aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, phenanthrenyl, or pyrenyl.

Unless otherwise specified, the term "heteroaryl" or "heteroaromatic ring group" means an aromatic monocyclic or polycyclic ring system containing a 5-14 membered structure, or preferably a 5-12 membered structure, or preferably a 5-10 membered structure, or preferably a 5-9 membered structure, or preferably a 5-8 membered structure, more preferably a 5-6 membered structure, wherein 1, 2, 3 or more ring atoms are heteroatoms and the remaining atoms are carbon, the heteroatoms are independently selected from O, N or S, and the number of heteroatoms is preferably 1, 2 or 3. Polycyclic heteroaryl is a fused heteroaryl. Embodiments of heteroaryl groups include, but are not limited to, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiodiazolyl, triazinyl, phthalazinyl, quinolyl, isoquinolyl, pteridinyl, purinyl, indolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, benzopyridinyl, benzopyrimidinyl, benzopyrazinyl, benzo imidazolyl, benzophthalazinyl, pyrrolo[2,3-b]pyridinyl, imidazo[1,2-a]pyridinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[4,3-b]pyridazinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-a]pyridinyl, etc.

Unless otherwise specified, the term "fused heteroaryl" refers to an aromatic ring system formed by two or

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more cyclic structures sharing two adjacent atoms, each ring in the fused heteroaryl is an unsaturated aromatic ring, which may contain 5-20 ring atoms, preferably 6-14 ring atoms, more preferably 7-10 ring atoms (e.g., 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms), wherein it includes 1-4 ring heteroatoms, preferably 1-3 (i.e., 1, 2 or 3) ring heteroatoms, and the heteroatoms are independently selected from N, O and S. Fused heteroaryls include bicyclic, tricyclic, tetracyclic, or polycyclic fused heteroaryls, preferably bicyclic, tricyclic, or tetracyclic fused heteroaryls, and more preferably bicyclic or tricyclic fused heteroaryls. Illustrative embodiments of fused heteroaryls include (but are not limited to)  and the like.

Herein,  indicates that q Re may be substituted at any position in the bicyclic ring system as long as a stable structure is formed. E.g.,  may be represented as  or ; this rule applies to the optional ring systems of the present invention and is provided for illustrative purposes only.

In various sections of the present invention, reference is made to linking substituents (e.g., L4x, L4y, etc.). Those skilled in the art will understand that when a linking group is clearly required in a compound structure, the Markush variable listed for that group should be understood to refer to the linking group. E.g., if the structure requires a linking group and the Markush group definition for that variable lists "alkyl" or "aryl," it should be understood that "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively. Therefore, when used as a linking group, "alkyl" and "alkylene" have the same definition, e.g., "alkyl" and "alkylene" have the same definition.

Unless otherwise specified, the term "pharmaceutically acceptable salt" or "pharmaceutically acceptable salt" refers to salts that are suitable for use in contact with mammalian tissues, particularly humans, without excessive toxicity, irritation, or allergic response, and are commensurate with a reasonable benefit/risk ratio, within the scope of sound medical judgment. Pharmaceutically acceptable salts of amines, carboxylic acids, and other types of compounds are well known in the art. Such salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or separately by reacting the free base or free acid with a suitable reagent.

Unless otherwise specified, the term "stereoisomer" refers to compounds that have the same chemical constitution but differ in the arrangement of the atoms or groups in space. Stereoisomers include enantiomers, diastereomers, conformational isomers (rotamers), geometric isomers (cis/trans), isomers, atropisomers, rotational isomers, and the like. Any resulting mixture of stereoisomers can be separated into pure or substantially pure geometric isomers, enantiomers, and diastereomers based on differences in the constituent physicochemical properties, e.g., by chromatography and/or fractional crystallization. Unless otherwise specified, the term "geometric (cis/trans) isomers" may contain carbon-carbon or carbon-nitrogen double bonds in the E or Z configuration, wherein, the term "E" represents higher-order substituents on opposite sides of the carbon-carbon or carbon-nitrogen double bond, and the term "Z" represents higher-order substituents on the same side of the carbon-carbon or carbon-nitrogen double bond (determined using the Cahn-Ingold Prelog priority rules). The compounds of the present invention may also exist as mixtures of "E" and "Z" isomers.

Unless otherwise specified, the term "tautomers" refers to structural isomers of different energies that are interconvertible across a low energy barrier. If tautomerism is possible (e.g., in solution), chemical equilibrium of the tautomers can be achieved. For example, proton tautomers (also known as prototropic tautomers) include interconversions via proton migration, such as keto-enol isomerization and imine-enamine isomerization. Valence tautomers include interconversions via reorganization of some of the bonding electrons.

Unless otherwise indicated, the structural formulae described herein encompass all isomeric forms (e.g., enantiomers, diastereomers, and geometric isomers (or conformers)): For example, R and S configurations containing asymmetric centers, (Z) and (E) isomers of double bonds, and (Z) and (E) conformers. Thus, individual

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stereochemical isomers of the compounds of the present invention, or mixtures of their enantiomers, diastereomers, or geometric isomers (or conformers), are encompassed by the present invention.

The compounds of the present invention also encompass isotopic derivatives thereof. Unless otherwise specified, the term "isotopic derivative" means that the compounds of the present invention may exist in isotopically traced or enriched form, containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number of the largest atom found in nature. Isotopes can be radioactive or non-radioactive. Commonly used isotope labels include: Hydrogen isotopes, 2H and 3H; Carbon isotopes, 13C and 14C; Chlorine isotopes, 35Cl and 37Cl; Fluorine isotopes, 18F; Iodine isotopes, 123I and 125I; nitrogen isotopes: 13N and 15N; oxygen isotopes: 15O, 17O, and 18O; and sulfur isotope 35S. These isotopically labeled compounds can be used to study the distribution of pharmaceutical molecules in tissues. 3H and 13C are particularly widely used due to their ease of labeling and convenient detection. Substitution with certain heavy isotopes, such as deuterium (2H), can enhance metabolic stability and prolong half-life, thereby reducing dosage and providing therapeutic advantages. Isotopically labeled compounds are generally synthesized from labeled starting materials using known synthetic techniques similar to those used for non-isotopically labeled compounds. Isotopic derivatives are preferably deuterated derivatives.

The compounds of the present invention also include solvates or solvates thereof. Unless otherwise specified, the terms "solvate" and "solvate" refer to a physical association between a compound of the present invention and one or more solvent molecules (whether organic or inorganic). This physical association includes hydrogen bonding. In certain cases, a solvate can be isolated, e.g., when one or more solvent molecules are incorporated into the crystal lattice of the crystalline solid. The solvent molecules in a solvate can exist in regular and/or disordered arrangements. Solvates can contain stoichiometric or non-stoichiometric amounts of solvent molecules. "Solvate" encompasses both solution-phase and isolatable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Solvation methods are well known in the art.

The compounds of the present invention also include cocrystals thereof. Unless otherwise specified, the term "cocrystal" is used to describe such situations. Wherein, the neutral molecular components are present in a crystalline compound in a well-defined stoichiometric ratio. The preparation of pharmaceutical cocrystals enables the modification of the crystalline form of the active pharmaceutical ingredient, which in turn can alter its physicochemical properties without compromising its desired biological activity (see Pharmaceutical Salts and Cocrystals, edited by J. Wouters and L. Quere, RSC Publishing, 2012).

The compounds of the present invention also include their polymorphs. Unless otherwise specified, the term "polymorph" refers to the different arrangements of chemical drug molecules, generally manifesting as the solid state form of the drug substance. A drug can exist in multiple crystalline forms. Different crystalline forms of the same drug may exhibit different solubility and absorption in the body, thus affecting the dissolution and release of the formulation.

The compounds of the present invention also include their metabolites. Unless otherwise specified, the term "metabolite" refers to products produced by the in vivo metabolism of a specific compound or its salt. The metabolites of a compound can be identified by techniques known in the art, and their activity can be characterized by assays as described herein. Such products can be obtained by administering the compound through oxidation, reduction, hydrolysis, amidation, deamidation, esterification, defatting, enzymatic cleavage, and the like. Accordingly, the present invention includes metabolites of the compounds, including those produced by contacting the compounds of the present invention with a mammal for a sufficient period of time.

The compounds of the present invention also include prodrugs thereof. Unless otherwise specified, the term "prodrug" refers to a drug that is converted in vivo to the parent drug. Prodrugs are often useful because they can improve certain, undesirable physical or biological properties. Physical properties are often related to solubility (excessive or insufficient lipid or water solubility) or stability, while problematic biological properties include rapid metabolism or poor bioavailability, which themselves may be related to physicochemical properties. For example, they may be bioavailable orally, whereas the parent drug is not. Prodrugs also have improved solubility in pharmaceutical compositions compared to the parent drug. An example, but not limited to, of a prodrug is any compound of the present invention administered as an ester ("prodrug") to facilitate transport across cell membranes, wherein the water solubility is detrimental to mobility, but once inside the cell, water solubility is beneficial, and the compound is subsequently metabolically hydrolyzed to the carboxylic acid, the active moiety. Another example of a prodrug is a short peptide (polyamino acid) conjugated to an acid group, wherein the peptide is metabolized to reveal the active moiety.

The word "comprise" or "includes" and its English variants, such as "comprises" or "comprising," should be understood as having an open, non-exclusive meaning, i.e., "including but not limited to."

The term "individual," also referred to as "subject" or "subject," refers to cells or animals, including but not limited to mammals, such as laboratory animals or humans.

Some compounds of the present invention are optically active. The compounds of the present invention may

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be racemates, optical isomers, or mixtures thereof. The synthesis of optical isomers in the compounds of the present invention may be prepared from optical isomer starting materials or by separation of racemates.

The above embodiments represent exemplary embodiments of the present invention, but the present invention is not limited to the above embodiments. In addition, the various technical features of the above embodiments of the present invention may be combined to form one or more new technical solutions, which also fall within the scope of the present invention, as long as such new technical solutions are technically feasible.

Unless otherwise specified, the term "treat" encompasses any treatment of a disease, disorder, or condition in a patient, including: (a) inhibiting the symptoms of the disease, disorder, or condition, i.e., arresting its development; or (b) relieving the symptoms of the disease, disorder, or condition, for example, causing regression of the disease or symptoms; or (c) ameliorating or eliminating the disease, disorder, or condition or one or more symptoms associated with the disease.

Abbreviations used in the Preparative Embodiments, Embodiments, and elsewhere herein are:

DCM	Dichloromethane
DCE	1,2-Dichloroethane
DIPEA	N,N-Diisopropylethylamine
DMF	N,N-Dimethylformamide
HATU	2-(7-Azobenzotriazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate
NMP	N-Methylpyrrolidone
THF	Tetrahydrofuran

This application designs a class of compounds with novel structures, providing a new approach for the treatment of diseases such as diabetes, non-alcoholic fatty liver disease, and Alzheimer's disease, as well as for weight loss.

The beneficial effects of this invention are as follows:

The compounds of this invention exhibit one or more of the following beneficial effects:

(1) Enzymatic tests indicate that the compounds of this invention have a strong agonist effect on GLP-1R;

(2) In vivo pharmacokinetic studies in mice and/or rats indicate that the compounds of this invention have good oral efficacy.

(3) In vivo efficacy in mice indicates that the compounds of this invention have excellent weight loss effects.

(4) In vivo efficacy in mice indicates that the compounds of this invention have excellent blood sugar-lowering efficacy.

(5) Safety assessment tests show that the compounds of the present application have no off-target risk or very low off-target risk and have good safety.

Description of Attached Drawings

Figure 1: H NMR spectrum (temperature: 60°C) of Embodiment 10 (Compound 10).
Figure 2: H NMR spectrum (temperature: 80°C) of Embodiment 8 (Compound 8).
Figure 3: H NMR spectrum (temperature: 80°C) of Embodiment 15 (Compound 65).
Figure 4: Weight gain rate spectrum of Test Example 4.

Specific Embodiments

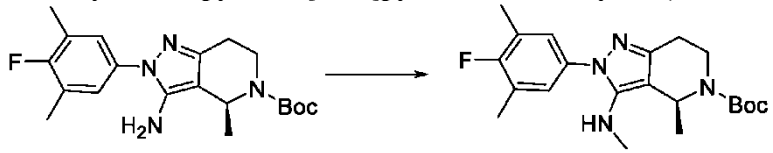
The present invention is further described below with reference to specific embodiments. It should be understood that these embodiments are intended to illustrate the present invention only and are not intended to limit its scope. In the following embodiments, experimental methods without specific conditions are generally performed under conventional conditions or according to the conditions recommended by the manufacturer. Unless otherwise defined, all technical and scientific terms used herein have the same meanings as those familiar to those skilled in the art. In addition, any methods and materials similar or equivalent to those described herein can be used in the methods of the present invention. The preferred embodiments and materials described herein are for illustrative purposes only.

The following are embodiments of the preparation of exemplary compounds of this application.

The structures of the compounds of the present invention are determined by nuclear magnetic resonance (NMR) and/or liquid chromatography-mass spectrometry (LC-MS), and/or liquid chromatography (HPLC), and/or high resolution mass spectrometry (HRMS). NMR measurements were performed using a Bruker Avanceneo 400 MHz (temperature: 60°C) or/and a Bruker AVANCE III 600; LC-MS measurements were performed using an Agilent 1260 Infinity II-6120/6125 MSD or/and a Waters ACQUITY QDa; HPLC measurements were performed

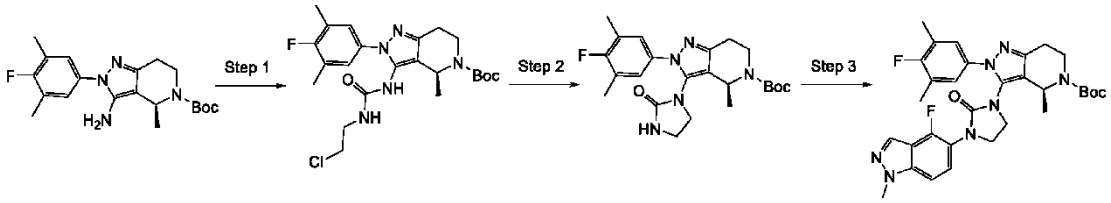
using a Waters e2695-2998 (column: Waters XBridge C18 4.6 x 250 mm, 5 μm; column temperature: 40°C; flow rate: 1 mL/min; wavelength: 216 nm; mobile phase A: water (containing 0.1% trifluoroacetic acid); mobile phase B: methanol); and HRMS measurements were performed using an Aglient Accurate-Mass Q-TOF 6530.
The starting materials in the embodiments of the present invention are known and commercially available, or can be synthesized using or according to methods known in the art.

Preparation Embodiment 1: Synthesis of (S)-tert-Butyl 2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(methylamino)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (intermediate 1.4-A)



(S)-tert-Butyl 3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (150 mg) was dissolved in THF (5 mL). Methyl iodide (62 mg) and sodium hydroxide (32 mg) were then added and stirred at room temperature for two hours. Water (40 mL) was added and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by column chromatography (n-hexane:ethyl acetate = 1:1, volume ratio) to afford intermediate 1.4-A (115 mg). ESI-MS (m/z): 389.2 [M+H].

Preparation Embodiment 2: (S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxoimidazolin-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7- Synthesis of tert-butyl tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (intermediate 1.5-A)



Step 1: Synthesis of tert-butyl (S)-3-(3-(2-chloroethyl)ureido)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

Tert-butyl (S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (2 g), chloroethyl isocyanate (734 mg), and tetrahydrofuran (40 mL) were added to a flask. Triethylamine (1.6 g) was added and the mixture was heated to 60°C and stirred for 8 hours. After completion of the reaction, the mixture was cooled and added to water (40 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (n-hexane:ethyl acetate = 3:1) to obtain the product (700 mg). ESI-MS (m/z): 480.2 [M+H]+.

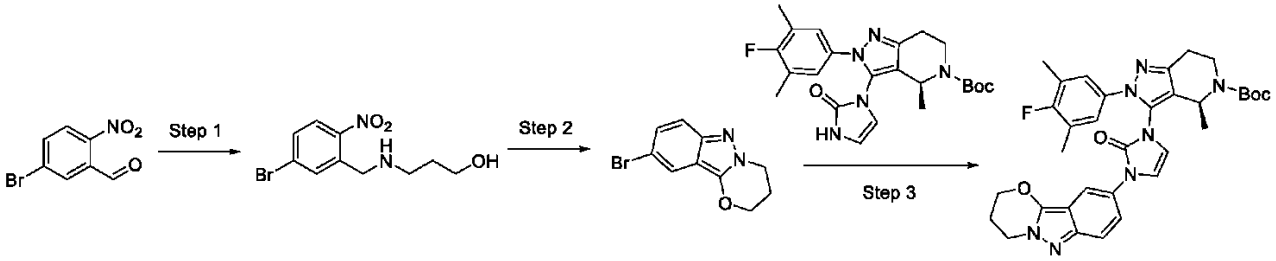
Step 2: Synthesis of (S)-tert-butyl 2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-oxoimidazolin-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

The product from Step 1 (700 mg) and N,N-dimethylformamide (10 mL) were added to a flask. NaH (88 mg) was added and the mixture was stirred at room temperature for 4 hours. After completion of the reaction, water (40 mL) was added to the mixture, and the mixture was extracted with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (n-hexane:ethyl acetate = 1:1) to obtain the product (300 mg). ESI-MS (m/z): 444.2 [M+H]+.

Step 3: Synthesis of intermediate 1.5-A

The product from Step 2 (60 mg), 5-bromo-4-fluoro-1-methyl-1H-indazole (62 mg), cuprous iodide (24 mg), (1S,2S)-(+)-N,N-dimethylcyclohexanediamine (18 mg), potassium phosphate (61 mg), and dioxane (5 mL) were added to a flask and heated to 120°C under a nitrogen atmosphere with stirring for 4 hours. After completion of the reaction, the mixture was cooled and water (40 mL) was added. The mixture was extracted with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by thin-layer chromatography (n-hexane:ethyl acetate = 1:2) to obtain intermediate 1.5-A (50 mg). ESI-MS (m/z): 592.3 [M+H]+.

Preparation Embodiment 3: Synthesis of (S)-tert-butyl 3-(3-(3,4-dihydro-2H-[1,3]oxazino[3,2-b]indazol-9-yl)-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 (intermediate 1.5-B)



Step 1: Synthesis of 3-((5-bromo-2-nitrobenzyl)amino)propan-1-ol

Dissolved 5-bromo-2-nitrobenzaldehyde (100 mg) and 3-amino-1-propanol (144 mg) in ethanol (10 mL), then added tetraisopropyl titanate. (1g) was stirred at room temperature for 1 hour, and then sodium borohydride (50 mg) was added. The mixture was stirred at room temperature for two hours, and then quenched with aqueous ammonia (6 mL). The reaction solution was filtered, and the filtrate was dried and concentrated. The crude product was purified by column chromatography (ethyl acetate) to obtain the product (78 mg). ESI-MS (m/z): 290.1 [M+H]+;

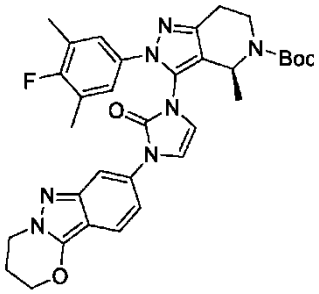
Step 2: Synthesis of 9-bromo-3,4-dihydro-2H-[1,3]oxazinyl[3,2-b]indazole

The product from step 1 (78 mg) was dissolved in a mixture of tert-butanol and water (15 mL/5 mL). Potassium hydroxide (61 mg) was added, and the mixture was reacted at 85°C for 5 hours. The mixture was diluted with water (40 mL) and extracted with ethyl acetate (30 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (ethyl acetate) to obtain the product (54 mg). ESI-MS (m/z): 253.2 [M+H]+.

Step 3: Synthesis of intermediate 1.5-B

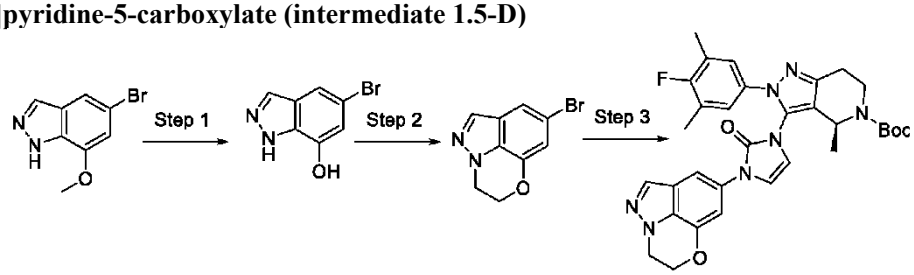
The product from Step 2 (54 mg), (S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (47 mg), cuprous iodide (8 mg), (1S,2S)-(+)-N,N'-dimethyl-1,2-cyclohexanediamine (12 mg), and potassium carbonate (87 mg) were dissolved in N-methylpyrrolidone (2 mL) and stirred at 130°C under nitrogen for 4 hours. After completion of the reaction, the reaction solution was directly concentrated, and the crude product was purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to obtain intermediate 1.5-B (27 mg). ESI-MS (m/z): 614.4 [M+H] +.

Preparation Embodiment 4: Synthesis of (S)-tert-butyl 3-(3-(3,4-dihydro-2H-[1,3]oxazino[3,2-b]indazol-8-yl)-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 (intermediate 1.5-C)



Referring to intermediate 1.5-B, intermediate 1.5-C (24 mg) was obtained using 4-bromo-2-nitrobenzaldehyde (100 mg). ESI-MS (m/z): 614.4 [M+H]+].

Preparation Embodiment 5: Synthesis of (S)-tert-butyl 3-(3-(2,3-dihydro-[1,4]oxazino[2,3,4,hi]indazol-8-yl)-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 (intermediate 1.5-D)



Step 1: Synthesis of 5-bromo-7-hydroxy-1H-indazole

5-Bromo-7-methoxy-1H-indazole (200 mg) was dissolved in dichloromethane (10 mL). Boron tribromide (440 mg) was added dropwise at 0°C. After stirring at room temperature for 1 hour, the mixture was quenched with water (40 mL). Dichloromethane (30 mL) was added to the mixture. The crude product was extracted with 1% paraformaldehyde (5 mL*3), dried over anhydrous sodium sulfate, filtered, and the filtrate was dried and

concentrated. The resulting crude product was purified by column chromatography (n-hexane:ethyl acetate = 5:1) to yield 5-bromo-7-hydroxy-1H-indazole (150 mg). ESI-MS (m/z): 213.1 [M+H]+].

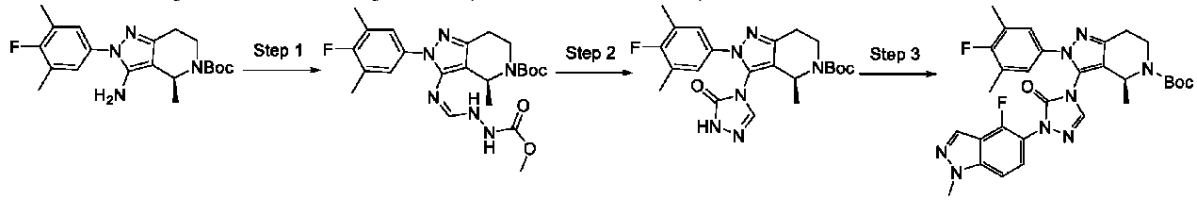
Step 2: Synthesis of 8-bromo-2,3-dihydro-[1,4]oxazino[2,3,4, hi]indazole

5-Bromo-7-hydroxy-1H-indazole (150 mg) was dissolved in N,N-dimethylformamide (20 mL), and 1-bromo-2-chloroethane (102 mg) was added. The mixture was reacted at room temperature for 4 hours, then heated to 70°C and continued to react for 2 hours. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (30 mL*3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (hexane:ethyl acetate = 10:1) to give 8-bromo-2,3-dihydro-[1,4]oxazinyl[2,3,4]indazole (100 mg). ESI-MS (m/z): 239.2 [M+H]+.

Step 3: Synthesis of intermediate 1.5-D

Referring to intermediate 1.5-B, 8-bromo-2,3-dihydro-[1,4]oxazinyl[2,3,4, 1]indazole (100 mg) was used as the starting material to obtain intermediate 1.5-D (30 mg). ESI-MS (m/z): 600.4 [M+H]+.

Preparation Embodiment 6: Synthesis of (S)-3-(1-(4-fluoro-1-methyl-1H-indazol-5-yl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (intermediate 1.5-E)



Step 1: Synthesis of tert-butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(((2-(methoxycarbonyl)hydrazino)methylene)amino)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

Tert-butyl (S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (5 g) and triethyl orthoformate (2.57 g) were added to a flask. The mixture was reacted at 90°C for 1 hour. After completion of the reaction, the temperature was lowered, the solvent was removed under reduced pressure, and methyl hydrazinecarboxylate (2.4 g) and p-toluenesulfonic acid (634 mg) were added. The mixture was stirred at 50°C for 2 hours. After completion of the reaction, the temperature was lowered, water (100 mL) was added, and the mixture was extracted with ethyl acetate (50 mL x 3). The solvent was removed under reduced pressure and column chromatography (n-hexane:ethyl acetate = 1:1) was performed to obtain the product (5.4 g). ESI-MS (m/z): 475.2 [M+H].

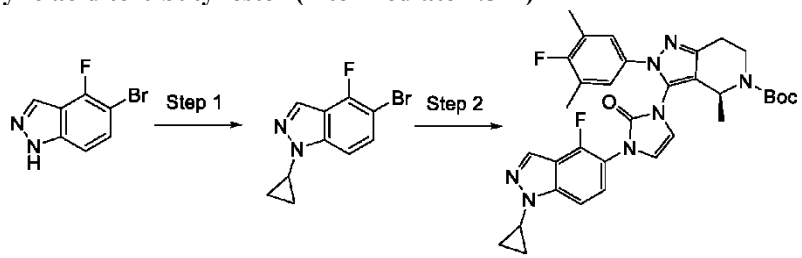
Step 2: Synthesis of tert-butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

The product from Step 1 (5.4 g) and methanol (100 mL) were added to a flask. A methanol solution of sodium methoxide (5 M, 4.5 mL) was added dropwise, and the mixture was stirred at room temperature for 12 h. After completion of the reaction, most of the methanol was removed under reduced pressure, and water (100 mL) was added. The mixture was filtered and dried to obtain the crude product (4.2 g). ESI-MS (m/z): 443.2 [M+H]+;

Step 3: Synthesis of intermediate 1.5-E

Referring to intermediate 1.5-A, the product from Step 2 (100 mg) was used as starting material to obtain intermediate 1.5-E (42 mg). ESI-MS (m/z): 591.3 [M+H].

Preparation Embodiment 7: Synthesis of (S)-3-(3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-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-carboxylic acid tert-butyl ester (intermediate 1.5-F)



Step 1: Synthesis of 5-bromo-1-cyclopropyl-4-fluoro-1H-indazole

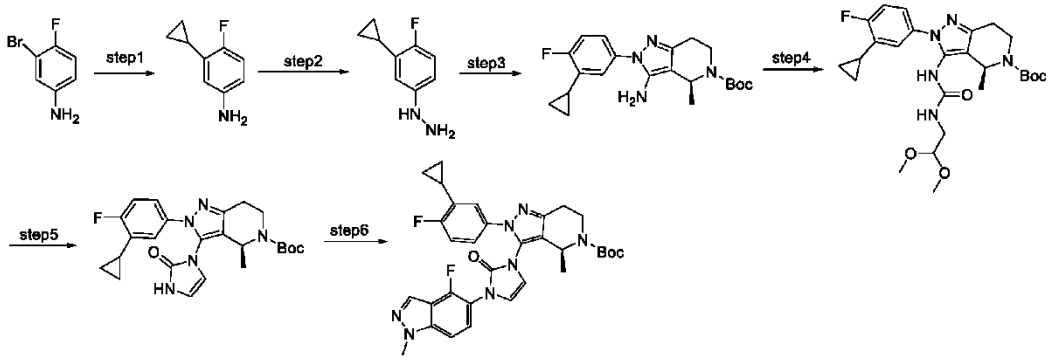
Take 5-bromo-4-fluoro-1H-indazole (1 g), cyclopropylboronic acid (0.8 g), anhydrous copper acetate (0.85 g), bipyridine (0.73 g), sodium carbonate (1 g). g) and 1,2-dichloroethane (20 mL) were added to a flask, heated to 70°C and stirred for two hours, filtered, and the filtrate was diluted with dichloromethane and washed with water (40 mL). The solvent was removed under reduced pressure and column chromatography (n-hexane:ethyl acetate = 5:1) was performed to obtain the product (0.8 g). ESI-MS (m/z): 254.9 [M+H]+;

Step 2: Synthesis of intermediate 1.5-F

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Referring to intermediate 1.5-A, the product of Step 1 (220 mg) and (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-carboxylic acid tert-butyl ester (200 mg) were used as starting materials to obtain intermediate 1.5-F (250 mg). mg), ESI-MS (m/z): 616.3 [M+H]+;

Preparation Embodiment 8: Synthesis of (S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (intermediate 1.5-G)



Step 1: Synthesis of 3-cyclopropyl-4-fluoroaniline

Take 3-bromo-4-fluoroaniline (10 g), cyclopropylboronic acid (5.9 g), potassium phosphate (39.1 g), palladium acetate (1.2 g), triphenylphosphine (1.4 g), toluene (200 mL), water (20 1 mL) was added to a flask, and the mixture was heated to 100°C and stirred under a nitrogen atmosphere for 15 hours. After completion of the reaction, water (200 mL) was added, and the mixture was extracted with ethyl acetate (150 mL x 3). The mixture was concentrated under reduced pressure and purified by column chromatography (n-hexane:ethyl acetate = 10:1) to obtain the product (6.9 g). ESI-MS (m/z): 152.1 [M+H]+].

Step 2: Synthesis of (3-cyclopropyl-4-fluorophenyl)hydrazine

The product from Step 1 (900 mg) and concentrated hydrochloric acid (30 mL) were added to a flask. A 0.12 M aqueous sodium nitrite solution (60 mL) was added dropwise at 0°C, and the mixture was stirred at 0°C for 1 hour. Subsequently, a 0.33 M stannous chloride solution in hydrochloric acid (50 mL) was added dropwise at 0°C, and the mixture was stirred at 0°C for 1 hour. After completion of the reaction, water (150 mL) was added, and the pH was adjusted to 8 with saturated sodium hydroxide solution. Ethyl acetate (200 mL) was added, and the insoluble matter was removed by filtration. The layers were separated, and the ethyl acetate layer was concentrated under reduced pressure to obtain the crude product. Finally, the product (210 mg) was purified by column chromatography (n-hexane:ethyl acetate = 1:1). ESI-MS (m/z): 167.1 [M+H]+.

Step 3: Synthesis of tert-butyl (S)-3-amino-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

The product from Step 2 (190 mg), tert-butyl (2S)-3-cyano-2-methyl-4-oxopiperidine-1-carboxylate (227 mg), ethanol (5 mL), and aqueous hydrochloric acid (2M, 100 μL) were added to a flask and stirred at 50°C. After completion of the reaction, the mixture was concentrated under reduced pressure and purified by column chromatography (hexane:ethyl acetate = 3:2) to obtain the product (258 mg). ESI-MS (m/z): 387.2 [M+H]+].

Step 4: Synthesis of tert-butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2,2-dimethoxyethyl)ureido)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

The product from Step 3 (87 mg) and dichloromethane (2 mL) were added to a flask. Triphosgene (22 mg) and N,N-diisopropylethylamine (58 mg) were dissolved in dichloromethane (2 mL) and added dropwise to the flask. The mixture was stirred at room temperature for 1 hour. 2,2-Dimethoxyethylamine (94 mg) was then added dropwise and the reaction was allowed to stir at room temperature. After completion of the reaction, water (20 mL) was added, and the mixture was extracted with dichloromethane (20 mL x 3). The mixture was concentrated under reduced pressure and purified by column chromatography (n-hexane:ethyl acetate = 1:1) to obtain the product (85 mg). ESI-MS (m/z): 518.3 [M+H].

Step 5: Synthesis of (S)-tert-butyl 2-(3-cyclopropyl-4-fluorophenyl)-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

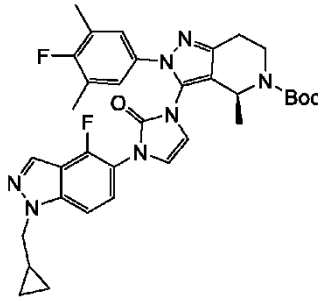
The product from step 4 (80 mg), trifluoromethanesulfonic acid (35 mL), and tetrahydrofuran (2 mL) were added to a flask and stirred at 60°C for 1 hour. The reaction mixture was cooled to room temperature, and triethylamine (47 mg) and di-tert-butyl dicarbonate (51 mg) were added and stirred at room temperature. After completion of the reaction, the product was concentrated under reduced pressure and purified by column chromatography (n-hexane:ethyl acetate = 1:1) to obtain the product (65 mg). ESI-MS (m/z): 454.2 [M+H]+.

Step 6: Synthesis of intermediate 1.5-G

Referring to the last step of the reaction of intermediate 1.5-A, 5-bromo-1-methyl-4-fluoro-1H-indazole (39

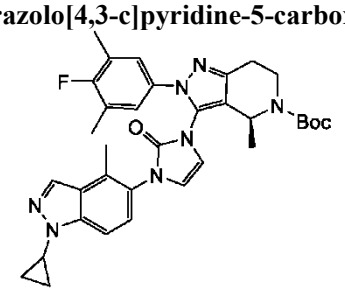
mg) and the product of Step 5 (50 mg) were used as starting materials to obtain intermediate 1.5-G (40 mg). ESI-MS (m/z): 602.3 [M+H] +.

Preparation Embodiment 9: Synthesis of (S)-tert-butyl 3-(3-(1-cyclopropylmethyl-4-fluoro-1H-indazol-5-yl)-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 (intermediate 1.5-H)



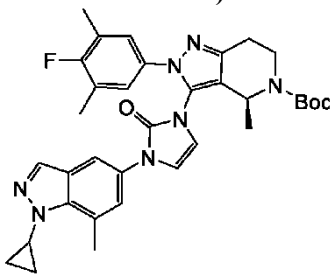
Referring to the synthesis of intermediate 1.5-F, starting from bromomethylcyclopropane (200 mg), intermediate 1.5-H (90 mg) was obtained. ESI-MS (m/z): 630.3 [M+H]+].

Preparation Embodiment 10: Synthesis of (S)-tert-butyl 3-(3-(1-cyclopropyl-4-methyl-1H-indazol-5-yl)-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 (intermediate 1.5-I)



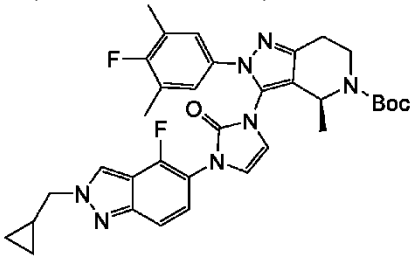
Referring to the synthesis of intermediate 1.5-F, starting from 5-bromo-4-methyl-1-H-indazole (140 mg), intermediate 1.5-I (48 mg) was obtained. ESI-MS (m/z): 612.2 [M+H]+].

Preparation Embodiment 11: Synthesis of (S)-tert-butyl 3-(3-(1-cyclopropyl-7-methyl-1H-indazol-5-yl)-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 (intermediate 1.5-J)



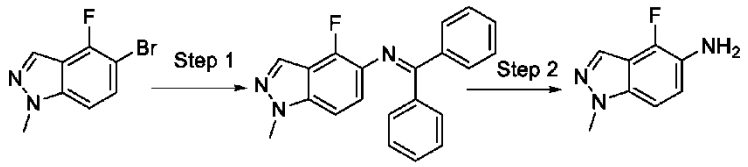
Referring to the synthesis of intermediate 1.5-F, 5-bromo-7-methyl-1-H-indazole (150 mg) was used as the starting material to obtain intermediate 1.5-J (280 mg). ESI-MS (m/z): 612.2 [M+H]+].

Preparation Embodiment 12: Synthesis of (S)-tert-butyl 3-(3-(2-cyclopropylmethyl-4-fluoro-2H-indazol-5-yl)-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 (intermediate 1.5-K)



Referring to the synthesis of intermediate 1.5-F, (3.15 g) was used as the starting material to obtain intermediate 1.5-K (4.20 g). ESI-MS (m/z): 630.3 [M+H]+].

Preparation Embodiment 13: Synthesis of 4-Fluoro-1-methyl-1H-indazol-5-amine (intermediate 2.1-A)



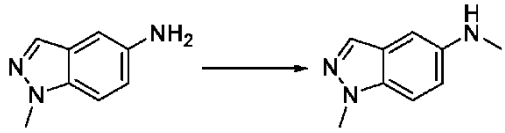
Step 1: Synthesis of N-(4-Fluoro-1-methyl-1H-indazol-5-yl)-1,1-diphenylcarbamylamine

5-Bromo-4-fluoro-1-methyl-1H-indazole (150 mg), benzophenone imine (142 mg), bis(dibenzylideneacetone)palladium (60 mg), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (152 mg), and cesium carbonate (429 mg) were added to a flask. Toluene (20 mL) was added and the mixture was heated to 130°C and stirred for 4 hours. After completion of the reaction, the mixture was cooled and added to water (40 mL). Extraction was performed with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The product (120 mg) was isolated by column chromatography (n-hexane:ethyl acetate = 5:1). ESI-MS (m/z): 330.1 [M+H]+.

Step 2: Synthesis of intermediate 2.1-A

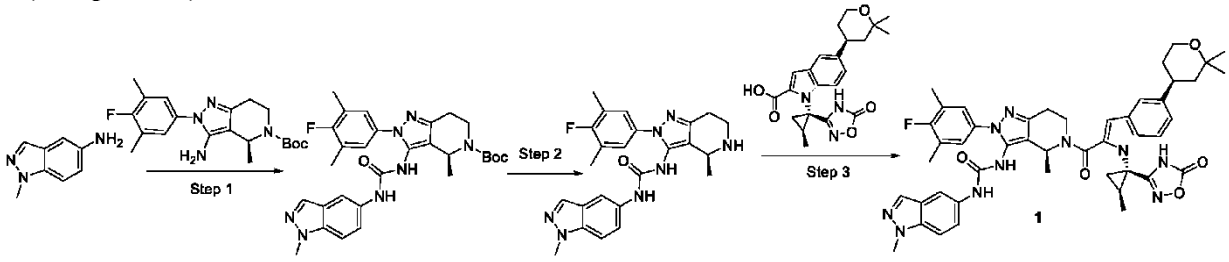
The product from Step 1 (120 mg) was added to a flask, followed by 10 mL each of tetrahydrofuran and water. Citric acid (200 mg) was added under ice-cooling, and the mixture was stirred at room temperature overnight. After completion of the reaction, the pH was adjusted to 9-10 with aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. intermediate 2.1-A (42 mg) was isolated by column chromatography (n-hexane:ethyl acetate = 5:1). ESI-MS (m/z): 166.1 [M+H]+.

Preparation Embodiment 14: Synthesis of N,1-Dimethyl-1H-indazol-5-amine (intermediate 2.2-A)



1-Methyl-1H-indazol-5-amine (150 mg) was dissolved in THF (5 mL), followed by the addition of iodomethane (160 mg) and sodium hydroxide (81 mg). The mixture was stirred at room temperature for two hours. After completion of the reaction, water (40 mL) was added and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by column chromatography (n-hexane:ethyl acetate = 5:1) to afford intermediate 2.2-A (103 mg). ESI-MS (m/z): 162.1 [M+H]+.

Embodiment 1: Synthesis of 1-((S)-5-(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-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(1-methyl-1H-indazol-5-yl)urea (Compound 1)



Step 1: Synthesis of (S)-tert-butyl 2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-1H-indazol-5-yl)ureido)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

1-Methyl-1H-indazol-5-amine (50 mg) was dissolved in dichloromethane (5 mL). Triphosgene (30 mg) and triethylamine (68 mg) were then added. After stirring at room temperature for two hours, (S)-tert-butyl 3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (127 mg, 0.34 mmol) was added and the reaction was stirred at room temperature overnight. After completion of the reaction, water (40 mL) was added and extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated by thin-layer chromatography (dichloromethane:methanol = 30:1, volume ratio) to afford the product (153 mg). ESI-MS (m/z): 548.3 [M+H]+;

Step 2: Synthesis 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-(1-methyl-1H-indazol-5-yl)urea

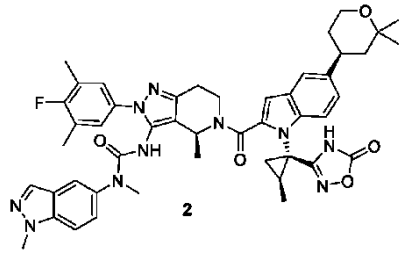
The product from Step 1 (153 mg) was dissolved in a 4 M solution of hydrochloric acid in dioxane (10 mL)

and stirred at room temperature for two hours. After completion of the reaction, the product was concentrated to give the crude product (105 mg). ESI-MS (m/z): 448.2 [M+H]+;

Step 3: 1-((S)-5-(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-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(1-methyl-1H-indazol-5-yl)urea

Take the product from step 2 (50 mg) and 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 (46 mg) was dissolved in anhydrous DMF (2 mL), and then HATU (85 mg) and DIPEA (29 mg) were added. The reaction was stirred at room temperature overnight. After completion of the reaction, water (40 mL) was added and extracted with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated by thin-layer chromatography (dichloromethane:methanol = 20:1) to afford compound 1 (65 mg). ESI-MS (m/z): 841.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C46H49N10O5F: 841.3944. Found: 841.3950. HPLC retention time: 18.820 min. The structure was confirmed by H NMR (600 MHz, DMSO-d6).

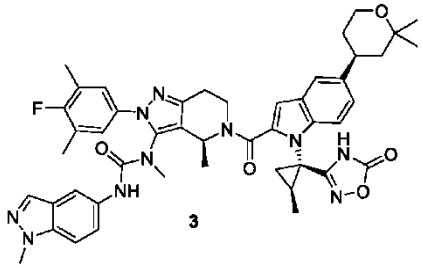
Embodiment 2: Synthesis of 3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1-methyl-1-(1-methyl-1H-indazol-5-yl)urea (Compound 2)



2

Following the method of Embodiment 1, N,1-dimethyl-1H-indazol-5-amine (intermediate 2.2-A) (50 mg) was used as the starting material to obtain Compound 2 (60 mg), ESI-MS (m/z): 855.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. For C47H51N10O5F: 855.4101. Found: 855.4098. HPLC retention time: 19.002 min.

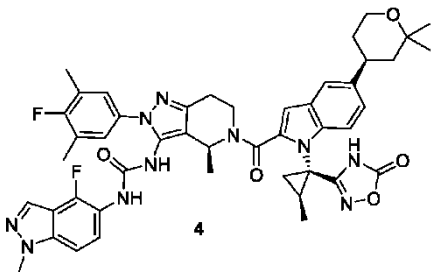
Embodiment 3: 1-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1-methyl-3-(1-methyl-1H-indazol-5-yl)urea (Compound 3) Synthesis of Compound 3



3

Following the method of Embodiment 1, compound 3 (63 mg) was obtained using (S)-tert-butyl 2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(methylamino)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (intermediate 1.4-A) (50 mg). ESI-MS (m/z): 855.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C47H51N10O5F: 855.4101. Found: 855.4100. HPLC retention time: 19.101 min.

Embodiment 4: Synthesis of 1-((S)-5-(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-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(4-fluoro-1-methyl-1H-indazol-5-yl)urea (Compound 4)

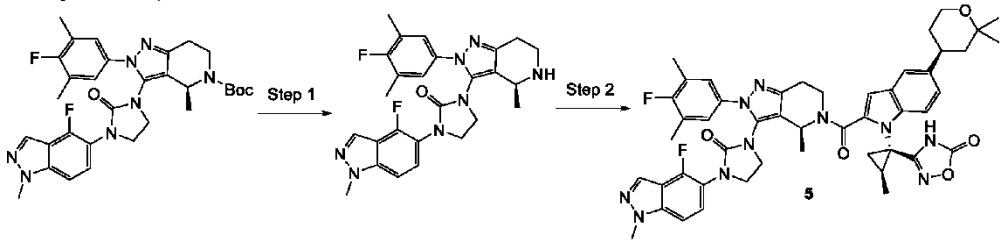


4

Following the method of Embodiment 1, 4-fluoro-1-methyl-1H-indazol-5-amine (intermediate 2.1-A) (50 mg)

was used as the starting material to obtain Compound 4 (53 mg), ESI-MS (m/z): 859.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C46H48N10O5F2: 859.3850. Found: 859.3843. HPLC retention time: 18.912 min.

Embodiment 5: Synthesis of 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxoimidazolin-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-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 (Compound 5)



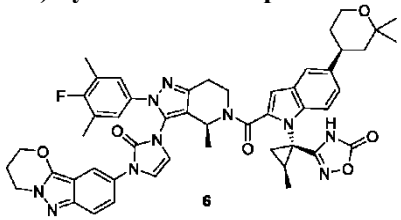
Step 1: Synthesis of (S)-1-(4-fluoro-1-methyl-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)imidazolin-2-one

(S)-tert-butyl 3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxoimidazolin-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (intermediate 1.5-A)) (66 mg) and dichloromethane (10 mL) were added to a flask. Trifluoroacetic acid (3 mL) was added, and the mixture was stirred at room temperature. After completion of the reaction, the solvent was concentrated and the crude product was purified by column chromatography (dichloromethane:methanol = 10:1) to obtain the product (50 mg). ESI-MS (m/z): 492.2 [M+H]+;

Step 2: Synthesis of Compound 5

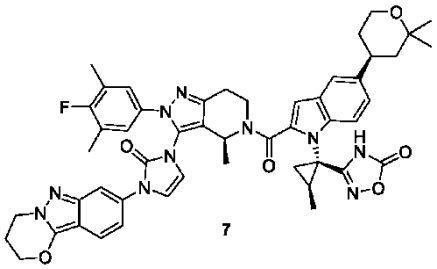
5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid (93 mg) and N,N-dimethylformamide (5 mL) were added to a flask. HATU (125 mg), triethylamine (56 mg), and the product from Step 1 (54 mg) were added and stirred at room temperature for 6 hours. After completion of the reaction, water (40 mL) was added to the mixture, and the mixture was extracted with ethyl acetate (30 mL*3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was separated and purified by column chromatography (dichloromethane: methanol = 20: 1) to give compound 5 (22 mg), ESI-MS (m/z): 885.4[M+H]+; HRMS (m/z): [M+H]+ Calcd. for C48H50N10O5F2: 885.4006. Found:885.4001; 1HNMR (600MHz,DMSO-d6) δ 11.80 (s, 1H), 8.25 (s, 1H),7.58(d, J=8.8 Hz, 1H), 7.54 (s,1H), 7.50-7.44 (m, 1H), 7.40(d,J=8.4 Hz, 1H), 7.31 (d,J=5.7Hz,2H), 7.27 (d, J=8.0Hz, 1H), 6.94 (s,1H), 5.68-5.63 (m, 1H), 4.39-4.33 (m, 1H), 4.09 (s, 3H), 4.06-4.02 (m, 1H), 3.96-3.86 (m, 2H), 3.66-3.60 (m, 2H), 3.18-3.10 (m, 1H), 3.08-3.00 (m, 2H), 2.90-2.80 (m, 2H), 2.32 (s, 6H), 1.75-1.62 (m, 4H), 1.55-1.52 (m, 3H), 1.29-1.22 (m,5H), 1.21-1.16 (m,7H). HPLC retention time: 20.381 min.

Embodiment 6: 3-((1S,2S)-1-(2-((S)-3-(3-(3,4-dihydro-2H-[1,3]oxazino[3,2-b]indazol-9-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound 6) Synthesis of Compound 6



Referring to the method of Embodiment 5, compound 6 (43 mg) was obtained from (S)-3-(3-(3,4-dihydro-2H-[1,3]oxazino[3,2-b]indazol-9-yl)-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-carboxylic acid tert-butyl ester (intermediate 1.5-B) (27 mg). ESI-MS (m/z): 907.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C50H51N10O6F: 907.4050. Found: 907.4058. HPLC retention time: 22.250 min.

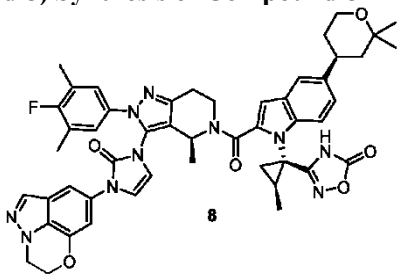
Embodiment 7: 3-((1S,2S)-1-(2-((S)-3-(3-(3,4-dihydro-2H-[1,3]oxazino[3,2-b]indazol-8-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound 7) Synthesis of Compound 7



7

Referring to the method of Embodiment 5, compound 7 (10 mg) was obtained using (S)-3-(3-(3,4-dihydro-2H-[1,3]oxazino[3,2-b]indazol-8-yl)-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-carboxylic acid tert-butyl ester (intermediate 1.5-C) (24 mg) as the starting material. ESI-MS (m/z): 907.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C50H51N10O6F: 907.4050. Found: 907.4044. HPLC retention time: 22.262 min.

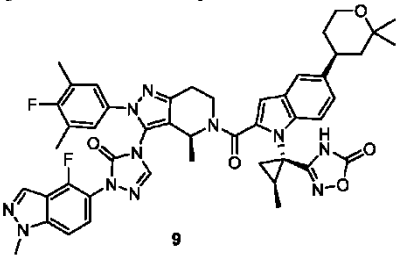
Embodiment 8: 3-((1S,2S)-1-(2-((S)-3-(3-(2,3-dihydro-[1,4]oxazino[2,3,4-hi]indazol-8-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound 8) Synthesis of Compound 8



8

Referring to the method of Embodiment 5, (S)-3-(3-(2,3-dihydro-[1,4]oxazino[2,3,4-hi]indazol-8-yl)-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-carboxylic acid tert-butyl ester (intermediate 1.5-D) (30 mg) was used as the starting material to obtain Compound 8 (42 mg). ESI-MS (m/z): 893.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C49H49N10O6F: 893.3893. Found: 893.3884. HPLC retention time: 20.210 min. 1HNMR (400 MHz, DMSO-d6, 80°C): See Figure 2.

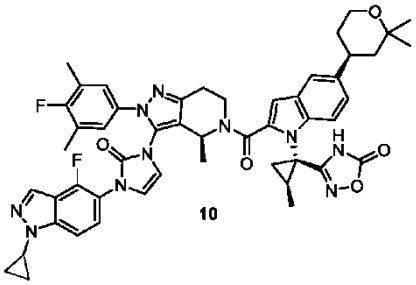
Embodiment 9: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl))-2-((S)-3-(1-(4-fluoro-1-methyl-1H-indazol-5-yl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound 9) Synthesis of Compound 9



9

Referring to the method of Embodiment 5, compound 9 (13 mg) was obtained using (S)-3-(1-(4-fluoro-1-methyl-1H-indazol-5-yl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (intermediate 1.5-E) (42 mg) as the starting material. ESI-MS (m/z): 884.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C47H47N11O5F2: 884.3802. Found: 884.3812. HPLC retention time: 20.090 min.

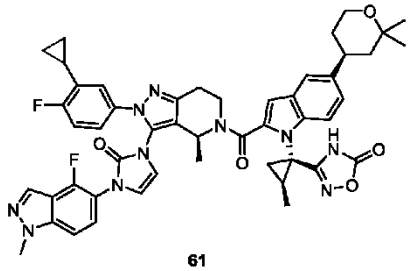
Embodiment 10: 3-((1S,2S)-1-(2-((S)-3-(3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound 10) Synthesis of Compound 10



10

Referring to the method of Embodiment 5, compound 10 (196 mg) was obtained using (S)-3-(3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-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-carboxylic acid tert-butyl ester (intermediate 1.5-F) (250 mg) as the starting material. ESI-MS (m/z): 909.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C50H50N10O5F2: 909.4006. Found: 909.4008. The 1H NMR (600 MHz, DMSO-d6, 60°C) results are shown in Figure 1. HPLC retention time: 21.060 min.

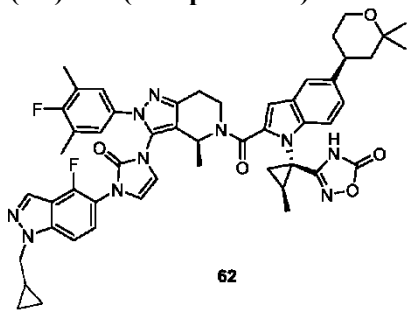
Embodiment 11: Synthesis of 3-((1S,2S)-1-(5-((4S)-2,2-dimethyloxan-4-yl)-2-((4S)-2-(4-fluoro-3-cyclopropylphenyl)-3-(3-(4-fluoro-1-cyclopropylindazol-5-yl)-2-oxoimidazol-1-yl)-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl)indol-1-yl)-2-methylcyclopropyl)-4H-1,2,4-oxadiazol-5-one (Compound 61)



61

Referring to the method of Embodiment 5, compound 61 (41 mg) was obtained using (S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (intermediate 1.5-G) (40 mg). ESI-MS (m/z): 895.3 [M+H] + ; HRMS (m/z): [M+H] + Calcd. for C49H48N10O5F2: 895.3850. Found: 895.3846. HPLC retention time: 19.834 min.

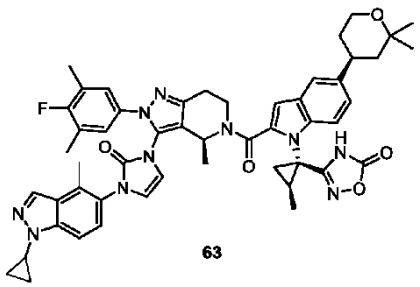
Embodiment 12: Synthesis of 3-((1S,2S)-1-(2-((S)-3-(3-(1-cyclopropylmethyl-4-fluoro-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound 62)



62

Referring to the method of Embodiment 5, compound 62 (40 mg) was obtained using (S)-3-(3-(1-cyclopropylmethyl-4-fluoro-1H-indazol-5-yl)-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-carboxylic acid tert-butyl ester (intermediate 1.5-H) (50 mg). ESI-MS (m/z): 923.4 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C51H52N10O5F2: 923.4163. Found: 923.4170. HPLC retention time: 21.515 min.

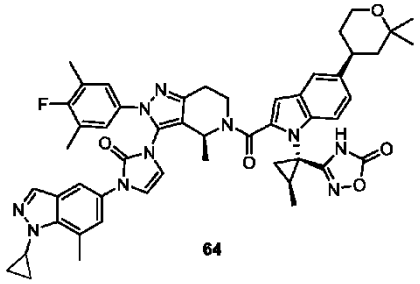
Embodiment 13: Synthesis of 3-((1S,2S)-1-(2-((S)-3-(3-(1-cyclopropyl-4-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound 63)



63

With reference to Embodiment 5, starting from (S)-3-(3-(1-cyclopropyl-4-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazolone-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (intermediate 1.5-I) (83 mg) was compound 63 (82 mg). ESI-MS (m/z): 905.4[M+H]+; HRMS (m/z): [M+H]+. Calcd. for C51H53N10O5F2: 905.4257. Found: 905.4266. HPLC retention time: 20.586 min.

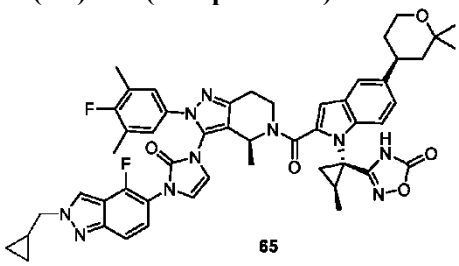
Embodiment 14: Synthesis of 3-((1S,2S)-1-(2-((S)-3-(3-(1-cyclopropyl-7-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound 64)



64

With reference to Embodiment 5, starting from (S)-3-(3-(1-cyclopropyl-7-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazolone-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (intermediate 1.5-J) (140 mg) was compound 64 (130 mg). ESI-MS (m/z): 905.3[M+H]+; HRMS (m/z): [M+H]+. Calcd. for C51H53N10O5F: 905.4257. Found: 905.4251. HPLC retention time: 21.285 min.

Embodiment 15: Synthesis of 3-((1S,2S)-1-(2-((S)-3-(3-(2-cyclopropylmethyl-4-fluoro-2H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (Compound 65)

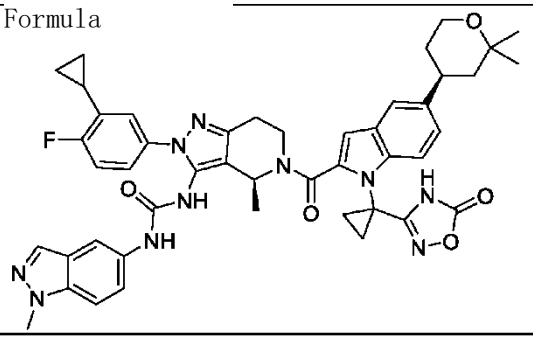
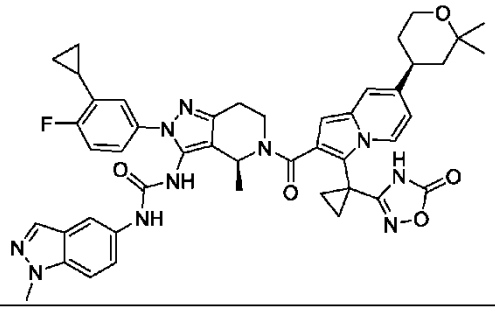


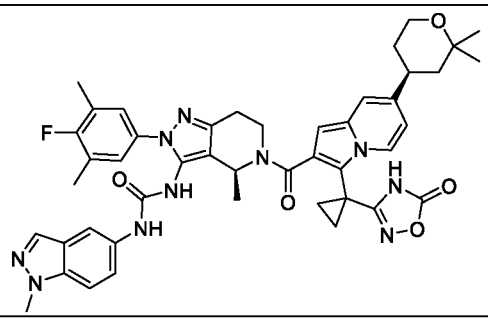
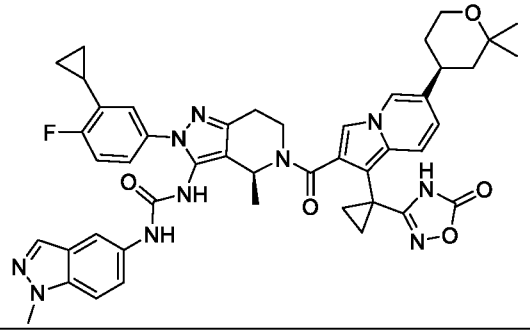
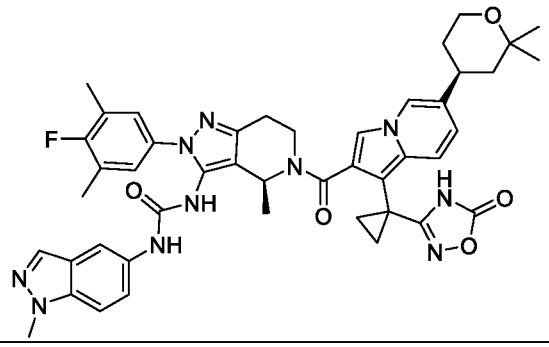
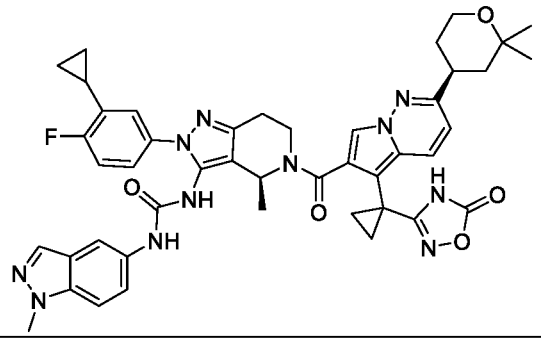
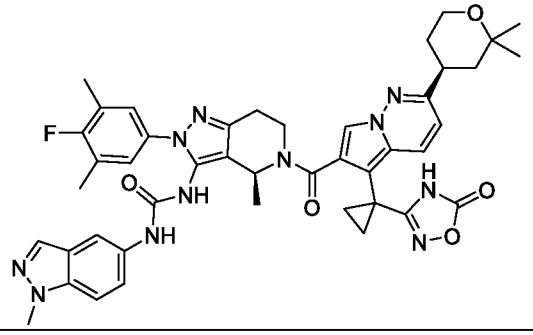
65

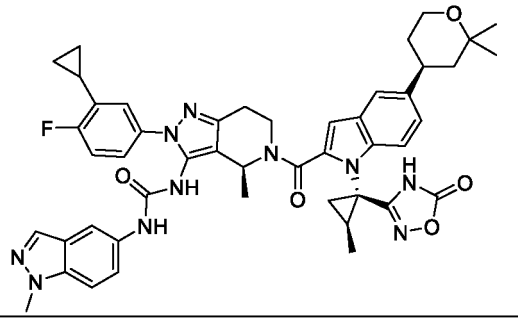
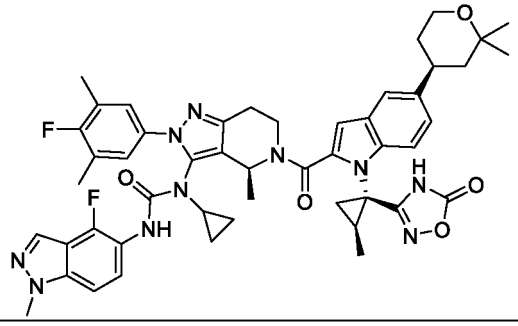
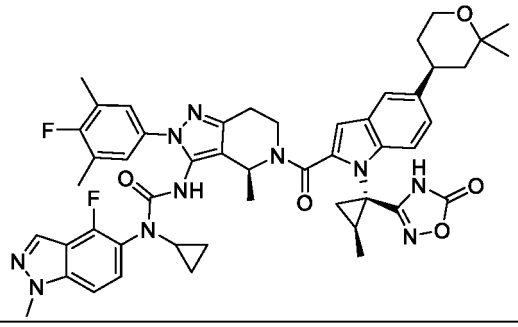
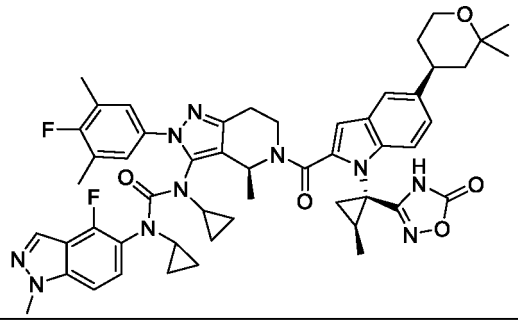
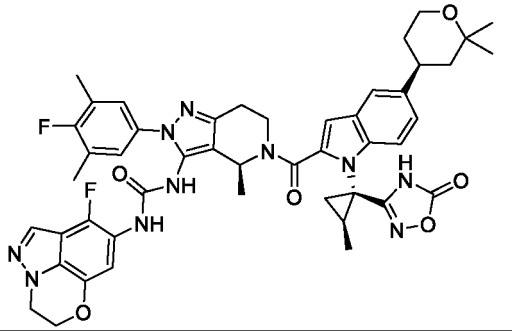
Referring to the method of Embodiment 5, compound 65 (5.22 g) was obtained using **(S)-3-(3-(2-cyclopropylmethyl-4-fluoro-2H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester** (intermediate 1.5-K) (3.71 g). ESI-MS (m/z): 923.3 [M+H]+; HRMS (m/z): [M+H]+. Calcd. for C51H52N10O5F2: 923.4163. Found: 923.4169. HPLC retention time: 20.656 min. 1H NMR (400 MHz, DMSO-d6, 80°C): See Figure 3.

By referring to the preparation methods of the above-mentioned embodiments and/or combining with preparation methods described in the literature, the following compounds were prepared. Their structures and characterization data are as follows:

Specifically, by referring to Embodiment 1 and/or combining with preparation methods described in the literature, the following compounds were prepared. Their structures and characterization data are as follows:

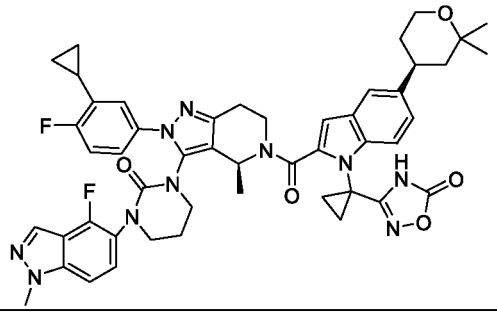
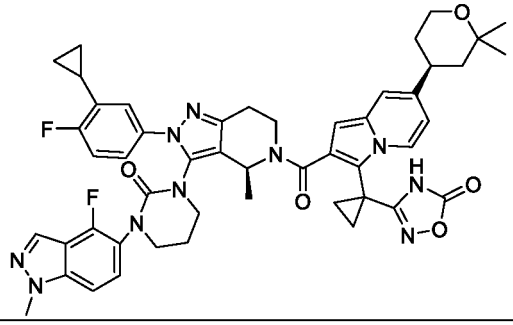
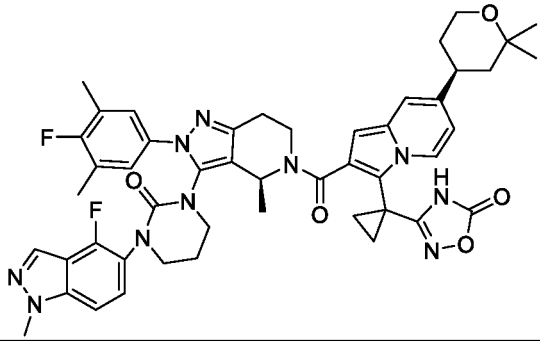
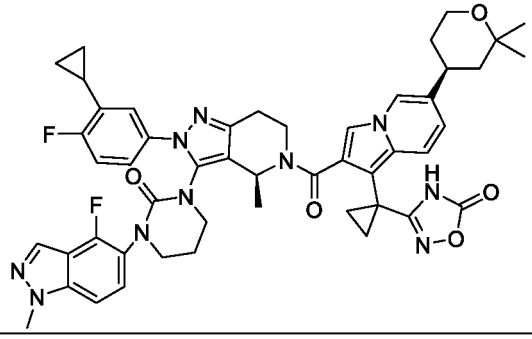
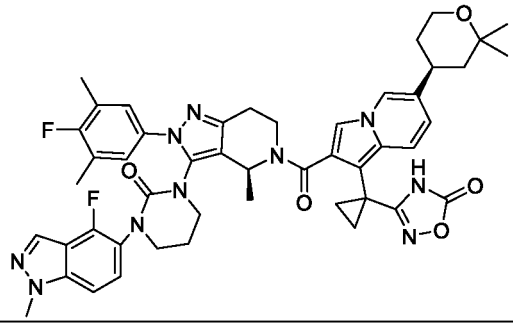
Number	Structural Formula	ESI-MS(m/z)
11		839.4[M+H]$^+$
12		839.4[M+H]$^+$

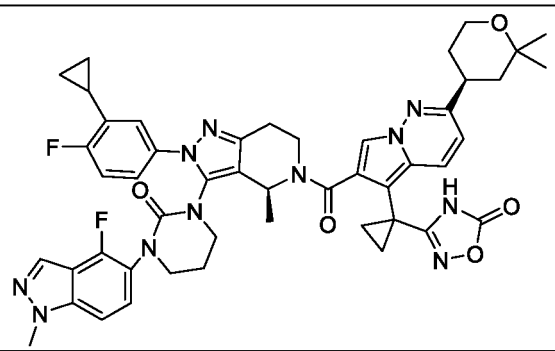
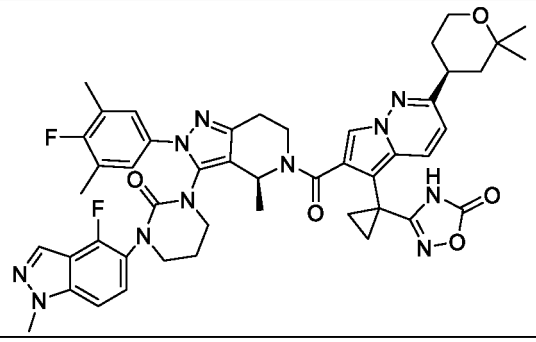
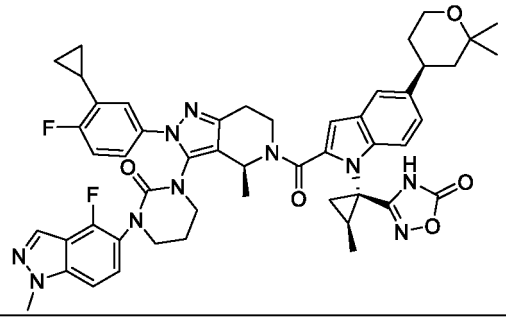
13		827.4[M+H]$^+$
14		839.4[M+H]$^+$
15		827.4[M+H]$^+$
16		840.4[M+H]$^+$
17		828.4[M+H]$^+$

18		853.4[M+H]$^+$
19		899.4[M+H]$^+$
20		899.4[M+H]$^+$
21		939.4[M+H]$^+$
22		887.4[M+H]$^+$

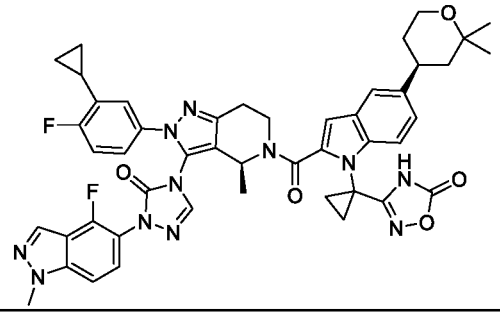
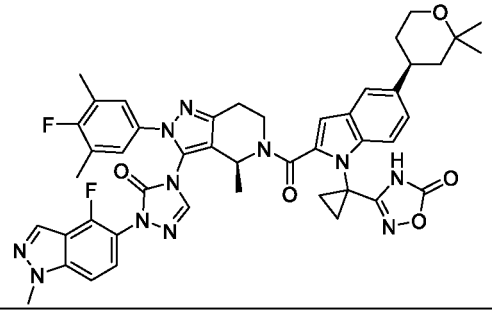
Specifically, referring to Embodiment 5 and/or in combination with preparation methods described in the literature, the following compound was prepared. The structure and characterization data are as follows:

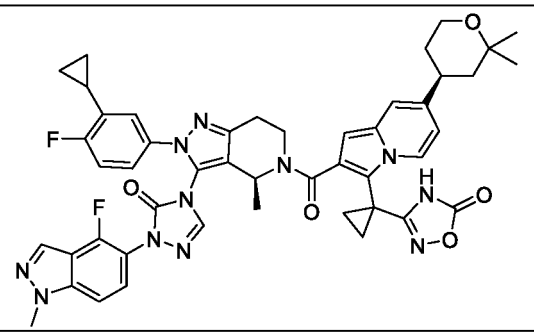
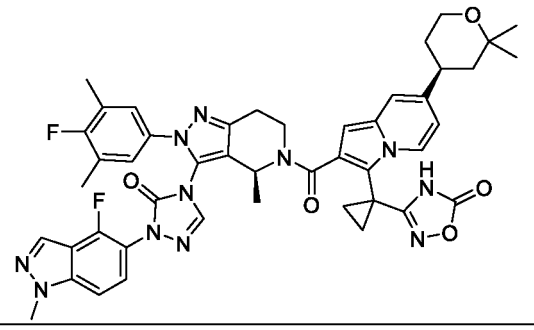
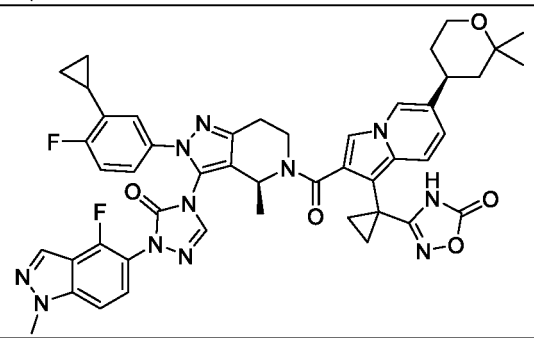
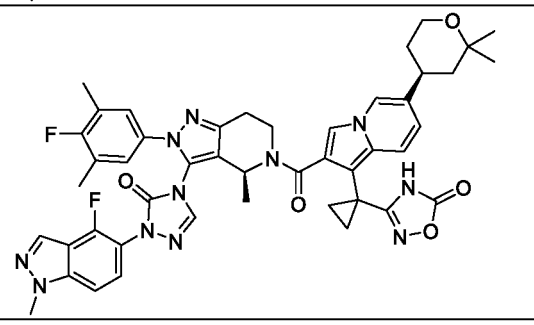
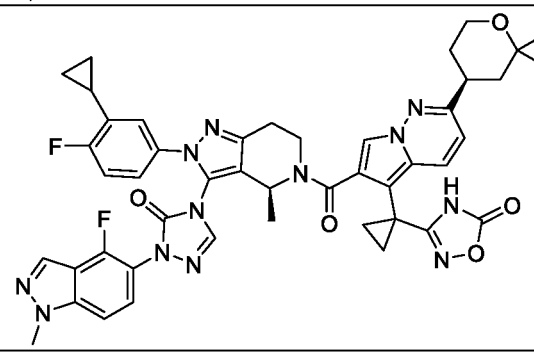
Number	Structural Formula	ESI-MS (m/z)

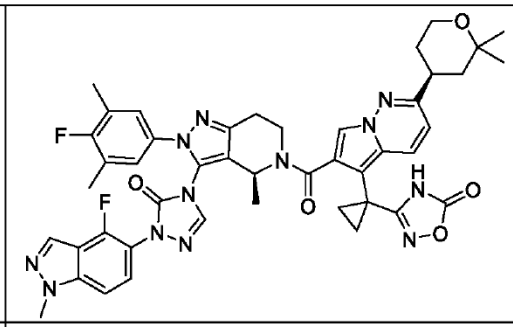
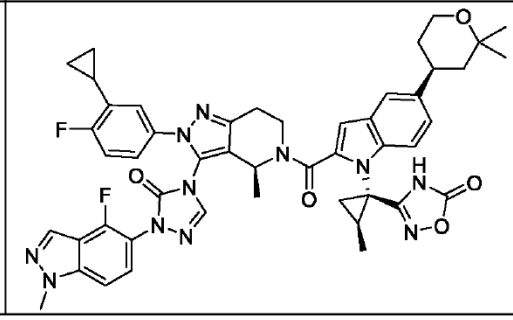
23		897.4[M+H]$^+$
24		897.4[M+H]$^+$
25		885.4[M+H]$^+$
26		897.4[M+H]$^+$
27		885.4[M+H]$^+$

28		898.4[M+H]$^+$
29		886.4[M+H]$^+$
30		911.4[M+H]$^+$

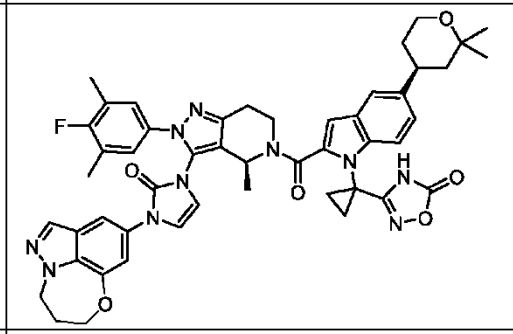
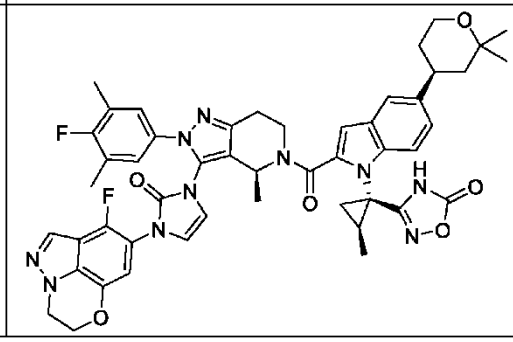
Specifically, referring to Embodiment 9 and/or in combination with preparation methods described in the literature, the following compound was prepared. The structure and characterization data are as follows:

Number	Structural Formula	ESI-MS(m/z)
31		882.4[M+H]$^+$
32		870.4[M+H]$^+$

33		882.4[M+H]$^+$
34		870.4[M+H]$^+$
35		882.4[M+H]$^+$
36		870.4[M+H]$^+$
37		883.4[M+H]$^+$

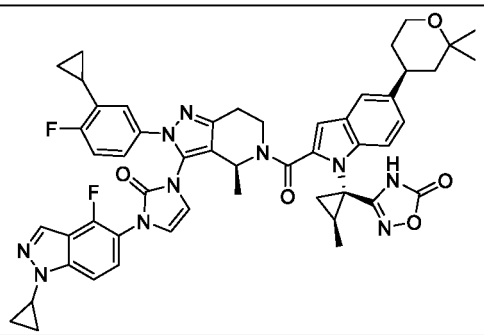
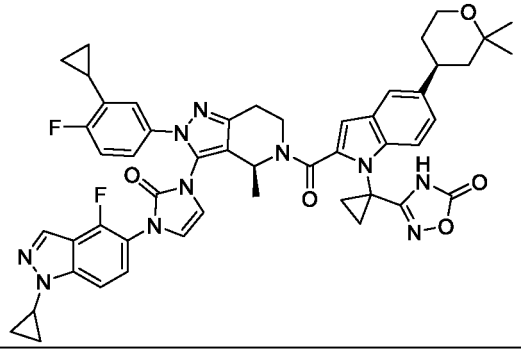
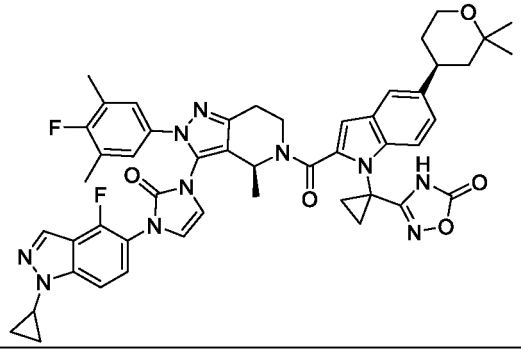
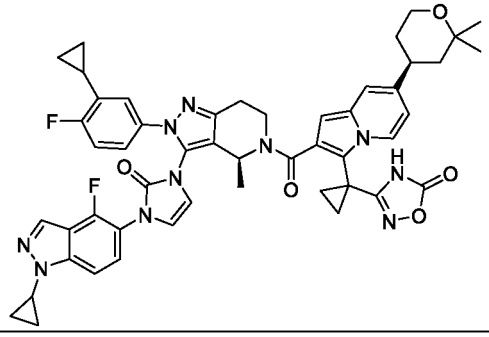
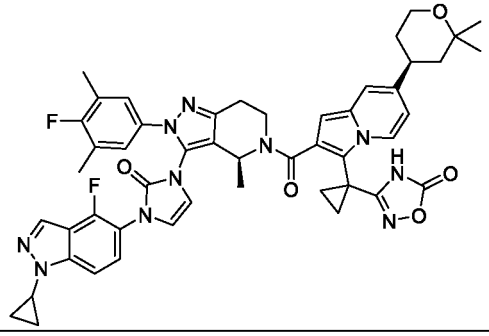
38		871.4[M+H]$^+$
39		896.4[M+H]$^+$

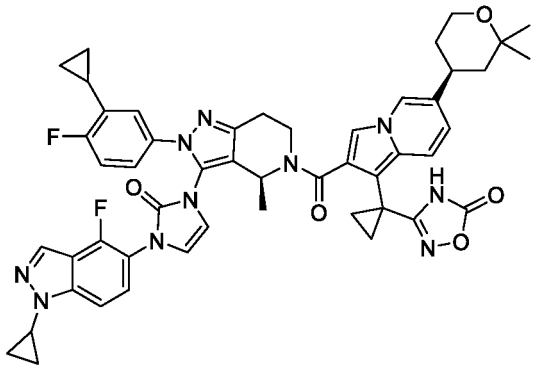
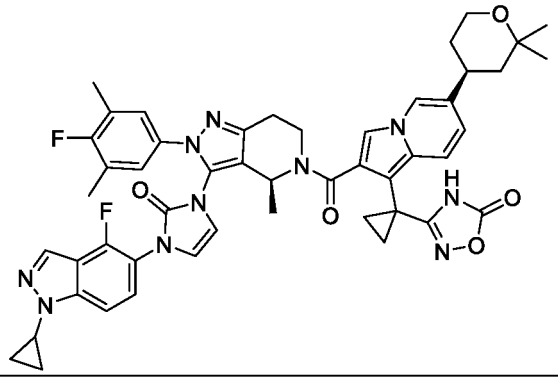
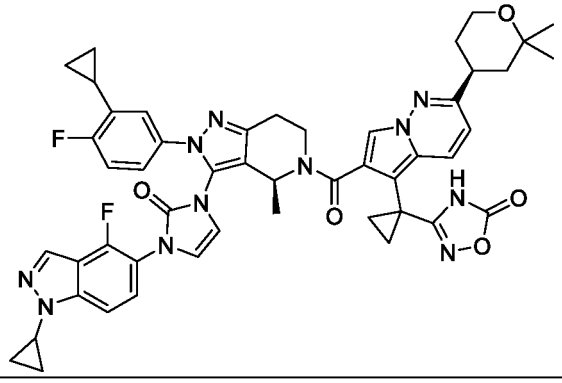
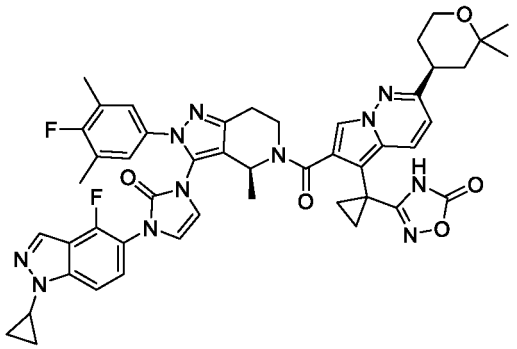
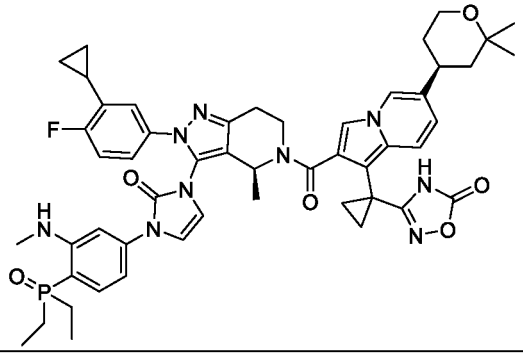
Specifically, referring to Embodiment 8 and/or in combination with preparation methods described in the literature, the following compound was prepared. The structure and characterization data are as follows:

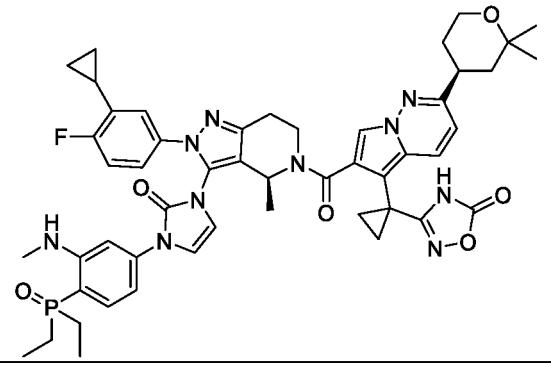
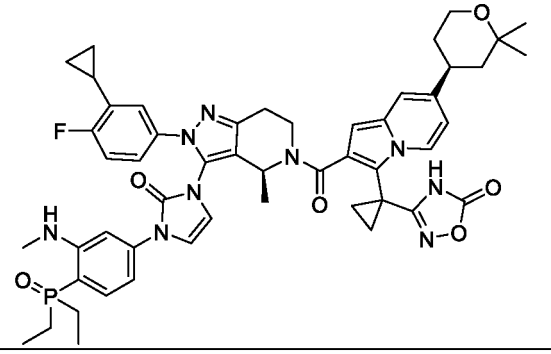
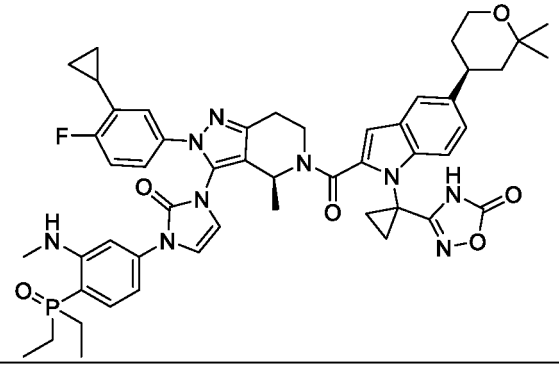
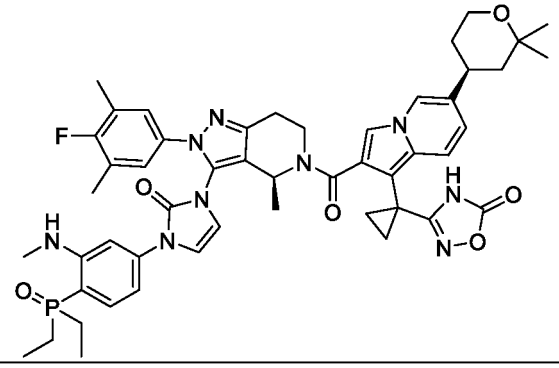
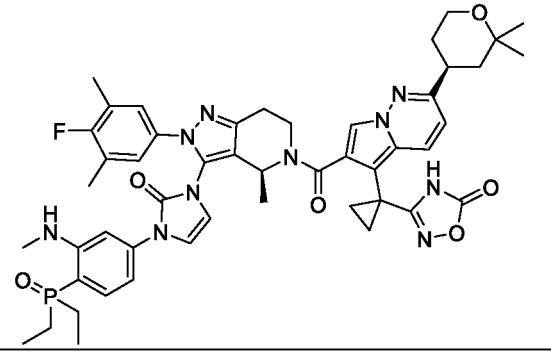
Number	Structural Formula	ESI-MS(m/z)
40		893.4[M+H]$^-$
41		911.4[M+H]$^+$

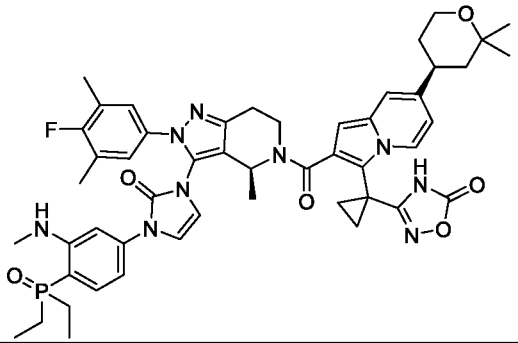
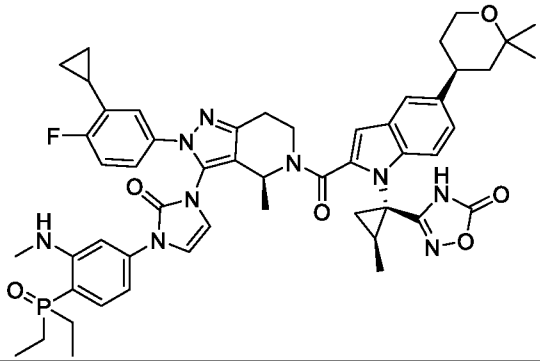
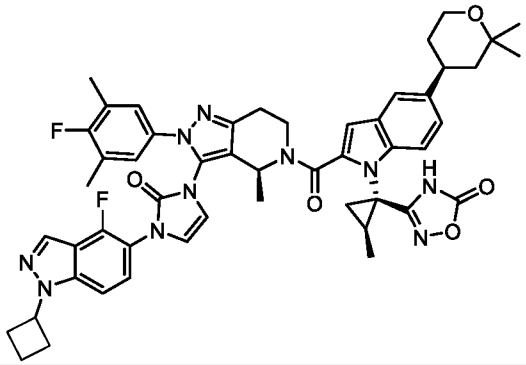
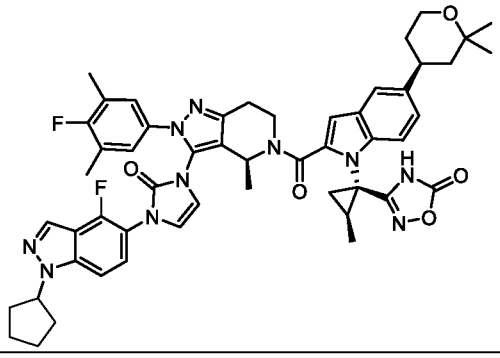
Specifically, referring to Embodiment 10 and/or in combination with preparation methods described in the literature, the following compound was prepared. The structure and characterization data are as follows:

Number	Structural Formula	ESI-MS (m/z)

42		921.4[M+H]$^+$
43		907.4[M+H]$^+$
44		895.4[M+H]$^+$
45		907.4[M+H]$^+$
46		895.4[M+H]$^+$

47		907.4[M+H]$^+$
48		895.4[M+H]$^+$
49		908.4[M+H]$^+$
50		896.4[M+H]$^+$
51		942.4[M+H]$^+$

52		943.4[M+H]$^+$
53		942.4[M+H]$^+$
54		942.4[M+H]$^+$
55		930.4[M+H]$^+$
56		931.4[M+H]$^+$

57		930.4[M+H]$^+$
58		956.4[M+H]$^+$
59		923.4[M+H]$^+$
60		937.4[M+H]$^+$

Test Example 1: In Vitro Enzymatic Assay

The agonistic effect of the test compound on GLP-1R was determined using GLP1R-cAmp-Luc cells. 1) Dissolve the test compound in DMSO and mix thoroughly until the test compound is completely dissolved. The test compounds were dissolved in DMSO and prepared into a stock solution with a concentration of 10 mM. All test compounds were diluted with DMEM medium (high glucose, Puromycin+, Hygromycin B+) to a starting concentration of 1250 nM and then diluted 5-fold to a total of 7 concentration gradients. Using white-walled 96-well cell culture plates, GLP1R-cAmp-Luc cells were seeded at a density of 1×105/mL, with 90 μL of cell suspension per well. 10 μL of the test compound was added to each well across all seven concentration gradients, with the actual working starting concentration of the test compound being 125 nM. The cells were incubated at 37°C, 5% CO2 for 4 hours. 2) 100 μL of luciferin potassium salt solution, diluted to 300 μg/mL in PBS, was added to each well, with a working concentration of 150 μL/mL, and the cells were incubated at room temperature for 30 minutes. 3) The fluorescence signal of firefly luciferin was measured using a multi-function microplate reader

(PerkinElmer, Nivo). Fluorescence values were processed using GraphPad Prism software, and the EC50 value was calculated.

The compounds of the present invention exhibit potent GLP-1R agonist activity. Preferred compounds exhibit agonist activity (EC50) of 20 nM or less, more preferred compounds exhibit agonist activity (EC50) of 10 nM or less, more preferred compounds exhibit agonist activity (EC50) of 5 nM or less, more preferred compounds exhibit agonist activity (EC50) of 2 nM or less, and even more preferred compounds exhibit agonist activity (EC50) of 1 nM or less. The activity results of exemplary compounds are shown in the table below.

Compound Number	**Agonist activity** (EC_{50}: nM)	**Compound Number**	**Agonist activity** (EC_{50}: nM)
1	A	6	A
2	A	7	A
3	A	8.	A
4	A	9	A
5	A	10	A
61	A	62	A
63	A	64	A
65	A	LY35029770	A

Note: A represents EC50 ≤ 10 nM.

Test Example 2: In Vivo Pharmacokinetic Study in Mice

Experimental Animals: ICR mice (female, 22-25 g) were purchased from Beijing Weitonglihua Laboratory Animal Technology Co., Ltd.

Experimental Procedure: ICR mice were administered the test compound via tail vein injection or oral gavage. Whole blood samples were collected from the mice 5 minutes (intravenous only), 15 minutes, 0.5 hours, 1 hour, 2 hours, 4 hours, 8 hours, 24 hours, 36 hours, 48 hours, and 72 hours after administration. Plasma was centrifuged and the compound concentration was determined by LC-MS/MS. Pharmacokinetic parameters such as plasma clearance (Cl), elimination half-life (T1/2), peak time (Tmax), peak concentration (Cmax), and area under the concentration-time curve (AUC) were calculated using Winnolin software.

Intravenous dose: 2 mg/kg; Oral gavage dose: 10 mg/kg.

Assay method: After pretreatment with protein precipitation, quantitative analysis was performed by LC/MS/MS.

The compounds of the present invention have excellent oral administration properties. The PK parameters of exemplary compounds are listed in the table below. Compared with LY3502970, they exhibit superior pharmacokinetic properties, particularly improved oral absorption.

Compound	iv（2 mg/kg）	po（10 mg/kg）		
	AUC_{inf} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (h*ng/mL)
8	7706	5377	1.33	41197

Note: 24-hour test results.

Compound	iv（2 mg/kg）			po（10 mg/kg）				
	Cl (mL/h/kg)	AUC_{inf} (h*ng/mL)	$T_{1/2}$ (h)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{inf} (h*ng/mL)	F (%)
10	92.7	21599	10	8197	1.67	9.56	103132	95.5

Note: 72-hour test results.

Compound	iv（2 mg/kg）			po（10 mg/kg）				
	Cl (mL/h/kg)	AUC_{inf} (h*ng/mL)	$T_{1/2}$ (h)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{inf} (h*ng/mL)	F (%)
10	102	19736	7.14	8197	1.67	7.77	95629	96.9

Note: 24-hour test results.

Compound	iv（2 mg/kg）	po（10 mg/kg）		
	AUC_{inf} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (h*ng/mL)
61	7077	5103	1.00	42906

Note: 24-hour test results.

Compound	iv（2 mg/kg）	po（10 mg/kg）		
	AUC_{inf} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (h*ng/mL)
41	7207	4557	1.67	43702

Note: 24-hour test results.

Compound	iv（2 mg/kg）	po（10 mg/kg）			
	AUC_{inf} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (h*ng/mL)	F (%)
65	17341	7807	1.67	85040	98.1

Note: 24-hour test results.

Compound	iv（2 mg/kg）	po（10 mg/kg）			
	AUC_{inf} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (h*ng/mL)	F (%)
LY3502970	10268	2660	1.17	23822	46.4

Note: 24-hour test results.

Test Example 3: In Vivo Pharmacokinetic Study in Rats

Experimental Animals: SD rats (female, 20-25 g) were purchased from Beijing Weitong Lihua Laboratory Animal Technology Co., Ltd.

Experimental Procedure: SD rats were administered the test compound via the tail vein and oral gavage. Whole blood samples were collected from the mice before administration, and at 15 minutes, 0.5 hours, 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours. Plasma was centrifuged and the compound concentration was determined by LC-MS/MS. Pharmacokinetic parameters such as plasma elimination half-life (T1/2), peak time (Tmax), peak concentration (Cmax), and area under the concentration-time curve (AUC) were calculated using Winnolin software.

Intravenous dose: 2 mg/kg; Oral gavage dose: 10 mg/kg

The compounds of the present invention have excellent oral administration properties. The oral PK parameters of exemplary compounds are listed in the table below. Compared with LY 3502970, they exhibit better pharmacokinetic properties, particularly improved oral absorption.

Compound	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{inf} (h*ng/mL)
8	2947	2.0	3.86	24500
65	3190	3.33	7.47	31480
LY3502970	1006	2.0	6.86	9190

Test Example 4: Weight Loss Efficacy Study in DIO C57BL/6 hGLP1R Mice

1. Test Purpose: To compare the weight loss efficacy of the test compound and LY3502970 administered orally at a dose of 0.3 mpk in obese mice.

2. Test Animals

Animals (species: C57BL/6 humanized transgenic (hGLP1R) mice; age: 6 weeks; sex: male) were purchased and fed a high-fat diet (60 kcal% Fat) for at least 12 weeks, until the animals reached a body weight of 40 g or more.

3. Test Groups

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Group	Drug	Number of Animals per Group	Dose	Dosage Concentration	Dosage Volume	Dosage Method	Dosage Frequency	Vehicle
			mg/kg	mg/mL	mL/kg			
G1	Vehicle	5	0	0	5	i.g.	qd	10% DMSO + 10% EL35 + 15% PEG400 + 65% (100mM glycine-NaOH buffer, pH-10)
G2	10	5	0.3	0.06		i.g.	qd	
G3	LY3502970	5	0.3	0.06		i.g.	qd	

Note: i.g. Stands for oral administration; qd stands for once daily.

4. Test Methods

Before dosing, mice were weighed and their daily food intake (one complete night plus daytime) was measured. Mice were then divided into groups based on their body weight and food intake.

Mice were weighed at fixed times daily, and their weight change rate was calculated. After the measurements, mice were given the appropriate drug based on their current body weight.

Mice were weighed daily, and their weight change rate was calculated, recorded, and graphed.

5. Test Results: After 18 days of continuous dosing, statistical analysis of the weight change rate of mice in each group revealed that Compound 10 of the present invention achieved significantly greater weight loss than the Vehicle group (average weight gain of Compound 10 was -20.2%, $p < 0.001$). Compound 10 of the present invention also achieved significantly greater weight loss than the LY3502970 group (average weight gain of LY3502970 was -15.1%) ($p < 0.05$).

After 20 days of continuous administration, statistical analysis of the weight change rate of mice in each group revealed that Compound 10 of the present invention achieved significantly greater weight loss than the vehicle group (average weight gain of Compound 10 was -20.3%, $p < 0.001$). Compound 10 of the present invention also achieved significantly greater weight loss than the LY3502970 group (average weight gain of LY3502970 was -15.7%) ($p < 0.05$). The weight gain curve is shown in Figure 4.

Test Example 5: Efficacy Study of Intraperitoneal Glucose Tolerance Test (IPGTT) in hGLP-1R Transgenic Mice

1. Test Purpose: The effects of different doses of the test compound on blood glucose levels at different times after glucose loading were investigated in hGLP-1R transgenic mice following a single oral gavage.

2. Test Animals: Male C57BL/6JSmoc-Glplrem2(hGLP1R)Smoc mice, approximately 23 g.

3. Test Grouping: Before the experiment, mice were fasted for approximately 16 hours. Basal blood glucose levels were measured, and the animals were randomly assigned to balanced groups based on baseline blood glucose and body weight, with 7 mice per group.

4. Experimental Methods: Each group was gavaged with the test compound at a volume of 10 mL/kg. The vehicle control group was gavaged with 2.5% DMSO, 10% Kolliphor® EL, 15% PEG400, and 72.5% (100 mM glycine-NaOH buffer, pH 10) at the same frequency and volume. Sixty minutes after administration, a glucose solution was intraperitoneally (i.p.) injected at a volume of 10 mL/kg at a rate of 2 g/kg based on mouse body weight. Time of glucose administration was designated as time zero. Blood glucose levels were measured before, and 15, 30, 60, and 120 minutes after glucose administration.

5. Specific groups are as follows:

Group	**Drug**	**Number of Animals**	**Dose**	**Dose Concentration**	**Dose Volume**	**Dose Method**	**Dose Frequency**
			mg/kg	mg/mL	mL/kg		
G1	vehicle	6	0	-	10	i.g.	Single
G4	Compound 10	6	0.05	0.005		i.g.	Single

6. Experimental Results:

Blood glucose testing showed that at a dose of 0.05 mg/kg, the blood glucose levels of mice in the Compound 10 group at 15, 30, 60, and 120 minutes after glucose loading showed a downward trend and were significantly lower than those in the vehicle group ($P<0.05$, $P<0.01$, $P<0.001$). Calculation of the area under the

blood glucose curve showed that AUC0-120min Glu was significantly lower in the Compound 10 group compared with the vehicle group after glucose loading (P<0.001). The results are shown in the table below.

Mean Blood Glucose AUC (mmol*min/L) (Mean±SD, n=5)		
Time Point (min)	G1 (Vehicle)	G4 (Compound 10) 0.05mg/kg
0-120	1790.5±176.4	949.6±87.6

Test Example 6: Safety Assessment of Off-Target Effects on 44 Targets

1. Test Purpose: This study primarily employed radioisotope binding, calcium flux assays, and enzyme fluorescence or chemiluminescence techniques to assess the off-target effects of test compounds on 44 selected targets at the cellular or molecular level in vitro, thereby evaluating the safety profile associated with the binding or inhibitory effects of the test compounds on these targets.

2. Test Methods: Test compound 10 (free acid) was tested for binding, inhibition, or agonism against 44 targets at a single concentration of 10 μM (12 μM for Eta agonism).

3. Test Procedure: Radioactive ligand competition assays were used to assess the binding of test compounds to 23 GPCRs (ADORA2A, AlphalA, Alpha2A, Beta1, Beta2, CB1, CB2, CCKa, D1, D2L, H1, H2, op-delta, op-kappa, op-mu, M1, M2, M3, 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, and V1A), eight ion channels (nAChR-Alpha7, Cav1.2 (Dihydropyridine Site), GABAA (alβ3γ2), hERG, NMDA (MK-801), 5-HT3, Na+, and Kv), three transporters (DAT, NET, and 5-HTT), and two nuclear receptors (AR and GR). Calcium flux assays were used to test the agonist and antagonist effects of the test compounds on Eta receptors. An in vitro biochemical platform was used to test the effects of the test compounds on seven enzyme targets.

4. Test Results:

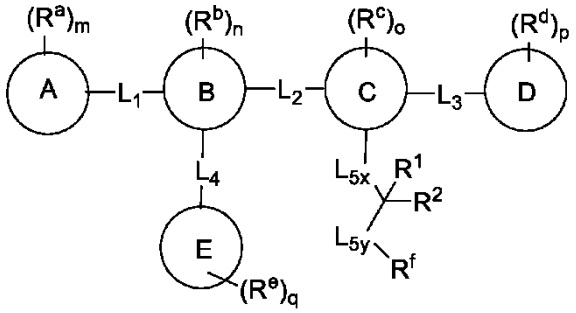
At a test concentration of 10 μM, compound 10 exhibited no significant binding, inhibitory (inhibition rate <50%), or agonist (agonist rate <50%) effects on any of the 44 targets at a single concentration of 10 μM (the test concentration for Eta agonism was 12 μM).

At a test concentration of 10 μM, LY3502970 exhibited mild inhibitory effects on Ca2+-L, 5HT2B, and op-delta (inhibition rate >50%). This may result in off-target effects on related targets.

The above describes the embodiments of the present invention. However, the present invention is not limited to these embodiments. Any modifications, equivalent substitutions, improvements, etc. made within the spirit and principles of the present invention shall be included within the scope of protection of the present invention.

Claims

1. Compounds represented by formula (I), stereoisomers, tautomers, or pharmaceutically acceptable salts thereof:



(I)

Wherein,

Ring A is selected from a C3-15 carbocyclyl, a 3-12-membered heterocyclyl, a C6-14 aryl, or a 5-12-membered heteroaryl;

Ring B is selected from a 3-12-membered heterocyclyl, a C6-14 aryl, or a 5-12-membered heteroaryl;

Ring C is selected from a 9-membered bicyclic heteroaryl;

Ring D is selected from a C3-15 carbocyclyl, a 3-12-membered heterocyclyl, a C6-14 aryl, or a 5-12-membered heteroaryl;

Ring E is selected from a C3-15 carbocyclyl, a 3-12-membered heterocyclyl, a C6-14 aryl, or a 5-12-membered heteroaryl;

Ra is independently selected each time from hydrogen, deuterium, halogen, hydroxy, amino, nitro, thio, cyano, oxo, -ORa1, -S(O)Ra1, -SO2(Ra1), -C(O)Ra1, -C(O)ORa1, -OC(O)Ra1, -N(Ra1)(R2), -C(O)N(Ra1)(R2), -N(Ra1)C(O)Ra2, -S(O)N(Ra1)(R2), -SON(Ra1)(R2), -N(Ra1)S(O)Ra2, -N(Ra1)S(O)Ra2, and the following groups optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) R3. C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl;

Alternatively, two Ra, together with the atoms to which they are attached, form an optionally substituted 3-10 membered heterocyclyl or an optionally substituted 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, thio, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl.

Ra1 and Ra2 are independently selected each time from hydrogen, deuterium, optionally substituted groups. C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl.

Ra3 is independently selected each time from hydrogen, deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, -Ra4, -ORa4, -SRa4, -S(O) Ra4, -S(O)2Ra4, -C(O)Ra4, -C(O)ORa4, -OC(O)Ra4, -N(Ra4)(Ra5), -C(O)N(Ra4)(Ra5), -N(Ra4) C(O)Ra5, -S(O)N(Ra4)(Ra5), -S(O)2N(Ra4)(Ra5), -N(Ra4)S(O)Ra5, -N(Ra4)S(O)2Ra5;

Ra4 and Ra5 are independently selected each time from hydrogen, deuterium, or optionally substituted with the following groups: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, or 5-12 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, 3-7 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl.

Rb is independently selected each time from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, C3-10 The term "optionally substituted" refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the substituted group independently substituted with Rb1.

Alternatively, two Rb together with the atoms to which they are attached form an optionally substituted 3-10 membered heterocyclyl or an optionally substituted 5-12 membered heteroaryl, optionally substituted refers to

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unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl.

Rb1 is independently selected each time from deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, -Rb2, -ORb2, -SRb2, -S(O)Rb2, -S(O)2Rb2, -C(O)Rb2, -C(O)ORb2, -OC(O)Rb2, -N(Rb2)(Rb3), -C(O)N(Rb2)(Rb3), -N(Rb2)C(O)Rb3, -S(O)N(Rb2)(Rb3), -S(O)2N(Rb2)(Rb3), -N(Rb2)S(O)Rb3, -N(Rb2)S(O)2Rb3;

Rb2 and Rb3 are independently selected each time from hydrogen, deuterium, and optionally substituted with the following groups: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) groups selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl.

Rc is independently selected each time from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, or optionally substituted with the following groups: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; optionally substituted refers to one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of an unsubstituted or substituted group are independently substituted with Rc1.

or two Rc together with the atoms to which they are attached form an optionally substituted 3-10 membered heterocyclyl or an optionally substituted 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl.

Rc1 is independently selected each time from deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, -Rc2, -ORc2, -SRc2, -S(O)Rc2, -S(O)2Rc2, -C(O)Rc2, -C(O)ORc2, -OC(O)Rc2, -N(Rc2)(Rc3), -C(O)N(Rc2)(Rc3), -N(Rc2)C(O)Rc3, -S(O)N(Rc2)(Rc3), -S(O)2N(Rc2)(Rc3), -N(Rc2)S(O)Rc3, -N(Rc2)S(O)Rc3;

Rc2 and Rc3 are independently selected each time from hydrogen, deuterium, and optionally substituted with the following groups: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, C3-10 The term "optionally substituted" refers to being unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, or 5-12 membered heteroaryl.

Rd is independently selected each time from hydrogen, deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, -ORd1, -S(O)Rd1, -S(O)2Rd1, -C(O)Rd1, -C(O)ORd1, -OC(O)Rd1, -N(Rd1)(Rd2), -C(O)N(Rd1)(Rd2), -N(Rd1)C(O)Rd2, -S(O)N(Rd1)(Rd2), -S(O)2N(Rd1)(Rd2), -N(Rd1)S(O)Rd2, -N(Rd1)S(O)2Rd2, and the following groups optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) Rd3: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl.

Alternatively, two Rd's, taken together with the atoms to which they are attached, form an optionally substituted 3-10 membered heterocyclyl, an optionally substituted 3-7 membered cycloalkyl, or an optionally substituted 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl.

Rd1 and Rd2 are each independently selected from hydrogen, deuterium, optionally substituted 5-12 membered heteroaryl. C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl. The term optionally substituted refers to being unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, and 5-6 membered heteroaryl.

Rd3 is independently selected from hydrogen, deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, and 5-6 membered heteroaryl. group, cyano group, oxo group, -Rd4, -ORd4, -SRd4, -S(O)Rd4, -S(O)2Rd4, -C(O)Rd4, -C(O)ORd4, -OC(O)Rd4, -N(Rd4)(Rd5), -C(O) N(Rd4)(Rd5), -N(Rd4)C(O)Rd5, -S(O)N(Rd4)(Rd5), -S(O)2N(Rd4)(Rd5), -N(Rd4)S(O)Rd5, -N(Rd4)S(O)2Rd5;

Rd4 and Rd5 are independently selected each time from hydrogen, deuterium, or optionally substituted groups. C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, or 5-12 membered heteroaryl; optionally substituted groups are unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6

alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, 3-7 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl.

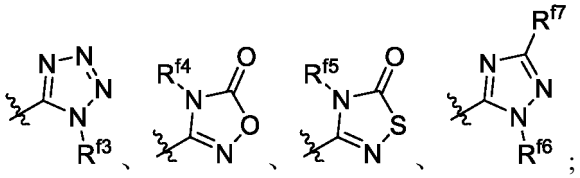
Re is independently selected each time from hydrogen, deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, -ORe1, -SRe1, -S(O)Re1, -S(O)2Re1, -C(O)Re1, -C(O)ORe1, -OC(O)Re1, -N(Re1)(Re2), -C(O)N(Re1)(Re2), -N(Re1)C(O)Re2, -S(O)N(Re1)(Re2), -S(O)2N(Re1)(Re2), -N(Re1)S(O)Re2, -N(Re1)S(O)2Re2, -C(O)N(Re1)S(O)2N(Re1)(Re2), -C(O)N(Re1)S(O)2Re2, -P(O)(Re1)Re2, and the following groups optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) Re3. C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl;

or two Re, together with the atoms to which they are attached, form an optionally substituted 3-10 membered heterocyclyl or an optionally substituted 5-12 membered heteroaryl, optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, and 5-12 membered heteroaryl.

Re1 and Re2 are independently selected each time from hydrogen, deuterium, or optionally substituted with the following groups: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, or 5-12 membered heteroaryl; optionally substituted refers to being unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from hydrogen, halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl.

Re3 is independently selected each time from hydrogen, deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, oxo, -Re4, -ORe4, -SRe4, -S(O)Re4, -S(O)2Re4, -C(O)Re4, -C(O)ORe4, -OC(O)Re4, -N(Re4)(Re5), -C(O)N(Re4)(Re5), -N(Re4)C(O)Re5, -S(O)N (Re4)(Re5), -S(O)2N(Re4)(Re5), -N(Re4)S(O)Re5, -N(Re4)S(O)2Re5, -C(O)N(Re4)S(O)2N(Re4)(Re5), -C(O)N(Re4)S(O)2Re5, -P(O)(Re4)Re5;

Re4 and Re5 are each independently selected from hydrogen, deuterium, and optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, 3-7 membered heterocyclyl, phenyl, 5-6 membered heteroaryl.

Rf is selected from -C(O)ORf1, -C(O)N(Rf1)(Rf2), ;

Rf1, Rf2, Rf3, Rf4, Rf5, Rf6, and Rf7 are each independently selected from hydrogen, deuterium, optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C3-10 cycloalkyl, 3-10 membered heterocyclyl, C6-14 aryl, 5-12 membered heteroaryl; the optionally substituted group refers to being unsubstituted or substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substituents selected from halogen, hydroxy, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-6 cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl.

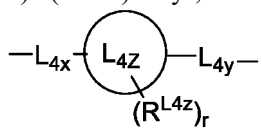
R1 and R2, together with the atoms to which they are attached, form a C3-15 carbocyclyl; the C3-15 carbocyclyl is optionally substituted with one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) R3. R3 is independently selected from hydrogen, deuterium, halogen, hydroxyl, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C3-10 cycloalkyl, 3-10 membered heterocyclyl; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) substitutable positions of the unsubstituted or substituted group are independently substituted by deuterium, halogen, hydroxyl, amino, cyano, oxo, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

L1 is selected from a bond, -C(RL1)2-, -O-, -C(RL1)2O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -N(RL1)C(O)-, -C(O)N(RL1)-, or -N(RL1)-; RL1 is independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) selected from deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 substituted with an alkynyl, C3-10 cycloalkyl, or 3-10 membered heterocyclyl.

L2 is independently selected from a bond, -C(RL2)2-, -O-, -C(RL2)2O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -N(RL2)C(O)-, -C(O)N(RL2)-, or -N(RL2)-; RL2 is independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, C1-6 alkyl,

C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

L3 is independently selected from a bond, -C(RL3)2-, -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -N(RL3)C(O)-, -C(O)N(RL3)-, or -N(RL3)-; RL3 is independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl, optionally substituted refers to unsubstituted or substituted by one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) groups selected from deuterium, halogen, hydroxy, amino, nitro, mercapto, cyano, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

L4 is independently selected from a bond, -L4x-C(RL4a)(RL4b)-L4y-, -L4x-O-L4y-, -L4x-S-L4y-, -L4x-C(O)-L4y-, -L4x-C(O)O-L4y-, -L4x-OC(O)-L4y-, -L4x-N(RL4a)C(O)-L4y-, -L4x-C(O)N(RL4a)-L4y-, -L4x-N(RL4a)-L4y-, -L4x-N(RL4a)C(O)N(RL4b)-L4y-, -L4x-N(RL4a)C(S)N(RL4b)-L4y- or 

;

L4x and L4y are each independently selected from a bond or an optionally substituted C1-10 alkylene group; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the unsubstituted or substituted group are independently substituted by deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, or a 3-10 membered heterocyclyl group.

RL4a and RL4b are each independently selected from hydrogen, deuterium, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5, 6, 7 or 8) substitutable positions of the unsubstituted or substituted group are independently substituted by deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

Ring L4Z is selected from a C3-15 carbocyclyl, a 3-12 membered heterocyclyl, a C6-14 aryl, or a 5-12 membered heteroaryl.

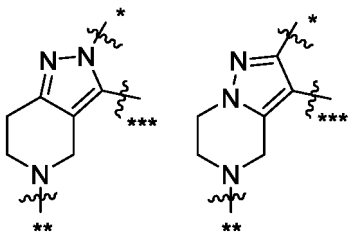
RL4z is independently selected from hydrogen, deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, or optionally substituted groups as follows: C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl; optionally substituted refers to that one or more substitutable positions of the unsubstituted or substituted group are independently substituted by deuterium, halogen, hydroxyl, amino, nitro, mercapto, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 3-10 membered heterocyclyl.

L5x and L5y are each independently selected from a bond or an optionally substituted C1-10 alkylene group; optionally substituted refers to that one or more (e.g., 2, 3, 4, 5, 6, 7, or 8) substitutable positions of the unsubstituted or substituted group are independently substituted with deuterium, halogen, hydroxyl, amino, nitro, thiol, cyano, oxo, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylamino, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, or a 3-10 membered heterocyclyl.

m, n, o, p, q, and r are each independently 0, 1, 2, or 3.

Unless otherwise specified, the heteroatoms in the heterocyclic and heteroaryl groups are independently selected from O, N, or S, and the number of heteroatoms is 1, 2, 3, or 4.

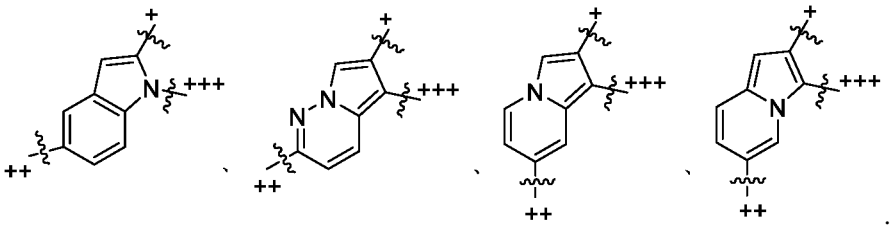
2. The compound according to claim 1, its stereoisomers, tautomers, or pharmaceutically acceptable salts, wherein, Ring A is selected from phenyl:

Ring B is selected from the group consisting of 

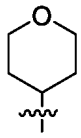
、 : wherein, the "*" end is connected to L1, the "**" end is connected to L2, and the "***" end is connected to L4;

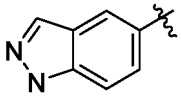
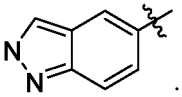
Ring C is selected from the group consisting of

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:

wherein, the "+" end is connected to L2, the "++" end is connected to L3, and the "+++" end is connected to L5x;

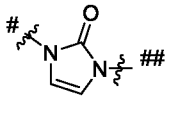
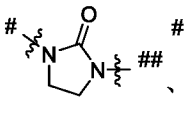
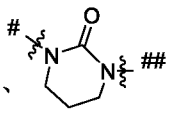
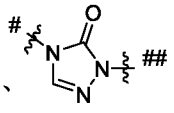
Ring D is :

Ring E is  or :

L1 is selected from a bond;

L2 is selected from -C(O)-;

L3 is selected from a bond;

L4 is selected from -NHC(O)NH-, -N(methyl)C(O)NH-, -N(cyclopropyl)C(O)NH-, -N(cyclopropyl)C(O)N(cyclopropyl)-, 、、、,wherein, the "#" end is connected to the end of ring B and the "##" end is connected to the end of ring E;

L5x and L5y are each independently selected from a bond;

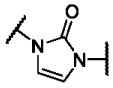
Ra is independently selected each time from halogen, methyl, and C3-5 cycloalkyl-(CH2)w-;

Rb is independently selected each time from fluorine, chlorine, oxo, and methyl;

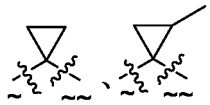
Rc is independently selected each time from hydrogen, fluorine, chlorine, oxo, methyl, ethyl, n-propyl, isopropyl, and n-butyl;

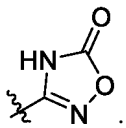
Rd is independently selected each time from optionally substituted C1-3 alkyl and optionally substituted C1-3 alkoxy; optionally substituted refers to unsubstituted or substituted with one or more (e.g., 2, 3, 4, or 5) substituents selected from hydrogen, deuterium, halogen, hydroxyl, and amino.

Re is independently selected each time from fluorine, or optionally substituted groups as follows: C1-3 alkyl (e.g., methyl, ethyl), C3-5 cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl), C3-5 cycloalkyl-(CH2)w-;

provided that, when L4 is , at least one (e.g., one or two) of Ra or the substituents on ring E (or Re) is C3-5 cycloalkyl-(CH2)w-;

Alternatively, two Re (preferably, two adjacent Re; further preferably, two adjacent Re on different rings) together with the atoms to which they are attached form an optionally substituted 5-7 membered heterocyclyl (e.g., a 5-, 6-, or 7-membered heterocyclyl) containing 1-3 (e.g., 1, 2, or 3) heteroatoms independently selected from N, O, or S; optionally substituted refers to that a hydrogen atom on the substituted group is unsubstituted or that one or more substitutable positions of the substituted group are independently substituted with Re3.

R1 and R2 together with the atoms to which they are attached form a carbon ring independently selected from the group consisting of , wherein, the "~" end is the end connected to L5x, and the "~~" end is the end connected to L5y;

Rf is selected from :

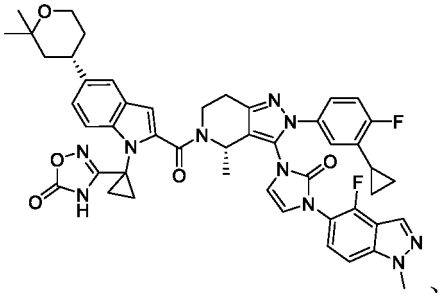
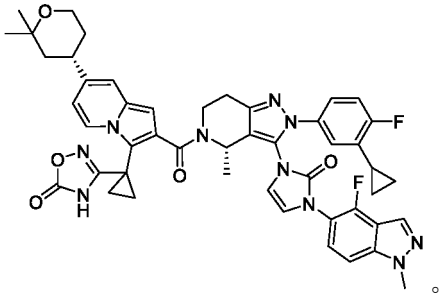
m is 2 or 3; q is 1, 2, or 3;

n, o, and p are each independently 0, 1, or 2;

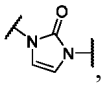
w is 0, 1, or 2;

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Re3 is as defined in claim 1;
provided that the following compounds are excluded:

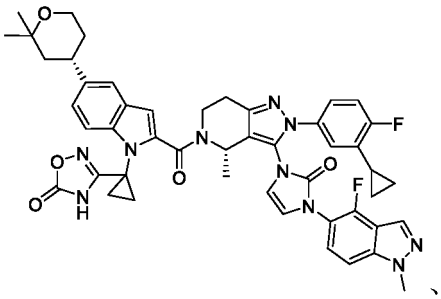
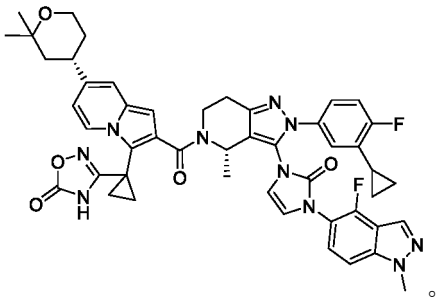
3. The compound according to claim 1 or 2, its stereoisomers, tautomers, or pharmaceutically acceptable salts, wherein:

Provided that, when L4 is , at least one (e.g., 1 or 2) of Ra or the substituents on ring E (or Re) is cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene or cyclopentyl-ethylene; alternatively, when neither Ra nor the substituents on ring E (or Re) is cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene or cyclopentyl-ethylene, two Re (preferably, two Re on different rings) together with the atoms to which they are attached form an optionally substituted 5-7 membered heterocyclyl, said heterocyclyl (preferably heterocycloalkyl) containing 1-3 (e.g., 1, 2 or 3) groups independently selected from N, O or S heteroatoms;

Optionally substituted refers to the hydrogen atoms on the substituted group are not replaced or one or more substitutable sites of the substituted group are independently replaced by Re3. Re3 is as defined for the compound of formula (I);

Preferably, the C3-5 cycloalkyl group is selected from cyclopropyl, cyclobutyl, and cyclopentyl; more preferably, cyclopropyl;

Provided that the following compounds are not included:

4. The compound according to any one of claims 1-3, its stereoisomers, tautomers, or pharmaceutically acceptable salts, wherein:

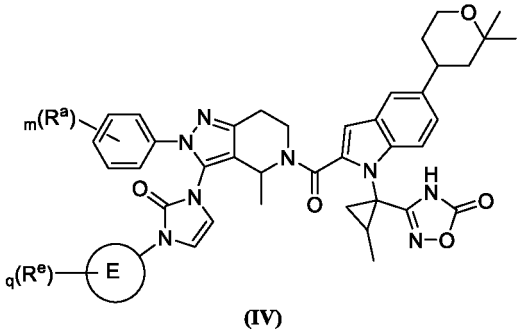
Provided that at least one (e.g., 1 or 2) of Ra or the substituents on ring E (or Re) is cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene or cyclopentyl-ethylene; alternatively, when neither Ra nor the substituents on ring E (or Re) are cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene or cyclopentyl-ethylene, two Re (preferably, two Re on different rings) together with the atoms to which they are attached form an optionally substituted 5-7 membered heterocyclyl, said heterocyclyl (preferably heterocycloalkyl) containing 1-3 (e.g., 1, 2 or 3) heteroatoms each independently selected from N, O or S;

Optionally substituted refers to hydrogen on the substituted group being unsubstituted or one or more substitutable sites of the substituted group are independently replaced by Re3. The Re3 is as defined in the compound of formula (I);

Preferably, the C3-5 cycloalkyl group is selected from cyclopropyl, cyclobutyl, and cyclopentyl; more preferably, cyclopropyl.

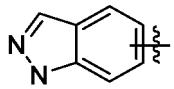
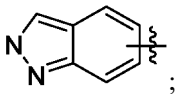
5. The compound according to any one of claims 1 to 4, its stereoisomers, tautomers, or pharmaceutically acceptable salts, wherein, the compound is represented by the following formula:

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(IV)

,

Ring E is selected from  and ;

Ra is independently selected each time from fluorine, methyl, and C3-5 cycloalkyl;

m is 2 or 3;

q is 2 or 3;

Re is independently selected each time from fluorine, or optionally substituted from the following groups: C1-3 alkyl (e.g., methyl, ethyl), C3-5 cycloalkyl; provided that at least one (e.g., one or two) of Ra or Re is cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl-methylene, cyclopropyl-ethylene, cyclobutyl-methylene, cyclobutyl-ethylene, cyclopentyl-methylene, or cyclopentyl-ethylene;

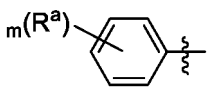
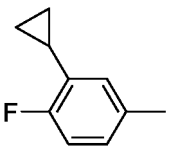
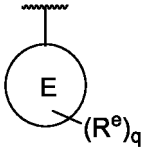
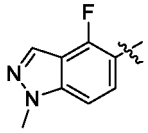
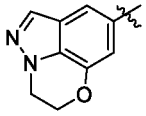
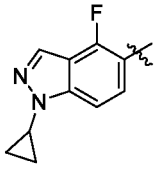
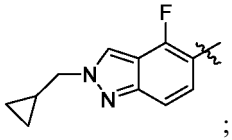
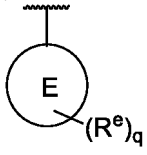
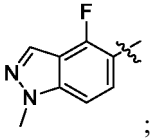
Alternatively, two Re (preferably, two adjacent Re; further preferably, two adjacent Re located on different rings) together with the atoms to which they are attached form an optionally substituted 5-7 membered heterocyclic group containing 1-3 (e.g., 1, 2 or 3) heteroatoms each independently selected from N, O or S;

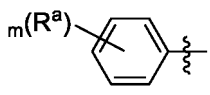
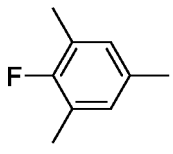
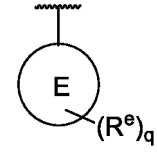
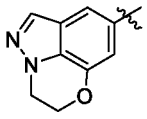
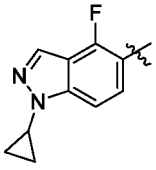
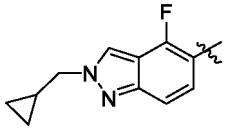
Optionally substituted refers to hydrogen on the substituted group being unsubstituted or one or more substitutable positions on the substituted group being independently substituted with Re3;

R3 is independently selected from deuterium, halogen (e.g., fluorine or chlorine), hydroxyl, amino, oxo, cyano, -R4, -ORe4, -S(O)2Re4, -C(O)Re4, -N(Re4)(Re5), -S(O)2N(Re4)(Re5), -N(Re4)S(O)2Re5, or -P(O)(Re4)Re5; R4 and R5 are independently selected from hydrogen or one or more (e.g., 2 or 3) optionally substituted with hydrogen, deuterium, halogen (e.g., fluorine or chlorine), hydroxyl, amino, cyano, oxo, or methoxy: C1-3 alkyl (e.g., methyl, ethyl, propyl) or C3-6 membered cycloalkyl (preferably 3-5 membered cycloalkyl, e.g., cyclopropyl, cyclobutyl, or cyclopentyl);

Preferably, the C3-5 cycloalkyl is selected from cyclopropyl, cyclobutyl, and cyclopentyl; more preferably cyclopropyl.

6. A compound according to any one of claims 1–5, or its stereoisomer, tautomer, or pharmaceutically acceptable salt, wherein,

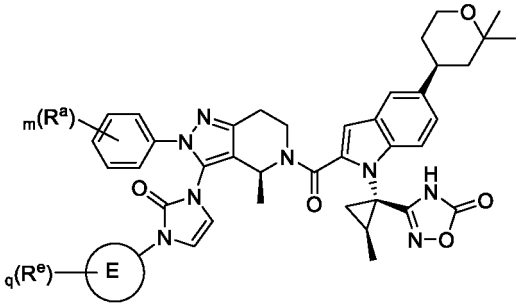
When  is ,  is 、、、 or ; preferably,  is ;

When  is ,  is 、、、 or .

7. A compound according to any one of claims 1–6, or its stereoisomer, tautomer, or pharmaceutically

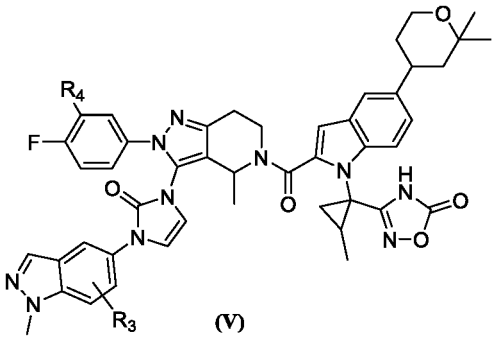
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acceptable salt, wherein, the compound is the compound shown in the formula below:

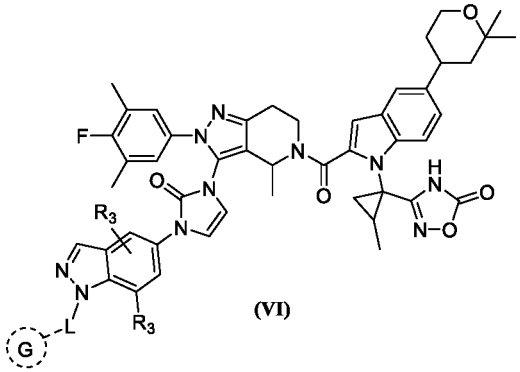


(IV-1)

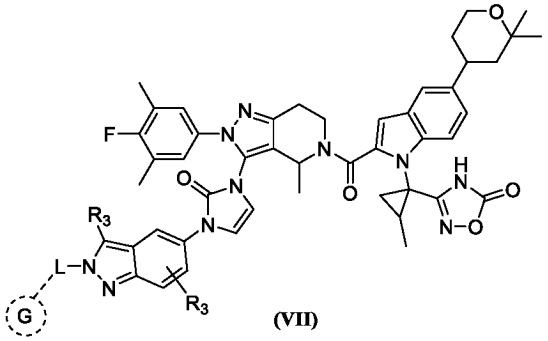
8. A compound according to any one of claims 1–7, or its stereoisomer, tautomer, or pharmaceutically acceptable salt, wherein, the compound is the compound shown in the formula below:



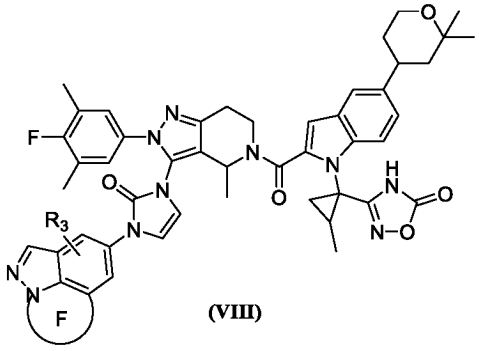
(V)



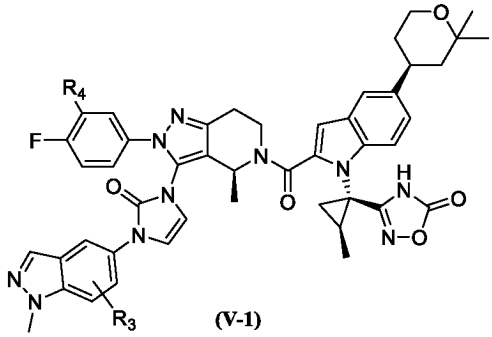
(VI)



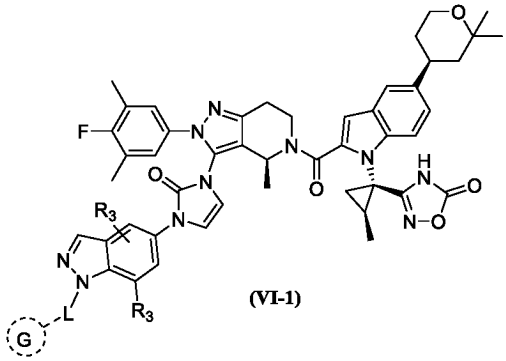
(VII)



(VIII)

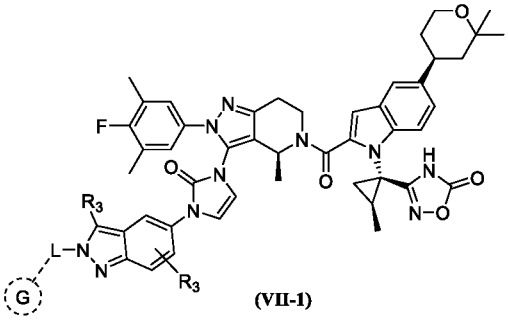


(V-1)

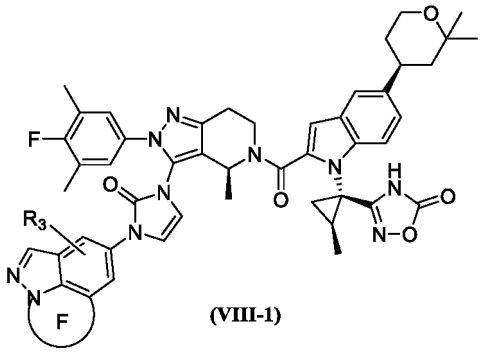


(VI-1)

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(VII-1)

or


(VIII-1)

, wherein, indicates the bond is present or absent;

G indicates ring G is present or absent; when ring G is present, ring G is a C3-5 cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl; preferably cyclopropyl);

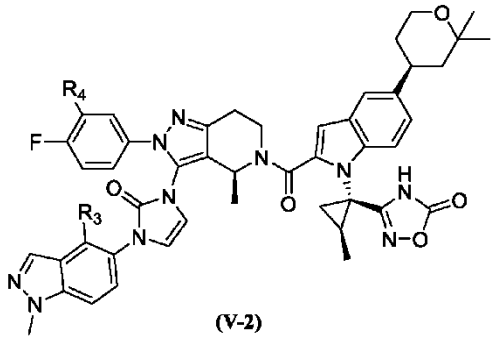
L is a bond, C1-3 alkylene (e.g., methylene, ethylene, propylene; preferably methylene), or C1-3 alkyl (e.g., methyl, ethyl, propyl; preferably methyl);

Alternatively, L and the adjacent R3 together form an optionally substituted 5-7 membered heterocyclic group, which contains 1–3 (e.g., 1, 2, or 3) heteroatoms each independently selected from N, O, or S, in which case ring G is absent; R3 is selected from H, F, or methyl; R4 is selected from C3-5 cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl; preferably cyclopropyl);

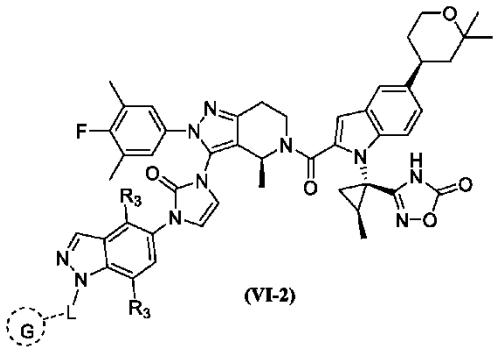
Ring F is an optionally substituted 5–7 membered heterocyclic group, containing 1–3 (e.g., 1, 2, or 3) heteroatoms each independently selected from N, O, or S;

Optionally substituted refers to the hydrogen on the substituted group being unsubstituted or one or more substitutable positions on the substituted group being independently substituted with Re3; Re3 is independently selected from deuterium, halogen (e.g., fluorine, chlorine), oxo group, hydroxyl, amino, cyano, -Re4, -ORe4, -SO2(Re4), -C(O)Re4, -N(Re4)(Re5), -SO2N(Re4)(Re5), -N(Re4)SO2(Re5), -P(O)(Re4)Re5; Re4 and Re5 are each independently selected from hydrogen or one or more (e.g., 2 or 3) substituents arbitrarily substituted with hydrogen, halogen (e.g., fluorine or chlorine), hydroxyl, amino, cyano, oxo, methoxy: C1-3 alkyl (e.g., methyl, ethyl, propyl) or C3-6 membered cycloalkyl (preferably 3–5 membered cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl).

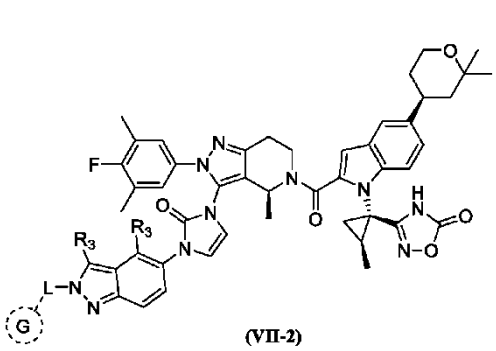
9. The compound, its stereoisomer, tautomer, or pharmaceutically acceptable salt according to any one of claims 1–8, wherein, the compound is a compound of the following formula:


(V-2)

,

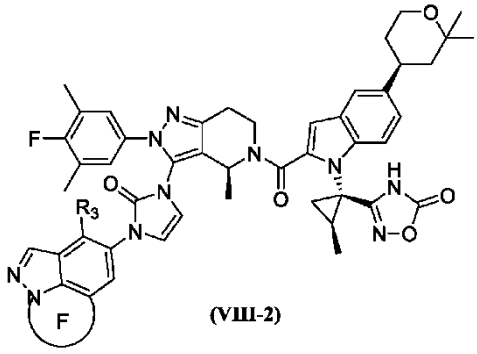

(VI-2)

,



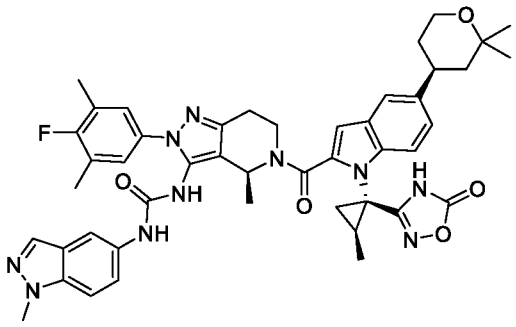
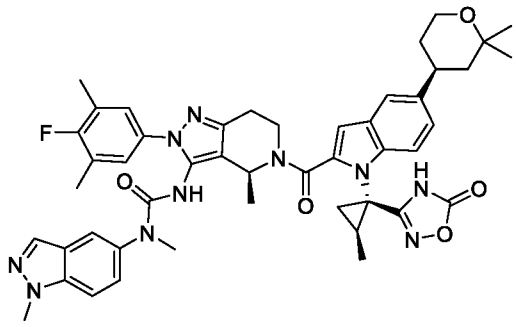
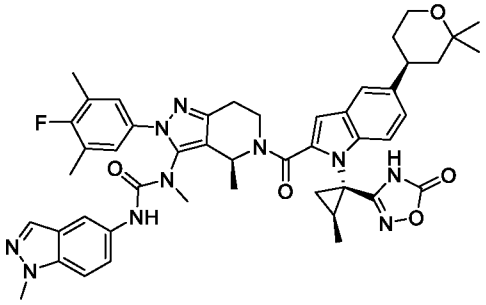
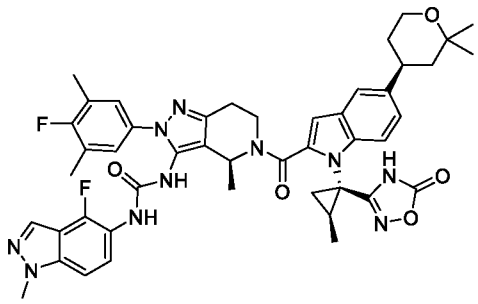
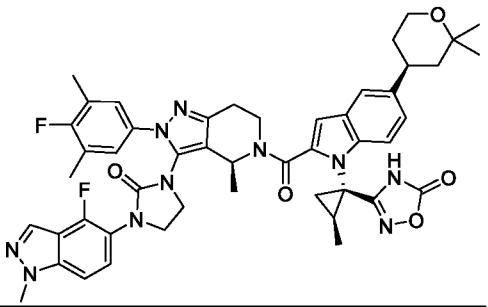
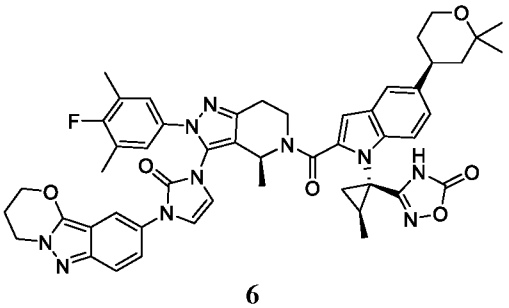
(VII-2)

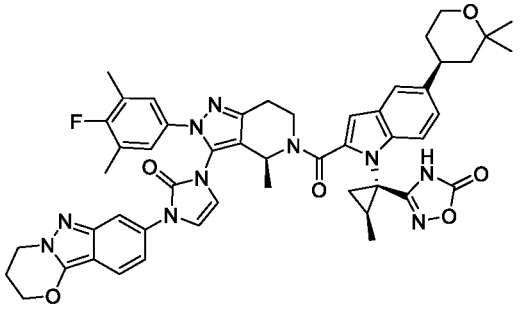
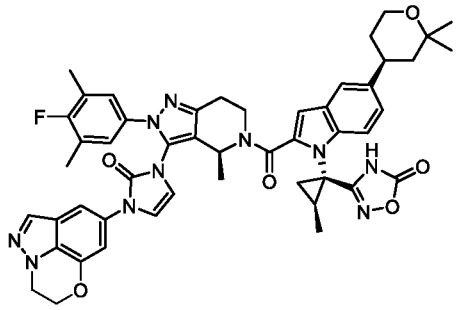
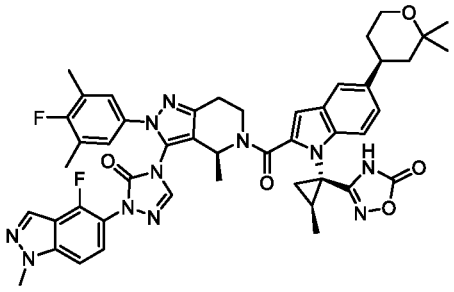
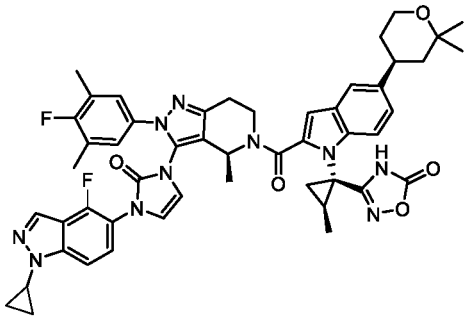
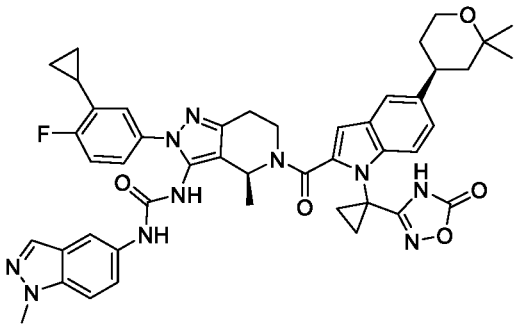
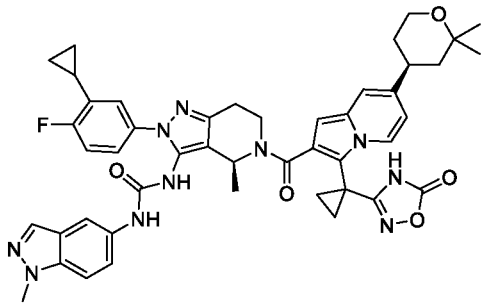
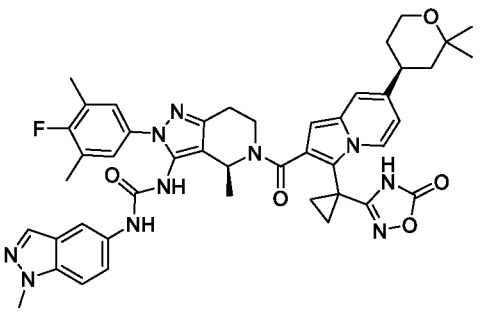
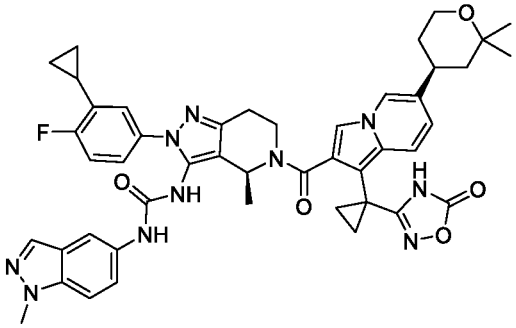
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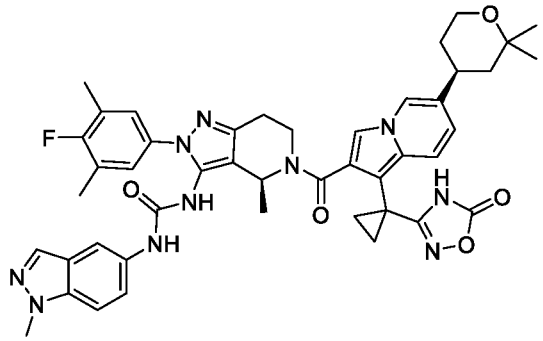
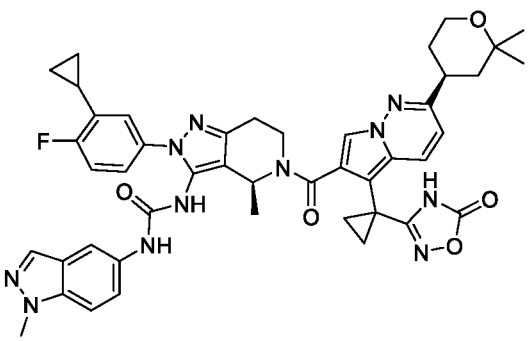
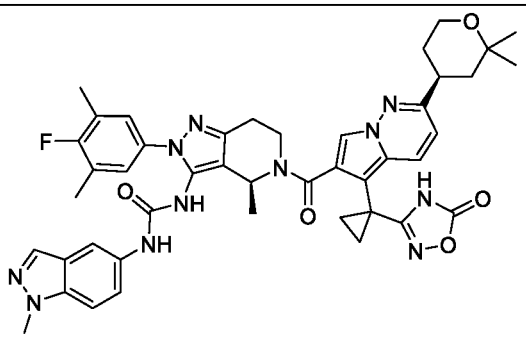
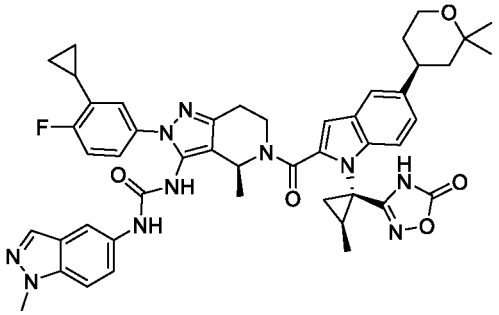
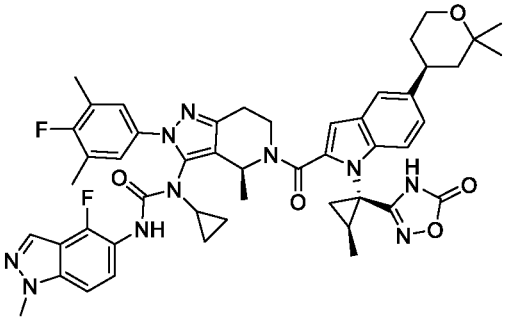
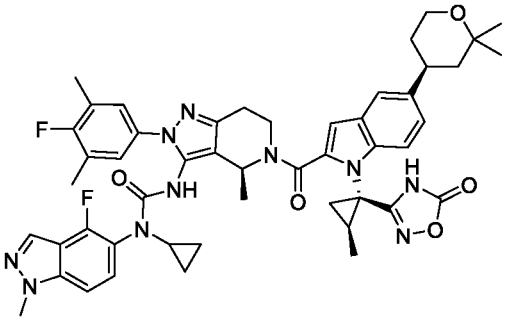
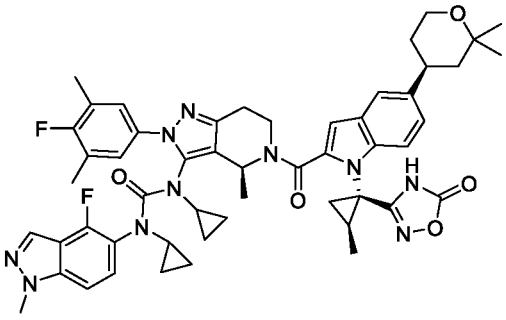
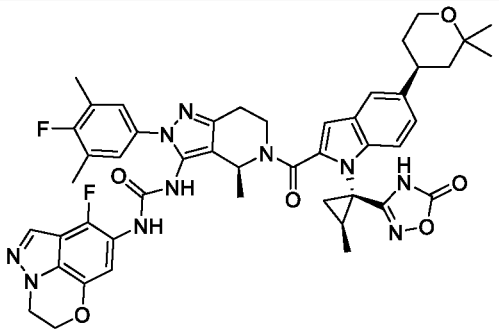
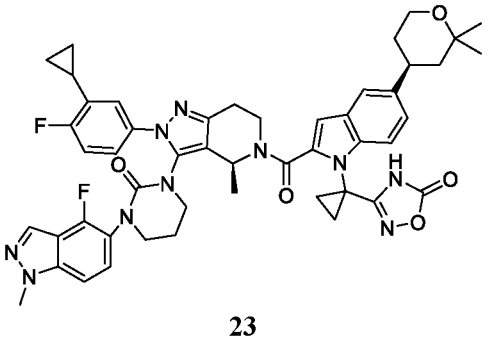
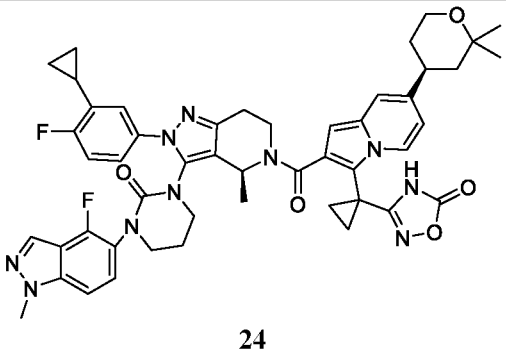


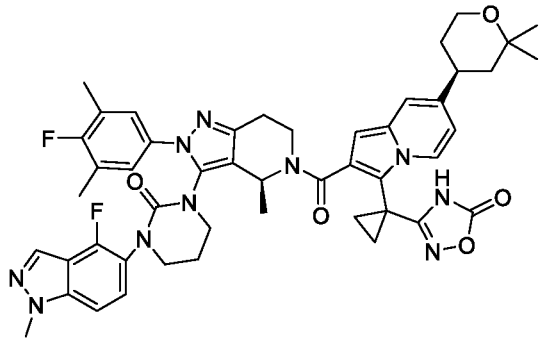
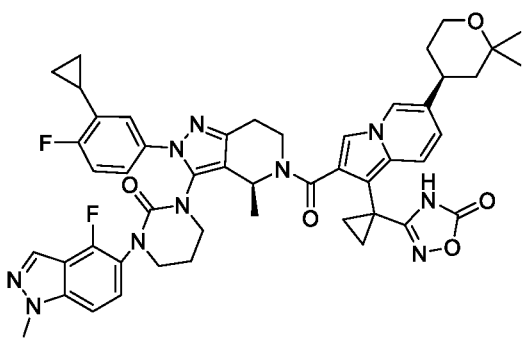
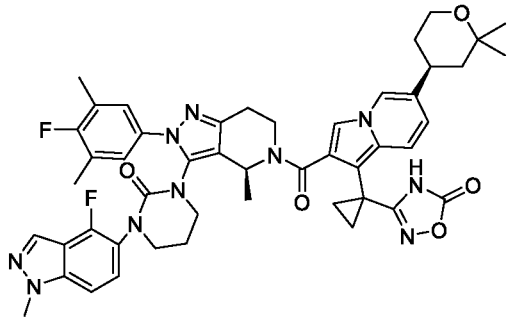
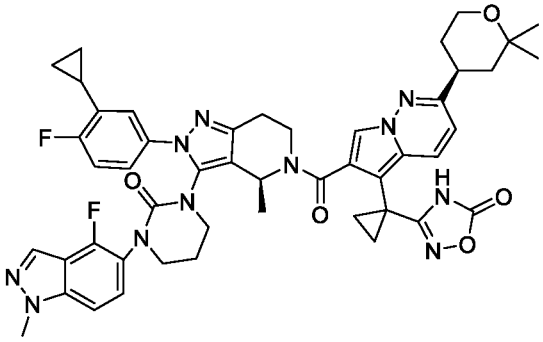
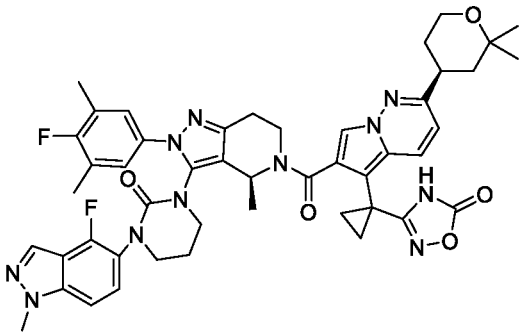
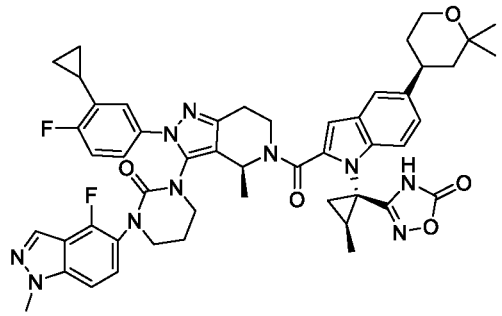
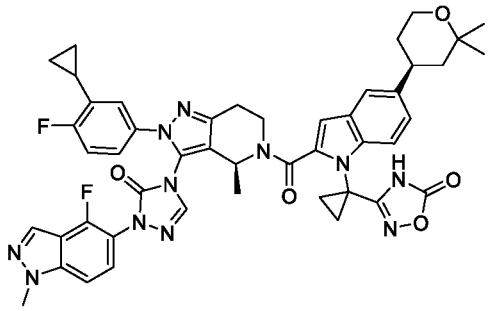
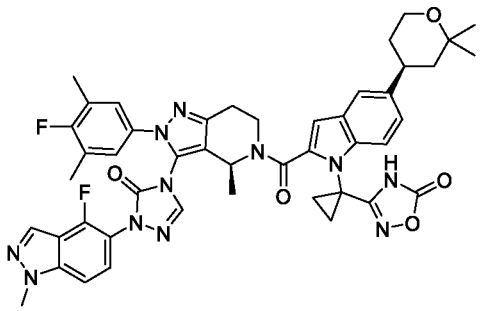
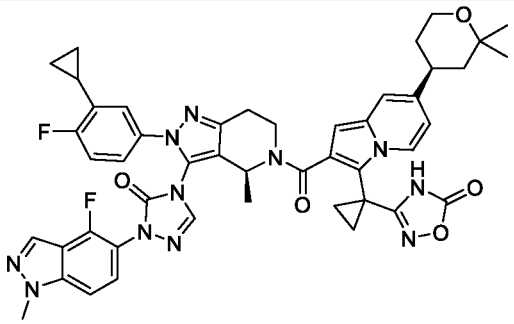
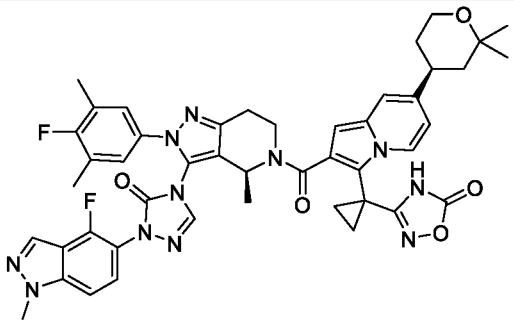
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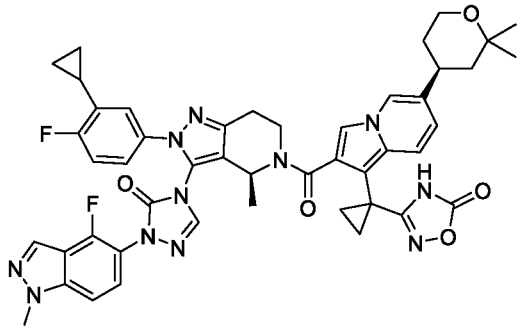
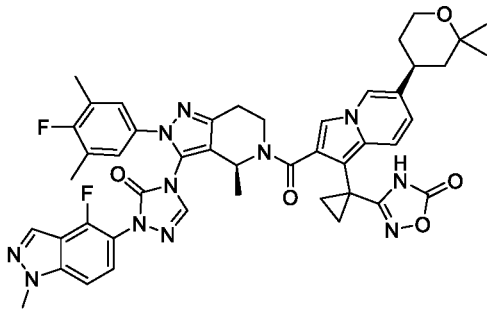
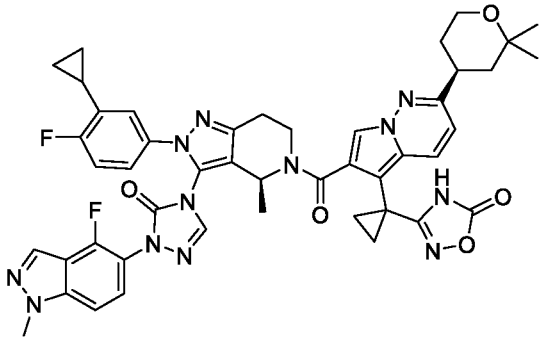
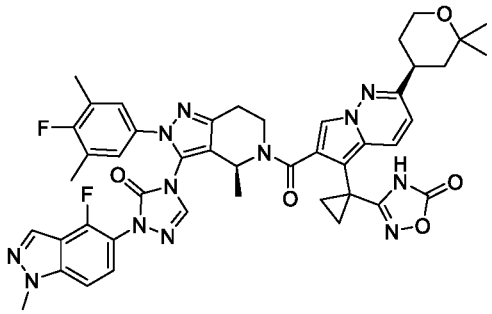
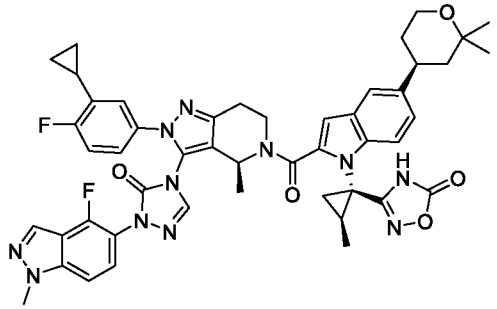
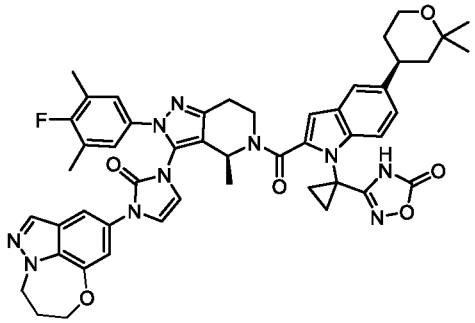
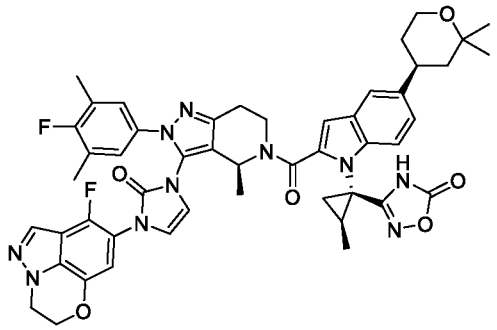
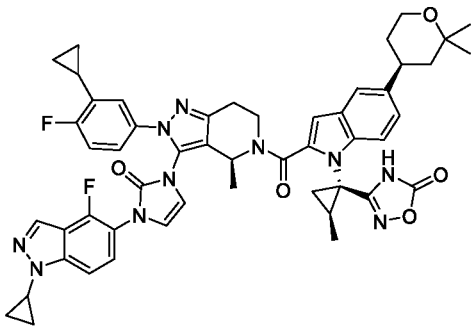
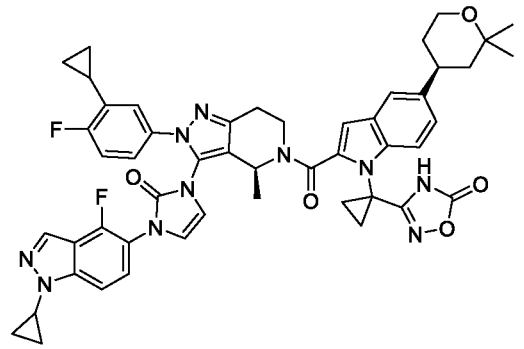
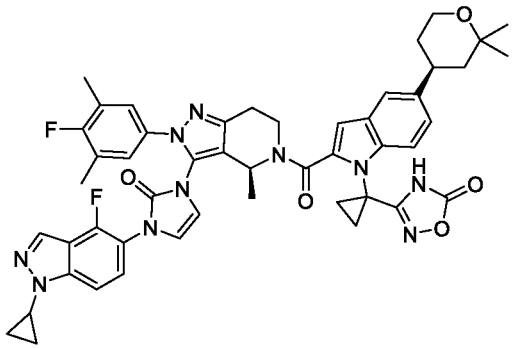
10. The following compounds, their stereoisomers, tautomers, or pharmaceutically acceptable salts, wherein, the compound is selected from:

Compound structure and number	Compound structure and number
 1	 2
 3	 4
	 6

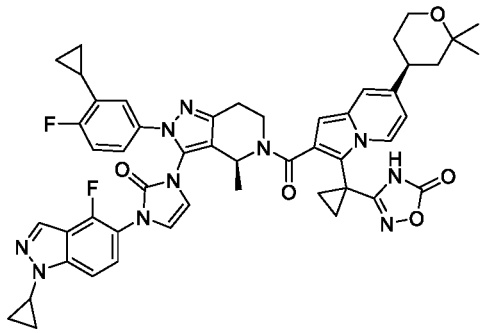
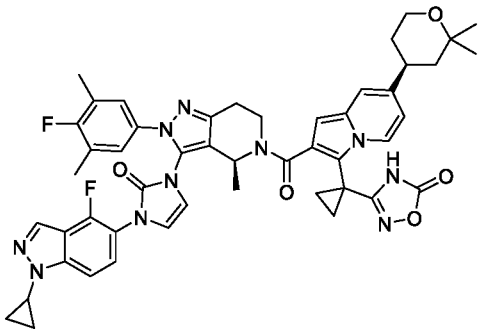
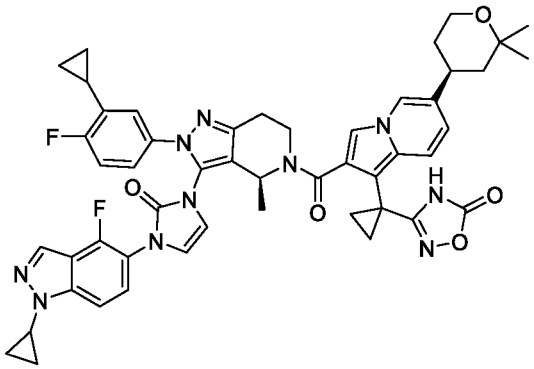
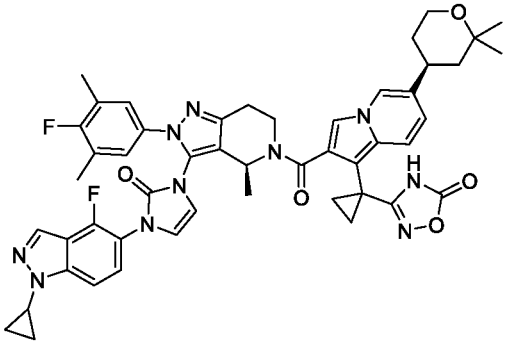
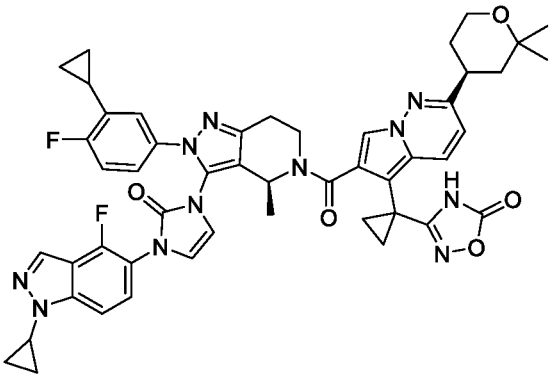
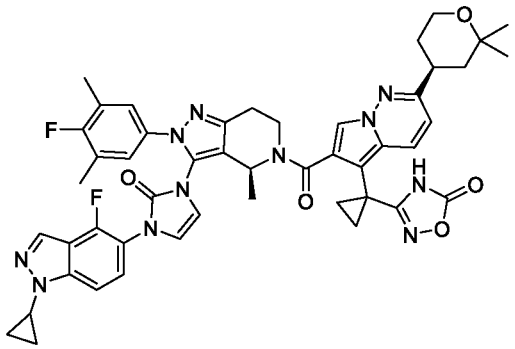
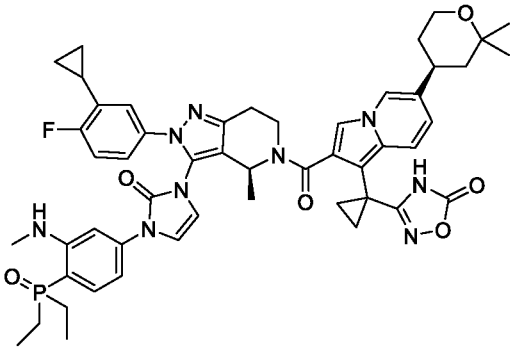
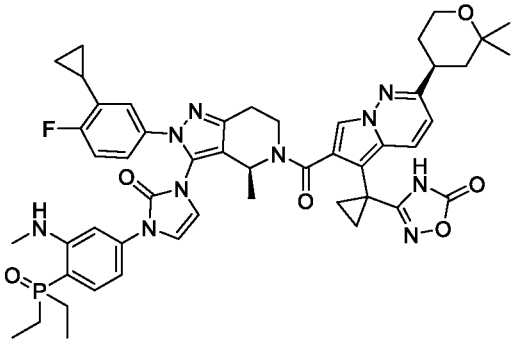
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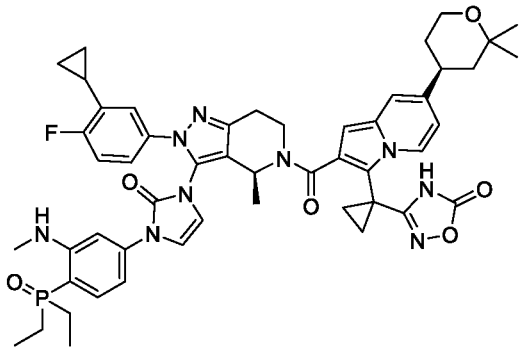
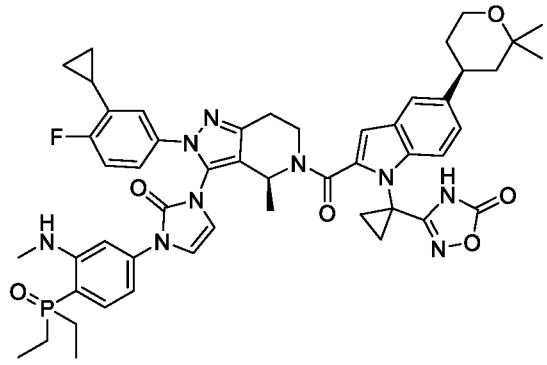
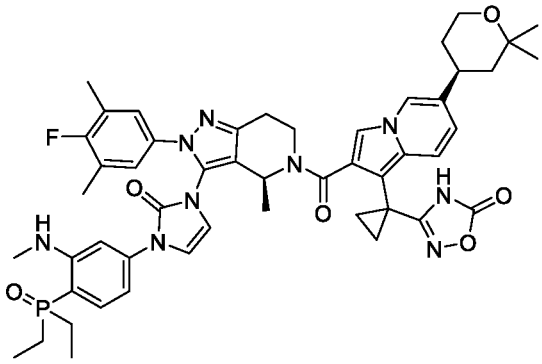
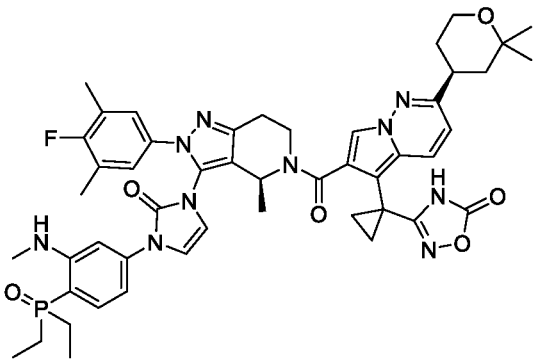
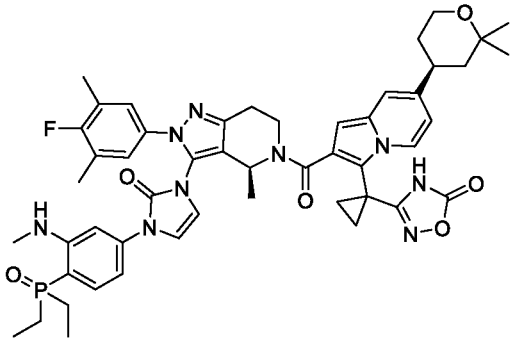
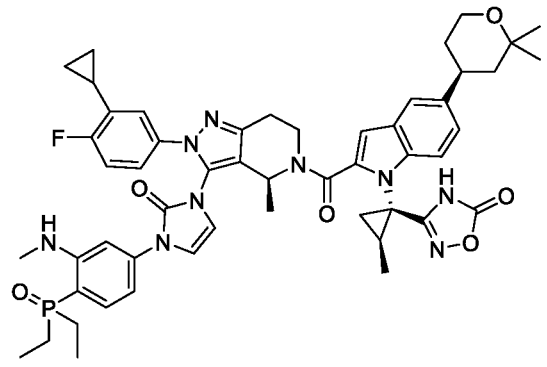
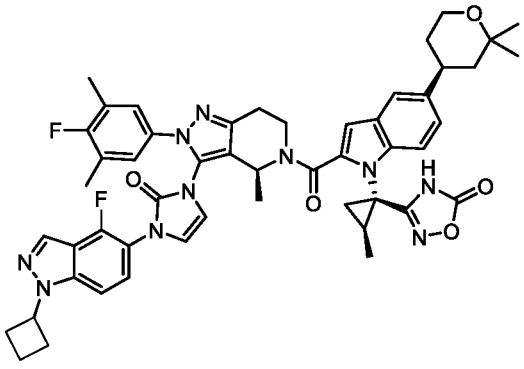
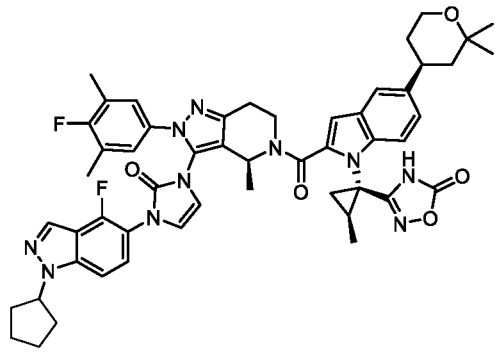
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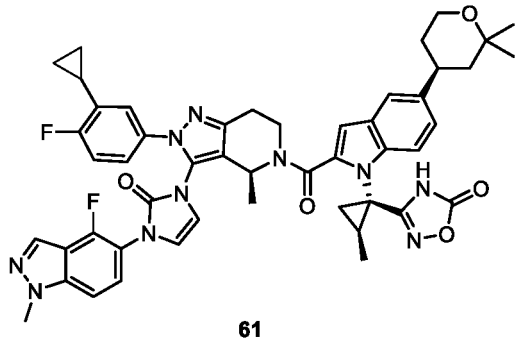
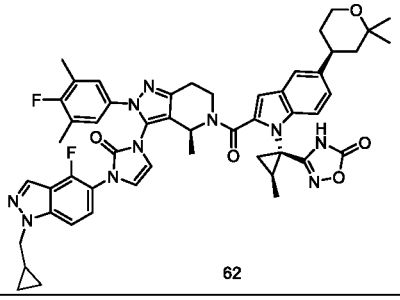
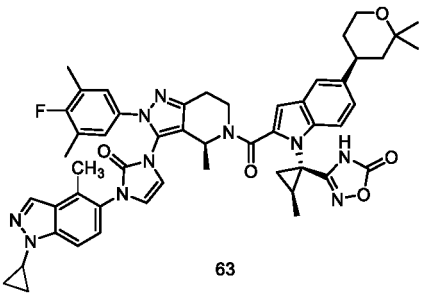
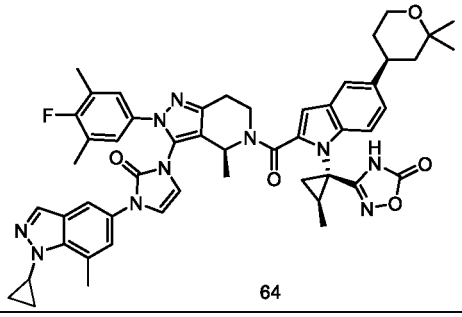
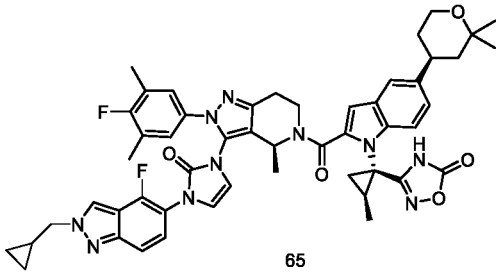
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11. A pharmaceutical composition comprising the compound, its stereoisomer, tautomer, or pharmaceutically acceptable salt according to any one of claims 1–10, optionally further comprising a pharmaceutically acceptable excipient.

12. The compound, its stereoisomer, tautomer, or pharmaceutically acceptable salt according to any one of claims 1–10, or the pharmaceutical composition according to claim 11, for use as a medication or in the manufacture of a medication.

13. The use according to claim 12, the medication is a GLP-1R agonist; more preferably, the medication is for treating and/or preventing GLP-1R-related disorders; more preferably, the medication is for treating and/or preventing GLP-1R-mediated disorders; more preferably, the medication is for treating and/or preventing disorders caused by or mediated by decreased GLP-1R activity; more preferably, the medication is for preventing and/or treating disorders mediated by GLP-1R agonism-induced cascade signaling; more preferably, the disorders include diabetes, overweight or obesity, nonalcoholic fatty liver disease, Alzheimer's disease, etc.; more preferably, the diabetes is type 2 diabetes.

14. The use according to claim 12, wherein, the medication is for treating and/or preventing diabetes, overweight or obesity, nonalcoholic fatty liver disease, or Alzheimer's disease; preferably, the medication is for treating and/or preventing diabetes, overweight or obesity; preferably, the diabetes is type 2 diabetes.

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Page 102 of 119

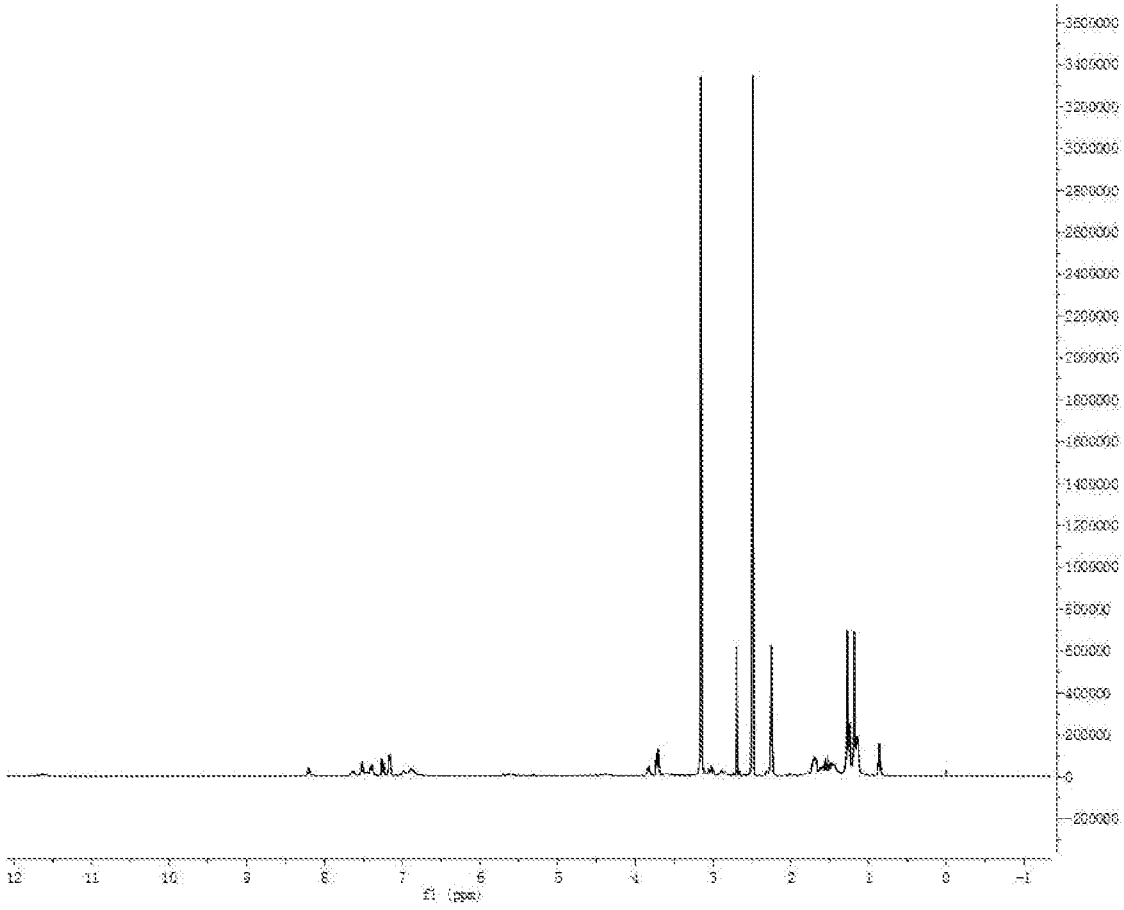


Figure 1

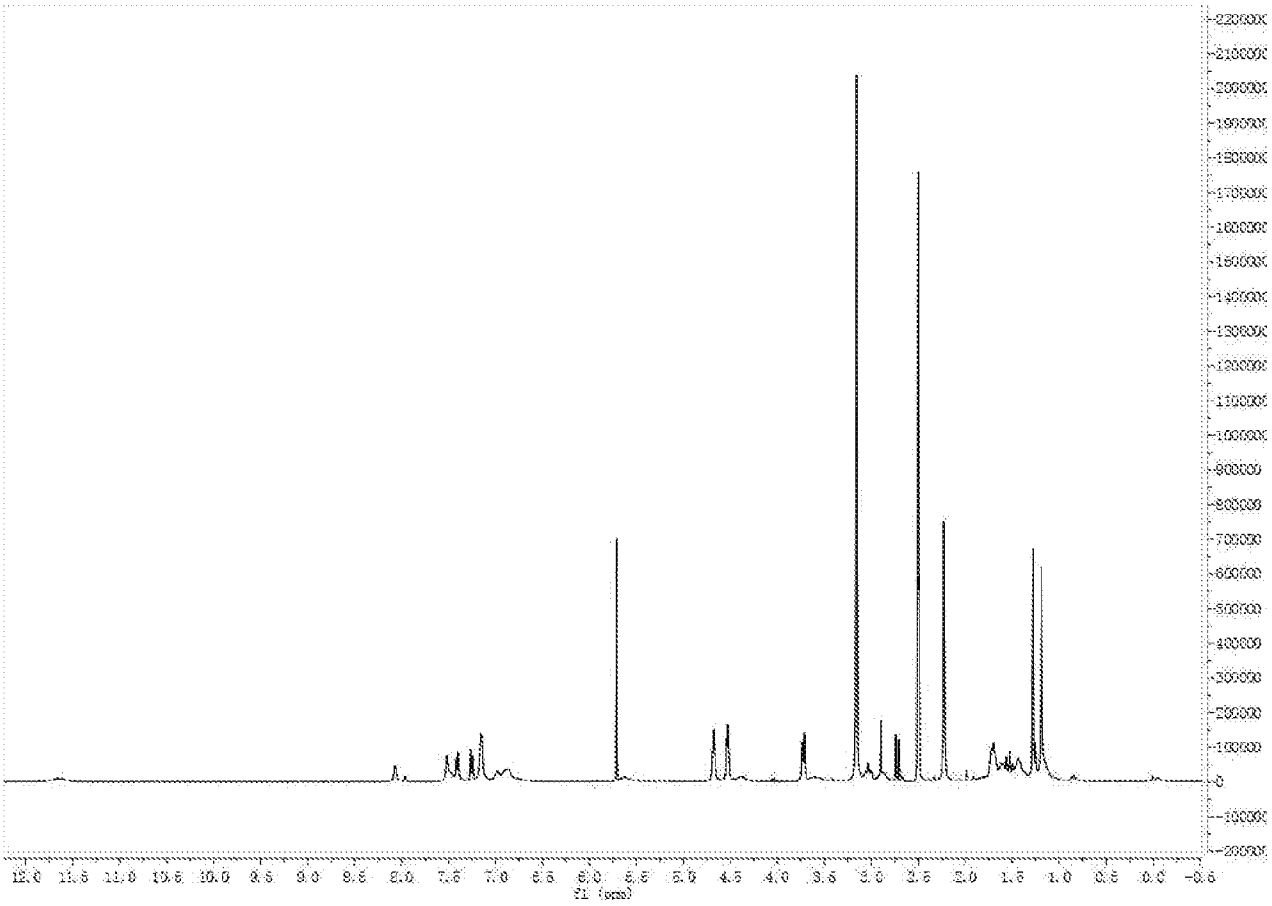


Figure 2

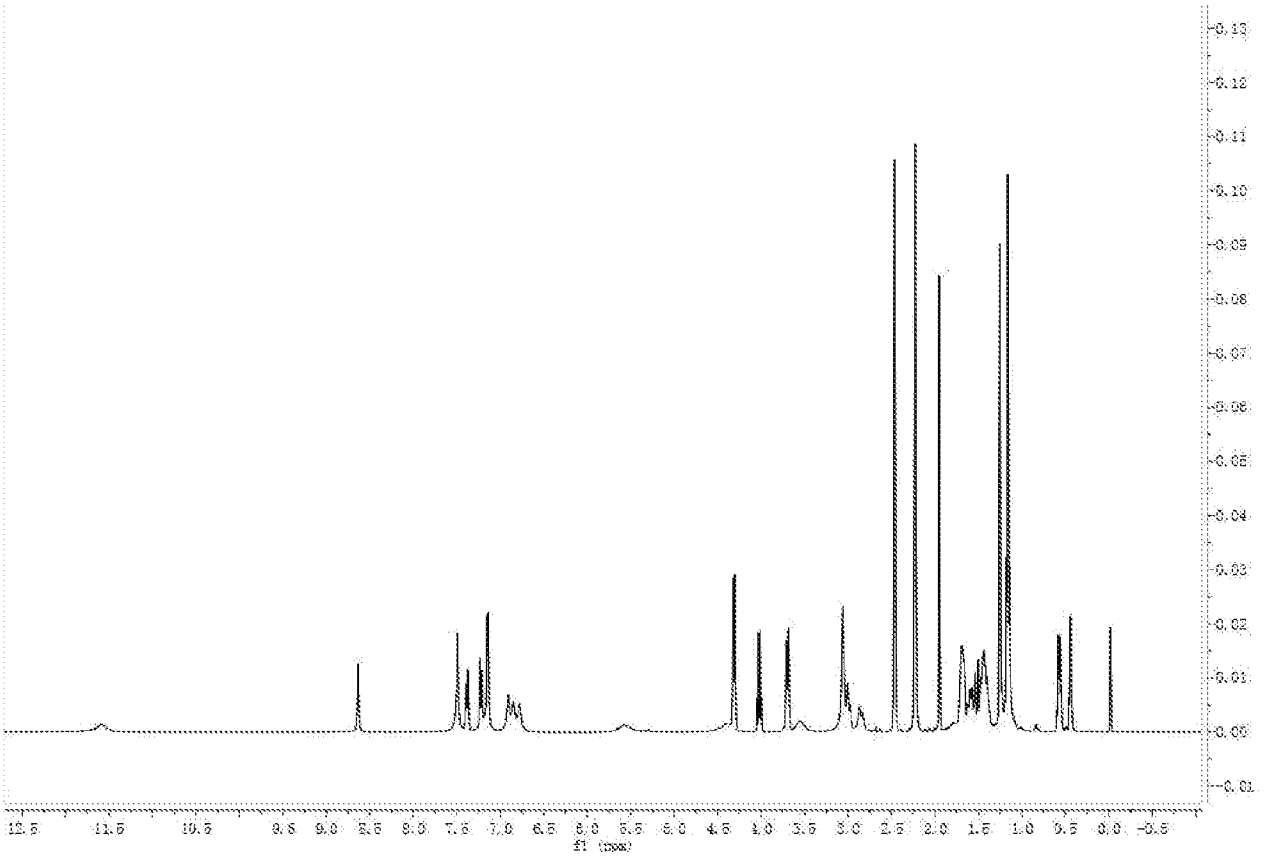


Figure 3

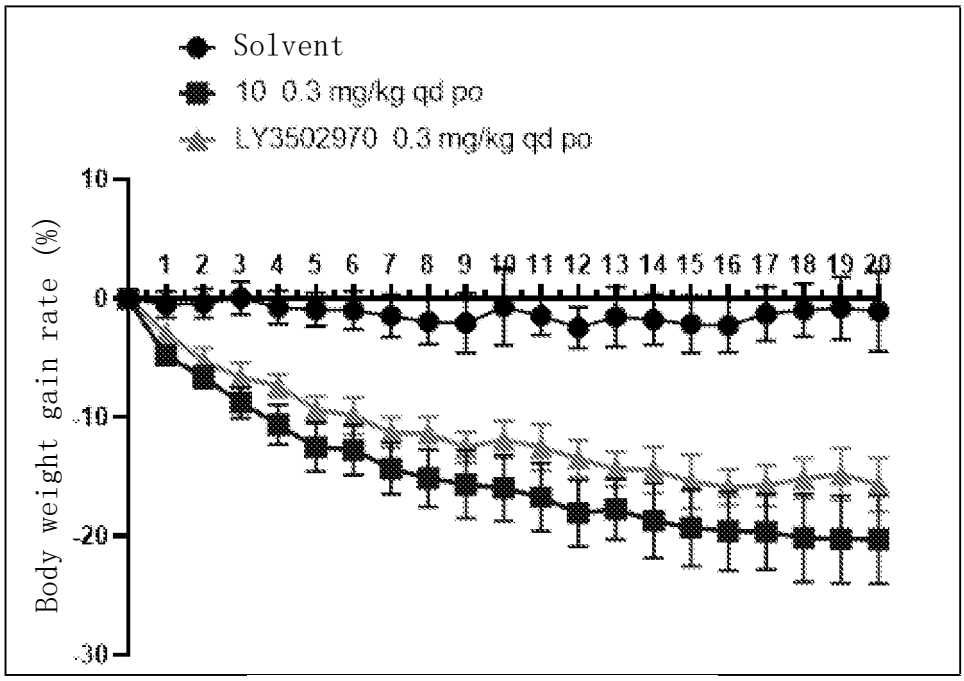


Figure 4

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Page 105 of 119

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/140920

A. CLASSIFICATION OF SUBJECT MATTER

C07D471/04(2006.01)i; C07D487/04(2006.01)i; C07D519/00(2006.01)i; A61K31/5377(2006.01)i; A61K31/437(2006.01)i; A61K31/444(2006.01)i; A61K31/4985(2006.01)i; A61P3/04(2006.01)i; A61P3/06(2006.01)i

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)

IPC:C07D471/-; C07D487/-; C07D519/-; A61K31/-; A61P3/-

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)

CNABS; CNTXT; VEN; WOTXT; USTXT; EPTXT; GBTXT; CATXT; CNKI; Wanfang; STN; GLP-1; GLP-1R; Diabetes; diabetes; Overweight or Obesity; overweight or obesity; Nonalcoholic Fatty Liver; nonalcoholic fatty 1w liver; Alzheimer; Alzheimer' s; CSPC Baike (Shandong) Biopharmaceutical Co., Ltd.; Wang Kuanglei; An Ran; Guo Jianqiao; Zhao Chuanwu; Song Yunlong; Wu Bin; Tian Jiahui; Chu Wenhao; Li Zizhen; Zhu Xingbo; structure of formula (I); structure of formula (IV); specific compound structure.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2025002250 A1 (WAYNE BIOTECHNOLOGY CO., LTD.) 02 January 2025 (2025-01-02) description, page 1, lines 28-30, page 10, line 17, first compound, and page 20, lines 5-16	1-14
E	WO 2025026270 A1 (SHANGHAI HANSOH BIOMEDICAL CO., LTD. et al.) 06 February 2025 (2025-02-06) claim 7, line 1, fifth compound, and claims 15-17	1-14
X	CN 109790161 A (CHUGAI PHARMACEUTICAL CO., LTD.) 21 May 2019 (2019-05-21) description, paragraphs [0022]-[0051] and [0075]-[0079], and paragraph [0995], compound 67	1-14
A	CN 116003403 A (YAOKANG ZHONGTUO (BEIJING) PHARMACEUTICAL TECHNOLOGY CO., LTD.) 25 April 2023 (2023-04-25) claims 1-8	1-14
A	CN 116390926 A (ECCOGENE (SHANGHAI) CO., LTD.) 04 July 2023 (2023-07-04) claims 1-62	1-14

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2025	**14 March 2025**

Name and mailing address of the ISA/CN	Authorized officer
China National Intellectual Property Administration (ISA/CN) **China No. 6, Xitucheng Road, Jimenqiao, Haidian District, Beijing 100088**	Telephone No.

Form PCT/ISA/210 (second sheet) (July 2022)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 4262873 A1 (THE CHINESE UNIVERSITY OF HONG KONG) 25 October 2023 (2023-10-25) claims 1-10	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/140920

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **12 (in part)-14 (in part)**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 12 (in part)-14 (in part) relate to the medicinal use of the compound and a stereoisomer, tautomer or pharmaceutically acceptable salt and pharmaceutical composition thereof. The designation of the subject matter thereof relates to a method for treatment of the human or animal body, which falls within the cases set out in PCT Rule 39.1(iv) for which a search is not required.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/140920

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2025002250	A1	02 January 2025	None			
WO	2025026270	A1	06 February 2025	None			
CN	109790161	A	21 May 2019	IL	287166	A	01 December 2021
				PE	20190709	A1	17 May 2019
				TW	201827426	A	01 August 2018
				TWI	753946	B	01 February 2022
				MX	2019003488	A	16 December 2019
				CR	20190149	A	27 August 2019
				UA	125586	C2	27 April 2022
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				DK	3517538	T3	25 March 2024
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				AU	2017330733	B2	28 May 2020
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				WO	2018056453	A1	29 March 2018
				US	2019225604	A1	25 July 2019
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				US	12187724	B2	07 January 2025
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				US	11814381	B2	14 November 2023
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				EA	037989	B1	21 June 2021
				NZ	751725	A	26 March 2021
				PT	3517538	T	09 April 2024
				AU	2022205222	A1	04 August 2022
				AU	2022205222	B2	04 April 2024
				RS	65398	B1	30 April 2024
				KR	20190039591	A	12 April 2019
				KR	102223227	B1	08 March 2021
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				JPWO	2018056453	A1	11 July 2019
				JP	6567778	B2	28 August 2019
				US	2024246971	A1	25 July 2024

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/140920

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
				EP	4134367	A1	15 February 2023
				CL	2019000663	A1	26 July 2019
				JOP	20190060	A1	26 March 2019
				US	2025002494	A1	02 January 2025
				ECSP	19020228	A	30 June 2019
				EA	202190802	A2	30 July 2021
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				WO	2022017338	A1	27 January 2022
				CO	2023001407	A2	16 February 2023
				AU	2021311567	A1	16 February 2023
				CA	3186217	A1	27 January 2022
				JP	2025004124	A	14 January 2025
				MX	2023000943	A	22 February 2023
				US	2023051320	A1	16 February 2023
				US	12037339	B2	16 July 2024
				PE	20230854	A1	29 May 2023
				KR	20230048056	A	10 April 2023
				CL	2023000196	A1	15 September 2023
				PH	12023550130	A1	24 June 2024
				US	11584751	B1	21 February 2023
EP	4262873	A1	25 October 2023	US	2024050531	A1	15 February 2024
				WO	2022127868	A1	23 June 2022
				AU	2021399517	A1	06 July 2023
				AU	2021399517	A9	20 June 2024

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/140920

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
		JP	2024500410	A	09 January 2024
		EP	4262873	A4	11 December 2024

Form PCT/ISA/210 (patent family annex) (July 2022)

International Search Report

International Application No.
PCT/CN2024/140920

A. Subject classification

C07D471/04(2006.01)i; C07D487/04(2006.01)i; C07D519/00(2006.01)i; A61K31/5377(2006.01)i; A61K31/437(2006.01)i; A61K31/444(2006.01)i; A61K31/4985(2006.01)i; A61P3/04(2006.01)i; A61P3/06(2006.01)i

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

B. Search field

Minimum documentation searched (classification system and codes indicated)

IPC: C07D471/-; C07D487/-; C07D519/-; A61K31/-; A61P3/-

Documents searched beyond the minimum documentation included in the search field

Electronic databases consulted during international search (name of database and search terms used, if any)

CNABS; CNTXT; VEN; WOTXT; USTXT; EPTXT; GBTXT; CATXT; CNKI; Wanfang; STN; GLP-1; GLP-1R; Diabetes; Diabetes; Overweight or Obesity; Overweight; Obesity; Nonalcoholic Fatty Liver; Nonalcoholic Fatty Liver; Alzheimer's; Alzheimer; CSPC Baike (Shandong) Biopharmaceutical Co., Ltd.; Wang Kuanglei; An Ran; Guo Jianqiao; Zhao Chuanwu; Song Yunlong; Wu Bin; Tian Jiahui; Chu Wenhao; Li Zizhen; Zhu Xingbo; Structure of formula (I); Structure of formula (IV); Specific compound structure.

C. Relevant documents

Type*	Cited document, specify relevant paragraphs if necessary	Relevant claims
E	WO 2025002250 A1 (WAYNE BIOTECHNOLOGY CO., LTD.) January 2, 2025 (2025 - 01 - 02) Specification page 1, lines 28–30; page 10, line 17, compound 1; page 20, lines 5–16	1-14
E	WO 2025026270 A1 (SHANGHAI HANSOH BIOMEDICAL CO., LTD. et al.) February 6, 2025 (2025 - 02 - 06) Claim 7, compound 5 on line 1; and claims 15–17	1-14
X	CN 109790161 A (CHUGAI PHARMACEUTICAL CO., LTD.) May 21, 2019 (2019 - 05 - 21) Specification [0022]–[0051], [0075]–[0079], and paragraph [0995], compound 67	1-14
A	CN 116003403 A (YAKANG ZHONGTUO (BEIJING) PHARMACEUTICAL TECHNOLOGY CO., LTD.) April 25, 2023 (2023 - 04 - 25) Claims 1–8	1-14
A	CN 116390926 A (SHANGHAI CHENGYI BIOTECHNOLOGY CO., LTD.) July 4, 2023 (2023 - 07 - 04) Claims 1–62	1-14

☑ The remaining documents are listed on the continuation of Column C.

☑ See the family patent attachment.

* Specific types of cited documents:

"A" Document reflecting the general state of the art, not particularly relevant

"D" Document cited by the applicant in the international application

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

"L" Document possibly casting doubt on the priority claim, or cited to determine the publication date of another document, or cited for other special reasons (as specifically described)

"O" Document relating to oral disclosure, use, exhibition, or other means of disclosure

"P" Document published before the international filing date but after the priority date

"T" Later document not conflicting with the application, but relevant for understanding the theory or principle of the invention

"X" Particularly relevant document, alone renders the claimed invention not novel or lacking inventive step

"Y" Particularly relevant document, in combination with one or more similar documents, renders the claimed invention obvious to a person skilled in the art

"&" Document from the same patent family

Date international search was actually completed	Date of mailing of the international search report
March 14, 2025	March 14, 2025

Name and mailing address of ISA/CN	Authorized Officer
China National Intellectual Property Administration No. 6 Xitucheng Road, Jimenqiao West, Haidian District, Beijing, China 100088	Huang Dazhi Telephone (+86) 028-62968525

C. Relevant documents

Type*	Cited document, specify relevant paragraphs if necessary	Relevant claims
A	EP 4262873 A1 (UNIV HONG KONG CHINESE) October 25, 2023 (2023 - 10 - 25) Claims 1–10	1-14

Section II Certain claims are considered unsearchable (continued from item 2 on page 1)

The reasons why certain claims were not searched under Article 17(2)(a) are as follows:

1. ☑ Claims: 12 (in part)–14 (in part)
Because they relate to subject matter on which this authority is not required to carry out a search, namely:

Claims 12 (in part)–14 (in part) relate to the use of the compound, its stereoisomers, tautomers, or pharmaceutically acceptable salts and pharmaceutical compositions thereof as a medicine, which constitutes a method of treatment of the human or animal body, falling under Rule 39.1(iv) of the PCT Regulations and hence not required to be searched.

2. ☐ Claims:
Because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims:
Because they are dependent claims, and have not been drafted in accordance with the requirements of Rules 6.4(a) second and third sentences.

International Search Report
Information on Family Patents

International Application Number
PCT/CN2024/140920

Patent Documents Cited in Search Report			Publication Date (Year/Month/Day)	Family Patents			Publication Date (Year/Month/Day)
WO	2025002250	A1	January 2, 2025	None			
WO	2025026270	A1	February 6, 2025	None			
CN	109790161	A	May 21, 2019	IL	287166	A	December 1, 2021
				PE	20190709	A1	May 17, 2019
				TW	201827426	A	August 1, 2018
				TWI	753946	B	February 1, 2022
				MX	2019003488	A	December 16, 2019
				CR	20190149	A	August 27, 2019
				UA	125586	C2	April 27, 2022
				PL	3517538	T3	June 10, 2024
				DK	3517538	T3	March 25, 2024
				BR	112019005322	A2	July 2, 2019
				EP	3517538	A1	July 31, 2019
				EP	3517538	A4	June 10, 2020
				EP	3517538	B1	March 13, 2024
				HRP	20240499	T1	July 5, 2024
				SG	11201901565	VA	March 28, 2019
				CO	2019002595	A2	March 29, 2019
				AU	2017330733	A1	March 14, 2019
				AU	2017330733	B2	May 28, 2020
				TN	2019000054	A1	July 15, 2020
				MX	2022004071	A	May 3, 2022
				WO	2018056453	A1	March 29, 2018
				US	2019225604	A1	July 25, 2019
				US	10858356	B2	December 8, 2020
				HUE	066583	T2	August 28, 2024
				IL	264945	A	May 30, 2019
				IL	264945	B	October 31, 2021
				FI	3517538	T3	May 20, 2024
				US	2023382912	A1	November 30, 2023
				US	12187724	B2	January 7, 2025
				US	2021017176	A1	January 21, 2021
				US	11814381	B2	November 14, 2023
				EA	201990518	A1	December 30, 2019
				EA	037989	B1	June 21, 2021
				NZ	751725	A	March 26, 2021
				PT	3517538	T	April 9, 2024
				AU	2022205222	A1	August 4, 2022
				AU	2022205222	B2	April 4, 2024
				RS	65398	B1	April 30, 2024
				KR	20190039591	A	April 12, 2019
				KR	102223227	B1	March 8, 2021
				JP	2023100963	A	July 19, 2023
				JP	7602573	B2	December 18, 2024
				AU	2024201884	A1	April 11, 2024
				MY	199663	A	November 15, 2023
				SA	519401409	B1	April 7, 2022
				JPWO	2018056453	A1	July 11, 2019
				JP	6567778	B2	August 28, 2019
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International Search Report
Information on Family Patents

International Application Number
PCT/CN2024/140920

Patent Documents Cited in Search Report			Publication Date (Year/Month/Day)	Family Patents			Publication Date (Year/Month/Day)
				EP	4134367	A1	February 15, 2023
				CL	2019000663	A1	July 26, 2019
				JOP	20190060	A1	March 26, 2019
				US	2025002494	A1	January 2, 2025
				ECSP	19020228	A	June 30, 2019
				EA	202190802	A2	July 30, 2021
				EA	202190802	A3	October 29, 2021
				EP	4349840	A2	April 10, 2024
				EP	4349840	A3	July 10, 2024
				ES	2987676	T3	November 15, 2024
				MD	3517538	T2	September 30, 2024
				AU	2020223687	A1	September 10, 2020
				AU	2020223687	B2	April 14, 2022
				CA	3038479	A1	March 29, 2018
				CA	3038479	C	June 22, 2021
				JP	2019203015	A	November 28, 2019
				JP	6957564	B2	November 2, 2021
				DOP	2019000074	A	May 31, 2019
				LT	3517538	T	May 10, 2024
				SI	3517538	T1	May 31, 2024
				MA	46286	A	July 31, 2019
				JP	2022003087	A	January 11, 2022
				JP	7280929	B2	May 24, 2023
				US	2024262824	A1	August 8, 2024
				PH	12019500659	A1	December 16, 2019
				ZA	201901070	B	June 30, 2021
CN	116003403	A	April 25, 2023	None			
CN	116390926	A	July 4, 2023	US	2025059192	A1	February 20, 2025
				BR	112023000932	A2	October 3, 2023
				EP	4182020	A1	May 24, 2023
				IL	299704	A	March 1, 2023
				JP	2023534983	A	August 15, 2023
				JP	7569443	B2	October 17, 2024
				WO	2022017338	A1	January 27, 2022
				CO	2023001407	A2	February 16, 2023
				AU	2021311567	A1	February 16, 2023
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				JP	2025004124	A	January 14, 2025
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				PH	12023550130	A1	June 24, 2024
				US	11584751	B1	February 21, 2023
EP	4262873	A1	October 25, 2023	US	2024050531	A1	February 15, 2024
				WO	2022127868	A1	June 23, 2022
				AU	2021399517	A1	July 6, 2023
				AU	2021399517	A9	June 20, 2024

International Search Report
Information on Family Patents

International Application Number
PCT/CN2024/140920

Patent Documents Cited in Search Report	Publication Date (Year/Month/Day)	Family Patents			Publication Date (Year/Month/Day)
		JP	2024500410	A	January 9, 2024
		EP	4262873	A4	December 11, 2024

PCT/ISA/210 Form (Family Patents Attachment) (July 2022)

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CERTIFICATION

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- WO2025131043A1

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Jacqueline Yorke, Project Manager

Sworn to before me this
Monday, September 08, 2025

Signature, Notary Public

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Notary Public - State of New York
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Qualified in Queens County
My Commission Expires February 02, 2027

Stamp, Notary Public