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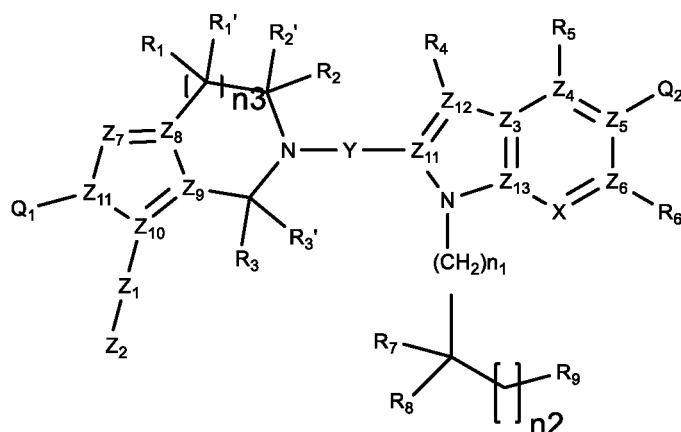
Application no.: 202410142451.2
Application type: Patent for invention
Title of invention/creation: GLP-1R AGONIST AND USE THEREOF
Filing date: January 31, 2024
Applicant: Ascletis BioScience (Hangzhou) Co., Ltd.
Inventors or designers: Liang Bin, Wu Jinzi

Commissioner
Shen Changyu

February 3, 2024

Claims

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



Formula I

wherein

X is selected from N or $-CR^a$; R^a is selected from 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 is optionally substituted by one to five substituents independently selected from halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy;

Q_2 is a 3- to 12-membered heterocyclyl, a bridged ring, a spiro ring or a 5- to 10-membered heteroaryl, wherein the 3- to 12-membered heterocyclyl and the 5- to 10-membered heteroaryl are optionally substituted by 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 groups together with the carbon atom to which they are attached 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 or cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from halogen atoms, C_{1-6} alkoxy and hydroxy;

wherein R_2 and R_3 together with the carbon atom to which they are attached form 4- to 8-membered heterocycloalkyl;

wherein R_1 and R_1' together with the carbon atom to which they are attached may form C_3-C_8 cycloalkyl, R_2 and R_2' together with the carbon atom to which they are attached may form C_3-C_8 cycloalkyl, and R_3 and R_3' together with the carbon atom to which they are attached may form C_3-

Claims

C₈ cycloalkyl;

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 by one or more substituents independently selected from halogen and C₃₋₁₅ cycloalkyl;

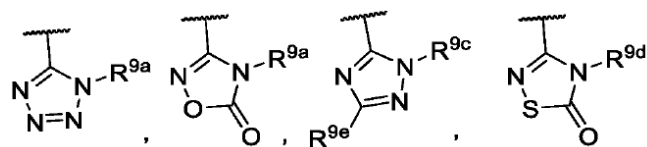
or R₇ and R₈ together with the carbon atom to which they are attached form a C₃₋₁₅ carbocyclic ring; wherein the C₃₋₁₅ carbocyclic ring formed by R₇ and R₈ together is optionally substituted by one to three C₁₋₆ alkyl groups, wherein the C₁₋₆ alkyl group is optionally substituted by one or more substituents independently selected from halogen, hydroxy, -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 groups together with the carbon atom to which they are attached may 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;

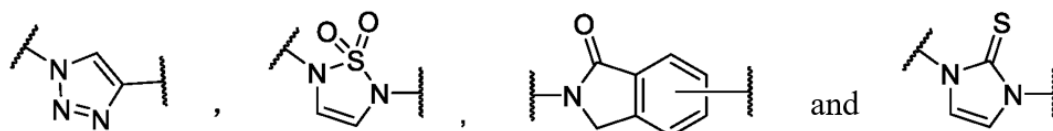
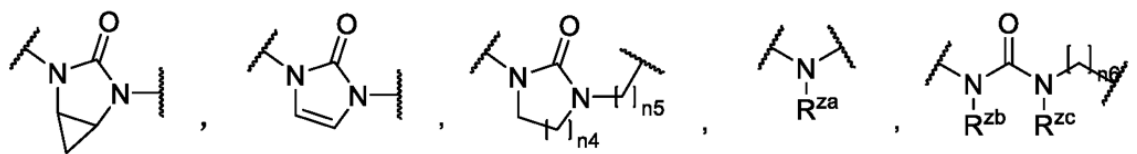
R₉ is selected from the following groups:



, -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 by one or more substituents independently selected from halogen and C₁₋₆ alkoxy; R^{9e} is hydrogen or C₁₋₆ alkyl optionally substituted by 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:



wherein R^{za} is selected from hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl, 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 and 5- to 10-membered heteroaryl, and the following groups:



R₁₀ and R₁₁ are selected from H, C₁₋₆ alkyl and (C₁₋₆ alkyl)aryl, C₁₋₆ haloalkyl, -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl;

a. 0X0;

b. halogen;

c. cyano;

d. -NR^{zd}R^{ze}; wherein R^{zd} and R^{ze} are independently selected from hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more substituents independently selected from hydroxy, halogen and C₁₋₆ alkoxy;

e. -C(=O)-NR^{zf}R^{zg}; wherein R^{zf} and R^{zg} are independently selected from hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more substituents independently selected from hydroxy, halogen and C₁₋₆ alkoxy;

f. $-S(=O)_{n7}-R^{zh}$; wherein $n7$ is 0, 1 or 2; R^{zh} is hydrogen or C_{1-6} alkyl;

g. C₁₋₆ alkyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxy, -NR^{zi}R^{zj}, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy and 3- to 12-membered heterocyclyl; wherein R^{zi} and R^{zj} are independently hydrogen or C₁₋₆ alkyl, and wherein the 3- to 12-membered heterocyclyl is optionally substituted by one or more cyano, C₁₋₆ alkyl and 3- to 12-membered heterocyclyl substituents;

h. C₁₋₆ alkoxy; wherein the C₁₋₆ alkoxy is optionally substituted by one or more hydroxy, halogen and C₁₋₆ alkoxy substituents;

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

j. C₆₋₁₀ aryl; wherein the C₆₋₁₀ aryl is optionally substituted by one or more (C₁₋₆ alkyl)carbonyl groups, and

k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally

Claims

substituted by one or more substituents independently selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, -NR^{zk}R^{zl} and 3- to 12-membered heterocyclyl; wherein R^{zk} and R^{zl} are independently selected from hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl, and wherein the 3- to 12-membered heterocyclyl is optionally substituted by one or more substituents independently selected from C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl;

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

m. -P(=O)R^{zm}R^{zn}, -(CH₂)_{n8}-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; n8 is 1 or 2;

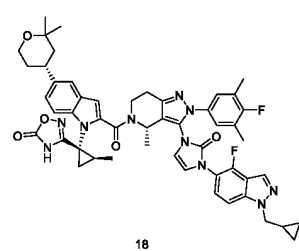
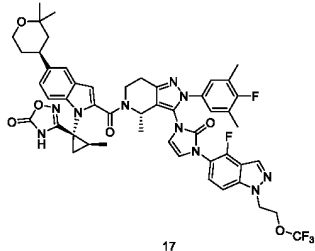
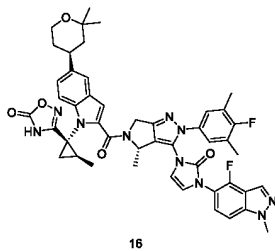
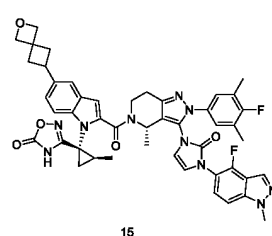
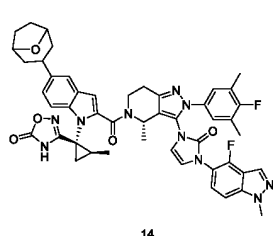
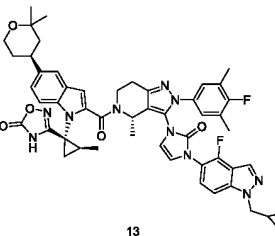
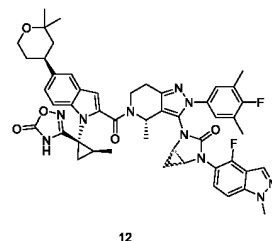
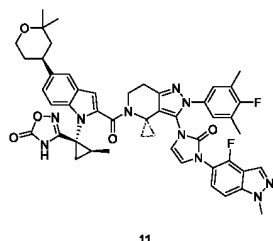
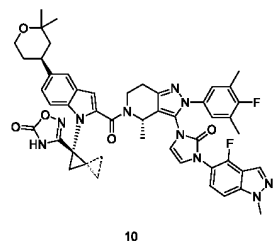
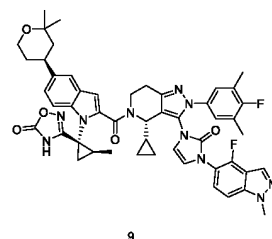
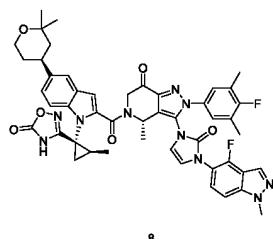
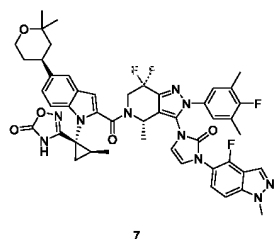
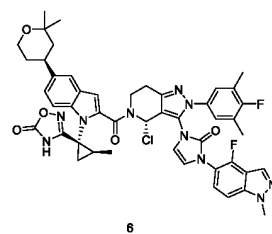
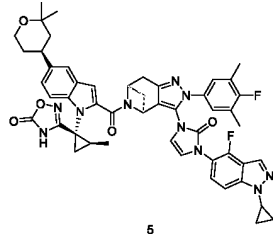
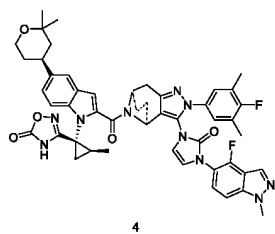
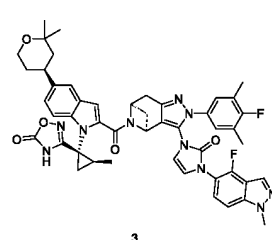
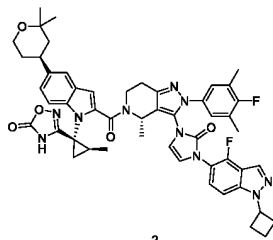
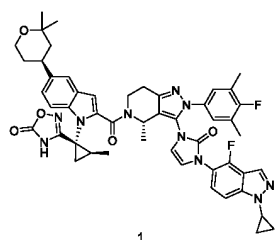
wherein the C₁₋₆ alkyl is optionally substituted by 1 to 6 substituents each independently selected from C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and halogen; wherein the C₃₋₆ cycloalkyl is optionally substituted by 1 to 3 substituents each independently selected from C₁₋₃ alkyl and halogen;

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

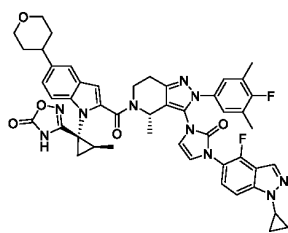
or R^{zm} and R^{zn} together with the phosphorus atom to which they are attached form a ring of 5-8 ring atoms, wherein 0-2 ring atoms, in addition to the phosphorus attached to R^{zm} and R^{zn}, are heteroatoms, each independently selected from: O, S and N, wherein the ring of 5-8 ring atoms is optionally substituted by 1-3 C₁₋₆ alkyl groups.

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

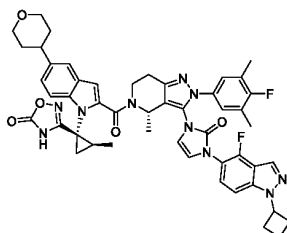
Claims



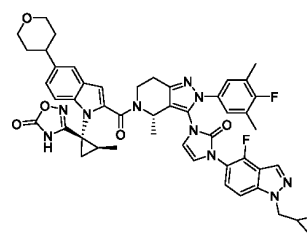
Claims



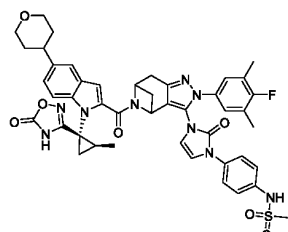
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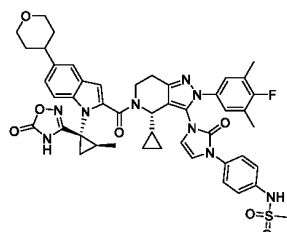
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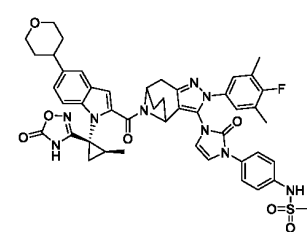
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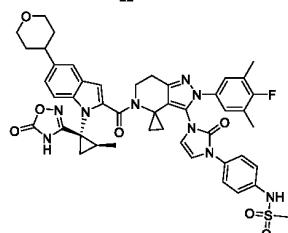
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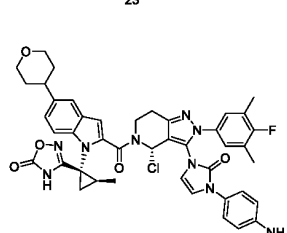
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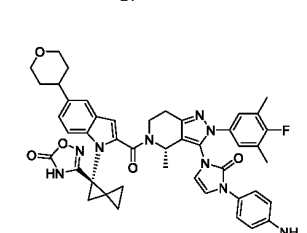
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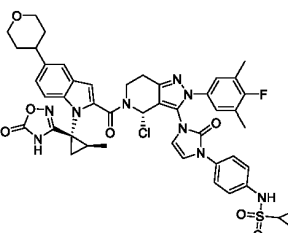
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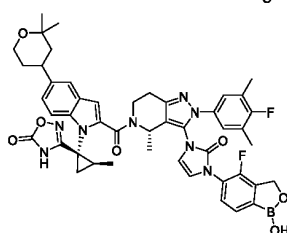
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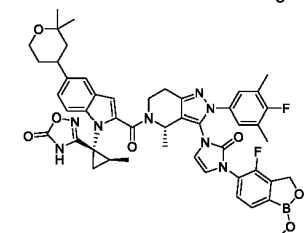
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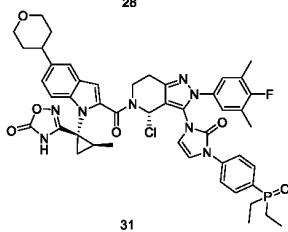
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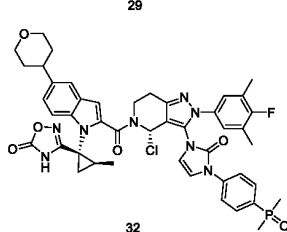
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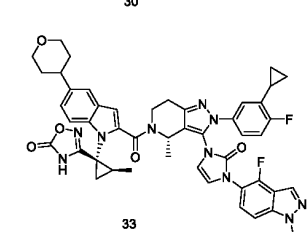
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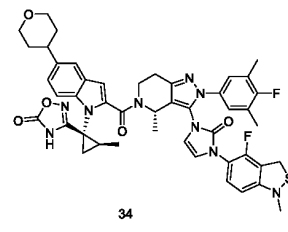
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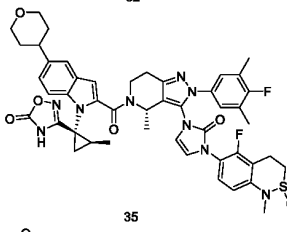
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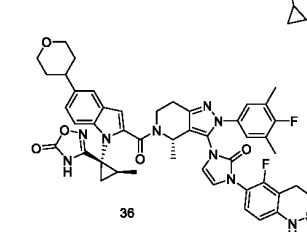
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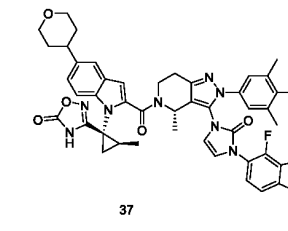
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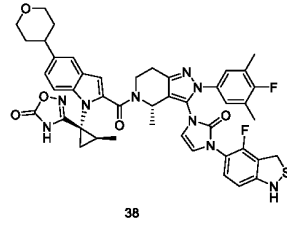
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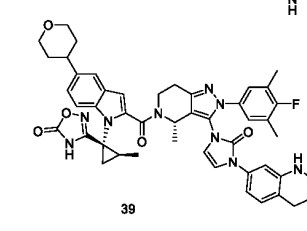
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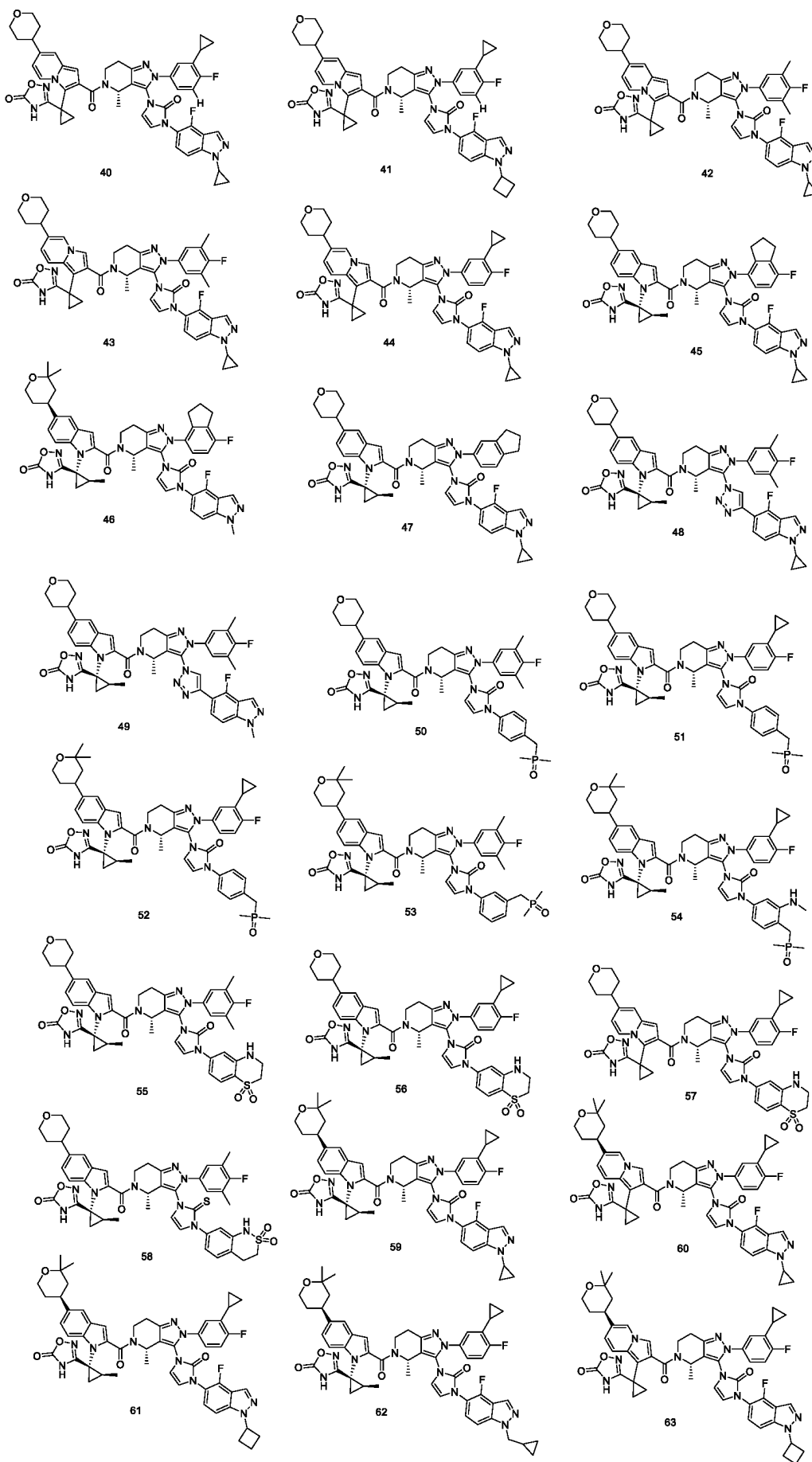


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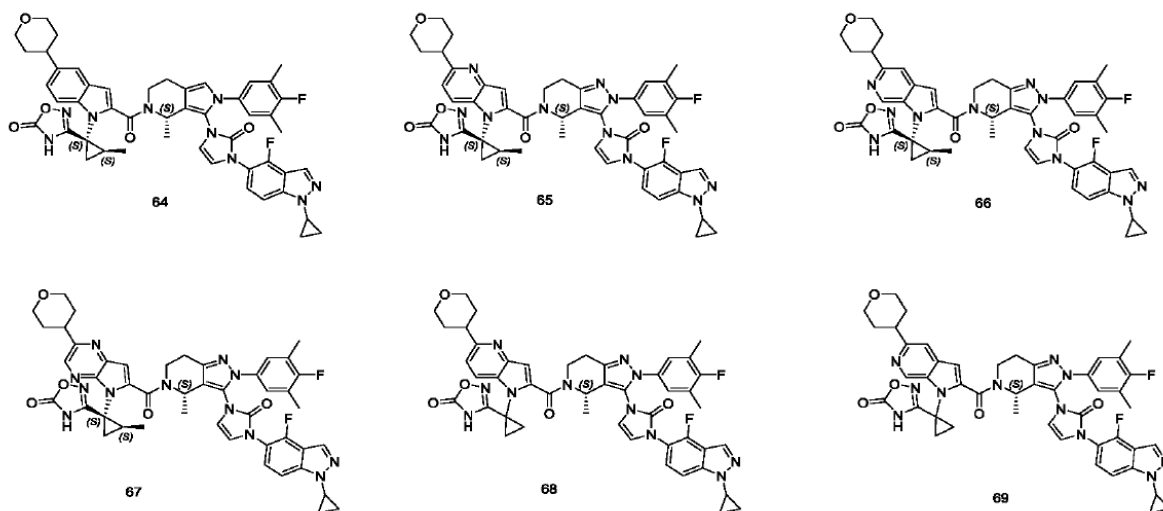


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Claims



Claims



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

3. A composition comprising the compound of formula (I) of claim 1 or 2 and the stereoisomer, pharmaceutically acceptable salt or deuterated compound thereof, as well as a pharmaceutically acceptable excipient.

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

5. The method of claim 3, wherein the GLP-1-mediated disease or symptom comprises T1 D, T2DM, prediabetes, idiopathic T1 D, 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 adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other drugs, excessive sugar craving, 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 pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, impaired fasting glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue diseases, psoriasis, foot ulcers, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's disease, schizophrenia, cognitive impairment,

Claims

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 acts 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

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

GLP-1R agonists are currently being extensively studied for diseases related to 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 drugs 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 endogenous GLP-1.

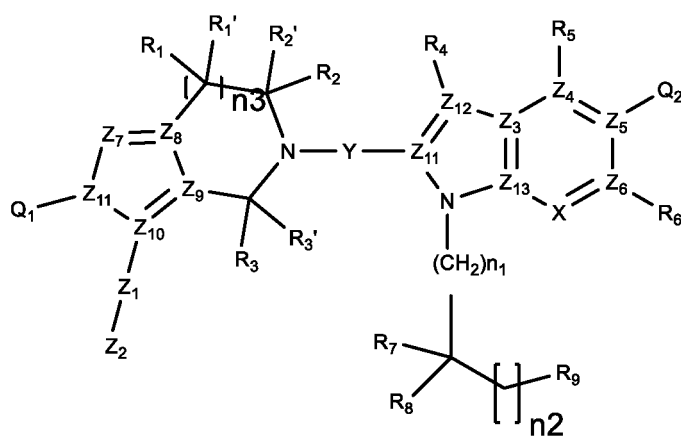
There remains a need for compounds, such as agonists of GLP-1R, that exhibit desirable therapeutic properties, metabolic properties, and/or ease of administration in the treatment of GLP-1R mediated diseases and conditions.

Summary of the Invention

Overview

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

Description



Formula I

wherein

X is selected from N or -CR^a; R^a is selected from 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 is optionally substituted by one to five substituents independently selected from halogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₁₋₆ haloalkyl and C₁₋₆ alkoxy;

Q₂ is a 3- to 12-membered heterocyclyl, a bridged ring, a spiro ring or a 5- to 10-membered heteroaryl, wherein the 3- to 12-membered heterocyclyl and the 5- to 10-membered heteroaryl are optionally substituted by 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 groups together with the carbon atom to which they are attached 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, R_{1'}, R_{2'} and R_{3'} are each independently selected from hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cycloalkyl or heterocycloalkyl;

wherein the C₁₋₆ alkyl or cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from halogen atoms, C₁₋₆ alkoxy and hydroxy;

wherein R₂ and R₃ together with the carbon atom to which they are attached form 4- to 8-membered heterocycloalkyl;

wherein R₁ and R_{1'} together with the carbon atom to which they are attached may form C₃-C₈ cycloalkyl, R₂ and R_{2'} together with the carbon atom to which they are attached may form C₃-C₈ cycloalkyl, and R₃ and R_{3'} together with the carbon atom to which they are attached may form C₃-C₈ cycloalkyl;

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

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

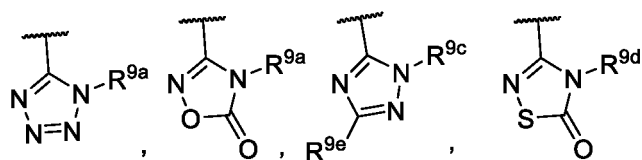
or R₇ and R₈ together with the carbon atom to which they are attached form a C₃₋₁₅ carbocyclic ring; wherein the C₃₋₁₅ carbocyclic ring formed by R₇ and R₈ together is optionally substituted by one to three C₁₋₆ alkyl groups, wherein the C₁₋₆ alkyl group is optionally substituted by one or more substituents independently selected from halogen, hydroxy, -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 groups together with the carbon atom to which they are attached may form a C₃₋₁₅ carbocyclic ring;

n₁ is 0, 1, 2, or 3;

n₂ is 0, 1, 2, 3, 4, or 5;

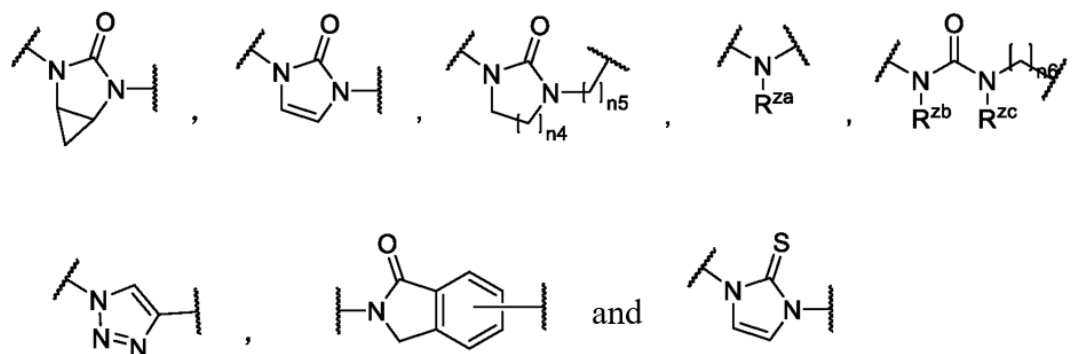
n₃ is 0 or 1;

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 by one or more substituents independently selected from halogen and C₁₋₆ alkoxy; R^{9e} is hydrogen or C₁₋₆ alkyl optionally substituted by 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;

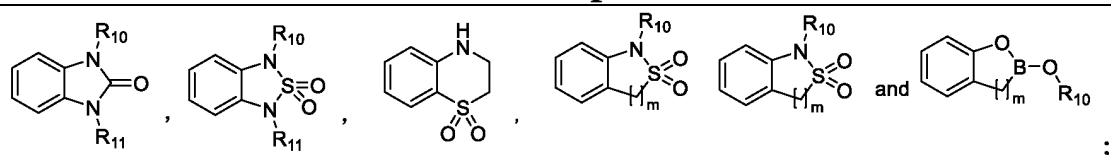
Z₁ is selected from the following groups:



wherein R^{za} is selected from hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl, 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 and 5- to 10-membered heteroaryl, and the following groups:

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

m is 1, 2, or 3;

R_{10} and R_{11} are 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 by one or more substituents independently selected from hydroxy, 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 by one or more substituents independently selected from hydroxy, 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 by one or more substituents independently selected from halogen, hydroxy, $-NR^{zi}R^{zj}$, 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 by one or more cyano, C_{1-6} alkyl and 3- to 12-membered heterocyclyl substituents;

h. C_{1-6} alkoxy; wherein the C_{1-6} alkoxy is optionally substituted by one or more hydroxy, halogen and C_{1-6} alkoxy substituents;

i. 3- to 12-membered heterocyclyl; wherein the 3- to 12-membered heterocyclyl is optionally substituted by 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 by one or more $(C_{1-6}$ alkyl)carbonyl groups, and

k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted by 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

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optionally substituted by 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 by one or more substituents independently selected from halogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl)carbonyl, wherein the alkyl or alkoxy is optionally substituted by halogen

m. -P(=O)R^{zm}R^{zn}, -(CH₂)_{n8}-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; n8 is 1 or 2;

wherein the C₁₋₆ alkyl is optionally substituted by 1 to 6 substituents each independently selected from C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and halogen; wherein the C₃₋₆ cycloalkyl is optionally substituted by 1 to 3 substituents each independently selected from C₁₋₃ alkyl and halogen;

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

or R^{zm} and R^{zn} together with the phosphorus atom to which they are attached form a ring of 5-8 ring atoms, wherein 0-2 ring atoms, in addition to the phosphorus attached to R^{zm} and R^{zn}, are heteroatoms, each independently selected from: O, S and N, wherein the ring of 5-8 ring atoms is optionally substituted by 1-3 C₁₋₆ alkyl groups.

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

The GLP-1-mediated disease or symptom comprises T1 D, T2DM, prediabetes, idiopathic T1 D, 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 adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other drugs, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular

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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 pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, impaired fasting glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue diseases, psoriasis, foot ulcers, ulcerative colitis, hyper apo 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.

I. Detailed Description

In the following description, certain specific details are included to provide a thorough understanding of various disclosed embodiments. One skilled in the relevant art will recognize, however, that the embodiments may be practiced without using one or more of these specific details, and instead using other methods, components, materials, etc.

Unless otherwise required by the present disclosure, throughout the description and claims that follow, the words "including" and "comprising" should be interpreted in an open, inclusive sense, i.e., "including, but not limited to".

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

Reference throughout the specification to "one embodiment" or "an embodiment" or "in another embodiment" or "in certain embodiments" means that a specific referenced element, structure or feature described in connection with the embodiment is included in at least one embodiment. Thus, the phrases "in one embodiment" or "in an embodiment" or "in another embodiment" or "in certain embodiments" appearing in various places throughout this specification do not necessarily all refer to the same embodiment. Furthermore, the specific elements, structures or features may be combined in any suitable manner in one or more embodiments.

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

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II. Definitions

Unless defined otherwise, all the technical and scientific terms used herein have the same meanings as commonly understood by those of ordinary skill in the art. A dash preceding or following a chemical group is provided for convenience to indicate the point of attachment to a parent moiety; a chemical group can be described with or without one or more dashes, which will not result in loss of its ordinary meaning. A prefix such as " C_{u-v} " or " C_{u-C_v} " indicates that the following group has from u to v carbon atoms, where u and v are integers. For example, " C_{1-6} alkyl" or " C_1-C_6 alkyl" means that the alkyl has 1 to 6 carbon atoms.

"Alkyl" is a monovalent or divalent, linear or branched, saturated hydrocarbon group. For example, an alkyl group can have 1 to 10 carbon atoms (i.e., C_{1-10} alkyl) or 1 to 8 carbon atoms (i.e., C_{1-8} alkyl) or 1 to 6 carbon atoms (i.e., C_{1-6} alkyl) or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl). Examples of alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)CH_2CH_3$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH(CH_3)CH_2CH_3$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$); 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)CH_2CH_2CH_3$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)CH_3$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$); 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)CH_2CH_2CH_2CH_3$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_2CH_3$); 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)CH_2CH_3$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)CH_2CH_2CH_3$); 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)CH_2CH_3$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)CH_2CH_3$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$), and octyl ($-(CH_2)_7CH_3$), and the alkyl may be unsubstituted or substituted.

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

"Alkoxyalkyl" is an alkoxy group attached to an alkyl group as defined above, thereby making the alkyl group divalent. For example, C_{2-6} alkoxyalkyl includes $-CH_2-OMe$, $-CH_2-O-iPr$, $-CH_2-$

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$\text{CH}_2\text{-OMe}$, $\text{-CH}_2\text{-CH}_2\text{-O-CH}_2\text{-CH}_3$ and $\text{-CH}_2\text{-CH}_2\text{-O-tBu}$. The alkoxyalkyl may be unsubstituted or substituted.

"Halogen" refers to fluorine (-F), chlorine (-Cl), bromine (-Br) and iodine (-I).

"Haloalkyl" is an alkyl group as defined herein in which one or more of the hydrogen atoms of the alkyl group are independently substituted with a halogen, which may be the same or different, so that the alkyl group is divalent. The alkyl and halogen may be any of those described above. In some embodiments, haloalkyl specifies the number of carbon atoms in the alkyl moiety, for example, C₁₋₄ 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 $\text{C}(\text{CH}_3)_2(\text{CF}_2\text{H})$. The haloalkyl may be unsubstituted or substituted.

"Haloalkoxy" is an alkoxy group as defined herein in which one or more of the hydrogen atoms of the alkoxy group are independently substituted with a halogen, which may be the same or different, so that the alkyl group is divalent. The 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, C₁₋₄ 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 $\text{OC}(\text{CH}_3)_2(\text{CF}_2\text{H})$. The haloalkoxy may be unsubstituted or substituted.

"Cycloalkyl" is a monovalent or divalent single all-carbon ring or a multiple condensed all-carbon ring system, in which the ring in each instance is a non-aromatic saturated or unsaturated ring. For example, in some embodiments, a cycloalkyl group has 3 to 12 carbon atoms, 3 to 10 carbon atoms, 3 to 8 carbon atoms, 3 to 6 carbon atoms, 3 to 5 carbon atoms, or 3 to 4 carbon atoms. Exemplary monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, cycloheptyl, cycloheptenyl, and cyclooctyl. The cycloalkyl group further includes a multiple condensed ring system (e.g., a ring system including 2 rings) having about 7 to 12 carbon atoms. Where valence requirements are met, the rings in the multiple condensed ring system may be interconnected by fusion bonds, spiro bonds, or bridging bonds. Exemplary multicyclic cycloalkyl groups include octahdropentene, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[2.2]oct-2-ene, and spiro[2.5]octane. The cycloalkyl group may be unsubstituted or substituted.

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

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As used herein, "aryl" refers to a monovalent or divalent single all-carbon aromatic ring or a multiple condensed all-carbon ring system, in which the ring is aromatic. For example, in some embodiments, an aryl group has 6 to 20 carbon atoms, 6 to 14 carbon atoms, 6 to 12 carbon atoms, or 6 to 10 carbon atoms. The aryl group includes a phenyl group. The aryl group further includes a multiple condensed ring system (e.g., a ring system consisting of 2, 3 or 4 rings) having about 9 to 20 carbon atoms, wherein the multiple rings are aromatic. Where valence requirements are met, the rings in the multiple condensed ring system may be interconnected by fusion bonds. It is also understandable that when referring to a membered aryl group within a certain atomic range (e.g., a 6- to 10-membered aryl group), the atomic range refers to the total ring atoms of the aryl group. For example, a 6-membered aryl group includes phenyl, and a 10-membered aryl group includes naphthyl. Non-limiting examples of aryl groups include, but are not limited to, phenyl, naphthyl, anthryl, and the like. The aryl may be unsubstituted or substituted.

"Alkylaryl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms of the alkyl group are independently substituted by an aryl group which may be the same or different. The alkyl and aryl may be any of those described above, and such alkyl is divalent. In some embodiments, an alkylaryl group 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 defined in the alkylaryl group refers to the total number of carbon atoms present in the alkyl and aryl. For example, C₇ alkylaryl refers to benzyl, while C₁₁ alkylaryl includes 1-methylnaphthalene and n-pentylphenyl. In some embodiments, the numbers of carbon atoms of the alkyl and aryl moieties can be specified separately, for example, C₁₋₆ alkyl-C₆₋₁₀ aryl. Non-limiting examples of alkylaryl groups include, but are not limited to, benzyl, 2,2-dimethylphenyl, n-pentylphenyl, 1-methylnaphthyl, 2-ethylnaphthyl, and the like. The alkylaryl may be unsubstituted or substituted.

As used herein, "heterocycle" or "heterocyclic ring" or "heterocyclyl" refers to a single saturated or partially unsaturated non-aromatic ring or a non-aromatic polycyclic ring system, having at least one heteroatom (i.e., at least one ring (i.e., cyclic) heteroatom selected from oxygen, nitrogen and sulfur). Unless otherwise specified, a heterocyclyl group has 3 to about 20 ring atoms, for example 3 to 12 ring atoms, for example 4 to 12 ring atoms, 4 to 10 ring atoms, or 3 to 8 ring atoms, or 3 to 6 ring atoms, or 4 to 6 ring atoms, or 4 to 5 ring atoms. Thus, the term includes a single saturated or partially unsaturated ring (e.g., a 3, 4, 5, 6, or 7-membered ring) having from about 1 to 6 ring carbon atoms and from about 1 to 3 ring heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. Where valence requirements are met, the rings in the multiple condensed ring system (e.g., bicyclic heterocycle) may be interconnected by fusion bonds, spiro bonds, and bridging bonds. Heterocycles include, but are not limited to, azetidine, azapyridine, imidazolidine, morpholine, oxirane, oxacycle, thiacycle, piperazine, piperidine,

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pyrazolidine, pyrrolidine, pyrrolidone, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, quinuclidine, 2-oxa-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 the like. The heteroaryl may be unsubstituted or substituted.

"Alkylheterocyclyl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms of the alkyl group are independently substituted by a heterocyclyl group which may be the same or different. The alkyl and heterocyclyl may be any of those described above, and such alkyl is divalent. In some embodiments, the numbers of atoms in the alkyl and heterocyclyl moieties can be specified separately, for example, C₁₋₆ alkyl-3- to 12-membered heterocyclyl having 1 to 3 heteroatoms, each heteroatom being independently N, O or S. The alkylheterocyclyl may be unsubstituted or substituted.

"5- to 10-membered heteroaryl" refers to a single aromatic ring having at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur; "5- to 10-membered heteroaryl" also includes a multiple condensed ring system having at least one such aromatic ring, and the multiple condensed ring system will be further described below. Thus, "5- to 10-membered heteroaryl" includes a single aromatic ring of about 1-6 carbon atoms and about 1-4 heteroatoms selected from the group of oxygen, nitrogen and sulfur. The sulfur and nitrogen atoms may also be present in oxidized forms, provided that the ring is aromatic. Exemplary 5- to 10-membered heteroaryl ring systems include, but are not limited to, pyridinyl, pyrimidinyl, oxazolyl, or furanyl. "5- to 10-membered heteroaryl" also includes a multiple condensed ring system (e.g., a ring system consisting of 2, 3 or 4 rings), wherein the 5- to 10-membered heteroaryl as defined above is condensed with one or more rings selected from 5- to 10-membered heteroaryl (forming, for example, 1,8-naphthyridinyl) and aryl (forming, for example, benzimidazolyl or indazolyl) to form a multiple condensed ring system. Thus, 5- to 10-membered heteroaryl (a single aromatic ring or a multiple condensed ring system) can have about 1 to 20 carbon atoms, and there are about 1 to 6 heteroatoms within the 5- to 10-membered heteroaryl ring. For example, tetrazolyl has 1 carbon atom and 4 nitrogen heteroatoms in the ring. Where valence requirements are met, the rings in the multiple condensed ring system may be interconnected by fusion bonds. It should be understood that the individual rings of the multiple condensed ring system may be interconnected in any order. It should be understood that the point of attachment 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 the 5- to 10-membered heteroaryl multiple condensed ring system, including carbon atoms and heteroatoms (e.g., nitrogen). It is also understood that when referring to a membered heteroaryl group within a certain atomic range (e.g., a 5- to 10-membered heteroaryl group), the atomic range refers to the total ring atoms of the heteroaryl group, including carbon atoms and heteroatoms. It is also understood that the ring of a

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multiple condensed ring system may include an aryl ring fused to a heterocycle (e.g., a 3-, 4-, 5-, 6-, or 7-membered ring) having saturated or partially unsaturated bonds, and the ring has about 1 to 6 ring carbon atoms and about 1 to 3 ring heteroatoms selected from oxygen, nitrogen, and sulfur in the ring. For example, 5- to 10-membered heteroaryl includes thiazolyl, and 5- to 10-membered heteroaryl includes quinolyl. Exemplary 5- to 10-membered heteroaryl groups include, but are not limited to, pyridinyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furanyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxazolyl, quinazolyl, benzofuranyl, benzimidazolyl, thiophenyl, pyrrolo[2,3-b]pyridinyl, quinazolinyl-4(3H)-one, triazolyl, and tetrazolyl. The 5- to 10-membered heteroaryl may be unsubstituted or substituted.

"Alkyl-heteroaryl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms of the alkyl group are independently substituted by a heteroaryl group which may be the same or different, so that the alkyl is divalent. The 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 heteroatom being independently N, O or S. The alkylheteroaryl may be unsubstituted or substituted.

As used herein, "oxo" refers to =O.

As used herein, "substituted" refers to a group in which one or more hydrogen atoms of the group are independently substituted by one or more (e.g., 1, 2, 3, or 4 or more) substituents, as indicated.

"Compounds of the present disclosure" include compounds disclosed herein, for example, compounds of the present disclosure include compounds of formula I, including the compounds in the Examples. In some embodiments, "compounds of the present disclosure" include compounds of formula I.

"Pharmaceutically acceptable excipients" include, but are 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 medical response, including 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 will vary depending on the compound, the disease and the severity thereof, as well as the age, body weight of the subject to be treated, and other factors. The effective amount may include a range of amounts. As understood in the art, an effective amount can be one or more doses, i.e., one dose or multiple doses may be required to achieve the desired therapeutic endpoint.

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An effective amount may be considered in the context of administration of one or more therapeutic agents, and a single agent may be considered to be administered in an effective amount if a desired or beneficial result may be or has been achieved when used together with one or more other agents. The appropriate dose of any co-administered compound may be optionally lowered due to the combined effect (e.g., additive or synergistic effect) of the compounds.

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

Also provided are pharmaceutically acceptable salts, hydrates, solubilized forms, isomeric forms, polymorphs, and prodrugs of the compounds described herein.

"Pharmaceutically acceptable" or "physiologically acceptable" means that compounds, salts, compositions, dosage forms, and other materials are useful in preparing pharmaceutical compositions suitable for veterinary or human pharmaceutical use.

The compounds described herein may be prepared and/or formulated as pharmaceutically acceptable salts or, where appropriate, as free bases. Pharmaceutically acceptable salts are non-toxic salts of the free base form of the compound which possess the desired pharmacological activity of the free base. These salts may be derived from inorganic or organic acids or bases. For example, a compound containing a basic nitrogen can be prepared as a pharmaceutically acceptable salt by contacting the compound with an inorganic or organic acid. Non-limiting examples of pharmaceutically acceptable salts include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, octanoate, acrylate, formate, isobutyrate,

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hexanoate, heptanoate, propanolate, oxalate, malonate, perferrite, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-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, gamma-hydroxybutyrate, glycolate, tartrate, and mandelate. Lists of other suitable pharmaceutically acceptable salts may be found in Remington: The Science and Practice of Pharmacy, 21st edition, Lippincott Williams and Wilkins, Philadelphia, Pa., 2006.

Examples of "pharmaceutically acceptable salts" of the compounds disclosed herein also include salts derived from appropriate bases, such as alkali metals (e.g., sodium, potassium), alkaline earth metals (e.g., magnesium), ammonium, and $N(C_1-C_4 \text{ alkyl})^{4+}$. Base addition salts, such as sodium or potassium salts, are also included.

Also provided are compounds or pharmaceutically acceptable salts, isomers or mixtures thereof described herein, wherein 1 to n hydrogen atoms attached to a carbon atom may be substituted by a deuterium atom or D, wherein n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds may increase resistance to metabolism and thus may be used to increase the half-lives of compounds described herein or pharmaceutically acceptable salts, isomers, or mixtures thereof when taken by a mammal. See Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends in Pharmacological Sciences 5(12): 524-527 (1984). Such compounds are synthesized by methods well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been substituted by deuterium.

Examples of isotopes that can be incorporated into the compounds disclosed herein also include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, 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 positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies, for examining substrate receptor occupancy. Isotopically labeled compounds of formula I can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples below using appropriate isotopically labeled reagents in place of the non-labeled reagents previously employed.

The compounds or pharmaceutically acceptable salts thereof in the embodiments disclosed herein may contain one or more asymmetric centers, and may thus give rise to enantiomeric, diastereomeric and other stereoisomeric forms which may be defined in terms of absolute stereochemistry as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant

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to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (R) and (S), or (D) and (L) isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers 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 the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that these compounds include both E and Z geometric isomers. Likewise, all isomeric forms are included. When a compound is represented in its chiral form, it is understood that this 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 this embodiment is directed to a specific diastereomer or enantiomerically enriched form; or a racemic or scalemic mixture of such a compound. As used herein, a "scalemic mixture" refers to a mixture of stereoisomers in a ratio other than 1:1.

As used herein, "stereoisomers" refer to compounds with identical atomic connectivity but with different three-dimensional structures, and they are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof, and includes "enantiomers", which refers to a pair of stereoisomers whose molecules are non-superimposable mirror images of each other.

As used herein, "tautomers" refers to isomers involving proton transfer from one atom of a molecule to another atom of the same molecule. In some embodiments, tautomers of said compounds are included in the present disclosure.

As used herein, "solvate" refers to the resultant of the interaction of a solvent and a compound. Also provided are solvates of salts of the compounds described herein. Also provided are hydrates of the compounds described herein.

As used herein, "hydrate" refers to a compound of the present invention chemically associated with one or more water molecules.

"Prevention" or "preventing" refers to any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. In some embodiments, the compound may be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

As used herein, "prodrug" refers to a derivative of a drug that upon administration to the human body is converted to the parent drug according to some chemical or enzymatic pathway. In some embodiments, a prodrug is a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathways.

As used herein, "treatment" or "treat" or "treating" refers to an approach for obtaining beneficial or desired results. For purposes of the present disclosure, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one embodiment,

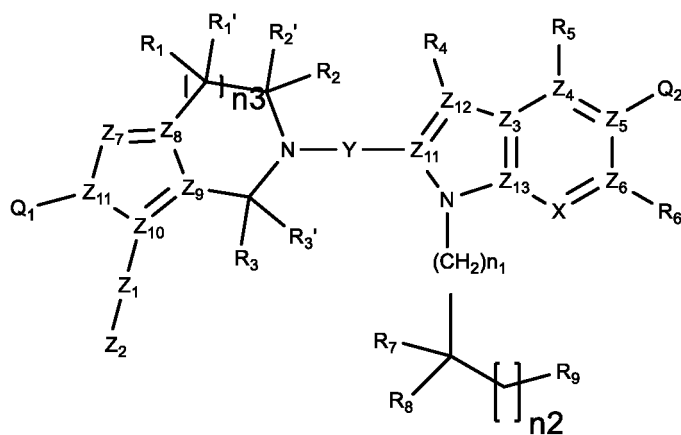
Description

"treatment" or "treating" includes one or more of: a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); and c) relieving the disease or condition, e.g., causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival. As used herein, an "individual at risk" refers to an individual who is at risk of developing a condition which needs to be treated. An individual "at risk" may or may not have detectable disease or condition, and may or may not have displayed detectable disease prior to the treatment methods described herein. "At risk" denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease or condition and are known in the art. An individual having one or more of these risk factors has a higher probability of developing the disease or condition than an individual without these risk factors.

III. Compounds

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

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



Formula I

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

wherein

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

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

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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 is optionally substituted by one to five substituents independently selected from halogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₁₋₆ haloalkyl and C₁₋₆ alkoxy;

Q₂ is a 3- to 12-membered heterocyclyl, a bridged ring, a spiro ring or a 5- to 10-membered heteroaryl, wherein the 3- to 12-membered heterocyclyl and the 5- to 10-membered heteroaryl are optionally substituted by 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 groups together with the carbon atom to which they are attached 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 or cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from halogen atoms, C₁₋₆ alkoxy and hydroxy;

wherein R₂ and R₃ together with the carbon atom to which they are attached form 4- to 8-membered heterocycloalkyl;

wherein R₁ and R₁' together with the carbon atom to which they are attached may form C₃-C₈ cycloalkyl, R₂ and R₂' together with the carbon atom to which they are attached may form C₃-C₈ cycloalkyl, and R₃ and R₃' together with the carbon atom to which they are attached may form C₃-C₈ cycloalkyl;

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 by one or more substituents independently selected from halogen and C₃₋₁₅ cycloalkyl;

or R₇ and R₈ together with the carbon atom to which they are attached form a C₃₋₁₅ carbocyclic ring; wherein the C₃₋₁₅ carbocyclic ring formed by R₇ and R₈ together is optionally substituted by one to three C₁₋₆ alkyl groups, wherein the C₁₋₆ alkyl group is optionally substituted by one or more substituents independently selected from halogen, hydroxy, -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 groups together with the carbon atom to which they are attached may form a C₃₋₁₅ carbocyclic ring;

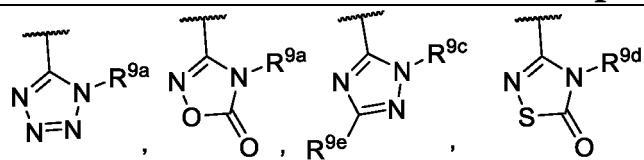
n₁ is 0, 1, 2, or 3;

n₂ is 0, 1, 2, 3, 4, or 5;

n₃ is 0 or 1;

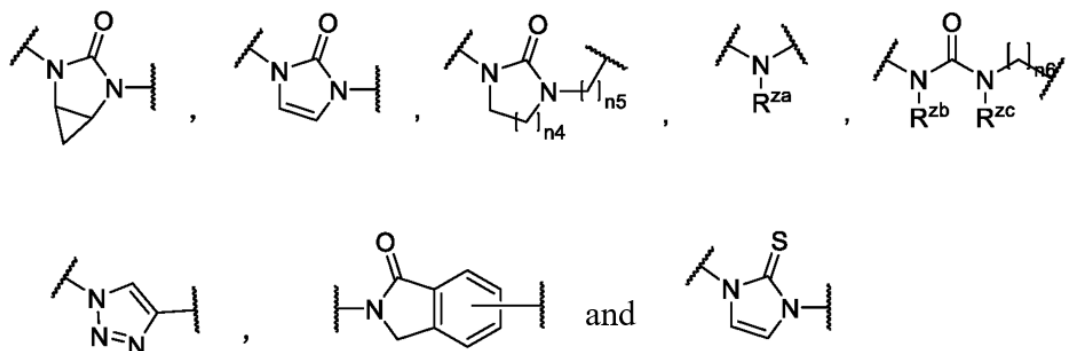
R₉ is selected from the following groups:

Description



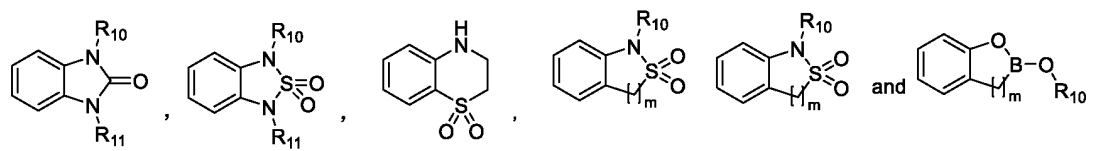
, $-\text{CO}_2\text{R}^{9f}$ and $-\text{C}(=\text{O})-\text{NR}^{9g}\text{R}^{9h}$; and R^{9a} , R^{9b} , R^{9c} , R^{9d} and R^{9g} are each independently selected from hydrogen, C_{1-6} alkyl and $(\text{C}_{1-6}$ alkyl)carbonyl, wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen and C_{1-6} alkoxy; R^{9e} is hydrogen or C_{1-6} alkyl optionally substituted by one or more halogen atoms; R^{9f} is hydrogen or C_{1-6} alkyl; R^{9h} is hydrogen, C_{1-6} alkyl, $(\text{C}_{1-6}$ alkyl)carbonyl, cyano or $-\text{S}(=\text{O})_{n3}-\text{R}^{9i}$; $n3$ is 0, 1 or 2; R^{9i} is C_{1-6} alkyl;

Z_1 is selected from the following groups:



wherein R^{za} is selected from hydrogen, C_{1-6} alkyl and $(\text{C}_{1-6}$ alkyl)carbonyl, R^{zb} and R^{zc} are independently hydrogen or C_{1-6} alkyl; $n4$ is 1, 2 or 3; $n5$ and $n6$ 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 and 5- to 10-membered heteroaryl, and the following groups:



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

m is 1, 2, or 3;

R_{10} and R_{11} are selected from H, C_{1-6} alkyl and $(\text{C}_{1-6}$ alkyl)aryl, C_{1-6} haloalkyl, $-\text{C}_3-\text{C}_{15}$ cycloalkyl or $-\text{C}_1-\text{C}_6$ alkyl- C_3-C_{15} cycloalkyl;

G is selected from the following groups:

- a. oxo;
- b. halogen;
- c. cyano;

Description

d. $-\text{NR}^{\text{zd}}\text{R}^{\text{ze}}$; wherein R^{zd} and R^{ze} are independently selected from hydrogen, C_{1-6} alkyl and $(\text{C}_{1-6} \text{ alkyl})\text{carbonyl}$; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from hydroxy, halogen and C_{1-6} alkoxy;

e. $-\text{C}(=\text{O})-\text{NR}^{\text{zf}}\text{R}^{\text{zg}}$; wherein R^{zf} and R^{zg} are independently selected from hydrogen, C_{1-6} alkyl and $(\text{C}_{1-6} \text{ alkyl})\text{carbonyl}$; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from hydroxy, halogen and C_{1-6} alkoxy;

f. $-\text{S}(=\text{O})_{\text{n7}}-\text{R}^{\text{zh}}$; 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 by one or more substituents independently selected from halogen, hydroxy, $-\text{NR}^{\text{zi}}\text{R}^{\text{zj}}$, 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 by one or more cyano, C_{1-6} alkyl and 3- to 12-membered heterocyclyl substituents;

h. C_{1-6} alkoxy; wherein the C_{1-6} alkoxy is optionally substituted by one or more hydroxy, halogen and C_{1-6} alkoxy substituents;

i. 3- to 12-membered heterocyclyl; wherein the 3- to 12-membered heterocyclyl is optionally substituted by one or more substituents independently selected from C_{1-6} alkyl and $(\text{C}_{1-6} \text{ alkyl})\text{carbonyl}$;

j. C_{6-10} aryl; wherein the C_{6-10} aryl is optionally substituted by one or more $(\text{C}_{1-6} \text{ alkyl})\text{carbonyl}$ groups, and

k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted by one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-\text{NR}^{\text{zk}}\text{R}^{\text{zl}}$ and 3- to 12-membered heterocyclyl; wherein R^{zk} and R^{zl} are independently selected from hydrogen, C_{1-6} alkyl and $(\text{C}_{1-6} \text{ alkyl})\text{carbonyl}$, and wherein the 3- to 12-membered heterocyclyl is optionally substituted by one or more substituents independently selected from C_{1-6} alkyl and $(\text{C}_{1-6} \text{ alkyl})\text{carbonyl}$;

l. $-\text{C}_3\text{-C}_{15}$ cycloalkyl or $-\text{C}_1\text{-C}_6$ alkyl- $\text{C}_3\text{-C}_{15}$ cycloalkyl; wherein the cycloalkyl or alkyl is optionally substituted by one or more substituents independently selected from halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and $(\text{C}_{1-6} \text{ alkyl})\text{carbonyl}$, wherein the alkyl or alkoxy is optionally substituted by halogen;

m. $-\text{P}(=\text{O})\text{R}^{\text{zm}}\text{R}^{\text{zn}}$, $-(\text{CH}_2)_{\text{n8}}-\text{P}(=\text{O})\text{R}^{\text{zm}}\text{R}^{\text{zn}}$, $\text{NR}^{\text{zm}}\text{S}(=\text{O})\text{R}^{\text{zn}}$ and $\text{NR}^{\text{zm}}\text{S}(=\text{O})_2\text{R}^{\text{zn}}$, wherein R^{zm} and R^{zn} are selected from H, C_{1-6} alkyl and C_{6-10} aryl; n8 is 1 or 2;

wherein the C_{1-6} alkyl is optionally substituted by 1 to 6 substituents each independently selected from C_{1-6} alkoxy, C_{3-6} cycloalkyl and halogen; wherein the C_{3-6} cycloalkyl is optionally substituted by 1 to 3 substituents each independently selected from C_{1-3} alkyl and halogen;

wherein the C_{6-10} aryl is optionally substituted by 1-3 C_{1-3} alkyl groups;

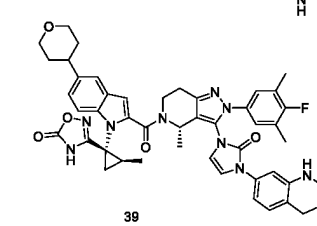
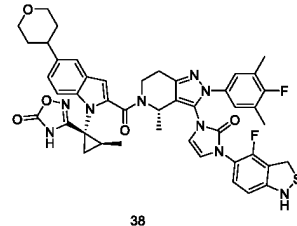
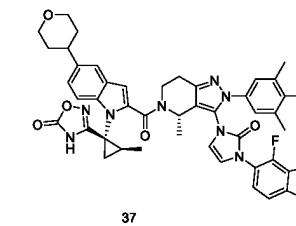
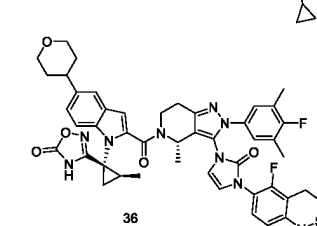
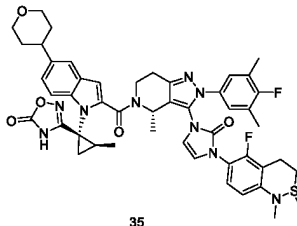
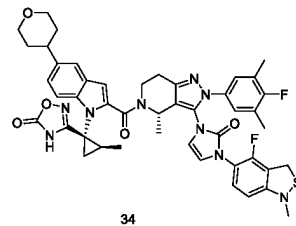
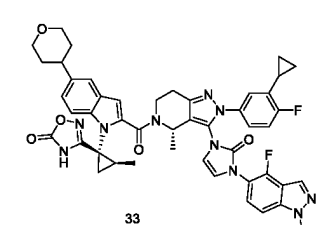
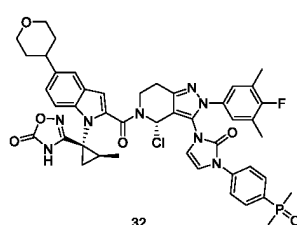
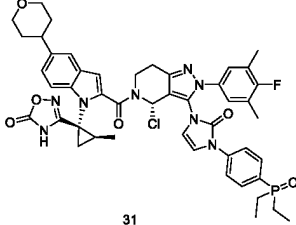
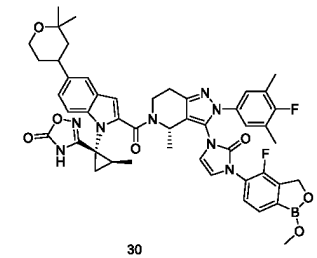
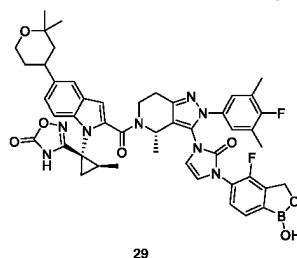
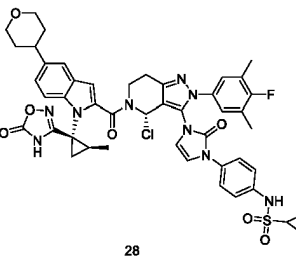
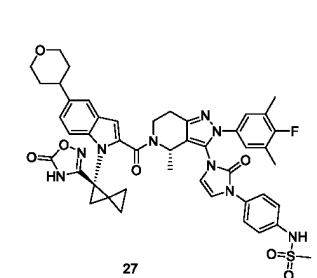
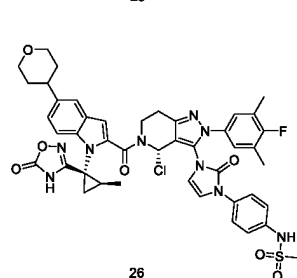
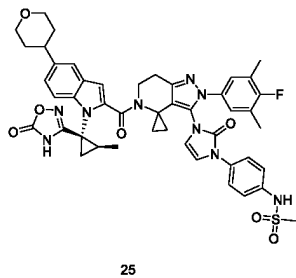
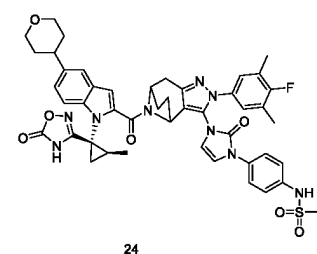
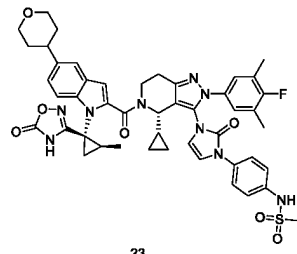
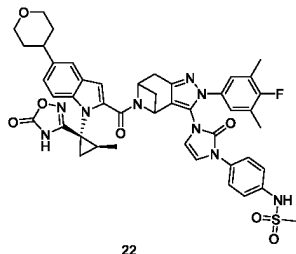
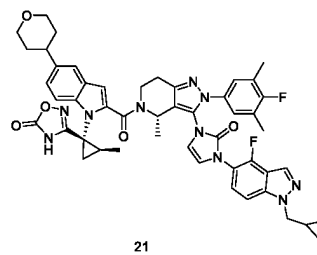
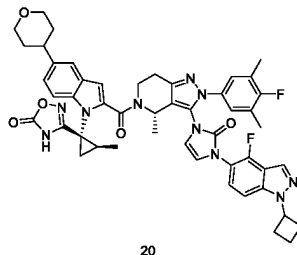
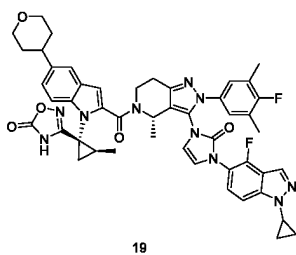
Description

or R^{zm} and R^{zn} together with the phosphorus atom to which they are attached form a ring of 5-8 ring atoms, wherein 0-2 ring atoms, in addition to the phosphorus attached to R^{zm} and R^{zn} , are heteroatoms, each independently selected from: O, S and N, wherein the ring of 5-8 ring atoms is optionally substituted by 1-3 C_{1-6} alkyl groups.

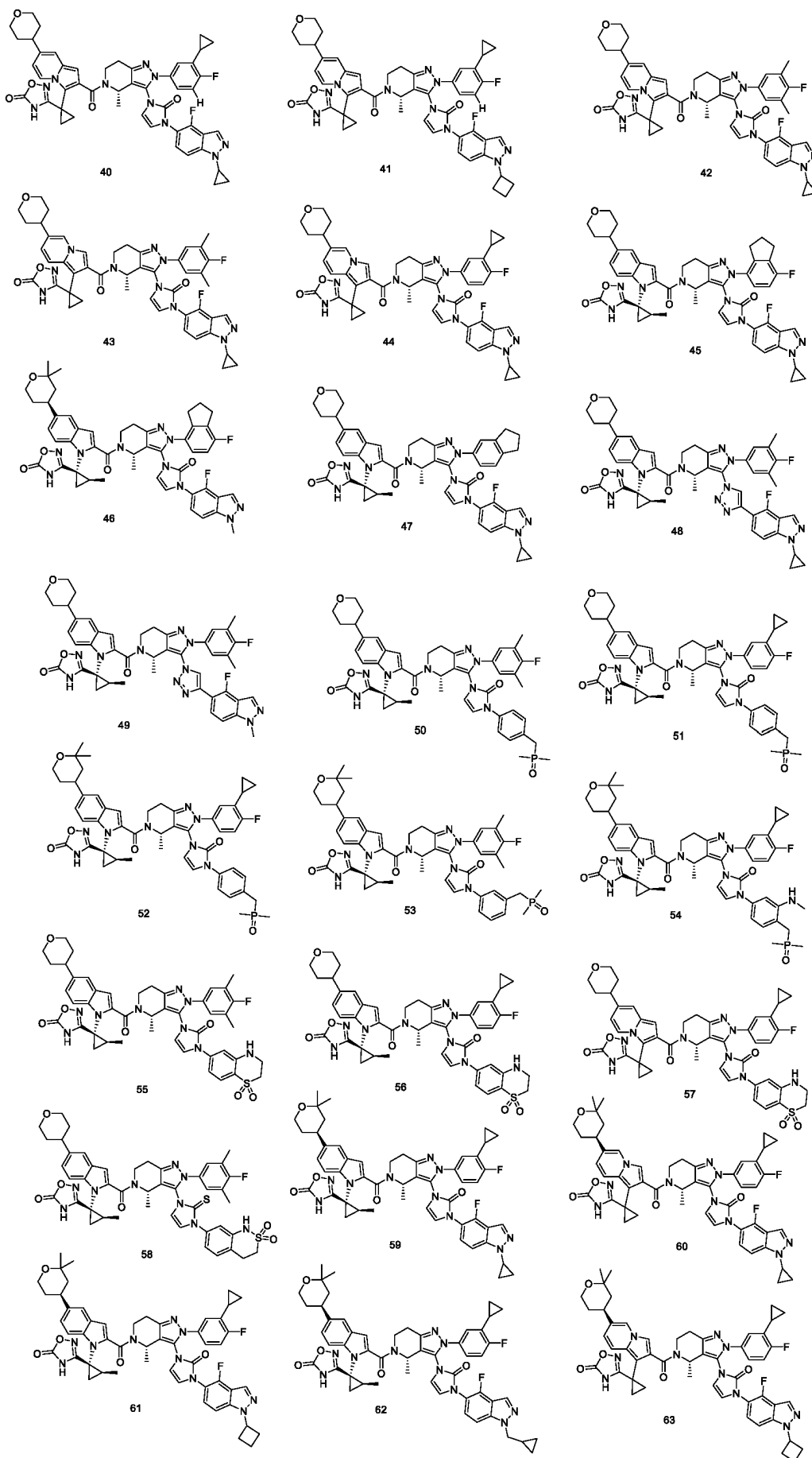
In some embodiments, the compound of formula (I) or the pharmaceutically acceptable salt thereof has the following structural formulas:



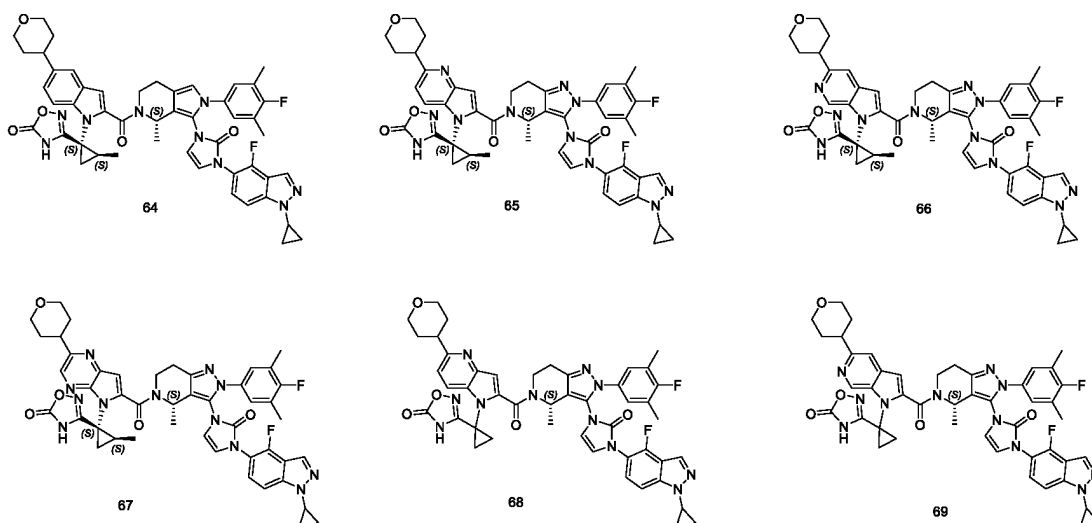
Description



Description



Description



, and

the stereoisomer, pharmaceutically acceptable salt or deuterated compound thereof.

IV. Pharmaceutical formulation

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

The pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof disclosed herein may be prepared with one or more pharmaceutically acceptable excipients, which may be selected according to conventional practice. Tablets may comprise excipients including glidants, fillers, binders and the like. The aqueous composition can be prepared in a sterile form, and the aqueous composition may generally be isotonic when it is intended to be delivered by a route other than oral administration. In some embodiments, the composition may comprise excipients, such as those set forth in Rowe et al., Handbook of Pharmaceutical Excipients, 6th edition, American Pharmacists Association, 2009. Excipients may include ascorbic acid and other antioxidants, chelating agents such as ethylenediaminetetraacetic acid, carbohydrates such as dextrans, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid, and the like. 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 may be present in a unit dosage form and may be prepared by any of the methods commonly known in the art of pharmacy. These methods include the step of bringing an active ingredient (e.g., a compound of the present disclosure or a pharmaceutically salt thereof) into association with one or more pharmaceutically acceptable excipients. The composition can be prepared by uniformly and intimately bringing the active ingredient into association with liquid excipients or finely divided solid excipients or both, and then, if necessary, shaping the product. Techniques and formulations can generally be found in Remington: The

Description

Science and Practice of Pharmacy, 21st Edition, Lippincott Williams and Wilkins, Philadelphia, Pa., 2006.

The composition described herein suitable for oral administration may be present in discrete units (unit dosage forms) including, but not limited to, capsules, sachets or tablets, each containing a predetermined amount of the active ingredient. In some embodiments, the pharmaceutical composition of the present disclosure is a tablet.

The pharmaceutical composition disclosed herein comprises one or more compounds or pharmaceutically acceptable salts thereof disclosed herein, 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 intended for oral use, for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. The composition for oral use may be prepared according to any method known in the art for the manufacture of a pharmaceutical composition, and such composition may comprise one or more excipients including sweeteners, flavoring agents, colorants and preservatives to provide a palatable preparation. A tablet containing an active ingredient and a non-toxic pharmaceutically acceptable excipient which is suitable for the manufacture of the tablet is acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as corn starch or alginic acid; binders, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricants, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract, thereby providing a sustained action over a longer period. For example, a retardant material such as glyceryl monostearate or glyceryl distearate may be used either alone or in combination with a wax.

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

In some embodiments, in one variation, the composition comprising the compound of the present disclosure or the pharmaceutically acceptable salt thereof does not comprise an agent that affects the rate at which the active ingredient is metabolized. Thus, it is understood that in one aspect, the composition comprising the compound of the present invention does not comprise an

Description

agent that would affect (e.g., slow, hinder or retard) 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 is also understood that in one aspect, any of the methods, kits, articles of manufacture and the like detailed herein does not comprise an agent that would affect (e.g., slow, hinder or retard) 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.

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

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

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

The compounds of the present disclosure may also be used in the form of prodrugs or other suitable modified forms which release the active ingredient in vivo.

V. Routes of administration

The compounds of the present disclosure, also referred to herein as active ingredients, may be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, local (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratumoral, intrathecal and epidural) routes, etc. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of certain compounds disclosed herein is that they are orally bioavailable and can be administered orally.

A compound of the present disclosure may be administered to an individual in accordance with 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 longer. In one embodiment, the compound is administered daily or intermittently for the duration of the individual's life.

The dosage or dosing frequency of a compound of the present disclosure may be adjusted over the course of the treatment, based on the judgment of the administering physician.

The compound can be administered to an individual (e.g., a human) in an effective amount. In some embodiments, the compound is administered once daily.

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

A compound of the present disclosure may be combined with one or more additional therapeutic agents in any dosage amount of the compound of the present disclosure (e.g., from 1 mg to 1000 mg of compound). Therapeutically effective amounts may include from about 1 mg per dose to about 1000 mg per dose, such as from about 50 mg per dose to about 500 mg per dose, or such as from about 100 mg per dose to about 400 mg per dose, or such as from about 150 mg per dose to about 350 mg per dose, or such as from about 200 mg per dose to about 300 mg per dose. Other therapeutically effective amounts of the compound of the present disclosure are 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 amounts of the compounds of the present disclosure are about 100 mg per dose, or about 125, 150, 175, 200, 225, 250, 275, 300, 350, 400, 450, or about 500 mg per dose. A single dose can be administered hourly, daily, or weekly. For example, a single dose can be administered once every 1 hour, 2, 3, 4, 6, 8, 12, 16 or 24 hours. A single dose can also be administered once every 1 day, 2, 3, 4, 5, 6, or 7 days. A single dose can also be administered once every 1 week, 2, 3, or 4 weeks. In some embodiments, a single dose can be administered once every week. A single dose can also be administered once every month.

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

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

Example 1:

Synthesis

The compound of the present invention may be prepared using the methods disclosed herein, and routine modifications thereof which will be obvious given the methods disclosed herein and methods well known in the art. Conventional and well-known synthesis methods may be used in addition to the teachings herein.

The synthesis of typical compounds of formula I, or pharmaceutically acceptable salts thereof, e.g., compounds having one or more depicted structures of formula I, or other formulas or compounds disclosed herein, may be accomplished as described in the following examples.

General synthesis methods

Typical embodiments of compounds in accordance with the present disclosure may be synthesized using the general reaction schemes and/or examples described below. It will be apparent given the description herein that the general schemes may be altered by substitution of the starting materials with other materials having similar structures to result in products that are correspondingly different. The subsequent descriptions of synthesis provide numerous examples of how the starting materials may vary to provide corresponding products. Starting materials are typically obtained from commercial sources or synthesized using published methods for synthesizing compounds which are embodiments of the present disclosure, inspection of the structure of the compound to be synthesized will provide the identity of each substituent. The identity of the final product will generally render the identity of the necessary starting materials apparent by a simple process of inspection, given the examples herein. Group labels (e.g., R₁, R₂) used in the reaction schemes herein are for illustrative purposes only, and unless otherwise specified do not necessarily match, by name or function, the labels used elsewhere to describe compounds of formula I or aspects or fragments thereof.

Synthesis reaction parameters

A compound of the disclosure can be prepared from readily available starting materials using, for example, the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimal reaction conditions may vary with the specific reactants or solvent used, but such conditions can be determined by those skilled in the art by routine optimization procedures.

Description

Additionally, for those skilled in the art, traditional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting specific functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts (1999) *Protecting Groups in Organic Synthesis*, 3rd Edition, Wiley, New York, and references cited therein.

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

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 of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). Others may be prepared by procedures or obvious modifications thereof, described in standard references such as Fieser's *Reagents for Organic Synthesis*, Volumes 1-15 (John Wiley, and Sons, 1991); Rodd's *Chemistry of Carbon Compounds*, Volumes 1-5, and Supplementary Edition (Elsevier Science Publishers, 1989); *Organic Reactions*, Volumes 1-40 (John Wiley, and Sons, 1991); March's *Advanced Organic Chemistry*, (John Wiley, and Sons, 5th Edition, 2001); and Larock's *Comprehensive Organic Transformations* (VCH Publishers Inc., 1989).

The terms "solvent," "inert organic solvent" or "inert solvent" refer to a solvent inert under the conditions of the reaction in conjunction therewith (including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), N,N-dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, pyridine and the like). Unless specified to the contrary, the solvents used in the reactions of the present disclosure are inert organic solvents, and the reactions are carried out under an inert gas, preferably nitrogen.

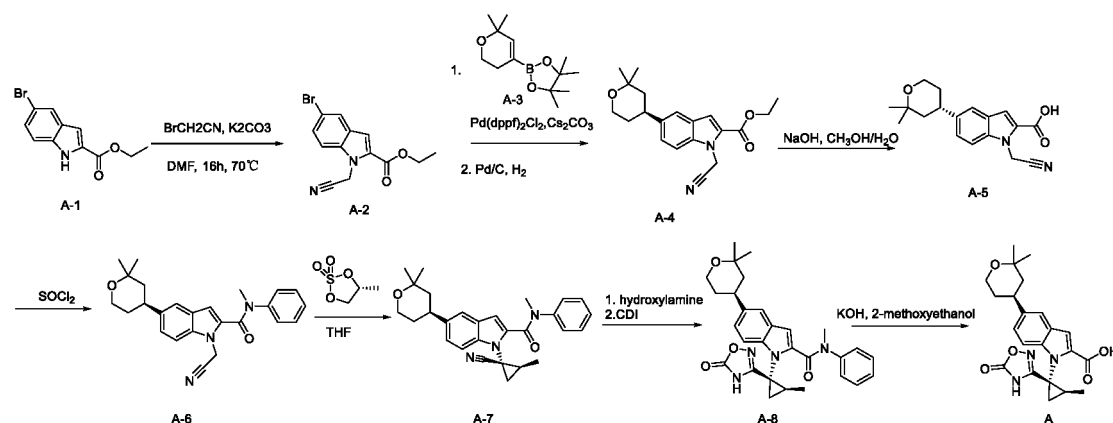
The term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to a desired volume (i.e., 100%).

Description

Compounds provided herein may be synthesized according to the general schemes provided below. In the schemes below, it should be appreciated that each of the compounds shown therein may have protecting groups as required present at any step. Standard protecting groups are within the purview of those skilled in the art.

Preparation of intermediates:

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 solution, and the mixture was heated to 70°C and reacted for 16 hours. After cooling to room temperature, water (60 ml) was added to precipitate a solid, the mixture was filtered to obtain 4 g of brown solid, with a yield of 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 under N₂ and reacted for 4 hours. The reaction solution was cooled, water (30 ml) and ethyl acetate (30 ml) were added, and the extraction afforded the organic phase. The organic phase was concentrated to dryness and purified by column chromatography to obtain 1.2 g of a white solid. The obtained solid was dissolved in methanol, and Pd/C (0.12 g, 30% wt.) was added, and the mixture was reacted at room temperature under hydrogen atmosphere overnight. The mixture was filtered, the filtrate was taken, concentrated to dryness, and the obtained solid was prepared by chiral preparative liquid chromatography (taking the fraction with a short retention time) to obtain 0.6 g of **A-4**, with a yield of 27.3%.

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

A-5 (300 mg, 1.1 mmol) was dissolved in dichloromethane (10 ml), thionyl chloride (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 solution was concentrated to dryness to obtain acyl chloride as an oil, which was dissolved completely by addition of 5 ml of dichloromethane for later use. *N*-methylaniline (180 mg, 1.65 mmol) and triethylamine (222 mg, 2.2 mmol) were dissolved in dichloromethane (10 ml). An acyl chloride solution was added dropwise under ice bath and the reaction was

Description

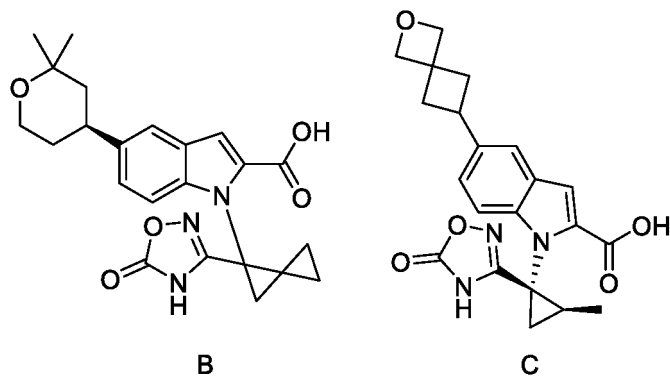
continued at room temperature for 1 hour. Water (10 ml) was added, and the extraction afforded the organic phase, which was concentrated to dryness under reduced pressure to obtain 350 mg of **A-6** with a yield of 87.9%.

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, and lithium bis(trimethylsilyl)amide (1 ml, 1 M in THF) was added dropwise. After the addition was completed, the mixture was reacted at room temperature for 24 hours. Water (5 ml) was added slowly dropwise to quench the reaction, 10 ml of ethyl acetate was added and the extraction afforded the organic phase, which was concentrated to dryness under reduced pressure to obtain an oil. The oil was purified by column chromatography to obtain 40 mg of **A-7** with a yield of 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. Water (10 ml) and ethyl acetate (10 ml) were added for extraction, 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. Water (10 ml) and ethyl acetate (10 ml) were added for extraction, and the organic phase was dried and concentrated to dryness to obtain 10 mg of **A-8** with a yield of 88.2%.

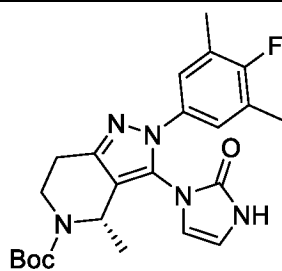
A-8 (220 mg, 0.44 mmol) was dissolved in ethylene glycol methyl ether (3 ml), potassium hydroxide (494 mg, 8.8 mmol) was added, and the mixture was heated to 130°C and reacted for 5 hours. The mixture was cooled to room temperature, and the pH was adjusted to 5.0 with hydrochloric acid (6N). Ethyl acetate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

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

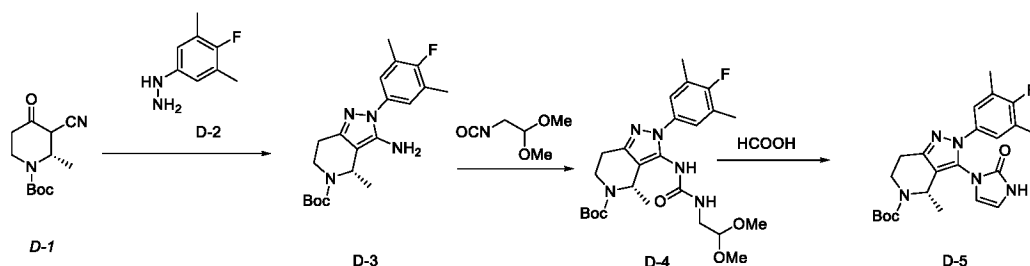


Preparation of intermediate D

Description



D



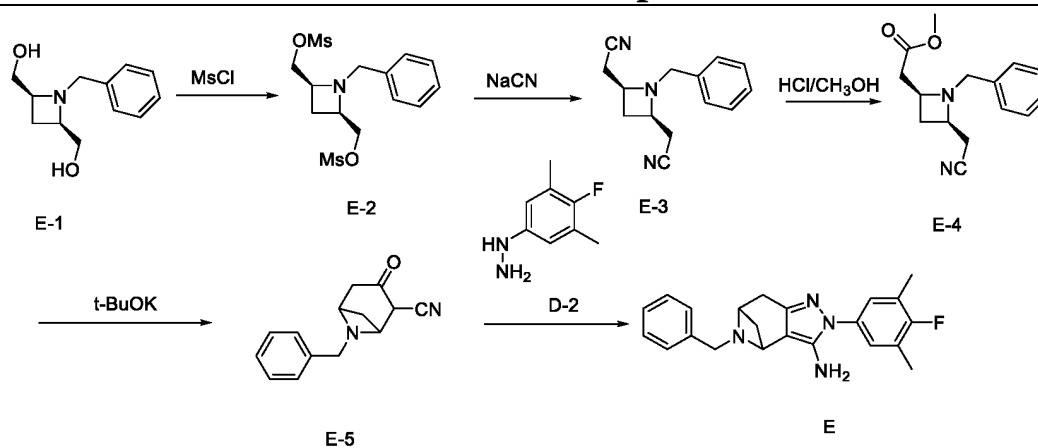
D-1 (2.0 g, 8.4 mmol), **D-2** (1.29 g, 8.4 mmol) and pyridine hydrochloride (0.97 g, 8.4 mmol) were dissolved in toluene (10 ml), and the mixture was heated to reflux and reacted for 1 hour. After the reaction solution was cooled, water (10 ml) and ethyl acetate (10 ml) were added, and the extraction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

D-3 (2.0 g, 5.34 mmol) was dissolved in DCM (20 ml), and 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. Water (20 ml) was added, and after the extraction, the organic phase was separated and subjected to reduced pressure to dryness to obtain an oil, which was directly used for the next reaction.

Under ice bath, **D-4** as an oil was dissolved in dichloromethane (20 ml), and then added to formic acid (10 ml), and the mixture was stirred at room temperature overnight. 20 ml of water was added, and after the extraction, the organic phase was separated and subjected to reduced pressure to dryness to obtain a crude product, which was then slurried with ethyl acetate and n-heptane to obtain 1.2 g of **D-5**.

Preparation of intermediates E and F:

Description



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

E-2 (3.0 g, 8.25 mmol) was dissolved in EMF (30 ml), and NaCN (850 mg, 17.3 mmol) was slowly added, and the mixture was reacted at 60°C for 1 hour. After cooling, a saturated sodium hypochlorite solution (30 ml) was added and stirred for 1 hour. Ethyl acetate (30 ml) was added, and the extraction afforded the organic phase which was concentrated to dryness to obtain 1.54 g of **E-3** with a yield of 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 stirred at room temperature overnight. Water was added and stirred for 2 hours. Ethyl acetate (20 ml) was added, and after the extraction, the organic phase was separated, which was evaporated to dryness under reduced pressure to obtain an oil. The oil was then purified by column chromatography to obtain 0.6 g of **E-4** with a yield of 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 at room temperature overnight. The pH was adjusted to neutral with dilute hydrochloric acid, and ethyl acetate was added for extraction. After evaporation to dryness under reduced pressure, 0.34 g of **E-5** was obtained by column chromatography with a yield of 68%.

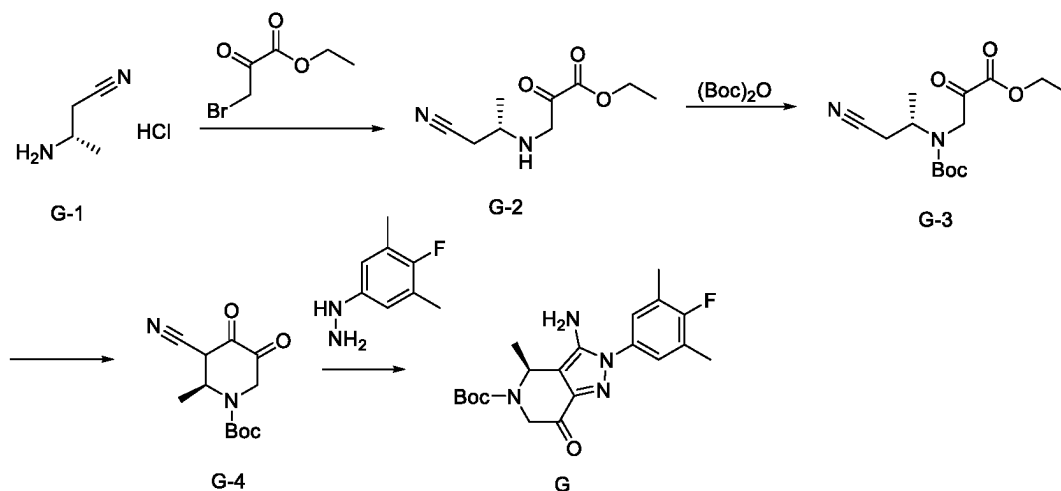
E-5 (0.2 g, 0.88 mmol), **D-2** (126 mg, 0.88 mmol) and pyridine hydrochloride (0.1 g, 0.88 mmol) were dissolved in toluene (4 ml), and the mixture was heated to reflux and reacted for 1 hour. After the reaction solution was cooled, water (10 ml) and ethyl acetate (10 ml) were added, and the extraction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

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



Description

Preparation of intermediate G:



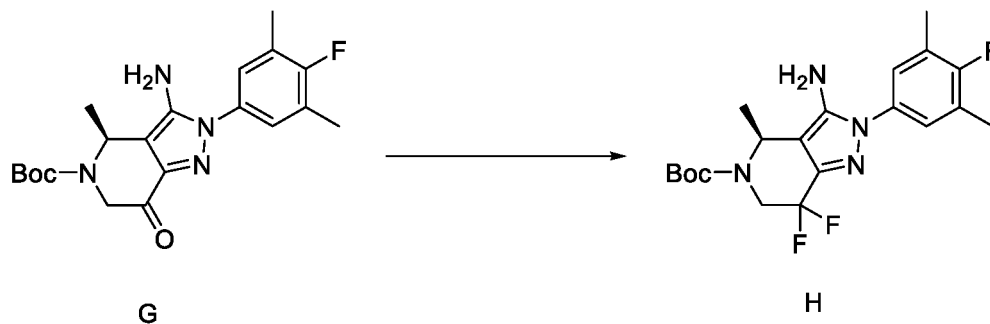
G-1 (5.0 g, 41.5 mmol), ethyl 3-bromopyruvate (8.90 g, 45.61 mmol) and cesium carbonate (20.3 g, 62.2 mmol) were dissolved in DMF (100 ml), and the mixture was heated to 65°C and reacted for 4 hours. After cooling to room temperature, 200 ml of water was added to precipitate a solid, the mixture was filtered to obtain 4.80 g of **G-2** with a yield of 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 stirred at room temperature overnight. Water (50 ml) and ethyl acetate (50 ml) were added, and the extraction afforded the organic phase which was concentrated under reduced pressure to obtain 5.6 g of **G-3** with a yield of 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 at room temperature overnight. The pH was adjusted to neutral with dilute hydrochloric acid, and ethyl acetate was added for extraction. After evaporation to dryness under reduced pressure, 3.6 g of **G-4** was obtained by column chromatography with a yield of 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. After the reaction solution was cooled, water (40 ml) and ethyl acetate (40 ml) were added, and the extraction afforded the organic phase which was concentrated under reduced pressure to obtain 1.2 g of the target compound **G** with a yield of 39%.

Preparation of intermediate H:

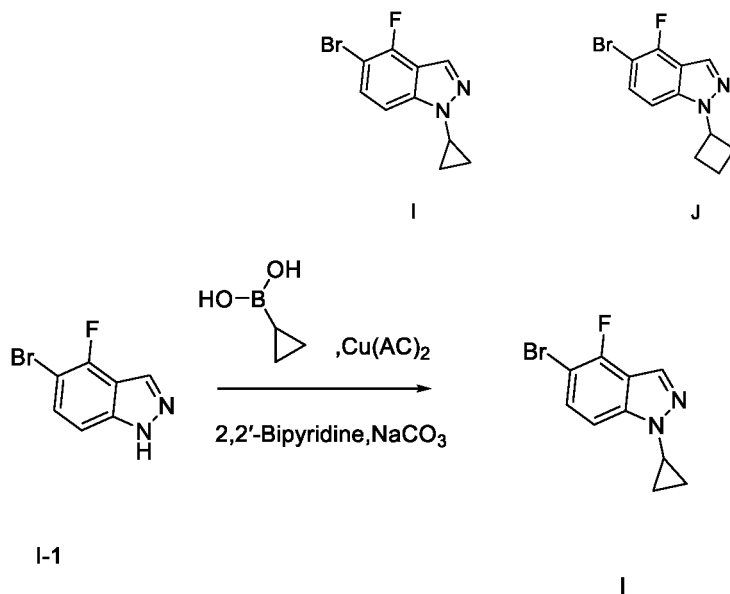


Compound **G** (200 mg, 0.52 mmol) was dissolved in DCM (2 ml), DAST (165 mg, 1.0 mmol)

Description

was added under ice bath, and the mixture was stirred at 0°C overnight. A saturated sodium bicarbonate solution (4 ml) and DCM (4 ml) were added, and after the extraction, the organic phase was separated, subjected to reduced pressure to dryness, and then purified by column chromatography to obtain 0.12 g of compound **H** with a yield of 56.8%.

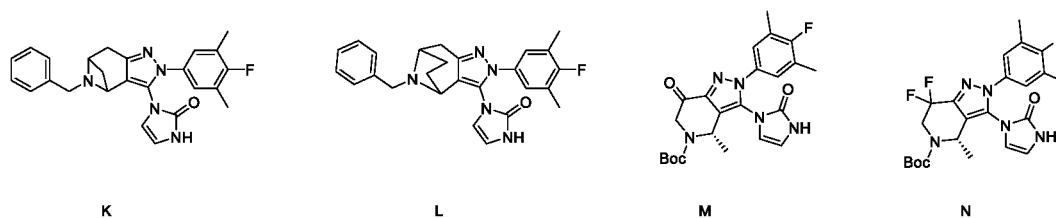
Preparation of intermediates **I** and **J**:



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 at room temperature under an oxygen balloon overnight. The reaction solution was filtered, and the filtrate was removed and extracted with water and dichloromethane. The organic phase was separated, and the organic phase was subjected to reduced pressure to dryness and then purified by column chromatography to obtain 3.6 g of **I** with a yield of 61%.

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

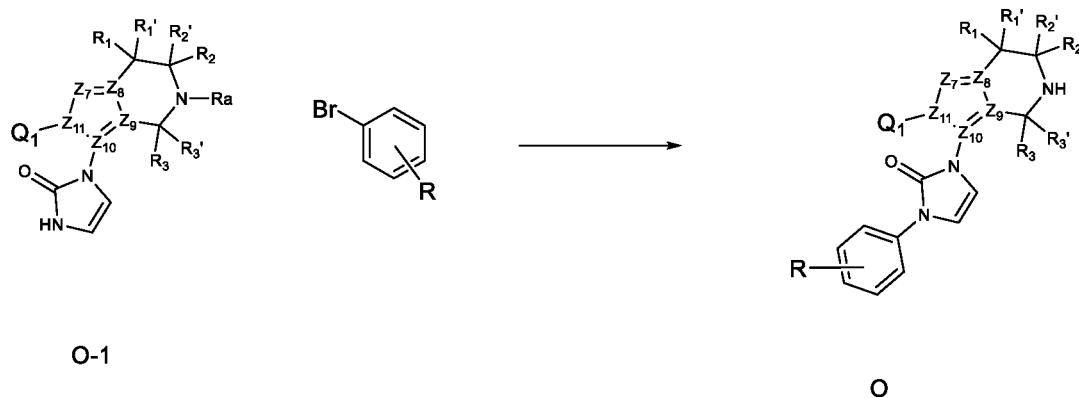
Preparation of intermediates **K**, **L**, **M** and **N**



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

Preparation of intermediate **O** (Ullmann reaction)

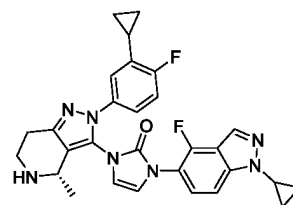
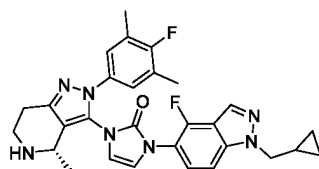
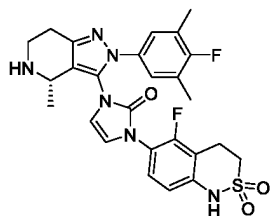
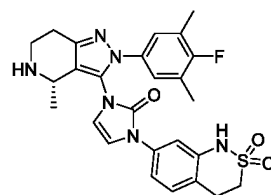
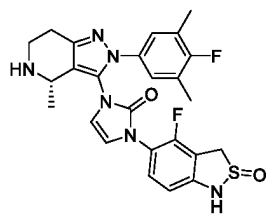
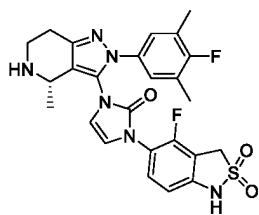
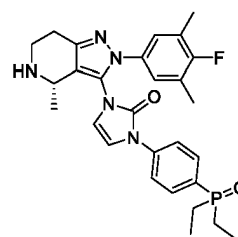
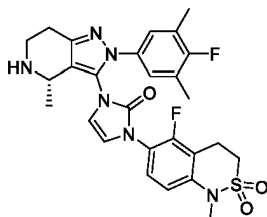
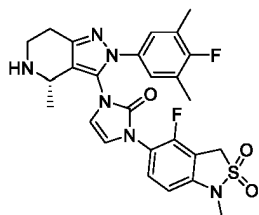
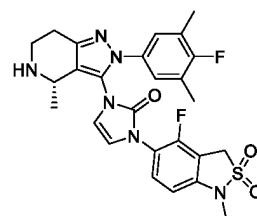
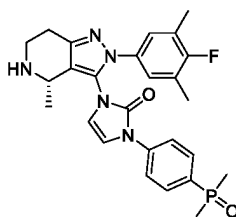
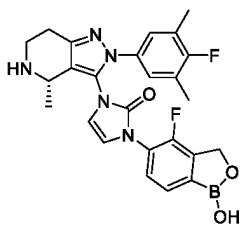
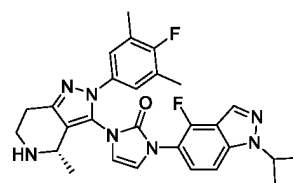
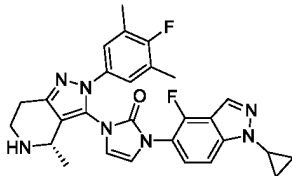
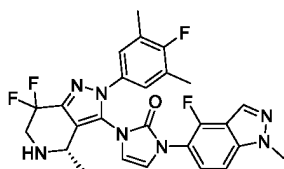
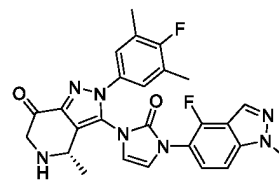
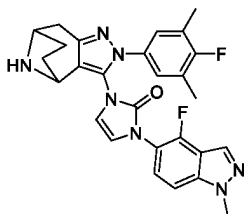
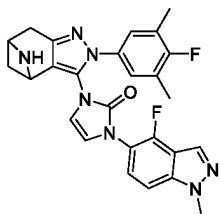
Description



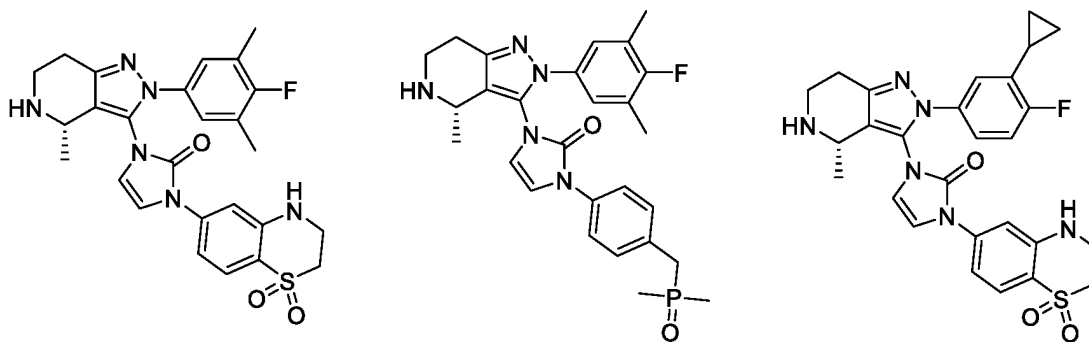
O-1 (1 eq.), (1R,2R)-(-)-N,N'-dimethyl-1,2-cyclohexanediamine (0.5 eq.), CuI (0.5 eq.), bromide (1.5 eq.), and potassium carbonate (3 eq.) were added to NMP, and the mixture was reacted at room temperature under an oxygen balloon overnight. The mixture was filtered, water and ethyl acetate were added to the filtrate, and after the extraction, the organic phase was separated. After the organic phase was subjected to reduced pressure, purification, and deprotection reaction (debenzylation or Boc-deprotection reaction), the target compound was obtained.

The following compounds can be obtained by this method:

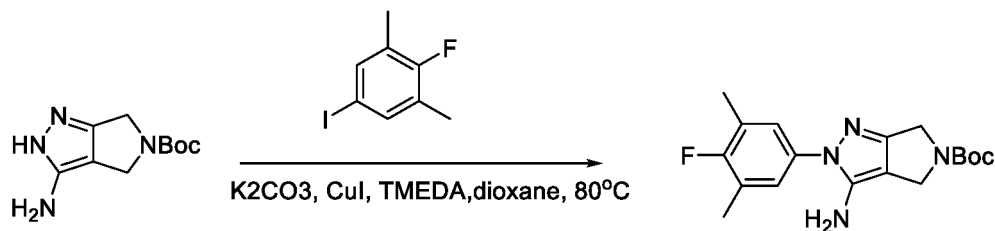
Description



Description



Preparation of intermediate P:



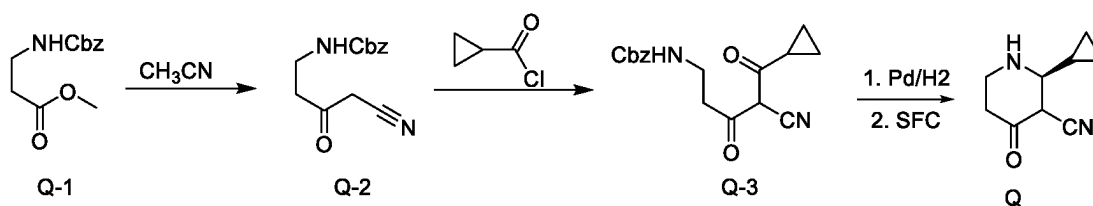
P-1

P

P-1 (1.0 g, 4.46

mmol), 2-fluoro-5-iodo-1,3-xylene (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. After cooling, the mixture was filtered, the filtrate was removed and extracted with ethyl acetate (20 ml) and water (20 ml), and the organic phase was separated, concentrated under reduced pressure, and purified by column chromatography to obtain 0.6 g of P with a yield of 38.8%.

Preparation of intermediate Q:



Under N₂ protection, acetonitrile (15.57 g, 379.34 mmol) was added to THF (300 ml). The temperature was lowered to below -78°C, LiHMDS (63.47 g, 379.34 mmol) was added dropwise, and the reaction was kept at this temperature for 1 hour. Then, a solution of compound Q1 (45.0 g, 189.67 mmol) in THF (5 ml) was added dropwise, and the temperature was raised to -50°C for reaction for 30 minutes. A saturated ammonium chloride solution was added dropwise to quench the reaction, and ethyl acetate (150 ml) was added for extraction. The organic phase was washed with brine, dried over anhydrous magnesium sulfate, concentrated under reduced pressure and purified by column chromatography to obtain a yellow oil.

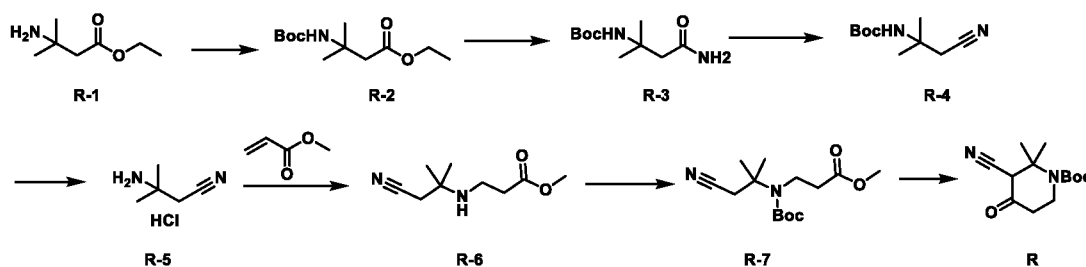
Q2 (246.26 mg, 1 mmol) and triethylamine (202.38 mg, 2 mmol) were dissolved in DCM (10 ml), cyclopropylcarbonyl chloride (209.06 mg, 2 mmol) was added dropwise, and the mixture was

Description

reacted at room temperature overnight. The reaction solution was quenched by adding water, then 10 ml of DCM was added, and after the extraction, the organic phase was separated. The organic phase was washed with brine, dried over magnesium sulfate, concentrated to dryness under reduced pressure and 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 under a hydrogen balloon for 3 hours. The reaction solution was filtered, and the filtrate was taken and purified by SFC to obtain 32 mg of Q3 with a yield of 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 at room temperature overnight. The reaction solution was quenched with 100 ml of water, and then extracted with 100 ml of DCM. The organic phase was separated, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to obtain 15.3 g of **R-2** with a yield of 90.56%.

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

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

R-4 (5.3 g, 26.7 mmol) was added to a solution of hydrogen chloride in ethyl acetate (4 M, 30 ml) and stirred at room temperature for 2 hours. The solid was precipitated, and the mixture was filtered to obtain 3.2 g of **R-5** with a yield of 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 methyl acrylate (2.15 g, 24.9 mmol) was added. The mixture was heated to 70°C and reacted for 3 hours. After cooling to room temperature, (Boc)₂O (6.74 g, 30.9 mmol) was added and the reaction was continued overnight. Water (50 ml) and ethyl acetate were added, and after the extraction, the organic phase was separated. The organic phase was washed with water and brine, dried over magnesium sulfate, concentrated under reduced pressure, and purified by column chromatography to obtain 4.3 g of **R-7** with a yield of 63.6%.

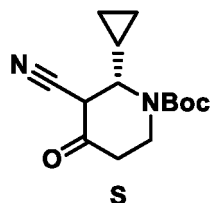
R-7 (4.0 g, 14.1 mmol) and potassium tert-butoxide (2.37 g, 21.1 mmol) were dissolved in THF

Description

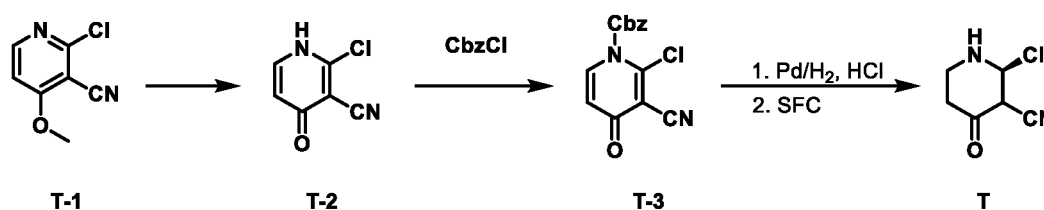
and the mixture was reacted at room temperature for 1 hour. The reaction was quenched by addition of 2N hydrochloric acid. Water and ethyl acetate were added for extraction, the organic phase was separated, washed with brine, dried over magnesium sulfate, concentrated under reduced pressure, and purified by column chromatography to obtain 2.5 g of **R** with a yield of 70.4%.

Preparation of intermediate **S**:

According to the preparation method of intermediate **R**, intermediate **S** can be obtained through SFC chiral separation.



Preparation of intermediate **T**:



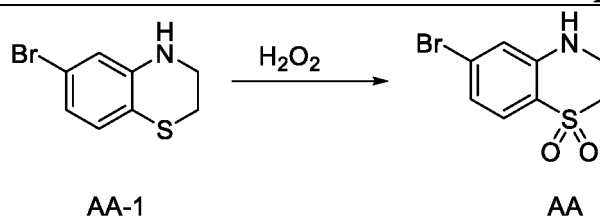
T-1 (10.0 g, 59.3 mmol) was dissolved in THF (100 ml), boron tribromide (120 ml, 1 M in DCM) was added dropwise, and the mixture was reacted at room temperature for 3 hours. The reaction solution was quenched with a saturated sodium carbonate solution, and then extracted with DCM. The organic phase was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

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

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 reacted under a hydrogen pressure of 50 Psi for 2 hours. The reaction solution was filtered and the solvent was removed under reduced pressure. DCM and a saturated sodium bicarbonate solution were added, and the extraction afforded the organic phase, which was then washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by FLASH to obtain a racemate. The racemate was then chirally purified by SFC to obtain 1.2 g of **T** with a yield of 21.8%.

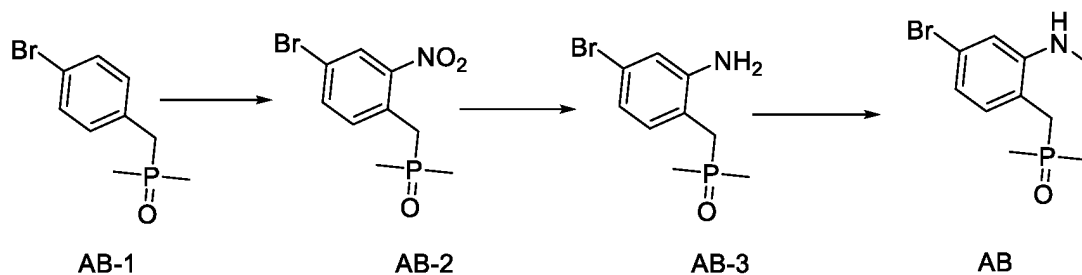
Preparation of intermediate **AA**:

Description



Compound AA-1 (1.0 g, 4.35 mmol) was dissolved in ethanol (10 ml), 5 ml of hydrogen peroxide (30%, 10 ml) was added at room temperature, and the mixture was reacted overnight. The reaction solution was filtered to obtain 1.1 g of AA with a yield of 96.6%.

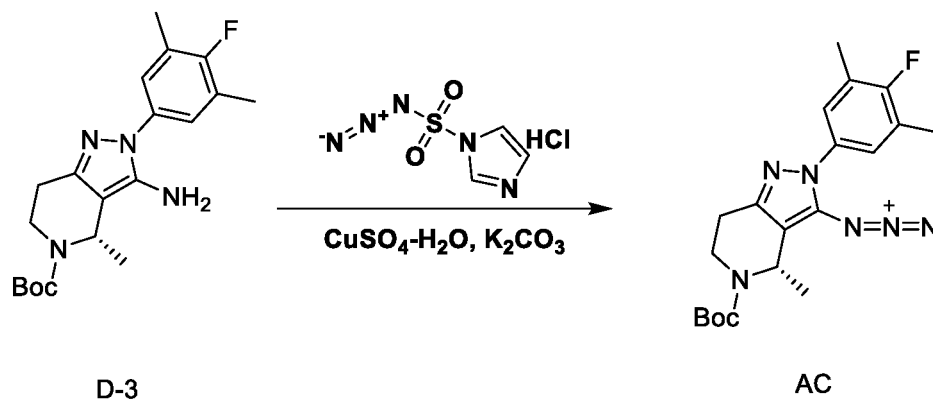
Preparation of intermediate AB:



AB-1 (5.0 g, 20.2 mmol) was dissolved in 25 ml of concentrated sulfuric acid. Potassium nitrate (2.1 g, 20.2 mmol) was added in batches at -20°C , and the reaction was kept at this temperature for 4 hours. The reaction solution was poured into ice water to precipitate a solid. After the solid was dried, 0.7 g of AB-2 was obtained by column chromatography with a yield of 11%.

AB-2 (0.7 g, 2.4 mmol) was dissolved in methanol (5 ml), and saturated ammonium chloride (5 ml) was added, and then iron powder (0.54 g, 9.6 mmol) was added, and the mixture was heated to 80°C and reacted for 3 hours. After cooling to room temperature, 20 ml of ethyl acetate was added for extraction to obtain 0.54 g of AB-3 with a yield of 86%.

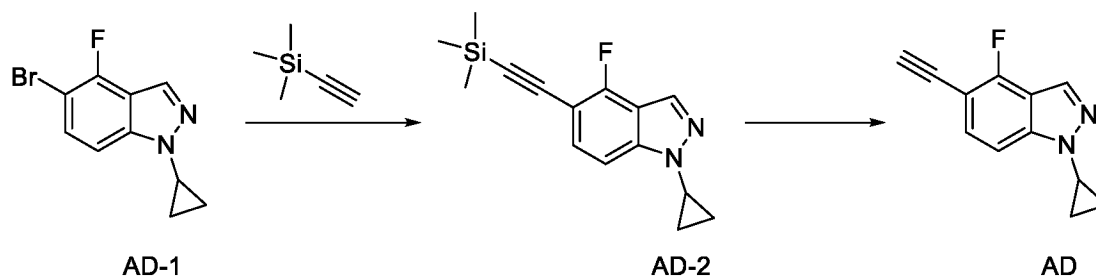
AB-3 (0.54 g, 2.0 mmol) was dissolved in dichloromethane (5 ml), triethylamine (0.20 g, 2.0 mmol) and (Boc) $_2$ O (0.45 mmol) were added at room temperature, and the mixture was stirred at room temperature overnight. Iodomethane (0.29 g, 2.0 mmol) was added dropwise to the reaction solution and the mixture was reacted for 1 hour. The reaction solution was concentrated to dryness, a solution of hydrogen chloride in ethyl acetate (5 ml, 2N) was added, and the mixture was stirred at room temperature for 1 hour. The solid was precipitated, and the mixture was filtered to obtain 0.32 g of AB with a yield of 49.7%. Preparation of intermediate AC:



Description

D-3 (290 mg, 0.77 mmol), 1H-imidazole-1-sulfonyl azide (139.99 mg, 0.81 mmol) and potassium carbonate (212.84 mg, 1.54 mmol) were added to methanol (3 mL) at 0°C, copper sulfate hydrate (1.9 mg, 0.0077 mmol) was added, and the mixture was reacted at room temperature for 12 hours. Ethyl acetate and water were added to the reaction solution for extraction. The organic phase was washed with 1N hydrochloric acid, saturated sodium bicarbonate and brine respectively, dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to obtain 0.15 g of AC as an oil with a yield of 48%.

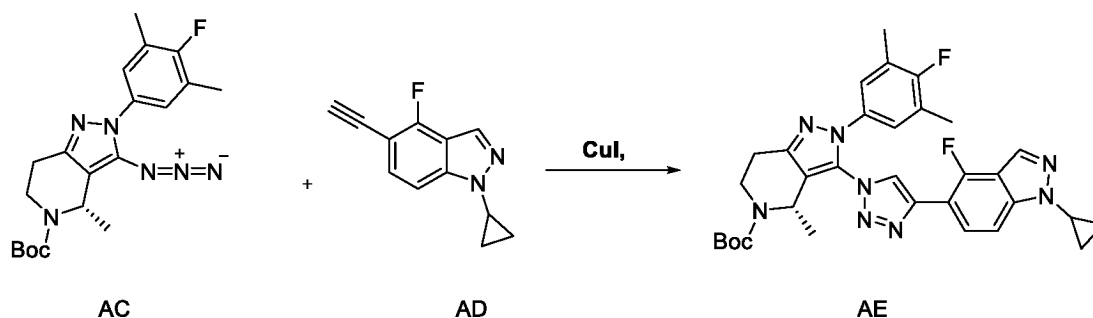
Preparation of intermediate AD:



AD-1 (2.0 g, 7.84 mmol), TMSCN (1.16 g, 11.8 mmol), triethylamine (1.59 g, 15.7 mmol), cuprous iodide (1.49 g, 7.8 mmol) and tetrakis(triphenyl)phosphine palladium (900 mg, 0.8 mmol) were added to dioxane (20 ml), and the mixture was heated to 70°C under nitrogen protection and reacted overnight. After cooling to room temperature, water and ethyl acetate were added, and after the extraction, concentration and purification by column chromatography, 1.1 g of AD-2 was obtained with a yield of 51.5%.

AD-2 (1.1 g, 4.0 mmol) was added to methanol, potassium carbonate (1.1 g, 8.1 mmol) was added, and the mixture was stirred at room temperature for 4 hours. Water and ethyl acetate were added for extraction. The organic phase was concentrated to dryness and purified by column chromatography to obtain 0.35 g of AD with a yield of 43.3%.

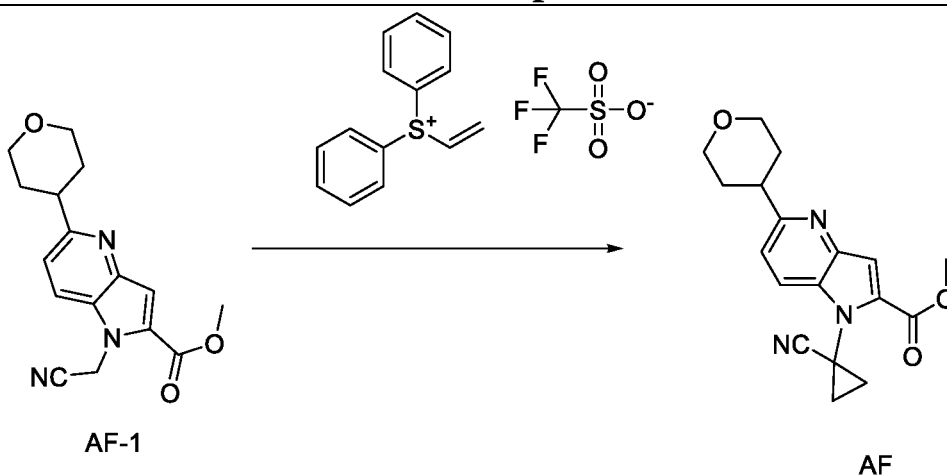
Preparation of intermediate AE



AC (100 mg, 0.25 mmol) and AD (55 mg, 0.27 mmol) were dissolved in PEG200 (2 ml), CuI (9.5 mg, 0.05 mmol) was added, and the mixture was reacted at 50°C for 2 hours. After cooling to room temperature, the reaction solution was filtered and purified by preparative liquid chromatography (C18) to obtain 123 mg of AE with a yield of 82%.

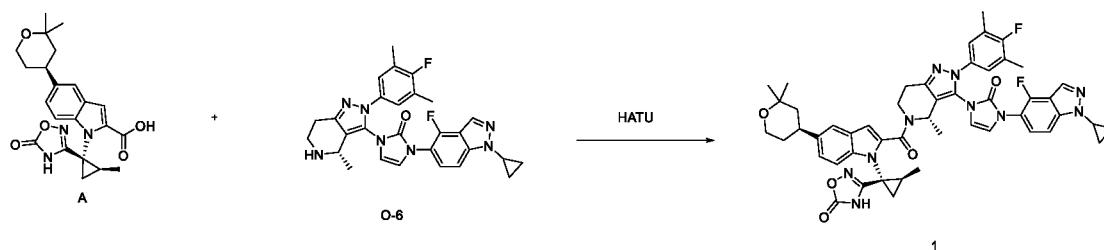
Preparation of intermediate AF

Description



Compound AF-1 (300 mg, 1.00 mmol) was dissolved in DMSO (10 ml), and diphenyl(vinyl)sulfonium trichloromethanesulfonate (0.40 g, 1.1 mmol) and DBU (0.46 g, 3 mmol) were added. The reaction was carried out at room temperature for 2 hours. Ethyl acetate (50 mL) and water (20 mL) were added dropwise to the reaction solution, and after the extraction, the organic phase was separated. The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The concentrate was purified by column chromatography to obtain 154 mg of AF with a yield of 47.22%.

Preparation of compound 1

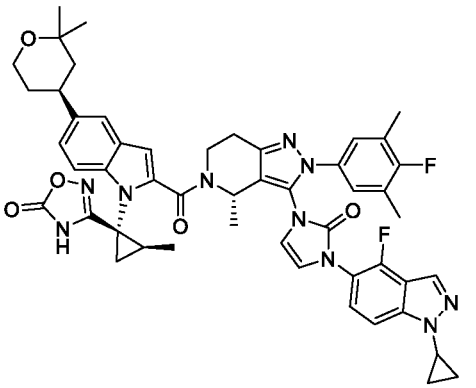
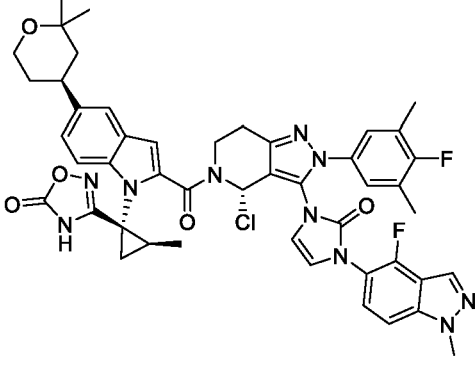


Intermediate **A** (180 mg, 0.44 mmol), **O-6** (280 mg, 0.57 mmol), HATU (250.95 mg, 0.66 mmol) and DIPEA (170 mg, 1.32 mmol) were dissolved in DMF (5 ml) and stirred at room temperature for 3 hours. 5 ml of water was added, the mixture was extracted three times with dichloromethane, and the organic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

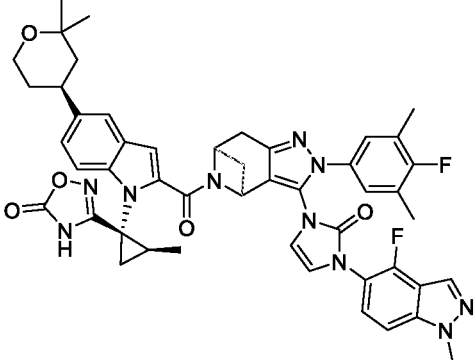
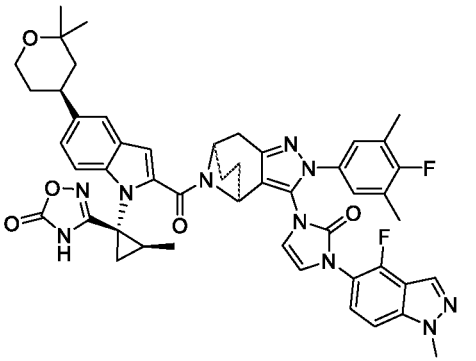
The following compounds were prepared according to the preparation methods described herein using appropriate starting materials and intermediates and, where necessary, appropriate protecting group chemistry, and the structures of these compounds were confirmed by MS and ¹HNMR.

Number	Structure	MS	¹ HNMR
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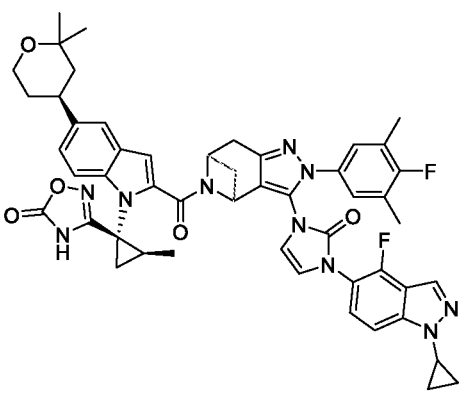
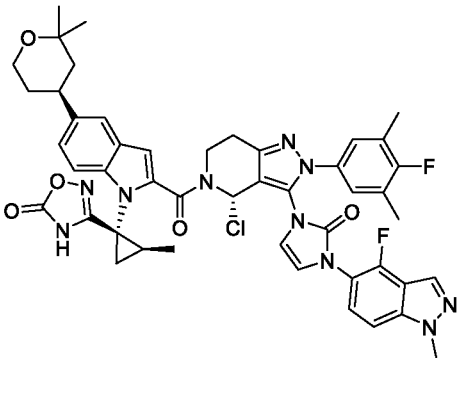
Description

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 – 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).

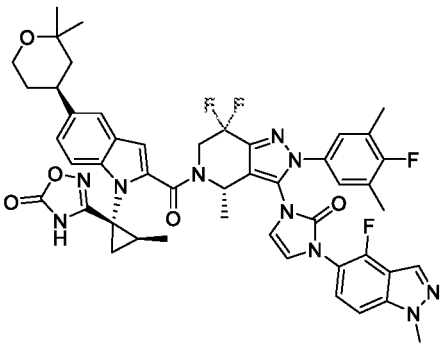
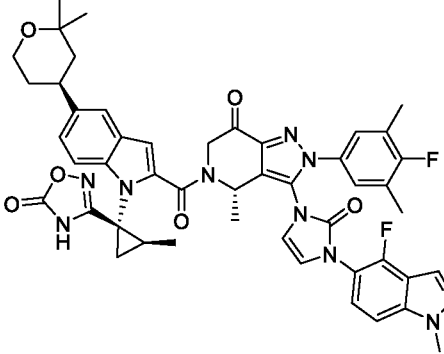
Description

3		881.36 ¹H 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 ¹H 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 – 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, <i>J</i> = 6.0 Hz, 3H).

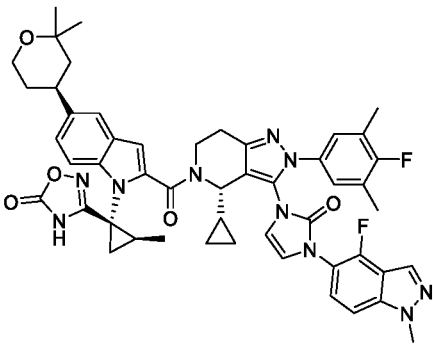
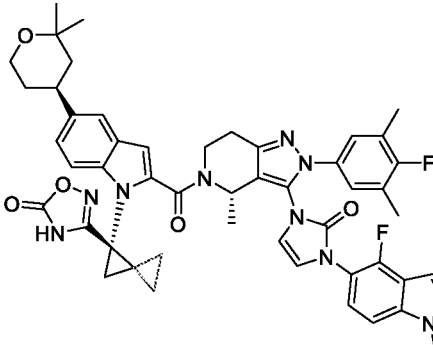
Description

5		907.38 ¹ H NMR (500 MHz, DMSO- <i>d</i> 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, <i>J</i> = 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), 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, <i>J</i> = 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, <i>J</i> = 4.9 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.68 – 7.63 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, <i>J</i> = 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, <i>J</i> = 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, 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, <i>J</i> = 7.8 Hz, 3H), 1.27 – 1.15 (m, 6H), 0.99 (d, <i>J</i> = 6.0 Hz, 3H).

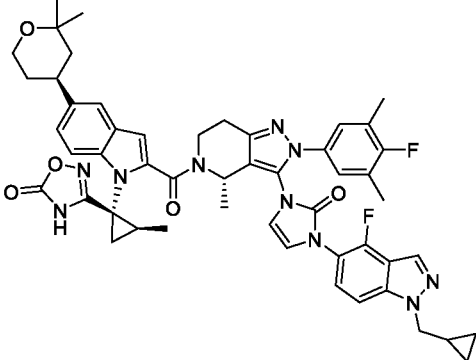
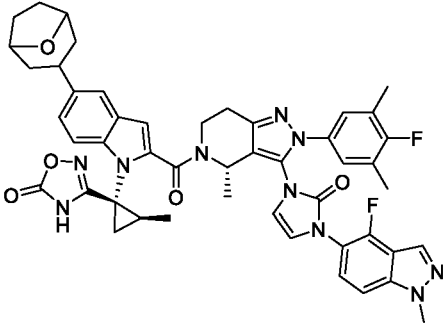
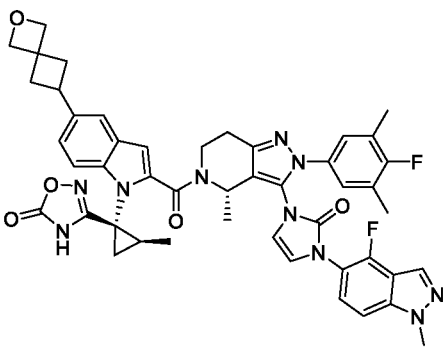
Description

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, <i>J</i> = 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, <i>J</i> = 2.0 Hz, 1H), 7.11 – 7.04 (m, 1H), 4.89 (d, <i>J</i> = 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, 1H), 1.25 – 1.15 (m, 6H), 0.99 (d, <i>J</i> = 6.0 Hz, 3H), 0.68 – 0.57 (m, 2H), 0.49 – 0.39 (m, 2H).
10		895.38 ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.76 (s, 1H), 8.36 – 8.29 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.67 – 7.64 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, <i>J</i> = 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).

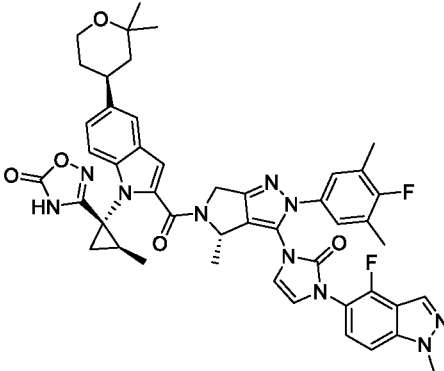
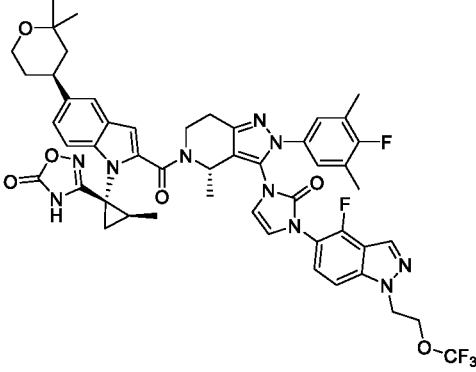
Description

11		895.38 ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.16 (s, 1H), 8.34–8.23 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.82–7.76 (m, 1H), 7.67–7.63 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.46–7.37 (m, 3H), 7.24 (d, <i>J</i> = 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, <i>J</i> = 6.0 Hz, 3H).
12		898.00 ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.16 (s, 1H), 8.13 (d, <i>J</i> = 5.2 Hz, 1H), 7.68–7.63 (m, 1H), 7.53 (d, <i>J</i> = 9.0 Hz, 1H), 7.51–7.41 (m, 2H), 7.37 (d, <i>J</i> = 4.9 Hz, 2H), 7.21 (d, <i>J</i> = 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, <i>J</i> = 8.0 Hz, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, <i>J</i> = 6.0 Hz, 3H).

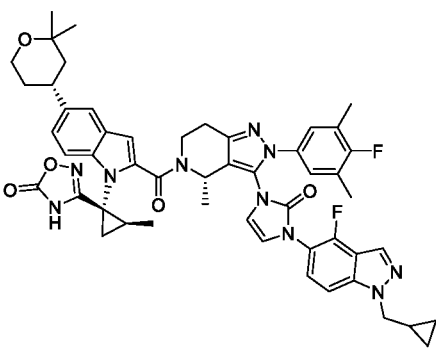
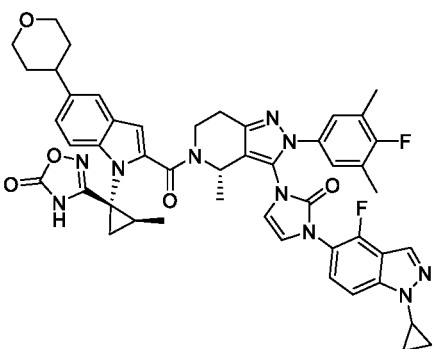
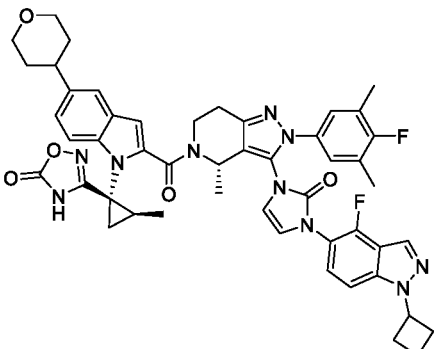
Description

13		923.41	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.37 – 8.29 (m, 2H), 8.25 (d, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 6.0 Hz, 3H), 0.61 – 0.38 (m, 4H).
14		881.36	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), 7.82 – 7.75 (m, 1H), 7.66 – 7.61 (m, 1H), 7.54 (d, <i>J</i> = 8.8 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.11 – 7.06 (m, 1H), 5.22 – 5.14 (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, <i>J</i> = 8.0 Hz, 3H), 0.99 (d, <i>J</i> = 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, <i>J</i> = 4.9 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.66 – 7.61 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.21 (d, <i>J</i> = 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),

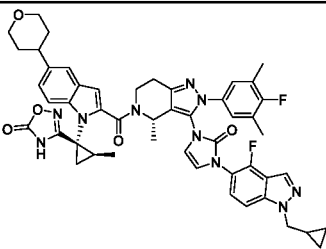
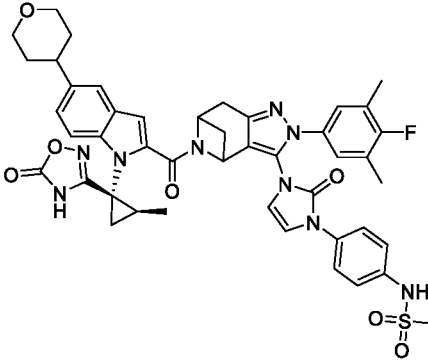
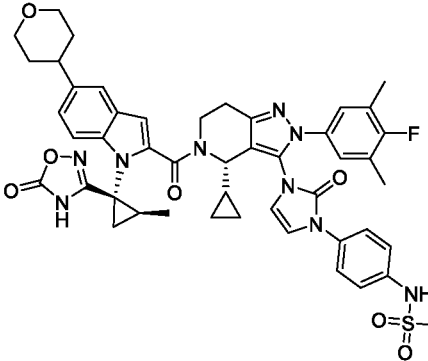
Description

			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).
16		869.36	^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), 7.81 – 7.76 (m, 1H), 7.66 – 7.64 (m, 1H), 7.54 (d, $J = 8.9$ Hz, 1H), 7.45 – 7.37 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.10 – 7.05 (m, 1H), 5.02 – 4.95 (m, 1H), 4.61 (d, $J = 1.0$ 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, $J =$ 7.0 Hz, 3H), 1.27 – 1.15 (m, 6H), 0.99 (d, $J = 6.0$ Hz, 3H).
17		981.38	^1H NMR (500 MHz, Chloroform- d) 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, 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,

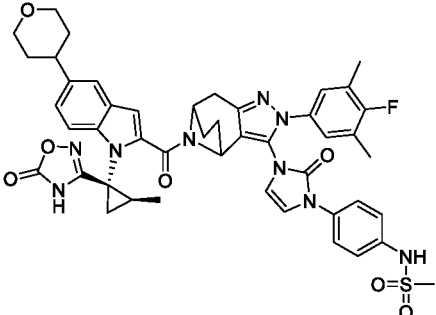
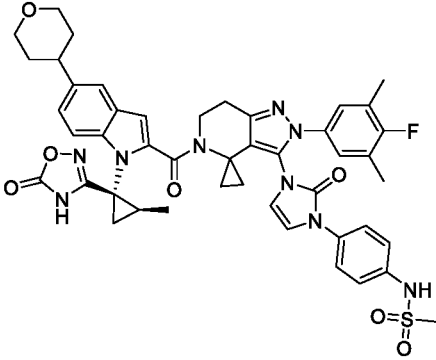
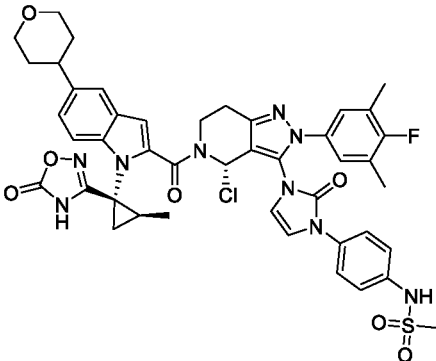
Description

18		923.04	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.37 – 8.29 (m, 2H), 8.25 (d, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 6.0 Hz, 3H), 0.61 – 0.38 (m, 4H).
19		881.36	¹ H 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 (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, <i>J</i> = 8.0 Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.95 (m, 3H).
20		895.38	¹ H NMR (500 MHz, DMSO- <i>d</i> 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

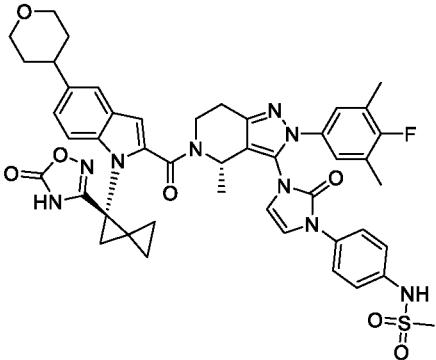
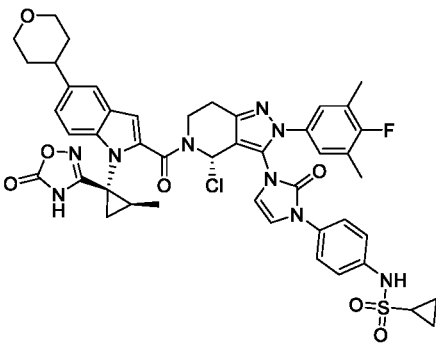
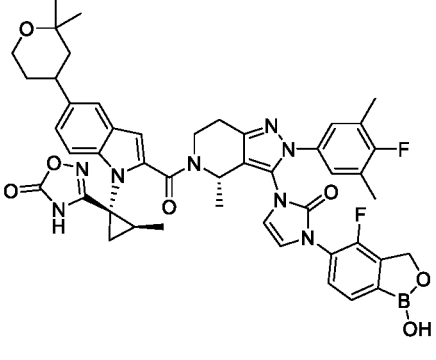
Description

			(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 (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), 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).

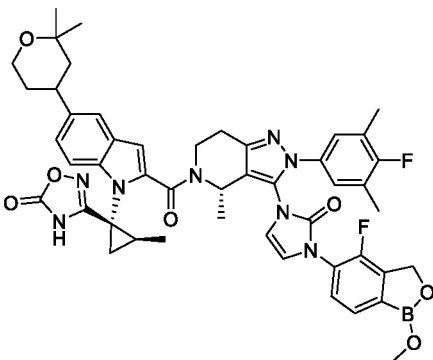
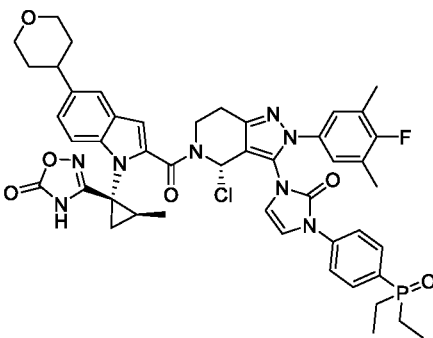
Description

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, <i>J</i> = 6.0 Hz, 1H), 8.17 (d, <i>J</i> = 6.0 Hz, 1H), 7.64 (t, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 6.0 Hz, 1H), 8.17 (d, <i>J</i> = 6.0 Hz, 1H), 7.64 (t, <i>J</i> = 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 (m, 2H), 2.40 – 2.18 (m, 13H), 2.15 – 2.07 (m, 2H), 1.88 – 1.80 (m, 2H), 0.99 (d, <i>J</i> = 5.8 Hz, 3H).
26		895.32	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.91 (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), 3.06 – 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, <i>J</i> = 5.8 Hz, 3H).

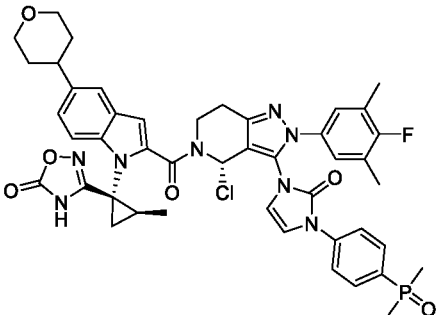
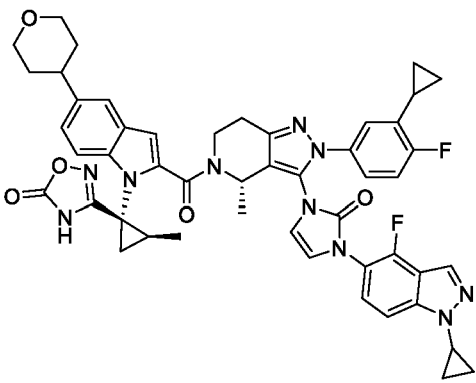
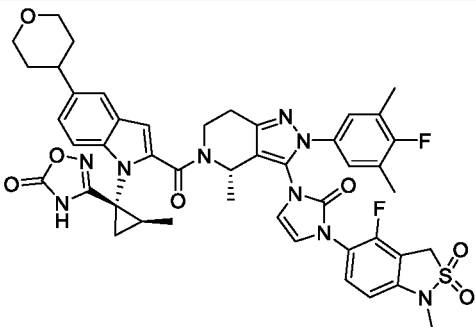
Description

27		888.32 ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.91 (s, 1H), 8.76 (s, 1H), 8.36 (d, <i>J</i> = 6.0 Hz, 1H), 8.17 (d, <i>J</i> = 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 – 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 ¹H 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 ¹H 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, 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,

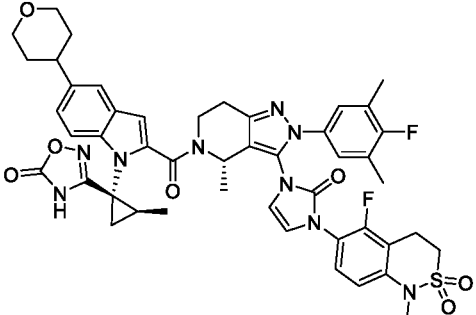
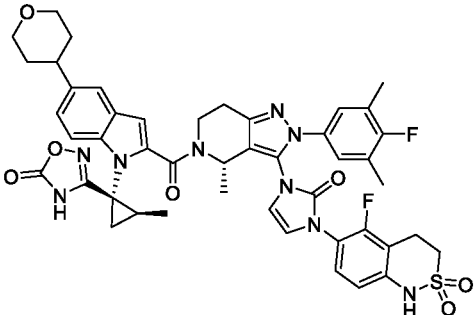
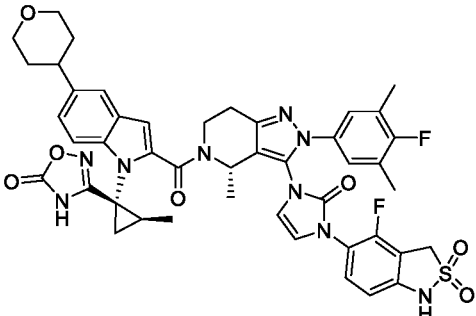
Description

			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).
31		907.34	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.37 (d, $J = 6.0$ Hz, 1H), 8.18 (d, $J = 6.0$ Hz, 1H), 7.81 – 7.75 (m, 2H), 7.75 – 7.69 (m, 2H), 7.66 – 7.62 (m, 1H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.40 (d, $J = 5.1$ Hz, 2H), 7.21 (d, $J = 2.0$ 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, $J = 5.8$ Hz, 3H).

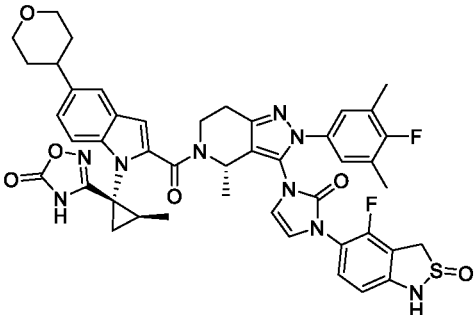
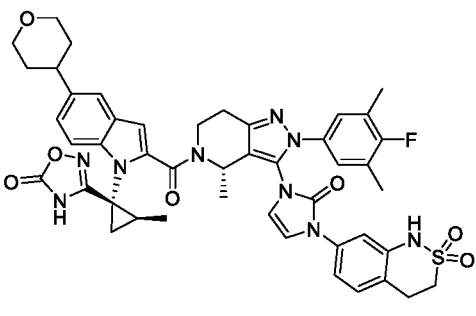
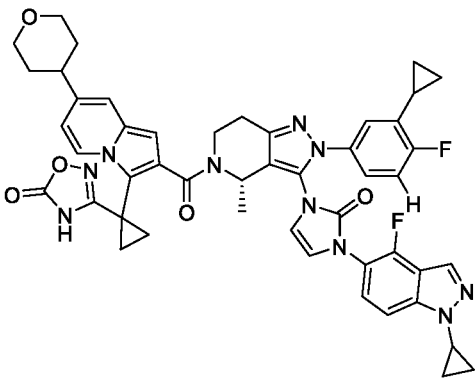
Description

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, 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, <i>J</i> = 5.8 Hz, 3H).
33		893.37	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 8.39 – 8.29 (m, 3H), 7.93 – 7.83 (m, 1H), 7.69 – 7.58 (m, 2H), 7.49 – 7.36 (m, 3H), 7.20 (s, 1H), 7.11 – 7.06 (m, 1H), 5.23 – 5.13 (m, 1H), 4.55 – 4.49 (m, 1H), 4.13 – 3.85 (m, 2H), 3.57 – 3.47 (m, 4H), 3.05 – 2.88 (m, 3H), 2.40 – 2.27 (m, 4H), 2.16 – 2.09 (m, 2H), 1.90 – 1.80 (m, 2H), 1.58 (d, <i>J</i> = 8.0 Hz, 3H), 1.40 – 1.22 (m, 8H), 1.11 – 1.05 (m, 3H).
34		906.32	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.18 (s, 1H), 8.41 – 8.29 (m, 2H), 7.99 – 7.89 (m, 1H), 7.64 – 7.54 (m, 2H), 7.46 – 7.36 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.11 – 7.08 (m, 1H), 5.26 – 5.16 (m, 1H), 4.57 – 4.52 (m, 3H), 4.11 – 3.81 (m, 2H), 3.55 – 3.49 (m, 4H), 3.13 – 2.85 (m, 6H), 2.42 – 2.33 (m, 3H), 2.30 (s, 6H), 2.15 – 2.11 (m, 2H), 1.88 – 1.79 (m, 2H), 1.61 (d, <i>J</i> = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).

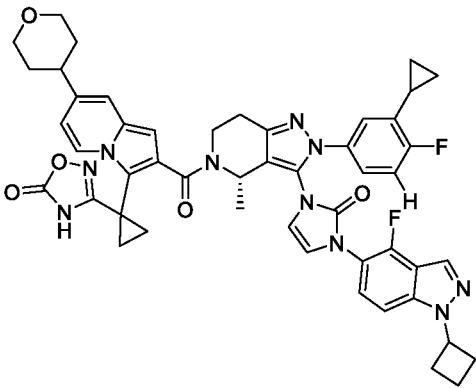
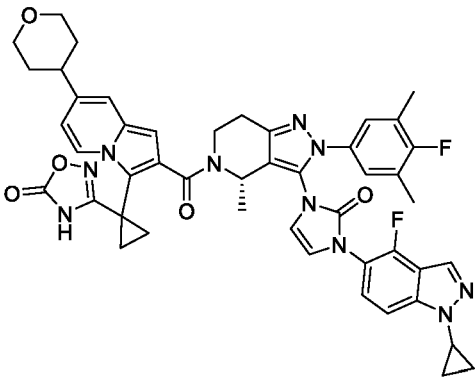
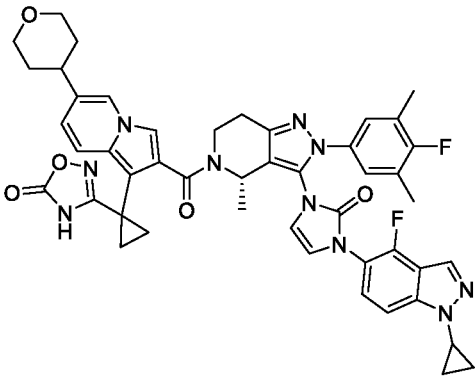
Description

35		920.34	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.17 (s, 1H), 8.40 – 8.29 (m, 2H), 7.97 – 7.87 (m, 1H), 7.65 – 7.55 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, <i>J</i> = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 5.29 – 5.19 (m, 1H), 4.55 – 4.52 (m, 1H), 4.13 – 3.80 (m, 2H), 3.79 – 3.61 (m, 2H), 3.58 – 3.49 (m, 4H), 3.16 – 2.89 (m, 8H), 2.43 – 2.35 (m, 3H), 2.28 (s, 6H), 2.16 – 2.13 (m, 2H), 1.85 – 1.79 (m, 2H), 1.63 (d, <i>J</i> = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).
36		906.32	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.17 (s, 1H), 8.40 – 8.29 (m, 2H), 7.97 – 7.87 (m, 1H), 7.65 – 7.55 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, <i>J</i> = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 5.29 – 5.19 (m, 1H), 4.55 – 4.52 (m, 1H), 4.13 – 3.80 (m, 2H), 3.79 – 3.61 (m, 2H), 3.58 – 3.49 (m, 4H), 3.16 – 2.89 (m, 5H), 2.43 – 2.35 (m, 3H), 2.28 (s, 6H), 2.16 – 2.13 (m, 2H), 1.85 – 1.79 (m, 2H), 1.63 (d, <i>J</i> = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).
37		892.30	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.18 (s, 1H), 8.41 – 8.29 (m, 2H), 7.99 – 7.89 (m, 1H), 7.64 – 7.54 (m, 2H), 7.46 – 7.36 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.11 – 7.08 (m, 1H), 5.26 – 5.16 (m, 1H), 4.57 – 4.52 (m, 3H), 4.11 – 3.81 (m, 2H), 3.55 – 3.49 (m, 4H), 3.13 – 2.85 (m, 3H), 2.42 – 2.33 (m, 3H), 2.30 (s, 6H), 2.15 – 2.11 (m, 2H), 1.88 – 1.79 (m, 2H), 1.61 (d, <i>J</i> = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).

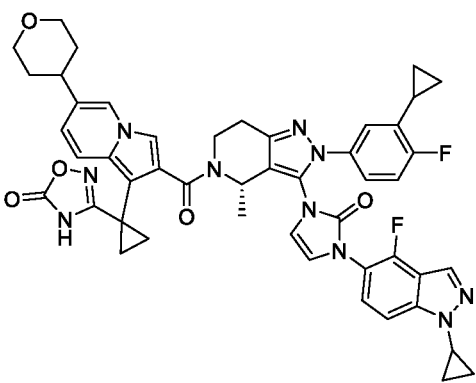
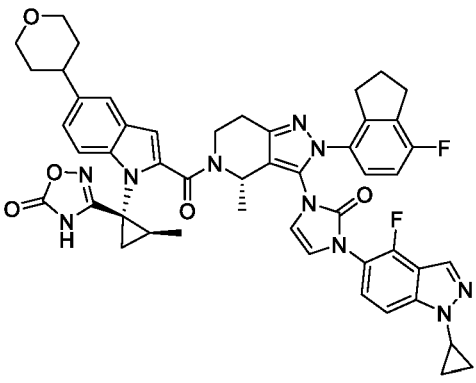
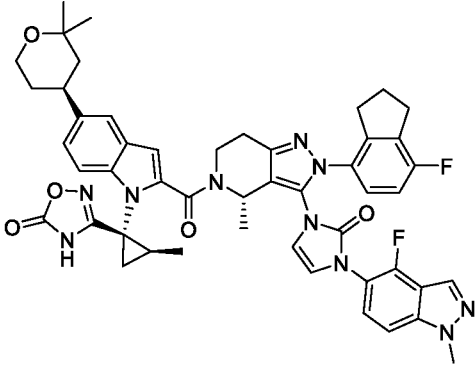
Description

38		876.31	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.18 (s, 1H), 8.41 – 8.29 (m, 2H), 7.99 – 7.89 (m, 1H), 7.64 – 7.54 (m, 2H), 7.46 – 7.36 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.11 – 7.08 (m, 1H), 5.26 – 5.16 (m, 1H), 4.57 – 4.52 (m, 1H), 4.11 – 3.81 (m, 4H), 3.55 – 3.49 (m, 4H), 3.13 – 2.85 (m, 3H), 2.42 – 2.33 (m, 3H), 2.30 (s, 6H), 2.15 – 2.11 (m, 2H), 1.88 – 1.79 (m, 2H), 1.61 (d, <i>J</i> = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).
39		888.33	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.20 (s, 1H), 8.43 – 8.33 (m, 2H), 7.95 – 7.87 (m, 1H), 7.69 – 7.59 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, <i>J</i> = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.29 – 5.19 (m, 1H), 4.55 – 4.52 (m, 1H), 4.13 – 3.80 (m, 2H), 3.79 – 3.61 (m, 2H), 3.58 – 3.49 (m, 4H), 3.16 – 2.89 (m, 5H), 2.43 – 2.35 (m, 3H), 2.28 (s, 6H), 2.16 – 2.13 (m, 2H), 1.85 – 1.79 (m, 2H), 1.63 (d, <i>J</i> = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).
40		879.35	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.42 – 8.37 (m, 3H), 7.91 – 7.81 (m, 1H), 7.65 – 7.54 (m, 2H), 7.45 – 7.36 (m, 2H), 7.12 – 7.09 (m, 1H), 6.51 – 6.46 (m, 2H), 5.33 – 5.23 (m, 1H), 4.61 – 4.49 (m, 1H), 4.15 – 3.85 (m, 2H), 3.67 – 3.47 (m, 4H), 3.09 – 2.91 (m, 3H), 2.42 – 2.29 (m, 4H), 2.18 – 2.11 (m, 2H), 1.92 – 1.82 (m, 2H), 1.42 – 1.25 (m, 9H), 1.13 – 1.07 (m, 3H).

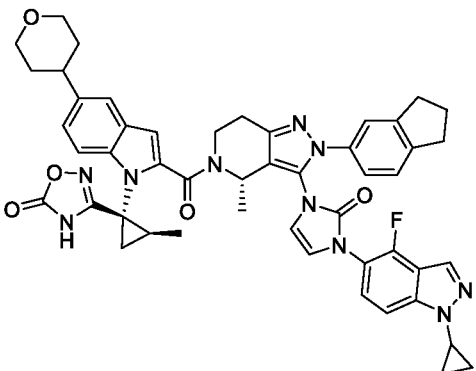
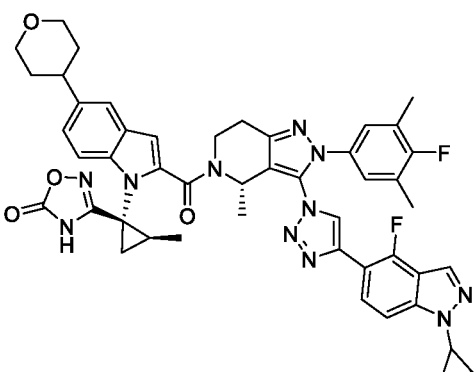
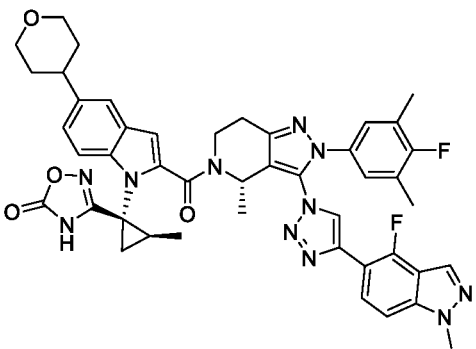
Description

41		893.37	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.42 – 8.37 (m, 3H), 7.91 – 7.81 (m, 1H), 7.65 – 7.54 (m, 2H), 7.45 – 7.36 (m, 2H), 7.12 – 7.09 (m, 1H), 6.51 – 6.46 (m, 2H), 5.33 – 5.23 (m, 1H), 4.61 – 4.49 (m, 1H), 4.15 – 3.85 (m, 2H), 3.67 – 3.47 (m, 4H), 3.09 – 2.91 (m, 3H), 2.42 – 2.29 (m, 4H), 2.18 – 2.11 (m, 2H), 1.92 – 1.82 (m, 2H), 1.42 – 1.25 (m, 9H), 1.13 – 1.07 (m, 5H).
42		867.35	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 8.41 – 8.36 (m, 3H), 7.90 – 7.80 (m, 1H), 7.67 – 7.55 (m, 2H), 7.46 – 7.37 (m, 2H), 7.11 – 7.07 (m, 1H), 6.52 – 6.43 (m, 2H), 5.34 – 5.25 (m, 1H), 4.63 – 4.51 (m, 1H), 4.17 – 3.87 (m, 2H), 3.69 – 3.49 (m, 4H), 3.12 – 2.96 (m, 3H), 2.44 – 2.33 (m, 9H), 2.22 – 2.13 (m, 2H), 1.91 – 1.83 (m, 2H), 1.45 – 1.25 (m, 9H), 1.14 – 1.08 (m, 5H).
43		867.35	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 8.42 – 8.38 (m, 3H), 7.88 – 7.77 (m, 2H), 7.69 – 7.59 (m, 2H), 7.49 – 7.39 (m, 2H), 6.73 – 6.54 (m, 1H), 6.44 – 6.35 (m, 1H), 5.33 – 5.24 (m, 1H), 4.65 – 4.53 (m, 1H), 4.19 – 3.88 (m, 2H), 3.71 – 3.59 (m, 4H), 3.16 – 2.99 (m, 3H), 2.48 – 2.38 (m, 9H), 2.26 – 2.16 (m, 2H), 1.97 – 1.87 (m, 2H), 1.43 – 1.23 (m, 9H), 1.12 – 1.08 (m, 5H).

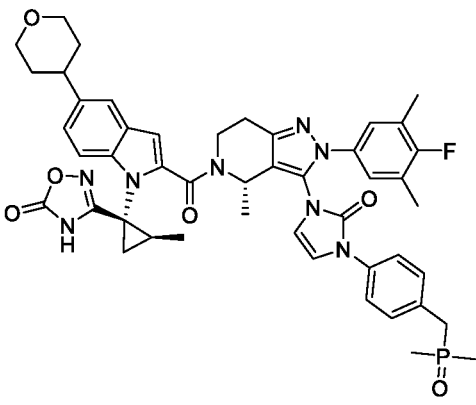
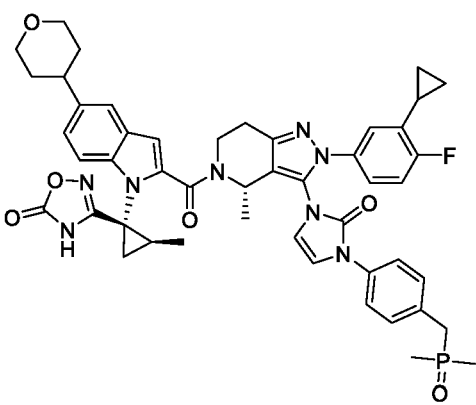
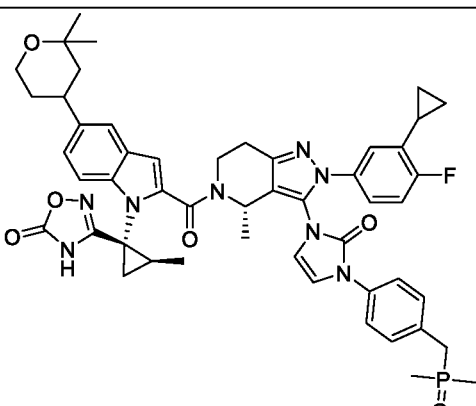
Description

44		879.35	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.18 (s, 1H), 8.44 – 8.38 (m, 3H), 7.89 – 7.79 (m, 2H), 7.65 – 7.62 (m, 2H), 7.55 – 7.45 (m, 2H), 6.75 – 6.55 (m, 1H), 6.46 – 6.36 (m, 1H), 5.34 – 5.25 (m, 1H), 4.66 – 4.56 (m, 1H), 4.29 – 3.98 (m, 2H), 3.75 – 3.69 (m, 4H), 3.14 – 2.94 (m, 3H), 2.45 – 2.35 (m, 7H), 2.28 – 2.18 (m, 2H), 1.95 – 1.85 (m, 2H), 1.41 – 1.23 (m, 10H), 1.13 – 1.08 (m, 6H).
45		893.37	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.20 (s, 1H), 8.43 – 8.33 (m, 2H), 7.95 – 7.87 (m, 1H), 7.69 – 7.59 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, <i>J</i> = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 4H), 3.16 – 2.96 (m, 3H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 7H), 1.12 – 1.08 (m, 6H).
46		895.38	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.19 (s, 1H), 8.44 – 8.34 (m, 2H), 7.94 – 7.86 (m, 1H), 7.67 – 7.57 (m, 2H), 7.47 – 7.38 (m, 3H), 7.23 (d, <i>J</i> = 2.0 Hz, 1H), 7.12 – 7.09 (m, 1H), 6.45 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 2H), 3.16 – 2.96 (m, 5H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 3H), 1.12 – 1.08 (m, 12H).

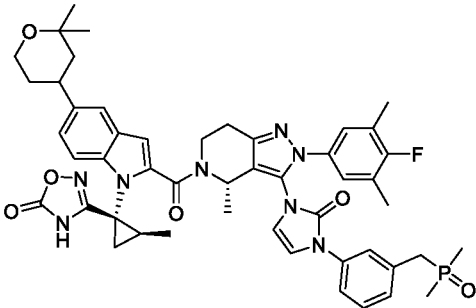
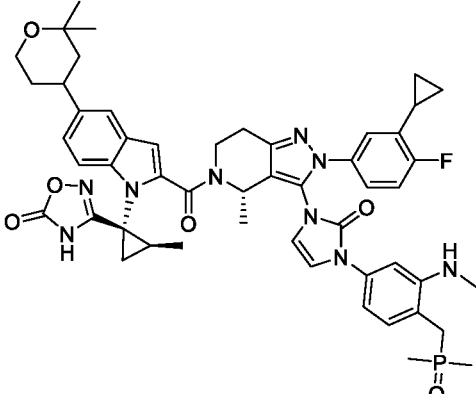
Description

47		875.37	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.21 (s, 1H), 8.47 – 8.37 (m, 2H), 7.97 – 7.87 (m, 1H), 7.69 – 7.59 (m, 2H), 7.49 – 7.39 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.14 – 7.12 (m, 1H), 6.48 – 6.44 (m, 1H), 5.36 – 5.26 (m, 1H), 4.71 – 4.62 (m, 1H), 4.36 – 3.95 (m, 2H), 3.79 – 3.68 (m, 4H), 3.12 – 2.96 (m, 3H), 2.45 – 2.38 (m, 7H), 2.25 – 2.16 (m, 5H), 1.95 – 1.87 (m, 2H), 1.45 – 1.24 (m, 7H), 1.11 – 1.08 (m, 6H).
48		866.37	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.20 (s, 1H), 8.48 – 8.38 (m, 2H), 7.98 – 7.88 (m, 1H), 7.68 – 7.58 (m, 2H), 7.47 – 7.37 (m, 3H), 7.20 (d, <i>J</i> = 2.0 Hz, 1H), 7.16 – 7.12 (m, 1H), 6.47 – 6.44 (m, 1H), 5.36 – 5.26 (m, 1H), 4.72 – 4.62 (m, 1H), 4.37 – 3.95 (m, 2H), 3.77 – 3.68 (m, 4H), 3.13 – 2.95 (m, 3H), 2.47 – 2.38 (m, 9H), 2.27 – 2.17 (m, 5H), 1.94 – 1.87 (m, 2H), 1.44 – 1.24 (m, 5H), 1.12 – 1.08 (m, 6H).
49		840.35	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.21 (s, 1H), 8.47 – 8.37 (m, 2H), 7.97 – 7.87 (m, 1H), 7.69 – 7.59 (m, 2H), 7.49 – 7.39 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.14 – 7.12 (m, 1H), 6.48 – 6.44 (m, 1H), 5.36 – 5.26 (m, 1H), 4.71 – 4.62 (m, 1H), 4.36 – 3.95 (m, 2H), 3.79 – 3.68 (m, 4H), 3.12 – 2.96 (m, 5H), 2.45 – 2.38 (m, 9H), 2.25 – 2.16 (m, 5H), 1.95 – 1.87 (m, 2H), 1.45 – 1.24 (m, 3H), 1.11 – 1.08 (m, 4H).

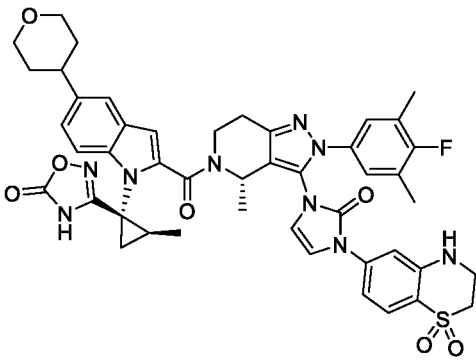
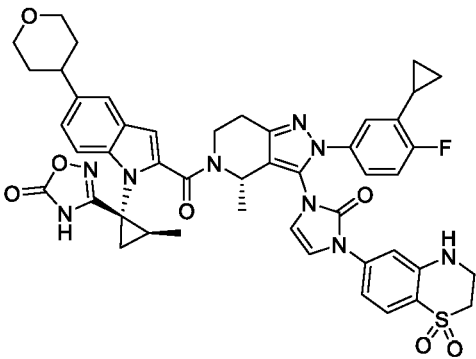
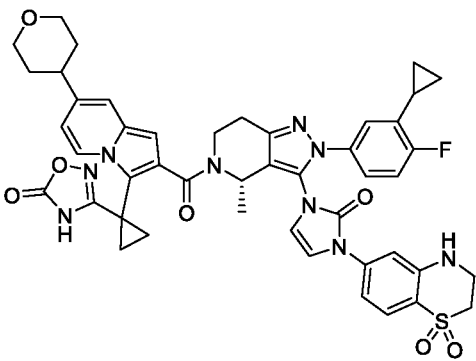
Description

50		873.36	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.20 (s, 1H), 8.48 – 8.38 (m, 2H), 7.98 – 7.88 (m, 1H), 7.68 – 7.58 (m, 2H), 7.47 – 7.37 (m, 3H), 7.20 (d, <i>J</i> = 2.0 Hz, 1H), 7.16 – 7.12 (m, 1H), 5.36 – 5.26 (m, 1H), 4.73 – 4.62 (m, 1H), 4.36 – 3.95 (m, 2H), 3.79 – 3.68 (m, 6H), 3.12 – 2.96 (m, 2H), 2.45 – 2.38 (m, 9H), 2.25 – 2.16 (m, 5H), 1.95 – 1.87 (m, 2H), 1.45 – 1.24 (m, 3H), 1.11 – 1.08 (m, 4H).
51		885.36	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 8.89 (s, 1H), 8.33 – 8.29 (m, 2H), 8.21 – 8.15 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 2H), 7.51 – 7.45 (m, 4H), 7.25 – 7.21 (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), 3.35(s, 2H), 3.86 – 3.61 (m, 2H), 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, 5H), 1.39 – 1.31 (m, 2H), , 1.01 – 0.98 (m, 3H).
52		913.39	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 8.89 (s, 1H), 8.33 – 8.29 (m, 2H), 8.21 – 8.15 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 2H), 7.51 – 7.45 (m, 4H), 7.25 – 7.21 (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), 3.35(s, 2H), 3.86 – 3.61 (m, 2H), 3.08 – 2.90 (m, 3H), 2.49 – 2.32 (m, 3H),

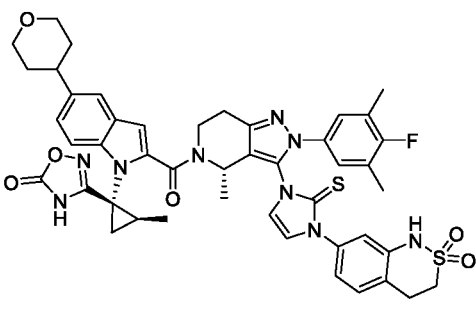
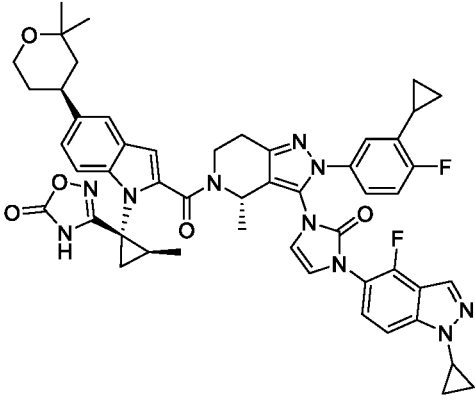
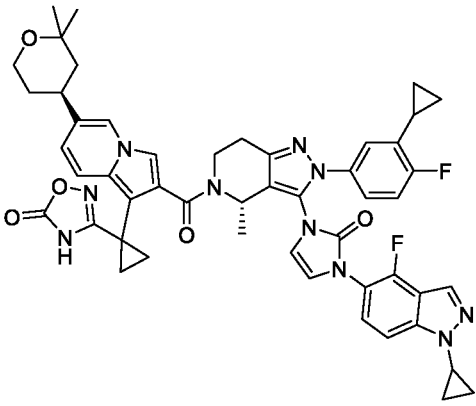
Description

			2.26 – 2.23 (m, 6H), 2.08 – 1.91 (m, 2H), 1.86 – 1.69 (m, 2H), 1.61 – 1.57 (m, 9H), 1.39 – 1.31 (m, 2H), 1.19-1.14 (m, 4H), 1.01 – 0.98 (m, 3H).
53		901.39	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 8.91 (s, 1H), 8.36 – 8.29 (m, 2H), 8.21 – 8.14 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 2H), 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), 3.35(s, 2H), 3.86 – 3.61 (m, 3H), 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, 7H), 1.39 – 1.31 (m, 5H), 1.19 (s, 6H), 1.01 – 0.98 (m, 3H).
54		942.42	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, 2H), 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), 3.35(s, 2H), 3.86 – 3.61 (m, 3H), 3.08 – 2.90 (m, 6H), 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, 9H), 1.39 – 1.31 (m, 2H), 1.19-1.13 (m, 3H), 1.01 – 0.98 (m, 3H).

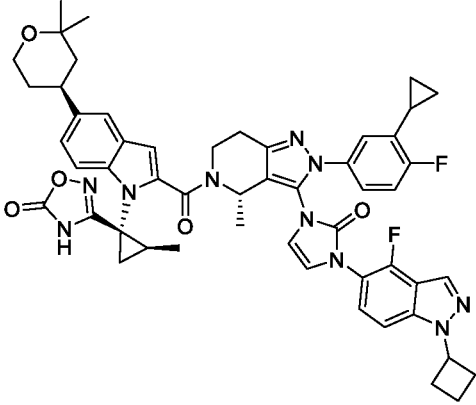
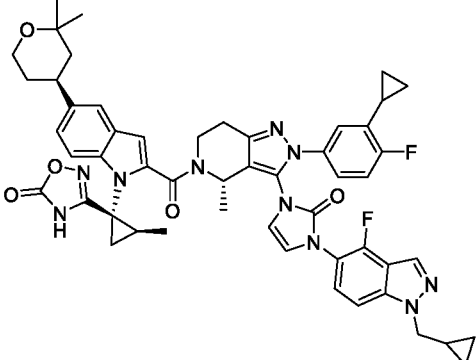
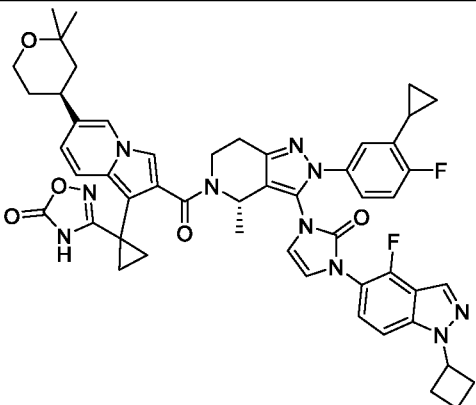
Description

55		888.32	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.15 (s, 1H), 8.42 – 8.38 (m, 3H), 7.90 – 7.82 (m, 1H), 7.65 – 7.56 (m, 1H), 7.44 – 7.41 (m, 2H), 7.13 – 7.09 (m, 1H), 6.54-6.53(m, 1H), 6.51 – 6.46 (m, 2H), 5.33 – 5.23 (m, 1H), 4.61 – 4.49 (m, 1H), 4.15 – 3.85 (m, 2H), 3.67 – 3.47 (m, 8H), 3.09 – 2.91 (m, 3H), 2.42 – 2.29 (m, 4H), 2.24 – 2.11 (m, 8H), 1.92 – 1.82 (m, 2H), 1.42 – 1.25 (m, 4H), 1.11 – 1.07 (m, 3H).
56		900.32	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.15 (s, 1H), 8.42 – 8.38 (m, 3H), 7.90 – 7.82 (m, 1H), 7.65 – 7.56 (m, 2H), 7.44 – 7.41 (m, 2H), 7.13 – 7.09 (m, 1H), 6.54-6.53(m, 1H), 6.51 – 6.46 (m, 2H), 5.33 – 5.23 (m, 1H), 4.61 – 4.49 (m, 1H), 4.15 – 3.85 (m, 2H), 3.67 – 3.47 (m, 8H), 3.09 – 2.91 (m, 3H), 2.42 – 2.29 (m, 4H), 2.18 – 2.11 (m, 2H), 1.92 – 1.82 (m, 2H), 1.42 – 1.25 (m, 4H), 1.13 – 1.07 (m, 6H).
57		886.31	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.13 (s, 1H), 8.42 – 8.38 (m, 3H), 7.91 – 7.82 (m, 1H), 7.65 – 7.56 (m, 2H), 7.45 – 7.39 (m, 2H), 7.12 – 7.09 (m, 1H), 6.54(s, 1H), 6.51 – 6.46 (m, 2H), 5.33 – 5.23 (m, 1H), 4.61 – 4.49 (m, 1H), 4.15 – 3.85 (m, 2H), 3.67 – 3.47 (m, 8H), 3.09 – 2.91 (m, 3H), 2.42 – 2.29 (m, 4H), 2.18 – 2.11 (m, 2H), 1.92 – 1.82 (m, 3H), 1.42 – 1.25 (m, 4H), 1.13 – 1.07 (m, 3H).

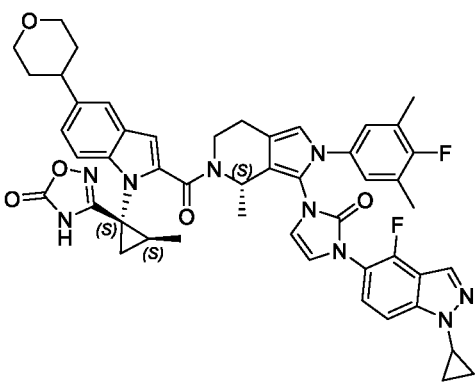
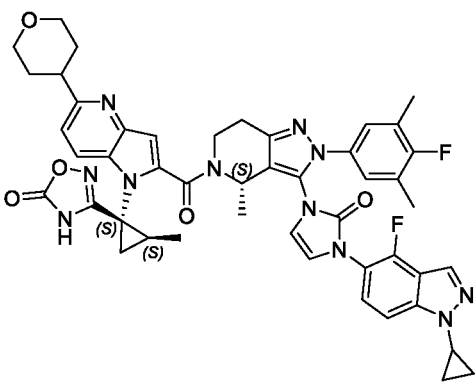
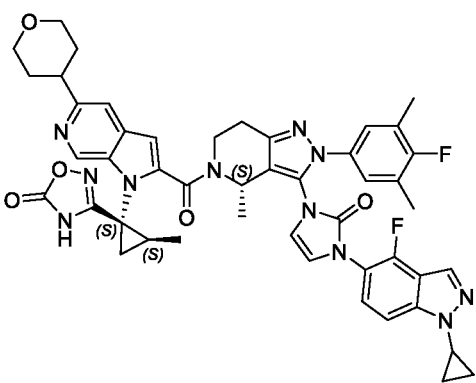
Description

58		904.30	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.17 (s, 1H), 8.40 – 8.29 (m, 2H), 7.97 – 7.87 (m, 1H), 7.65 – 7.55 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, <i>J</i> = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.29 – 5.19 (m, 1H), 4.55 – 4.52 (m, 1H), 4.13 – 3.80 (m, 2H), 3.79 – 3.61 (m, 2H), 3.58 – 3.49 (m, 4H), 3.16 – 2.89 (m, 5H), 2.43 – 2.35 (m, 3H), 2.28 (s, 6H), 2.16 – 2.13 (m, 2H), 1.85 – 1.79 (m, 2H), 1.63 (d, <i>J</i> = 8.0 Hz, 3H), 1.02 – 0.96 (m, 3H).
59		921.39	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 8.39 – 8.29 (m, 3H), 7.93 – 7.83 (m, 1H), 7.69 – 7.58 (m, 2H), 7.49 – 7.36 (m, 3H), 7.20 (s, 1H), 7.11 – 7.06 (m, 1H), 5.23 – 5.13 (m, 1H), 4.55 – 4.49 (m, 1H), 4.13 – 3.85 (m, 2H), 3.57 – 3.47 (m, 4H), 3.05 – 2.88 (m, 3H), 2.40 – 2.27 (m, 4H), 2.16 – 2.09 (m, 2H), 1.58 (d, <i>J</i> = 8.0 Hz, 3H), 1.40 – 1.22 (m, 8H), 1.11 – 1.05 (m, 9H).
60		907.38	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.18 (s, 1H), 8.44 – 8.38 (m, 3H), 7.89 – 7.79 (m, 2H), 7.65 – 7.62 (m, 2H), 7.55 – 7.45 (m, 2H), 6.75 – 6.55 (m, 1H), 6.46 – 6.36 (m, 1H), 5.34 – 5.25 (m, 1H), 4.66 – 4.56 (m, 1H), 4.29 – 3.98 (m, 2H), 3.75 – 3.69 (m, 4H), 3.14 – 2.94 (m, 3H), 2.45 – 2.35 (m, 7H), 2.28 – 2.18 (m, 2H), 1.41 – 1.23 (m, 10H), 1.13 – 1.08 (m, 12H).

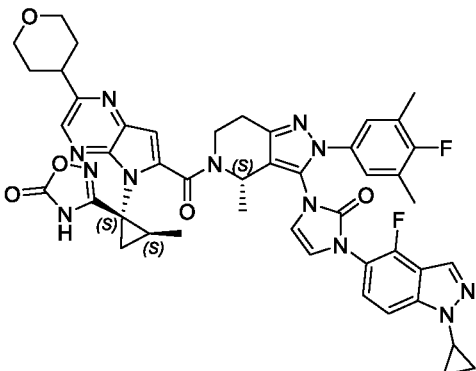
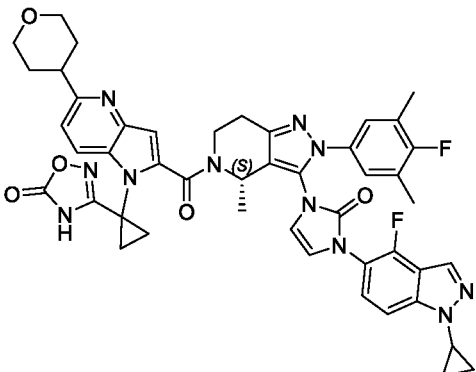
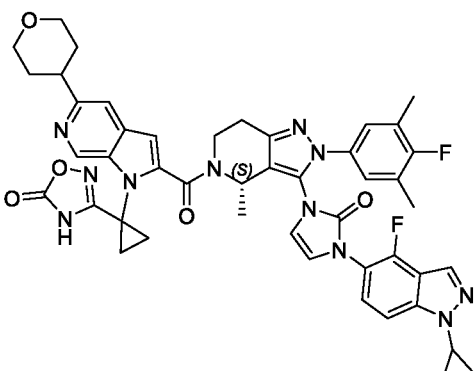
Description

61		935.41	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.14(s, 1H), 8.39 – 8.29 (m, 3H), 7.93 – 7.83 (m, 1H), 7.69 – 7.58 (m, 2H), 7.49 – 7.36 (m, 3H), 7.20 (s, 1H), 7.11 – 7.06 (m, 1H), 5.23 – 5.13 (m, 1H), 4.55 – 4.49 (m, 1H), 4.13 – 3.85 (m, 2H), 3.57 – 3.47 (m, 4H), 3.05 – 2.88 (m, 3H), 2.40 – 2.27 (m, 4H), 2.16 – 2.09 (m, 2H), 1.58 (d, <i>J</i> = 8.0 Hz, 3H), 1.40 – 1.22 (m, 9H), 1.11 – 1.05 (m, 10H).
62		935.41	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15(s, 1H), 8.39 – 8.29 (m, 3H), 7.93 – 7.83 (m, 1H), 7.69 – 7.58 (m, 2H), 7.49 – 7.36 (m, 3H), 7.20 (s, 1H), 7.11 – 7.06 (m, 1H), 5.23 – 5.13 (m, 1H), 4.55 – 4.49 (m, 1H), 4.13 – 3.85 (m, 2H), 3.57 – 3.47 (m, 4H), 3.05 – 2.88 (m, 3H), 2.40 – 2.27 (m, 4H), 2.16 – 2.09 (m, 2H), 1.58 (d, <i>J</i> = 8.0 Hz, 3H), 1.40 – 1.22 (m, 8H), 1.11 – 1.05 (m, 11H).
63		921.39	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.18 (s, 1H), 8.44 – 8.38 (m, 3H), 7.89 – 7.79 (m, 2H), 7.65 – 7.62 (m, 2H), 7.55 – 7.45 (m, 2H), 6.75 – 6.55 (m, 1H), 6.46 – 6.36 (m, 1H), 5.34 – 5.25 (m, 1H), 4.66 – 4.56 (m, 1H), 4.29 – 3.98 (m, 2H), 3.75 – 3.69 (m, 4H), 3.14 – 2.94 (m, 3H), 2.45 – 2.35 (m, 7H), 2.28 – 2.18 (m, 2H), 1.41 – 1.23 (m, 12H), 1.13 – 1.08 (m, 12H).

Description

64		880.37	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.11 (s, 1H), 8.40 – 8.29 (m, 3H), 7.96 – 7.86 (m, 1H), 7.67 – 7.58 (m, 3H), 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 (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, <i>J</i> = 8.0 Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.95 (m, 3H).
65		882.36	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.12 (s, 1H), 8.40 – 8.28 (m, 3H), 7.96 – 7.86 (m, 1H), 7.60 – 7.58 (m, 1H), 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 (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, <i>J</i> = 8.0 Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.95 (m, 3H).
66		882.36	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.12 (s, 1H), 8.40 – 8.28 (m, 3H), 7.96 – 7.86 (m, 1H), 7.62 – 7.58 (m, 2H), 7.47 – 7.33 (m, 2H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.09 – 7.03 (m, 1H), 5.23 – 5.13 (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, <i>J</i> = 8.0 Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.95 (m, 3H).

Description

67		883.35	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.10 (s, 1H), 8.40 – 8.28 (m, 3H), 7.96 – 7.86 (m, 1H), 7.60 – 7.58 (m, 1H), 7.47 – 7.34 (m, 2H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.09 – 7.03 (m, 1H), 5.23 – 5.13 (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, <i>J</i> = 8.0 Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.95 (m, 3H).
68		868.34	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 8.40 – 8.28 (m, 3H), 7.96 – 7.86 (m, 1H), 7.60 – 7.58 (m, 1H), 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 (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), 1.39 – 1.20 (m, 4H), 1.01 – 0.95 (m, 4H).
69		868.34	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 8.40 – 8.28 (m, 3H), 7.96 – 7.86 (m, 1H), 7.63 – 7.58 (m, 2H), 7.47 – 7.33 (m, 2H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.09 – 7.03 (m, 1H), 5.23 – 5.13 (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), 1.39 – 1.20 (m, 4H), 1.01 – 0.95 (m, 4H).

Description

Example 2. In vitro activity evaluation

GLP-1R cAMP Assay

1. Cell line and reagent preparation

- 1) Cell line: Flp-In-293-GLP1R
- 2) Culture medium: DMEM + 10% FBS + 1 X Penicillin-Streptomycin + 200 µg/mL HB
- 3) Assay buffer: 1 X HBSS + 20mM HEPES + 0.1%BSA+ 500µM IBMX

2. Agonist testing

a) Flpin-293-GLP1R cells were seeded in a complete medium at 2,000 cells per well in a 384-well assay plate (6007680-50, PE).

b) 4X complex working solution was prepared in an assay buffer.

c) 5 µL of 4X compound working solution was added to the cell plate and incubated at 37°C for 30 minutes.

d) Eu-cAMP tracer was diluted (1/50) with a lysis buffer and added to the assay plate at 10 µl/well.

e) Ulight-anti-cAMP was diluted (1/150) with a lysis buffer and added to the assay plate at 10 µl/well.

f) The plate was incubated at constant temperature for 1 hour.

g) The plate was read on an Envision 2105 plate reader at 665 nM and 615 nM wavelengths.

3. Data analysis

3.1 The calculation formula for % 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 Calculation of EC50 and drawing of the effect-dose curve of the compounds:

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

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

Table 2 shows the biological activity of the compounds in the GLP-1R agonist cAMP stimulation assay, as follows.

Table 2: The biological activity of some compounds in the GLP-1R agonist cAMP stimulation assay

Compound ID	GLP-1R cAMP:EC ₅₀ /nM
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Description

1	0.094
9	1.995
11	>10
13	0.228
16	>10
18	0.265
19	0.012
20	0.018
21	0.044
25	>10
29	0.063
33	0.020
35	0.025
36	0.050
37	0.060
51	0.028

Example 3. Pharmacokinetic study

PK study in SD rats

PK study of the compounds of the present invention after single subcutaneous administration.

Protocol: animal: SD rats; vehicle formula: 80% MCT + 20% benzyl alcohol; dose: 30 mg/kg; dosing concentration: 30 mg/mL; dosing volume: 1 mL/kg; dosing site: the dorsal skin used for the subcutaneous injection uniformly.

A 1 mL syringe (0.45 mm*16 mm needle) with a precision of 0.01 mL was used to administer the drug, and the dosing volume was calculated based on the body weight. At each time point, approximately 100 μ L of blood sample was collected and placed in an anticoagulant tube containing EDTA-K2 anticoagulant, and the plasma was obtained by centrifugation within 30 minutes. Whole blood samples were placed on wet ice before centrifugation. All collected plasma samples were stored on dry ice or in a freezer until analysis and detection. WinNonlin 8.0 was used to calculate the PK parameters. The concentrations and AUC_{0-t} at each blood sampling time point are shown in Table 3.

Table 3. Blood drug concentrations of different compounds after subcutaneous injection

Compound	1	13	18	19	21	20
T/hour	Blood drug concentration (ng/ml)					
0	0	0	0	0	0	0
1	0	2.56	8.58	39	7.34	9.56
3	10.9	9.98	33.8	381	35.7	34
8	164	48.2	107	1220	137	152

Description

24	561	97.2	218	2603	275	298
48	347	87.6	131	993	199	237
72	165	48.5	133	763	152	173
96	176	36.4	128	621	125	143
120	119	28.9	126	561	122	132
144	103	41.6	134	488	116	108
216	85.7	37.5	127	402	119	181
312	57.6	32.3	90.4	150	70.5	170
480	28.7	/	16.5	84.9	55.8	46.9
696	24.7	/	9.55	41.1	41.2	15.1
1056	25.6					
1224	20.5					
1392	10.4					
AUC _{0-t} (ng.hr/ml)	75191	14020	51234	234473	61479	77688



April 17, 2025

Certification

Welocalize Translations

TRANSLATOR'S DECLARATION:

I, Lili Wang, hereby declare:

That I possess advanced knowledge of the Chinese and English languages. The attached Chinese into English translation has been translated by me and to the best of my knowledge and belief, it is a true and accurate translation of:
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