UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
63/603,854	**11/29/2023 03:13:56 PM Z ET**	**HRT-021US0**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Provisional Application under 35 USC 111(b)	PATENT #	-
CONFIRMATION #	4616	FILED BY	Daniel Nevrivy
PATENT CENTER #	63419282	FILING DATE	-
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 5

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
ADS_.pdf		8	Application Data Sheet	2174 KB
Application_filed_11_29_2023.pdf		92	-	800 KB
Application_filed_11_29_2023-SPEC.pdf	(1-82)	82	Specification	686 KB
Application_filed_11_29_2023-CLM.pdf	(83-91)	9	Claims	150 KB
Application_filed_11_29_2023-ABST.pdf	(92-92)	1	Abstract	24 KB

COVER_SHEET_.pdf	3	Provisional Cover Sheet (SB16)	2561 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
ADS_.pdf	2DD3910F3E1AEB0970A37CDCD78D212531F02386D36D143BD BA4B6865D8883ED0ADB551FCFC5FC0E944700D764EA73D38 06DDAAAC54AE76C57F0AD5C56D37F3F
Application_filed_11_29_2023.pdf	CE7A5A34E4354838A29E41E8E95DAA3806B37E587BFA7DE4B C8D9CF7A4094BCBCD29C28ED2D9069C34DBECBFDC325D90 4C6742FDB9DE02400EB7033D722C0A62
Application_filed_11_29_2023-SPEC.pdf	022065930 5B1DA527AEB4F078FA80EA8173969F787EE9FB5E3 AE224C49301B00CFB0BAF4A1E8598A2172439A2F20DAA2BFE 5890A6F9AEBCE73C3148108C6518A
Application_filed_11_29_2023-CLM.pdf	469FD4FEDADBBBE80BAC8C465FB46B1817E341178186B0142 9F3912AE6B506A45360EA03258E7F39D8282FF82198711C0224 50A430E851AE082178CBF7C21730
Application_filed_11_29_2023-ABST.pdf	22FB65196CC07130ECBF10E6DEA7BFF625A227A3A13080062 130D20DE25861CE1D1B26A4C924817393913DA7667C70F13B D40690B756681D9FBEFF9452627FFE
COVER_SHEET_.pdf	F6AD2EFB04F5A095AC6E61FA5C4C2136D74F0ACED5E0A331 8967CF91806FCC022487A0FAF277481473BE8CD2CF58E4FED 3EBC2E57E7FEBE2EA0C3EB6080525C2

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-021US0
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bin		Liang	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Hangzhou	Country of Residence	CN

Mailing Address of Inventor:

Address 1	3-1201, No. 371 Mingxing Road		
Address 2	HIPARK, Xiaoshan District		
City	Hangzhou	**State/Province**	
Postal Code	311202	**Country**	CN

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jinzi	Jason	Wu	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Hangzhou	Country of Residence	CN

Mailing Address of Inventor:

Address 1	3-1201, No. 371 Mingxing Road		
Address 2	HIPARK, Xiaoshan District		
City	Hangzhou	**State/Province**	
Postal Code	311202	**Country**	CN

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Bin		Liang	Hangzhou		CN

Inventor 2 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Jinzi	Jason	Wu	Hangzhou		CN

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof
Attorney Docket Number (if applicable)	HRT-021US0

Correspondence Address

Direct all correspondence to (select one):

◉ The address corresponding to Customer Number	○ Firm or Individual Name
Customer Number	83682

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ◉ No.
- ○ Yes, the invention was made by an agency of the United States Government. The U.S. Government agency name is:
- ○ Yes, the invention was under a contract with an agency of the United States Government. The name of the U.S. Government agency and Government contract number are:

PTO/SB/16 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

Entity Status
Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29

- (●) Applicant asserts small entity status under 37 CFR 1.27
- ( ) Applicant certifies micro entity status under 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
- ( ) No

Warning

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Daniel Nevrivy/			Date (YYYY-MM-DD)	2023-11-29
First Name	Daniel	Last Name	Nevrivy	Registration Number (If appropriate)	59,118

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or paten. Accordingly, pursuant to the requirements of the Act, please be advised that : (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, t o a n other federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

GLP-1R Agonist and Therapeutic Method Thereof

FIELD

[0001] The present application generally relates to compounds that bind to and act as agonists or modulators of the glucagon-like peptide-1 receptor (GLP-1R), as well as the use of such compounds for the treatment and/or prevention of GLP-1R-mediated diseases and conditions.

BACKGROUND

[0002] Glucagon-like peptide-1 (GLP-1) is a peptide hormone that is secreted from the enteroendocrine cells in the gut in response to a meal. GLP-1 is believed to play a role in regulation of post-prandial glycemia, via directly augmenting meal-induced insulin secretion from the pancreatic beta-cells, as well as in promoting satiety by delaying the transit of food through the gut. GLP-1 mediates intracellular signaling via the GLP-1 receptor (GLP-1R) which belongs to a family of G-protein coupled receptors that are present on the cell membrane and can result in accumulation of the secondary messenger cyclic adenosine monophosphate (cAMP) upon activation. Non-alcoholic steatohepatitis (NASH) can be associated with features of metabolic syndrome, including obesity, type 2 diabetes, insulin resistance and cardiovascular disease.

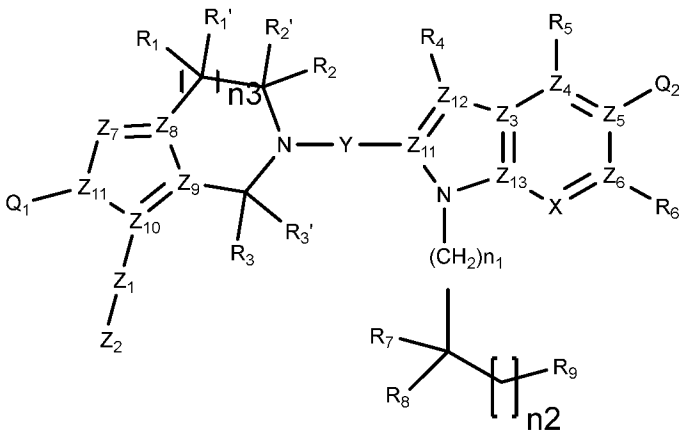
[0003] GLP-1R agonists are currently being investigated in connection with diabetes, obesity, and NASH. GLP-1R agonists include peptides, such as exenatide, liraglutide, and dulaglutide, that have been approved for the management of type 2 diabetes. Such peptides are predominantly administered by subcutaneous injection. Oral GLP-1 agonists are also under investigation for 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 longer half-lives than endogenous GLP-1.

[0004] There remains a need for compounds, such as agonists of GLP-1R, with desirable therapeutic properties, metabolic properties, and/or easy administration in the treatment of GLP-1R-mediated diseases and conditions.

SUMMARY

Conjupro EX1025
Page 8 of 106

[0005] One aspect of the present application relates to a compound of Formula I and stereoisomers, pharmaceutically acceptable salts or deuterated compounds thereof;



Formula I

wherein X is selected from the group consisting of N and -CR^a; wherein R^a is selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

wherein Y is -C(=O)-;

wherein each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

wherein Q_1 is selected from the group consisting of C_{6-10} aryl and C_{5-10} heteroaryl, wherein C_{6-10} aryl or C_{5-10} heteroaryl is optionally substituted by one to five substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy;

wherein Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl are optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy and -$NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl;

wherein each of R_1, R_2, R_3, R_1', R_2' and R_3' is independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} ahaloalkoxy, cycloalkyl and

Conjupro EX1025
Page 9 of 106

heterocycloalkyl; wherein C_{1-6} alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen , C_{1-6} alkoxy and hydroxyl;

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

wherein R_1 and R_1' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl, and R_2 and R_2' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl ; and R_3 and R_3' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl;

each of R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

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

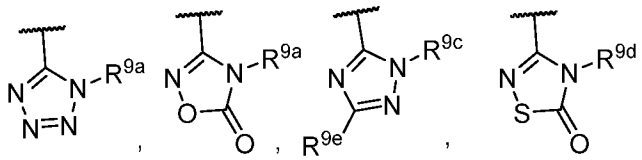
or R_7 and R_8 together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring, wherein the C_{3-15} carbocyclic ring is optionally substituted by one to three C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclic , and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl groups and (C_{1-6} alkyl) carbonyl; and any two C_{1-6} alkyl groups optionally form C_{3-15} carbon ring together with the carbon atom to which they are attached;

n_1 is 0, 1, 2 or 3;

n2 is 0, 1, 2, 3, 4 or 5;

n3 is 0, 1 or 2;

R_9 is selected from the group consisting of:



, $-CO_2R^{9f}$ and $-C(=O)-NR^{9g}R^{9h}$; and each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{1-6} alkoxy;

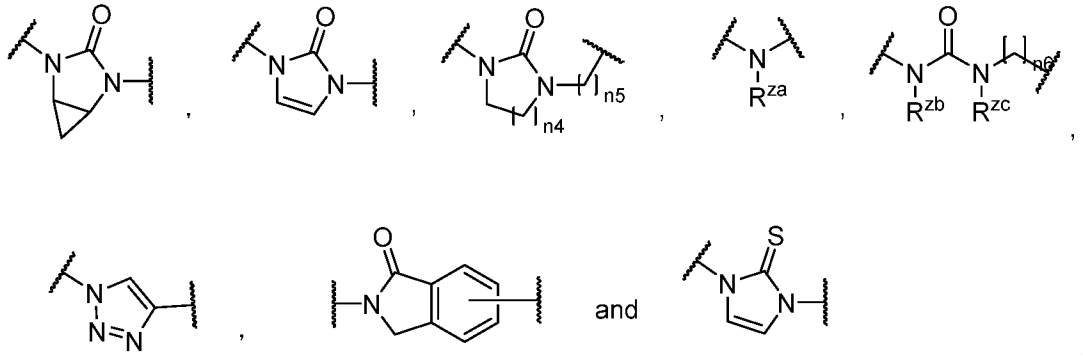
R^{9e} is selected from the group consisting of hydrogen and C_{1-6} alkyl optionally substituted by one or more halogen atoms;

R^{9f} is selected from the group consisting of hydrogen or C_{1-6} alkyl;

R^{9h} is selected from the group consisting of hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl) carbonyl, cyano and $-S(=O)_{n3}-R^{9i}$;

R^{9i} is C_{1-6} alkyl;

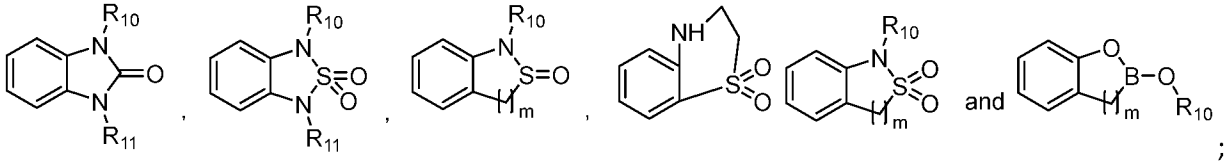
Z_1 is selected from the group consisting of:



wherein R^{za} is selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, and each of R^{zb} and R^{zc} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

n4 is 1, 2 or 3; each of n5 and n6 is independently integers from 0 to 10;

Z_2 is selected from the group consisting of C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12-membered heterocyclic, C_{6-10} aryl and 5 to 10-membered heteroaryl,



;

wherein Z_2 is independently optionally substituted with one to five G's; and m is 1, 2, 3;

wherein each of R_{11} and R_{10} is independently selected from the group consisting of H, C_{1-6} alkyl and (C_{1-6} alkyl) aryl, C_{1-6} haloalkyl, $-C_3-C_{15}$ cycloalkyl and $-C_1-C_6$ alkyl-C_3-C_{15} cycloalkyl;

wherein G' is selected from the group consisting of:

a. Oxygen;

b. Halogen;

c. Cyano;

d. $-NR^{zd}R^{ze}$; wherein R^{zd} and R^{ze} are independently selected from the group consisting of

hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and C_{1-6} alkoxy;

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

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

g. C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, -$NR^{zi}R^{zj}$, C_{1-6} alkoxy, C_{1-6} alkoxy and 3- to 12-membered heterocyclic groups; wherein each of R^{zi} and R^{zj} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein the 3- to 12-membered heterocyclic groups are optionally substituted with one or more substituents selected from the group consisting of cyano, C_{1-6} alkyl and 3 to 12-membered heterocyclic;

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

i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic 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 C_{6-10} aryl is optionally substituted by one or more (C_{1-6} alkyl) carbonyl;

k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, -$NR^{zk}R^{zl}$, and 3- to 12-membered heterocyclic; wherein R^{zk} and R^{zl} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and (C_{1-6} alkyl)carbonyl and wherein the 3- to 12-membered heterocyclic is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, and C_{1-6} alkoxy;

l. -C_3-C_{15} cycloalkyl or -C_1-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein -C_3-C_{15} cycloalkyl or -C_1-

Conjupro EX1025
Page 12 of 106

C_6 alkyl-C_3-C_{15} cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl is optionally substituted by halogen;

m. $-P(=O)R^{zm}R^{zn}$, $NR^{zm}S(=O)R^{zn}$ and $NR^{zm}S(=O)_2R^{zn}$, wherein R^{zm} and R^{zn} are independently selected from the group consisting of H, C_{1-6} alkyl and C_{6-10} aryl, wherein C_{1-6} alkyl is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo; wherein C_{3-6} cycloalkyl is optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo;

wherein C_{6-10} aryl is optionally substituted with 1-3 independently selected from C_{1-3} alkyl;

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

[0006] Another aspect of the present application relates to a composition comprising a compound of formula (I), stereoisomers, pharmaceutically acceptable salts or deuterated compounds thereof.

[0007] Another aspect of the present application relates to methods for treating GLP-1R mediated diseases or conditions with the compounds of the present application.

DETAILED DESCRIPTION

I. Definitions

[0008] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. A dash at the front or end of a chemical group is a matter of convenience to indicate the point of attachment to a parent moiety; chemical groups may be depicted with or without one or more dashes without losing

their 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" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0009] "Alkyl" is a monovalent or divalent linear or branched saturated hydrocarbon radical. 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, $-CH(CH_3)_2$), 1-butyl (*n*-Bu, *n*-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (*s*-Bu, *s*-butyl, $-CH(CH_3)CH_2CH_3$), 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 ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 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 ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2, 3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3, 3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, and octyl ($-(CH_2)_7CH_3$). Alkyl groups can be unsubstituted or substituted.

[0010] "Alkoxy" refers to the group -O-alkyl, where alkyl is as defined above. For example, C_{1-4} alkoxy refers to an -O-alkyl group having 1 to 4 carbons. Alkoxy groups can be unsubstituted or substituted.

[0011] "Alkoxyalkyl" is an alkoxy group attached to an alkyl as defined above, such that the alkyl is divalent. For example, C_{2-6} alkoxyalkyl includes $-CH_2$-OMe, $-CH_2$-O-*i*Pr, $-CH_2$-CH_2-OMe, $-CH_2$-CH_2-O-CH_2-CH_3, and $-CH_2$-CH_2-O-*t*Bu. Alkoxyalkyl groups can be unsubstituted or substituted.

[0012] "Alkenyl" is a monovalent or divalent linear or branched hydrocarbon radical with at least one carbon-carbon double bond. For example, an alkenyl group can have 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl) or 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl) or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include, but are not limited to, ethenyl (-

$CH=CH_2$), allyl ($-CH_2CH=CH_2$), and $-CH_2-CH=CH-CH_3$. Alkenyl groups can be unsubstituted or substituted.

[0013] "Alkynyl" is a monovalent or divalent linear or branched hydrocarbon radical with at least one carbon-carbon triple bond. For example, an alkynyl group can have 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl) or 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl) or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). Examples of alkynyl groups include, but are not limited to, acetylenyl ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), and -CH2-$C\equiv C-CH_3$. Alkynyl groups can be unsubstituted or substituted.

[0014] "Halogen" refers to fluoro (-F), chloro (-Cl), bromo (-Br) and iodo (-I).

[0015] "Haloalkyl" is an alkyl as defined herein, wherein one or more hydrogen atoms of the alkyl are independently replaced by a halogen, which may be the same or different, such that the alkyl is divalent. The alkyl group and the halogen can be any of those described above. In some embodiments, the haloalkyl defines the number of carbon atoms in the alkyl portion, e.g., C_{1-4} haloalkyl includes CF_3, CH_2F, CHF_2, CH_2CF_3, $CH_2CH_2CF_3$, $CCl_2CH_2CH_2CH_3$, and $C(CH_3)_2(CF_2H)$. Haloalkyl groups can be unsubstituted or substituted.

[0016] "Haloalkoxy" is an alkoxy as defined herein, wherein one or more hydrogen atoms of the alkyl in the alkyoxy are independently replaced by a halogen, which may be the same or different, such that the alkyl is divalent. The alkoxy group and the halogen can be any of those described above. In some embodiments, the haloalkoxy defines the number of carbon atoms in the alkyl portion, e.g., C_{1-4} haloalkoxy includes OCF_3, OCH_2F, OCH_2CF_3, $OCH_2CH_2CF_3$, $OCCl_2CH_2CH_2CH_3$, and $OC(CH_3)_2(CF_2H)$. Haloalkoxy groups can be unsubstituted or substituted.

[0017] "Cycloalkyl" is a monovalent or divalent single all carbon ring or a multiple condensed all carbon ring system wherein 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 single ring cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, and cyclooctyl. Cycloalkyl also includes multiple condensed ring systems (e.g., ring systems comprising 2 rings) having about 7 to 12 carbon atoms. The rings of the multiple condensed ring system can be connected to each other via fused, spiro, or bridged bonds when allowed by

valency requirements. Exemplary multiple ring cycloalkyl groups include octahydropentalene, bicyclo[2. 2. 1]heptane, bicyclo[2. 2. 2]octane, bicyclo[2. 2. 2]oct-2-ene, and spiro[2. 5]octane. Cycloalkyl groups can be unsubstituted or substituted.

[0018] Alkylcycloalkyl" refers to an alkyl as defined herein, wherein one or more hydrogen atoms of the alkyl are independently replaced by a cycloalkyl group, which may be the same or different. The alkyl group and the cycloalkyl group can be any of those described above. In some embodiments, the number of carbon atoms in the alkyl and cycloalkyl portion can be designated separately, e.g., C_{1-6} alkyl-C_{3-12} cycloalkyl. Alkylcycloalkyl groups can be unsubstituted or substituted.

[0019] "Aryl" as used herein refers to a monovalent or divalent single all carbon aromatic ring or a multiple condensed all carbon ring system wherein 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. Aryl includes a phenyl radical. Aryl also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) having about 9 to 20 carbon atoms in which multiple rings are aromatic. The rings of the multiple condensed ring system can be connected to each other via fused bonds when allowed by valency requirements. It is also understood that when reference is made to a certain atom-range membered aryl (e.g., 6-10 membered aryl), the atom range is for the total ring atoms of the aryl. For example, a 6-membered aryl would include phenyl and a 10-membered aryl would include naphthyl. Non-limiting examples of aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, and the like. Aryl groups can be unsubstituted or substituted.

[0020] "Alkylaryl" refers to an alkyl as defined herein, wherein one or more hydrogen atoms of the alkyl are independently replaced by an aryl group, which may be the same or different. The alkyl group and the aryl group can be any of those described above, such that the 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. An alkylaryl group defined by the number of carbon atoms refers to the total number of carbon atoms present in the constitutive alkyl and aryl groups combined. For example, C_7 alkylaryl refers to benzyl, while C_{11} alkylaryl includes 1-methylnaphthyl and n-pentylphenyl. In some embodiments the number of carbon atoms in the alkyl and aryl portion can be designated separately, e.g., C_{1-6} alkyl-C_{6-10} 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. Alkylaryl groups can be unsubstituted or substituted.

[0021] "Heterocyclyl" or "heterocycle" or "heterocycloalkyl" as used herein refers to a single saturated or partially unsaturated non-aromatic ring or a non-aromatic multiple ring system that has at least one heteroatom in the ring (i.e., at least one annular (i.e., ring-shaped) heteroatom selected from oxygen, nitrogen, and sulfur). Unless otherwise specified, a heterocyclyl group has from 3 to about 20 annular atoms, for example from 3 to 12 annular atoms, for example from 4 to 12 annular atoms, 4 to 10 annular atoms, or 3 to 8 annular atoms, or 3 to 6 annular atoms, or 3 to 5 annular atoms, or 4 to 6 annular atoms, or 4 to 5 annular atoms. Thus, the term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6 or 7- membered rings) having from about 1 to 6 annular carbon atoms and from about 1 to 3 annular heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The rings of the multiple condensed ring (e.g. bicyclic heterocyclyl) system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. Heterocycles include, but are not limited to, azetidine, aziridine, imidazolidine, morpholine, oxirane (epoxide), oxetane, thietane, piperazine, piperidine, pyrazolidine, piperidine, pyrrolidine, pyrrolidinone, 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]hexanyl, 2-azabicyclo[2. 1. 1]hexanyl, 2-azabicyclo[2. 2. 1]heptan-2-yl, 4-azaspiro[2. 4]heptanyl, 5-azaspiro[2. 4]heptanyl, and the like. Heterocyclyl groups can be unsubstituted or substituted.

[0022] "Alkylheterocyclyl" refers to an alkyl as defined herein, wherein one or more hydrogen atoms of the alkyl are independently replaced by a heterocyclyl group, which may be the same or different. The alkyl group and the heterocyclyl group can be any of those described above, such that the alkyl is divalent. In some embodiments, the number of atoms in the alkyl and heterocyclyl portion can be designated separately, e.g., $C_{1\text{-}6}$ alkyl-3 to 12 membered heterocyclyl having one to three heteroatoms each independently N, O, or S. Alkylheterocyclyl groups can be unsubstituted or substituted.

[0023] "5-10 membered heteroaryl" refers to a single aromatic ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of

Conjupro EX1025
Page 17 of 106

oxygen, nitrogen and sulfur; "5-10 membered heteroaryl" also includes multiple condensed ring systems that have at least one such aromatic ring, which multiple condensed ring systems are further described below. Thus, "5-10 membered heteroaryl" includes single aromatic rings of from about 1 to 6 carbon atoms and about 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. The sulfur and nitrogen atoms may also be present in an oxidized form provided the ring is aromatic. Exemplary 5-10 membered heteroaryl ring systems include but are not limited to pyridyl, pyrimidinyl, oxazolyl or furyl. "5-10 membered heteroaryl" also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) wherein a 5-10 membered heteroaryl group, as defined above, is condensed with one or more rings selected from 5-10 membered heteroaryls (to form for example 1, 8-naphthyridinyl) and aryls (to form, for example, benzimidazolyl or indazolyl) to form the multiple condensed ring system. Thus, a 5-10 membered heteroaryl (a single aromatic ring or multiple condensed ring system) can have about 1-20 carbon atoms and about 1-6 heteroatoms within the 5-10 membered heteroaryl ring. For example, tetrazolyl has 1 carbon atom and 4 nitrogen heteroatoms within the ring. The rings of the multiple condensed ring system can be connected to each other via fused bonds when allowed by valency requirements. It is to be understood that the individual rings of the multiple condensed ring system may be connected in any order relative to one another. It is to be understood that the point of attachment for a 5-10 membered heteroaryl or 5-10 membered heteroaryl multiple condensed ring system can be at any suitable atom of the 5-10 membered heteroaryl or 5-10 membered heteroaryl multiple condensed ring system including a carbon atom and a heteroatom (e.g., a nitrogen). It also to be understood that when a reference is made to a certain atom-range membered (e.g., a 5-10 membered heteroaryl), the atom range is for the total ring atoms of the 5-10 membered heteroaryl and includes carbon atoms and heteroatoms. It is also to be understood that the rings of the multiple condensed ring system may include an aryl ring fused to a heterocyclic ring with saturated or partially unsaturated bonds (e.g., 3, 4, 5, 6 or 7-membered rings) having from about 1 to 6 annular carbon atoms and from about 1 to 3 annular heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. For example, a 5-10 membered heteroaryl includes thiazolyl and a 5-10 membered heteroaryl includes quinolinyl. Exemplary 5-10 membered heteroaryls include but are not limited to pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl,

isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxalyl, quinazolyl, benzofuranyl, benzimidazolyl, thianaphthenyl, pyrrolo[2, 3-b]pyridinyl, quinazolinyl-4(3H)-one, triazolyl, and tetrazolyl. 5-10 membered heteroaryl groups can be unsubstituted or substituted.

[0024] "Alkylheteroaryl" refers to an alkyl as defined herein, wherein one or more hydrogen atoms of the alkyl are independently replaced by a heteroaryl group, which may be the same or different, such that the alkyl is divalent. The alkyl group and the heteroaryl group can be any of those described above. In some embodiments, the number of atoms in the alkyl and heteroaryl portion are designated separately, e.g., C_{1-6} alkyl-5 to 10 membered heteroaryl having one to four heteroatoms each independently N, O, or S. Alkylheteroaryl groups can be unsubstituted or substituted.

[0025] "Oxo" as used herein refers to =O.

[0026] "Substituted" as used herein refers to wherein one or more hydrogen atoms of the group are independently replaced by one or more substituents (e.g., 1, 2, 3, or 4 or more) as indicated.

[0027] A "compound of the present application" includes compounds disclosed herein, for example a compound of the present application includes compounds of Formula I, including the compounds of the Examples. In some embodiments, a "compound of the present application" includes compounds of Formula I.

[0028] "Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0029] "Therapeutically effective amount" or "effective amount" as used herein refers to an amount that is effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to affect such treatment for the disease. The effective amount will vary depending on the compound, the disease, and its severity and the age, weight, etc., of the subject to be treated. The effective amount can include a range of amounts. As is understood in the art, an effective amount may be in one or more doses, i.e., a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of

administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any co-administered compounds may optionally be lowered due to the combined action (e.g., additive or synergistic effects) of the compounds.

[0030] "Co-administration" as used herein refers to administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound of the present application is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound of the present application within seconds or minutes. In some embodiments, a unit dose of a compound of the present application is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the present application. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of each agent are present in the body of the subject.

[0031] Provided are also pharmaceutically acceptable salts, hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein.

[0032] Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0033] The compounds described herein may be prepared and/or formulated as pharmaceutically acceptable salts or when appropriate as a free base. Pharmaceutically acceptable salts are non-toxic salts of a free base form of a compound that possesses the desired pharmacological activity of the free base. These salts may be derived from inorganic or organic

acids or bases. For example, a compound that contains a basic nitrogen may 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 sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1, 4-dioates, hexyne-1, 6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, and mandelates. Lists of other suitable pharmaceutically acceptable salts are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Wiliams and Wilkins, Philadelphia, Pa., 2006.

[0034] Examples of "pharmaceutically acceptable salts" of the compounds disclosed herein also include salts derived from an appropriate base, such as an alkali metal (for example, sodium, potassium), an alkaline earth metal (for example, magnesium), ammonium and $N(C_1-C_4\ alkyl)_4^+$. Also included are base addition salts, such as sodium or potassium salts.

[0035] Provided are also compounds described herein or pharmaceutically acceptable salts, isomers, or a mixture thereof, in which from 1 to n hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D, in which 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 useful for increasing the half-life of the compounds described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof when administered to a mammal. See, e.g., Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

[0036] Examples of isotopes that can be incorporated into the disclosed compounds also include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and

Conjupro EX1025
Page 21 of 106

iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. 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 as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0037] The compounds of the embodiments disclosed herein, or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, tautomer, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, as well as deuterated analogs thereof. The chemical formula shown in the present application is meant 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 the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. Where compounds are represented in their chiral form, it is understood that the embodiment encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form. Where chirality is not specified but is present, it is understood that the embodiment is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound(s). As used herein, "scalemic mixture" is a mixture of stereoisomers at a ratio other than 1:1

[0038] "Stereoisomer" as used herein refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present application contemplates various stereoisomers and mixtures

thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are non-superimposable mirror images of one another.

[0039] "Tautomer" as used herein refers to a proton shift from one atom of a molecule to another atom of the same molecule. In some embodiments, the present application includes tautomers of said compounds.

[0040] "Solvate" as used herein refers to the result of the interaction of a solvent and a compound. Solvates of salts of the compounds described herein are also provided. Hydrates of the compounds described herein are also provided.

[0041] "Hydrate" as used herein refers to a compound of the disclosure that is chemically associated with one or more molecules of water.

[0042] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

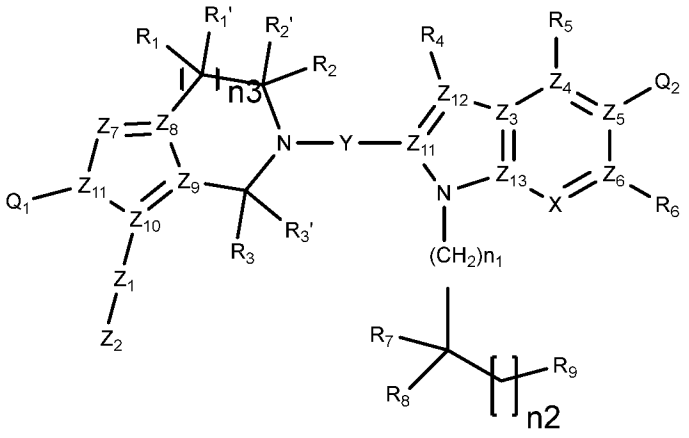
[0043] "Prodrug" as used herein refers to a derivative of a drug that upon administration to the human body is converted to the parent drug according to some chemical or enzymatic pathway. In some embodiments, a prodrug is a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathway.

[0044] "Treatment" or "treat" or "treating" as used herein refers to an approach for obtaining beneficial or desired results. For purposes of the present application, 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, "treatment" or "treating" includes one or more of the following: 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. "At risk individual" as

used herein refers to an individual who is at risk of developing a condition 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 of 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 factor(s).

II. Compounds

[0045] One aspect of the present application relates to a compound of Formula I and stereoisomers, pharmaceutically acceptable salts or deuterated compounds thereof;



Formula I

wherein X is selected from the group consisting of N and -CR^a; wherein R^a is selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

wherein Y is -C(=O)-;

wherein each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

wherein Q_1 is selected from the group consisting of C_{6-10} aryl and C_{5-10} heteroaryl, wherein C_{6-10} aryl or C_{5-10} heteroaryl is optionally substituted by one to five substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy;

Conjupro EX1025
Page 24 of 106

wherein Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl are optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy and $-NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl;

wherein each of R_1, R_2, R_3, R_1', R_2' and R_3' is independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} ahaloalkoxy, cycloalkyl and heterocycloalkyl; wherein C_{1-6} alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkoxy and hydroxyl;

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

wherein R_1 and R_1' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl, and R_2 and R_2' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl ; and R_3 and R_3' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl;

each of R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

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

or R_7 and R_8 together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring, wherein the C_{3-15} carbocyclic ring is optionally substituted by one to three C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclic , and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl groups and (C_{1-6} alkyl) carbonyl; and any two C_{1-6} alkyl groups optionally form C_{3-15} carbon ring together with the carbon atom to which they are attached;

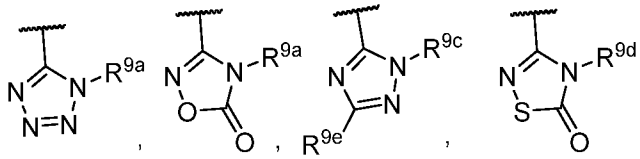
n_1 is 0, 1, 2 or 3;

Conjupro EX1025
Page 25 of 106

n2 is 0, 1, 2, 3, 4 or 5;

n3 is 0, 1 or 2;

R_9 is selected from the group consisting of:


, $-CO_2R^{9f}$ and $-C(=O)-NR^{9g}R^{9h}$; and each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{1-6} alkoxy;

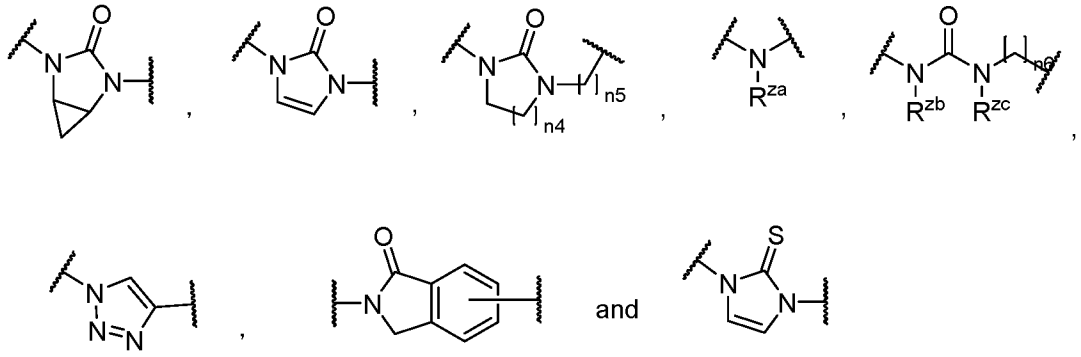
R^{9e} is selected from the group consisting of hydrogen and C_{1-6} alkyl optionally substituted by one or more halogen atoms;

R^{9f} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{9h} is selected from the group consisting of hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl) carbonyl, cyano and $-S(=O)_{n3}-R^{9i}$;

R^{9i} is C_{1-6} alkyl;

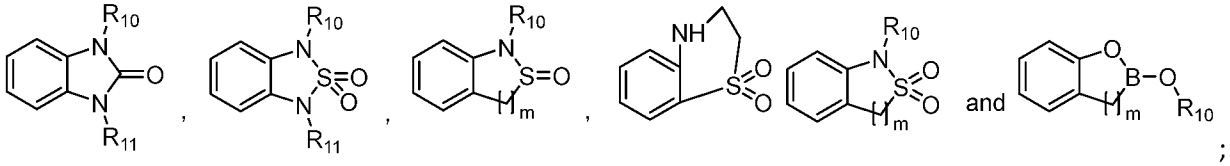
Z_1 is selected from the group consisting of:


wherein R^{za} is selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, and each of R^{zb} and R^{zc} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

n4 is 1, 2 or 3; each of n5 and n6 is independently integers from 0 to 10;

Conjupro EX1025
Page 26 of 106

Z_2 is selected from the group consisting of C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12-membered heterocyclic, C_{6-10} aryl , 5 to 10-membered heteroaryl,



;

wherein Z_2 is independently optionally substituted with one to five G's; and m is 1, 2, 3;

wherein each of R_{11} and R_{10} is independently selected from the group consisting of 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;

wherein G' is selected from the group consisting of:

a. Oxygen;
b. Halogen;
c. Cyano;
d. $-NR^{zd}R^{ze}$; wherein R^{zd} and R^{ze} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and C_{1-6} alkoxy;
e. $-C(=O)-NR^{zf}R^{zg}$; wherein R^{zf} and R^{zg} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and C_{1-6} alkoxy;
f. $-S(=O)_{n7}-R^{zh}$; wherein n7 is 0, 1 or 2; R^{zh} is selected from the group consisting of hydrogen and C_{1-6} alkyl;
g. C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, $-NR^{zi}R^{zj}$, C_{1-6} alkoxy, C_{1-6} alkoxy and 3- to 12-membered heterocyclic groups; wherein each of R^{zi} and R^{zj} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein the 3- to 12-membered heterocyclic groups are optionally substituted with one or more substituents selected from the group consisting of cyano, C_{1-6} alkyl and 3 to 12-membered heterocyclic;
h. C_{1-6} alkoxy; wherein C_{1-6} alkoxy is optionally substituted by one or more substituents of hydroxyl, halogen and C_{1-6} alkoxy;

Conjupro EX1025
Page 27 of 106

i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic 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 C_{6-10} aryl is optionally substituted by one or more (C_{1-6} alkyl) carbonyl;

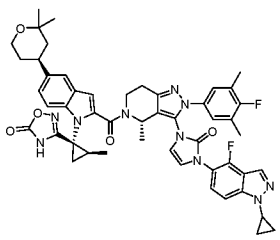
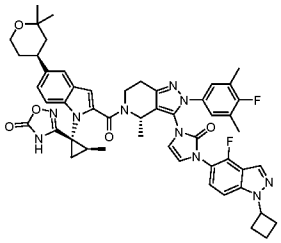
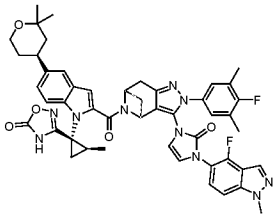
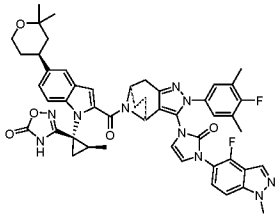
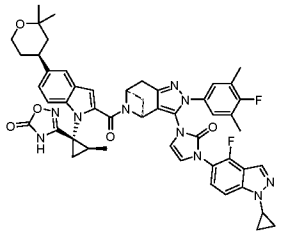
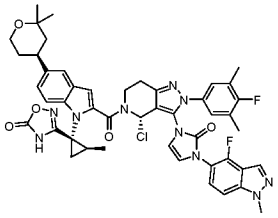
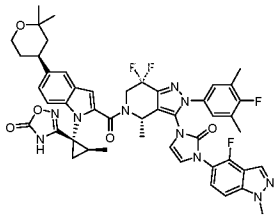
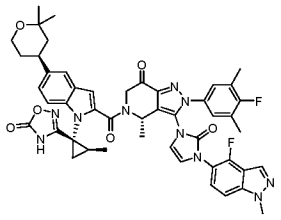
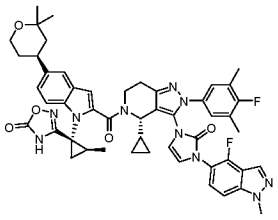
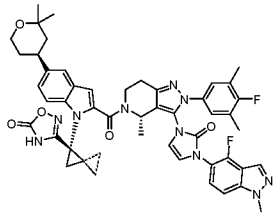
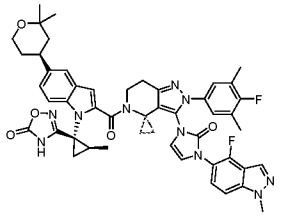
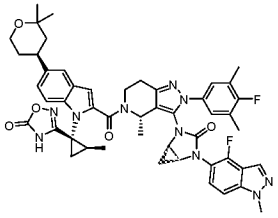
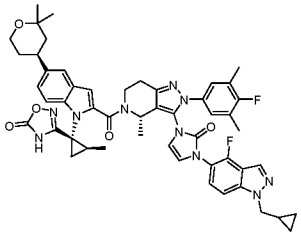
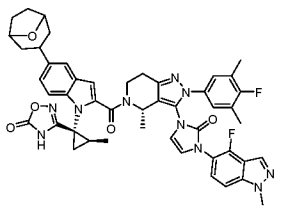
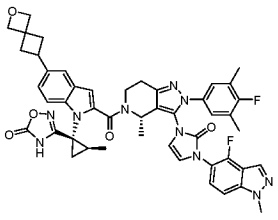
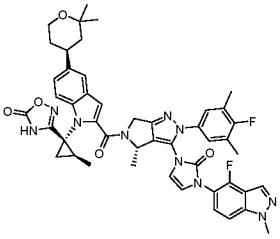
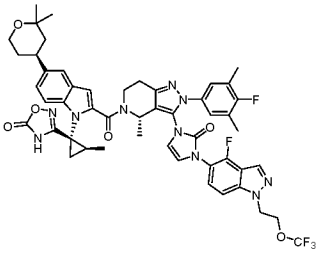
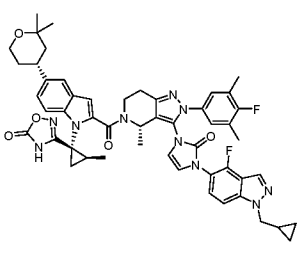
k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{zk}R^{zl}$, and 3- to 12-membered heterocyclic; wherein R^{zk} and R^{zl} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and (C_{1-6} alkyl)carbonyl and wherein the 3- to 12-membered heterocyclic is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, and C_{1-6} alkoxy;

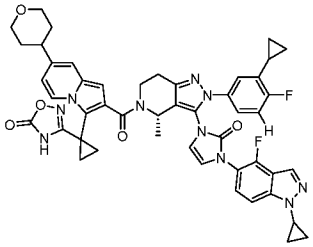
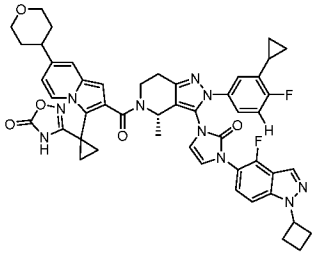
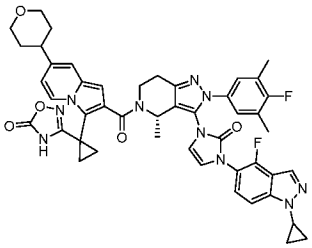
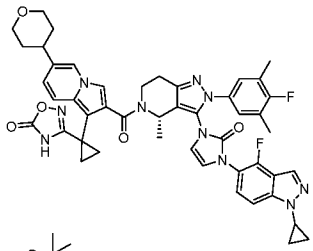
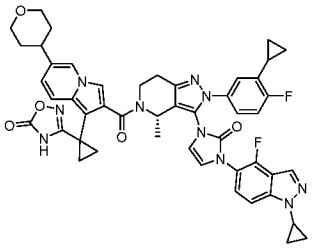
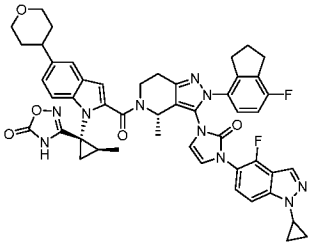
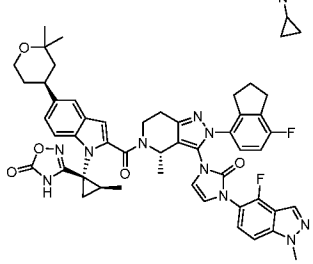
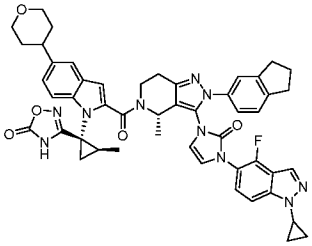
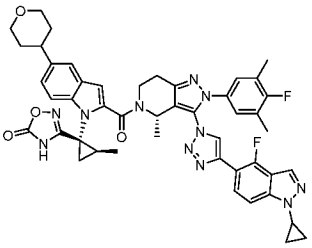
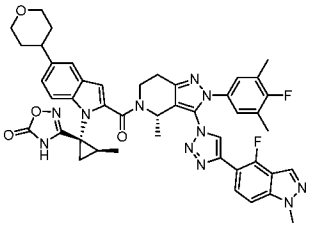
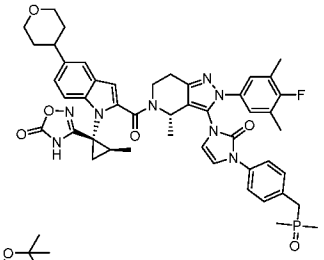
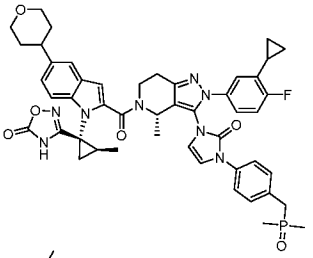
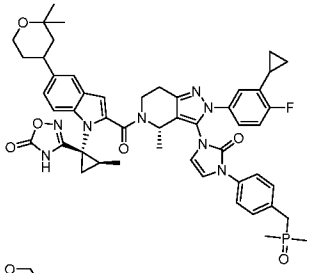
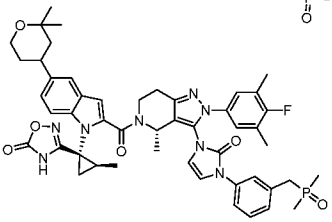
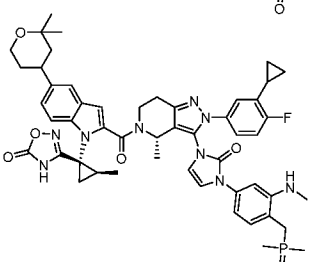
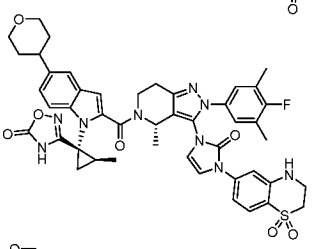
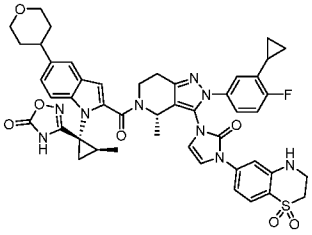
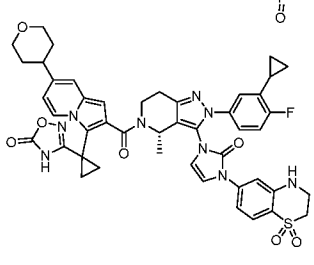
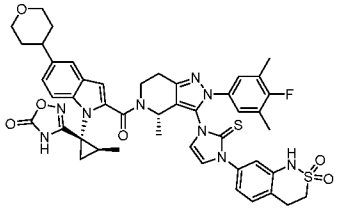
l. $-C_3$-C_{15} cycloalkyl or $-C_1$-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein $-C_3$-C_{15} cycloalkyl or $-C_1$-C_6 alkyl-C_3-C_{15} cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl is optionally substituted by halogen;

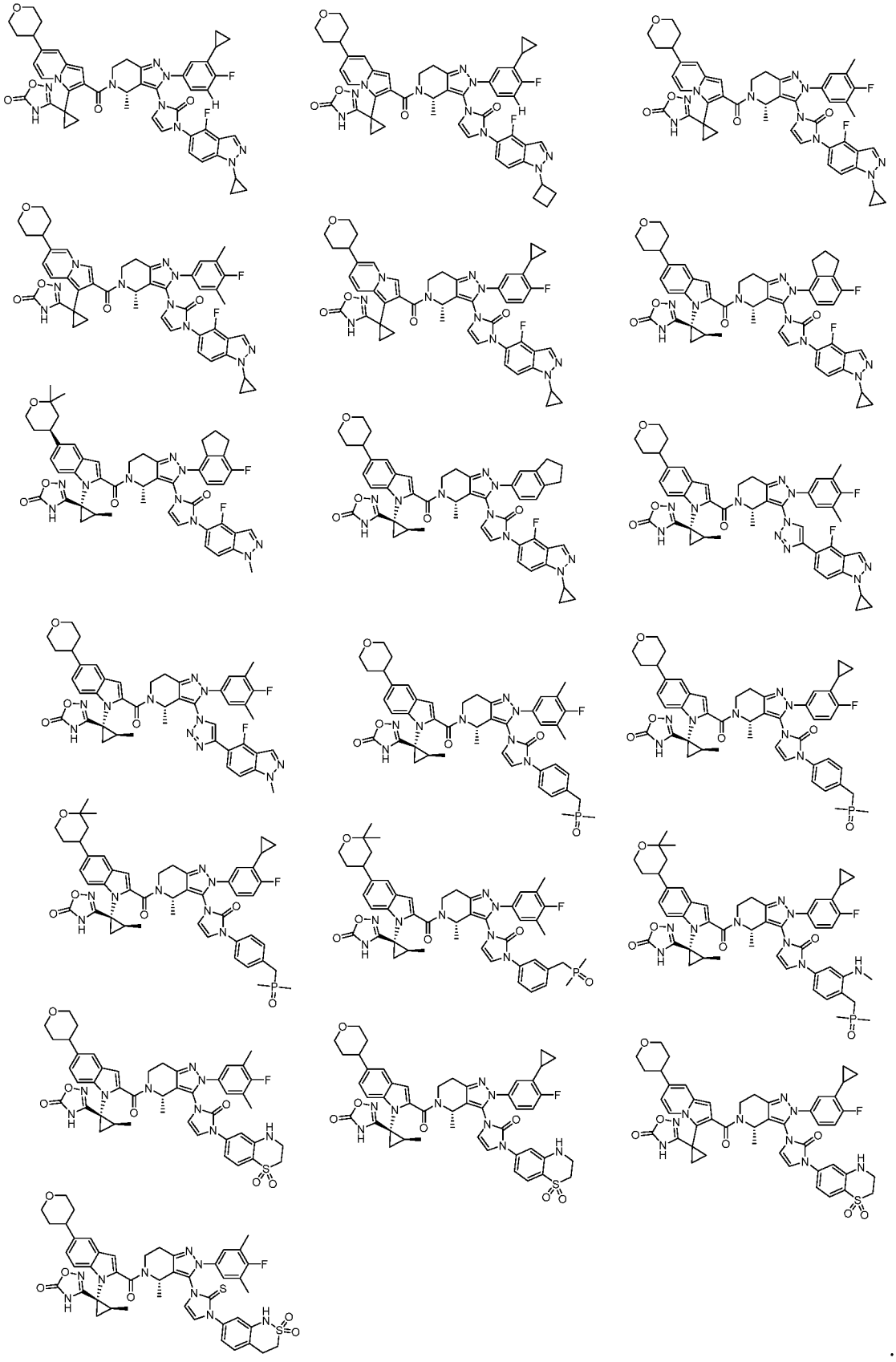
m. $-P(=O)R^{zm}R^{zn}$, $NR^{zm}S(=O)R^{zn}$ and $NR^{zm}S(=O)_2R^{zn}$, wherein R^{zm} and R^{zn} are independently selected from the group consisting of H, C_{1-6} alkyl and C_{6-10} aryl , wherein C_{1-6} alkyl is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo; wherein C_{3-6} cycloalkyl is optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo;
wherein C_{6-10} aryl is optionally substituted with 1-3 independently selected from C_{1-3} alkyl;
or R^{zm} and R^{zn} taken together with the phosphorous atom to which each is attached form a ring including from 5-8 ring atoms, wherein 0-2 ring atoms (in addition to the phosphorous attached to R^{zm} and R^{zn}) are heteroatoms each independently selected from the group consisting of: O, S, and N, wherein the ring is optionally substituted with 1-3 independently selected from C_{1-6} alkyl.

Conjupro EX1025
Page 28 of 106

In some embodiments, the compound of Formula I, and stereoisomers, pharmaceutically acceptable salts or deuterated compounds thereof has one of the structures listed below:



III. Pharmaceutical compositions

[0046] Another aspect of the present application relates to pharmaceutical compositions that contains the compounds of the present application. In some embodiments, the present application provides a pharmaceutical composition comprising a compound of the present application, and one or more pharmaceutically acceptable excipient.

[0047] In some embodiments, the pharmaceutical composition comprises a compound of Formula I or a pharmaceutically acceptable salt thereof.

[0048] In some embodiments, the pharmaceutical composition of the present application further comprises one or more additional therapeutic agents. Examples of the additional therapeutic agents include, but are not limited to, those therapeutic agents listed in the Combination therapy section of this application.

[0049] Pharmaceutical compositions of the present application may be in any form suitable for the intended method of administration. In some embodiments, the pharmaceutical composition is in the form of tablets, sachets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs for oral administration.

[0050] In some embodiments, the pharmaceutical compositions of the present application are presented in unit dosage form, including but not limited to, capsules, sachets or tablets each containing a predetermined amount of the active ingredient. In one embodiment, the pharmaceutical composition is a tablet.

[0051] The pharmaceutical composition may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient (*e.g.*, a compound of the present application or a pharmaceutical salt thereof) with the one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid excipients or finely divided solid excipients or both, and then, if desired, shaping the product. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Wiliams and Wilkins, Philadelphia, Pa., 2006.

[0052] Examples of the one or more excipients include, but not limited to, fillers, binders, bulking agent, glidants, sweetening agents, flavoring agents, coloring agents and

preserving agents. In some embodiments, the pharmaceutical composition is in tablet form and comprises one or more pharmaceutically acceptable excipients which are suitable for manufacture of tablets. 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 maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, 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 and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0053] The amount of active ingredient that may be combined with the inactive ingredients to produce a dosage form may vary depending upon the intended treatment subject and the mode of administration. For example, in some embodiments, a dosage form for oral administration to humans may contain approximately 1 to 1000 mg of active material formulated with an appropriate and convenient amount of a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutically acceptable excipient varies from about 5% to about 95% of the total compositions (weight:weight).

[0054] In some embodiments, the pharmaceutical composition of the present application does not contain an agent that affects the rate at which the active ingredient is metabolized. Thus, it is understood that pharmaceutical compositions comprising a compound of the present application in one aspect do not comprise an agent that would affect (e.g., slow, hinder or retard) the metabolism of a compound of the present application or any other active ingredient administered separately, sequentially or simultaneously with a compound of the present application. It is also understood that any of the methods, kits, articles of manufacture and the like detailed herein in one aspect do not comprise an agent that would affect (e.g., slow, hinder or retard) the metabolism of a compound of the present application or any other active ingredient administered separately, sequentially or simultaneously with a compound of the present application.

IV. Methods of treatment

[0055] Another aspect of the present application relates to a method for preventing, treating or ameliorating a symptom of a GLP-1R-mediated disease or condition with the compound of the present application. In some embodiments, the method comprises the step of administering to a subject in need of such treatment an effective amount of a compound of Formula I, or stereoisomers, pharmaceutically acceptable salts or deuterated compounds thereof.

[0056] Examples of GLP-1R-mediated diseases or conditions include, but are not limited to, present application chronic intrahepatic or some forms extrahepatic cholestatic conditions, liver fibrosis, acute intrahepatic cholestatic conditions, obstructive or chronic inflammatory disorders that arise out of improper bile composition, gastrointestinal conditions with a reduced uptake of dietary fat and fat-soluble dietary vitamins, inflammatory bowel diseases, lipid and lipoprotein disorders, type II diabetes and clinical complications of type I and type II diabetes, conditions and diseases which result from chronic fatty and fibrotic degeneration of organs due to enforced lipid and specifically triglyceride accumulation and subsequent activation of profibrotic pathways, of obesity and metabolic syndrome (combined conditions of dyslipidemia, diabetes and abnormally high body-mass index), acute myocardial infarction, acute stroke, thrombosis which occurs as an endpoint of chronic obstructive atherosclerosis, persistent infections by intracellular bacteria or parasitic protozoae, non-malignant hyperproliferative disorders, malignant hyperproliferative disorders, colon adenocarcinoma and hepatocellular carcinoma for instance, liver steatosis and associated syndromes, liver failure or liver malfunction as an outcome of chronic liver diseases or of surgical liver resection, Hepatitis B infection, Hepatitis C infection and/or of cholestatic and fibrotic effects that are associated with alcohol-induced cirrhosis or with viral-borne forms of hepatitis, type I diabetes, pre-diabetes, idiopathic type 1 diabetes, latent autoimmune diabetes, maturity onset diabetes of the young, early onset diabetes, 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, obesity, eating disorders, sleep apnea, weight gain, sugar craving, dyslipidemia, hyperinsulinemia, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, left

Conjupro EX1025
Page 34 of 106

ventricular hypertrophy, Parkinson's Disease, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, angina pectoris, premenstrual syndrome, thrombosis, atherosclerosis, impaired glucose metabolism, or vascular restenosis.

[0057] In some embodiments, the GLP-1R-mediated disease or condition is selected from the group consisting of type I diabetes (T1D), type II diabetes mellitus (T2DM), pre-diabetes, idiopathic T1D, late-onset autoimmune diabetes of adulthood (LADA), early-onset T2DM (EOD), youth-onset atypical diabetes (YOAD), maturity-onset diabetes of the young (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 agents, 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, post-prandial 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, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, prevention or treatment of Polycystic Ovary Syndrome and treatment of addiction.

[0058] In some embodiments, the GLP-1R-mediated disease or condition is a liver disease, e.g., liver fibrosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), liver cirrhosis, compensated liver fibrosis, decompensated liver

fibrosis, hepatocellular carcinoma, Primary Biliary Cirrhosis (PBC), or Primary Sclerosing Cholangitis (PSC).

[0059] In some embodiments, the GLP-1R-mediated disease or condition is a metabolic disease.

[0060] In some embodiments, the present application relates to a method for treating and/or preventing NAFLD, comprises administering to a subject in need thereof n effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

[0061] In some embodiments, the present application relates to a method for treating and/or preventing NASH. In some embodiments, the method comprises administering an effective amount of a compound of Formula I to a subject in need thereof.

[0062] In some embodiments, the present application relates to preventive and posttraumatic treatment of a cardiovascular disorder, such as acute myocardial infarction, acute stroke, or thrombosis which occur as an endpoint of chronic obstructive atherosclerosis. In some embodiments, the method comprises administering an effective amount of a compound of Formula I, to a subject in need thereof.

[0063] In some embodiments, the present application relates to a method for the treatment and/or prevention of obesity and associated disorders such as metabolic syndrome (combined conditions of dyslipidemias, diabetes and abnormally high body-mass index), which can be overcome by GLP1R-mediated lowering of serum triglycerides, blood glucose and increased insulin sensitivity and GLP1R-mediated weight loss. In some embodiments, the method comprises administering an effective amount of a compound of Formula I to a subject in need thereof.

[0064] In some embodiments, the present application relates to a method for preventing and/or treating clinical complications of Type I and Type II Diabetes. Examples of such complications include diabetic nephropathy, diabetic retinopathy, diabetic neuropathies, or Peripheral Arterial Occlusive Disease (PAOD). Other clinical complications of diabetes are also encompassed by the present application. In some embodiments, the method comprises administering an effective amount of a compound of Formula I to a subject in need thereof.

[0065] Furthermore, conditions and diseases which result from chronic fatty and fibrotic degeneration of organs due to enforced lipid and/or triglyceride accumulation and subsequent activation of profibrotic pathways may also be prevented and/or treated by administering the

compounds or pharmaceutical compositions of the present application. Such conditions and diseases include, but are not limited to, NASH and chronic cholestatic conditions in the liver, Glomerulosclerosis and Diabetic Nephropathy in the kidney, Macular Degeneration and Diabetic Retinopathy in the eye and neurodegenerative diseases, such as Alzheimer´s Disease in the brain, or Diabetic Neuropathies in the peripheral nervous system.

[0066] In some embodiments, the present application relates to a method for treating and/or preventing conditions and diseases which result from chronic fatty and fibrotic degeneration of organs due to enforced lipid and/or triglyceride accumulation and subsequent activation of profibrotic pathways. In some embodiments, the method comprises administering an effective amount of a compound of Formula I to a subject in need thereof.

[0067] In some embodiments, the compound of the present application is used in the form of a prodrug or other suitably modified form, which releases the active ingredient in vivo.

[0068] The compounds of the present application (also referred to herein as the active ingredients) or pharmaceutical compositions of the present application can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratumoral, intrathecal and epidural), and the like. 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 dosed orally.

[0069] A compound of the present application 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 one 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 variation, the compound is administered on a daily or intermittent schedule for the duration of the individual's life.

[0070] The dosage or dosing frequency of a compound of the present application may be adjusted over the course of the treatment, based on the judgment of the administering physician.

[0071] The compound may be administered to an individual (e.g., a human) in an effective amount. In some embodiments, the compound is administered once daily.

[0072] The compound can 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.

[0073] A compound of the present application may be combined with one or more additional therapeutic agents in any dosage amount of the compound of the present application (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 application 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 compound of the present application 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 once every 24 hours. A single dose can also be administered once every 1 day, 2, 3, 4, 5, 6, or once every 7 days. A single dose can also be administered once every 1 week, 2, 3, or once every 4 weeks. In some embodiments, a single dose can be administered once every week. A single dose can also be administered once every month.

[0074] Kits that comprise a compound of the present application, or pharmaceutically acceptable salt thereof, are also included in the present application. In one embodiment, a kit further includes a label and/or instructions for use of the compounds in the treatment of the indications, such as the diseases or conditions described herein. In one embodiment, the kit comprises a compound of the present application, or pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, four, one or two, or one to three, or one to four) additional therapeutic agents.

V. Combination therapy

[0075] Also provided herein is the use of a compound of the present application in combination with one or more additional therapeutic agents having a synergistic effect with the compound of the present application.

[076] In some embodiments, the one or more additional therapeutic agents comprise an apoptotic signal-regulating kinase (ASK-1) inhibitor, a farnesoid X receptor (FXR) agonist, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, fish oil, an acetyl-coA carboxylase (ACC) inhibitor, or a TGFβ antagonist, or a combination thereof.

[077] In some embodiments, the one or more additional therapeutic agents are selected from the group consisting of ACE inhibitors, 2-acylglycerol O-acyltransferase 2 (DGAT2) inhibitors, acetaldehyde dehydrogenase inhibitors, acetyl CoA carboxylase inhibitors, adrenergic receptor agonists, Alstrom syndrome protein 1(ALMS1)/PKC alpha protein interaction inhibitors, apelin receptor agonists, diacylglycerol O acyltransferase 2 inhibitors, adenosine A3 receptor agonists, adenosine A3 receptor antagonists, adiponectin receptor agonists, aldehyde dehydrogenase 2 stimulators, AKT protein kinase inhibitors, AMP-activated protein kinases (AMPK), AMP kinase activators, ATP citrate lyase inhibitors, AMP activated protein kinase stimulators, endothelial nitric oxide synthase stimulators, NAD-dependent deacetylase sirtuin-1 stimulators, androgen receptor agonists, amylin receptor agonists, angiotensin II AT-1 receptor antagonists, autophagy protein modulators, autotaxin inhibitors, Axl tyrosine kinase receptor inhibitors, Bax protein stimulators, beta-catenin inhibitors, bioactive lipids, aalcitonin agonists, cannabinoid receptor modulators, Caspase inhibitors, Caspase-3 stimulators, cathepsin inhibitors, caveolin 1 inhibitors, CCK receptor antagonists, CCL26 gene inhibitors, CCR2 chemokine antagonists, CCR2 chemokine antagonists, angiotensin II AT-1 receptor antagonists, CCR3 chemokine antagonists, CCR5 chemokine antagonists, CD3 antagonists, CDGSH iron sulfur domain protein modulators, chitinase inhibitors, chloride channel stimulators, chitotriosidase 1 inhibitors, CNR1 inhibitors, connective tissue growth factor ligand inhibitors, cyclin D1 inhibitors, cytochrome P4507A1 inhibitors, DGAT1/2 inhibitors, diacylglycerol O acyltransferase 1 (DGAT1) inhibitors, cytochrome P4502E1 (CYP2E1) inhibitors, CXCR4 chemokine antagonists, dihydroceramide delta 4 desaturase inhibitors, dihydroorotate dehydrogenase inhibitors, dipeptidyl peptidase IV inhibitors, endosialin modulators, eotaxin ligand inhibitors, extracellular matrix protein

modulators, farnesoid X receptor agonists, fatty acid synthase inhibitors, FGF1 receptor agonists, fibroblast growth factor (FGF-15, FGF-19, FGF-21) ligands, fibroblast activation protein inhibitors, free fatty acid receptor 1 agonists, galectin-3 inhibitors, GDNF family receptor alpha like agonists, glucagon receptor agonists, glucagon-like peptide 1 agonists, glucocorticoid receptor antagonists, glucose 6-phosphate 1-dehydrogenase inhibitors, G-protein coupled bile acid receptor 1 agonists, G-protein coupled receptor-119 agonists, G-protein coupled receptor 84 antagonists, hedgehog (Hh) modulators, hepatitis C virus NS3 protease inhibitors, hepatocyte nuclear factor 4 alpha (HNF4A) modulators, hepatocyte growth factor modulators, histone deacetylase inhibitors, STAT-3 modulators, HMG CoA reductase inhibitors, HSD17B13 gene inhibitors, 5-HT 2a receptor antagonists, hydrolase inhibitors, hypoxia inducible factor-2 alpha inhibitors, IL-10 agonists, IL-17 antagonists, IL-22 agonists, ileal sodium bile acid cotransporter inhibitors, insulin sensitizers, insulin ligand agonists, insulin receptor agonists, integrin modulators, integrin antagonists, integrin alpha-V/beta-1 antagonists, integrin alpha-V/beta-6 antagonists, intereukin-1 receptor-associated kinase 4 (IRAK4) inhibitors, IL-6 receptor agonists, interleukin 17 ligand inhibitors, Jak2 tyrosine kinase inhibitors, Jun N terminal kinase-1 inhibitors, Kelch like ECH associated protein 1 modulators, ketohexokinase (KHK) inhibitors, klotho beta stimulators, leukotriene A4 hydrolase inhibitors, 5-lipoxygenase inhibitors, lipoprotein lipase inhibitors, liver X receptors, LPL gene stimulators, lysophosphatidate-1 receptor antagonists, lysyl oxidase homolog 2 inhibitors, LXR inverse agonists, macrophage mannose receptor 1 modulators, matrix metalloproteinases (MMPs) inhibitors, MEKK-5 protein kinase inhibitors, MCH receptor-1 antagonists, membrane copper amine oxidase (VAP-1) inhibitors, methionine aminopeptidase-2 inhibitors, methyl CpG binding protein 2 modulators, microRNA-132 (miR-132) antagonists, microRNA-21(miR-21) inhibitors, mitochondrial uncouplers, mixed lineage kinase-3 inhibitors, motile sperm domain protein 2 inhibitors, myelin basic protein stimulators, NACHT LRR PYD domain protein 3 (NLRP3) inhibitors, NAD-dependent deacetylase sirtuin stimulators, NADPH oxidase (NOX) inhibitors, NFE2L2 gene inhibitors, nicotinic acid receptor 1 agonists, opioid receptor mu antagonists, P2Y13 purinoceptor stimulators, nuclear erythroid 2-related factor 2 stimulators, nuclear receptor modulators, P2X7 purinoceptor modulators, PACAP type I receptor agonists, PDE 3 inhibitors, PDE 4 inhibitors, PDE 5 inhibitors, PDGF receptor beta modulators, phenylalanine hydroxylase stimulators, phospholipase C inhibitors, phosphoric

diester hydrolase inhibitors, PPAR alpha agonists, PPAR delta agonists, PPAR gamma agonists, peptidyl-prolyl cis-trans isomerase A inhibitors, PNPLA3 gene inhibitors, PPAR gamma modulators, protease-activated receptor-2 antagonists, protein kinase modulators, protein NOV homolog modulators, PTGS2 gene inhibitors, renin inhibitors, resistin/CAP1 (adenylyl cyclase associated protein 1) interaction inhibitors, rho associated protein kinase inhibitors, snitrosoglutathione reductase (GSNOR) enzyme inhibitors, sodium glucose transporter-2 inhibitors, sphingolipid delta 4 desaturase DES1 inhibitors, SREBP transcription factor inhibitors, STAT-1 inhibitors, stearoyl CoA desaturase-1 inhibitors, STK25 inhibitors, suppressor of cytokine signalling-1 stimulators, suppressor of cytokine signalling-3 stimulators, telomerase stimulators, TERT gene modulators, TGF beta (TGFB1) ligand inhibitors, TNF antagonists, transforming growth factor β (TGF-β), transforming growth factor β activated Kinase 1 (TAK1), thyroid hormone receptor beta agonists, TLR-4 antagonists, transglutaminase inhibitors, tyrosine kinase receptor modulators, GPCR modulators, nuclear hormone receptor modulators, TLR-9 antagonists, VDR agonists, WNT modulators, YAP/TAZ modulators and zonulin inhibitors.

[078] Non-limiting examples of the one or more additional therapeutic agents include:

- ACE inhibitors, such as enalapril;
- Acetaldehyde dehydrogenase inhibitors, such as ADX-629;
- Acetyl CoA carboxylase (ACC) inhibitors, such as NDI-010976 (firsocostat), DRM-01, gemcabene, GS-834356, PF-05175157, QLT-091382, PF-05221304;;
- Acetyl CoA carboxylase/Diacylglycerol O acyltransferase 2 inhibitors, such as PF-07055341;
- Adenosine receptor agonists, such as CF-102 (namodenoson), CF-101, CF-502, CGS21680;
-Adenosine A3 receptor antagonist, such as FM-101;
- Adiponectin receptor agonists, such as ADP-355, ADP-399;
- Adrenergic receptor antagonist, such as bromocriptine, phentermine, VI-0521
- Aldehyde dehydrogenase 2 stimulators, such as FP-045;
- Alpha glucosidase inhibitors (e.g. voglibose, acarbose, or miglitol);
- Amylin/calcitonin receptor agonists, such as KBP-042, KBP-089;
- AMP activated protein kinase stimulators, such as, C-455, PXL-770, O-304;

- AMP kinase activators/ATP citrate lyase inhibitors, such as bempedoic acid (ETC-1002, ESP-55016)
- AMP activated protein kinase/Endothelial nitric oxide synthase/NAD-dependent deacetylase sirtuin-1 stimulators, such as NS-0200 (leucine + metformin + sildenafil); - Androgen receptor agonists, such as LPCN-1144, LPCN-1148, testosterone prodrug; - Angiotensin II AT-1 receptor antagonists, such as irbesartan; Angiopoietin-related protein-3 inhibitors, such as vupanorsen (IONIS-ANGPTL3-LRx);
- Apelin receptor agonist, such as CB-5064, MBT-2;
- Autophagy protein modulators, such as A-2906;
- Autotaxin (ectonucleotide pyrophosphatase/phosphodiesterase 2 (NPP2 or ENPP2)) inhibitors, such as FP10.47, PAT-505, PAT-048, GLPG-1690, X-165, PF-8380, TJC- 0265, TJC-0316, AM-063, BBT-877;
- Axl tyrosine kinase receptor inhibitors, such as bemcentinib (BGB-324, R-428);
- Bax protein stimulators, such as CBL-514;
- Bioactive lipids, such as DS-102;
- Cannabinoid receptor modulators, such as namacizumab (nimacimab), GWP-42004, REV-200, CRB-4001, INV-101, SCN-002;
- Caspase inhibitors, such as emricasan;
- Pan cathepsin B inhibitors, such as VBY-376;
- Pan cathepsin inhibitors, such as VBY-825;
- CCK receptor antagonist, such as proglumide;
- CCL26 gene inhibitor, such as mosedipimod, KDDF-201410-10
- CCR2/CCR5 chemokine antagonists, such as BMS-687681, cenicriviroc, maraviroc, CCX-872, leronlimab, WXSH-0213;
- CCR2/CCR5 chemokine antagonists and FXR agonists, such as LJC-242 (tropifexor + cenivriviroc);
- CCR2 chemokine antagonists, such as propagermanium;
- CCR2 chemokine/Angiotensin II AT-1 receptor antagonists, such as DMX-200, DMX-250;
- CCR3 chemokine antagonists, such as bertilimumab;
- CD3 antagonists, such as NI-0401 (foralumab);

Conjupro EX1025
Page 42 of 106

- CDGSH iron sulfur domain protein modulators, such as EYP-002;
- Chitinase inhibitor, such as OATD-01;
- Chitotriosidase 1 inhibitors, such as OAT-2068;
- Chloride channel stimulators, such as cobiprostone, and lubiprostone;
- Casein kinase-1 (CK1) delta/epsilon inhibitors, such as PF-05006739;
- Connective tissue growth factor ligand inhibitor, such as PBI-4050;
- CXCR4 chemokine antagonists, such as AD-214;
- Diglyceride acyltransferase 2 (DGAT2) inhibitors, such as IONIS-DGAT2Rx, PF-06865571;
- Diglyceride acyltransferase 1 (DGAT1) inhibitors, such as GSK-3008356;
- Diacylglycerol O acyltransferase 1 (DGAT1)/ Cytochrome P4502E1 inhibitors (CYP2E1), such as SNP-610;
- Dihydroorotate dehydrogenase inhibitor, such as vidofludimus;
- Dipeptidyl peptidase IV inhibitors, such as linagliptin, evogliptin;
- Eotaxin ligand inhibitors, such as bertilimumab, CM-101;
- Extracellular matrix protein modulators, such as CNX-024;
- Farnesoid X receptor (FXR) agonists, such as AGN-242266, AGN-242256, ASC-42, EDP-297 (EP-024297), RDX-023, BWL-200, AKN-083, EDP-305, GNF-5120, cilofexor tromethamine (GS-9674), HPG-1860, IOT-022, LMB-763, obeticholic acid, Px-102, Px- 103, M790, M780, M450, M-480, MET-409, MET-642, PX20606, SYHA-1805, vonafexor (EYP-001), TERN-101, TC-100, INT-2228, TQA-3526, ZG-5266;
- Farnesoid X receptor (FXR)/ G-protein coupled bile acid receptor 1(TGR5) agonists, such as INT-767;
- Fatty acid synthase inhibitors, such as TVB-2640, FT-8225;
- Fibroblast growth factor 19 (rhFGF19)/cytochrome P450 (CYP) 7A1 inhibitors, such as aldafermin (NGM-282);
- Fibroblast growth factor 21(FGF-21) ligand modulators, such as AP-025, BMS-986171, B-1654, BIO89-100, BOS-580,
- Pegbelfermin (BMS-986036), B-1344;

- Fibroblast growth factor 21(FGF-21)/glucagon like peptide 1 (GLP-1) agonists, such as YH-25723 (YH-25724; YH-22241), efruxifermin (AKR-001);
- FGF receptor agonists/Klotho beta stimulators, such as BFKB-8488A (RG-7992);
- Free fatty acid receptor 1 agonist, such as SCO-267;
- Galectin-3 inhibitors, such as belapectin (GR-MD-02), GB-1107 (Gal-300), GB-1211 (Gal-400);
- GDNF family receptor alpha like agonist, such as NGM-395
- Glucagon-like peptide 1(GLP1R) agonists, such as ALT-801, AC-3174, liraglutide, cotadutide (MEDI-0382), SAR-425899, LY-3305677, HM-15211, YH-25723, YH-GLP1, RPC-8844, PB-718, PF-06882961, semaglutide;
- Glucagon-like peptide 1 receptor agonist; Oxyntomodulin ligand; Glucagon receptor agonist, such as efinopegdutide;
- Gastric inhibitory polypeptide/Glucagon-like peptide-1(GIP/GLP-1) receptor co-agonist, such as tirzepatide (LY-3298176);
- PEGylated long-acting glucagon-like peptide-1/glucagon (GLP-1R/GCGR) receptor dual agonist, such as DD-01;
- Glucagon/GLP1-receptor agonist, such as BI-456906;
- Glucocorticoid receptor antagonists, such as CORT-118335 (miricorilant);
- Glucose 6-phosphate 1-dehydrogenase inhibitors, such as ST001;
- Glucokinase stimulator, such as dorzagliatin, sinogliatin (RO-5305552)
- G-protein coupled bile acid receptor 1(TGR5) agonists, such as RDX-009, INT-777, HY-209;
- G-protein coupled receptor 84 antagonist, such as PBI-4547;
- G-protein coupled receptor-119 agonist, such as DA-1241;
- Heat shock protein 47 (HSP47) inhibitors, such as ND-L02-s0201;
- Hedgehog protein and/or TGF beta ligand inhibitors, such as Oxy-210
- Histone deacetylase inhibitors/ STAT-3 modulators, such as SFX-01;
- HMG CoA reductase inhibitors, such as atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin;
- HSD17B13 gene inhibitor, such as ALN-HSD, ARO-HSD
- Hydrolase inhibitor, such as ABD-X;

- Hypoxia inducible factor-2 alpha inhibitors, such as PT-2567;
- IL-10 agonists, such as peg-ilodecakin;
- Ileal sodium bile acid cotransporter inhibitors, such as odevixibat (A-4250), volixibat potassium ethanolate hydrate (SHP-262), GSK2330672, CJ-14199, elobixibat (A-3309); - Insulin sensitizers, such as, KBP-042, azemiglitazone potassium (MSDC-0602K), ION- 224, MSDC-5514, Px-102, RG-125 (AZD4076), Tolimidone, VVP-100X, CB-4211, ETI-101, pioglitazone;
- Insulin ligand/dsInsulin receptor agonists, such as ORMD-0801;
- Integrin antagonists, such as IDL-2965;
- IL-6 receptor agonists, such as KM-2702;
- Integrin alpha-V/beta-6 and alpha-V/beta-1 dual inhibitor; such as PLN-74809;
- Interleukin 17 ligand inhibitor, such as netakimab
- Jak1/2 tyrosine kinase inhibitor, such as baricitinib
- Jun N terminal kinase-1 inhibitor, such as CC-90001
- Kelch like ECH associated protein 1 modulator, such as alpha-cyclodextrin-stabilized sulforaphane;
- Ketohexokinase (KHK) inhibitors, such as PF-06835919, LY-3478045;
- beta Klotho (KLB)- FGF1c agonists, such as MK-3655 (NGM-313);
- Leukotriene A4 hydrolase inhibitor, such as LYS-006;
- 5-Lipoxygenase inhibitors, such as tipelukast (MN-001), epeleuton (DS-102, (AF-102); - Lipoprotein lipase inhibitors, such as CAT-2003;
- LPL gene stimulators, such as alipogene tiparvovec;
- Liver X receptor (LXR) inhibitors, such as PX-665, PX-L603, PX-L493, BMS-852927, T-0901317, GW-3965, SR-9238;
- Lysophosphatidate-1 receptor antagonists, such as BMT-053011, UD-009 (CP-2090), AR-479, ITMN-10534, BMS-986020, KI-16198;
- Lysyl oxidase homolog 2 inhibitors, such as simtuzumab, PXS-5382A (PXS-5338); - Macrophage mannose receptor 1 modulators, such as tilmanocept-Cy3 (technetium Tc 99m tilmanocept);
- Matrix metalloprotease inhibitors, such as ALS-L1023;

- Membrane copper amine oxidase (VAP-1) inhibitors, such as TERN-201, TT-01025; - MEKK-5 protein kinase (ASK-1) inhibitors, such as CJ-16871, CS-17919, selonsertib (GS-4997), SRT-015, GS-444217, GST-HG-151, TERN-301;
- MCH receptor-1 antagonists, such as CSTI-100 (ALB-127158);
- Semicarbazide-Sensitive Amine Oxidase/Vascular Adhesion Protein-1 (SSAO/VAP-1) Inhibitors, such as PXS-4728A (BI-1467335);
- Methionine aminopeptidase-2 inhibitors, such as ZGN-1061, ZGN-839, ZN-1345;
- Methyl CpG binding protein 2 modulators, such as mercaptamine;
- Mineralocorticoid receptor antagonists (MCRA), such as MT-3995 (apararenone);
- Mitochondrial uncouplers, such as 2, 4-dinitrophenol, HU6, Mito-99-0053;
- Mixed lineage kinase-3 inhibitors, such as URMC-099-C;
- Motile sperm domain protein 2 inhibitors, such as VB-601;
- Myelin basic protein stimulators, such as olesoxime;
- Myeloperoxidase inhibitors, such as PF-06667272, AZM-198;
- NADPH oxidase inhibitors, such as GKT-831, GenKyoTex, APX-311, setanaxib;
- Nicotinic acid receptor 1 agonists, such as ARI-3037MO;
- NACHT LRR PYD domain protein 3 (NLRP3) inhibitors, such as KDDF-201406-03, NBC-6, IFM-514, JT-194 (JT-349);
- NFE2L2 gene inhibitor, such as GeRP-amiR-144
- Nuclear receptor modulators, such as DUR-928 (DV-928);
- Opioid receptor mu antagonists, such as methylnaltrexone;
- P2X7 purinoceptor modulators, such as SGM-1019;
- P2Y13 purinoceptor stimulators, such as CER-209;
- PDE 3/4 inhibitors, such as tipelukast (MN-001);
- PDE 5 inhibitors, such as sildenafil, MSTM-102;
- PDGF receptor beta modulators, such as BOT-191, BOT-509;
- Peptidyl-prolyl cis-trans isomerase inhibitors, such as CRV-431 (CPI-432-32), NVP-018, NV-556 (NVP-025);
- Phenylalanine hydroxylase stimulators, such as HepaStem;
- Phosphoric diester hydrolase inhibitor, such as ZSP-1601;
- PNPLA3 gene inhibitor, such as AZD-2693;

- PPAR agonists, such as Chiglitazar, elafibranor (GFT-505), seladelpar lysine (MBX-8025), deuterated pioglitazone R-enantiomer, pioglitazone, PXL-065 (DRX-065), saroglitazar, lanifibranor (IVA-337), CHS-131, pemafibrate (K-877), ZG-0588, ZSP-0678; ZSYM-008;
- Protease-activated receptor-2 antagonists, such as PZ-235;
- Protein kinase modulators, such as CNX-014;
- Protein NOV homolog modulators, such as BLR-200;
- PTGS2 gene inhibitors, such as STP-705, STP-707;
- Renin inhibitors, such as PRO-20;
- Resistin/CAP1 (adenylyl cyclase associated protein 1) interaction inhibitors, such as DWJ-211
- Rev protein modulator, such as ABX-464;
- Rho associated protein kinase (ROCK) inhibitors, such as REDX-10178 (REDX-10325), KD-025, RXC-007, TDI-01;
- Snitrosoglutathione reductase (GSNOR) enzyme inhibitors, such as SL-891;
- Sodium glucose transporter-2(SGLT2) inhibitors, such as ipragliflozin, remogliflozin etabonate, ertugliflozin, dapagliflozin, tofogliflozin, sotagliflozin,
- Sodium glucose transporter-1/2 (SGLT 1/2) inhibitors, such as licogliflozin bis(prolinate) (LIK-066);
- SREBP transcription factor inhibitors, such as CAT-2003, HPN-01, MDV-4463;
- Stearoyl CoA desaturase-1 inhibitors, such as aramchol;
- Thyroid hormone receptor beta agonists, such as ALG-009, ASC-41, CNPT-101101; CNPT-101207, CS-27186, KY-41111, resmetirom (MGL-3196), MGL-3745, TERN-501, VK-2809;
- TLR-2/TLR-4 antagonists, such as VB-201 (CI-201);
- TLR-4 antagonists, such as JKB-121, JKB-122, naltrexone;
- Tyrosine kinase receptor modulators, such as CNX-025, GFE-2137 (repurposed nitazoxanide);
- TLR-9 antagonist, such as GNKS-356
- TNF antagonist, such as ALF-421
- GPCR modulators, such as CNX-023;

- Nuclear hormone receptor modulators, such as Px-102;

- VDR agonist, such as CK-15;

- Xanthine oxidase inhibitors, such as ACQT-1127;

- Xanthine oxidase/Urate anion exchanger 1 (URAT1) inhibitors, such as RLBN-1001, RLBN-1127; and

- Zonulin Inhibitors, such as lorazotide acetate (INN-202).

[079] In some embodiments, the one or more additional therapeutic agents are selected from A-4250, AC-3174, acetylsalicylic acid, AK-20, alipogene tiparvovec, AMX-342, AN-3015, anti-TAGE antibody, aramchol, ARI-3037MO, ASP-8232, AZD-2693, bertilimumab, Betaine anhydrous, BI-1467335, BMS-986036, BMS-986171, BMT-053011, BOT-191, BTT-1023, budesonide, BX-003, CAT-2003, cenicriviroc, CBW-511, CER-209, CF-102, CGS21680, CNX-014, CNX-023, CNX-024, CNX-025, cobiprostone, colesevelam, dabigatran etexilate mesylate, dapagliflozin, DCR-LIV1, deuterated pioglitazone R-enantiomer, 2, 4-dinitrophenol, DRX-065, DS-102, DUR-928, EDP-305, elafibranor (GFT-505), emricasan, enalapril, ertugliflozin, evogliptin, F-351, fluasterone (ST-002), FT-4101, GDD-3898, GH-509, GKT-831, GNF-5120, GRI-0621, GR-MD-02, GS-300, GS-4997, GS-9674, HEC-96719, HTD-1801, HS-10356, HSG-4112, HST-202, HST-201, HU-6, hydrochlorothiazide, icosabutate (PRC-4016), icosapent ethyl ester, IMM-124-E, INT-767, INV-240, IONIS-DGAT2Rx, ipragliflozin, Irbesarta, propagermanium, IVA-337, J2H-1702, JKB-121, KB-GE-001, KBLP-004, KBLP-009, KBP-042, KD-025, M790, M780, M450, metformin, sildenafil, LB-700, LC-280126, linagliptin, liraglutide, (LJN-452) (tropifexor), LM-011, LM-002 (CVI-LM-002), LMB-763, LYN-100, MB-N-008, MBX-8025, MDV-4463, mercaptamine, MGL-3196, MGL-3745, MP-301, MSDC-0602K, namacizumab, NC-101, NDI-010976, ND-L02-s0201 (BMS-986263), NGM-282, NGM-313, NGM-386, NGM-395, NP-011, NP-135, NP-160, , norursodeoxycholic acid, NV-422, NVP-022, O-304, obeticholic acid (OCA), 25HC3S, olesoxime, PAT-505, PAT-048, PBI-4547, peg-ilodecakin, pioglitazone, pirfenidone, PRI-724, PX20606, Px-102, PX-L603, PX-L493, PXS-4728A, PZ-235, PZH-2109, RCYM-001, RDX-009, remogliflozin etabonate, RG-125 (AZD4076), RPI-500, S-723595, saroglitazar, SBP-301, semaglutide, SH-2442, SHC-028, SHC-023, simtuzumab, solithromycin, sotagliflozin, statins (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin), symbiotic, TCM-606F, TEV-45478, TQA-3526,

TQA-3563, tipelukast (MN-001), TLY-012, TRX-318, TVB-2640, TXR-612, TS-20004, UD-009, UN-03, ursodeoxycholic acid, VBY-376, VBY-825, VK-2809, vismodegib, volixibat potassium ethanolate hydrate (SHP-626), VVP-100X, WAV-301, WNT-974, WXSH-0038, WXSH-0078, XEN-103, XRx-117, XTYW-003, XW-003, XW-004, ZGN-839, ZG-5216, ZSYM-008, ZYSM-007.

[080] In some embodiments, the compound of present application is administered in combination with one or more thereapeutic agents selected from the group consisting of anti-obesity agents, peptide YY and analogues thereof, neuropeptide Y receptor type 2 (NPYR2) agonists, NPYR1 agonists, NPYR5 antagonists, cannabinoid receptor type 1 (CB1 R) antagonists, lipase inhibitors (e.g., orlistat), human proislet peptides (HIP), melanocortin receptor 4 agonists (e.g., setmelanotide), melanin concentrating hormone receptor 1 antagonists, famesoid X receptor (FXR) agonists (e.g. obeticholic acid), apoptotic signal-regulating kinase (ASK-1) inhibitors, zonisamide, phentermine (alone or in combination with topiramate), norepinephrine/dopamine reuptake inhibitors (e.g., buproprion), opioid receptor antagonists (e.g., naltrexone), combinations of norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonists (e.g., a combination of bupropion and naltrexone), GDF-15 analogs, sibutramine, cholecystokinin agonists, amylin and analogues thereof (e.g., pramlintide), leptin and analogues thereof (e.g., metroleptin), serotonergic agents (e.g., lorcaserin), methionine aminopeptidase 2 (MetAP2) inhibitors (e.g., beloranib or ZGN-1061), phendimetrazine, diethylpropion, benzphetamine, SGLT2 inhibitors (e.g., empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, tofogliflozin, sergliflozin etabonate, remogliflozin etabonate, or ertugliflozin), SGLTL1 inhibitors, dual SGLT2/SGLT1 inhibitors, fibroblast growth factor receptor (FGFR) modulators, AMP-activated protein kinase (AMPK) activators, biotin, MAS receptor modulators, glucagon receptor agonists (alone or in combination with another GLP-1 R agonist, e.g., liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, or semaglutide), insulin sensitizers such as thiazolidinediones (TZDs), peroxisome proliferator-activated receptor alpha (PPARα) agonists, fish oil, acetyl-coA carboxylase (ACC) inhibitors, transforming growth factor beta (TGFβ) antagonists, GDNF family receptor alpha like (GFRAL) agonists, a melanocortin-4 receptor (MC4R) agonists, including the pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

EXAMPLES

Synthesis

[081] The compounds of the disclosure may be prepared using methods disclosed herein and routine modifications thereof which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds of Formula I, or a pharmaceutically acceptable salt thereof, e.g., compounds having structures described by one or more of Formula I, or other formulas or compounds disclosed herein, may be accomplished as described in the following examples.

General Syntheses

[082] Typical embodiments of compounds in accordance with the present application 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. Descriptions of syntheses follow to 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 application, inspection of the structure of the compound to be synthesized will provide the identity of each substituent group The identity of the final product will generally render apparent the identity of the necessary starting materials 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.

Synthetic Reaction Parameters

[083] The compounds of this 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. Optimum reaction conditions may vary with the

particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[084] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular 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.

[085] Furthermore, the compounds of the present application 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 enriched mixtures) are included within the scope of this disclosure, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

[086] 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 reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplemental (Elsevier Science Publishers, 1989) organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5thEdition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[087] The terms "solvent, " "inert organic solvent" or "inert solvent" refer to a solvent inert under the conditions of the reaction being described in conjunction therewith (including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), N, N-dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl

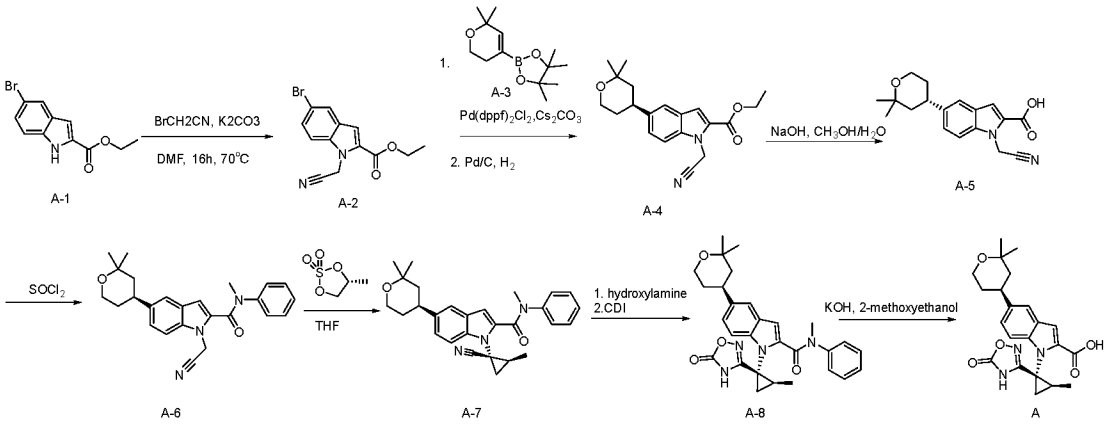
ether, methanol, pyridine and the like). Unless specified to the contrary, the solvents used in the reactions of the present application are inert organic solvents, and the reactions are carried out under an inert gas, preferably nitrogen.

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

Compounds as 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 well within the purview of one skilled in the art.

Intermediate preparation:

Preparation of intermediates A, B and C



A-1(5g, 18.65mmol), potassium carbonate (5.16g, 37.3mmol) and sodium iodide (0.28g, 1.86mmol) were dissolved in DMF(30ml), and bromoacetonitrile (3.36g, 28.0mmol) was added dropwise to the reaction solution and heated to 70℃ for 16 hours. Cooling to room temperature, adding water (60ml) to precipitate solid, and filtering to obtain brown solid 4g, with a yield of 49.0%.

A-2(2.0g, 6.51mmol), A-3(1.71g, 7.16mmol), cesium carbonate (3.18g, 9.77mmol) and Pd(dppf)2Cl2(0.5g, 0.6mmol) were dissolved in dioxane (20ml) and heated to 100 under N_2. The reaction solution was cooled, and water (30ml) and ethyl acetate (30ml) were added to extract the organic phase. The organic phase was concentrated to dryness, and then purified by column chromatography to obtain 1.2g of white solid. The obtained solid was dissolved in methanol, and Pd/C(0.12g, 30%wt.) was added to react overnight at room temperature under hydrogen. Filtering, collecting filtrate, and concentrating to dryness. The obtained solid was

prepared by manual preparation of liquid phase (with short retention time) to obtain A-4, 0.6g, with a yield of 27.3%.

A-4(0.6g, 1.76mmol) was dissolved in methanol/water (4ml/2ml), and sodium hydroxide (0.28g, 7.05mmol) was added to react at room temperature for 4 hours. Adjust the pH to 5.0 with dilute hydrochloric acid, add ethyl acetate (5ml) to extract the organic phase, and concentrate under reduced pressure to get solid A-5, 0.53g, with a yield of 96.3%.

A-5(300mg, 1.1mmol) was dissolved in dichloromethane (10ml), thionyl dichloride (520mg, 4.4mmol) and 1 drop of DMF were added and reacted at room temperature for 6 hours. Concentrate the reaction solution to dryness to obtain acyl chloride oil, and add 5ml of dichloromethane to dissolve it for use. N- methylaniline (180mg, 1.65mmol) and triethylamine (222mg, 2.2mmol) were dissolved in dichloromethane (10ml), and the solution of acyl chloride was added dropwise under ice bath, and the reaction continued for 1 hour at room temperature. Add water (10ml) to extract the organic phase, and concentrate it under reduced pressure to dryness to obtain A-6, 350 mg, 87.9%.

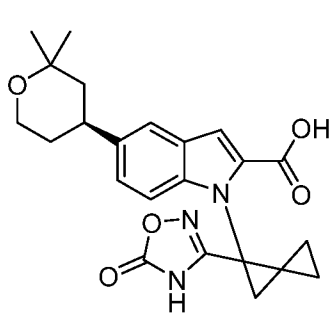
A-6(100mg, 0.25mmol), (4R)-4- methyl -1, 3, 2- dioxolane 2, 2- dioxide (103.6g, 0.75mmol) was dissolved in THF(5ml). Cooling to -20℃, dropwise adding lithium bis (trimethylsilylamine) (1ml, 1M in THF), and reacting at room temperature for 24 hours. Slowly add water (5ml) to quench the reaction, add 10ml of ethyl acetate, extract the organic phase, concentrate it under reduced pressure to dryness to obtain an oil, and then purify it by column chromatography to obtain A-7, 40 40mg with a yield of 36.4%.

A-7(10mg, 0.023mmol) was dissolved in DMSO(2ml), and hydroxylamine aqueous solution (0.6ml, 50%) was added to react at room temperature for 16 hours. Water (10ml) and ethyl acetate (10ml) were added for extraction, and the organic phase was dried and concentrated to dryness to obtain an oil. Dissolve the oil in DMSO (3ml), add CDI(10mg, 0.062mmol) and DBU(10mg, 0.066mmol) and react at room temperature for 6 hours. Water (10ml) and ethyl acetate (10ml) were added for extraction, and the organic phase was dried and concentrated to obtain A-8, 10 mg, with a yield of 88.2%.

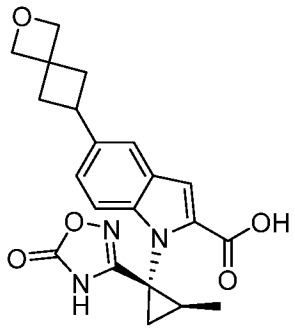
A-8(220mg, 0.44mmol) was dissolved in ethylene glycol methyl ether (3ml), potassium hydroxide (494mg, 8.8mmol) was added, and the reaction was heated to 130℃ for 5 hours. Cooling to room temperature, adjusting pH to 5.0 with hydrochloric acid (6N), adding ethyl

acetate (10ml) for extraction, drying the organic phase with anhydrous sodium sulfate, and concentrating under reduced pressure to obtain intermediate A, 180mg, with a yield of 99.0%.

Intermediate B and C were prepared by the same method:

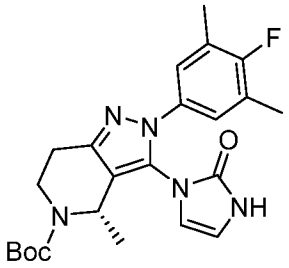


B

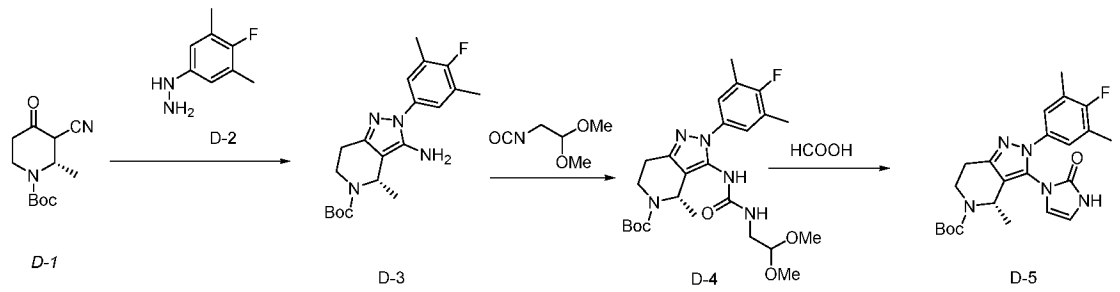


C

Preparation of intermediate D



D



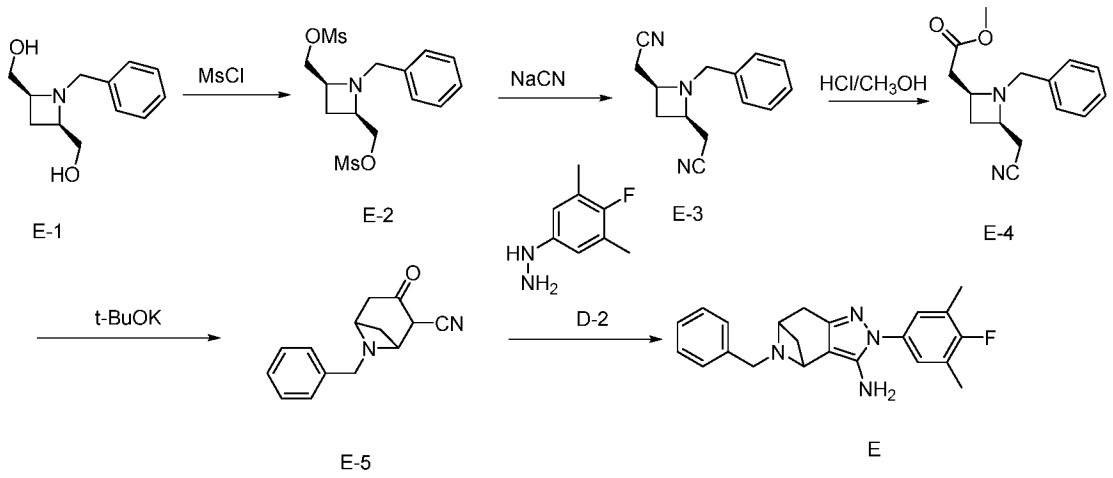
D-1(2.0g, 8.4mmol), D-2(1.29g, 8.4mmol) and pyridine hydrochloride (0.97g, 8.4mmol) were dissolved in toluene (10ml) and heated to reflux for 1 hour. After cooling the reaction solution, water (10ml) and ethyl acetate (10ml) were added to extract the organic phase, and the target compound D-3, 2.4g, was obtained by vacuum concentration with a yield of 76.4%.

D-3(2.0g, 5.34mmol) was dissolved in DCM (20ml), and a dichloromethane (5ml) solution of 2- isocyanate -1, 1- dimethoxyethane (0.84g, 6.41mmol) was added dropwise at room temperature, and the mixture was stirred at room temperature for 2 hours. Add water (20ml),

extract, separate the organic phase, and reduce the pressure to dryness to obtain oil, which can be directly reacted in the next step.

Under ice bath, the oil of D-4 was dissolved in dichloromethane (20ml), then added to formic acid (10ml), and stirred overnight at room temperature. Add 20ml of water, extract to separate out the organic phase, reduce the pressure to dryness to obtain a crude product, and then pulping with ethyl acetate and n-heptane to obtain D-5, 1.2g.

Preparation of intermediates E and F;



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

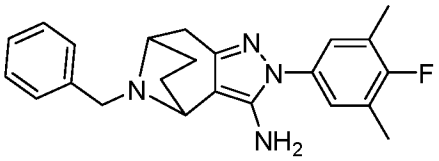
E-2(3.0g, 8.25mmol) was dissolved in EMF (30ml), then NaCN(850mg, 17.3mmol) was slowly added and reacted at 60℃ for 1h. After cooling, sodium hypochlorite saturated solution (30ml) was added and stirred for 1 hour. Ethyl acetate (30ml) was added, and the organic phase was extracted and concentrated to obtain E-3, 1.54g, with a yield of 82.8%.

E-3(1.2g, 5.33mmol) was dissolved in methanol solution of hydrogen chloride (1M, 7ml) and stirred overnight at room temperature, followed by adding water and stirring for 2h. Ethyl acetate (20ml) was added, and the organic phase was separated by extraction. After vacuum evaporation, an oil was obtained, and then E-4, 0.6g, was purified by column chromatography with a yield of 43.6%.

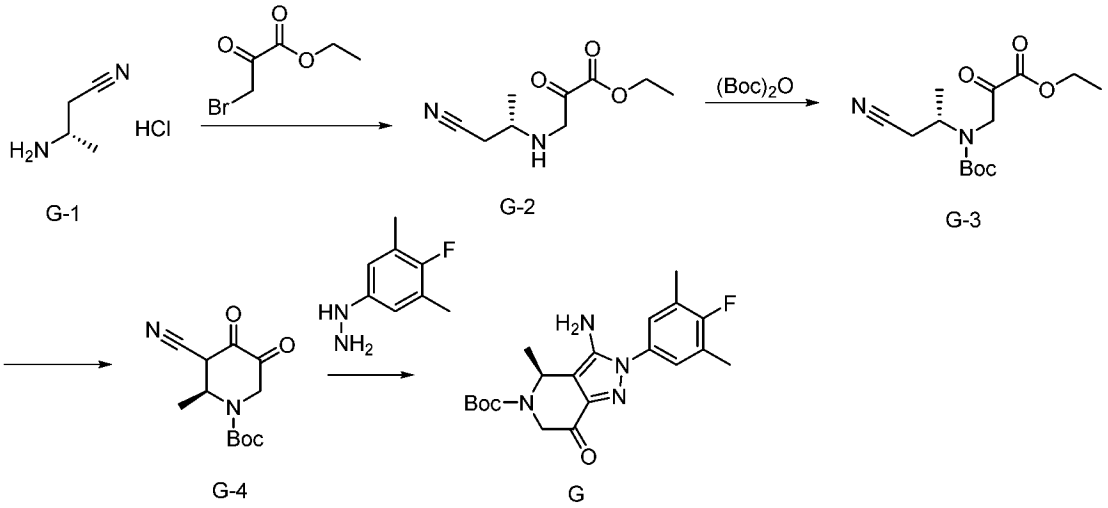
E-4(0.5g, 1.9mmol) was dissolved in THF(5ml), and potassium tert-butoxide (1.09g, 9.7mmol) was added to react overnight at room temperature. Adjust the pH to neutrality with dilute hydrochloric acid, add ethyl acetate for extraction, evaporate under reduced pressure, and then get E-5, 0.34g by column chromatography with a yield of 68%.

E-5(0.2g, 0.88mmol), D-2(126mg, 0.88mmol) and pyridine hydrochloride (0.1g, 0.88mmol) were dissolved in toluene (4ml) and heated to reflux for 1 hour. After cooling the reaction solution, water (10ml) and ethyl acetate (10ml) were added to extract the organic phase, and the target compound E, 260mg, was obtained by vacuum concentration with a yield of 81.2%.

Intermediate F was prepared by the same method:



Preparation of intermediate G:



G-1(5.0g, 41.5mmol), ethyl 3- bromopyruvate (8.90g, 45.61mmol) and cesium carbonate (20.3g, 62.2mmol) were dissolved in DMF(100ml), heated to 65°C and reacted for 4 hours. Cooling to room temperature, adding 200ml of water, precipitating solid, and filtering to obtain G-2, 4.80g, with a yield of 58.4%.

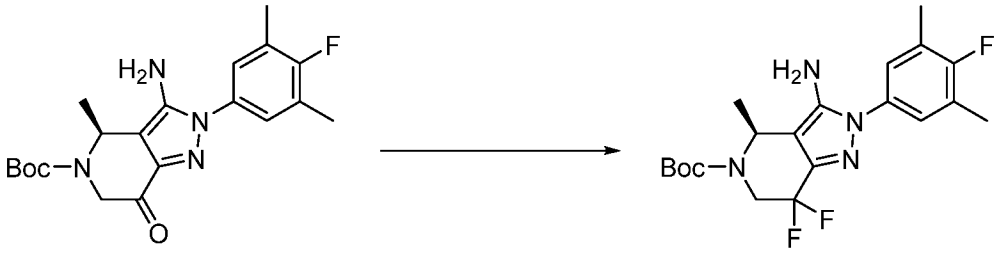
G-2(4.0g, 20.2mmol), (Boc)2O(6.6g, 30.3mmol) and triethylamine (6.13g, 60.5mmol) were dissolved in THF(40ml) and stirred overnight at room temperature. Adding water (50ml)

and ethyl acetate (50ml), extracting to separate out the organic phase, and then concentrating under reduced pressure to obtain G-3, 5.6g and 93.2%.

G-3(5.6g, 18.8mmol) was dissolved in THF(50ml), and potassium tert-butoxide (10.5g, 94mmol) was added to react overnight at room temperature. Adjust pH to neutrality with dilute hydrochloric acid, add ethyl acetate for extraction, evaporate under reduced pressure, and then prepare G-4, 3.6g by column chromatography with a yield of 76%.

G-4(2.0g, 7.93mmol), D-2(1.22g, 7.93mmol) and pyridine hydrochloride (0.9g, 7.93mmol) were dissolved in toluene (40ml) and heated to reflux for 1 hour. After cooling the reaction solution, water (40ml) and ethyl acetate (40ml) were added to extract the organic phase, and the target compound G, 1.2g, was obtained by vacuum concentration with a yield of 39%.

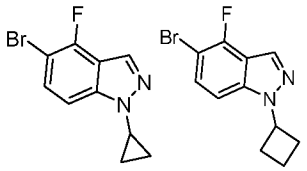
Preparation of intermediate H:



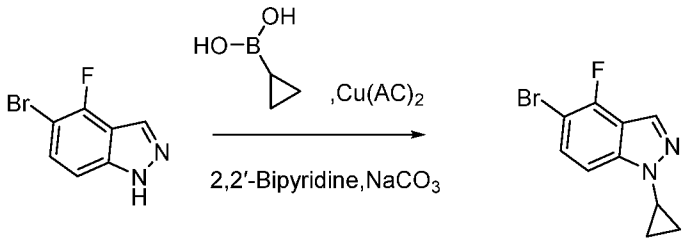
G H

Compound G (200mg, 0.52mmo) was dissolved in DCM(2ml), and DAST(165mg, 1.0mmol) was added under ice bath, and stirred at 0°C overnight. Adding saturated sodium bicarbonate solution (4ml) and DCM(4ml), extracting, separating organic phase, vacuum drying, and purifying by column chromatography to obtain compound H, 0.12g, with a yield of 56.8%.

Preparation of intermediates I and J;



I J

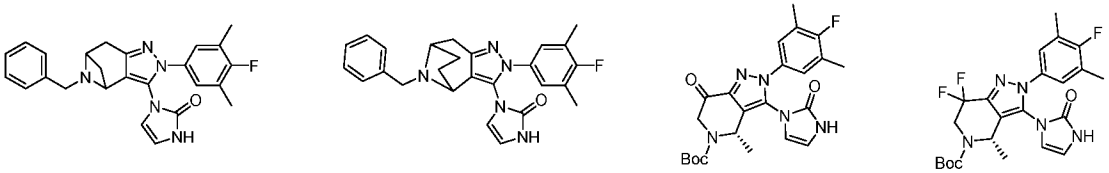


I-1 I

Compound I-1(50ml, 23.3mmol), cyclopropylboronic acid (3.99g, 46.5mmol), copper acetate (3.48g, 23.2mmol), 2 , 2' bipyridine (3.9g, 23.3mmol) and sodium carbonate (4.9g, 46.5mmol) were added to dichloroethane. The reaction solution was filtered, the filtrate was extracted with water and dichloromethane, and the organic phase was separated. The organic phase was decompressed to dryness, and then purified by column chromatography to obtain I, 3.6g, with a yield of 61%.

Intermediate j can be obtained by the same method.

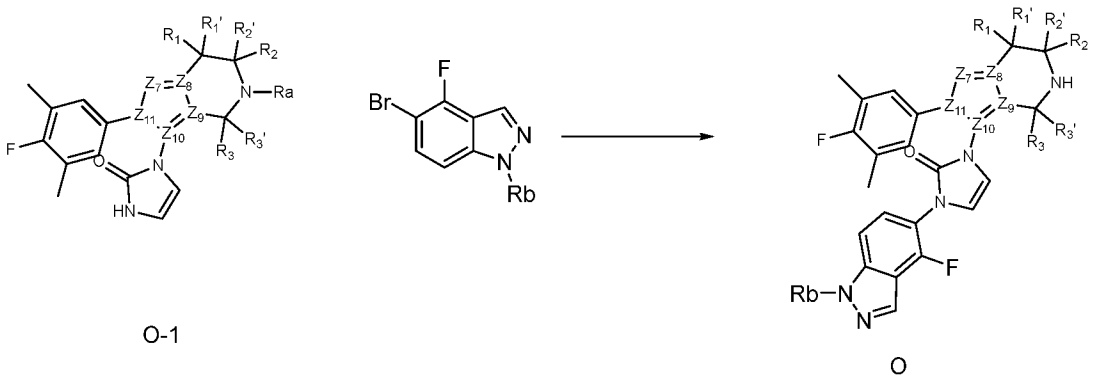
Preparation of intermediates K, L, M and N



K L M N

According to the preparation method of intermediate D, K, L, M and N can be obtained.

Preparation of intermediate O



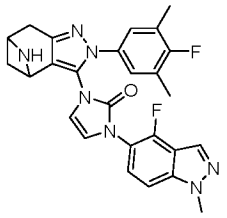
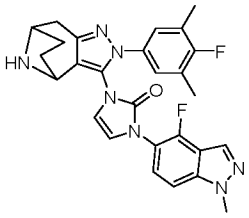
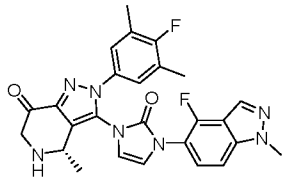
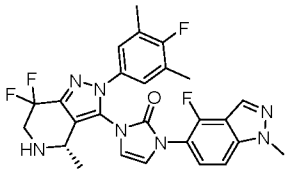
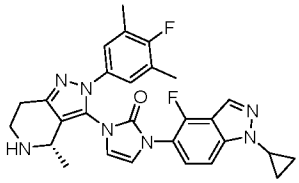
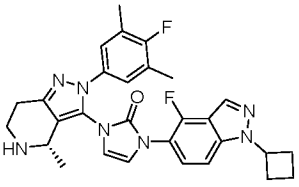
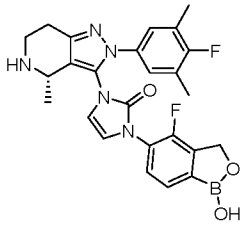
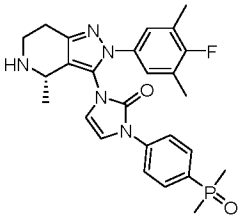
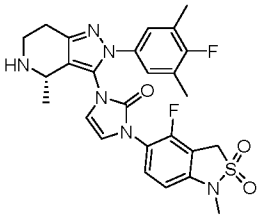
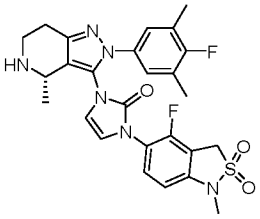
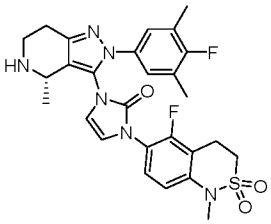
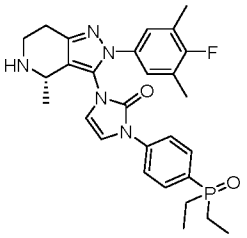
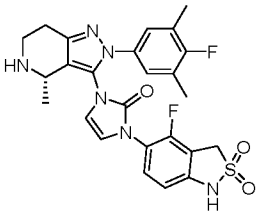
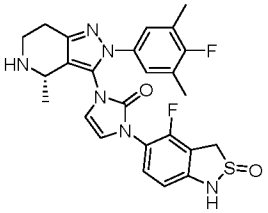
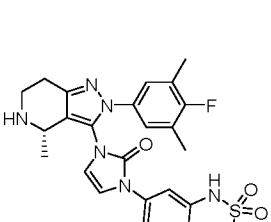
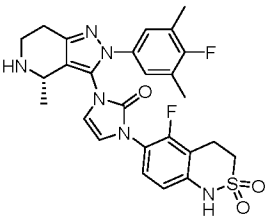
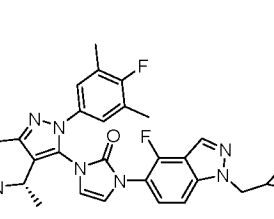
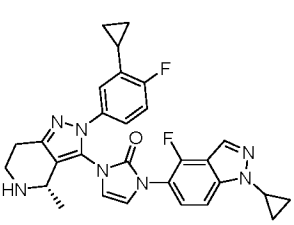
O-1 O

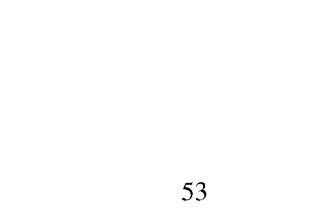
O-1(1eq.) and (1R, 2R)-(-)-N, N'- dimethyl -1, 2- cyclohexanediamine (0.5eq.), CuI(0.5eq.), bromide (1.5eq.) and potassium carbonate (3eq.) were added to NMP. Filtering, adding water

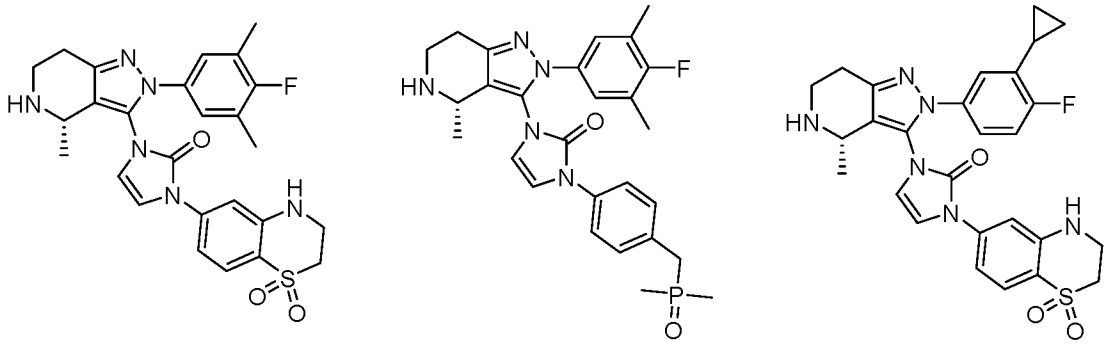
Conjupro EX1025
Page 58 of 106

and ethyl acetate to the filtrate, extracting to separate out the organic phase, depressurizing, purifying, and deprotecting (debenzylation or Boc removal) to obtain the target compound.

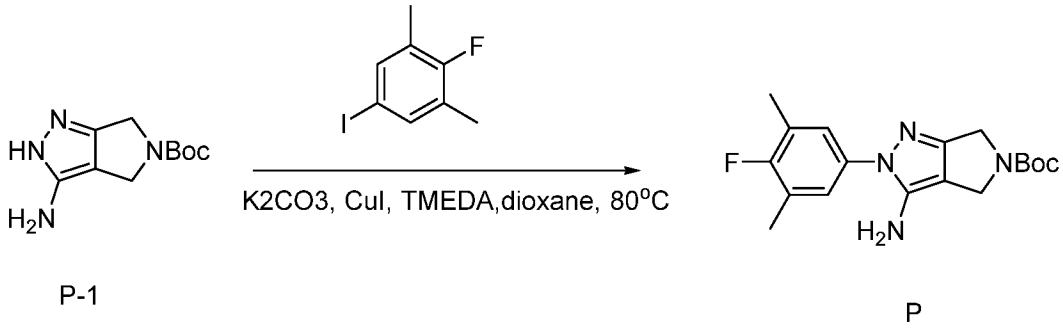
The following compounds can be prepared by this method:



Preparation of intermediate P:

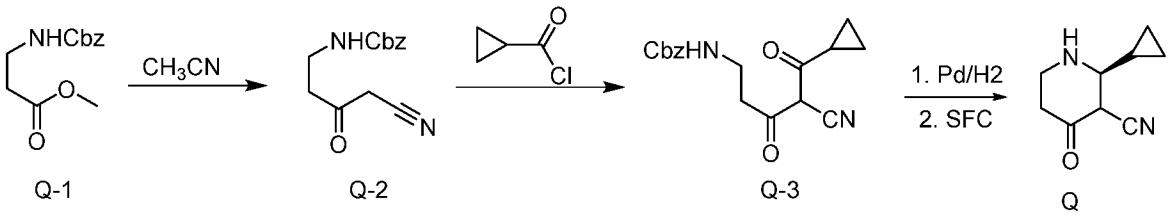


P-1

P

P-1(1.0g, 4.46mmol), 2- fluoro -5- iodo -1.3- xylene (1.12g, 4.46mmol), CuI(0.8g, 4.46mmol), TMEDA(0.52g, 4.46mmol) and potassium carbonate (0.92g, 6.69mmol) were added. After cooling, filtering, removing filtrate, adding ethyl acetate (20ml) and water (20ml), extracting to separate organic phase, concentrating under reduced pressure, and purifying by column chromatography to obtain P, 0.6g, with a yield of 38.8%.

Preparation of intermediate Q:



Q-1 Q-2 Q-3 Q

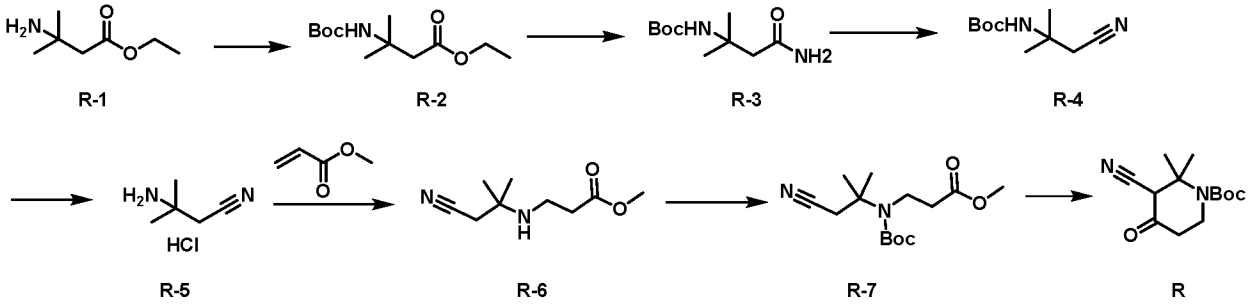
To a solution of acetonitrile (15.57 g, 379.34 mmol, Purity 100 %) in Tetrahydrofuran (300 mL) at -78°C under N_2 was added dropwise Lithium bis(trimethylsilyl)amide (63.47 g, 379.34 mmol), and then the mixture was stirred for 1h at -78°C. A solution of Q1 (45.0 g, 189.67 mmol) in 5ml THF was added dropwise. The resulting mixture was allowed to warm to -50°C over 30min. The reaction mixture was quenched with 100ml Saturated NH4Cl(aq.) and extracted with 150ml EA, and separated organic layer was washed with brine, dried over $MgSO_4$,

concentrated under reduced pressure and purified by silica gel column chromatography (PE / EtOAc =0%-50%) to give yellow oil.

To a solution of benzyl N-(4-cyano-3-oxobutyl)carbamate (246.26 mg, 1 mmol) and Triethylamine (202.38 mg, 2 mmol) in dichloromethane (10 mL), was added dropwise cyclopropanecarbonyl chloride (209.06 mg, 2 mmol), and then the mixture was stirred for overnight at r.t. The reaction mixture was quenched with 10ml water and extracted with 10ml dichloromethane, and separated organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by silica gel column chromatography (PE / EtOAc =0%-50%) to give an oil.

Q-3(150mg, 0.47mmol) and Pd/C (15mg, 30%wt) was dissolved into MeOH(15ml), and stirred 3 hours under H_2. The mixture was filtrated and concentrated under reduced pressure and purified by SFC to get the title compound, 32mg, yield: 40.8%. ^{1}HNMR(d-DMSO， 500MHZ): δ4.12(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:



To a solution of **R-1**(10.0g, 68.87mmol) and Triethylamine (13.9g , 138 mmol) in dichloromethane (100 mL), was added $(Boc)_2O$(18.0g, 82.64mmol), and then the mixture was stirred for overnight at r.t. The reaction mixture was quenched with 100ml water and extracted with 100ml dichloromethane, and separated organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure to get **R-2**, 15.3g, yield: 90.56%.

R-2(15.0g, 61.1mmol) was dissolved in NH_3/CH_3OH(10M, 300ml), and stirred for 4hours in a autoclave at 90~100°C. After cooling, the mixture was concentrated under reduced pressure to get a crude **R-3**, without purification for next step reaction.

R-3, TFAA (6.90ml, 49.5mml) and pyridine(8.0ml, 99.0mmol) was added into a three-neck bottle, and stirred at room temperature for 1 h. The reaction was quenched with H_2O (100 mL) and extracted with EtOAc. The organic layers were washed with brine (100 mL), dried over

Na_2SO_4, concentrated in vacuo and purified by flash chromatography (PE / EtOAc = 20 / 1) to afford **R-4**, 5.3g.

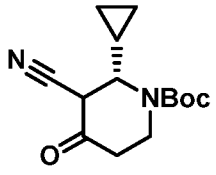
R-4 (5.3g, 26.7mmol) was dissolved in HCl/EtOAc(4M, 30ml), and stirred 2 hour at r.t. A solid was Precipitated and filtrated to afford **R-5**, 3.2g, 88.9%.

To a solution of **R-5**(3.2g, 23.7mmol) in EtOH(20ml), was added Et_3N(7.22g, 71.3mmol) and methyl acrylate(2.15g, 24.9mmol),) at room temperature. After stirred at 70°C for 3 h, the reaction mixture was cooled to room temperature and $(Boc)_2O$ (6.74g, 30.9mmol) was added. The solution was stirred at room temperature overnight and then diluted with H_2O (50 mL). The mixture was extracted with EtOAc. The organic layers were washed with brine (50 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (PE / EtOAc = 10 / 1) to afford **R-7**, 4.3g, yield: 63.6%.

To a solution of **R-7** (4.0g, 14.1mmol) in THF(50 mL) was added t-BuOK (2.37 g, 21.1mmol). The mixture was stirred at room temperature for 1 h and then quenched with 2N HCl solution. The mixture was diluted with H2O (50 mL) and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by flash chromatography to afford **R**, 2.5g, yield: 70.4%.

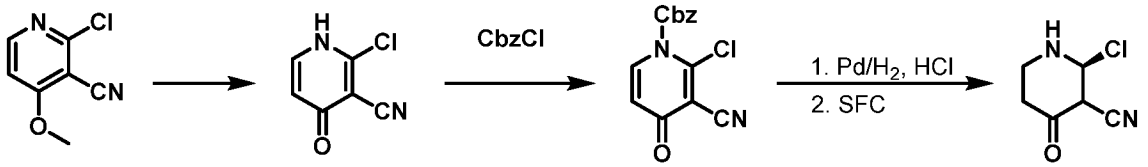
Preparation of intermediate S:

Following the synthetic route of intermediate R, the intermediate S was obtained by another SFC enantioseparation.



S

Preparation of intermediate T:



T-1 **T-2** **T-3** **T**

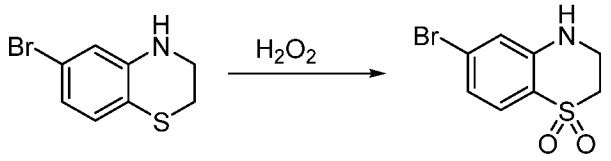
To a solution of **T-1**(10.0g, 59.3mmol) in THF(100ml), was added Boron tribromide (120ml, 1M in DCM), and stirred 3 hours at r.t. The mixture quenched with Na2CO3(aq.) and

extracted with DCM. The organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo to afford **T-2**, 8.5g, yield: 92.7%.

To a solution of **T-2**(8.0g, 51.8mmol) in DCM, was added Et_3N(7.8g, 77.6mmol). The mixture was cooled to 0 °C， and was dropwise added Cbz-Cl(9.71g, 56.9mmol). After stirred 2 hours, the mixture quenched with Na2CO3(aq.) and extracted with DCM. The organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo to afford **T-3**, 11.2g, yield: 74.9%.

A solution of **T-3** (10.0g, 34.6mmol), Pd/C(1.0g, 30%wt) and 0.5ml HCl(1M in H_2O) in MeOH 150ml saturated with H2 was stirred under 50 Psi at r.t. for 2 hours. The mixture was filtrated and concentrated in vacuo, then dissolved into DCM and washed by NaHCO3(aq) and brine. The organic layers were dried over Na_2SO_4, concentrated in vacuo and purified by flash chromatography to afford a racemate. Then the racemate was purified by SFC to afford **T**, 1.2g, yield: 21.8%.

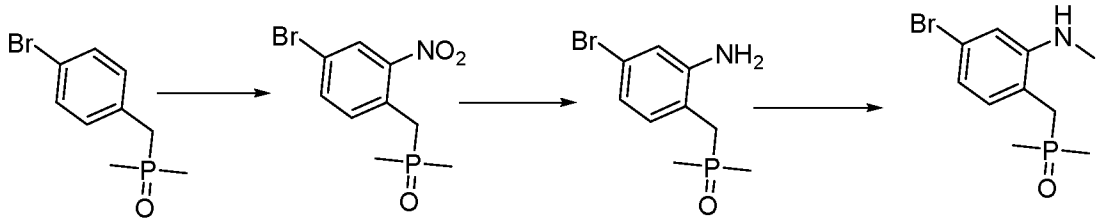
Preparation of intermediate AA:



AA-1 AA

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

Preparation of intermediate AB:



AB-1 AB-2 AB-3 AB

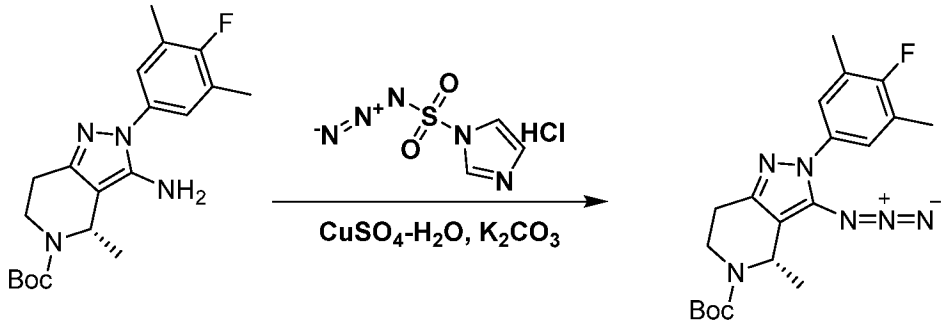
AB-1 (5.0 g, 20.2 mmol) was dissolved in 25 ml of concentrated sulfuric acid at -20 °C. Potassium nitrate (2.1 g, 20.2 mmol) was added in batches and the reaction was held for 4 hours.

The reaction solution was poured into ice water and a solid was precipitated. The solid was dried and then prepared by column chromatography to obtain AB-2 0.7g, yield: 11%.

AB-2 (0.7g, 2.4mmol) was dissolved in methanol (5ml), saturated ammonium chloride (5ml) was added, iron powder (0.54g, 9.6mmol) was added, and the reaction was heated to 80°C for 3 hours. Cooled to room temperature, added ethyl acetate 20ml, extracted to produce AB-3, 0.54g, yield: 86%.

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

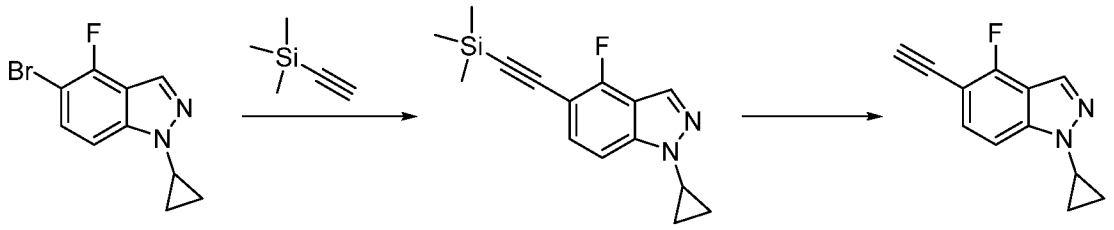
Preparation of intermediate AC:



D-3 AC

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, followed by the addition of copper sulfate hydrate (1.9 mg, 0.0077 mmol) and the reaction was allowed to run for 12 h at room temperature. The reaction solution was extracted with ethyl acetate and water. The organic phase was washed with 1N hydrochloric acid, saturated sodium bicarbonate, and brine, respectively, and then dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to obtain AC as an oil, 0.15 g, 48%.

Preparation of intermediate AD:

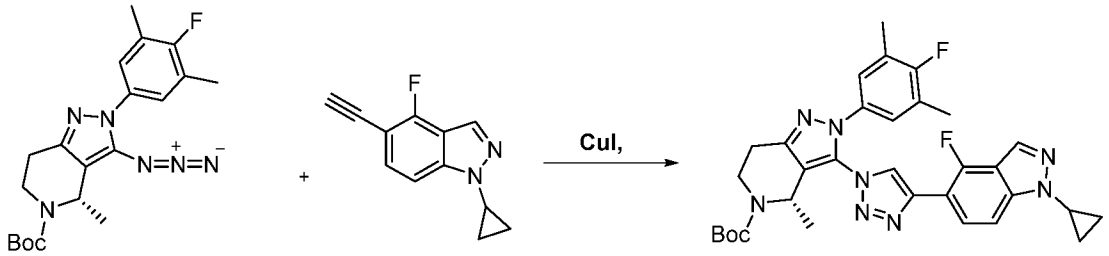


AD-1 AD-2 AD

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 palladium tetrakis(triphenylphosphine) (900 mg, 0.8 mmol) were added to dioxane (20 ml) and heated under nitrogen protection to 70 C. The reaction was carried out overnight. Cooled to room temperature, added water and ethyl acetate, extracted, concentrated and then purified by column chromatography to produce AD-2, 1.1 g, yield: 51.5%.

AD-2 (1.1g, 4.0mmol) was added to methanol, potassium carbonate (1.1g, 8.1mmol) was added, stirred at room temperature for 4 hours. Add water and ethyl acetate extraction, the organic phase was concentrated to dry, and then purified by column chromatography to obtain AD, 0.35g, yield: 43.3%.

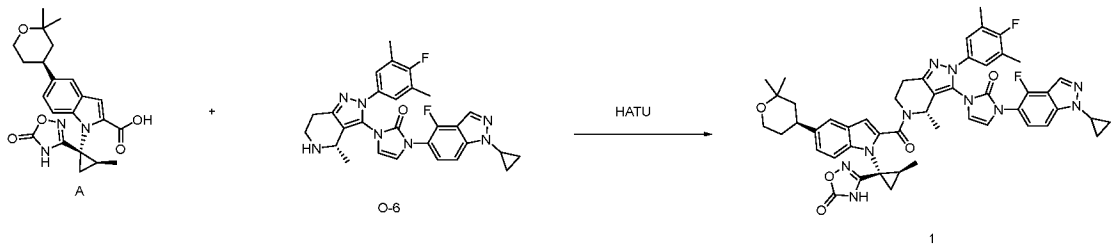
Preparation of intermediate AE



AC AD AE

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

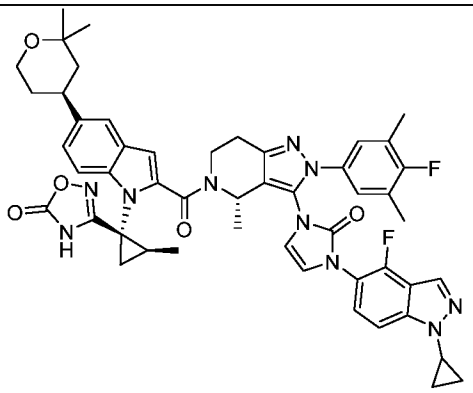
Preparation of compound 1

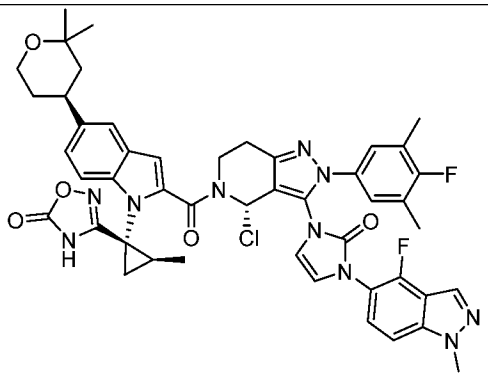
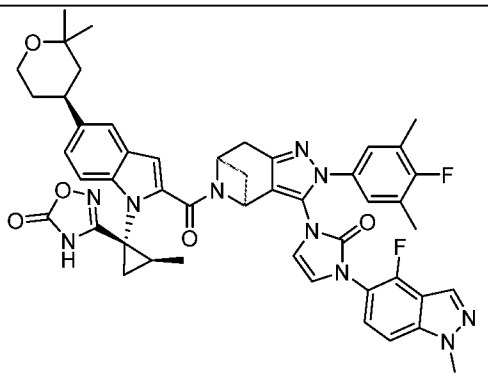


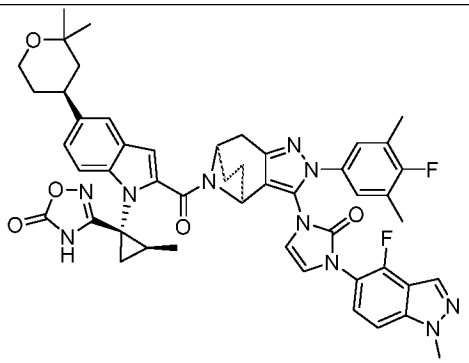
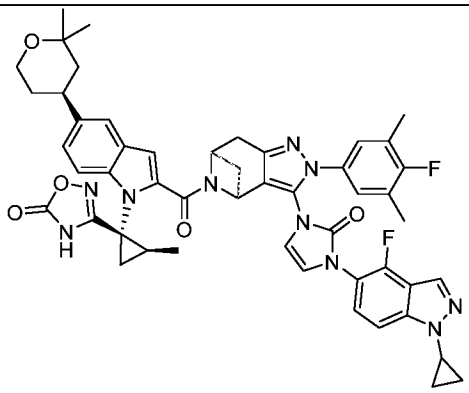
A　　O-6　　1

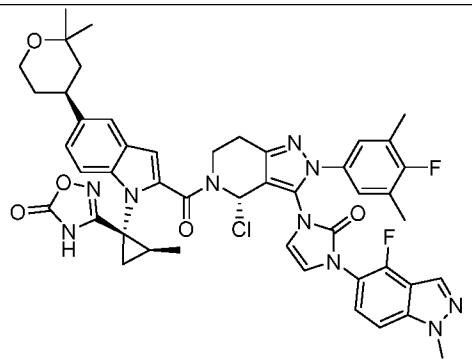
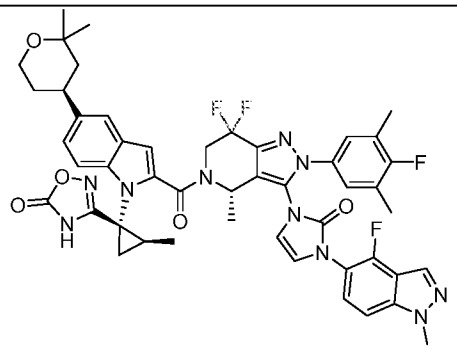
Intermediate A(180mg, 0.44mmol), O-6(280mg, 0.57mmol), HATU(250.95mg, 0.66mmol) and DIPEA(170mg, 1.32mmol) were dissolved in DMF(5ml) and stirred at room temperature for 3 hours. Add 5ml of water, extract with dichloromethane for 3 times, and combine the organic phases. Concentrated under reduced pressure, and purified by preparative liquid phase (acetonitrile: 0.1% formic acid aqueous solution), 1, 200 mg of the target compound was obtained with a yield of 51%.

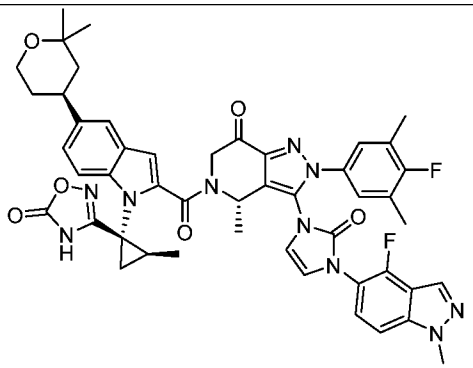
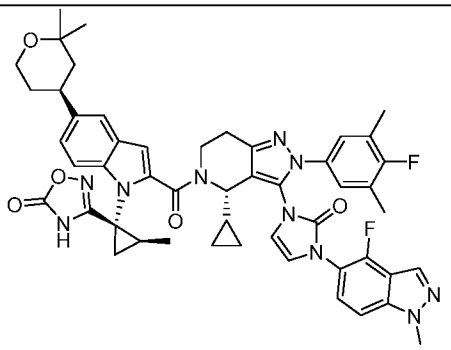
According to the preparation method described in this paper, the following compounds were prepared by using appropriate starting materials and intermediates and, if necessary, appropriate protective group chemistry. The structures were confirmed by MS and *1H*NMR.

序号	结构	MS	^{1}*H*NMR
1		909.39	^{1}H 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), 4.57 – 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).

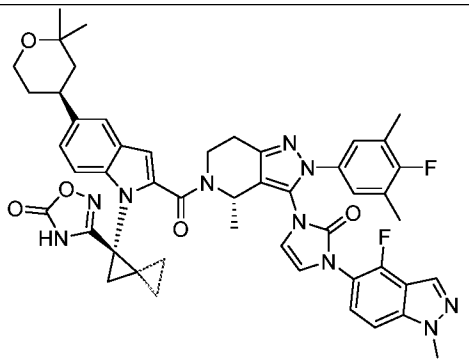
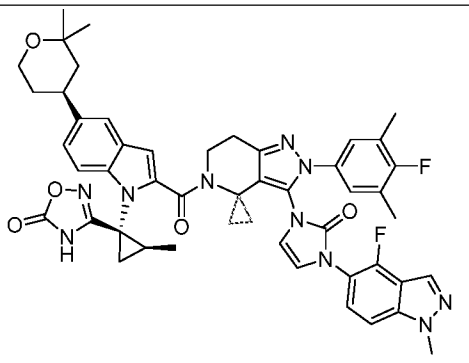
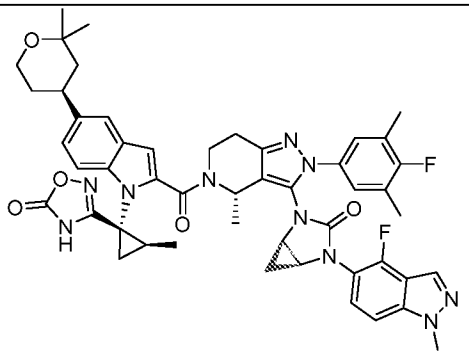
2		923.41	^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.79 (s, 1H), 8.38 – 8.28 (m, 2H), 8.18 (d, *J* = 6.0 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.63 – 7.57 (m, 1H), 7.52 – 7.40 (m, 4H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.12 – 7.04 (m, 1H), 5.23 – 5.13 (m, 1H), 4.53 – 4.47 (m, 1H), 4.14 – 4.05 (m, 1H), 3.86 – 3.78 (m, 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, *J* = 7.8 Hz, 3H), 1.24 (s, 3H), 1.19 (s, 3H), 1.00 (d, *J* = 6.0 Hz, 3H).
3		881.36	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.36 – 8.27 (m, 2H), 8.14 (d, *J* = 4.9 Hz, 1H), 7.83 – 7.75 (m, 1H), 7.67 – 7.63 (m, 1H), 7.54 (d, *J* = 8.9 Hz, 1H), 7.47 – 7.36 (m, 3H), 7.25 (d, *J* = 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, *J* = 5.9 Hz, 3H).

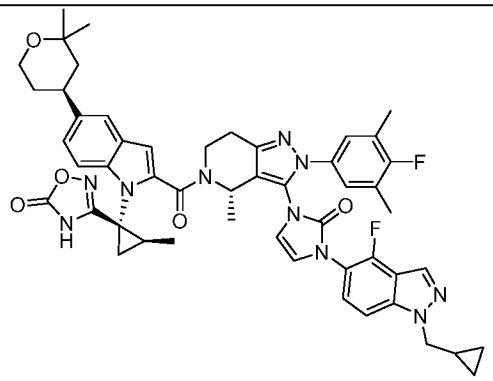
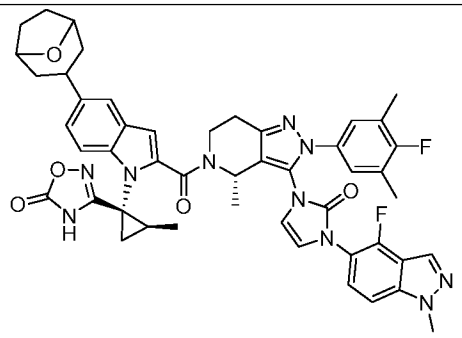
4		895.38	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.36 – 8.28 (m, 2H), 8.14 (d, J = 4.9 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.67 – 7.62 (m, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.25 (d, J = 2.0 Hz, 1H), 7.10 – 7.04 (m, 1H), 5.07 – 5.00 (m, 1H), 4.55 – 4.46 (m, 1H), 3.93 (s, 3H), 3.71 – 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, J = 6.0 Hz, 3H).
5		907.38	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.39 – 8.29 (m, 3H), 7.94 – 7.88 (m, 1H), 7.68 – 7.58 (m, 2H), 7.46 – 7.38 (m, 3H), 7.25 (d, J = 2.0 Hz, 1H), 7.09 – 7.05 (m, 1H), 5.63 – 5.57 (m, 1H), 4.70 – 4.63 (m, 1H), 4.56 – 4.50 (m, 1H), 3.74 – 3.59 (m, 2H), 3.10 – 3.03 (m, 1H), 3.02 – 2.94 (m, 2H), 2.67 – 2.60 (m, 1H), 2.49 – 2.39 (m, 2H), 2.36 – 2.30 (m, 1H), 2.27 – 2.17 (m, 7H), 2.08 – 2.01 (m, 1H), 1.97 – 1.92 (m, 1H), 1.86 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.39 – 1.29 (m, 2H), 1.29 – 1.20 (m, 5H), 1.18 (s, 3H), 0.99 (d, J = 6.0 Hz, 3H).

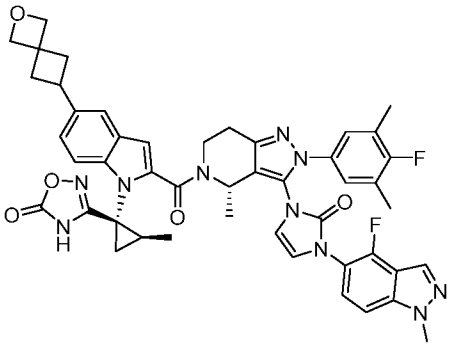
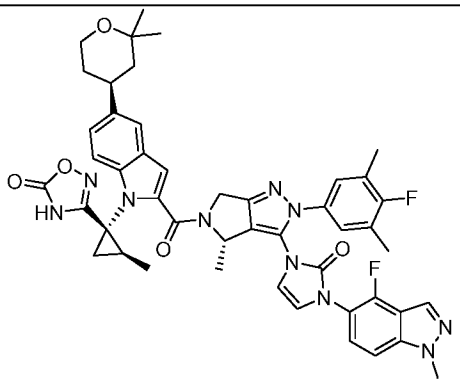
6		903.32	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.38 – 8.28 (m, 2H), 8.14 (d, J = 4.9 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.68 – 7.63 (m, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, J = 2.0 Hz, 1H), 7.10 – 7.04 (m, 1H), 6.94 (s, 1H), 4.33 – 4.25 (m, 1H), 4.09 – 4.03 (m, 1H), 3.93 (s, 3H), 3.74 – 3.67 (m, 1H), 3.66 – 3.58 (m, 1H), 3.07 – 2.94 (m, 3H), 2.49 – 2.41 (m, 1H), 2.38 – 2.28 (m, 2H), 2.24 (s, 6H), 2.07 – 2.00 (m, 1H), 1.99 – 1.91 (m, 1H), 1.87 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, J = 6.0 Hz, 3H).
7		919.36	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.39 – 8.28 (m, 2H), 8.14 (d, J = 4.9 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.68 – 7.64 (m, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.21 (d, J = 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, J = 7.5 Hz, 3H), 1.25 – 1.15 (m, 6H), 0.99 (d, J = 6.0 Hz, 3H).

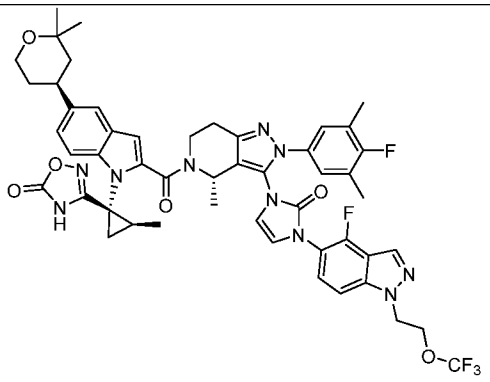
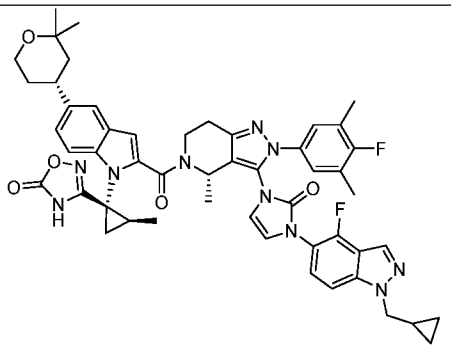
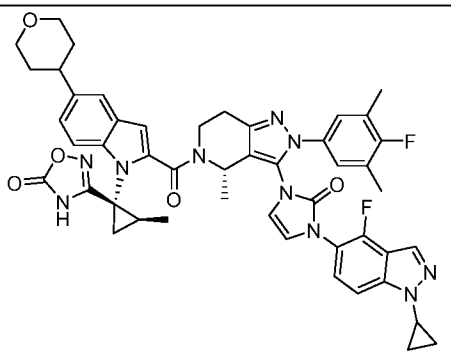
8		897.36	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.36 – 8.29 (m, 2H), 8.17 – 8.11 (m, 1H), 7.83 – 7.75 (m, 1H), 7.68 – 7.63 (m, 1H), 7.57 – 7.51 (m, 1H), 7.47 – 7.40 (m, 3H), 7.21 (d, J = 2.0 Hz, 1H), 7.10 – 7.03 (m, 1H), 5.11 – 4.96 (m, 3H), 3.93 (s, 3H), 3.74 – 3.58 (m, 2H), 3.02 – 2.95 (m, 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, J = 7.8 Hz, 3H), 1.27 – 1.15 (m, 6H), 0.99 (d, J = 6.0 Hz, 3H).
9		895.38	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.36 – 8.29 (m, 2H), 8.14 (d, J = 4.9 Hz, 1H), 7.83 – 7.76 (m, 1H), 7.68 – 7.63 (m, 1H), 7.57 – 7.51 (m, 1H), 7.48 – 7.37 (m, 3H), 7.21 (d, J = 2.0 Hz, 1H), 7.11 – 7.04 (m, 1H), 4.89 (d, J = 6.7 Hz, 1H), 4.18 – 4.08 (m, 1H), 3.93 (s, 3H), 3.87 – 3.79 (m, 1H), 3.75 – 3.58 (m, 2H), 3.05 – 2.88 (m, 3H), 2.51 – 2.44 (m, 1H), 2.37 – 2.29 (m, 2H), 2.24 (s, 6H), 2.08 – 2.00 (m, 1H), 1.98 – 1.89 (m, 2H), 1.87 – 1.78 (m, 1H), 1.75 – 1.69 (m, 1H), 1.25 – 1.15 (m, 6H), 0.99 (d, J = 6.0 Hz, 3H), 0.68 – 0.57 (m, 2H), 0.49 – 0.39 (m, 2H).

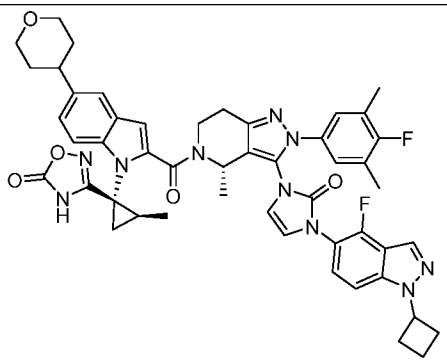
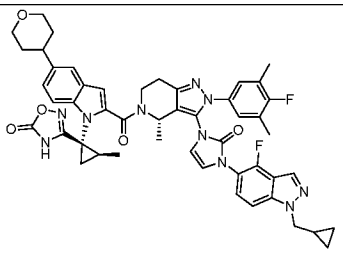
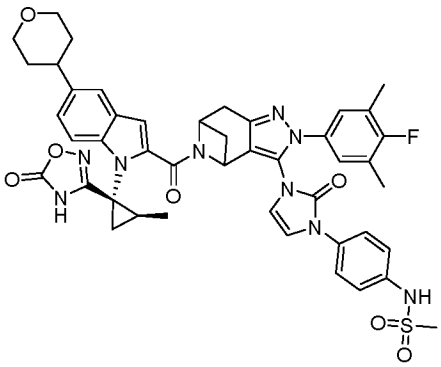
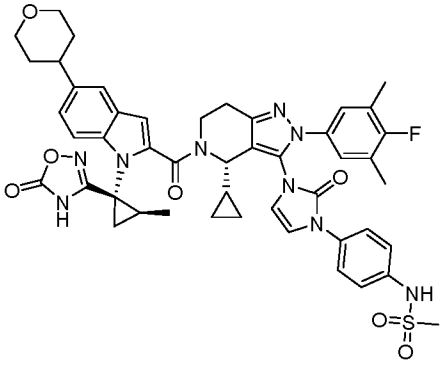
Conjupro EX1025
Page 71 of 106

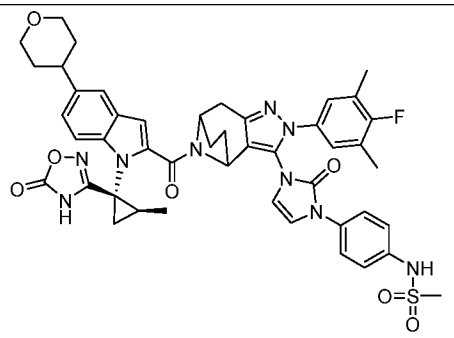
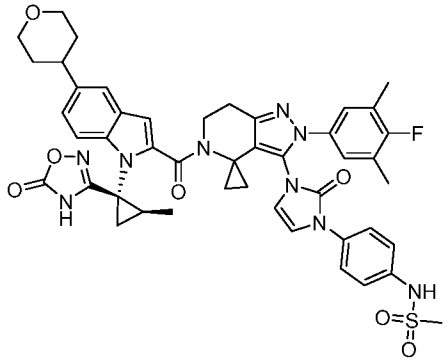
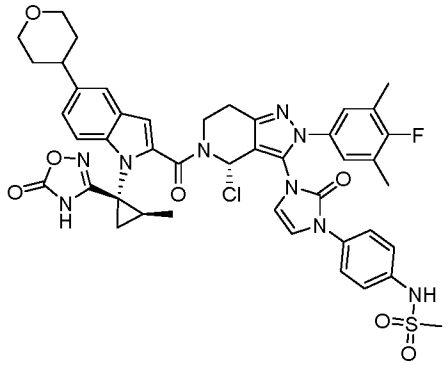
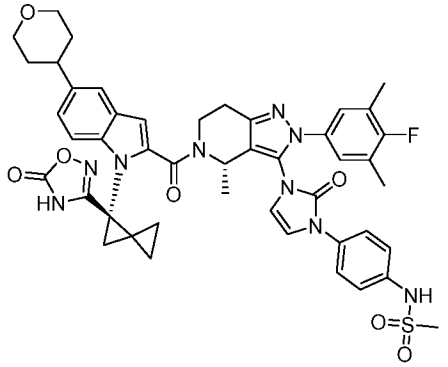
10		895.38	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.36 – 8.29 (m, 2H), 8.14 (d, J = 4.9 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.67 – 7.64 (m, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, J = 2.0 Hz, 1H), 7.10 – 7.04 (m, 1H), 5.22 – 5.14 (m, 1H), 4.11 – 4.05 (m, 1H), 3.96 – 3.85 (m, 4H), 3.74 – 3.58 (m, 2H), 3.04 – 2.90 (m, 3H), 2.35 (s, 2H), 2.24 (s, 6H), 2.07 – 1.91 (m, 2H), 1.86 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.65 – 1.47 (m, 7H), 1.25 – 1.16 (m, 6H).
11		895.38	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.34 – 8.23 (m, 2H), 8.14 (d, J = 4.9 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.67 – 7.63 (m, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.24 (d, J = 2.0 Hz, 1H), 7.11 – 7.04 (m, 1H), 3.96 – 3.83 (m, 5H), 3.74 – 3.59 (m, 2H), 3.01 – 2.95 (m, 1H), 2.91 – 2.84 (m, 2H), 2.51 – 2.44 (m, 1H), 2.37 – 2.19 (m, 12H), 2.07 – 2.00 (m, 1H), 1.97 – 1.92 (m, 1H), 1.87 – 1.79 (m, 1H), 1.75 – 1.69 (m, 1H), 1.26 – 1.16 (m, 6H), 0.99 (d, J = 6.0 Hz, 3H).
12		898.00	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.13 (d, J = 5.2 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.53 (d, J = 9.0 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.37 (d, J = 4.9 Hz, 2H), 7.21 (d, J = 2.0 Hz, 1H), 7.10 – 7.05 (m, 1H), 5.22 – 5.11 (m, 1H), 4.34 – 4.29 (m, 2H), 4.10 – 4.03

			(m, 1H), 3.96 – 3.87 (m, 4H), 3.74 – 3.59 (m, 2H), 3.04 – 2.89 (m, 3H), 2.48 – 2.42 (m, 1H), 2.38 – 2.29 (m, 2H), 2.24 (s, 6H), 2.07 – 1.91 (m, 3H), 1.86 – 1.68 (m, 3H), 1.60 (d, J = 8.0 Hz, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, J = 6.0 Hz, 3H).
13		923.41	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.37 – 8.29 (m, 2H), 8.25 (d, J = 4.9 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.67 – 7.62 (m, 1H), 7.48 – 7.37 (m, 4H), 7.21 (d, J = 2.0 Hz, 1H), 7.09 – 7.04 (m, 1H), 5.22 – 5.13 (m, 1H), 4.13 – 3.84 (m, 4H), 3.73 – 3.59 (m, 2H), 3.03 – 2.89 (m, 3H), 2.49 – 2.20 (m, 9H), 2.08 – 1.91 (m, 2H), 1.87 – 1.68 (m, 2H), 1.63 – 1.45 (m, 4H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.61 – 0.38 (m, 4H).
14		881.36	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.37 – 8.28 (m, 2H), 8.14 (d, J = 4.9 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.66 – 7.61 (m, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, J = 2.0 Hz, 1H), 7.11 – 7.06 (m, 1H), 5.22 – 5.14 (m, 1H), 4.12 – 4.03 (m, 3H), 3.95 – 3.85 (m, 4H), 3.07 – 2.89 (m, 3H), 2.42 – 2.21 (m, 9H), 1.99 – 1.73 (m, 8H), 1.60 (d, J = 8.0 Hz, 3H), 0.99 (d, J = 5.8 Hz, 3H).

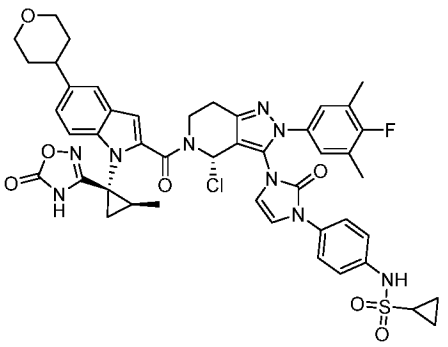
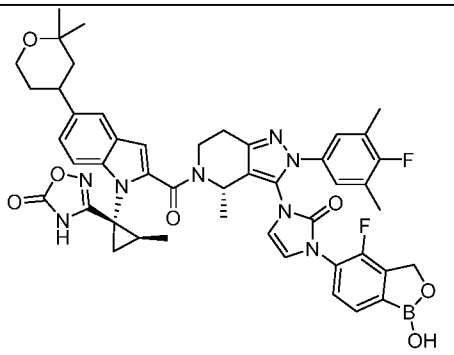
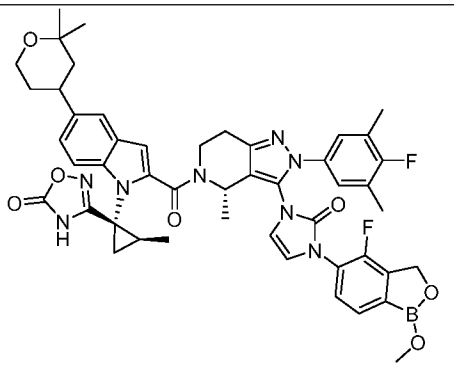
15		867.35	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.36 – 8.28 (m, 2H), 8.14 (d, J = 4.9 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.66 – 7.61 (m, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.21 (d, J = 2.0 Hz, 1H), 7.08 – 7.03 (m, 1H), 5.24 – 5.12 (m, 1H), 4.11 – 4.02 (m, 1H), 3.96 – 3.87 (m, 4H), 3.81 (d, J = 6.0 Hz, 2H), 3.72 (d, J = 6.2 Hz, 2H), 3.04 – 2.80 (m, 3H), 2.52 – 2.43 (m, 1H), 2.39 – 2.28 (m, 2H), 2.24 (s, 6H), 2.15 – 2.00 (m, 4H), 1.60 (d, J = 8.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H).
16		869.36	^{1}H 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	^{1}H 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, 3H), 1.01 – 0.98 (m, 3H).
18		923.04	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.37 – 8.29 (m, 2H), 8.25 (d, *J* = 4.9 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.67 – 7.62 (m, 1H), 7.48 – 7.37 (m, 4H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.09 – 7.04 (m, 1H), 5.22 – 5.13 (m, 1H), 4.13 – 3.84 (m, 4H), 3.73 – 3.59 (m, 2H), 3.03 – 2.89 (m, 3H), 2.49 – 2.20 (m, 9H), 2.08 – 1.91 (m, 2H), 1.87 – 1.68 (m, 2H), 1.63 – 1.45 (m, 4H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, *J* = 6.0 Hz, 3H), 0.61 – 0.38 (m, 4H).
19		881.36	^{1}H NMR (500 MHz, DMSO-d_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, *J* = 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, *J* = 8.0 Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.95 (m, 3H).

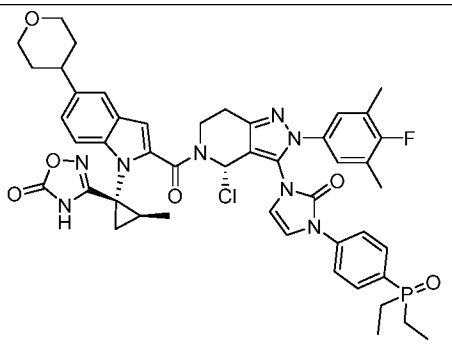
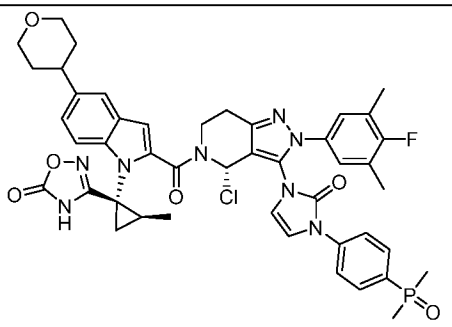
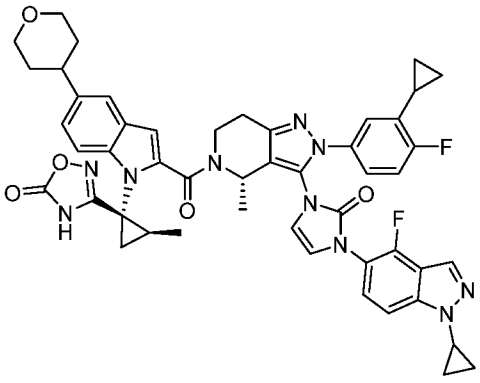
20		895.38	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.38 – 8.29 (m, 3H), 7.94 – 7.88 (m, 1H), 7.66 – 7.58 (m, 2H), 7.46 – 7.37 (m, 3H), 7.23 – 7.20 (m, 1H), 7.08 – 7.03 (m, 1H), 5.23 – 5.11 (m, 1H), 4.53 – 4.47 (m, 1H), 4.09 – 3.87 (m, 2H), 3.59 – 3.46 (m, 4H), 3.03 – 2.88 (m, 3H), 2.41 – 2.26 (m, 3H), 2.24 (s, 6H), 2.15 – 1.98 (m, 6H), 1.88 – 1.79 (m, 4H), 1.62 – 1.58 (m, 3H), 0.99 (d, *J* = 5.8 Hz, 3H).
21		895.44	^{1}H 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	^{1}H 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	^{1}H 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).

24		888.34	^{1}H 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 = 2.1 Hz, 1H), 7.48 – 7.35 (m, 5H), 7.31 – 7.18 (m, 3H), 7.08 – 7.03 (m, 1H), 5.04 (t, J = 4.8 Hz, 1H), 4.55 – 4.48 (m, 1H), 3.59 – 3.48 (m, 4H), 3.02 – 2.86 (m, 6H), 2.48 – 2.42 (m, 1H), 2.37 – 2.28 (m, 2H), 2.24 (s, 6H), 2.23 – 2.16 (m, 1H), 2.15 – 2.01 (m, 3H), 2.00 – 1.89 (m, 2H), 1.88 – 1.80 (m, 2H), 0.99 (d, J = 6.0 Hz, 3H).
25		888.32	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.16 (s, 1H), 8.34 (d, J = 6.0 Hz, 1H), 8.17 (d, J = 6.0 Hz, 1H), 7.64 (t, J = 2.1 Hz, 1H), 7.47 – 7.36 (m, 5H), 7.27 – 7.16 (m, 3H), 7.10 – 7.02 (m, 1H), 3.92 – 3.83 (m, 2H), 3.57 – 3.48 (m, 4H), 3.01 – 2.96 (m, 1H), 2.95 (s, 3H), 2.91 – 2.85 (m, 2H), 2.40 – 2.18 (m, 13H), 2.15 – 2.07 (m, 2H), 1.88 – 1.80 (m, 2H), 0.99 (d, J = 5.8 Hz, 3H).
26		895.32	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.16 (s, 1H), 8.37 (d, J = 6.0 Hz, 1H), 8.18 (d, J = 6.0 Hz, 1H), 7.64 (s, 1H), 7.64 (d, J = 4.1 Hz, 0H), 7.43 (d, J = 7.5 Hz, 1H), 7.42 – 7.37 (m, 4H), 7.23 – 7.17 (m, 3H), 7.08 – 7.03 (m, 1H), 6.94 (s, 1H), 4.31 – 4.23 (m, 1H), 4.11 – 4.03 (m, 1H), 3.59 – 3.47 (m, 4H), 3.06 – 2.96 (m, 3H), 2.95 (s, 3H), 2.40 – 2.33 (m, 1H), 2.36 – 2.26 (m, 2H), 2.24 (s, 6H), 2.16 – 2.07 (m, 2H), 1.88 – 1.79 (m, 2H), 0.99 (d, J = 5.8 Hz, 3H).
27		888.32	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.76 (s, 1H), 8.36 (d, J = 6.0 Hz, 1H), 8.17 (d, J = 6.0 Hz, 1H), 7.64 (s, 1H), 7.46 – 7.37 (m, 5H), 7.23 – 7.17 (m, 3H), 7.08 – 7.03 (m, 1H), 5.22 – 5.14 (m, 1H), 4.10 – 4.02 (m, 1H), 3.95 – 3.87 (m, 1H), 3.59 – 3.47 (m, 4H), 3.03 – 2.89 (m, 6H), 2.43 – 2.37 (m, 1H), 2.30 – 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 –

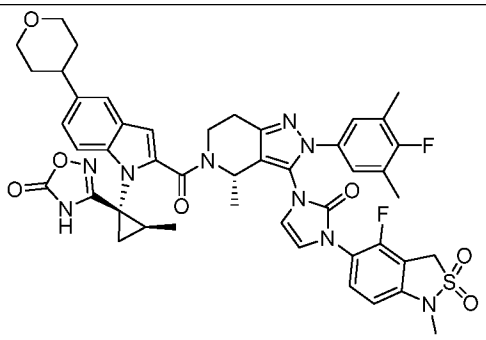
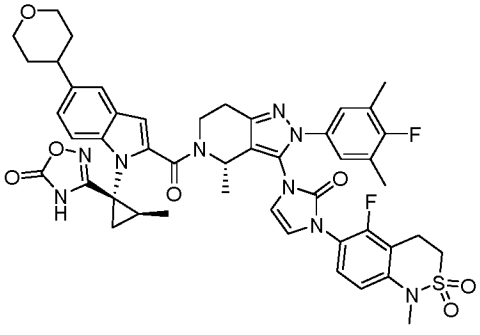
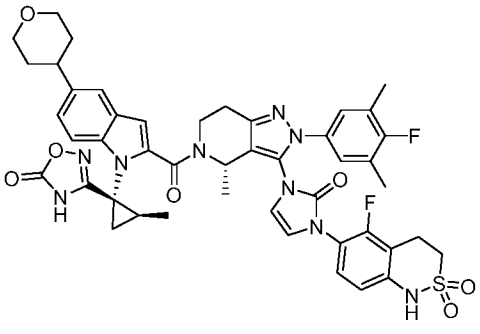
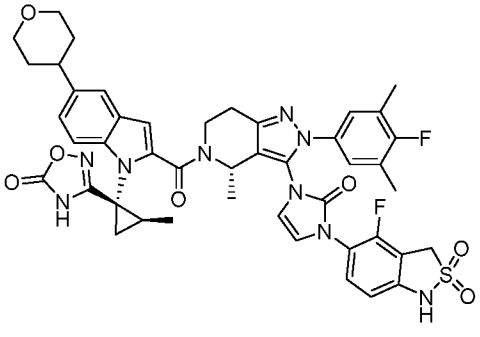
Conjupro EX1025
Page 77 of 106

			1.50 (m, 1H), 1.53 – 1.46 (m, 1H).
28		922.28	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (s, 1H), 9.16 (s, 1H), 8.37 (d, J = 6.0 Hz, 1H), 8.18 (d, J = 6.0 Hz, 1H), 7.64 (s, 1H), 7.64 (d, J = 4.1 Hz, 0H), 7.43 (d, J = 7.5 Hz, 1H), 7.42 – 7.37 (m, 4H), 7.23 – 7.17 (m, 3H), 7.08 – 7.03 (m, 1H), 6.94 (s, 1H), 4.31 – 4.23 (m, 1H), 4.11 – 4.03 (m, 1H), 3.59 – 3.47 (m, 4H), 3.47 – 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, J = 5.8 Hz, 3H).
29		885.34	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.36 – 8.29 (m, 2H), 7.65 (d, J = 3.8 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.47 – 7.33 (m, 4H), 7.21 (d, J = 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, 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-d_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).

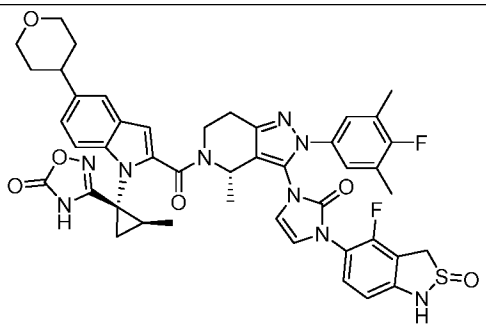
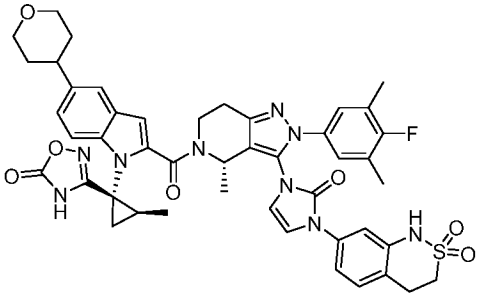
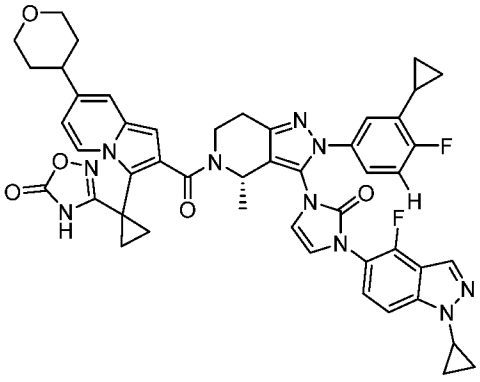
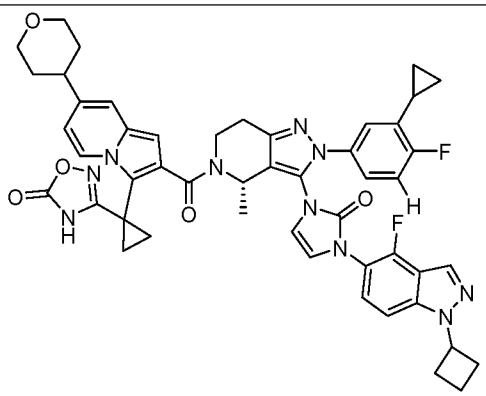
Conjupro EX1025
Page 78 of 106

31		907.34	^{1}H NMR (500 MHz, DMSO-d_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).
32		879.29	^{1}H NMR (500 MHz, DMSO-d_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), 2.41 – 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).
33		893.37	^{1}H NMR (500 MHz, DMSO-d_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, J = 8.0 Hz, 3H), 1.40 – 1.22 (m, 8H), 1.11 – 1.05 (m, 3H).

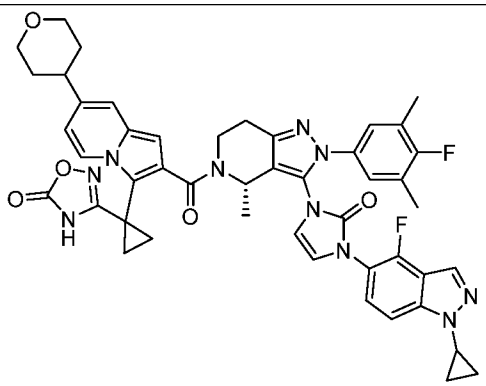
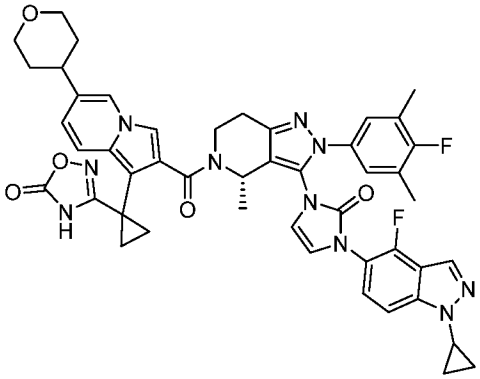
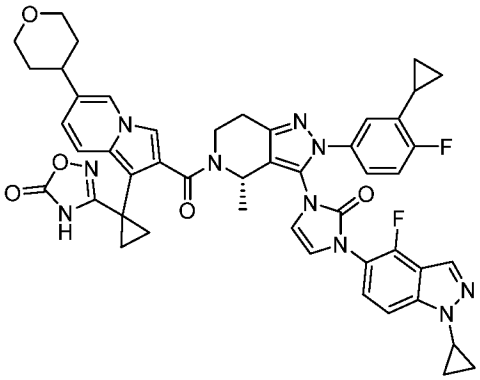
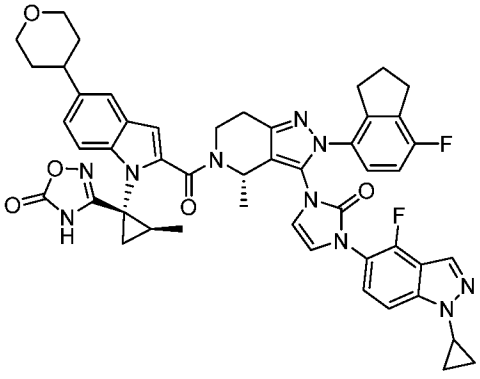
Conjupro EX1025
Page 79 of 106

34		906.32	^{1}H NMR (500 MHz, DMSO-d_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, J = 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, J = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).
35		920.34	^{1}H NMR (500 MHz, DMSO-d_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, J = 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, J = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).
36		906.32	^{1}H NMR (500 MHz, DMSO-d_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, J = 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, J = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).
37		892.30	^{1}H NMR (500 MHz, DMSO-d_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, J = 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, J = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).

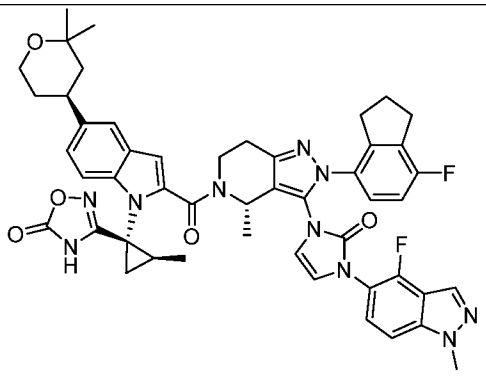
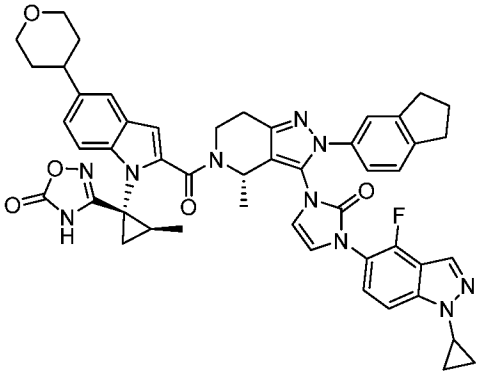
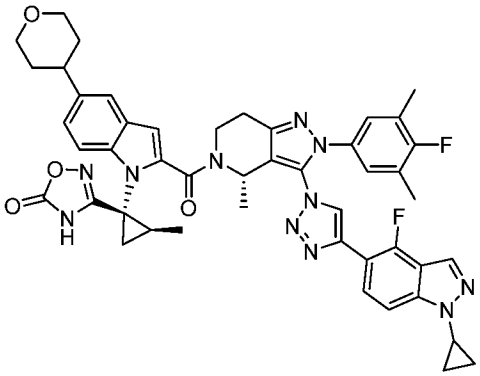
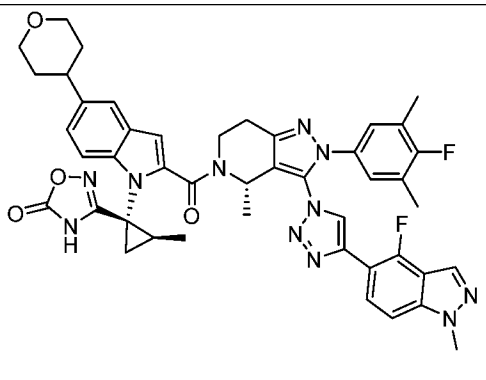
Conjupro EX1025
Page 80 of 106

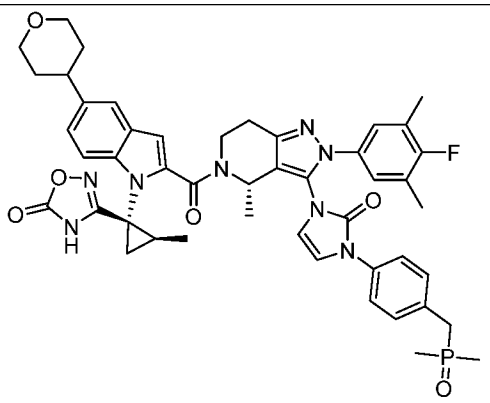
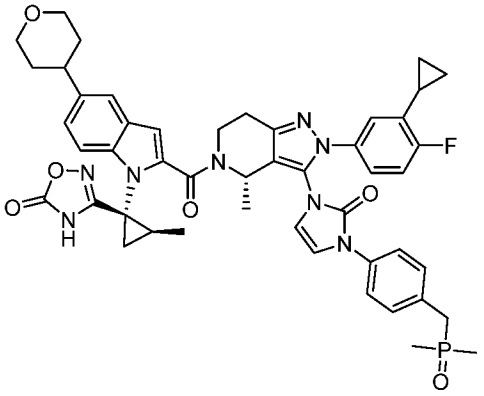
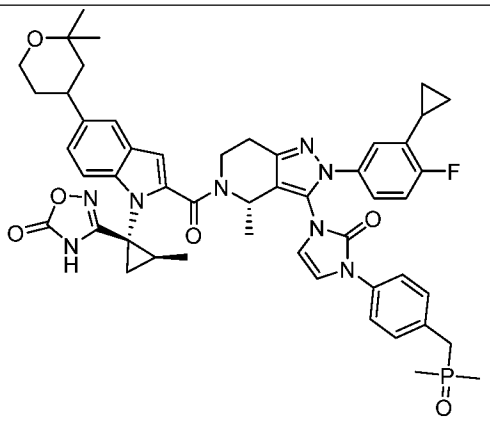
38		876.31	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.41 – 8.29 (m, 2H), 7.99 – 7.89 (m, 1H), 7.64 – 7.54 (m, 2H), 7.46 – 7.36 (m, 3H), 7.21 (d, J = 2.0 Hz, 1H), 7.11 – 7.08 (m, 1H), 5.26 – 5.16 (m, 1H), 4.57 – 4.52 (m, 1H), 4.11 – 3.81 (m, 4H), 3.55 – 3.49 (m, 4H), 3.13 – 2.85 (m, 3H), 2.42 – 2.33 (m, 3H), 2.30 (s, 6H), 2.15 – 2.11 (m, 2H), 1.88 – 1.79 (m, 2H), 1.61 (d, J = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).
39		888.33	^{1}H NMR (500 MHz, DMSO-d_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, J = 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, J = 8.0 Hz, 3H), 1.01 – 0.95 (m, 3H).
40		879.35	1H NMR (500 MHz, DMSO-d6) 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).
41		893.37	^{1}H NMR (500 MHz, DMSO-d_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).

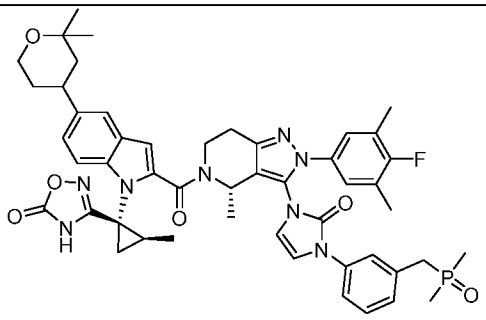
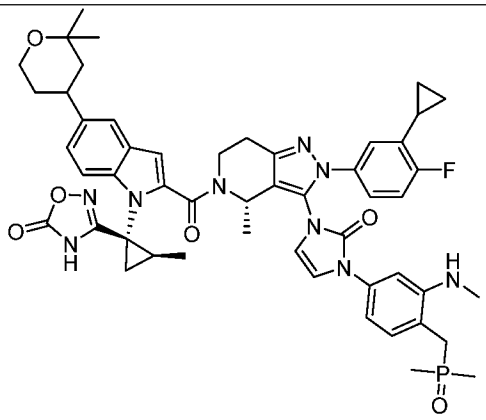
Conjupro EX1025
Page 81 of 106

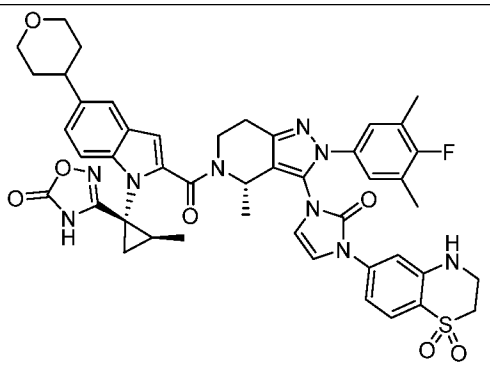
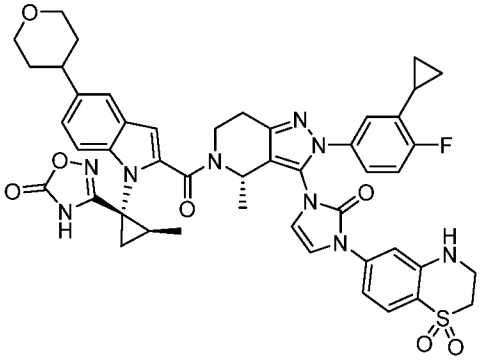
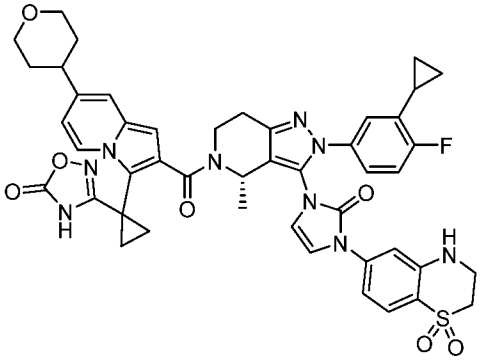
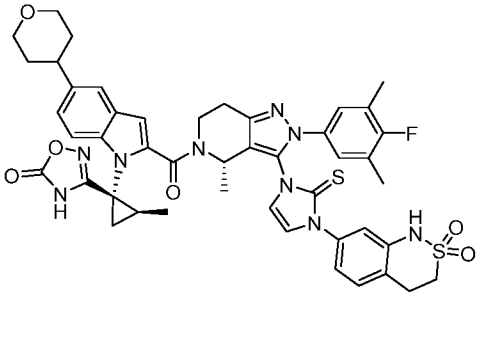
42		867.35	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.41 – 8.36 (m, 3H), 7.90 – 7.80 (m, 1H), 7.67 – 7.55 (m, 2H), 7.46 – 7.37 (m, 2H), 7.11 – 7.07 (m, 1H), 6.52 – 6.43 (m, 2H), 5.34 – 5.25 (m, 1H), 4.63 – 4.51 (m, 1H), 4.17 – 3.87 (m, 2H), 3.69 – 3.49 (m, 4H), 3.12 – 2.96 (m, 3H), 2.44 – 2.33 (m, 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-d_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).
44		879.35	^{1}H NMR (500 MHz, DMSO-d_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-d_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, J = 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).

Conjupro EX1025
Page 82 of 106

46		895.38	^{1}H NMR (500 MHz, DMSO-d_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, *J* = 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).
47		875.37	^{1}H NMR (500 MHz, DMSO-d_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, *J* = 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-d_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, *J* = 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-d_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, *J* = 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).

50		873.36	^{1}H NMR (500 MHz, DMSO-d_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, J = 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-d) 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-d) 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, 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-*d*) 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-*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, 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).

55		888.32	1H NMR (500 MHz, DMSO-d6) 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	1H NMR (500 MHz, DMSO-d6) 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	1H NMR (500 MHz, DMSO-d6) 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).
58		904.30	^{1}H NMR (500 MHz, DMSO-d_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, J = 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, *J* = 8.0 Hz, 3H), 1.02 – 0.96 (m, 3H).

Example 2 In vitro activity evaluation

GLP-1R cAMP Assay

1. Cell line and reagent preparation

1) Cell line: Flp-In-293-GLP1R

2) Medium: DMEM + 10% FBS + 1 X Penicillin-Streptomycin + 200 μg/mL HB

3) Test buffer: 1 X HBSS + 20 mM HEPES + 0.1%BSA + 500 μM IBMX

2. Agonist test

a) Inoculate Flpin-293-GLP1R cells in a 384-well assay plate (6007680-50, PE) using complete medium with 2,000 cells per well.

b) Prepare a 4 X complex working solution with assay buffer.

c) Add 5 μL of 4 X Compound Working Solution to the cell plate and incubate at 37°C for 30 minutes.

d) Dilute Eu-cAMP tracer (1/50) with lysis buffer and add 10 μl/well to the assay plate.

e) Dilute Ulight-anti-cAMP (1/150) with lysis buffer and add 10 μl/well to the assay plate.

f) Incubate at constant temperature for 1 hour.

g) Read the plate on Envision 2105 plate reader at 665 nM and 615 nM.

3. Data Analysis

3.1 The formula for calculating % Activity is as follows

% Activity =100-(Signalcmpd-SignalAve_PC)/(SignalAve_VC-SignalAve_PC)×100.

3.2 Calculate EC50 and plot the effect-dose curve for cmpds:

Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))

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

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

Table 2: Bioactivity of compounds in GLP-1R agonist cAMP stimulation assay

Compound ID	GLP-1R cAMP:EC_{50}/nM
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

Note: EC50 range: A: 0 ≤ EC50 < 0.1nM; B: 0.1nM ≤ EC50 < 1nM; C: 1nM ≤ EC50 < 10nM.

Example 3 Pharmacokinetic study

PK study in SD rats

PK study of single subcutaneous administration of the compounds of the present invention. Protocol: Animal: SD rat: Solvent prescription: 80% MCT + 20% benzyl alcohol; Dose: 30 mg/kg; Administration concentration: 30 mg/mL; Administration volume: 1 mL/kg. blood samples were collected, and the blood samples were analyzed by LCMSMS, and the time point of each blood sampling and the concentration of the blood drug were shown in Table 3, and the blood samples were analyzed by LCMSMS, and the concentration of the blood drug was found in Table 4.

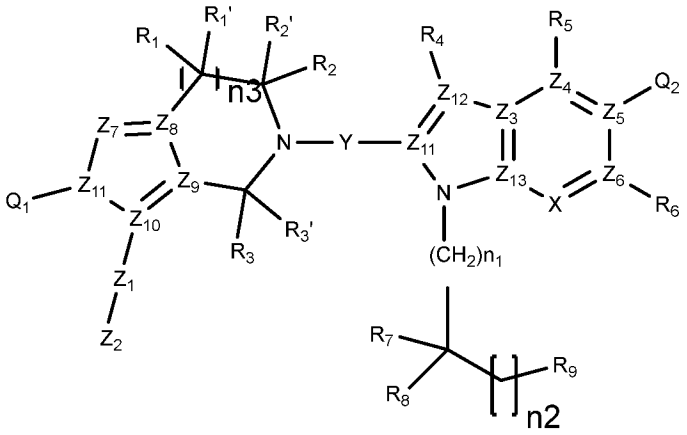
Table 3 Blood concentrations of different compounds after subcutaneous injection

Compound	1	13	18	19	21	20
T/time	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
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	/
696	24.7	/	9.55	41.1	41.2	/
AUC_{0-t} (ng.hr/ml)	60272	14020	51234	234473	61479	52740

WHAT IS CLAIMED IS:

1. A compound of Formula I:



Formula I

stereoisomers, pharmaceutically acceptable salts or deuterated compounds thereof,

wherein X is selected from the group consisting of N and -CR^a; wherein R^a is selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

wherein Y is -C(=O)-;

wherein each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

wherein Q_1 is selected from the group consisting of C_{6-10} aryl and C_{5-10} heteroaryl, wherein C_{6-10} aryl or C_{5-10} heteroaryl is optionally substituted by one to five substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy;

wherein Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl are optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy and -$NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl;

wherein each of R_1, R_2, R_3, R_1', R_2' and R_3' is independently selected from the group

consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cycloalkyl and heterocycloalkyl; wherein C_{1-6} alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkoxy and hydroxyl;

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

wherein R_1 and R_1' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl, and R_2 and R_2' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl ; and R_3 and R_3' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl;

each of R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

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

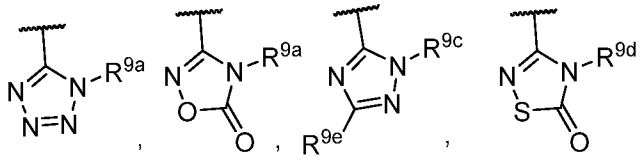
or R_7 and R_8 together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring, wherein the C_{3-15} carbocyclic ring is optionally substituted by one to three C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclic, and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl groups and (C_{1-6} alkyl) carbonyl; and any two C_{1-6} alkyl groups optionally form C_{3-15} carbon ring together with the carbon atom to which they are attached;

n_1 is 0, 1, 2 or 3;

n2 is 0, 1, 2, 3, 4 or 5;

n3 is 0, 1 or 2;

R_9 is selected from the group consisting of:



, $-CO_2R^{9f}$ and $-C(=O)-NR^{9g}R^{9h}$; and each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is independently selected from the group consisting of hydrogen,

C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{1-6} alkoxy;

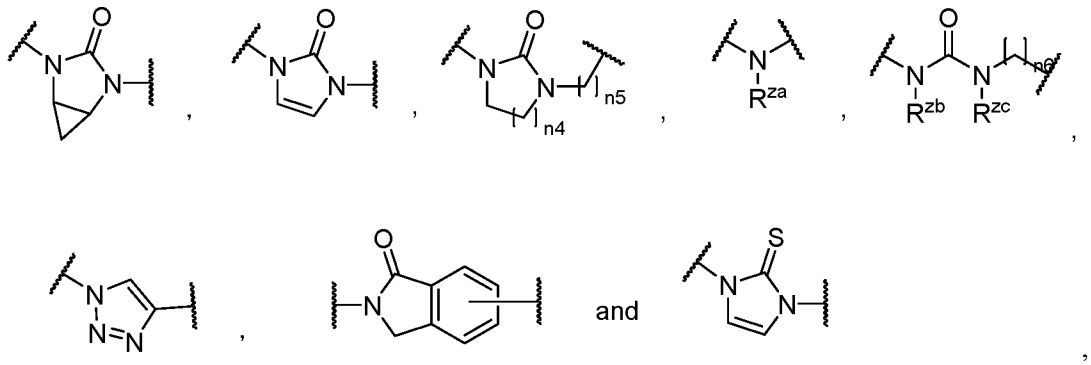
R^{9e} is selected from the group consisting of hydrogen and C_{1-6} alkyl optionally substituted by one or more halogen atoms;

R^{9f} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{9h} is selected from the group consisting of hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl) carbonyl, cyano and $-S(=O)_{n3}-R^{9i}$;

R^{9i} is C_{1-6} alkyl;

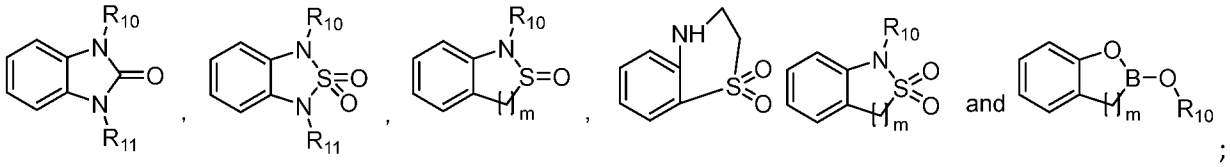
Z_1 is selected from the group consisting of:



wherein R^{za} is selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, and each of R^{zb} and R^{zc} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

n4 is 1, 2 or 3; each of n5 and n6 is independently integers from 0 to 10;

Z_2 is selected from the group consisting of C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12-membered heterocyclic, C_{6-10} aryl , 5 to 10-membered heteroaryl,



;

wherein Z_2 is independently optionally substituted with one to five G's; and m is 1, 2, 3;

wherein each of R_{11} and R_{10} is independently selected from the group consisting of H, C_{1-6} alkyl , (C_{1-6} alkyl) aryl, C_{1-6} haloalkyl, $-C_3-C_{15}$ cycloalkyl and $-C_1-C_6$ alkyl-C_3-C_{15} cycloalkyl;

wherein G' is selected from the group consisting of:

a. Oxygen;

b. Halogen;

c. Cyano;

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

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

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

g. C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, $-NR^{zi}R^{zj}$, C_{1-6} alkoxy, C_{1-6} alkoxy and 3- to 12-membered heterocyclic groups; wherein each of R^{zi} and R^{zj} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein the 3- to 12-membered heterocyclic groups are optionally substituted with one or more substituents selected from the group consisting of cyano, C_{1-6} alkyl and 3 to 12-membered heterocyclic;

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

i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic 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 C_{6-10} aryl is optionally substituted by one or more (C_{1-6} alkyl) carbonyl;

k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{zk}R^{zl}$, and 3- to 12-membered heterocyclic; wherein R^{zk} and R^{zl} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and (C_{1-6} alkyl)carbonyl and wherein the 3- to 12-membered heterocyclic is optionally substituted with one or more substituents independently selected from the

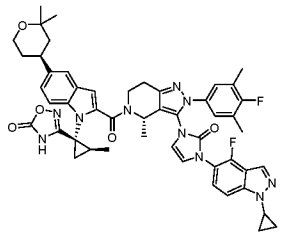
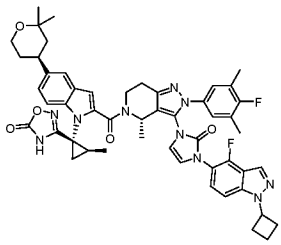
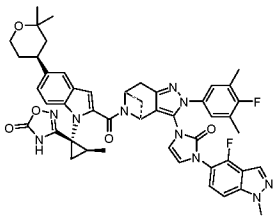
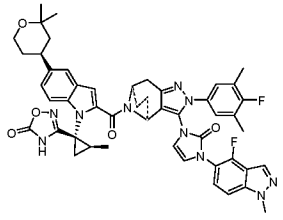
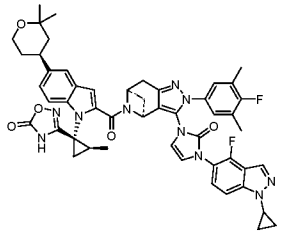
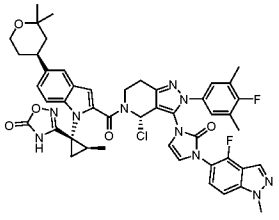
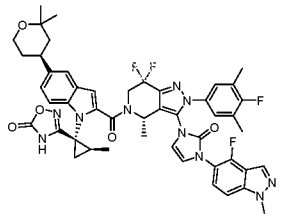
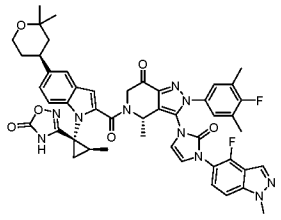
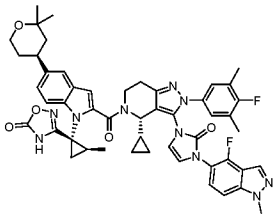
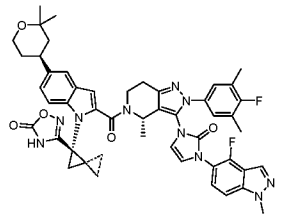
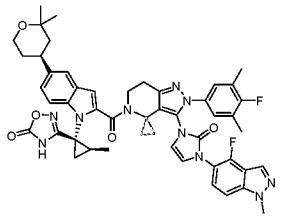
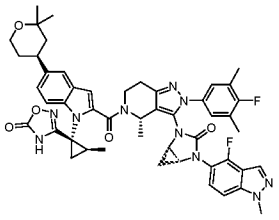
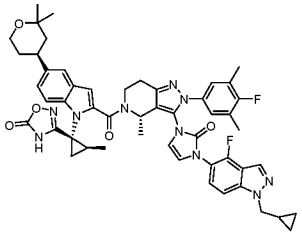
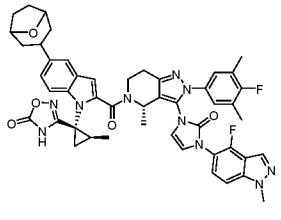
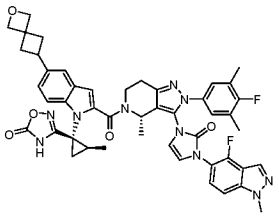
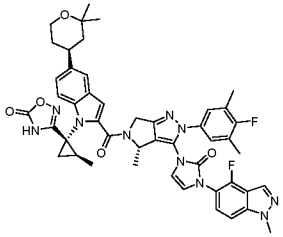
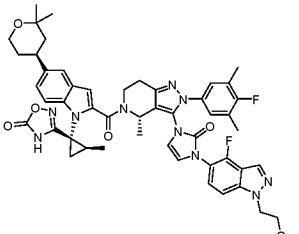
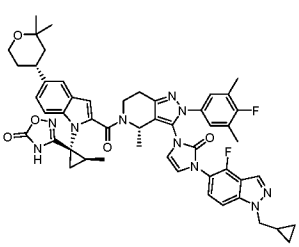
Conjupro EX1025
Page 93 of 106

group consisting of C_{1-6} alkyl, and C_{1-6} alkoxy;

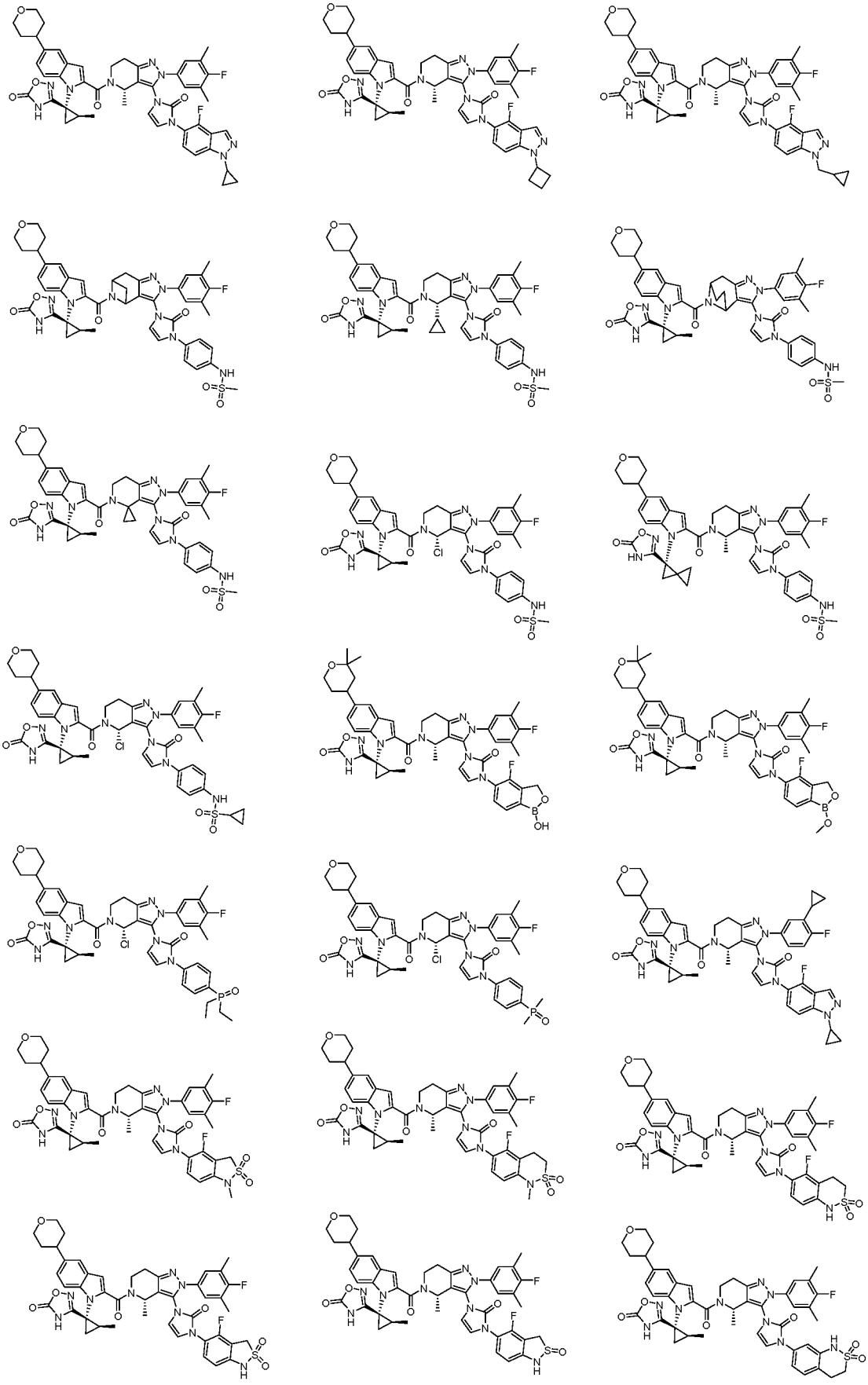
l. -C_3-C_{15} cycloalkyl or -C_1-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein -C_3-C_{15} cycloalkyl or -C_1-C_6 alkyl-C_3-C_{15} cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl is optionally substituted by halogen;

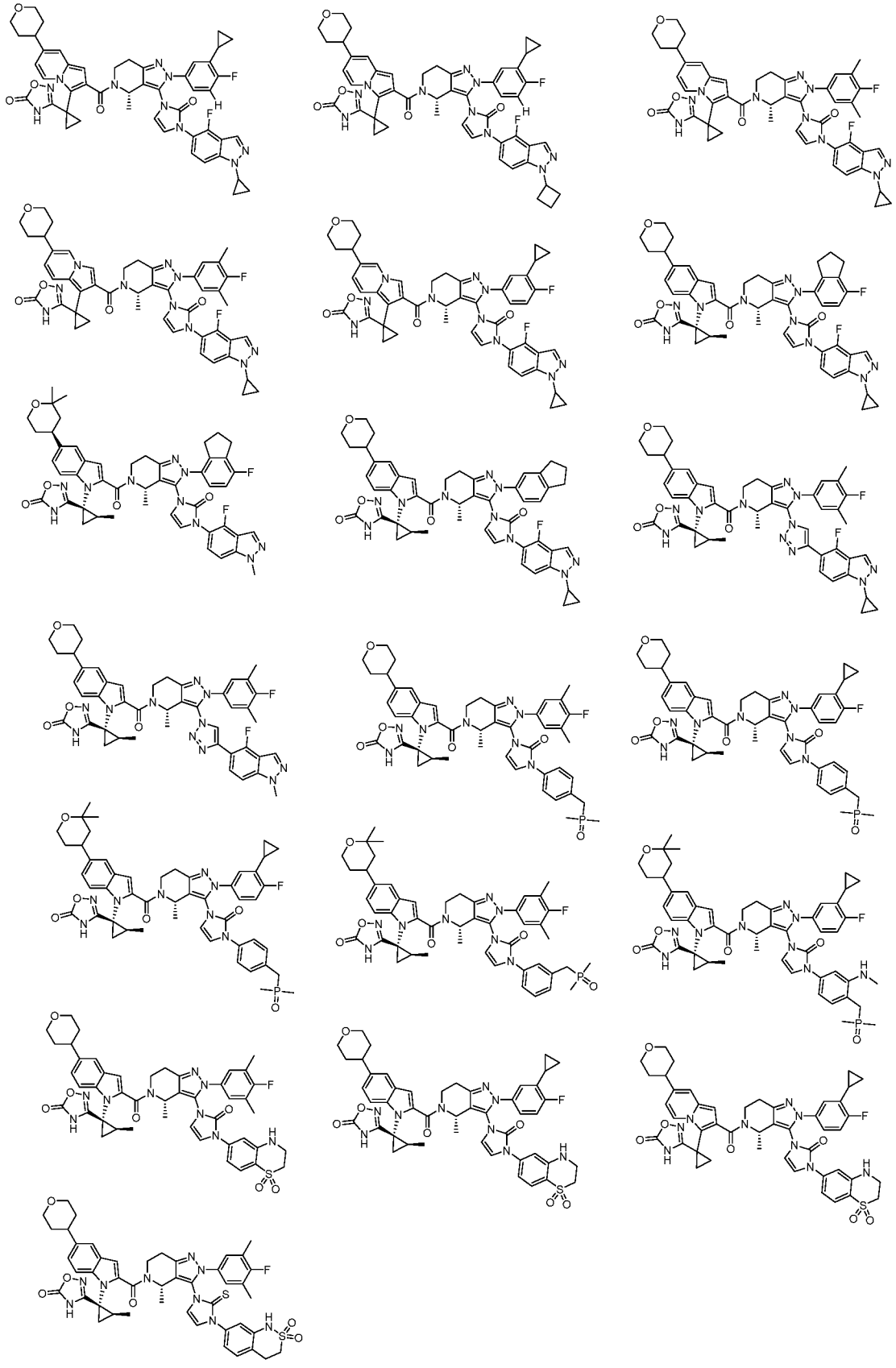
m. -$P(=O)R^{zm}R^{zn}$, $NR^{zm}S(=O)R^{zn}$ and $NR^{zm}S(=O)_2R^{zn}$, wherein R^{zm} and R^{zn} are independently selected from the group consisting of H, C_{1-6} alkyl and C_{6-10} aryl,
wherein C_{1-6} alkyl is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo; wherein C_{3-6} cycloalkyl is optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo;
wherein C_{6-10} aryl is optionally substituted with 1-3 independently selected from C_{1-3} alkyl;
or R^{zm} and R^{zn} taken together with the phosphorous atom to which each is attached form a ring including from 5-8 ring atoms, wherein 0-2 ring atoms (in addition to the phosphorous attached to R^{zm} and R^{zn}) are heteroatoms each independently selected from the group consisting of: O, S, and N, wherein the ring is optionally substituted with 1-3 independently selected from C_{1-6} alkyl.

2. The compound of claim 1, stereoisomers, pharmaceutically acceptable salts or deuterated compounds thereof, wherein the compound is selected from the group consisting of:





3. A pharmaceutical composition, comprising the compound of claim 1 or claim 2, stereoisomers, pharmaceutically acceptable salts or deuterated compounds thereof, and a pharmaceutically acceptable excipient.

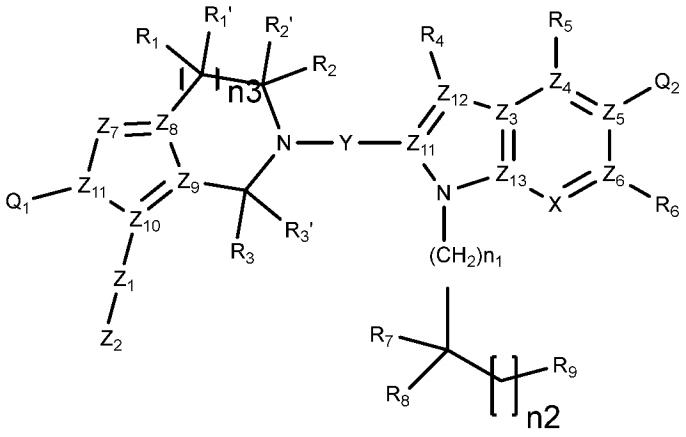
4. A method for treating a GLP-1R-mediated disease or condition, comprising administering to a subject in need thereof a therapeutically effective amount of the compound of claim 1 or claim 2, stereoisomers, pharmaceutically acceptable salts or deuterated compounds thereof.

5. The method of claim 4, wherein the GLP-1R-mediated disease or condition is selected from the group consisting of T1D, T2DM, pre-diabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, 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, post-prandial 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, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, polycystic ovary syndrome and substance addiction.

Conjupro EX1025
Page 98 of 106

ABSTRACT

The present application describes GLP-1R modulating compounds that are useful for treating GLP-1R-mediated diseases or conditions.



Formula I

Conjupro EX1025
Page 99 of 106

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-021US0
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).			
☐ An Address is being provided for the correspondence Information of this application.			
Customer Number	83682		
Email Address	dnevrivy@nevrivylaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	GLP-1R Agonist and Therapeutic Method Thereof		
Attorney Docket Number	HRT-021US0	**Small Entity Status Claimed**	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	0	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	83682		

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-021US0
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-021US0
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-021US0
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	ASCLETIS BIOSCIENCE CO., LTD		
Mailing Address Information For Applicant:			
Address 1	3-1201, No. 371 Mingxing Road		
Address 2	HIPARK, Xiaoshan District		
City	Hangzhou	**State/Province**	
Country	CN	Postal Code	311202
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-021US0
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Daniel Nevrivy/			Date (YYYY-MM-DD)	2023-11-29
First Name	Daniel	Last Name	Nevrivy	Registration Number	59,118

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-021US0
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.