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Title of Invention:	GLP-1R Agonist and Therapeutic Method Thereof
First Named Inventor/Applicant Name:	Bin Liang
Customer Number:	83682
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Page 1 of 71

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2		application.pdf	494613	yes	66
			153b9913b6b7706bd306c20787ebf5fbcd03a978		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	58	
	Claims		59	65	
	Abstract		66	66	
Warnings:					
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3	Application Data Sheet	ADS_filed.pdf	144528	no	9
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4	Fee Worksheet (SB06)	fee-info.pdf	37264	no	2
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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					<input type="button" value="Remove"/>
Given Name	Middle Name	Family Name	City	State	Country
Bin		Liang	Hangzhou		CN
Inventor 2					<input type="button" value="Remove"/>
Given Name	Middle Name	Family Name	City	State	Country
Bailing		Yang	Hangzhou		CN
Inventor 3					<input type="button" value="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.					<input type="button" value="Add"/>
Title of Invention		GLP-1R Agonist and Therapeutic Method Thereof			
Attorney Docket Number (if applicable)		HRT-016US0			
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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:	

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

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Signature

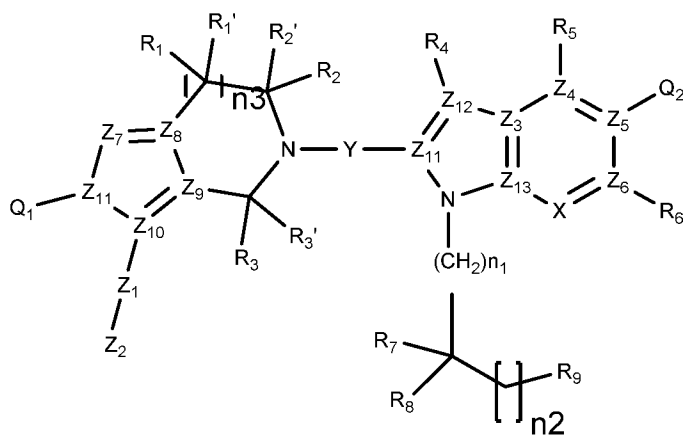
Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Daniel Nevrvy/			Date (YYYY-MM-DD)	2023-09-18
First Name	Daniel	Last Name	Nevrvy	Registration Number (If appropriate)	59118

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ABSTRACT

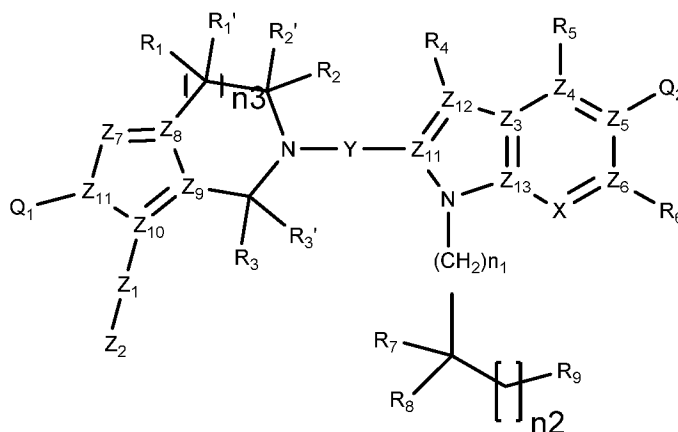
The present application describes GLP-IR modulating compounds that are useful for treating GLP-IR-mediated diseases or conditions.



Formula I

WHAT IS CLAIMED IS:

1. A compound of Formula I:



Formula I

stereoisomers, pharmaceutically acceptable salts or deuterated compounds,

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 C₁₋₆ alkyl;

wherein Y is -C(=O)-;

wherein each of Z₃, Z₄, Z₅, Z₆, Z₇, Z₈, Z₉, Z₁₀, Z₁₁, Z₁₂ and Z₁₃ is independently selected from the group consisting of N and C;

wherein Q₁ is selected from the group consisting of C₆₋₁₀ aryl and C₅₋₁₀ heteroaryl, wherein C₆₋₁₀ aryl or C₅₋₁₀ heteroaryl is optionally substituted by one to five substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and C₁₋₆ alkoxy;

wherein Q₂ 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, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy and -NR^{Qa}R^{Qb}, wherein two C₁₋₆ alkyl groups together with the carbon atoms to which they are attached form a C₃₋₈ carbocyclic ring; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and (C₁₋₆ alkyl) carbonyl;

wherein each of R₁, R₂, R₃, R₁' , R₂' and R₃' is independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cycloalkyl and

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

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

wherein R₁ and R₁' optionally together with the carbon atom to which they are attached form C₃₋₈ cycloalkyl, and R₂ and R₂' optionally together with the carbon atom to which they are attached form C₃₋₈ cycloalkyl; and R₃ and R₃' optionally together with the carbon atom to which they are attached form C₃₋₈ cycloalkyl;

each of R₄, R₅ and R₆ is independently selected from the group consisting of hydrogen, halogen and C₁₋₆ alkyl;

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

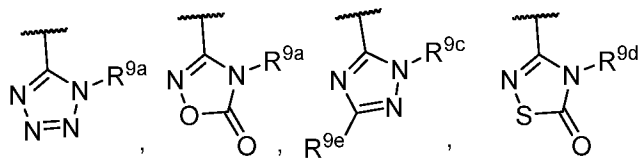
or R₇ and R₈ together with the carbon atom to which they are attached form C₃₋₁₅ carbocyclic ring, wherein the C₃₋₁₅ carbocyclic ring is optionally substituted by one to three C₁₋₆ alkyl, wherein each C₁₋₆ alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, -NR^{7a}R^{7b}, C₁₋₆ alkoxy and 3- to 12-membered heterocyclic, and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl groups and (C₁₋₆ alkyl) carbonyl; and any two C₁₋₆ alkyl groups optionally form a C₃₋₁₅ carbon ring together with the carbon atom to which they are attached;

n₁ is 0, 1, 2 or 3;

n₂ is 0, 1, 2, 3, 4 or 5;

n₃ is 0, 1 or 2;

R₉ is selected from the group consisting of:

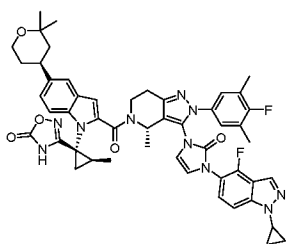
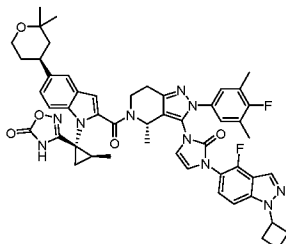
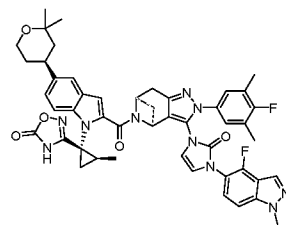
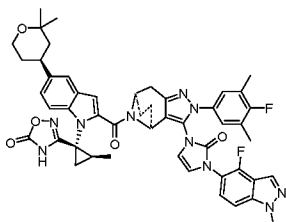
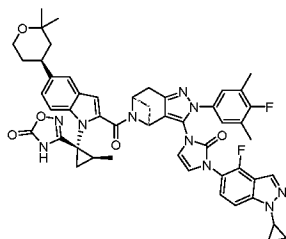
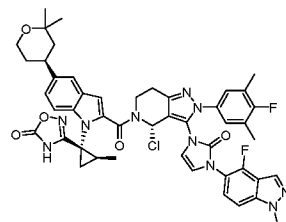
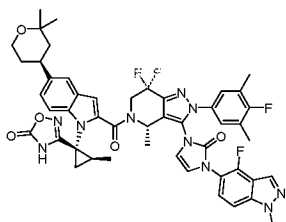
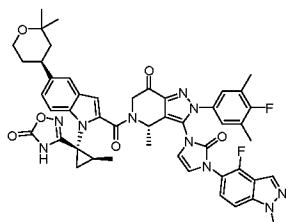
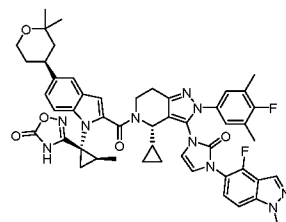
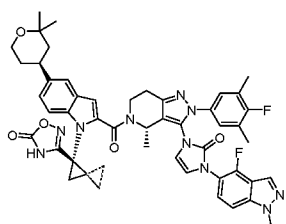
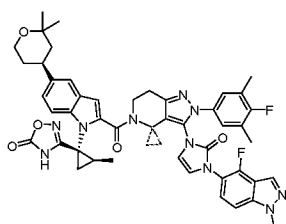
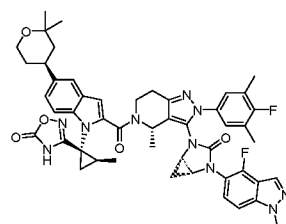
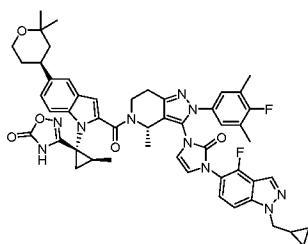
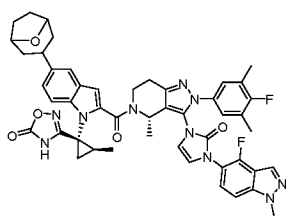
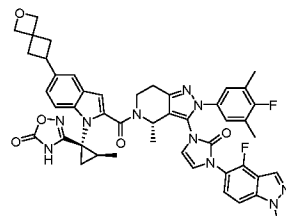
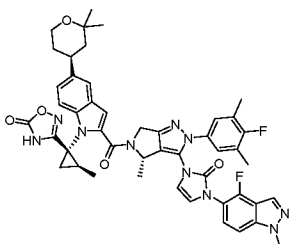
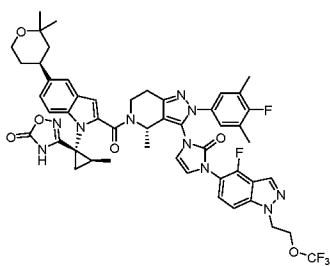


, -CO₂R^{9f} and -C(=O)-NR^{9g}R^{9h}; and each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl) carbonyl, wherein C₁₋₆ alkyl is optionally substituted with

hydrogen and C₁₋₆ alkyl;

- g. C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, -NR^{zi}R^{zj}, C₁₋₆ alkoxy, C₁₋₆ 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 or C₁₋₆ alkyl, wherein the 3- to 12-membered heterocyclic groups are optionally substituted with one or more substituents selected from the group consisting of cyano, C₁₋₆ alkyl and 3 to 12-membered heterocyclic;
- h. C₁₋₆ alkoxy; wherein C₁₋₆ alkoxy is optionally substituted by one or more substituents of hydroxyl, halogen and C₁₋₆ alkoxy;
- i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic is optionally substituted by one or more substituents independently selected from C₁₋₆ alkyl and (C₁₋₆ alkyl) carbonyl;
- j. C₆₋₁₀ aryl; wherein C₆₋₁₀ aryl is optionally substituted by one or more (C₁₋₆ 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 C₁₋₆ alkyl, C₁₋₆ 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, C₁₋₆ alkyl, and (C₁₋₆ 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 C₁₋₆ alkyl, and C₁₋₆ alkoxy;
- l. -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl; wherein -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl) carbonyl, wherein each of C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl) carbonyl is optionally substituted by halogen.

2. The compound of claim 1, its stereoisomers, pharmaceutically acceptable salts or deuterated compounds, 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, and a pharmaceutically acceptable excipient.

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

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.

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

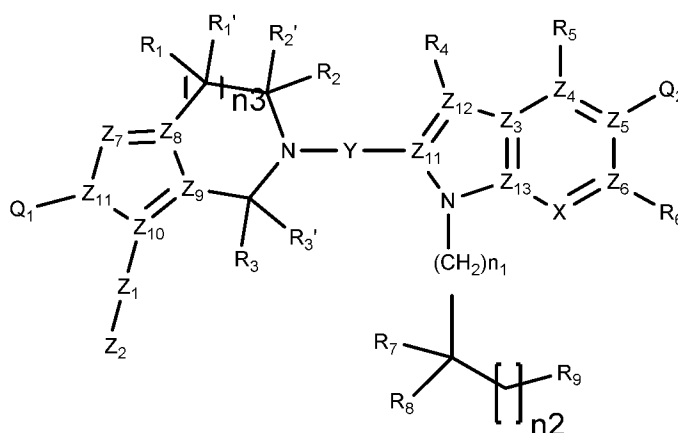
[0002] Glucagon-like peptide-1 (GLP-1) is a peptide hormone that is secreted from the enteroendocrine cells in the gut in response to a meal. GLP-1 is believed to play a role in regulation of post-prandial glycemia, via directly augmenting meal-induced insulin secretion from the pancreatic beta-cells, 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

[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_{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 a 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 C₁₋₆ alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C₁₋₆ alkoxy and hydroxyl;

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

wherein R₁ and R₁' optionally together with the carbon atom to which they are attached form C₃₋₈ cycloalkyl, and R₂ and R₂' optionally together with the carbon atom to which they are attached form C₃₋₈ cycloalkyl; and R₃ and R₃' optionally together with the carbon atom to which they are attached form C₃₋₈ cycloalkyl;

each of R₄, R₅ and R₆ is independently selected from the group consisting of hydrogen, halogen and C₁₋₆ alkyl;

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

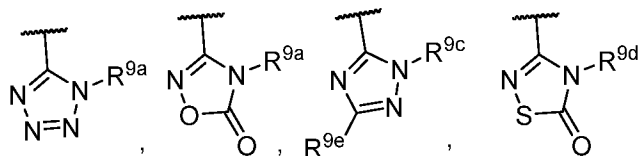
or R₇ and R₈ together with the carbon atom to which they are attached form C₃₋₁₅ carbocyclic ring, wherein the C₃₋₁₅ carbocyclic ring is optionally substituted by one to three C₁₋₆ alkyl, wherein each C₁₋₆ alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, -NR^{7a}R^{7b}, C₁₋₆ alkoxy and 3- to 12-membered heterocyclic, and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl groups and (C₁₋₆ alkyl) carbonyl; and any two C₁₋₆ alkyl groups optionally form a C₃₋₁₅ carbon ring together with the carbon atom to which they are attached;

n₁ is 0, 1, 2 or 3;

n₂ is 0, 1, 2, 3, 4 or 5;

n₃ is 0, 1 or 2;

R₉ is selected from the group consisting of:



, -CO₂R^{9f} and -C(=O)-NR^{9g}R^{9h}; and each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl) carbonyl, wherein C₁₋₆ alkyl is optionally substituted with

hydrogen and C₁₋₆ alkyl;

- g. C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, -NR^{zi}R^{zj}, C₁₋₆ alkoxy, C₁₋₆ 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 or C₁₋₆ alkyl, wherein the 3- to 12-membered heterocyclic groups are optionally substituted with one or more substituents selected from the group consisting of cyano, C₁₋₆ alkyl and 3 to 12-membered heterocyclic;
- h. C₁₋₆ alkoxy; wherein C₁₋₆ alkoxy is optionally substituted by one or more substituents of hydroxyl, halogen and C₁₋₆ alkoxy;
- i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic is optionally substituted by one or more substituents independently selected from C₁₋₆ alkyl and (C₁₋₆ alkyl) carbonyl;
- j. C₆₋₁₀ aryl; wherein C₆₋₁₀ aryl is optionally substituted by one or more (C₁₋₆ 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 C₁₋₆ alkyl, C₁₋₆ 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, C₁₋₆ alkyl, and (C₁₋₆ 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 C₁₋₆ alkyl, and C₁₋₆ alkoxy;
- l. -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl; wherein -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl) carbonyl, wherein each of C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl) carbonyl is optionally substituted by halogen.

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

[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, “C₁₋₆ alkyl” or “C₁-C₆ 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., C₁₋₁₀ alkyl) or 1 to 8 carbon atoms (i.e., C₁₋₈ alkyl) or 1 to 6 carbon atoms (i.e., C₁₋₆ alkyl) or 1 to 4 carbon atoms (i.e., C₁₋₄ alkyl). Examples of alkyl groups include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (*n*-Pr, *n*-propyl, -CH₂CH₂CH₃), 2-propyl (*i*-Pr, *i*-Propyl, -CH(CH₃)₂), 1-butyl (*n*-Bu, *n*-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, -CH₂CH(CH₃)₂), 2-butyl (*s*-Bu, *s*-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, -C(CH₃)₃), 1-pentyl (*n*-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2, 3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3, 3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), and octyl (-CH₂)₇CH₃). Alkyl groups can be unsubstituted or substituted.

[0010] “Alkoxy” refers to the group -O-alkyl, where alkyl is as defined above. For example, C₁₋₄ 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, C₂₋₆ alkoxyalkyl includes -CH₂-OMe, -CH₂-O-*i*Pr, -CH₂-CH₂-OMe, -CH₂-CH₂-O-CH₂-CH₃, and -CH₂-CH₂-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., C₂₋₈ alkenyl) or 2 to 6 carbon atoms (i.e., C₂₋₆ alkenyl) or 2 to 4 carbon atoms (i.e., C₂₋₄ alkenyl). Examples of alkenyl groups include, but are not limited to, ethenyl (-CH=CH₂), allyl (-CH₂CH=CH₂), and -CH₂-CH=CH-CH₃. 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., C₂₋₈ alkynyl) or 2 to 6 carbon atoms (i.e., C₂₋₆ alkynyl) or 2 to 4 carbon atoms (i.e., C₂₋₄ alkynyl). Examples of alkynyl groups include, but are not limited to, acetylenyl (-C≡CH), propargyl (-CH₂C≡CH), and -CH₂-C≡C-CH₃. 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., C₁₋₄ haloalkyl includes CF₃, CH₂F, CHF₂, CH₂CF₃, CH₂CH₂CF₃, CCl₂CH₂CH₂CH₃, and C(CH₃)₂(CF₂H). 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 alkoxy 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., C₁₋₄ haloalkoxy includes OCF₃, OCH₂F, OCH₂CF₃, OCH₂CH₂CF₃, OCCl₂CH₂CH₂CH₃, and OC(CH₃)₂(CF₂H). 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., C₁₋₆ alkyl-C₃₋₁₂ 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, C₇ alkylaryl refers to benzyl, while C₁₁ 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., C₁₋₆ alkyl-C₆₋₁₀ aryl. Non-limiting examples of alkylaryl groups include, but are not limited to, benzyl, 2, 2-dimethylphenyl, n-pentylphenyl, 1-methylnaphthyl, 2-ethylnaphthyl, and the like. 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., C₁₋₆ 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 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., C₁₋₆ 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, isobutyrate, 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 Williams 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 $N(C_1-C_4 \text{ alkyl})_4^+$. 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 iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , 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.

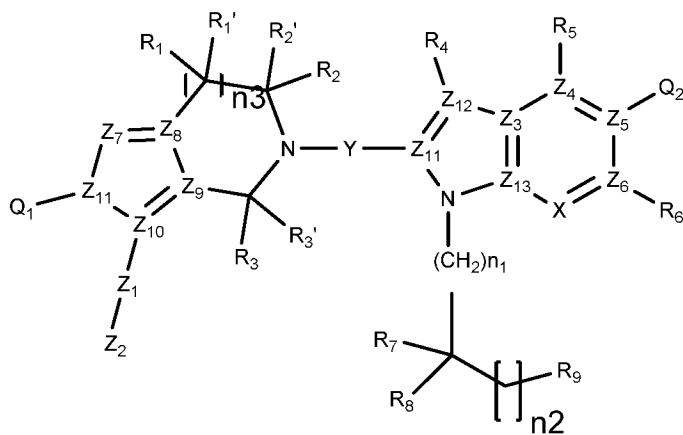
[0043] “Prodrug” as used herein refers to a derivative of a drug that upon administration to the human body is converted to the parent drug according to some chemical or enzymatic pathway. In some embodiments, a prodrug is a biologically inactive derivative of a drug that upon administration to the human 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 C₁₋₆ alkyl;

wherein Y is -C(=O)-;

wherein each of Z₃, Z₄, Z₅, Z₆, Z₇, Z₈, Z₉, Z₁₀, Z₁₁, Z₁₂ and Z₁₃ is independently selected from the group consisting of N and C;

wherein Q₁ is selected from the group consisting of C₆₋₁₀ aryl and C₅₋₁₀ heteroaryl, wherein C₆₋₁₀ aryl or C₅₋₁₀ heteroaryl is optionally substituted by one to five substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and C₁₋₆ alkoxy;

wherein Q₂ 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, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy and -NR^{Qa}R^{Qb}, wherein two C₁₋₆ alkyl groups together with the carbon atoms to which they are attached form a C₃₋₈ carbocyclic ring; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and (C₁₋₆ alkyl) carbonyl;

wherein each of R₁, R₂, R₃, R₁' , R₂' and R₃' is independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cycloalkyl and heterocycloalkyl; wherein C₁₋₆ alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C₁₋₆ alkoxy and hydroxyl;

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

wherein R₁ and R₁' optionally together with the carbon atom to which they are attached form C₃₋₈ cycloalkyl, and R₂ and R₂' optionally together with the carbon atom to which they are attached form C₃₋₈ cycloalkyl; and R₃ and R₃' optionally together with the carbon atom to which they are attached form C₃₋₈ cycloalkyl;

each of R₄, R₅ and R₆ is independently selected from the group consisting of hydrogen, halogen and C₁₋₆ alkyl;

each of R₇ and R₈ is independently selected from the group consisting of hydrogen and C₁₋₆

alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C₃₋₁₅ cycloalkyl;

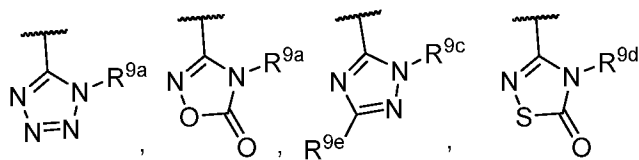
or R₇ and R₈ together with the carbon atom to which they are attached form C₃₋₁₅ carbocyclic ring, wherein the C₃₋₁₅ carbocyclic ring is optionally substituted by one to three C₁₋₆ alkyl, wherein each C₁₋₆ alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, -NR^{7a}R^{7b}, C₁₋₆ alkoxy and 3- to 12-membered heterocyclic, and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl groups and (C₁₋₆ alkyl) carbonyl; and any two C₁₋₆ alkyl groups optionally form a C₃₋₁₅ carbon ring together with the carbon atom to which they are attached;

n₁ is 0, 1, 2 or 3;

n₂ is 0, 1, 2, 3, 4 or 5;

n₃ is 0, 1 or 2;

R₉ is selected from the group consisting of:



, -CO₂R^{9f} and -C(=O)-NR^{9g}R^{9h}; and each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl and (C₁₋₆ alkyl) carbonyl, wherein C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C₁₋₆ alkoxy;

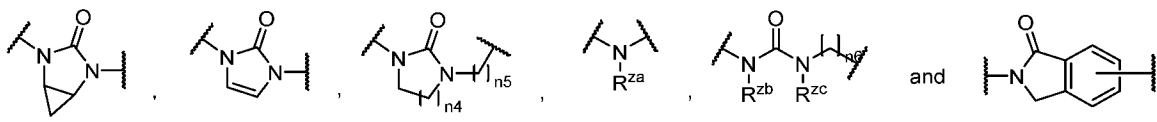
R^{9e} is selected from the group consisting of hydrogen and C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

R^{9f} is selected from the group consisting of hydrogen and C₁₋₆ alkyl;

R^{9h} is selected from the group consisting of hydrogen, C₁₋₆ alkyl, (C₁₋₆ alkyl) carbonyl, cyano and -S(=O)_{n3}-R⁹ⁱ;

R⁹ⁱ is C₁₋₆ alkyl;

Z₁ 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;

n_4 is 1, 2 or 3; each of n_5 and n_6 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 the C_{3-15} cycloalkyl, and 3 to 12-membered heterocyclic group are independently optionally substituted with one to five G's;

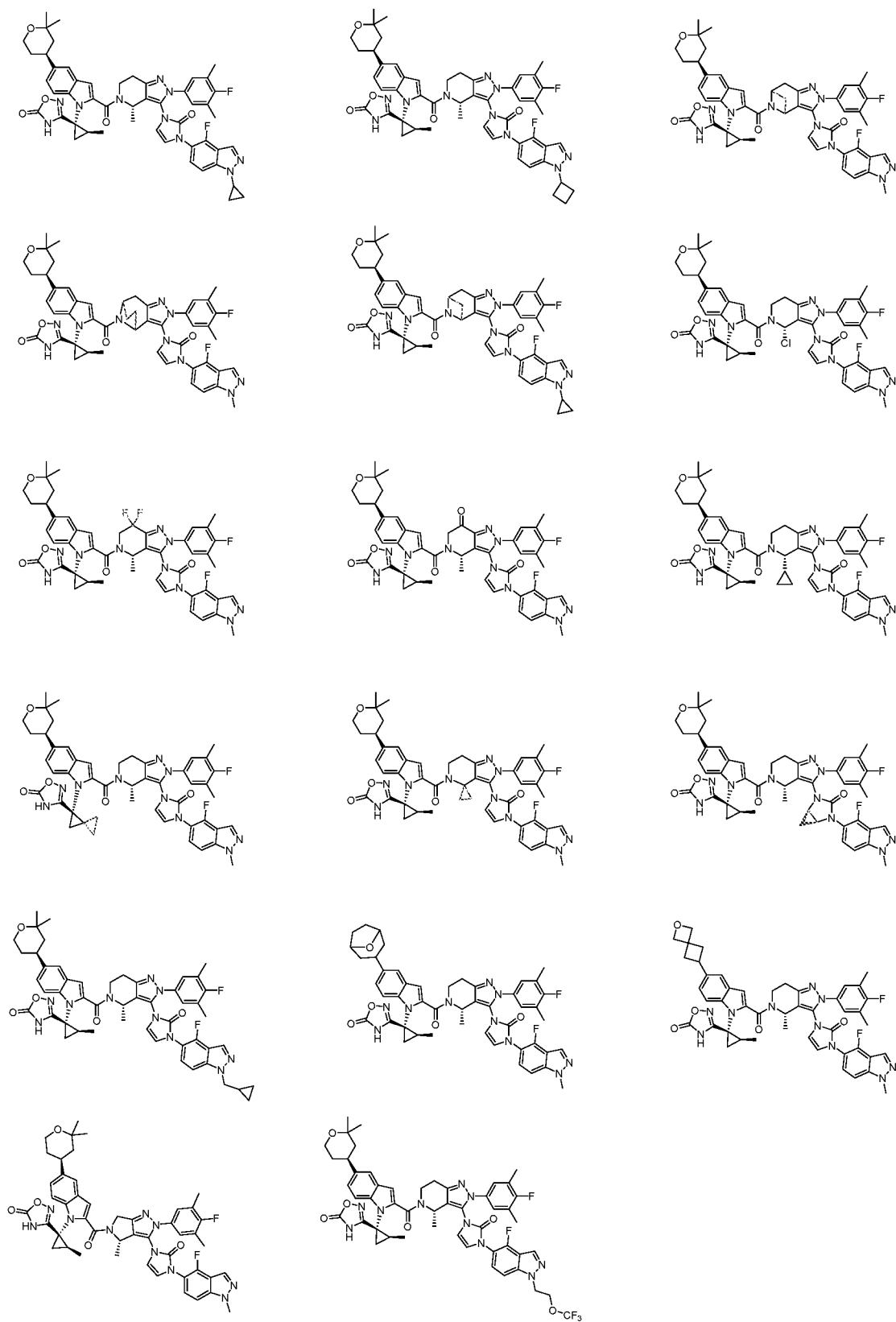
wherein G's is selected from the group consisting of:

- 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 n_7 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 or 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 C₁₋₆ alkyl and (C₁₋₆ alkyl) carbonyl;

- j. C₆₋₁₀ aryl; wherein C₆₋₁₀ aryl is optionally substituted by one or more (C₁₋₆ 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 C₁₋₆ alkyl, C₁₋₆ 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, C₁₋₆ alkyl, and (C₁₋₆ 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 C₁₋₆ alkyl, and C₁₋₆ alkoxy;
- l. -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl; wherein -C₃-C₁₅ cycloalkyl or -C₁-C₆ alkyl-C₃-C₁₅ cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl) carbonyl, wherein each of C₁₋₆ alkyl, C₁₋₆ alkoxy and (C₁₋₆ alkyl) carbonyl is optionally substituted by halogen.

[0046] 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

[0047] 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.

[0048] In some embodiments, the pharmaceutical composition comprises a compound of Formula I or a pharmaceutically acceptable salt thereof.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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 Williams and Wilkins, Philadelphia, Pa., 2006.

[0053] 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.

[0054] 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).

[0055] 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

[0056] 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.

[0057] 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

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.

[0058] 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.

[0059] 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).

[0060] In some embodiments, the GLP-1R-mediated disease or condition is a metabolic disease.

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

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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

[0076] 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.

[077] 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 (PPAR α) agonist, fish oil, an acetyl-coA carboxylase (ACC) inhibitor, or a TGF β antagonist, or a combination thereof.

[078] 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, interleukin-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, stearyl 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.

[079] 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 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 nacamizumab (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);

- 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 tiplelukast (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 URM-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 tiplelukast (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).

[080] 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, tielukast (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, WXS-0038, WXS-0078, XEN-103, XR-117, XTYW-003, XW-003, XW-004, ZGN-839, ZG-5216, ZSYM-008, ZSYM-007.

[081] In some embodiments, the compound of present application is administered in combination with one or more therapeutic 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, farnesoid 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., bupropion), 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., metreleptin), 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), SGLT1 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 (PPAR α) agonists, fish oil, acetyl-coA carboxylase (ACC) inhibitors, transforming growth factor beta (TGF β) antagonists, GDNF family receptor type 1 (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

[082] 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

[083] 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

[084] 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.

[085] 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.

[086] 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.

[087] 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, 5th Edition, 2001), and *Larock's Comprehensive Organic Transformations* (VCH Publishers Inc., 1989).

[088] 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

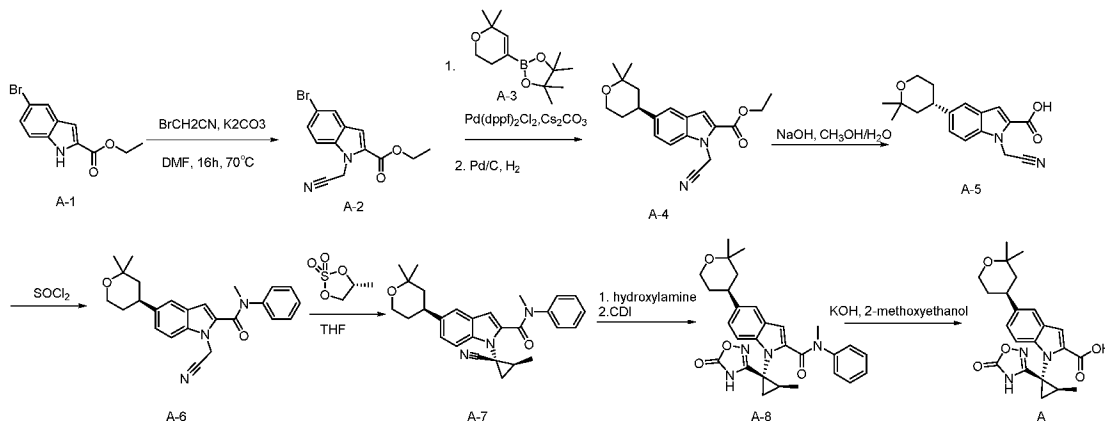
ether, methanol, pyridine and the like). Unless specified to the contrary, the solvents used in the reactions of the present application are inert organic solvents, and the reactions are carried out under an inert gas, preferably nitrogen.

[089] 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°C 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 N₂. 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%.

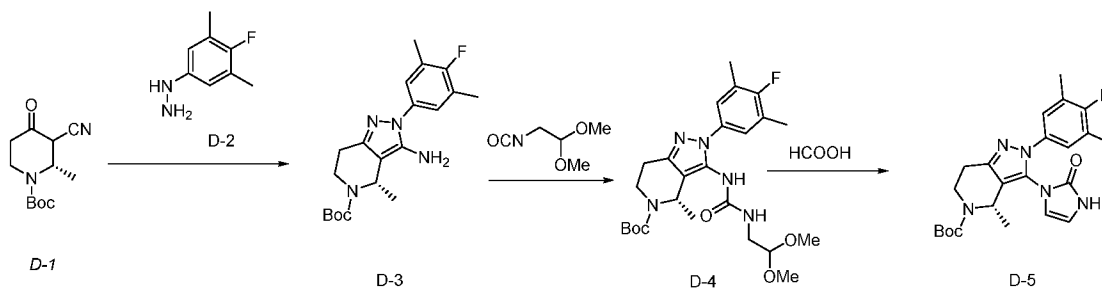
A-5(300mg, 1.1mmol) was dissolved in dichloromethane (10ml), thionyl dichloride (520mg, 4.4mmol) and 1 drop of DMF were added and reacted at room temperature for 6 hours. Concentrate the reaction solution to dryness to obtain acyl chloride oil, and add 5ml of dichloromethane to dissolve it for use. N- 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°C , 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°C for 5 hours. Cooling to room temperature, adjusting pH to 5.0 with hydrochloric acid (6N), adding ethyl

Intermediate B and C were prepared by the same method:

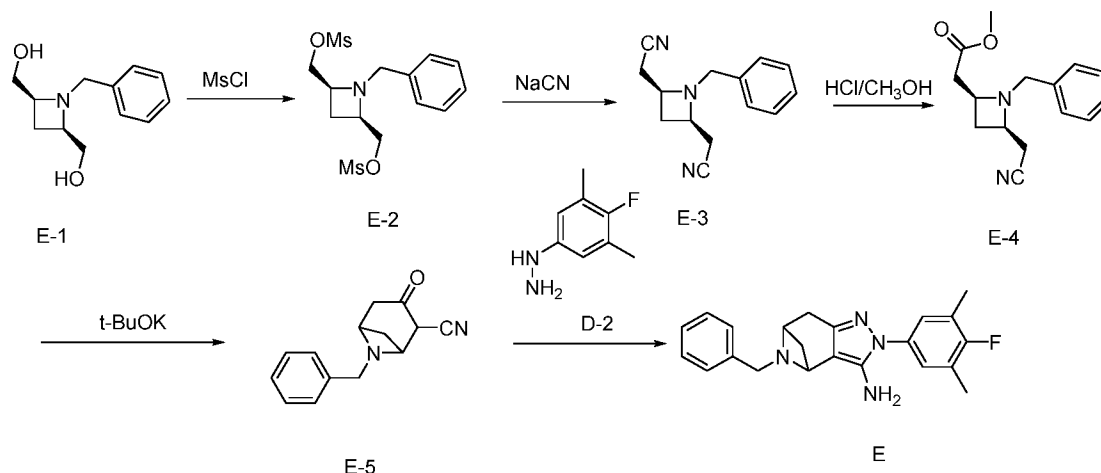


D-3(2.0g, 5.34mmol) was dissolved in DCM (20ml), and a dichloromethane (5ml) solution of 2- isocyanate -1, 1- dimethoxyethane (0.84g, 6.41mmol) was added dropwise at room temperature, and the mixture was stirred at room temperature for 2 hours. Add water (20ml),

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°C 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%.

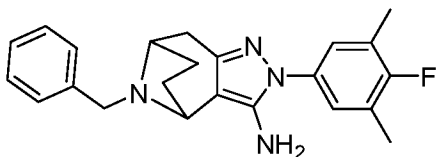
E-3(1.2g, 5.33mmol) was dissolved in methanol solution of hydrogen chloride (1M, 7ml) and stirred overnight at room temperature, followed by adding water and stirring for 2h. Ethyl acetate (20ml) was added, and the organic phase was separated by extraction. After vacuum evaporation, an oil was obtained,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

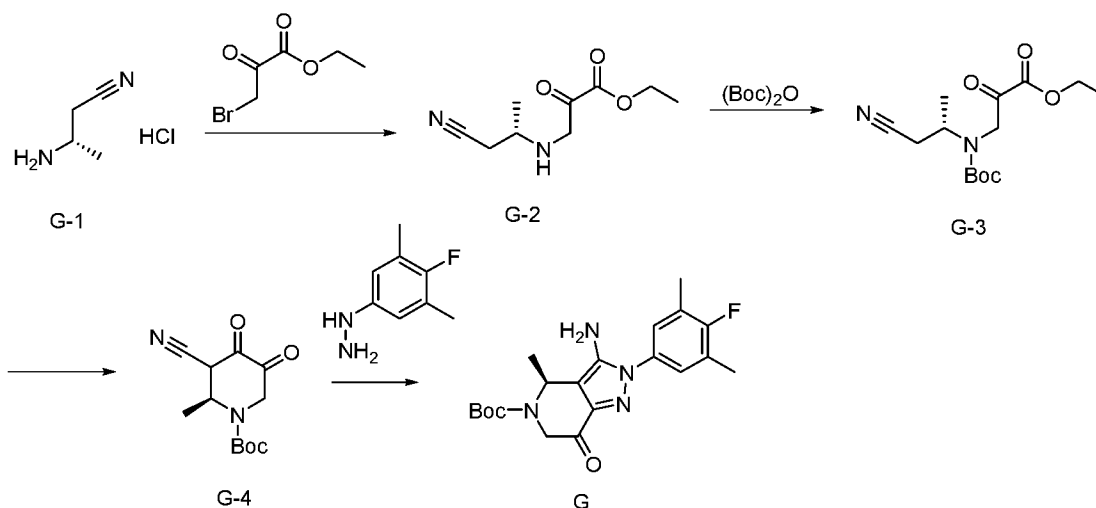
acid, add ethyl acetate for extraction, evaporate under reduced pressure, and then get E-5, 0.34g by column chromatography with a yield of 68%.

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%.

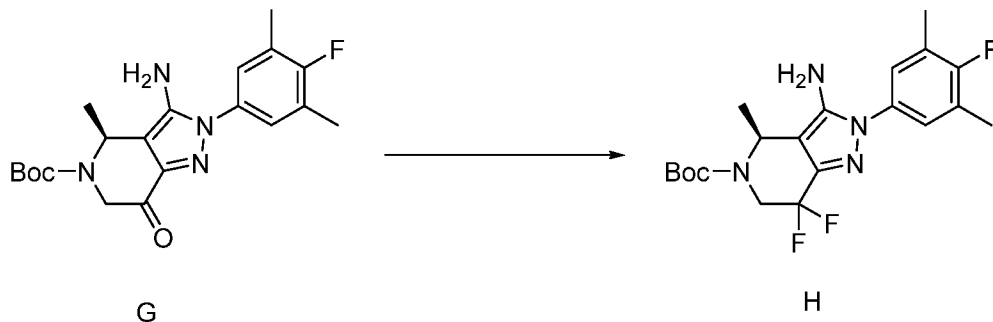
G-2(4.0g, 20.2mmol), (Boc)₂O(6.6g, 30.3mmol) and triethylamine (6.13g, 60.5mmol) were dissolved in THF(40ml) and stirred overnight at room temperature. Adding water (50ml) and ethyl acetate (50ml), extracting to separate out the organic phase, and then concentrating under reduced pressure to obtain G-3, 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%.

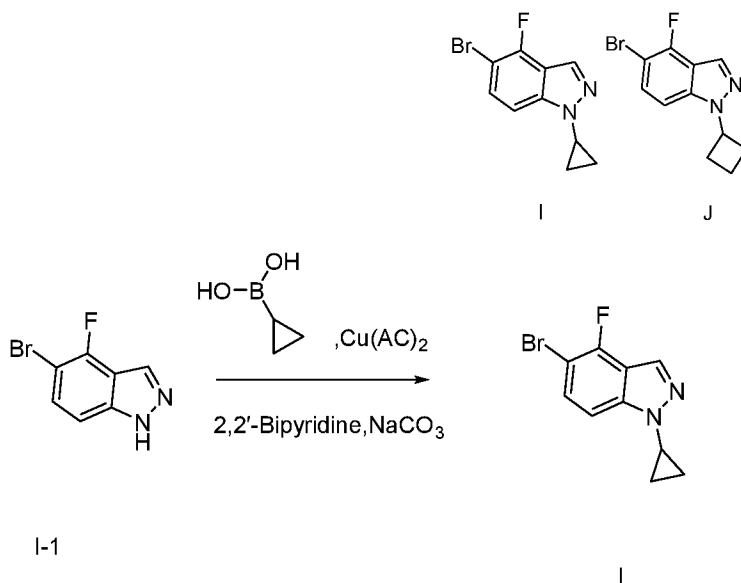
G-4(2.0g, 7.93mmol), D-2(1.22g, 7.93mmol) and pyridine hydrochloride (0.9g, 7.93mmol) were dissolved in toluene (40ml) and heated to reflux for 1 hour. After cooling the reaction solution, water (40ml) and ethyl acetate (40ml) were added to extract the organic phase, and the target compound G, 1.2g,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

Preparation of intermediate H:



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;

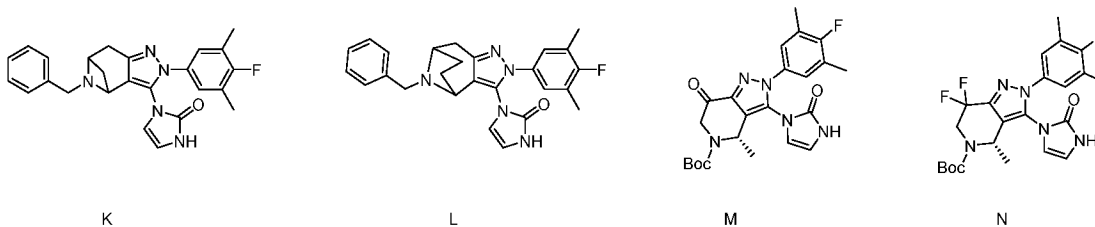


Compound I-1(50ml, 23.3mmol), cyclopropylboronic acid (3.99g, 46.5mmol), copper acetate (3.48g, 23.2mmol), 2, 2' bipyridine (3.9g, 23.3mmol) and sodium carbonate (4.9g, 46.5mmol) were added to dichloroethane. The reaction solution was filtered, the filtrate was extracted with water and

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%.

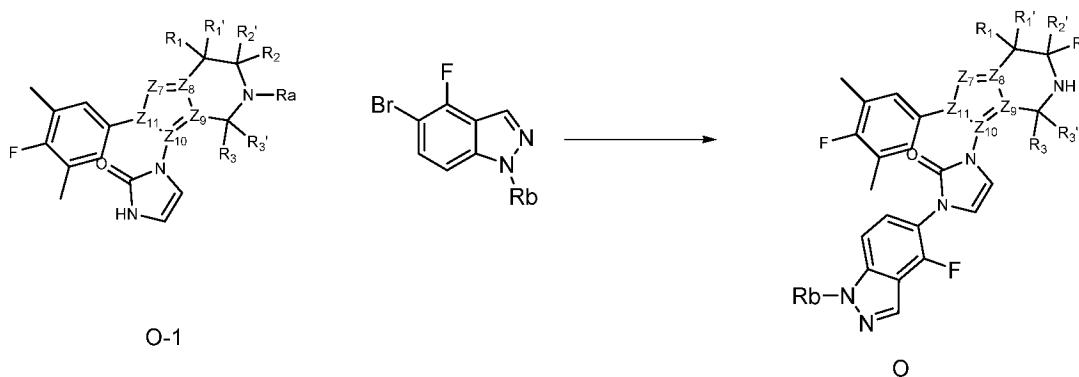
Intermediate j can be obtained by the same method.

Preparation of intermediates K, L, M and N



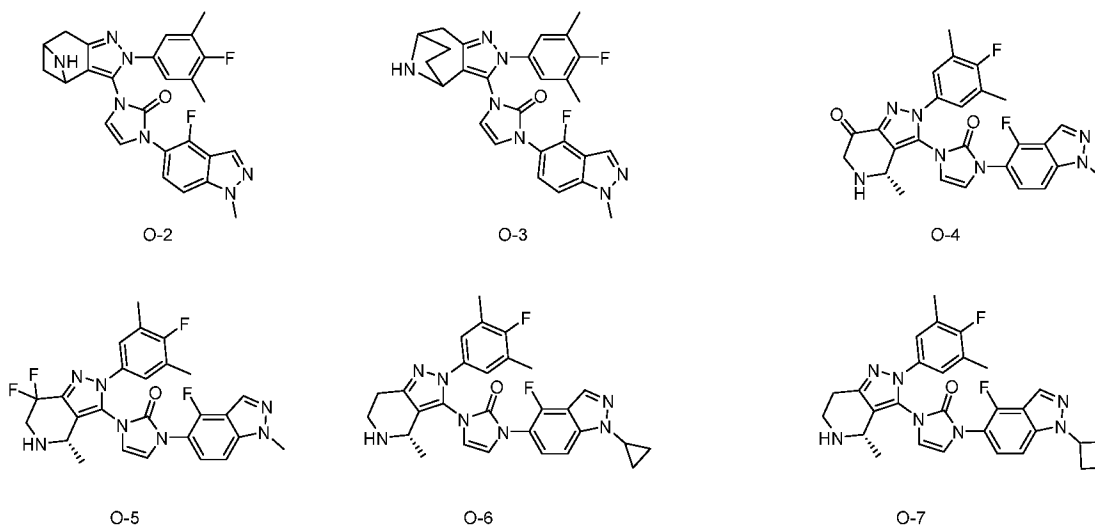
According to the preparation method of intermediate D, K, L, M and N can be obtained.

Preparation of intermediate O

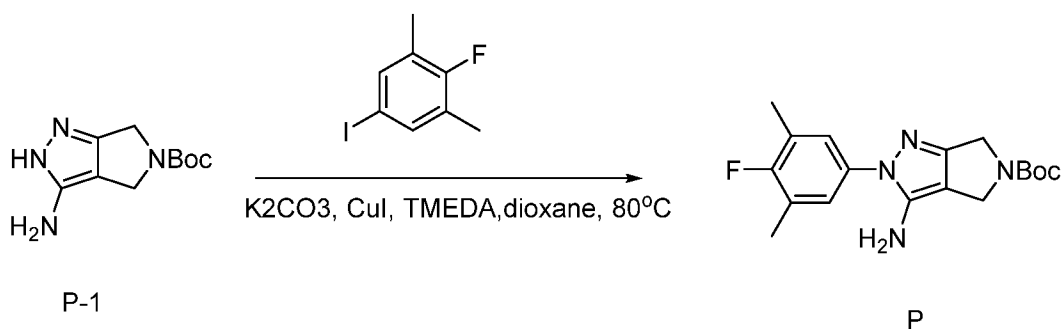


O-1(1eq.) and (1R, 2R)-(-)-N, N'- dimethyl -1, 2- cyclohexanediamine (0.5eq.), CuI(0.5eq.), bromide (1.5eq.) and potassium carbonate (3eq.) were added to NMP. Filtering, adding water and ethyl acetate to the filtrate, extracting to separate out the organic phase, depressurizing, purifying, and deprotecting (debenzylation or Boc removal) to obtain the target compound.

The following compounds can be prepared by this method:

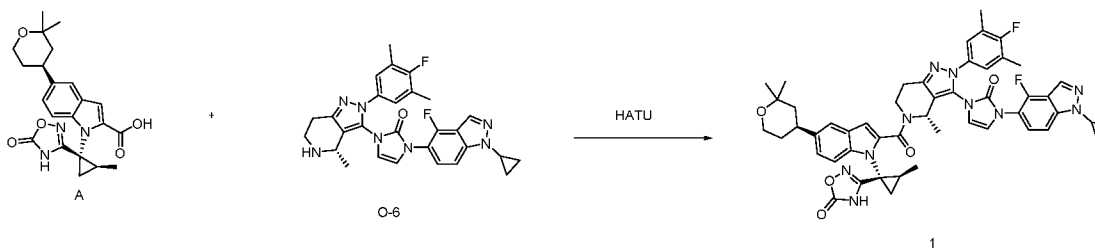


Preparation of intermediate P:



P-1(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%.

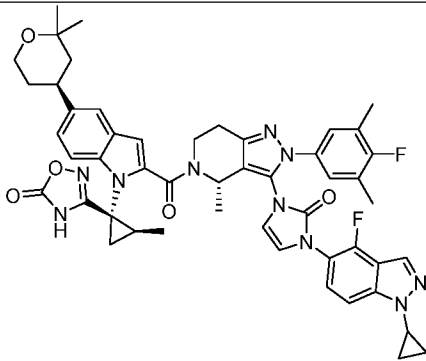
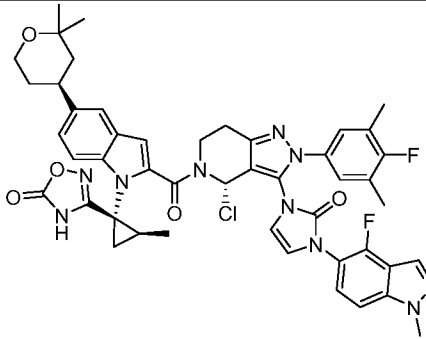
Preparation of compound 1

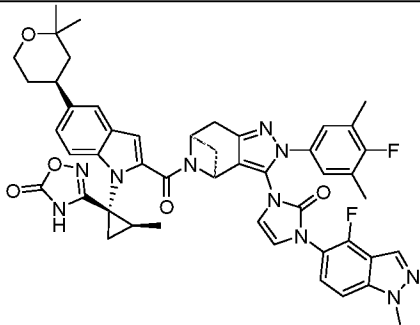


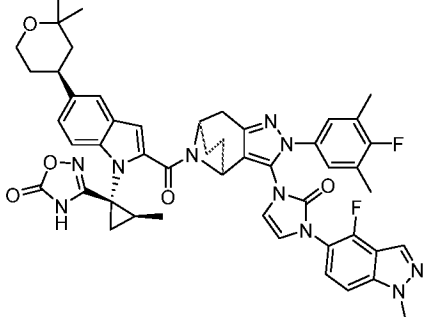
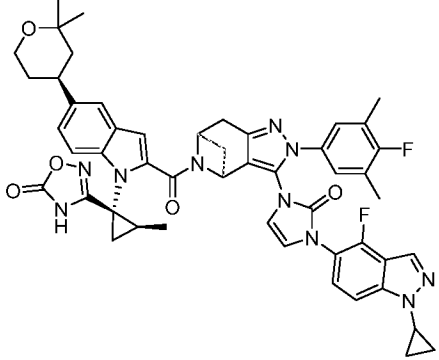
Intermediate A(180mg, 0.44mmol), O-6(280mg, 0.57mmol), HATU(250.95mg, 0.66mmol) and DIPEA(170mg, 1.32mmol) were dissolved in DMF(5ml) and stirred at room temperature for 3 hours. Add 5ml of water, extract with dichloromethane for 3 times, and combine the organic phases.

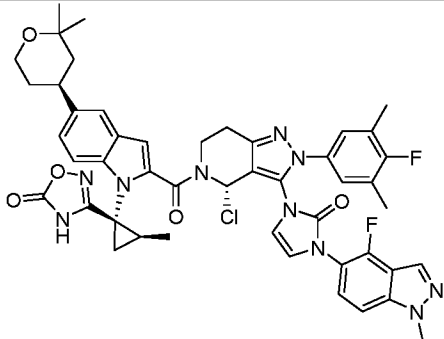
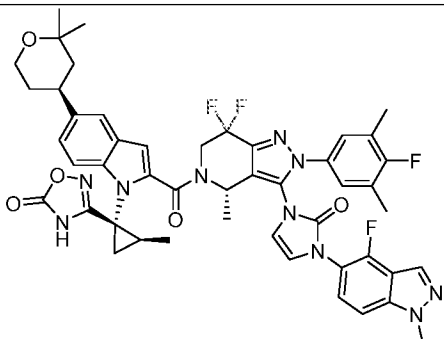
Concentrated under reduced pressure, and purified by preparative liquid phase (acetonitrile: 0.1% formic acid aqueous solution), 1, 200 mg of the target compound was obtained with a yield of 51%.

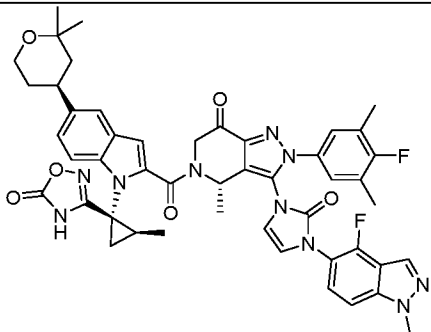
According to the preparation method described in this paper, the following compounds were prepared by using appropriate starting materials and intermediates and, if necessary, appropriate protective group chemistry. The structures were confirmed by MS and ^1H NMR.

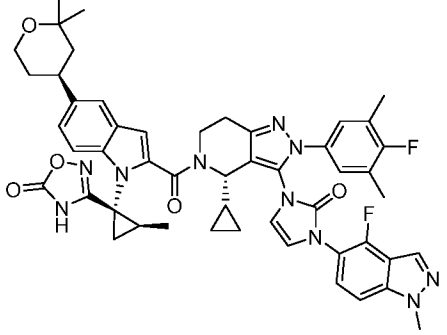
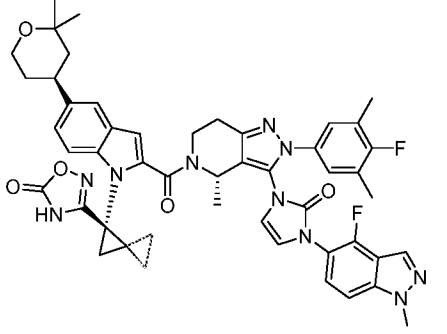
Number	Structure	MS	^1H NMR
1		909.39	^1H NMR (500 MHz, Chloroform- <i>d</i>) δ 8.79 (s, 1H), 8.37 – 8.29 (m, 2H), 8.21 – 8.14 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 1H), 7.51 – 7.41 (m, 4H), 7.25 – 7.20 (m, 1H), 7.11 – 7.04 (m, 1H), 5.24 – 5.14 (m, 1H), 4.57 – 4.49 (m, 1H), 4.14 – 4.05 (m, 1H), 3.86 – 3.61 (m, 3H), 3.08 – 2.90 (m, 3H), 2.49 – 2.32 (m, 3H), 2.26 – 2.23 (m, 6H), 2.08 – 1.91 (m, 2H), 1.86 – 1.69 (m, 2H), 1.61 – 1.57 (m, 3H), 1.39 – 1.31 (m, 2H), 1.29 – 1.22 (m, 5H), 1.19 (s, 3H), 1.01 – 0.98 (m, 3H).
2		923.41	^1H NMR (500 MHz, Chloroform- <i>d</i>) 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),

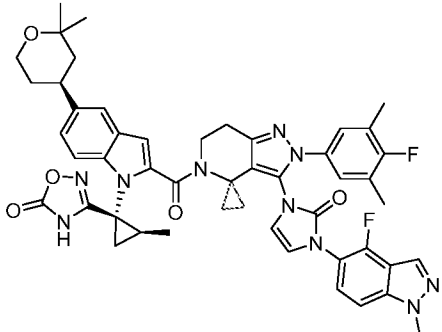
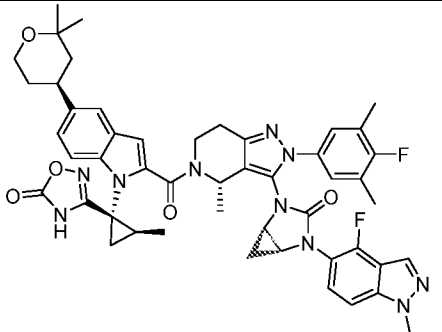
			4.53 – 4.47 (m, 1H), 4.14 – 4.05 (m, 1H), 3.86 – 3.78 (m, 1H), 3.76 – 3.62 (m, 2H), 3.08 – 2.90 (m, 3H), 2.48 – 2.31 (m, 3H), 2.24 (s, 6H), 2.14 – 1.98 (m, 5H), 1.97 – 1.92 (m, 1H), 1.87 – 1.77 (m, 3H), 1.75 – 1.69 (m, 1H), 1.59 (d, $J = 7.8$ Hz, 3H), 1.24 (s, 3H), 1.19 (s, 3H), 1.00 (d, $J = 6.0$ Hz, 3H).
3		881.36	¹ H NMR (500 MHz, DMSO- <i>d</i> 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).

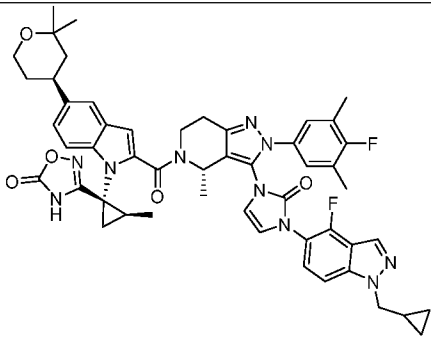
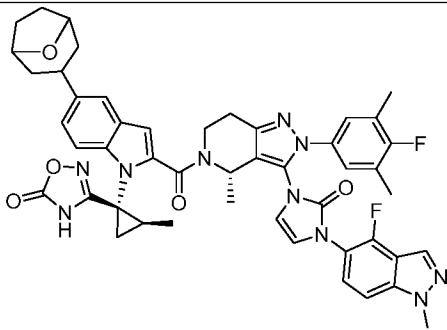
4		895.38	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.36 – 8.28 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.67 – 7.62 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.25 (d, <i>J</i> = 2.0 Hz, 1H), 7.10 – 7.04 (m, 1H), 5.07 – 5.00 (m, 1H), 4.55 – 4.46 (m, 1H), 3.93 (s, 3H), 3.71 – 3.61 (m, 2H), 3.05 – 2.85 (m, 3H), 2.49 – 2.42 (m, 1H), 2.37 – 2.29 (m, 2H), 2.26 – 2.16 (m, 7H), 2.08 – 1.89 (m, 5H), 1.89 – 1.81 (m, 1H), 1.77 – 1.71 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, <i>J</i> = 6.0 Hz, 3H).
5		907.38	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.39 – 8.29 (m, 3H), 7.94 – 7.88 (m, 1H), 7.68 – 7.58 (m, 2H), 7.46 – 7.38 (m, 3H), 7.25 (d, <i>J</i> = 2.0 Hz, 1H), 7.09 – 7.05 (m, 1H), 5.63 – 5.57 (m, 1H), 4.70 – 4.63 (m, 1H), 4.56 – 4.50 (m, 1H), 3.74 – 3.59 (m, 2H), 3.10 – 3.03 (m, 1H), 3.02 – 2.94 (m, 2H), 2.67 – 2.60 (m, 1H), 2.49 – 2.39 (m, 2H), 2.36 – 2.30 (m, 1H), 2.27 – 2.17 (m, 7H), 2.08 – 2.01 (m, 1H), 1.97 – 1.92 (m, 1H),

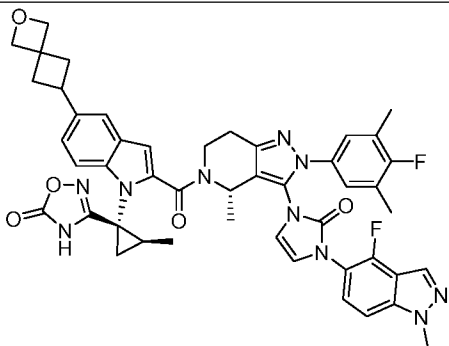
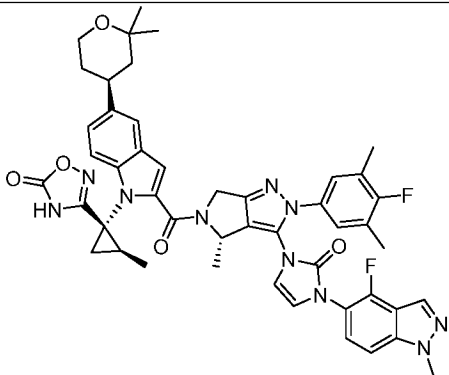
			1.86 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.39 – 1.29 (m, 2H), 1.29 – 1.20 (m, 5H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H).
6		903.32	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.38 – 8.28 (m, 2H), 8.14 (d, $J = 4.9$ Hz, 1H), 7.81 – 7.75 (m, 1H), 7.68 – 7.63 (m, 1H), 7.54 (d, $J = 8.9$ Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.10 – 7.04 (m, 1H), 6.94 (s, 1H), 4.33 – 4.25 (m, 1H), 4.09 – 4.03 (m, 1H), 3.93 (s, 3H), 3.74 – 3.67 (m, 1H), 3.66 – 3.58 (m, 1H), 3.07 – 2.94 (m, 3H), 2.49 – 2.41 (m, 1H), 2.38 – 2.28 (m, 2H), 2.24 (s, 6H), 2.07 – 2.00 (m, 1H), 1.99 – 1.91 (m, 1H), 1.87 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H).
7		919.36	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.39 – 8.28 (m, 2H), 8.14 (d, $J = 4.9$ 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,

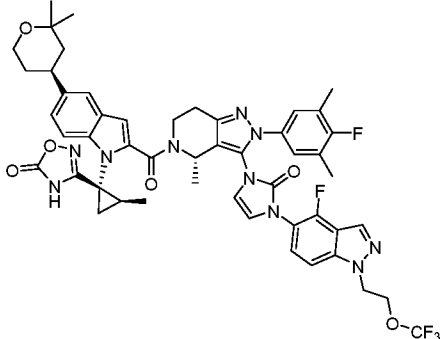
			<p>1H), 7.09 – 7.05 (m, 1H), 5.27 – 5.19 (m, 1H), 4.89 – 4.76 (m, 2H), 3.93 (s, 3H), 3.74 – 3.58 (m, 2H), 3.03 – 2.94 (m, 1H), 2.50 – 2.38 (m, 1H), 2.38 – 2.28 (m, 2H), 2.24 (s, 6H), 2.08 – 1.99 (m, 1H), 1.98 – 1.90 (m, 1H), 1.87 – 1.78 (m, 1H), 1.76 – 1.68 (m, 1H), 1.60 (d, $J = 7.5$ Hz, 3H), 1.25 –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

9		895.38	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.36 – 8.29 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.83 – 7.76 (m, 1H), 7.68 – 7.63 (m, 1H), 7.57 – 7.51 (m, 1H), 7.48 – 7.37 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.11 – 7.04 (m, 1H), 4.89 (d, <i>J</i> = 6.7 Hz, 1H), 4.18 – 4.08 (m, 1H), 3.93 (s, 3H), 3.87 – 3.79 (m, 1H), 3.75 – 3.58 (m, 2H), 3.05 – 2.88 (m, 3H), 2.51 – 2.44 (m, 1H), 2.37 – 2.29 (m, 2H), 2.24 (s, 6H), 2.08 – 2.00 (m, 1H), 1.98 – 1.89 (m, 2H), 1.87 – 1.78 (m, 1H), 1.75 – 1.69 (m, 1H), 1.25 – 1.15 (m, 6H), 0.99 (d, <i>J</i> = 6.0 Hz, 3H), 0.68 – 0.57 (m, 2H), 0.49 – 0.39 (m, 2H).
10		895.38	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.76 (s, 1H), 8.36 – 8.29 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.67 – 7.64 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.10 – 7.04 (m, 1H), 5.22 – 5.14 (m, 1H), 4.11 – 4.05 (m, 1H), 3.96 – 3.85 (m, 4H), 3.74 – 3.58 (m, 2H), 3.04 – 2.90 (m, 3H), 2.35 (s, 2H), 2.24 (s, 6H), 2.07 – 1.91

			(m, 2H), 1.86 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.65 – 1.47 (m, 7H), 1.25 – 1.16 (m, 6H).
11		895.38	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.34 – 8.23 (m, 2H), 8.14 (d, <i>J</i> = 4.9 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.67 – 7.63 (m, 1H), 7.54 (d, <i>J</i> = 8.9 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.24 (d, <i>J</i> = 2.0 Hz, 1H), 7.11 – 7.04 (m, 1H), 3.96 – 3.83 (m, 5H), 3.74 – 3.59 (m, 2H), 3.01 – 2.95 (m, 1H), 2.91 – 2.84 (m, 2H), 2.51 – 2.44 (m, 1H), 2.37 – 2.19 (m, 12H), 2.07 – 2.00 (m, 1H), 1.97 – 1.92 (m, 1H), 1.87 – 1.79 (m, 1H), 1.75 – 1.69 (m, 1H), 1.26 – 1.16 (m, 6H), 0.99 (d, <i>J</i> = 6.0 Hz, 3H).
12		898.00	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.13 (d, <i>J</i> = 5.2 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.53 (d, <i>J</i> = 9.0 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.37 (d, <i>J</i> = 4.9 Hz, 2H), 7.21 (d, <i>J</i> = 2.0 Hz, 1H), 7.10 – 7.05 (m, 1H), 5.22 – 5.11 (m, 1H), 4.34 – 4.29 (m, 2H), 4.10 – 4.03 (m, 1H), 3.96 – 3.87 (m, 4H), 3.74 – 3.59 (m, 2H),

			3.04 – 2.89 (m, 3H), 2.48 – 2.42 (m, 1H), 2.38 – 2.29 (m, 2H), 2.24 (s, 6H), 2.07 – 1.91 (m, 3H), 1.86 – 1.68 (m, 3H), 1.60 (d, $J = 8.0$ Hz, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H).
13		923.41	^1H NMR (500 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.37 – 8.29 (m, 2H), 8.25 (d, $J = 4.9$ Hz, 1H), 7.85 – 7.78 (m, 1H), 7.67 – 7.62 (m, 1H), 7.48 – 7.37 (m, 4H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.09 – 7.04 (m, 1H), 5.22 – 5.13 (m, 1H), 4.13 – 3.84 (m, 4H), 3.73 – 3.59 (m, 2H), 3.03 – 2.89 (m, 3H), 2.49 – 2.20 (m, 9H), 2.08 – 1.91 (m, 2H), 1.87 – 1.68 (m, 2H), 1.63 – 1.45 (m, 4H), 1.23 (s, 3H), 1.18 (s, 3H), 0.99 (d, $J = 6.0$ Hz, 3H), 0.61 – 0.38 (m, 4H).
14		881.36	^1H NMR (500 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.37 – 8.28 (m, 2H), 8.14 (d, $J = 4.9$ Hz, 1H), 7.82 – 7.75 (m, 1H), 7.66 – 7.61 (m, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 7.46 – 7.37 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.11 – 7.06 (m, 1H), 5.22 – 5.14 (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	^1H 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	^1H NMR (500 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.37 – 8.28 (m, 2H), 8.14 (d, $J = 4.9$ Hz, 1H), 7.81 – 7.76 (m, 1H), 7.66 – 7.64 (m, 1H), 7.54 (d, $J = 8.9$ Hz, 1H), 7.45 – 7.37 (m, 3H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.10 – 7.05 (m, 1H), 5.02 – 4.95 (m, 1H), 4.61 (d,

			$J = 1.0$ Hz, 2H), 3.93 (s, 3H), 3.71 – 3.62 (m, 2H), 3.03 – 2.94 (m, 1H), 2.49 – 2.40 (m, 1H), 2.38 – 2.21 (m, 8H), 2.06 – 1.81 (m, 3H), 1.77 – 1.70 (m, 1H), 1.57 (d, $J = 7.0$ Hz, 3H), 1.27 – 1.15 (m, 6H), 0.99 (d, $J = 6.0$ Hz, 3H).
17		981.38	^1H NMR (500 MHz, Chloroform- d) δ 8.79 (s, 1H), 8.37 – 8.29 (m, 2H), 8.21 – 8.14 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 1H), 7.51 – 7.41 (m, 4H), 7.25 – 7.20 (m, 1H), 7.11 – 7.04 (m, 1H), 5.24 – 5.14 (m, 1H), 4.59 – 4.49 (m, 3H), 4.14 – 4.05 (m, 1H), 3.86 – 3.61 (m, 5H), 3.08 – 2.90 (m, 3H), 2.49 – 2.32 (m, 3H), 2.26 – 2.23 (m, 6H), 2.08 – 1.91 (m, 2H), 1.86 – 1.69 (m, 2H), 1.61 – 1.57 (m, 3H), 1.39 – 1.31 (m, 2H), 1.19 (s, 3H), 1.01 – 0.98 (m, 3H).