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Certificate

The annex to this certificate is a copy of the following patent application document submitted to the Office.

Application number: 202311371725.7

Application type: Patent of Invention

Title of the invention: GLP-1R AGONIST AND USE THEREOF

Application date: October 23, 2023

Applicant: Ascletis Bioscience Co., Ltd, Hangzhou

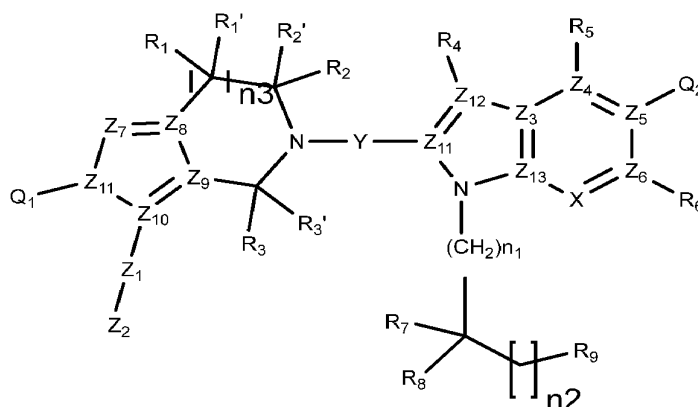
Inventor or designer: Liang Bin, Yang Bailing, Wu Jinzi

Director
Shen Changyu

October 26, 2023

Claims

1. A GLP-1R agonist or modulator compound having a structure of formula (I) and a stereoisomer, a pharmaceutically acceptable salt or a deuterated compound thereof:



formula I

wherein

X is selected from N or -CR^a; R^a is selected from a hydrogen atom, halogen and C₁₋₆ alkyl;

Y is selected from -C(=O)-;

Z₃, Z₄, Z₅, Z₆, Z₇, Z₈, Z₉, Z₁₀, Z₁₁, Z₁₂, and Z₁₃ are selected from N or C;

Q₁ is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl or 5- to 10-membered heteroaryl are optionally substituted with one to five substituents independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and C₁₋₆ alkoxy;

Q₂ is 3- to 12-membered heterocyclyl, a bridged ring, a spiro ring or 5- to 10-membered heteroaryl, wherein the 3- to 12-membered heterocyclyl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 substituents independently selected from a halogen atom, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy and -NR^{Qa}R^{Qb}, and two C₁₋₆ alkyl together with the carbon atom connected thereto form a C₃₋₈ carbocyclic ring; and R^{Qa} and R^{Qb} are independently selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and (C₁₋₆ alkyl)carbonyl;

R₁, R₂, R₃, R₁', R₂' and R₃' are each independently selected from hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cycloalkyl or heterocycloalkyl;

wherein the C₁₋₆ alkyl, cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from a halogen atom, C₁₋₆ alkoxy and hydroxyl;

wherein R₂ and R₃ together with the carbon atom connected thereto form 4-membered to 8-membered heterocycloalkyl;

wherein R₁ and R₁' together with the carbon atom connected thereto can form C₃₋₈ cycloalkyl, R₂ and R₂' together with the carbon atom connected thereto can form C₃₋₈ cycloalkyl, and R₃ and R₃' together with the carbon atom connected thereto can form C₃₋₈ cycloalkyl;

Claims

R₄, R₅ and R₆ are each independently selected from hydrogen, halogen and C₁₋₆ alkyl;

R₇ and R₈ are independently selected from hydrogen or C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from halogen and C₃₋₁₅ cycloalkyl;

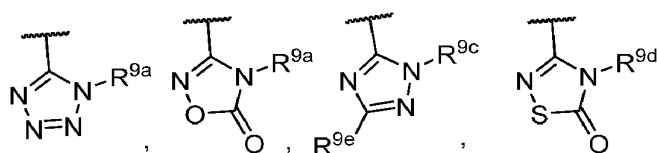
alternatively, R₇ and R₈ together with the carbon atom connected thereto form a C₃₋₁₅ carbocyclic ring; wherein the C₃₋₁₅ carbocyclic ring formed by R₇ and R₈ is optionally substituted with one to three C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, -NR^{7a}R^{7b}, C₁₋₆ alkoxy and 3- to 12-membered heterocyclyl, and R^{7a} and R^{7b} are independently selected from hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl; any two C₁₋₆ alkyl together with the carbon atom connected thereto can form a C₃₋₁₅ carbocyclic ring;

n₁ is 0, 1, 2, or 3;

n₂ is 0, 1, 2, 3, 4 or 5;

n₃ is 0 or 1;

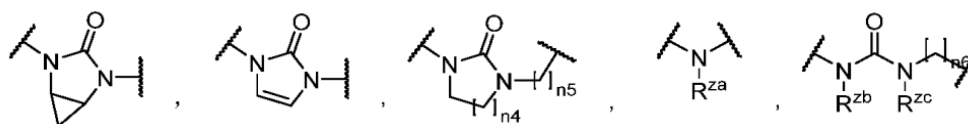
R₉ is selected from the following groups:



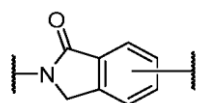
, -CO₂R^{9f} and -C(=O)-NR^{9g}R^{9h}; and R^{9a},

R^{9b}, R^{9c}, R^{9d} and R^{9g} are each independently selected from hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl, wherein the C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from halogen and C₁₋₆ alkoxy; R^{9e} is hydrogen or C₁₋₆ alkyl optionally substituted with one or more halogen atoms; R^{9f} is hydrogen or C₁₋₆ alkyl; R^{9h} is hydrogen, C₁₋₆ alkyl, (C₁₋₆ alkyl)carbonyl, cyano or -S(=O)_{n3}-R⁹ⁱ; n₃ is 0, 1 or 2; R⁹ⁱ is C₁₋₆ alkyl;

Z₁ is selected from the following groups:



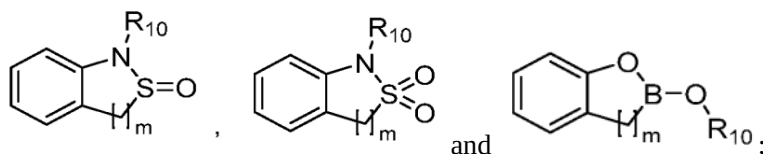
and



, wherein R^{za} is selected from hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl, and R^{zb} and R^{zc} are independently hydrogen or C₁₋₆ alkyl; n₄ is 1, 2 or 3; n₅ and n₆ are independently integers from 0 to 10;

Z₂ is selected from C₁₋₆ alkyl, C₃₋₁₅ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, and the following groups:

Claims



wherein Z_2 is independently optionally substituted with 1 to 5 G;

m is 1, 2, or 3;

R_{10} is selected from H, C_{1-6} alkyl and $(C_{1-6}$ alkyl)aryl, C_{1-6} haloalkyl, $-C_3-C_{15}$ cycloalkyl or $-C_1-C_6$ alkyl- C_3-C_{15} cycloalkyl;

G is selected from the following groups:

- a. oxo;
- b. halogen;
- c. cyano;
- d. $-NR^{zd}R^{ze}$; wherein R^{zd} and R^{ze} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl; wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from hydroxyl, halogen and C_{1-6} alkoxy;
- e. $-C(=O)-NR^{zf}R^{zg}$; wherein R^{zf} and R^{zg} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl; wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from hydroxyl, halogen and C_{1-6} alkoxy;
- f. $-S(=O)_n-R^{zh}$; wherein n is 0, 1 or 2; R^{zh} is hydrogen or C_{1-6} alkyl;
- g. C_{1-6} alkyl; wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, $-NR^{zi}R^{zj}$, C_{1-6} alkoxy, C_{1-6} haloalkoxy and 3- to 12-membered heterocyclyl; wherein R^{zi} and R^{zj} are independently hydrogen or C_{1-6} alkyl, and wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituents selected from cyano, C_{1-6} alkyl and 3- to 12-membered heterocyclyl;
- h. C_{1-6} alkoxy; wherein the C_{1-6} alkoxy is optionally substituted with one or more substituents selected from hydroxyl, halogen and C_{1-6} alkoxy;
- i. 3- to 12-membered heterocyclyl; wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl;
- j. C_{6-10} aryl; wherein the C_{6-10} aryl is optionally substituted with one or more $(C_{1-6}$ alkyl)carbonyl, and
- k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{zk}R^{zl}$ and 3- to 12-membered heterocyclyl; wherein R^{zk} and R^{zl} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl,

Claims

and wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituents independently selected from C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl;

l. -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl; wherein the cycloalkyl or alkyl is optionally substituted with one or more substituents independently selected from halogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl)carbonyl, and wherein the alkyl or alkoxy is selectively substituted with halogen;

m. -P(=O)R^{zm}R^{zn}, NR^{zm}S(=O)R^{zn} and NR^{zm}S(=O)₂R^{zn}, wherein R^{zm} and R^{zn} are selected from H, C₁₋₆ alkyl and C₆₋₁₀ aryl;

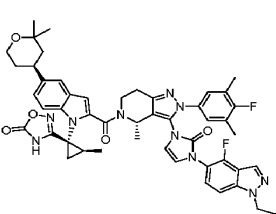
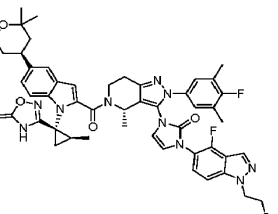
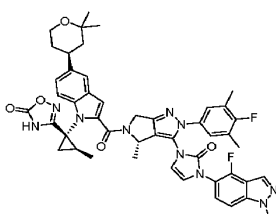
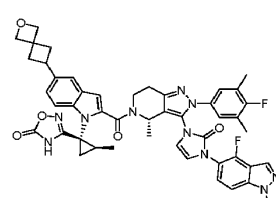
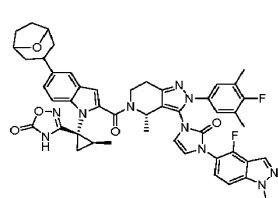
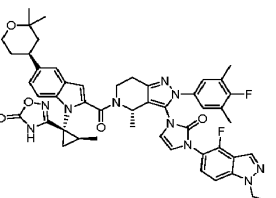
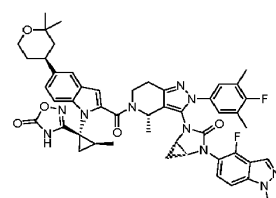
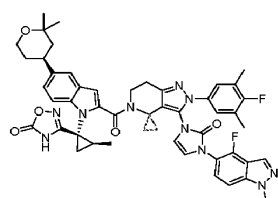
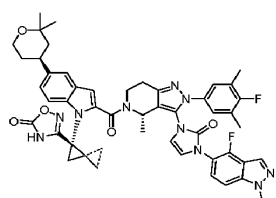
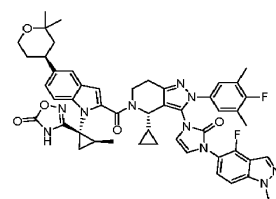
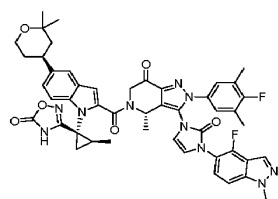
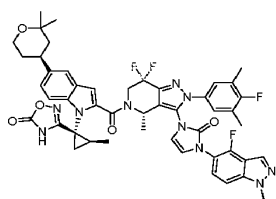
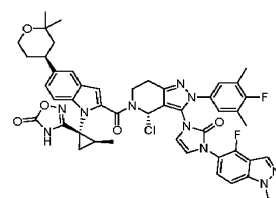
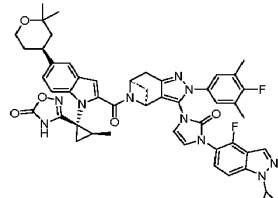
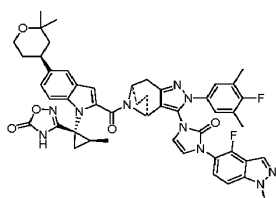
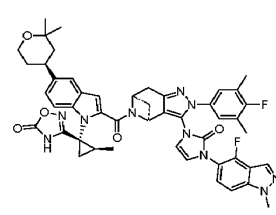
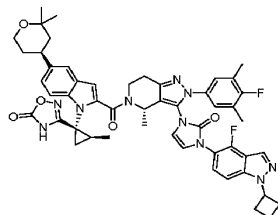
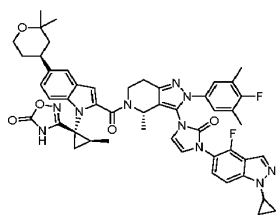
wherein the C₁₋₆ alkyl may be optionally substituted with 1-6 substituents each independently selected from C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and halogen; wherein the C₃₋₆ cycloalkyl may be optionally substituted with 1-3 substituents each independently selected from C₁₋₃ alkyl and halogen;

wherein the C₆₋₁₀ aryl is optionally substituted with 1-3 C₁₋₃ alkyl;

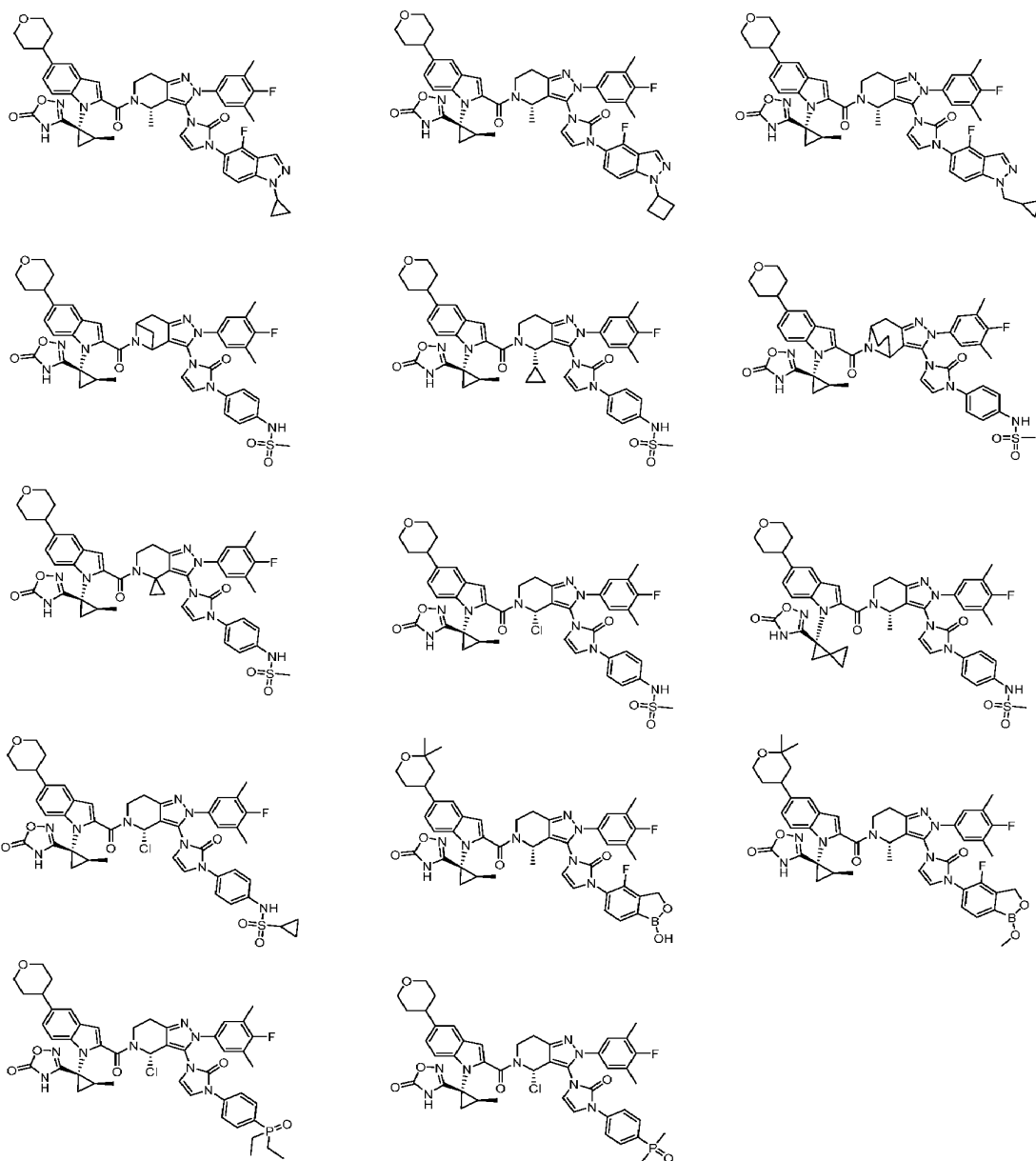
or R^{zm} and R^{zn} together with the phosphorus atom connected thereto form a ring having 5-8 ring atoms, wherein 0-2 ring atoms other than the phosphorus atom connected to R^{zm} and R^{zn} are heteroatoms, and are each independently selected from: O, S and N, wherein the ring having 5-8 ring atoms is optionally substituted with 1-3 C₁₋₆ alkyl.

2. The compound of formula (I) of claim 1, wherein the compound is selected from:

Claims



Claims



3. A method for treating a GLP-1-mediated disease or symptom, comprising the following step: administering to a subject an effective amount of the compound of formula (I) of claim 1 or 2, and the stereoisomer, the pharmaceutically acceptable salt or the deuterated compound thereof.

4. The method of claim 3, wherein the GLP-1-mediated disease or symptom includes: T1D, T2DM, prediabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral fat deposition, sleep apnea, obesity, eating disorders, weight gain due to other medications,

Claims

excessive sugar addiction, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, postprandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina, thrombosis, atherosclerosis, transient ischemic attack, vascular restenosis, impaired glucose metabolism, impaired fasting glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue diseases, psoriasis, foot ulcers, ulcerative colitis, hyper-apolipoprotein B lipoproteinemia, Alzheimer's disease, schizophrenia, cognitive impairment, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, polycystic ovary syndrome, and substance addiction.

Description

GLP-1R AGONIST AND USE THEREOF

Technical Field

The present application relates to a compound that binds to the glucagon-like peptide 1 receptor (GLP-1R) and is used as an agonist or modulator thereof, and the use of such compound for treating and/or preventing a GLP-1R-mediated disease and condition.

Background Art

Glucagon-like peptide 1 (GLP-1) is a peptide hormone secreted by enteroendocrine cells in the intestine in response to a meal. GLP-1 is considered to play a role in the regulation of postprandial blood glucose, and promote satiety by directly increasing meal-induced insulin secretion from pancreatic β cells and by delaying the transit of food through the intestine. GLP-1 mediates intracellular signaling by the GLP-1 receptor (GLP-1R). The GLP-1 receptor belongs to a family of G protein-coupled receptors present on cell membranes and can lead to the accumulation of the second messenger cyclic adenosine monophosphate (cAMP) upon activation. Non-alcoholic steatohepatitis (NASH) may be associated with features of the metabolic syndrome, including obesity, type 2 diabetes, insulin resistance, and cardiovascular disease.

GLP-1R agonists are currently being studied extensively in diseases associated with diabetes, obesity, and NASH. GLP-1R agonists include peptides, such as exenatide, liraglutide, and dulaglutide, which have been approved for the treatment of type 2 diabetes. Such peptide medications are mainly administered by subcutaneous injection. Oral GLP-1 agonists are also being studied for the treatment of type 2 diabetes. Some GLP-1R agonists, such as liraglutide, dulaglutide, and exenatide, are resistant to rapid degradation by dipeptidyl peptidase 4, resulting in a longer half-life than that of endogenous GLP-1.

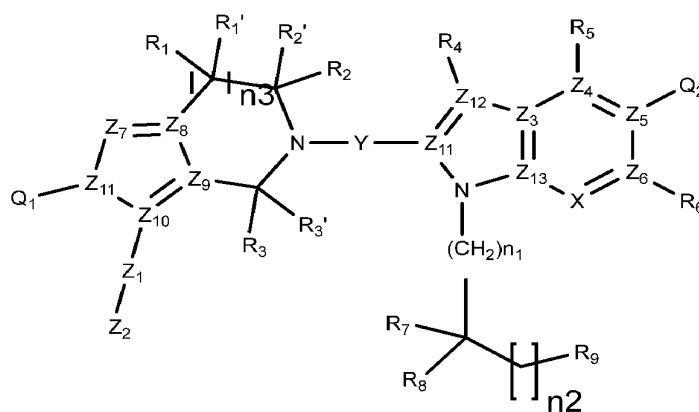
There remains a need for a compound, such as a GLP-1R agonist, that has desirable therapeutic properties, metabolic properties, and/or ease of administration for the treatment of a GLP-1R-mediated disease and condition.

Summary of the Invention

Summary

In one aspect, the present application relates to a compound of formula I and a stereoisomer, a pharmaceutically acceptable salt or a deuterated compound thereof:

Description



formula I

wherein

X is selected from N or -CR^a; R^a is selected from a hydrogen atom, halogen and C₁₋₆ alkyl;

Y is selected from -C(=O)-;

Z₃, Z₄, Z₅, Z₆, Z₇, Z₈, Z₉, Z₁₀, Z₁₁, Z₁₂, and Z₁₃ are selected from N or C;

Q₁ is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl or 5- to 10-membered heteroaryl are optionally substituted with one to five substituents independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and C₁₋₆ alkoxy;

Q₂ is 3- to 12-membered heterocyclyl, a bridged ring, a spiro ring or 5- to 10-membered heteroaryl, wherein the 3- to 12-membered heterocyclyl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 substituents independently selected from a halogen atom, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy and -NR^{Qa}R^{Qb}, and two C₁₋₆ alkyl together with the carbon atom connected thereto form a C₃₋₈ carbocyclic ring; and R^{Qa} and R^{Qb} are independently selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and (C₁₋₆ alkyl)carbonyl;

R₁, R₂, R₃, R₁', R₂' and R₃' are each independently selected from hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cycloalkyl or heterocycloalkyl;

wherein the C₁₋₆ alkyl, cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from a halogen atom, C₁₋₆ alkoxy and hydroxyl;

wherein R₂ and R₃ together with the carbon atom connected thereto form 4-membered to 8-membered heterocycloalkyl;

wherein R₁ and R₁' together with the carbon atom connected thereto can form C₃₋₈ cycloalkyl, R₂ and R₂' together with the carbon atom connected thereto can form C₃₋₈ cycloalkyl, and R₃ and R₃' together with the carbon atom connected thereto can form C₃₋₈ cycloalkyl;

R₄, R₅ and R₆ are each independently selected from hydrogen, halogen and C₁₋₆ alkyl;

Description

R_7 and R_8 are independently selected from hydrogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen and C_{3-15} cycloalkyl;

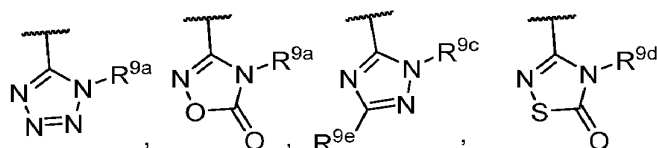
alternatively, R_7 and R_8 together with the carbon atom connected thereto form a C_{3-15} carbocyclic ring; wherein the C_{3-15} carbocyclic ring formed by R_7 and R_8 is optionally substituted with one to three C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclyl, and R^{7a} and R^{7b} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl; any two C_{1-6} alkyl together with the carbon atom connected thereto can form a C_{3-15} carbocyclic ring;

n_1 is 0, 1, 2, or 3;

n_2 is 0, 1, 2, 3, 4 or 5;

n_3 is 0 or 1;

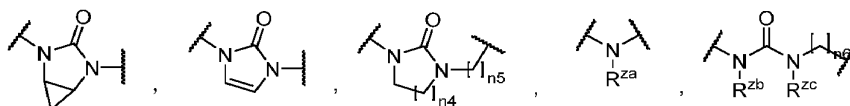
R_9 is selected from the following groups:



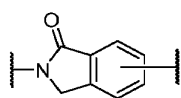
, $-CO_2R^{9f}$ and $-C(=O)-NR^{9g}R^{9h}$; and R^{9a} ,

R^{9b} , R^{9c} , R^{9d} and R^{9g} are each independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen and C_{1-6} alkoxy; R^{9e} is hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen atoms; R^{9f} is hydrogen or C_{1-6} alkyl; R^{9h} is hydrogen, C_{1-6} alkyl, $(C_{1-6}$ alkyl)carbonyl, cyano or $-S(=O)_{n3}-R^{9i}$; n_3 is 0, 1 or 2; R^{9i} is C_{1-6} alkyl;

Z_1 is selected from the following groups:

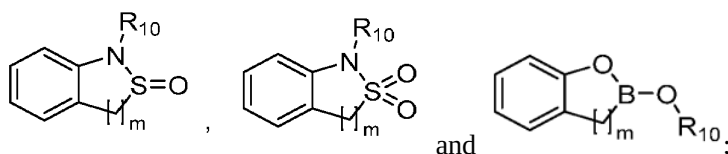


and



, wherein R^{za} is selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl, and R^{zb} and R^{zc} are independently hydrogen or C_{1-6} alkyl; n_4 is 1, 2 or 3; n_5 and n_6 are independently integers from 0 to 10;

Z_2 is selected from C_{1-6} alkyl, C_{3-15} cycloalkyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, and the following groups:



Description

wherein Z_2 is independently optionally substituted with 1 to 5 G;

m is 1, 2, or 3;

R_{10} is selected from H, C_{1-6} alkyl and $(C_{1-6}$ alkyl)aryl, C_{1-6} haloalkyl, $-C_3-C_{15}$ cycloalkyl or $-C_1-C_6$ alkyl- C_3-C_{15} cycloalkyl;

G is selected from the following groups:

- a. oxo;
- b. halogen;
- c. cyano;
- d. $-NR^{zd}R^{ze}$; wherein R^{zd} and R^{ze} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl; wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from hydroxyl, halogen and C_{1-6} alkoxy;
- e. $-C(=O)-NR^{zf}R^{zg}$; wherein R^{zf} and R^{zg} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl; wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from hydroxyl, halogen and C_{1-6} alkoxy;
- f. $-S(=O)_n-R^{zh}$; wherein n7 is 0, 1 or 2; R^{zh} is hydrogen or C_{1-6} alkyl;
- g. C_{1-6} alkyl; wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, $-NR^{zi}R^{zj}$, C_{1-6} alkoxy, C_{1-6} haloalkoxy and 3- to 12-membered heterocyclyl; wherein R^{zi} and R^{zj} are independently hydrogen or C_{1-6} alkyl, and wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituents selected from cyano, C_{1-6} alkyl and 3- to 12-membered heterocyclyl;
- h. C_{1-6} alkoxy; wherein the C_{1-6} alkoxy is optionally substituted with one or more substituents selected from hydroxyl, halogen and C_{1-6} alkoxy;
- i. 3- to 12-membered heterocyclyl; wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl;
- j. C_{6-10} aryl; wherein the C_{6-10} aryl is optionally substituted with one or more $(C_{1-6}$ alkyl)carbonyl, and
- k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{zk}R^{zl}$ and 3- to 12-membered heterocyclyl; wherein R^{zk} and R^{zl} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl, and wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl;
- l. $-C_3-C_{15}$ cycloalkyl or $-C_1-C_6$ alkyl- C_3-C_{15} cycloalkyl; wherein the cycloalkyl or alkyl is optionally substituted with one or more substituents independently selected from halogen,

Description

oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl)carbonyl, and wherein the alkyl or alkoxy is selectively substituted with halogen;

m. $-P(=O)R^{zm}R^{zn}$, $NR^{zm}S(=O)R^{zn}$ and $NR^{zm}S(=O)_2R^{zn}$, wherein R^{zm} and R^{zn} are selected from H, C₁₋₆ alkyl and C₆₋₁₀ aryl;

wherein the C₁₋₆ alkyl may be optionally substituted with 1-6 substituents each independently selected from C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and halogen; wherein the C₃₋₆ cycloalkyl may be optionally substituted with 1-3 substituents each independently selected from C₁₋₃ alkyl and halogen;

wherein the C₆₋₁₀ aryl is optionally substituted with 1-3 C₁₋₃ alkyl;

or R^{zm} and R^{zn} together with the phosphorus atom connected thereto form a ring having 5-8 ring atoms, wherein 0-2 ring atoms other than the phosphorus atom connected to R^{zm} and R^{zn} are heteroatoms, and are each independently selected from: O, S and N, wherein the ring having 5-8 ring atoms is optionally substituted with 1-3 C₁₋₆ alkyl.

In another aspect, the present application relates to a composition comprising a compound of formula (I) and a stereoisomer, a pharmaceutically acceptable salt or a deuterated compound thereof, and a pharmaceutically acceptable excipient.

In another aspect, the present application relates to a method for treating a GLP-1-mediated disease or symptom, comprising the following step: administering to a subject an effective amount of the compound of formula (I), and the stereoisomer, the pharmaceutically acceptable salt or the deuterated compound thereof, or administering to a subject an effective amount of the composition comprising the compound of formula (I).

In another aspect, the present application relates to the use in a medication for treating a GLP-1-mediated disease or symptom, which use comprises: administering to a subject an effective amount of the compound of formula (I), and the stereoisomer, the pharmaceutically acceptable salt or the deuterated compound thereof, or administering to a subject an effective amount of the composition comprising the compound of formula (I).

I. Details

In the following description, certain specific details are included to provide a comprehensive understanding of each disclosed embodiment. However, a person skilled in the relevant art will recognize that embodiments may be implemented without one or more of these specific details and with other methods, components, materials, etc.

Unless otherwise required in the present disclosure, throughout the specification and the following claims, the words "include" and "comprise" should be construed as open-ended, inclusive meanings, i.e., "include, but is/are not limited to".

As used in the present disclosure and the appended claims, singular references without quantity indications include plural references unless the context clearly dictates otherwise.

Description

"One embodiment", "an embodiment", "in another embodiment" or "in certain embodiments" mentioned throughout the specification means that at least one embodiment includes the specific referenced element, structure, or feature related to the description of the embodiment. Therefore, the phrase "in one embodiment", "in an embodiment", "in another embodiment" or "in certain embodiments" appearing in different places throughout the specification is not necessarily all referring to the same embodiment. In addition, the specific element, structure, or feature may be combined in any appropriate manner in one or more embodiments.

It should be understood that the singular articles "a", "an" and "the" used in the specification and the appended claims of the present disclosure includes plural objects unless the context clearly dictates otherwise. Therefore, for example, the mentioned sustained-release tablet comprising "a pharmaceutically acceptable excipient" includes one pharmaceutically acceptable excipient, or two or more pharmaceutically acceptable excipients.

II. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. A dash at the beginning or end of a chemical group is for convenience to indicate the point connected to the parent moiety; and a chemical group may be described with or without one or more dashes without losing the ordinary meaning thereof. A prefix, such as "C_{u-v}" or "C_u-C_v" indicates that the following group has u to v carbon atoms, where u and v are integers. For example, "C₁₋₆ alkyl" or "C₁-C₆ alkyl" indicates that the alkyl has 1 to 6 carbon atoms.

"Alkyl" is a monovalent or divalent linear or branched saturated hydrocarbon group. For example, one alkyl can have 1 to 10 carbon atoms (i.e., C₁₋₁₀ alkyl), 1 to 8 carbon atoms (i.e., C₁₋₈ alkyl), 1 to 6 carbon atoms (i.e., C₁₋₆ alkyl) or 1 to 4 carbon atoms (i.e., C₁₋₄ alkyl). Examples of alkyl include, but are not limited to: methyl (Me, or -CH₃), ethyl (Et, or -CH₂CH₃), 1-propyl (n-Pr, n-propyl, or -CH₂CH₂CH₃), 2-propyl (i-Pr, i-Propyl, or -CH(CH₃)CH₂CH₃), 1-butyl (n-Bu, n-butyl, or -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i-Bu, i-butyl, or -CH₂CH(CH₃)CH₂CH₃), 2-butyl (s-Bu, s-butyl, or -CH(CH₃)CH₂CH₂CH₃), 2-methyl-2-propyl (t-Bu, t-butyl, or -C(CH₃)₃); 1-pentyl (n-pentyl, or -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH₂CH(CH₃)CH₂CH₂CH₃), 2-methyl-2butyl (-C(CH₃)₂CH₂CH₃); 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)CH₃), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃); 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃),

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2-hexyl $(-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)$, 3-hexyl $(-\text{CH}(\text{CH}_2\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CH}_3))$, 2-methyl-2-pentyl $(-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_3)$; 3-methyl-2-pentyl $(-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3)$, 4-methyl-2-pentyl $(-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)_2)$, 3-methyl-3-pentyl $(-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_3)_2)$; 2-methyl-3-pentyl $(-\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}(\text{CH}_3)_2)$, 2,3-dimethyl-2-butyl $(-\text{C}(\text{CH}_3)_2\text{CH}(\text{CH}_3)_2)$, 3,3-dimethyl-2-butyl $(-\text{CH}(\text{CH}_3)\text{C}(\text{CH}_3)_3)$, and octyl $(-(\text{CH}_2)_7\text{CH}_3)$, and alkyl can be unsubstituted or substituted.

"Alkoxy" refers to a group $-\text{O-alkyl}$, wherein the alkyl is as defined above. For example, C_{1-4} alkoxy refers to $-\text{O-alkyl}$ group having 1 to 4 carbon atoms. Alkoxy can be unsubstituted or substituted.

"Alkoxyalkyl" is alkoxy connected to alkyl as defined above, such that the alkyl is divalent. For example, C_{2-6} alkoxyalkyl includes $-\text{CH}_2\text{-OMe}$, $-\text{CH}_2\text{-O-iPr}$, $-\text{CH}_2\text{-CH}_2\text{-OMe}$, $-\text{CH}_2\text{-CH}_2\text{-O-CH}_2\text{-CH}_3$, and $-\text{CH}_2\text{-CH}_2\text{-O-tBu}$. Alkoxyalkyl can be unsubstituted or substituted.

"Halogen" refers to fluorine $(-\text{F})$, chlorine $(-\text{Cl})$, bromine $(-\text{Br})$ and iodine $(-\text{I})$.

"Haloalkyl" is alkyl as defined herein with one or more hydrogen atoms independently substituted with one halogen, which halogen can be the same or different, such that the alkyl is divalent. Alkyl and halogen may be any of those described above. In some embodiments, haloalkyl determines the number of carbon atoms in the alkyl moiety. For example, C_{1-4} haloalkyl includes CF_3 , CH_2F , CHF_2 , CH_2CF_3 , $\text{CH}_2\text{CH}_2\text{CF}_3$, $\text{CCl}_2\text{CH}_2\text{CH}_3$ and $\text{C}(\text{CH}_3)_2(\text{CF}_2\text{H})$. Halogenated hydrocarbon can be unsubstituted or substituted.

"Haloalkoxy" is alkoxy as defined herein with one or more hydrogen atoms independently substituted with halogen, which halogen can be the same or different, such that the alkyl is divalent. Alkoxy and halogen may be any of those described above. In some embodiments, haloalkoxy defines the number of carbon atoms in the alkyl moiety. For example, C_{1-4} haloalkoxy includes OCF_3 , OCH_2F , OCH_2CF_3 , $\text{OCH}_2\text{CH}_2\text{CF}_3$, $\text{OCCl}_2\text{CH}_2\text{CH}_3$ and $\text{OC}(\text{CH}_3)_2(\text{CF}_2\text{H})$. Haloalkoxy can be unsubstituted or substituted.

"Cycloalkyl" is a monovalent or divalent single all-carbon ring or multiple condensed all-carbon ring system, in which the ring in each example is a non-aromatic saturated or unsaturated ring. For example, in some embodiments, cycloalkyl has 3 to 12 carbon atoms, 3 to 10 carbon atoms, 3 to 8 carbon atoms, 3 to 6 carbon atoms,

Description

3 to 5 carbon atoms, or 3 to 4 carbon atoms. Exemplary monocyclic cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, cycloheptyl, cycloheptenyl and cyclooctyl. Cycloalkyl also includes a multiple condensed ring system having about 7 to 12 carbon atoms (such as a ring system including 2 rings). As the valence requirements permit, the rings of the multiple condensed ring system can be interconnected via a fusion bond, a spiral bond, or a bridging bond. Exemplary polycyclic cycloalkyl includes octahydropentenyl, bicyclo[2. 2. 1]heptanyl, bicyclo[2. 2. 2]octanyl, bicyclo[2. 2]oct-2enyl and spiro[2. 5]octanyl. Cycloalkyl group can be unsubstituted or substituted.

"Alkylcycloalkyl" refers to alkyl as defined herein with one or more hydrogen atoms independently substituted with cycloalkyl, which cycloalkyl can be the same or different. Alkyl and cycloalkyl may be any of those described above. In some embodiments, the numbers of carbon atoms of the alkyl and cycloalkyl moieties may be specified separately, for example, C1-6 alkyl-C3-12 cycloalkyl. Alkylcycloalkyl group can be unsubstituted or substituted.

As used herein, "aryl" refers to a monovalent or divalent single all-carbon aromatic ring or multiple condensed all-carbon ring system, in which the ring is aromatic. For example, in some embodiments, one aryl has 6 to 20 carbon atoms, 6 to 14 carbon atoms, 6 to 12 carbon atoms, or 6 to 10 carbon atoms. Aryl includes one phenyl. Aryl also includes a multiple condensed ring system (such as a ring system consisting of 2, 3, or 4 rings) having about 9 to 20 carbon atoms, wherein multiple rings are aromatic. As the valence requirements permit, the rings of the multiple condensed ring system can be interconnected via a fusion bond. It can also be understood that when referring to aryl having members within a certain atomic number range (such as aryl having 6-10 members), the atomic number range refers to the total ring atoms of the aryl. For example, aryl having 6 members includes phenyl, and aryl having 10 members includes naphthyl. Non-limiting examples of aryl include, but are not limited to, phenyl, naphthyl, anthryl, etc. Aryl can be unsubstituted or substituted.

"Alkylaryl" refers to alkyl as defined herein with one or more hydrogen atoms independently substituted with one aryl, which aryl can be the same or different. Alkyl and aryl may be any of those described above, and the alkyl is divalent. In some embodiments, one alkylaryl has 7 to 24 carbon atoms, 7 to 16 carbon atoms, 7 to 13 carbon atoms, or 7 to 11 carbon atoms. The number of carbon atoms for defining alkylaryl refers to the total number of carbon atoms present in the constituent alkyl and aryl. For example, C₇ alkylaryl refers to benzyl, and C₁₁ alkylaryl includes 1-methylnaphthyl and n-pentylphenyl. In some embodiments, the numbers of carbon atoms of the alkyl and aryl moieties may be specified separately, for example, C₁₋₆ alkyl-C₆₋₁₀ aryl.

Description

Non-limiting examples of alkylaryl include, but are not limited to, benzyl, 2,2-dimethylphenyl, n-pentylphenyl, 1-methylnaphthyl, 2-ethylnaphthyl, etc. Alkylaryl can be unsubstituted or substituted.

As used herein, "heterocycle", "heterocyclic ring" or "heterocyclyl" refers to a single saturated or partially unsaturated non-aromatic ring or non-aromatic polycyclic ring system, wherein the ring has at least one heteroatom (i.e., at least one ring (i.e., cyclic) heteroatom selected from oxygen, nitrogen and sulfur). Unless otherwise specified, heterocyclyl group has 3 to about 20 ring atoms, such as 3 to 12 ring atoms, 4 to 12 ring atoms, 4 to 10 ring atoms, 3 to 8 ring atoms, 3 to 6 ring atoms, 4 to 6 ring atoms, or 4 to 5 ring atoms. Therefore, the term includes a single saturated or partially unsaturated ring (such as 3, 4, 5, 6, or 7-membered ring) having about 1 to 6 ring carbon atoms and about 1 to 3 ring heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. As the valence requirements permit, the rings of the multiple condensed ring system (bicyclic heterocycle) can be interconnected via a fusion bond, a spiral bond, and a bridging bond. Heterocycle includes, but is not limited to, azetidine, azepyrindine, imidazolidine, morpholine, ethylene oxide, oxygen-containing heterocycle, sulfur-containing heterocycle, piperazine, piperidine, pyrazolidine, pyrrolidine, pyrrolidinone, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, quinuclidine, 2-oxo-6-azaspiro[3.3]heptan-6-yl, 6-oxa-1-azaspiro[3.3]heptan-1-yl, 2-thia-6-azaspiro[3.3]heptan-6-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 2-azabicyclo[3.1.0]hexan-2-yl, 3-azabicyclo[3.1.0]hexyl, 2-azabicyclo[2.1.1]hexyl, 2-azabicyclo[2.2.1]hept-2-yl, 4-azaspiro[2.4]heptyl, 5-azaspiro[2.4]heptyl, and an analog thereof. Heterocyclyl can be unsubstituted or substituted.

"Alkylheterocyclyl" refers to alkyl as defined herein with one or more hydrogen atoms independently substituted with heterocyclyl, which heterocyclyl can be the same or different. Alkyl and heterocyclyl may be any of those described above, and the alkyl is divalent. In some embodiments, the numbers of carbon atoms of the alkyl and heterocyclyl moieties may be specified separately, for example, C₁₋₆ alkyl-3 to 12-membered heterocyclyl having 1 to 3 heteroatoms each independently selected from N, O or S. Alkylheterocyclyl can be unsubstituted or substituted.

"5- to 10-membered heteroaryl" refers to a single aromatic ring having at least one atom other than carbon atom in the ring, in which the atom is selected from the group consisting of oxygen, nitrogen and sulfur; and "5- to 10-membered heteroaryl" also includes a multiple condensed ring system having at least one such aromatic ring, which multiple condensed ring system is further described below. Therefore, "5- to 10-membered heteroaryl" includes a single aromatic ring having about 1 to 6 carbon atoms and about 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. The sulfur and nitrogen atoms may also be present in an oxidized form, provided that the ring is aromatic. Exemplary 5- to 10-membered heteroaryl ring system includes, but is not limited to pyridyl, pyrimidinyl, oxazolyl or furyl.

Description

"5- to 10-membered heteroaryl" also includes a multiple condensed ring system (such as a ring system consisting of 2, 3 or 4 rings), in which the 5- to 10-membered heteroaryl as defined above is condensed with one or more rings selected from 5- to 10-membered heteroaryl (to form, for example, 1,8-naphthyridinyl) and aryl (to form, for example, benzimidazolyl or indazolyl) to form a multiple condensed ring system. Therefore, 5- to 10-membered heteroaryl (single aromatic ring or multiple condensed ring system) can have about 1 to 20 carbon atoms, and the ring of the 5-10 membered heteroaryl has about 1 to 6 heteroatoms. For example, the ring of tetrazolyl has 1 carbon atom and 4 nitrogen heteroatoms. As the valence requirements permit, the rings of the multiple condensed ring system can be interconnected via a fusion bond. It should be understood that the rings of the multiple condensed ring system can be connected to each other in any order. It should be understood that the connection point of 5- to 10-membered heteroaryl or 5- to 10-membered heteroaryl multiple condensed ring system can be any suitable atom of the 5- to 10-membered heteroaryl or 5- to 10-membered heteroaryl multiple condensed ring system, including a carbon atom and a heteroatom (such as nitrogen). It should also be understood that when referring to heteroaryl having members within a certain atomic number range (such as heteroaryl having 5 to 10 members), the atomic number range is for the total ring atoms of the heteroaryl, including the carbon atom and the heteroatom. It should also be understood that the rings of the multiple condensed ring system may include an aryl ring fused to heterocycle (such as 3-, 4-, 5-, 6-, or 7-membered ring) having a saturated or partially unsaturated bond, wherein the heterocycle has about 1 to 6 ring carbon atoms and about 1 to 3 ring heteroatoms selected from oxygen, nitrogen, and sulfur in ring. For example, 5- to 10-membered heteroaryl includes thiazolyl, and 5- to 10-membered heteroaryl includes quinolyl. Exemplary 5- to 10-membered heteroaryl includes, but is not limited to pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxazolyl, quinazolyl, benzofuryl, benzoimidazolyl, thiophenyl, pyrrolo[2,3-b]pyridyl, quinazolinyl-4 (3H)-one, triazolyl and tetrazolyl. 5- to 10-membered heteroaryl can be unsubstituted or substituted.

"Alkyl-heteroaryl" refers to alkyl as defined herein with one or more hydrogen atoms independently substituted with heteroaryl, which heteroaryl can be the same or different, such that the alkyl is divalent. Alkyl and heteroaryl may be any of those described above. In some embodiments, the numbers of atoms in the alkyl and heteroaryl moieties are specified separately, for example, C₁₋₆ alkyl-5 to 10-membered heteroaryl, having 1 to 4 heteroatoms each independently selected N, O or S. Alkylheteroaryl can be unsubstituted or substituted.

"Oxo" herein refers to =O.

As used herein, "substituted" refers to that one or more hydrogen atoms of the group are independently substituted with one or more substituents (such as 1, 2, 3, 4 or more), as indicated.

Description

"The compound of the disclosure" includes the compound disclosed herein, for example, the compound of the disclosure includes the compound of formula I, including the compound of the examples. In some embodiments, "the compound of the disclosure" includes the compound of formula I.

The term "pharmaceutically acceptable excipient" includes, but is not limited to any adjuvant, carrier, excipient, lubricant, sweetener, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersant, suspending agent, stabilizer, isotonic agent, solvent or emulsifier that has been approved by the U.S. Food and Drug Administration for use in humans or livestock.

As used herein, "therapeutically effective amount" or "effective amount" refers to an amount effective to elicit a desired biological or medicinal response and includes an amount of a compound sufficient to affect treatment of a disease when administered to a subject for treatment of the disease. The effective amount would vary depending on factors, such as the compound, the disease and the severity thereof, and the age and weight of the subject to be treated. The effective amount may include a range of amounts. As is understood in the art, the effective amount may be one or more doses, i.e., one dose or more doses may be required to achieve the desired therapeutic endpoint. The effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be administered in an effective amount if, when used in combination with one or more other agents, a desired or beneficial result may be or has been achieved. The appropriate dosages of any co-administered compounds may be selectively lowered due to the combined action of the compounds (such as additive or synergistic effect).

As used herein, "co-administration" refers to administration of a unit dose of the compound of the present disclosure before or after administration of a unit dose of one or more additional therapeutic agents, for example, administration of the compound of the present disclosure within seconds, minutes, or hours of administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of the compound of the present disclosure is administered first, followed within seconds or minutes by a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed within seconds or minutes by a unit dose of the compound of the present disclosure. In some embodiments, a unit dose of the compound of the present disclosure is administered first, followed a few hours (such as 1-12 hours) later by a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed a few hours (such as 1-12 hours) later by a unit dose of the compound of the present disclosure. Co-administration of the compound disclosed herein with one or more additional therapeutic agents generally refers to the simultaneous or sequential administration of the compound disclosed herein and the one or more additional therapeutic agents, such that a therapeutically effective amount of each agent is present in the subject.

Description

Further provided are a pharmaceutically acceptable salt, a hydrate, a solubilized substance, an isomeric form, a polymorph, and a prodrug of the compound described herein.

"Pharmaceutically acceptable" or "physiologically acceptable" refers to that the compound, salt, composition, dosage form, and other material are useful in the preparation of a pharmaceutical compositions suitable for veterinary or human pharmaceutical use.

The compound described herein can be prepared and/or formulated as a pharmaceutically acceptable salt or, where appropriate, as a free base. The pharmaceutically acceptable salt is a non-toxic salt of the free base form of the compound that has the desired pharmacological activity as the free base. These salts can be prepared from an inorganic or organic acid or base. For example, a compound containing a basic nitrogen can be prepared into a pharmaceutically acceptable salt by contacting the compound with an inorganic or organic acid. Non-limiting examples of the pharmaceutically acceptable salt include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, octanoate, acrylate, formate, isobutyrate, hexanoate, heptanoate, propanolate, oxalate, malonate, ferrite, sebacate, fumarate, maleate, butyn-1,4-dioate, hexyn-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, methanesulfonate, propanesulfonate, benzenesulfonate, xylenesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ -hydroxybutyrate, glycolate, tartrate, and mandelate. Lists of other suitable pharmaceutically acceptable salts may be found in Remington: The Science and Practice of Pharmacy, 21st ed., Lippincott Williams & Wilkins, Philadelphia, PA, 2006.

Examples of the "pharmaceutically acceptable salt" of the compound disclosed herein also include the salt from an appropriate base, e.g., alkali metal (such as sodium and potassium), alkaline earth metal (such as magnesium), ammonium, and N (C₁-C₄ alkyl)⁴⁺. Examples of the pharmaceutically acceptable salt also include a base addition salt, such as sodium or potassium salt.

Further provided are the compound, or the pharmaceutically acceptable salt or isomer described herein, or a mixture thereof, wherein 1 to n hydrogen atoms connected to a carbon atom can be substituted with deuterium atoms or D, and n is the number of hydrogen atoms in the molecule. As is known in the art, the deuterium atom is a non-radioactive isotope of a hydrogen atom. Such compound may increase resistance to metabolism and thus can be used to increase the half-life of the compound, or the pharmaceutically acceptable salt or isomer described herein, or the mixture thereof when administered to mammals. See "Forster, "Deuterium isotope effects in studies of drug metabolism" Trends in Pharmacological Sciences, Science 5(12):524-527 (1984)".

Description

Such compound is synthesized by a method well known in the art, for example, using a starting material with one or more hydrogen atoms substituted with deuterium.

Examples of the isotope that can be incorporated into the disclosed compound also include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I and ^{125}I . Substitution with a positron emitting isotope, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be used in the positron emission topography (PET) study to examine substrate receptor occupancy. An isotopically labeled compound of formula I can generally be prepared by substituting the non-labeled reagent previously used with an appropriate isotopically labeled reagent by conventional techniques known to a person skilled in the art or by a process analogous to that described in the examples below.

The compounds of the embodiments disclosed herein or the pharmaceutically acceptable salts thereof may contain one or more asymmetric centers and may therefore have enantiomer, diastereomer, and other stereoisomeric forms. The forms may be defined in terms of absolute stereochemistry as (R)- or (S)-, or, in the case of amino acids, as (D)- or (L)-. This statement is meant to include all such possible isomers, as well as the racemate and optically pure form thereof. Optically active (+) and (-), (R) and (S), or (D) and (L)-isomers can be prepared using chiral syntheses or chiral reagents, or resolved using conventional techniques, such as chromatography and fractional crystallization. Conventional techniques for the preparation/separation of single enantiomer include chiral synthesis from a suitable optically pure precursor, or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, unless otherwise specified, such compounds are intended to include E and Z geometric isomers. Similarly, all isomeric forms are also included. When a compound is indicated in a chiral form thereof, it is understood that the embodiment includes, but is not limited to, the specific diastereomer or enantiomerically enriched form. If chirality is not specified but is present, it is understood that the embodiment is directed to a particular diastereomer or enantiomerically enriched form; or a racemic or scalar mixture of such compound. As used herein, "scalar mixture" refers to a mixture of stereoisomers in a non-1 : 1 ratio.

As used herein, "stereoisomer" refers to compounds that are bound by the same atoms but have different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and a mixture thereof, and includes "enantiomers", which refer to two stereoisomers whose molecules are non-superimposable mirror images of each other.

As used herein, "tautomer" refers to that a proton transfers from one atom of a molecule to another atom of the same molecule. In some embodiments, the present disclosure includes the tautomer of the compound.

Description

As used herein, “solvate” refers to the result of the interaction of a solvent and a compound. Further provided is a solvate of the salt of the compound described herein. Further provided is a hydrate of the compound described herein.

As used herein, “hydrate” refers to a compound of the invention chemically bound to one or more water molecules.

“Prevention” or “preventing” refers to any treatment of a disease or condition that results in the non-development of clinical symptoms of the disease or condition. In some embodiments, the compound can be administered to a subject (including human) who is at risk for or have a family history of the disease or condition.

As used herein, “prodrug” refers to a derivative of a medicament that is converted to the parent drug according to some chemical or enzymatic pathway after administration to the human body. In some embodiments, a prodrug is a biologically active derivative of a medicament that is converted to the biologically active parent drug according to some chemical or enzymatic pathway after administration to the human body.

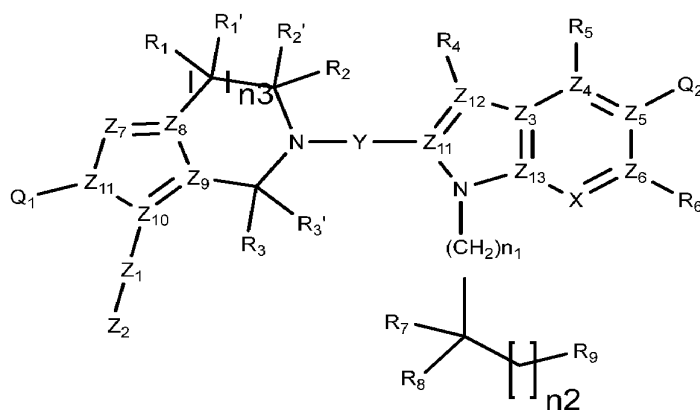
As used herein, “treat”, “treating” or “treatment” refers to a method of obtaining a beneficial or desired result. For the purpose of the present disclosure, the beneficial or desired result includes, but is not limited to, reducing symptoms and/or reducing the extent of symptoms and/or preventing worsening of symptoms associated with a disease or condition. In one embodiment, “treating” or “treatment” includes one or more of the followings: a) inhibiting a disease or condition (such as reducing one or more symptoms caused by a disease or condition, and/or reducing the extent of a disease or condition); b) slowing or preventing the development of one or more symptoms associated with a disease or condition (such as stabilizing a disease or condition, slowing the worsening or progression of a disease or condition); and c) alleviating a disease or condition, for example, resulting in regression of clinical symptoms, improving the disease state, slowing disease progression, improving quality of life, and/or prolonging survival. As used herein, “individual at risk” refers to an individual who is at risk of developing a disease for which treatment is required. An individual who is “at risk” may or may not have a detectable disease or condition and may or may not have manifested a detectable disease prior to the treatment method described herein. “At risk” means that the individual has one or more so-called risk factors, which are measurable parameters associated with the development of a disease or condition, and it is known in the art that the individual with one or more of these risk factors have a higher probability of developing a disease or condition than an individual without these risk factors.

III. Compound

One aspect of the present application relates to compounds that bind to GLP-1R and are used as GLP-1R agonists or modulators.

In some embodiments, the compound of the present disclosure is a compound of formula (I):

Description



formula I

or a stereoisomer, a pharmaceutically acceptable salt or a deuterated compound thereof;

wherein

X is selected from N or $-CR^a$; R^a is selected from a hydrogen atom, halogen and C_{1-6} alkyl;

Y is selected from $-C(=O)-$;

$Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12}$, and Z_{13} are selected from N or C;

Q_1 is C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{6-10} aryl or 5- to 10-membered heteroaryl are optionally substituted with one to five substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy;

Q_2 is 3- to 12-membered heterocyclyl, a bridged ring, a spiro ring or 5- to 10-membered heteroaryl, wherein the 3- to 12-membered heterocyclyl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 substituents independently selected from a halogen atom, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy and $-NR^{Qa}R^{Qb}$, and two C_{1-6} alkyl together with the carbon atom connected thereto form a C_{3-8} carbocyclic ring; and R^{Qa} and R^{Qb} are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and $(C_{1-6}$ alkyl)carbonyl;

$R_1, R_2, R_3, R_1', R_2'$ and R_3' are each independently selected from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cycloalkyl or heterocycloalkyl;

wherein the C_{1-6} alkyl, cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from a halogen atom, C_{1-6} alkoxy and hydroxyl;

wherein R_2 and R_3 together with the carbon atom connected thereto form 4-membered to 8-membered heterocycloalkyl;

wherein R_1 and R_1' together with the carbon atom connected thereto can form C_3-C_8 cycloalkyl, R_2 and R_2' together with the carbon atom connected thereto can form C_3-C_8 cycloalkyl, and R_3 and R_3' together with the carbon atom connected thereto can form C_3-C_8 cycloalkyl;

Description

R_4 , R_5 and R_6 are each independently selected from hydrogen, halogen and C_{1-6} alkyl;

R_7 and R_8 are independently selected from hydrogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen and C_{3-15} cycloalkyl;

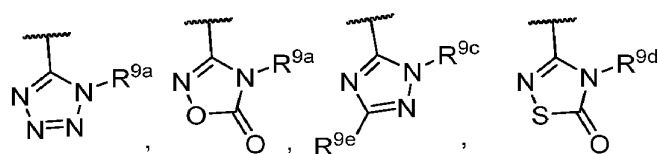
alternatively, R_7 and R_8 together with the carbon atom connected thereto form a C_{3-15} carbocyclic ring; wherein the C_{3-15} carbocyclic ring formed by R_7 and R_8 is optionally substituted with one to three C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclyl, and R^{7a} and R^{7b} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6} \text{ alkyl})\text{carbonyl}$; any two C_{1-6} alkyl together with the carbon atom connected thereto can form a C_{3-15} carbocyclic ring;

n_1 is 0, 1, 2, or 3;

n_2 is 0, 1, 2, 3, 4 or 5;

n_3 is 0 or 1;

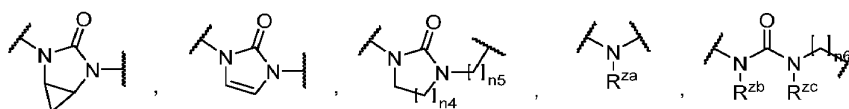
R_9 is selected from the following groups:



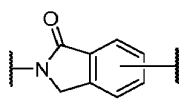
, $-\text{CO}_2R^{9f}$ and $-\text{C}(=\text{O})-\text{NR}^{9g}R^{9h}$; and R^{9a} ,

R^{9b} , R^{9c} , R^{9d} and R^{9g} are each independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6} \text{ alkyl})\text{carbonyl}$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen and C_{1-6} alkoxy; R^{9e} is hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen atoms; R^{9f} is hydrogen or C_{1-6} alkyl; R^{9h} is hydrogen, C_{1-6} alkyl, $(C_{1-6} \text{ alkyl})\text{carbonyl}$, cyano or $-\text{S}(=\text{O})_{n_3}-R^{9i}$; n_3 is 0, 1 or 2; R^{9i} is C_{1-6} alkyl;

Z_1 is selected from the following groups:



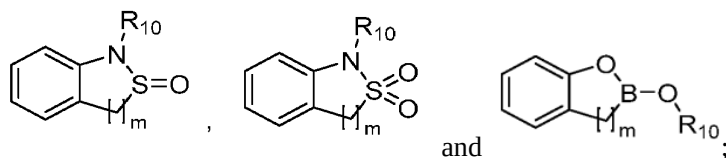
and



, wherein R^{za} is selected from hydrogen, C_{1-6} alkyl and $(C_{1-6} \text{ alkyl})\text{carbonyl}$, and R^{zb} and R^{zc} are independently hydrogen or C_{1-6} alkyl; n_4 is 1, 2 or 3; n_5 and n_6 are independently integers from 0 to 10;

Z_2 is selected from C_{1-6} alkyl, C_{3-15} cycloalkyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, and the following groups:

Description



wherein Z_2 is independently optionally substituted with 1 to 5 G;

m is 1, 2, or 3;

R_{10} is selected from H, C_{1-6} alkyl and $(C_{1-6}$ alkyl)aryl, C_{1-6} haloalkyl, $-C_3-C_{15}$ cycloalkyl or $-C_1-C_6$ alkyl- C_3-C_{15} cycloalkyl;

G is selected from the following groups:

- a. oxo;
- b. halogen;
- c. cyano;
- d. $-NR^{zd}R^{ze}$; wherein R^{zd} and R^{ze} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl; wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from hydroxyl, halogen and C_{1-6} alkoxy;
- e. $-C(=O)-NR^{zf}R^{zg}$; wherein R^{zf} and R^{zg} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl; wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from hydroxyl, halogen and C_{1-6} alkoxy;
- f. $-S(=O)_n-R^{zh}$; wherein n is 0, 1 or 2; R^{zh} is hydrogen or C_{1-6} alkyl;
- g. C_{1-6} alkyl; wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, $-NR^{zi}R^{zj}$, C_{1-6} alkoxy, C_{1-6} haloalkoxy and 3- to 12-membered heterocyclyl; wherein R^{zi} and R^{zj} are independently hydrogen or C_{1-6} alkyl, and wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituents selected from cyano, C_{1-6} alkyl and 3- to 12-membered heterocyclyl;
- h. C_{1-6} alkoxy; wherein the C_{1-6} alkoxy is optionally substituted with one or more substituents selected from hydroxyl, halogen and C_{1-6} alkoxy;
- i. 3- to 12-membered heterocyclyl; wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl;
- j. C_{6-10} aryl; wherein the C_{6-10} aryl is optionally substituted with one or more $(C_{1-6}$ alkyl)carbonyl, and
- k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{zk}R^{zl}$ and 3- to 12-membered heterocyclyl; wherein R^{zk} and R^{zl} are independently selected from hydrogen, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl,

Description

and wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituents independently selected from C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl;

l. -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl; wherein the cycloalkyl or alkyl is optionally substituted with one or more substituents independently selected from halogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl)carbonyl, and wherein the alkyl or alkoxy is selectively substituted with halogen;

m. -P(=O)R^{zm}R^{zn}, NR^{zm}S(=O)R^{zn} and NR^{zm}S(=O)₂R^{zn}, wherein R^{zm} and R^{zn} are selected from H, C₁₋₆ alkyl and C₆₋₁₀ aryl;

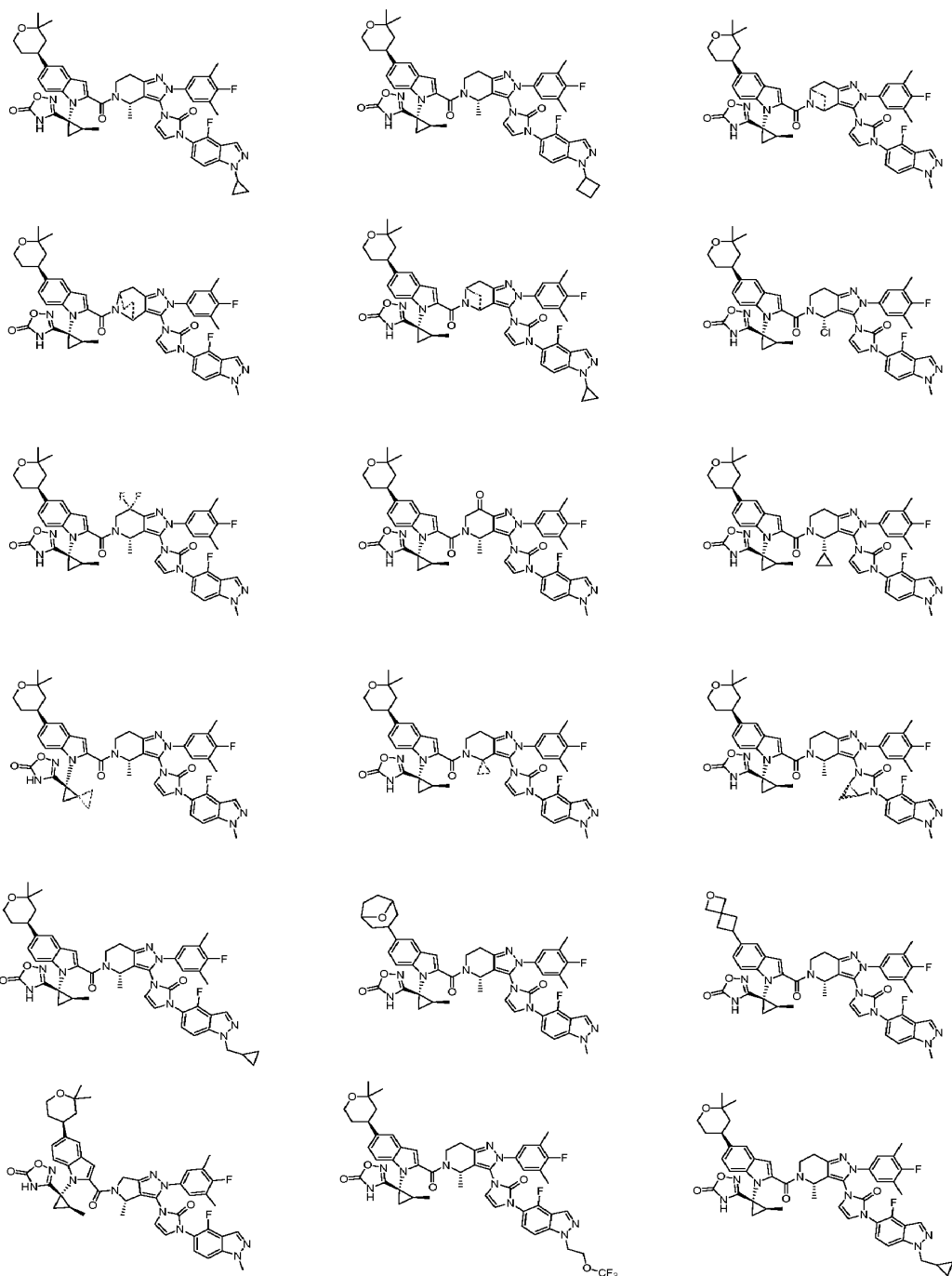
wherein the C₁₋₆ alkyl may be optionally substituted with 1-6 substituents each independently selected from C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and halogen; wherein the C₃₋₆ cycloalkyl may be optionally substituted with 1-3 substituents each independently selected from C₁₋₃ alkyl and halogen;

wherein the C₆₋₁₀ aryl is optionally substituted with 1-3 C₁₋₃ alkyl;

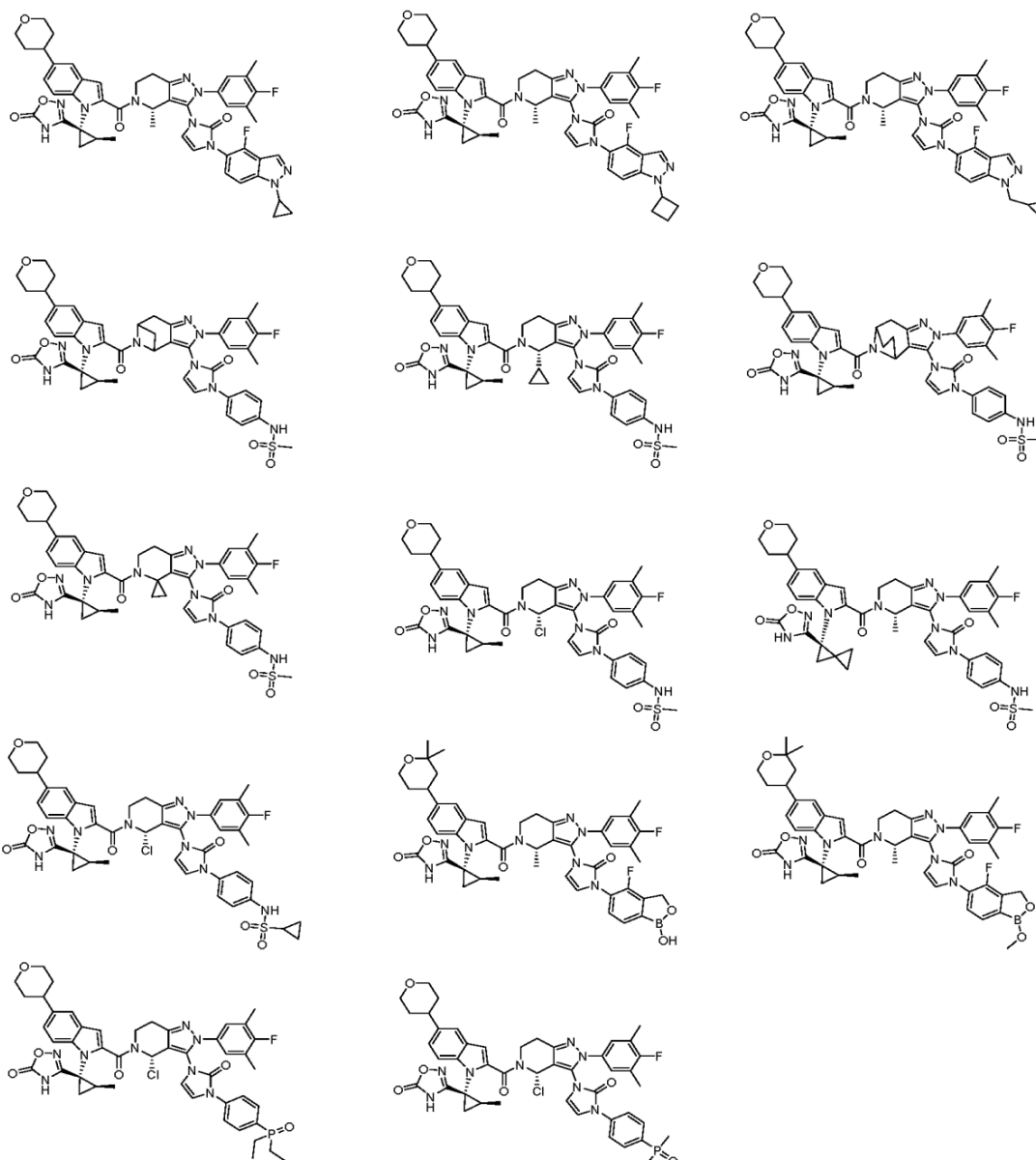
or R^{zm} and R^{zn} together with the phosphorus atom connected thereto form a ring having 5-8 ring atoms, wherein 0-2 ring atoms other than the phosphorus atom connected to R^{zm} and R^{zn} are heteroatoms, and are each independently selected from: O, S and N, wherein the ring having 5-8 ring atoms is optionally substituted with 1-3 C₁₋₆ alkyl.

In some embodiments, the compound of formula (I) or the pharmaceutically acceptable salt thereof has the following structural formula:

Description



Description



, and a stereoisomer, a pharmaceutically acceptable salt or a deuterated compound thereof.

IV. Pharmaceutical formulation

In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, such as the compound of formula I or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In some embodiments of the present disclosure, the pharmaceutical composition comprises the compound of formula I or the pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents, as more fully described below.

The pharmaceutical composition comprising the compound disclosed herein or the pharmaceutically acceptable salt thereof can be prepared with one or more pharmaceutically acceptable excipients, which can be selected according to conventional practice. Tablets can comprise excipients, including glidants, fillers, binders, etc. Aqueous compositions can be prepared in a sterile form,

Description

and when intended for delivery other than oral administration, can generally be isotonic. In some embodiments, the composition can comprise an excipient, such as those described in Rowe et al., Handbook of Pharmaceutical Excipients, 6th edition, American Pharmacists Association, 2009. Excipients can include antioxidants such as ascorbic acid, chelating agents such as ethylenediaminetetraacetic acid, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid, etc. In some embodiments, the composition is provided in a solid dosage form, including a solid oral dosage form.

The composition includes those suitable for various routes of administration, including oral administration. The composition can be in unit dosage form and may be prepared by any methods known in the pharmaceutical art. These methods include the step of combining the active ingredient (e.g., the compound of the present disclosure or the pharmaceutically acceptable salt thereof) with one or more pharmaceutically acceptable excipients. The composition can be prepared by uniformly and intimately combining the active ingredient with a liquid excipient, a finely divided solid excipient or both, and then, if desired, shaping the product. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams and Wilkins, Philadelphia, Pa., 2006.

The composition described herein suitable for oral administration can be presented in a discrete unit (unit dosage form) including, but not limited to, a capsule, a sachet or a tablet, each containing a predetermined amount of the active ingredient. In one embodiment, the pharmaceutical composition of the present disclosure is a tablet.

The pharmaceutical composition disclosed herein comprises one or more compounds disclosed herein or the pharmaceutically acceptable salts thereof, as well as pharmaceutically acceptable excipients and optionally other therapeutic agents. The pharmaceutical composition containing the active ingredient may be in any form suitable for the intended method of administration. When for oral administration, for example, tablets, lozenges, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. The composition for oral administration may be prepared according to any method known in the art for making pharmaceutical compositions, and such composition may contain one or more excipients including sweeteners, flavoring agents, coloring agents and preservatives in order to provide a palatable preparation. Tablets containing the active ingredient and nontoxic pharmaceutically acceptable excipients suitable for the production of tablets are acceptable. These excipients can be, for example, inert diluents such as calcium carbonate, sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium phosphate or sodium phosphate; granulating agents and disintegrants such as corn starch or alginic acid; binders such as cellulose, microcrystalline cellulose, starch, gelatin or gum arabic; and lubricants such as magnesium stearate, stearic acid or talc. Tablets can be uncoated,

Description

or can be coated by known techniques, including microencapsulation, to delay disintegration and adsorption in the gastrointestinal tract, thereby providing a longer sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be used alone or with a wax.

The amount of the active ingredient that can be combined with the inactive ingredient to produce the dosage form may vary depending on the intended subject to be treated and the mode of administration. For example, in some embodiments, dosage forms for oral administration to human can contain about 1 to 1000 mg of the active material formulated with an appropriate and convenient amount of a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutically acceptable excipient comprises about 5% to about 95% (weight: weight) of the total composition.

In some embodiments, in one variation, the composition comprising the compound of the present disclosure or the pharmaceutically acceptable salt thereof does not comprise a reagent that affects the metabolic rate of the active ingredient. Therefore, it should be understood that, in one aspect, the composition comprising the compound of the present invention does not comprise a reagent that affects (e.g., slows, hinders, or delays) the metabolism of the compound of the present invention or any other active ingredient administered separately, sequentially, or simultaneously with the compound of the present invention. It should also be understood that, in one aspect, any method, kit, product, etc. detailed herein does not comprise a reagent that affects (e.g., slows, hinders, or delays) the metabolism of the compound of the present disclosure or any other active ingredient administered separately, sequentially, or simultaneously with the compound of the present disclosure.

In some embodiments, the pharmaceutical composition described above is for use in humans or animals.

The present disclosure also includes the compound of the present disclosure administered as a single active ingredient of a pharmaceutically acceptable composition, which composition can be prepared by conventional methods known in the art, such as by combining the active ingredient with a pharmaceutically acceptable, therapeutically inert organic and/or inorganic carrier or excipient, or by mixing the two.

In one aspect, provided herein is the use of the compound of the present disclosure as a second or other active ingredient, in which the second or other active ingredient has a synergistic effect with other active ingredients in known medicaments, or the compound of the present disclosure is administered together with these medicaments.

The compound of the present disclosure can also be used in the form of the prodrug or other suitable modified form that releases the active ingredient in vivo.

V. Route of administration

The compound of the present disclosure (also referred to herein as an active ingredient) may be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal, parenteral (including subcutaneous, intramuscular injection, intravenous injection, intradermal, intratumoral,

Description

intrathecal, and epidural) etc. It can be understood that the preferred route may vary, for example, depending on the condition of the recipient. Certain compounds disclosed herein have the advantage that they are orally bioavailable and can be administered orally.

The compound of the present disclosure can be administered to an individual according to an effective dosing regimen for a desired period of time or duration, such as at least about 1 month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or more. In one embodiment, the compound is administered daily or intermittently for the duration of the individual's life.

The dosage or frequency of administration of the compound of the present disclosure may be adjusted during the treatment based on the judgment of the administering physician.

The compound can be administered to an individual (such as human) in an effective amount. In some embodiments, the compound is administered once a day.

The compound can be administered by any useful route and means, such as by oral or parenteral (such as intravenous) administration. The therapeutically effective amount of the compound can include about 0.00001 mg/kg body weight per day to about 10 mg/kg body weight per day, such as about 0.0001 mg/kg body weight per day to about 10 mg/kg body weight per day, about 0.001 mg/kg body weight per day to about 1 mg/kg body weight per day, about 0.01 mg/kg body weight per day to about 1 mg/kg body weight per day, about 0.05 mg/kg body weight per day to about 0.5 mg/kg body weight per day, about 0.3 mg to about 30 mg per day, or about 30 mg to about 300 mg per day.

The compound of the present disclosure can be combined with one or more additional therapeutic agents at any dosage amount of the compound of the present disclosure (such as 1 mg to 1000 mg of the compound). The therapeutically effective amount can include about 1 mg per dose to about 1000 mg per dose, such as about 50 mg per dose to about 500 mg per dose, about 100 mg per dose to about 400 mg per dose, about 150 mg per dose to about 350 mg per dose, or about 200 mg per dose to about 300 mg per dose. Other therapeutically effective amount of the compound disclosed herein is about 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, or about 500 mg per dose. Other therapeutically effective amount of the compound disclosed herein is about 100 mg per dose, or about 125, 150, 175, 200, 225, 250, 275, 300, 350, 400, 450 or about 500 mg per dose. Single dose can be administered hourly, daily, or weekly. For example, single dose can be administered once every 1 hour, or 2, 3, 4, 6, 8, 12, 16 or 24 hours. Single dose can also be administered once every 1 day, or 2, 3, 4, 5, 6 or 7 days. Single dose can also be administered once every 1 week, or 2, 3 or 4 weeks.

Description

In some embodiments, single dose can be administered once a week. Single dose can also be administered once a month.

A kit comprising the compound of the present disclosure or the enantiomer thereof or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising any of the foregoing is also included in the present disclosure. In one embodiment, a kit further comprises instructions for use. In one aspect, the kit comprises the compound of the present disclosure or the pharmaceutically acceptable salt, isomer, mixture of stereoisomers, bulk drug, or deuterated analog thereof, and a label and/or instructions for using the compound in treating the indication, such as disease or condition, as described herein. In one embodiment, provided is a kit comprising the compound of the present disclosure or the pharmaceutically acceptable salt thereof and one or more (such as one, two, three, four, one or two, or one to three, or one to four) additional therapeutic agents.

Also provided herein is an article of manufacture comprising the compound of the present disclosure or the pharmaceutically acceptable salt, isomer, mixture of stereoisomers, prodrug, or deuterated analog thereof in a suitable container. The container can be a vial, a jar, an ampoule, a prefilled syringe and an intravenous bag.

Example 1:

Synthesis

The compound of the present invention can be prepared by the method disclosed herein and conventional modifications thereof, which modifications are obvious in view of the method disclosed herein and methods well known in the art. In addition to the teachings herein, conventional and well-known synthetic methods can also be used.

The typical compound of formula I or the pharmaceutically acceptable salt thereof, such as compounds having one or more structures described in formula I, or other formulas or compounds disclosed herein, can be synthesized as described in the following examples.

General synthesized method

Typical embodiments of the compound according to the present disclosure can be synthesized using the general reaction schemes and/or examples described below. In view of the descriptions herein, it is obvious that the general schemes can be altered by replacing the starting materials with other materials having similar structures to produce corresponding different products. The following synthetic descriptions provide many examples of how the starting materials can be varied to provide corresponding products. The starting materials are generally obtained from commercial sources or synthesized using published methods for synthesizing compounds that are embodiments of the present disclosure. Inspection of the structure of the compound to be synthesized will provide the identity of each substituent. In view of the examples herein, the identity of the final product will generally make the identity of the necessary starting materials apparent by a simple inspection process.

Description

The group labels (e.g., R₁ and R₂) used in the reaction schemes herein are for illustrative purposes only and, unless otherwise indicated, are not necessarily identical in name or function to labels used elsewhere to describe compounds of formula I or aspects or fragments thereof.

Synthesized reaction parameters

The compound of the present disclosure can be prepared from readily available starting materials using, for example, the following general methods and procedures. It can be understood that where typical or preferred process conditions (i.e., reaction temperature, time, molar ratio of reactants, solvent, pressure, etc.) are given; other process conditions may also be used unless otherwise indicated. Optimal reaction conditions may vary depending on the use of specific reactants or solvents, but such conditions can be determined by a person skilled in the art through conventional optimization procedures.

In addition, it is known to a person skilled in the art that conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Protecting groups for various functional groups and suitable conditions for protecting and deprotecting specific functional groups are well known in the art. For example, many protecting groups are described in T.W. Greene and G.M. Wuts (1999), *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, and references cited therein.

In addition, the compound of the present disclosure may comprise one or more chiral centers. Therefore, if desired, such compounds may be prepared or isolated as pure stereoisomers, i.e., prepared or isolated as individual enantiomers or diastereomers or as stereoisomer-enriched mixtures. Unless otherwise indicated, all such stereoisomers (and enriched mixtures) are included within the scope of this statement. Pure stereoisomers (or enriched mixtures) may be prepared, for example, using optically active starting materials or stereoselective reagents well known in the art. In addition, racemic mixtures of such compounds may be separated using, for example, chiral column chromatography, chiral resolving agents, etc.

The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many starting materials are available from commercial suppliers, such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). Others can be prepared by procedures described in standard references, or obvious modifications thereof, such as Fieser's *Reagents for Organic Synthesis*: vol. 1-15 (John Wiley, and Sons, 1991); *Rodd's Chemistry of Carbon Compounds*: vol. 1-5, and *Supplementary Editions* (Elsevier Science Publisher, 1989); *Organic Reactions*, vol. 1-40 (John Wiley, and Sons, 1991), *March's Advanced Organic Chemistry* (John Wiley, and Sons, 5th Edition, 2001), and *Larock, Comprehensive Organic Transformations* (VCH Publishing Company, 1989).

Description

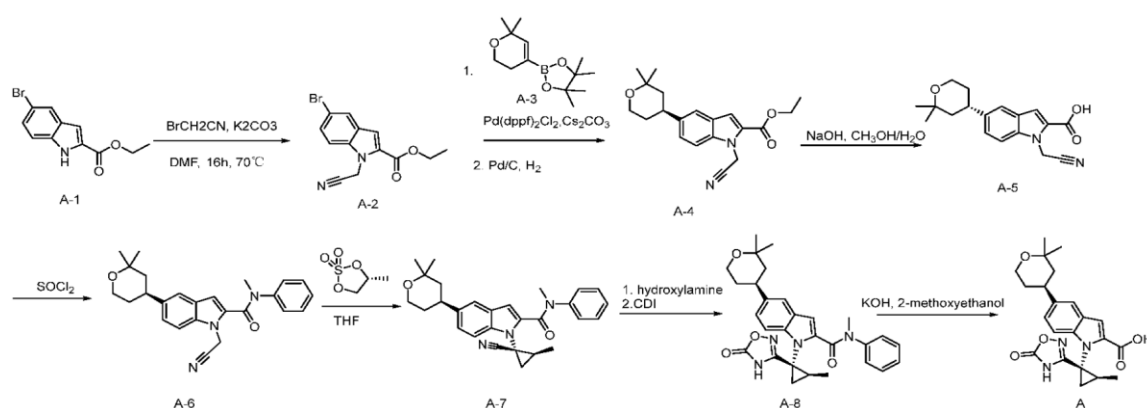
The terms "solvent", "inert organic solvent" or "inert solvent" refer to a solvent that is inert under the reaction conditions associated therewith (such as including benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), N,N-dimethylformamide ("DMF"), chloroform, dichloromethane (or methylene chloride), diethyl ether, methanol, pyridine, etc.). Unless otherwise specified, the solvent used in the reaction of the present disclosure is an inert organic solvent and the reaction is carried out under an inert gas, preferably nitrogen.

The term "q.s." refers to adding an amount sufficient to achieve the function described, for example, to bring the solution to the desired volume (i.e., 100%).

The compound provided herein can be synthesized according to the general schemes provided below. In the schemes below, it should be understood that each compound shown therein can have a protecting group present as desired in any step. Standard protecting groups are within the scope of a person skilled in the art.

Preparation of intermediate:

Preparation of intermediates A, B and C



A-1 (5 g, 18.65 mmol), potassium carbonate (5.16 g, 37.3 mmol) and sodium iodide (0.28 g, 1.86 mmol) were dissolved in DMF (30 ml), bromoacetonitrile (3.36 g, 28.0 mmol) was added dropwise to the reaction liquid, and the mixture was heated to 70°C and reacted for 16 hours. The reaction was cooled to room temperature, water (60 ml) was added to precipitate a solid, and the mixture was filtered to obtain a brown solid (4 g, yield: 49.0%).

A-2 (2.0 g, 6.51 mmol), **A-3** (1.71 g, 7.16 mmol), cesium carbonate (3.18 g, 9.77 mmol) and Pd(dppf)₂Cl₂ (0.5 g, 0.6 mmol) were dissolved in dioxane (20 ml), and the mixture was heated to 100°C and reacted for 4 hours under N₂. The reaction liquid was cooled, and extracted with water (30 ml) and ethyl acetate (30 ml), the organic phase was concentrated to dryness, and the residue was purified by column chromatography to obtain a white solid (1.2 g). The obtained solid was dissolved in methanol, Pd/C (0.12 g, 30%wt.) was added, and the mixture was reacted overnight at room temperature under hydrogen gas. The reaction was filtered, the filtrate was

Description

concentrated to dryness, and the obtained solid was subjected to chiral preparative liquid phase (taking the one with smaller retention time) to prepare **A-4** (0.6 g, yield: 27.3%).

A-4 (0.6 g, 1.76 mmol) was dissolved in methanol/water (4 ml/2 ml), sodium hydroxide (0.28 g, 7.05 mmol) was added, and the mixture was reacted at room temperature for 4 hours. The reaction was adjusted to pH 5.0 with dilute hydrochloric acid and extracted with ethyl acetate (5 ml), and the organic phase was concentrated to dryness under reduced pressure to obtain solid **A-5** (0.53 g, yield: 96.3%).

A-5 (300 mg, 1.1 mmol) was dissolved in dichloromethane (10 ml), thionyl dichloride (520 mg, 4.4 mmol) and 1 drop of DMF were added, and the mixture was reacted at room temperature for 6 hours. The reaction liquid was concentrated to dryness to obtain an acyl chloride oil, and 5 ml of dichloromethane was added to yield a clear solution for later use. *N*-methylaniline (180 mg, 1.65 mmol) and triethylamine (222 mg, 2.2 mmol) were dissolved in dichloromethane (10 ml). In ice bath, the acyl chloride solution was added dropwise, and the mixture was further reacted at room temperature for 1 hour. The reaction was extracted with water (10 ml), and the organic phase was concentrated to dryness under reduced pressure to obtain **A-6** (350 mg, 87.9%).

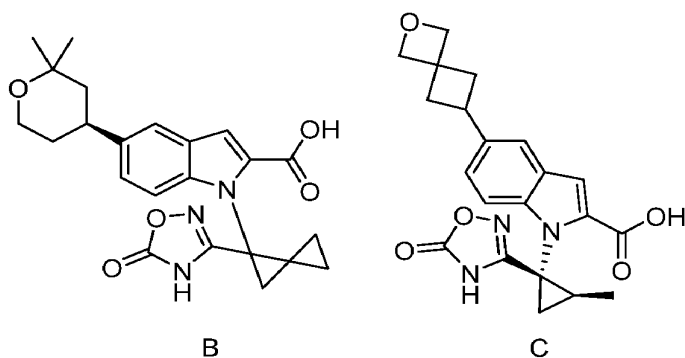
A-6 (100 mg, 0.25 mmol) and (4*R*)-4-methyl-1,3,2-dioxathiolane 2,2-dioxide (103.6 g, 0.75 mmol) were dissolved in THF (5 ml). The mixture was cooled to -20°C, lithium bis(trimethylsilyl)amide (1 ml, 1 M in THF) was added dropwise, and then the mixture was reacted at room temperature for 24 hours. The reaction was quenched by slowly dropwise addition of water (5 ml), the mixture was extracted with ethyl acetate (10 ml), and the organic phase was concentrated to dryness under reduced pressure to obtain an oil, which was then purified by column chromatography to obtain **A-7** (40 mg, yield: 36.4%).

A-7 (10 mg, 0.023 mmol) was dissolved in DMSO (2 ml), aqueous hydroxylamine solution (0.6 ml, 50%) was added, and the mixture was reacted at room temperature for 16 hours. The reaction was extracted with water (10 ml) and ethyl acetate (10 ml), and the organic phase was dried and concentrated to dryness to obtain an oil. The oil was dissolved in DMSO (3 ml), CDI (10 mg, 0.062 mmol) and DBU (10 mg, 0.066 mmol) were added, and the mixture was reacted at room temperature for 6 hours. The reaction was extracted with water (10 ml) and ethyl acetate (10 ml), and the organic phase was dried and concentrated to dryness to obtain **A-8** (10 mg, yield: 88.2%).

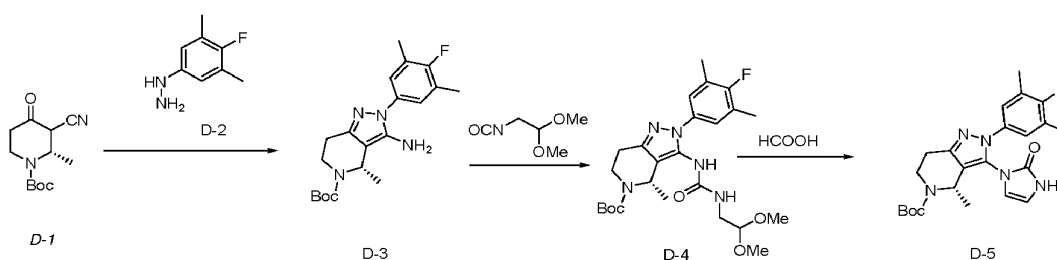
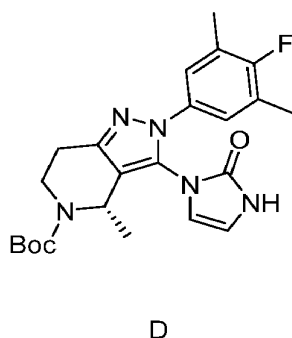
A-8 (220 mg, 0.44 mmol) was dissolved in ethylene glycol methyl ether (3 ml), potassium hydroxide (494 mg, 8.8 mmol) was added, and the mixture was heated to 130°C and reacted for 5 hours. The reaction was cooled to room temperature, adjusted to pH 5.0 with hydrochloric acid (6 N), and extracted with ethyl acetate (10 ml). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain intermediate A (180 mg, yield: 99.0%).

B and **C** were prepared in the same method:

Description



Preparation of intermediate D



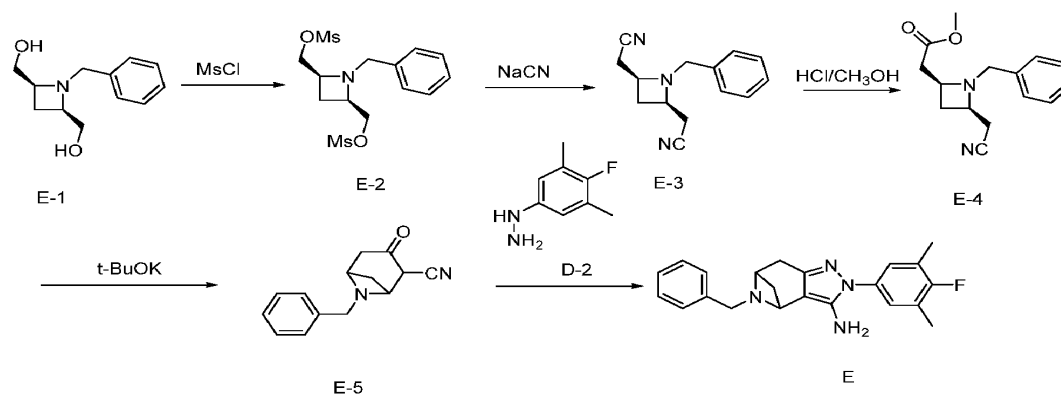
D-1 (2.0 g, 8.4 mmol), **D-2** (1.29 g, 8.4 mmol) and pyridine hydrochloride (0.97 g, 8.4 mmol) were dissolved in toluene (10 ml), and the mixture was heated to reflux and reacted for 1 hour. The reaction liquid was cooled, and extracted with water (10 ml) and ethyl acetate (10 ml), and the organic phase was concentrated under reduced pressure to obtain target compound **D-3** (2.4 g, yield: 76.4%).

D-3 (2.0 g, 5.34 mmol) was dissolved in DCM (20 ml), a solution of 2-isocyanato-1,1-dimethoxyethane (0.84 g, 6.41 mmol) in dichloromethane (5 ml) was added dropwise at room temperature, and the mixture was stirred at room temperature for 2 hours. The mixture was extracted with water (20 ml), and the organic phase was concentrated to dryness under reduced pressure to obtain an oil, which was directly used in the next reaction.

In ice bath, the oil of **D-4** was dissolved in dichloromethane (20 ml), and then the mixture was added to formic acid (10 ml). The mixture was stirred overnight at room temperature. The mixture was extracted with water (20 ml), and the organic phase was concentrated to dryness under reduced pressure to obtain a crude. Then, the crude was slurried by using ethyl acetate and n-heptane to obtain **D-5** (1.2 g).

Description

Preparation of intermediates E and F:



E-1 (5.0 g, 24.12 mmol) and triethylamine (7.31 g, 72.36 mmol) were dissolved in dichlorohexane (25 ml). In ice bath, MsCl (6.08 g, 53.07 mmol) was added dropwise, and then the mixture was stirred at room temperature for 30 minutes. The mixture was extracted with water (20 ml), and the organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain **E-2** (7.5 g, yield: 85.6%).

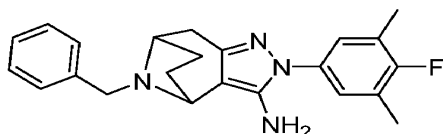
E-2 (3.0 g, 8.25 mmol) was dissolved in EMF (30 ml), NaCN (850 mg, 17.3 mmol) was slowly added, and the mixture was reacted at 60°C for 1 hour. The reaction was cooled, saturated sodium hypochlorite solution (30 ml) was added, and the mixture was stirred for 1 hour. The mixture was extracted with ethyl acetate (30 ml), and the organic phase was concentrated to dryness to obtain **E-3** (1.54 g, yield: 82.8%).

E-3 (1.2 g, 5.33 mmol) was dissolved in a solution of hydrogen chloride in methanol (1 M, 7 ml), and the mixture was stirred overnight at room temperature. Water was added, and the mixture was stirred for 2 hours. The mixture was extracted with ethyl acetate (20 ml), and the organic phase was evaporated to dryness under reduced pressure to obtain an oil, which was then purified by column chromatography to obtain **E-4** (0.6 g, yield: 43.6%).

E-4 (0.5 g, 1.9 mmol) was dissolved in THF (5 ml), potassium tert-butoxide (1.09 g, 9.7 mmol) was added, and the mixture was reacted overnight at room temperature. The reaction was adjusted to pH as neutral with dilute hydrochloric acid, and extracted with ethyl acetate, and the phase was evaporated to dryness under reduced pressure and subjected to column chromatography to obtain **E-5** (0.34 g, yield: 68%).

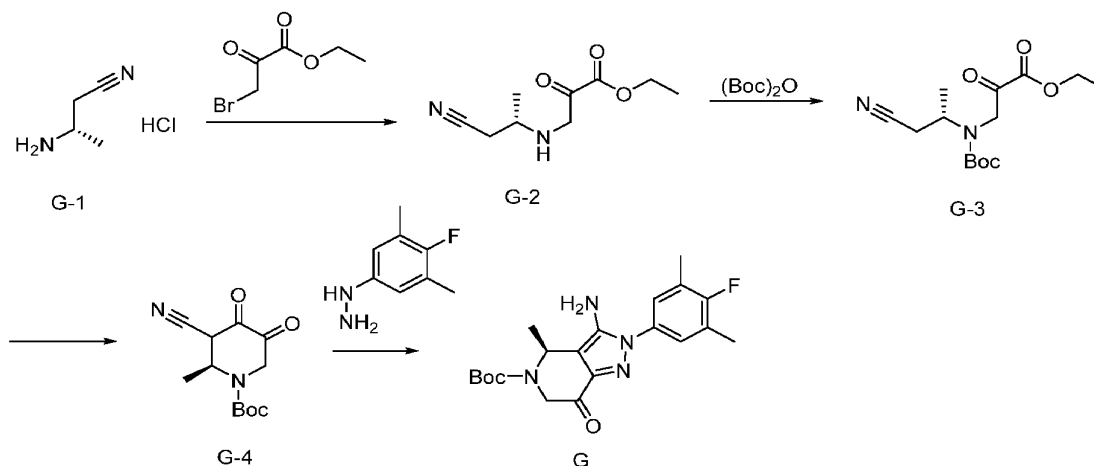
E-5 (0.2 g, 0.88 mmol), **D-2** (126 mg, 0.88 mmol) and pyridine hydrochloride (0.1 g, 0.88 mmol) were dissolved in toluene (4 ml), and the mixture was heated to reflux and reacted for 1 hour. The reaction liquid was cooled, and extracted with water (10 ml) and ethyl acetate (10 ml), and the organic phase was concentrated under reduced pressure to obtain target compound **E** (260 mg, yield: 81.2%).

Intermediate **F** was prepared by the same method:



Preparation of intermediate G:

Description



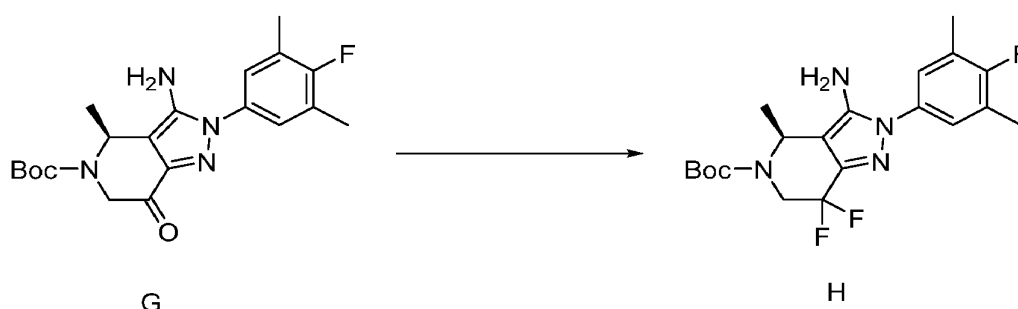
G-1 (5.0 g, 41.5 mmol), ethyl 3-bromopyruvate (8.90 g, 45.61 mmol) and cesium carbonate (20.3 g, 62.2 mmol) were dissolved in DMF (100 ml), and the mixture was heated to 65°C and reacted for 4 hours. The reaction was cooled to room temperature, water (200 ml) was added to precipitate a solid, and the mixture was filtered to obtain **G-2** (4.80 g, yield: 58.4%).

G-2 (4.0 g, 20.2 mmol), (Boc)₂O (6.6 g, 30.3 mmol) and triethylamine (6.13 g, 60.5 mmol) were dissolved in THF (40 ml), and the mixture was stirred overnight at room temperature. The mixture was extracted with water (50 ml) and ethyl acetate (50 ml), and then the organic phase was concentrated under reduced pressure to obtain **G-3** (5.6 g, 93.2%).

G-3 (5.6 g, 18.8 mmol) was dissolved in THF (50 ml), potassium tert-butoxide (10.5 g, 94 mmol) was added, and the mixture was reacted overnight at room temperature. The reaction was adjusted to pH as neutral with dilute hydrochloric acid, and extracted with ethyl acetate, and the phase was evaporated to dryness under reduced pressure and subjected to column chromatography to obtain **G-4** (3.6 g, yield: 76%).

G-4 (2.0 g, 7.93 mmol), **D-2** (1.22 g, 7.93 mmol) and pyridine hydrochloride (0.9 g, 7.93 mmol) were dissolved in toluene (40 ml), and the mixture was heated to reflux and reacted for 1 hour. The reaction liquid was cooled, and extracted with water (40 ml) and ethyl acetate (40 ml), and the organic phase was concentrated under reduced pressure to obtain target compound **G** (1.2 g, yield: 39%).

Preparation of intermediate H:

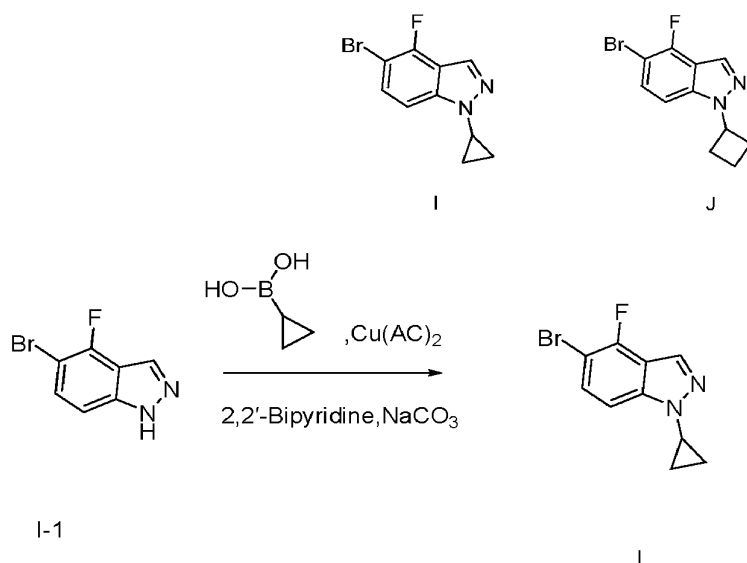


Compound **G** (200 mg, 0.52 mmol) was dissolved in DCM (2 ml). In ice bath, DAST (165 mg, 1.0 mmol) was added, and the mixture was stirred overnight at 0°C. The mixture was extracted with saturated sodium bicarbonate solution (4 ml) and DCM (4 ml), the organic phase

Description

was concentrated to dryness under reduced pressure, and the residue was then purified by column chromatography to obtain compound **H** (0.12 g, yield: 56.8%).

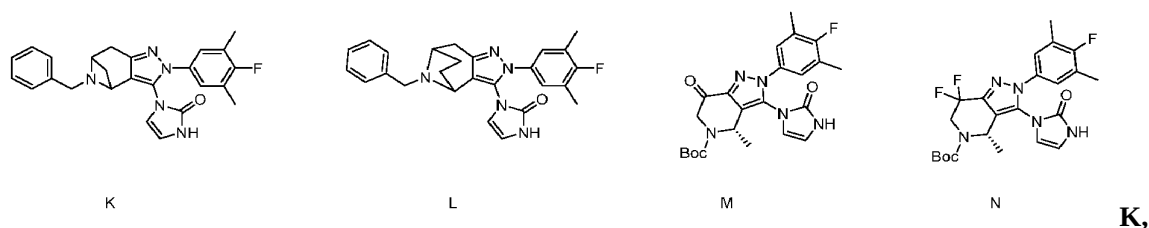
Preparation of intermediates **I** and **J**:



Compound **I-1** (5.0 g, 23.3 mmol), cyclopropylboronic acid (3.99 g, 46.5 mmol), copper acetate (3.48 g, 23.2 mmol), 2,2'-bipyridine (3.9 g, 23.3 mmol) and sodium carbonate (4.9 g, 46.5 mmol) were added to dichloroethane (50 ml), and the mixture was reacted overnight at room temperature under an oxygen balloon. The reaction liquid was filtered, the filtrate was extracted with water and dichloromethane, and the organic phase was concentrated to dryness under reduced pressure. The residue was then purified by column chromatography to obtain **I** (3.6 g, yield: 61%).

Intermediate **J** can be prepared by the same method:

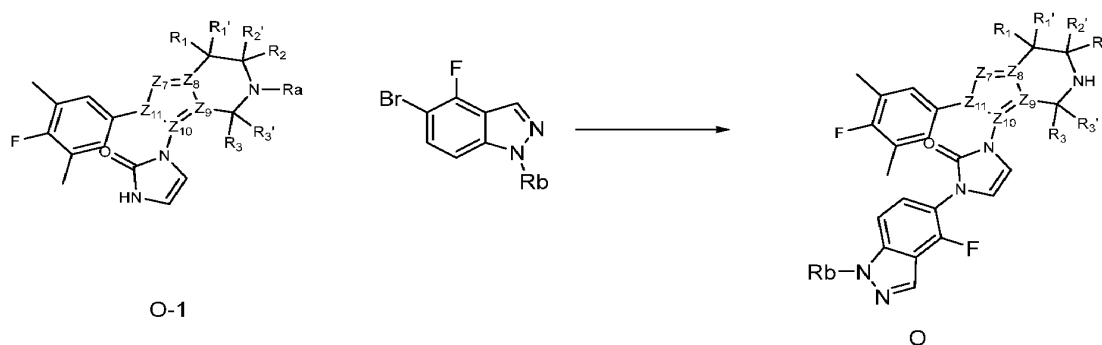
Preparation of intermediates **K**, **L**, **M** and **N**



L, **M** and **N** can be prepared according to the preparation method of intermediate **D**.

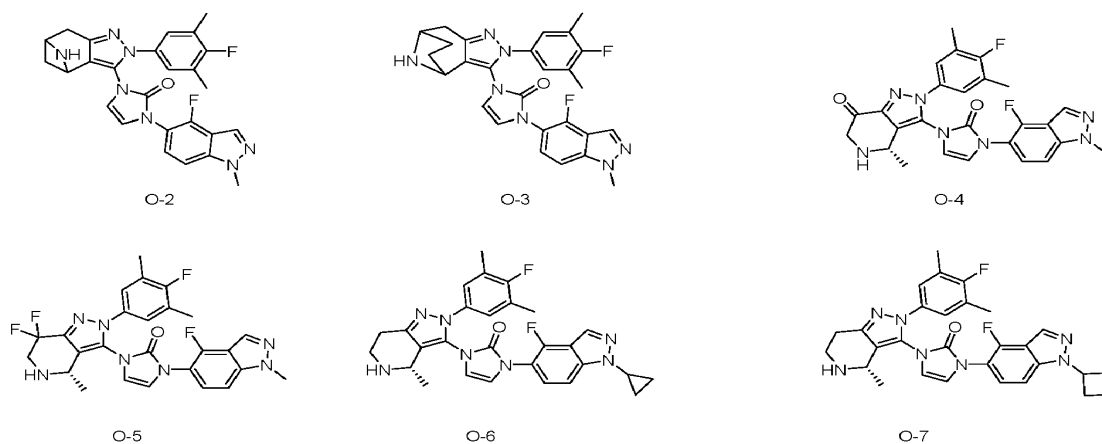
Preparation of intermediate **O**

Description

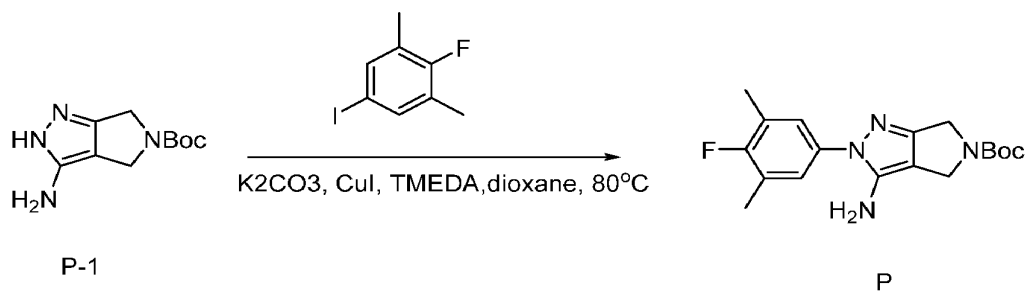


O-1 (1 eq.), (1R, 2R)-(-)-N,N'-dimethyl-1,2-cyclohexanediamine (0.5 eq.), CuI (0.5 eq.), bromide (1.5 eq.) and potassium carbonate (3 eq.) were added to NMP, and the mixture was reacted overnight at room temperature under an oxygen balloon. The reaction was filtered, the filtrate was extracted with water and ethyl acetate, and the organic phase was concentrated under reduced pressure. The residue was purified, and then subjected to a deprotection reaction (debenzylation or Boc removal reaction) to obtain the target compound.

The following compounds can be prepared by the method:



Preparation of intermediate P:

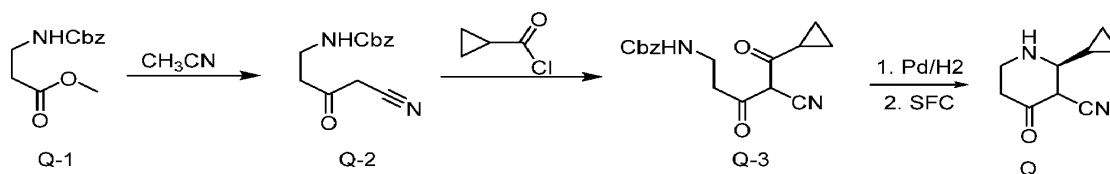


P-1 (1.0 g, 4.46 mmol), 2-fluoro-5-iodo-1,3-dimethylbenzene (1.12 g, 4.46 mmol), CuI (0.8 g, 4.46 mmol), TMEDA (0.52 g, 4.46 mmol) and potassium carbonate (0.92 g, 6.69 mmol) were dissolved in dioxane, and the mixture was reacted at 80°C for 4 hours.

Description

The reaction was cooled and filtered, the filtrate was extracted with ethyl acetate (20 ml) and water (20 ml), and the organic phase was concentrated under reduced pressure. The residue was purified by column chromatography to obtain P (0.6 g, yield: 38.8%).

Preparation of intermediate Q:

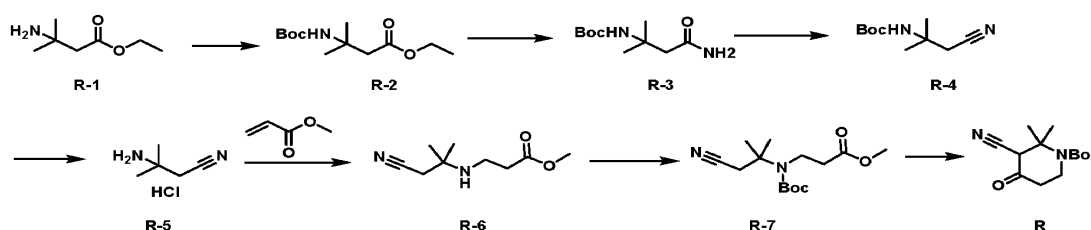


Under N₂ protection, acetonitrile (15.57 g, 379.34 mmol) was added to THF (300 ml), and the mixture was cooled down to below -78°C. LiHMDS (63.47 g, 379.34 mmol) was added dropwise, and the mixture was reacted with the temperature maintained constant for 1 hour. Then, a solution of compound Q1 (45.0 g, 189.67 mmol) in THF (5 ml) was added dropwise, and the mixture was warmed to -50°C and reacted for 30 minutes. The reaction was quenched by dropwise addition of saturated ferric chloride solution, and extracted with ethyl acetate (150 ml). The organic phase was washed with saline, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure, and then the residue was purified by column chromatography to obtain a yellow oil.

Q2 (246.26 mg, 1 mmol) and triethylamine (202.38 mg, 2 mmol) were dissolved in DCM (10 ml), cyclopropanecarbonyl chloride (209.06 mg, 2 mmol) was added dropwise, and the mixture was reacted overnight at room temperature. The reaction liquid was quenched with water, and extracted with DCM (10 ml), the organic phase was washed with saline, dried over magnesium sulfate, and concentrated to dryness under reduced pressure, and then the residue was purified by column chromatography to obtain an oil.

Q3 (150 mg, 0.47 mmol) and Pd/C (15 mg, 30%wt) were dissolved in methanol (15 ml), and the mixture was reacted at room temperature for 3 hours under a hydrogen balloon. The reaction liquid was filtered, and the filtrate was purified by SFC to obtain Q3 (32 mg, yield: 40.8%). ¹HNMR (d-DMSO, 500MHz): δ 4.12(d, 1H, J=8.0Hz), 3.35(m, 1H), 3.12-3.07(m, 2H), 2.63-2.55(m, 2H), 1.47-1.32(m, 5H).

Preparation of intermediate R:



R-1 (10.0 g, 68.87 mmol) and triethylamine (13.9 g, 138 mmol) were dissolved in DCM, (Boc)₂O (18.0 g, 82.64 mmol) was added, and the mixture was reacted overnight at room temperature. The reaction liquid was quenched with water (100 ml), and extracted with DCM (100 ml), and the organic phase was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to obtain **R-2** (15.3 g, yield: 90.56%).

R-2 (15.0 g, 61.1 mmol) was dissolved in a solution of ammonia in methanol (10 M, 300 ml), and the mixture was transferred to an autoclave, heated to 90°C-100°C and reacted for 4 hours. The reaction liquid was cooled and concentrated to dryness under reduced pressure to obtain **R-3**, which was directly used in the next reaction without purification.

Description

R-3, TFAA (6.90 ml, 49.5 mmol) and pyridine (8.0 ml, 99.0 mmol) were added to a three-necked flask, and reacted at room temperature for 1 hour. The reaction liquid was extracted with water and ethyl acetate, the organic phase was washed with saline, dried over magnesium sulfate, and concentrated under reduced pressure, and the residue was purified by column chromatography to obtain **R-4** (5.3 g).

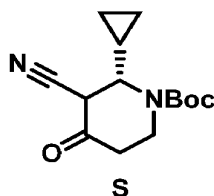
R-4 (5.3 g, 26.7 mmol) was added to a solution of hydrogen chloride in ethyl acetate (4 M, 30 ml), and the mixture was stirred at room temperature for 2 hours. A solid was precipitated, and the mixture was filtered to obtain **R-5** (3.2 g, yield: 88.9%).

R-5 (3.2 g, 23.7 mmol) and triethylamine (7.22 g, 71.3 mmol) were dissolved in ethanol (20 ml), and then methyl acrylate (2.15 g, 24.9 mmol) was added. The mixture was heated to 70°C and reacted for 3 hours. The reaction was cooled to room temperature, (Boc)₂O (6.74 g, 30.9 mmol) was added, and the mixture was further reacted overnight. The reaction was extracted with water (50 ml) and ethyl acetate, the organic phase was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure, and then the residue was purified by column chromatography to obtain **R-7** (4.3 g, yield: 63.6%).

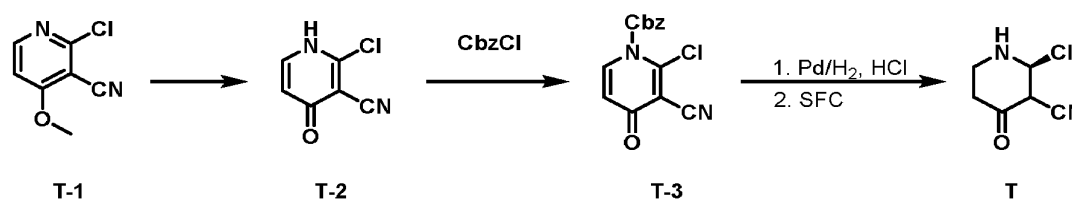
R-7 (4.0 g, 14.1 mmol) and potassium tert-butoxide (2.37 g, 21.1 mmol) were dissolved in THF, and the mixture was reacted at room temperature for 1 hour. The reaction was quenched with 2 N hydrochloric acid, and extracted with water and ethyl acetate, the organic phase was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure, and then the residue was purified by column chromatography to obtain **R** (2.5 g, yield: 70.4%).

Preparation of intermediate S:

Intermediate S can be prepared according to the preparation method of intermediate **R** and by SFC chiral separation.



Preparation of intermediate T:



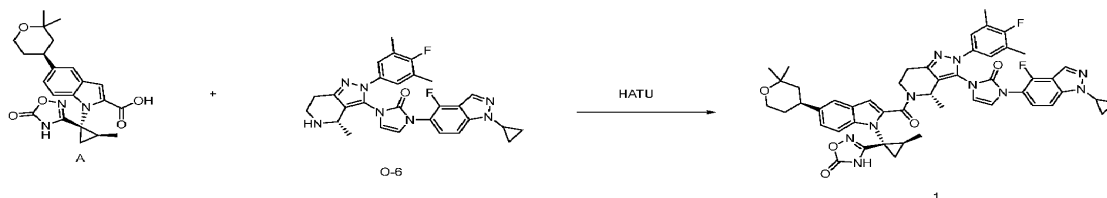
T-1 (10.0 g, 59.3 mmol) was dissolved in THF (100 ml), boron tribromide (120 ml, 1 M in DCM) was added dropwise, and the mixture was reacted at room temperature for 3 hours. The reaction liquid was quenched with saturated sodium carbonate solution and extracted with DCM, and the organic phase was washed brine, dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure to obtain **T-2** (8.5 g, yield: 92.7%).

T-2 (8.0 g, 51.8 mmol) and triethylamine (7.8 g, 77.6 mmol) were dissolved in DCM and cooled down to 0°C, and Cbz-Cl (9.71 g, 56.9 mmol) was added dropwise. The mixture was reacted for 2 hours, the reaction liquid was quenched with saturated sodium carbonate solution and extracted with DCM, and the organic phase was washed brine, dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure to obtain **T-3** (11.2 g, yield: 74.9%).

Description

T-3 (10.0 g, 34.6 mmol), Pd/C (1.0 g, 30%wt) and 0.5 ml HCl (1 M in H₂O) were dissolved in methanol, and the mixture was reacted under a hydrogen pressure of 50 Psi for 2 hours. The reaction liquid was filtered and concentrated under reduced pressure to remove a solvent. The residue was extracted with DCM and saturated sodium bicarbonate solution, the organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure, and the residue was purified by FLASH to obtain a racemate, which was further purified by chiral SFC to obtain T (1.2 g, yield: 21.8%).

Preparation of compound 1

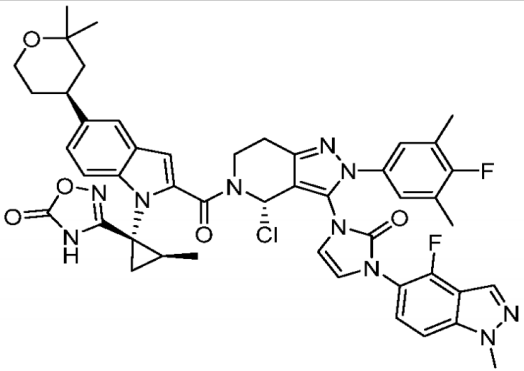


Intermediate **A** (180 mg, 0.44 mmol), **O-6** (280 mg, 0.57 mmol), HATU (250.95 mg, 0.66 mmol) and DIPEA (170 mg, 1.32 mmol) were dissolved in DMF (5 ml), and the mixture was stirred at room temperature for 3 hours. Water (5 ml) was added, and the mixture was extracted 3 times with dichloromethane. The organic phases were combined and concentrated under reduced pressure, and the residue was purified by preparative liquid phase chromatography (acetonitrile: 0.1% formic acid aqueous solution) to obtain target compound **1** (200 mg, yield: 51%).

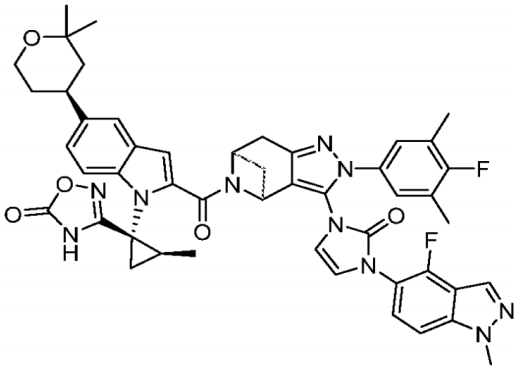
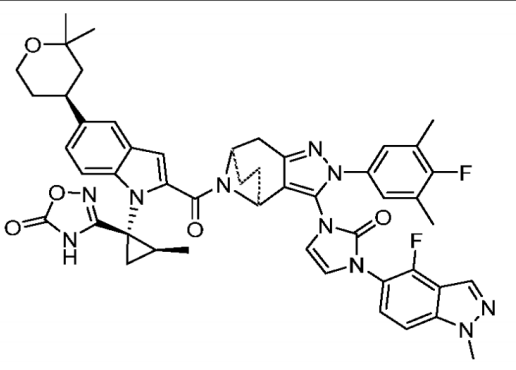
The following compounds were prepared according to the preparation methods described herein using appropriate starting materials and intermediates and appropriate protecting group chemistry when necessary, and the structures were confirmed by MS and ¹H NMR.

Serial number	Structure	MS	¹ H NMR
1		909.39	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 8.79 (s, 1H), 8.37 – 8.29 (m, 2H), 8.21 – 8.14 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 1H), 7.51 – 7.41 (m, 4H), 7.25 – 7.20 (m, 1H), 7.11 – 7.04 (m, 1H), 5.24 – 5.14 (m, 1H), 4.57 – 4.49 (m, 1H), 4.14 – 4.05 (m, 1H), 3.86 – 3.61 (m, 3H), 3.08 – 2.90 (m, 3H), 2.49 –

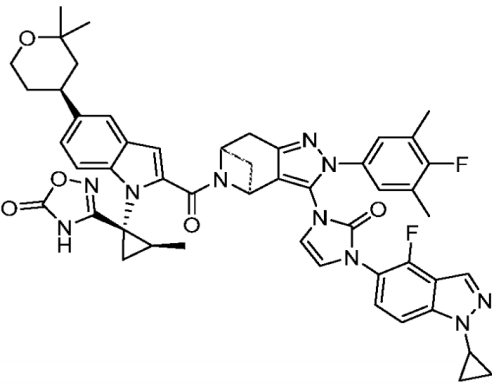
Description

			2.32 (m, 3H), 2.26 – 2.23 (m, 6H), 2.08 – 1.91 (m, 2H), 1.86 – 1.69 (m, 2H), 1.61 – 1.57 (m, 3H), 1.39 – 1.31 (m, 2H), 1.29 – 1.22 (m, 5H), 1.19 (s, 3H), 1.01 – 0.98 (m, 3H).
2		923.41	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 8.79 (s, 1H), 8.38 – 8.28 (m, 2H), 8.18 (d, <i>J</i> = 6.0 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.63 – 7.57 (m, 1H), 7.52 – 7.40 (m, 4H), 7.22 (d, <i>J</i> = 2.0 Hz, 1H), 7.12 – 7.04 (m, 1H), 5.23 – 5.13 (m, 1H), 4.53 – 4.47 (m, 1H), 4.14 – 4.05 (m, 1H), 3.86 – 3.78 (m, 1H), 3.76 – 3.62 (m, 2H), 3.08 – 2.90 (m, 3H), 2.48 – 2.31 (m, 3H), 2.24 (s, 6H), 2.14 – 1.98 (m, 5H), 1.97 – 1.92 (m, 1H), 1.87 – 1.77 (m, 3H), 1.75 – 1.69 (m, 1H), 1.59 (d, <i>J</i> = 7.8 Hz, 3H), 1.24 (s, 3H), 1.19 (s, 3H), 1.00 (d, <i>J</i> = 6.0 Hz, 3H).

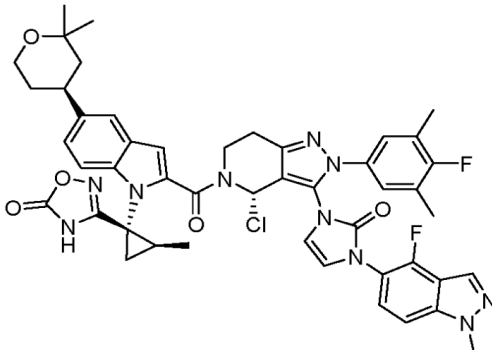
Description

3		881.36	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.36 – 8.27 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.83 – 7.75 (m, 1H), 7.67 – 7.63 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.47 – 7.36 (m, 3H), 7.25 (d, <i>J</i> = 2.0 Hz, 1H), 7.10 – 7.03 (m, 1H), 5.68 – 5.50 (m, 1H), 4.74 – 4.60 (m, 1H), 3.93 (s, 3H), 3.78 – 3.57 (m, 2H), 3.09 – 2.94 (m, 3H), 2.67 – 2.60 (m, 1H), 2.52 – 2.39 (m, 3H), 2.24 (s, 6H), 2.21 – 2.14 (m, 1H), 2.08 – 2.00 (m, 1H), 1.98 – 1.92 (m, 1H), 1.86 – 1.79 (m, 1H), 1.75 – 1.68 (m, 1H), 1.26 – 1.15 (m, 6H), 0.99 (d, <i>J</i> = 5.9 Hz, 3H).
4		895.38	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.36 – 8.28 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.67 – 7.62 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.25 (d, <i>J</i> = 2.0 Hz, 1H), 7.10 –

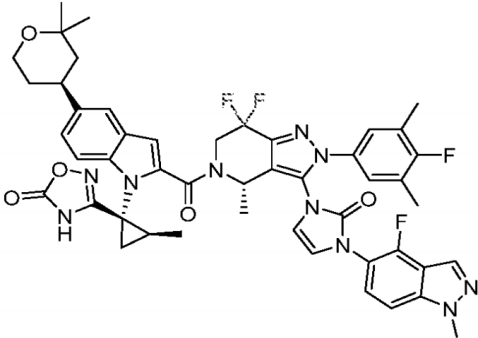
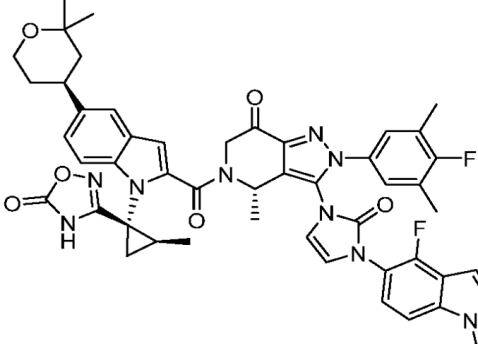
Description

			7.04 (m, 1H), 5.07 – 5.00 (m, 1H), 4.55 – 4.46 (m, 1H), 3.93 (s, 3H), 3.71 – 3.61 (m, 2H), 3.05 – 2.85 (m, 3H), 2.49 – 2.42 (m, 1H), 2.37 – 2.29 (m, 2H), 2.26 – 2.16 (m, 7H), 2.08 – 1.89 (m, 5H), 1.89 – 1.81 (m, 1H), 1.77 – 1.71 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H).
5		907.38	^1H NMR (500 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.39 – 8.29 (m, 3H), 7.94 – 7.88 (m, 1H), 7.68 – 7.58 (m, 2H), 7.46 – 7.38 (m, 3H), 7.25 (d, $J = 2.0$ Hz, 1H), 7.09 – 7.05 (m, 1H), 5.63 – 5.57 (m, 1H), 4.70 – 4.63 (m, 1H), 4.56 – 4.50 (m, 1H), 3.74 – 3.59 (m, 2H), 3.10 – 3.03 (m, 1H), 3.02 – 2.94 (m, 2H), 2.67 – 2.60 (m, 1H), 2.49 – 2.39 (m, 2H), 2.36 – 2.30 (m, 1H), 2.27 – 2.17 (m, 7H), 2.08 – 2.01 (m, 1H), 1.97 – 1.92 (m, 1H), 1.86 – 1.78 (m, 1H),

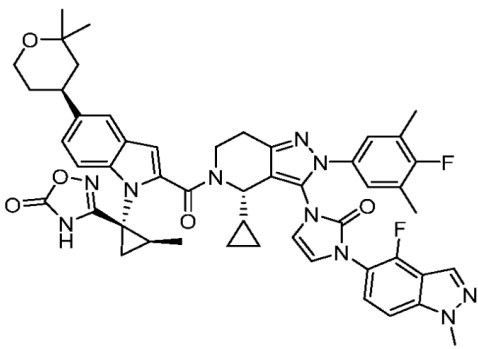
Description

			1.75 – 1.68 (m, 1H), 1.39 – 1.29 (m, 2H), 1.29 – 1.20 (m, 5H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H).
6		903.32	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.38 – 8.28 (m, 2H), 8.14 (d, $J = 4.9$ Hz, 1H), 7.81 – 7.75 (m, 1H), 7.68 – 7.63 (m, 1H), 7.54 (d, $J = 8.9$ Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.10 – 7.04 (m, 1H), 6.94 (s, 1H), 4.33 – 4.25 (m, 1H), 4.09 – 4.03 (m, 1H), 3.93 (s, 3H), 3.74 – 3.67 (m, 1H), 3.66 – 3.58 (m, 1H), 3.07 – 2.94 (m, 3H), 2.49 – 2.41 (m, 1H), 2.38 – 2.28 (m, 2H), 2.24 (s, 6H), 2.07 – 2.00 (m, 1H), 1.99 – 1.91 (m, 1H), 1.87 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H).

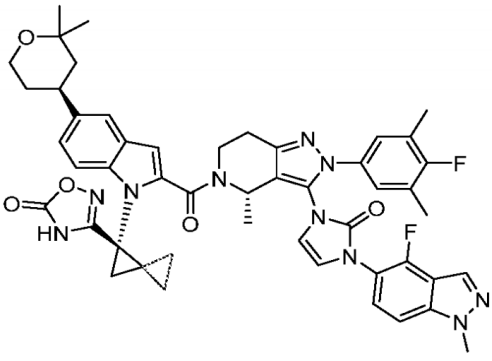
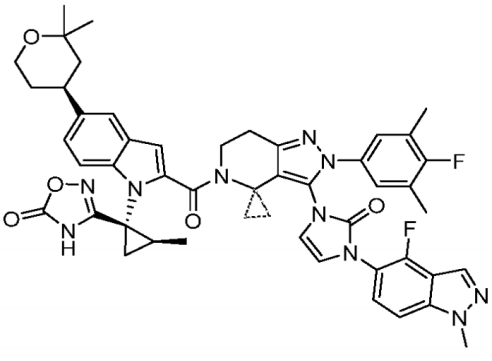
Description

7		919.36	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.39 – 8.28 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.68 – 7.64 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.09 – 7.05 (m, 1H), 5.27 – 5.19 (m, 1H), 4.89 – 4.76 (m, 2H), 3.93 (s, 3H), 3.74 – 3.58 (m, 2H), 3.03 – 2.94 (m, 1H), 2.50 – 2.38 (m, 1H), 2.38 – 2.28 (m, 2H), 2.24 (s, 6H), 2.08 – 1.99 (m, 1H), 1.98 – 1.90 (m, 1H), 1.87 – 1.78 (m, 1H), 1.76 – 1.68 (m, 1H), 1.60 (d, <i>J</i> = 7.5 Hz, 3H), 1.25 – 1.15 (m, 6H), 0.99 (d, <i>J</i> = 6.0 Hz, 3H).
8		897.36	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.36 – 8.29 (m, 2H), 8.17 – 8.11 (m, 1H), 7.83 – 7.75 (m, 1H), 7.68 – 7.63 (m, 1H), 7.57 – 7.51 (m, 1H), 7.47 – 7.40 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.10 – 7.03 (m,

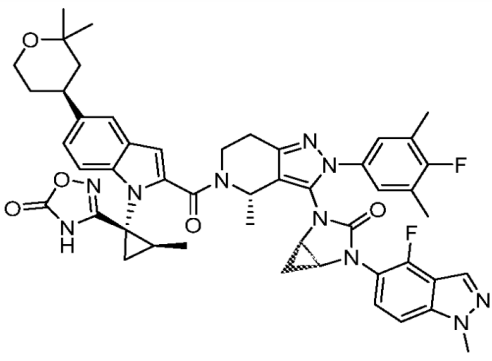
Description

			1H), 5.11 – 4.96 (m, 3H), 3.93 (s, 3H), 3.74 – 3.58 (m, 2H), 3.02 – 2.95 (m, 1H), 2.49 – 2.28 (m, 3H), 2.24 (s, 6H), 2.08 – 2.00 (m, 1H), 1.98 – 1.91 (m, 1H), 1.87 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.60 (d, $J = 7.8$ Hz, 3H), 1.27 – 1.15 (m, 6H), 0.99 (d, $J = 6.0$ Hz, 3H).
9		895.38	¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.16 (s, 1H), 8.36 – 8.29 (m, 2H), 8.14 (d, $J = 4.9$ Hz, 1H), 7.83 – 7.76 (m, 1H), 7.68 – 7.63 (m, 1H), 7.57 – 7.51 (m, 1H), 7.48 – 7.37 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.11 – 7.04 (m, 1H), 4.89 (d, $J = 6.7$ Hz, 1H), 4.18 – 4.08 (m, 1H), 3.93 (s, 3H), 3.87 – 3.79 (m, 1H), 3.75 – 3.58 (m, 2H), 3.05 – 2.88 (m, 3H), 2.51 – 2.44 (m, 1H), 2.37 – 2.29 (m, 2H), 2.24 (s, 6H), 2.08 – 2.00 (m, 1H), 1.98 – 1.89 (m, 2H), 1.87 – 1.78 (m, 1H), 1.75 – 1.69 (m,

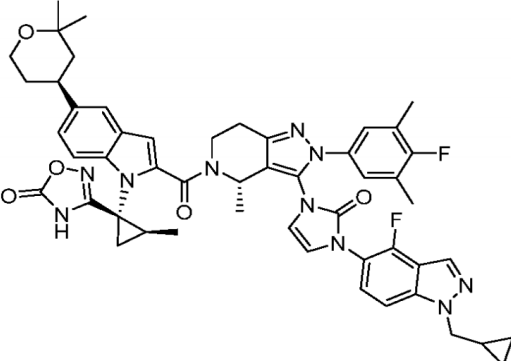
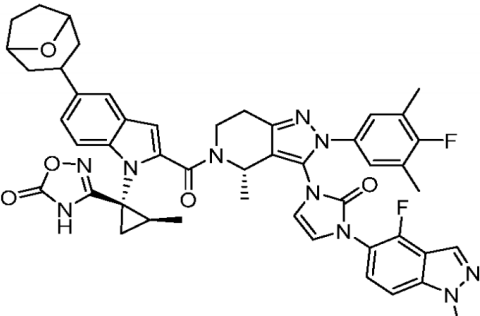
Description

			1H), 1.25 – 1.15 (m, 6H), 0.99 (d, $J = 6.0$ Hz, 3H), 0.68 – 0.57 (m, 2H), 0.49 – 0.39 (m, 2H).
10		895.38	^1H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.36 – 8.29 (m, 2H), 8.14 (d, $J = 4.9$ Hz, 1H), 7.81 – 7.76 (m, 1H), 7.67 – 7.64 (m, 1H), 7.54 (d, $J = 8.9$ Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.10 – 7.04 (m, 1H), 5.22 – 5.14 (m, 1H), 4.11 – 4.05 (m, 1H), 3.96 – 3.85 (m, 4H), 3.74 – 3.58 (m, 2H), 3.04 – 2.90 (m, 3H), 2.35 (s, 2H), 2.24 (s, 6H), 2.07 – 1.91 (m, 2H), 1.86 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.65 – 1.47 (m, 7H), 1.25 – 1.16 (m, 6H).
11		895.38	^1H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.34 – 8.23 (m, 2H), 8.14 (d, $J = 4.9$ Hz, 1H), 7.82 – 7.76 (m, 1H), 7.67 – 7.63 (m, 1H), 7.54 (d, $J = 8.9$ Hz, 1H), 7.46 – 7.37 (m, 3H), 7.24

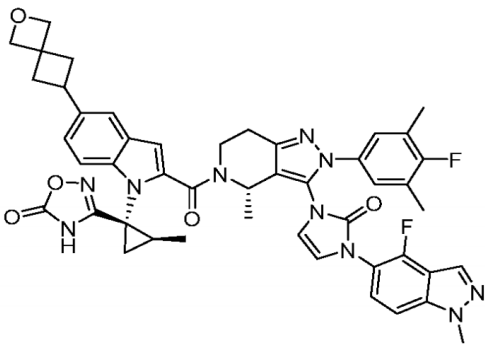
Description

			(d, $J = 2.0$ Hz, 1H), 7.11 – 7.04 (m, 1H), 3.96 – 3.83 (m, 5H), 3.74 – 3.59 (m, 2H), 3.01 – 2.95 (m, 1H), 2.91 – 2.84 (m, 2H), 2.51 – 2.44 (m, 1H), 2.37 – 2.19 (m, 12H), 2.07 – 2.00 (m, 1H), 1.97 – 1.92 (m, 1H), 1.87 – 1.79 (m, 1H), 1.75 – 1.69 (m, 1H), 1.26 – 1.16 (m, 6H), 0.99 (d, $J = 6.0$ Hz, 3H).
12		898.00	^1H NMR (500 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.13 (d, $J = 5.2$ Hz, 1H), 7.68 – 7.63 (m, 1H), 7.53 (d, $J = 9.0$ Hz, 1H), 7.51 – 7.41 (m, 2H), 7.37 (d, $J = 4.9$ Hz, 2H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.10 – 7.05 (m, 1H), 5.22 – 5.11 (m, 1H), 4.34 – 4.29 (m, 2H), 4.10 – 4.03 (m, 1H), 3.96 – 3.87 (m, 4H), 3.74 – 3.59 (m, 2H), 3.04 – 2.89 (m, 3H), 2.48 – 2.42 (m, 1H), 2.38 – 2.29 (m, 2H), 2.24 (s, 6H), 2.07 – 1.91 (m, 3H), 1.86 – 1.68 (m, 3H), 1.60 (d, $J = 8.0$

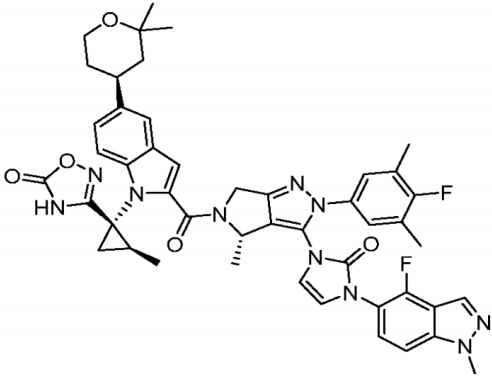
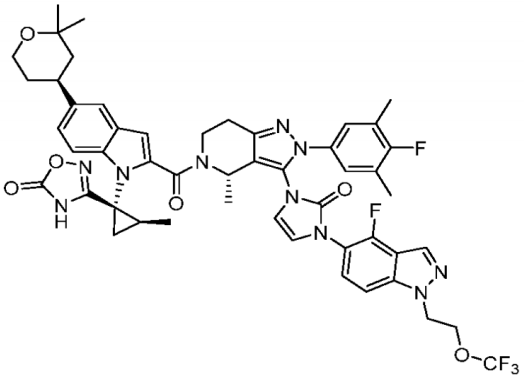
Description

			Hz, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H).
13		923.41	^1H NMR (500 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.37 – 8.29 (m, 2H), 8.25 (d, $J = 4.9$ Hz, 1H), 7.85 – 7.78 (m, 1H), 7.67 – 7.62 (m, 1H), 7.48 – 7.37 (m, 4H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.09 – 7.04 (m, 1H), 5.22 – 5.13 (m, 1H), 4.13 – 3.84 (m, 4H), 3.73 – 3.59 (m, 2H), 3.03 – 2.89 (m, 3H), 2.49 – 2.20 (m, 9H), 2.08 – 1.91 (m, 2H), 1.87 – 1.68 (m, 2H), 1.63 – 1.45 (m, 4H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H), 0.61 – 0.38 (m, 4H).
14		881.36	^1H NMR (500 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.37 – 8.28 (m, 2H), 8.14 (d, $J = 4.9$ Hz, 1H), 7.82 – 7.75 (m, 1H), 7.66 – 7.61 (m, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.11 – 7.06 (m, 1H), 5.22 – 5.14

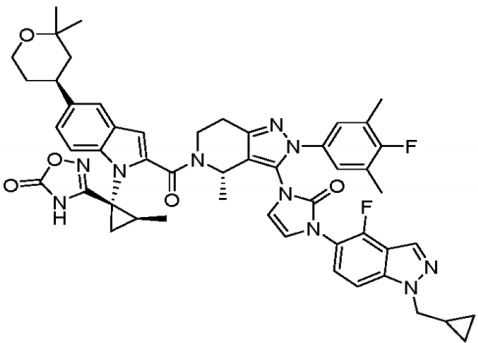
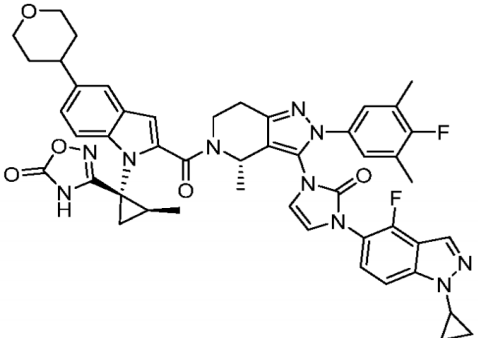
Description

			(m, 1H), 4.12 – 4.03 (m, 3H), 3.95 – 3.85 (m, 4H), 3.07 – 2.89 (m, 3H), 2.42 – 2.21 (m, 9H), 1.99 – 1.73 (m, 8H), 1.60 (d, $J = 8.0$ Hz, 3H), 0.99 (d, $J = 5.8$ Hz, 3H).
15		867.35	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.36 – 8.28 (m, 2H), 8.14 (d, $J = 4.9$ Hz, 1H), 7.82 – 7.76 (m, 1H), 7.66 – 7.61 (m, 1H), 7.54 (d, $J = 8.9$ Hz, 1H), 7.46 – 7.38 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.08 – 7.03 (m, 1H), 5.24 – 5.12 (m, 1H), 4.11 – 4.02 (m, 1H), 3.96 – 3.87 (m, 4H), 3.81 (d, $J = 6.0$ Hz, 2H), 3.72 (d, $J = 6.2$ Hz, 2H), 3.04 – 2.80 (m, 3H), 2.52 – 2.43 (m, 1H), 2.39 – 2.28 (m, 2H), 2.24 (s, 6H), 2.15 – 2.00 (m, 4H), 1.60 (d, $J = 8.0$ Hz, 3H), 0.99 (d, $J = 6.0$ Hz, 3H).

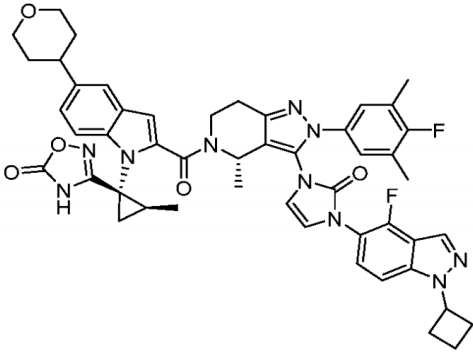
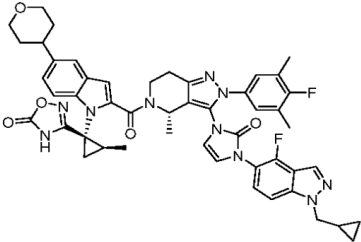
Description

16		869.36	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.37 – 8.28 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.66 – 7.64 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.10 – 7.05 (m, 1H), 5.02 – 4.95 (m, 1H), 4.61 (d, <i>J</i> = 1.0 Hz, 2H), 3.93 (s, 3H), 3.71 – 3.62 (m, 2H), 3.03 – 2.94 (m, 1H), 2.49 – 2.40 (m, 1H), 2.38 – 2.21 (m, 8H), 2.06 – 1.81 (m, 3H), 1.77 – 1.70 (m, 1H), 1.57 (d, <i>J</i> = 7.0 Hz, 3H), 1.27 – 1.15 (m, 6H), 0.99 (d, <i>J</i> = 6.0 Hz, 3H).
17		981.38	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 8.79 (s, 1H), 8.37 – 8.29 (m, 2H), 8.21 – 8.14 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 1H), 7.51 – 7.41 (m, 4H), 7.25 – 7.20 (m, 1H), 7.11 – 7.04 (m, 1H), 5.24 – 5.14 (m, 1H), 4.59 – 4.49 (m, 3H), 4.14 – 4.05 (m, 3H).

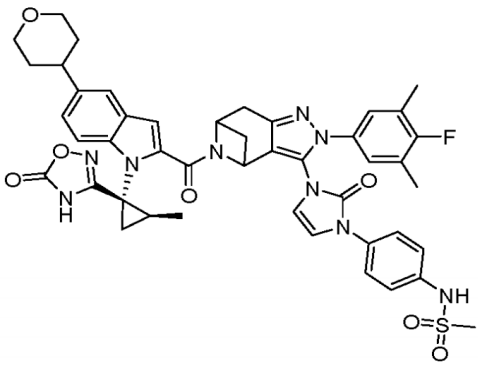
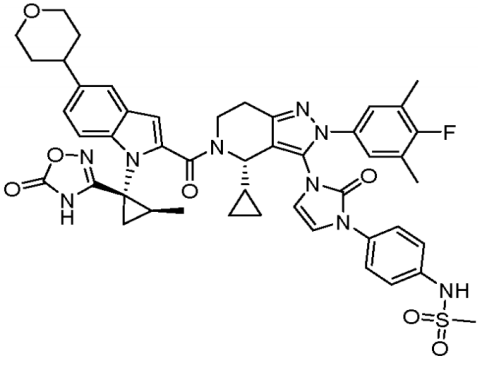
Description

			1H), 3.86 – 3.61 (m, 5H), 3.08 – 2.90 (m, 3H), 2.49 – 2.32 (m, 3H), 2.26 – 2.23 (m, 6H), 2.08 – 1.91 (m, 2H), 1.86 – 1.69 (m, 2H), 1.61 – 1.57 (m, 3H), 1.39 – 1.31 (m, 2H), 1.19 (s, 3H), 1.01 – 0.98 (m, 3H).
18		923.04	¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.16 (s, 1H), 8.36 – 8.23 (m, 3H), 7.85 – 7.78 (m, 1H), 7.68 – 7.63 (m, 1H), 7.48 – 7.38 (m, 4H), 7.23 – 7.18 (m, 1H), 7.10 – 7.04 (m, 1H), 5.20 – 5.14 (m, 1H), 4.12 – 3.85 (m, 4H), 3.74 – 3.59 (m, 2H), 3.03 – 2.89 (m, 3H), 2.48 – 2.42 (m, 1H), 2.37 – 2.28 (m, 2H), 2.24 (s, 6H), 2.07 – 1.92 (m, 2H), 1.86 – 1.79 (m, 1H), 1.75 – 1.67 (m, 1H), 1.63 – 1.46 (m, 4H), 1.24 – 1.16 (m, 6H), 1.00 – 0.97 (m, 3H), 0.61 – 0.38 (m, 4H).
19		881.36	¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.16 (s, 1H), 8.40 – 8.28 (m, 3H), 7.96 – 7.86 (m, 1H), 7.67 – 7.58 (m, 2H), 7.47 – 7.36 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.09 – 7.03 (m, 1H), 5.23 – 5.13

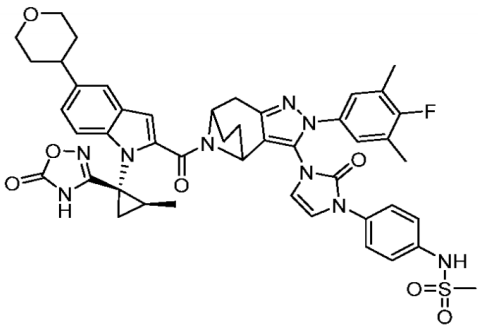
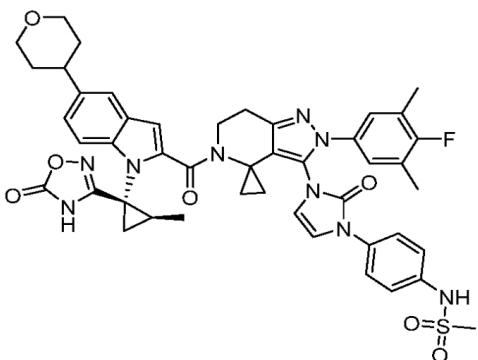
Description

			(m, 1H), 4.56 – 4.49 (m, 1H), 4.12 – 3.85 (m, 2H), 3.59 – 3.47 (m, 4H), 3.04 – 2.88 (m, 3H), 2.39 – 2.27 (m, 3H), 2.24 (s, 6H), 2.14 – 2.08 (m, 2H), 1.88 – 1.79 (m, 2H), 1.60 (d, $J = 8.0$ Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.95 (m, 3H).
20		895.38	^1H NMR (500 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.38 – 8.29 (m, 3H), 7.94 – 7.88 (m, 1H), 7.66 – 7.58 (m, 2H), 7.46 – 7.37 (m, 3H), 7.23 – 7.20 (m, 1H), 7.08 – 7.03 (m, 1H), 5.23 – 5.11 (m, 1H), 4.53 – 4.47 (m, 1H), 4.09 – 3.87 (m, 2H), 3.59 – 3.46 (m, 4H), 3.03 – 2.88 (m, 3H), 2.41 – 2.26 (m, 3H), 2.24 (s, 6H), 2.15 – 1.98 (m, 6H), 1.88 – 1.79 (m, 4H), 1.62 – 1.58 (m, 3H), 0.99 (d, $J = 5.8$ Hz, 3H).
21		895.44	^1H NMR (500 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.35 – 8.23 (m, 3H), 7.86 – 7.78 (m, 1H), 7.66 – 7.62 (m, 1H), 7.48 – 7.38 (m, 4H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.09 – 7.03 (m, 1H), 5.21 – 5.13 (m, 1H), 4.10 – 3.87 (m, 4H), 3.60 – 3.46 (m, 4H), 3.02 – 2.88

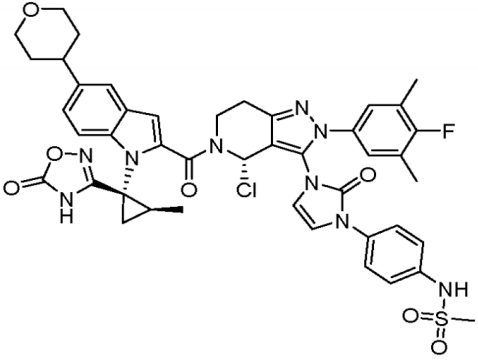
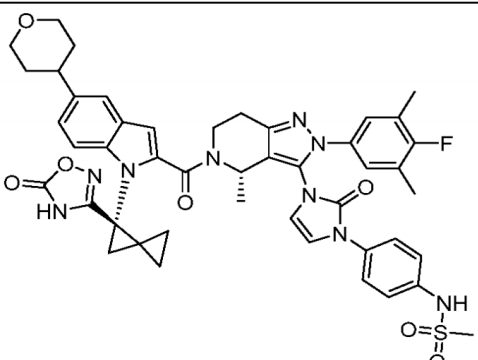
Description

			(m, 3H), 2.53 – 2.28 (m, 3H), 2.24 (s, 6H), 2.17 – 2.07 (m, 2H), 1.89 – 1.79 (m, 2H), 1.60 (d, $J = 8.0$ Hz, 3H), 1.53 – 1.45 (m, 1H), 0.99 (d, $J = 6.0$ Hz, 3H), 0.59 – 0.39 (m, 4H).
22		874.44	^1H NMR (500 MHz, DMSO- d_6) δ 9.91 (s, 1H), 9.16 (s, 1H), 8.36 (d, $J = 6.0$ Hz, 1H), 8.17 (d, $J = 6.0$ Hz, 1H), 7.64 (t, $J = 2.0$ Hz, 1H), 7.46 – 7.35 (m, 5H), 7.29 – 7.15 (m, 3H), 7.09 – 7.02 (m, 1H), 5.60 (t, $J = 5.7$ Hz, 1H), 4.70 – 4.62 (m, 1H), 3.58 – 3.47 (m, 4H), 3.09 – 2.96 (m, 3H), 2.95 (s, 3H), 2.67 – 2.61 (m, 1H), 2.45 – 2.26 (m, 4H), 2.24 (s, 6H), 2.17 – 2.06 (m, 2H), 1.89 – 1.76 (m, 2H), 0.99 (d, $J = 5.8$ Hz, 3H).
23		902.33	^1H NMR (500 MHz, DMSO- d_6) δ 9.91 (s, 1H), 9.16 (s, 1H), 8.36 (d, $J = 6.0$ Hz, 1H), 8.17 (d, $J = 6.0$ Hz, 1H), 7.64 (t, $J = 2.0$ Hz, 1H), 7.47 – 7.36 (m, 5H), 7.25 – 7.15 (m, 3H), 7.09 – 7.03 (m, 1H), 4.89 (d, $J = 6.7$ Hz, 1H), 4.16 – 4.07 (m, 1H), 3.89 – 3.81 (m, 1H), 3.58 – 3.47 (m, 4H),

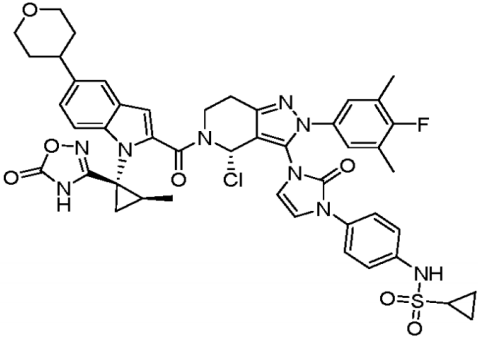
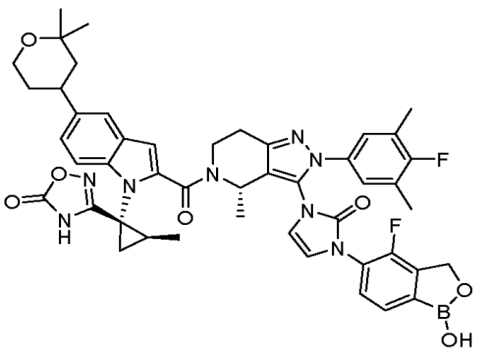
Description

			3.04 – 2.89 (m, 6H), 2.40 – 2.26 (m, 3H), 2.24 (s, 6H), 2.16 – 2.07 (m, 2H), 1.97 – 1.79 (m, 3H), 0.99 (d, $J = 5.8$ Hz, 3H), 0.58 – 0.54 (m, 4H).
24		888.34	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 9.16 (s, 1H), 8.36 (d, $J = 6.0$ Hz, 1H), 8.17 (d, $J = 6.0$ Hz, 1H), 7.64 (t, $J = 2.1$ Hz, 1H), 7.48 – 7.35 (m, 5H), 7.31 – 7.18 (m, 3H), 7.08 – 7.03 (m, 1H), 5.04 (t, $J = 4.8$ Hz, 1H), 4.55 – 4.48 (m, 1H), 3.59 – 3.48 (m, 4H), 3.02 – 2.86 (m, 6H), 2.48 – 2.42 (m, 1H), 2.37 – 2.28 (m, 2H), 2.24 (s, 6H), 2.23 – 2.16 (m, 1H), 2.15 – 2.01 (m, 3H), 2.00 – 1.89 (m, 2H), 1.88 – 1.80 (m, 2H), 0.99 (d, $J = 6.0$ Hz, 3H).
25		888.32	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 9.16 (s, 1H), 8.34 (d, $J = 6.0$ Hz, 1H), 8.17 (d, $J = 6.0$ Hz, 1H), 7.64 (t, $J = 2.1$ Hz, 1H), 7.47 – 7.36 (m, 5H), 7.27 – 7.16 (m, 3H), 7.10 – 7.02 (m, 1H), 3.92 – 3.83 (m, 2H), 3.57 – 3.48 (m, 4H), 3.01 – 2.96 (m, 1H), 2.95 (s, 3H), 2.91 – 2.85

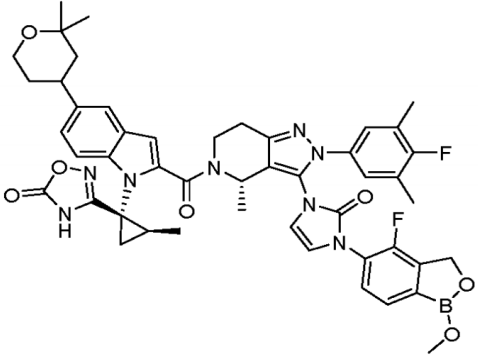
Description

			(m, 2H), 2.40 – 2.18 (m, 13H), 2.15 – 2.07 (m, 2H), 1.88 – 1.80 (m, 2H), 0.99 (d, $J = 5.8$ Hz, 3H).
26		895.32	^1H NMR (500 MHz, DMSO- d_6) δ 9.91 (s, 1H), 9.16 (s, 1H), 8.37 (d, $J = 6.0$ Hz, 1H), 8.18 (d, $J =$ 6.0 Hz, 1H), 7.64 (s, 1H), 7.64 (d, $J = 4.1$ Hz, 0H), 7.43 (d, $J =$ 7.5 Hz, 1H), 7.42 – 7.37 (m, 4H), 7.23 – 7.17 (m, 3H), 7.08 – 7.03 (m, 1H), 6.94 (s, 1H), 4.31 – 4.23 (m, 1H), 4.11 – 4.03 (m, 1H), 3.59 – 3.47 (m, 4H), 3.06 – 2.96 (m, 3H), 2.95 (s, 3H), 2.40 – 2.33 (m, 1H), 2.36 – 2.26 (m, 2H), 2.24 (s, 6H), 2.16 – 2.07 (m, 2H), 1.88 – 1.79 (m, 2H), 0.99 (d, $J = 5.8$ Hz, 3H).
27		888.32	^1H NMR (500 MHz, DMSO- d_6) δ 9.91 (s, 1H), 8.76 (s, 1H), 8.36 (d, $J = 6.0$ Hz, 1H), 8.17 (d, $J =$ 6.0 Hz, 1H), 7.64 (s, 1H), 7.46 – 7.37 (m, 5H), 7.23 – 7.17 (m, 3H), 7.08 – 7.03 (m, 1H), 5.22 – 5.14 (m, 1H), 4.10 – 4.02 (m, 1H), 3.95 – 3.87 (m, 1H), 3.59 – 3.47 (m, 4H), 3.03 – 2.89 (m, 6H), 2.43 – 2.37 (m, 1H), 2.30 –

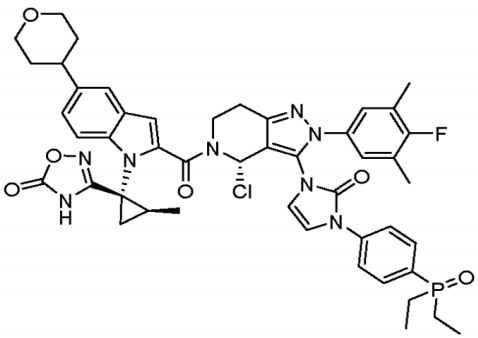
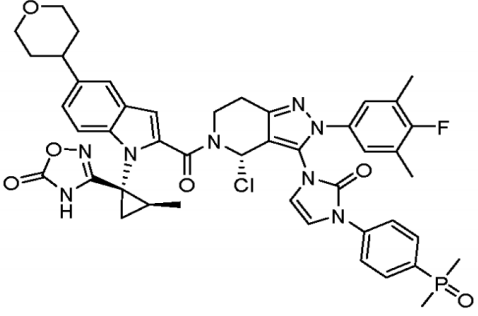
Description

			2.25 (m, 1H), 2.24 (s, 6H), 2.16 – 2.07 (m, 2H), 1.88 – 1.79 (m, 2H), 1.66 – 1.56 (m, 5H), 1.56 – 1.50 (m, 1H), 1.53 – 1.46 (m, 1H).
28		922.28	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.72 (s, 1H), 9.16 (s, 1H), 8.37 (d, <i>J</i> = 6.0 Hz, 1H), 8.18 (d, <i>J</i> = 6.0 Hz, 1H), 7.64 (s, 1H), 7.64 (d, <i>J</i> = 4.1 Hz, 0H), 7.43 (d, <i>J</i> = 7.5 Hz, 1H), 7.42 – 7.37 (m, 4H), 7.23 – 7.17 (m, 3H), 7.08 – 7.03 (m, 1H), 6.94 (s, 1H), 4.31 – 4.23 (m, 1H), 4.11 – 4.03 (m, 1H), 3.59 – 3.47 (m, 4H), 3.47 – 3.40 (m, 1H), 3.06 – 2.99 (m, 1H), 3.03 – 2.94 (m, 2H), 2.40 – 2.33 (m, 1H), 2.36 – 2.26 (m, 2H), 2.24 (s, 6H), 2.16 – 2.07 (m, 2H), 1.88 – 1.79 (m, 2H), 1.79 – 1.58 (m, 4H), 0.99 (d, <i>J</i> = 5.8 Hz, 3H).
29		885.34	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.36 – 8.29 (m, 2H), 7.65 (d, <i>J</i> = 3.8 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.47 – 7.33 (m, 4H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.11 – 7.04 (m, 1H), 5.23 – 5.11 (m, 3H), 4.11 – 4.02 (m,

Description

			1H), 3.96 – 3.87 (m, 1H), 3.74 – 3.62 (m, 2H), 3.13 – 2.89 (m, 3H), 2.51 – 2.43 (m, 1H), 2.38 – 2.29 (m, 2H), 2.24 (s, 6H), 2.17 – 2.09 (m, 1H), 2.00 – 1.87 (m, 2H), 1.78 – 1.71 (m, 1H), 1.60 (d, $J = 8.0$ Hz, 3H), 1.20 (d, $J = 25.2$ Hz, 6H), 0.99 (d, $J = 6.0$ Hz, 3H).
30		899.38	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.36 – 8.29 (m, 2H), 7.67 – 7.63 (m, 1H), 7.57 – 7.51 (m, 1H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.41 – 7.36 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.10 – 7.04 (m, 1H), 5.22 – 5.15 (m, 1H), 5.14 (s, 1H), 5.12 (s, 1H), 4.10 – 4.02 (m, 1H), 3.95 – 3.87 (m, 1H), 3.74 – 3.61 (m, 2H), 3.65 (s, 3H), 3.13 – 3.04 (m, 1H), 3.03 – 2.89 (m, 2H), 2.52 – 2.43 (m, 1H), 2.38 – 2.28 (m, 2H), 2.24 (s, 6H), 2.18 – 2.09 (m, 1H), 1.99 – 1.86 (m, 2H), 1.79 – 1.71 (m, 1H), 1.60 (d, $J = 8.0$ Hz, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H).

Description

31		907.34	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.37 (d, <i>J</i> = 6.0 Hz, 1H), 8.18 (d, <i>J</i> = 6.0 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.75 – 7.69 (m, 2H), 7.66 – 7.62 (m, 1H), 7.43 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 (d, <i>J</i> = 5.1 Hz, 2H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.94 (s, 1H), 4.31 – 4.23 (m, 1H), 4.11 – 4.03 (m, 1H), 3.59 – 3.47 (m, 4H), 3.06 – 2.99 (m, 1H), 3.03 – 2.94 (m, 2H), 2.72 – 2.63 (m, 4H), 2.41 – 2.26 (m, 3H), 2.24 (s, 6H), 2.16 – 2.07 (m, 2H), 1.88 – 1.79 (m, 2H), 1.51 – 1.47 (m, 6H), 0.99 (d, <i>J</i> = 5.8 Hz, 3H).
32		879.29	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.37 (d, <i>J</i> = 6.0 Hz, 1H), 8.18 (d, <i>J</i> = 6.0 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.75 – 7.69 (m, 2H), 7.66 – 7.62 (m, 1H), 7.43 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 (d, <i>J</i> = 5.1 Hz, 2H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.94 (s, 1H), 4.31 – 4.23 (m, 1H), 4.11 – 4.03 (m, 1H), 3.59 – 3.47 (m, 4H), 3.06 – 2.99 (m, 1H), 3.03 – 2.94 (m,

Description

			2H), 2.41 – 2.26 (m, 3H), 2.24 (s, 6H), 2.16 – 2.07 (m, 2H), 1.88 – 1.79 (m, 2H), 1.51 – 1.47 (m, 6H), 0.99 (d, $J = 5.8$ Hz, 3H).
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Description

Example 2 In vitro activity evaluation

GLP-1R cAMP Assay

1. Preparation of cell line and reagent
 - 1) Cell line: Flp-In-293-GLP1R
 - 2) Culture medium: DMEM + 10% FBS + 1 X Penicillin-Streptomycin + 200 µg/mL HB
 - 3) Test buffer: 1 X HBSS+20 mM HEPES + 0.1%BSA+ 500 µM IBMX
2. Agonist test
 - a) Flpin-293-GLP1R cells were inoculated into complete medium at 2,000 cells per well in a 384-well assay plate (6007680-50, PE).
 - b) 4X complex working solution was prepared with the test buffer.
 - c) 5 µL OF 4X compound working solution was added to the cell plate, and the cell plate was incubated at 37°C for 30 minutes.
 - d) Eu-cAMP tracer was diluted in a lysis buffer (1/50) and then added to the assay plate at 10 µl/well.
 - e) Ulight-anti-cAMP was diluted in a lysis buffer (1/150) and then added to the assay plate at 10 µl/well.
 - f) The plate was incubated at a constant-temperature for 1 hour.
 - g) The plate was read on Envision 2105 microplate reader at the wavelength of 665 nM and 615 nM.
3. Data analysis
 - 3.1 The calculation formula of % Activity is as follows:

$$\% \text{ Activity} = 100 - (\text{Signal}_{\text{cmpd}} - \text{Signal}_{\text{Ave_PC}}) / (\text{Signal}_{\text{Ave_VC}} - \text{Signal}_{\text{Ave_PC}}) \times 100.$$
 - 3.2 EC50 was calculated and the response-dose curve of cmpds was plotted:

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC50} - X) * \text{HillSlope}))}$$

X: logarithm of agonist concentration agonist; Y: activity percentage.

The biological activities of compounds in the GLP-1R agonist cAMP stimulation assay were shown in Table 2 below.

Table 2: Biological activities of compounds in the GLP-1R agonist cAMP stimulation assay

Compound ID	GLP-1R cAMP:EC ₅₀	Compound ID	GLP-1R cAMP:EC ₅₀
1	A	17	A
2	A	18	A

Description

3	A	19	A
4	A	20	A
5	A	21	A
6	A	22	A
7	A	23	A
8	A	24	A
9	A	25	A
10	A	26	A
11	A	27	A
12	B	28	A
13	A	29	A
14	A	30	A
15	A	31	A
16	C	32	A

Note: Range of EC₅₀: A: $0 \leq EC_{50} < 0.1$ nM; B: $0.1 \text{ nM} \leq EC_{50} < 1$ nM; C: $1 \text{ nM} \leq EC_{50} < 10$ nM.

TRANSLATION CERTIFICATION

Date: April 20, 2025

To whom it may concern:

This is to certify that the attached translation is an accurate representation of the documents CN202311371725.7 filed October 23, 2023, which is a certified copy of priority document of US12234236B1 received by this office. The translation was completed from:

- Simplified Chinese

To:

- English

Min ZHANG, Senior Reviser in RWS, attests to the following:

“To the best of my knowledge, the aforementioned documents are a true, full and accurate translation of the specified documents.”



Signature of Min ZHANG