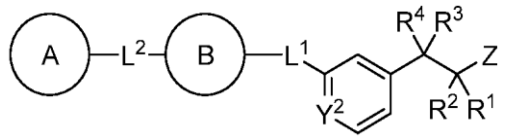
GPR40 AGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of US Provisional Application No. 62/983,438 filed on February 28, 2020, US Provisional Application No. 63/076,113 filed on September 9, 2020, US Provisional Application No. 63/117,074 filed on November 23, 2020, and US Provisional Application No. 63/147,980 filed on February 10, 2021, each of which is incorporated herein by reference in its entirety.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0001a] In an aspect of the present disclosure, there is provided a compound of Formula (2):



Formula (2)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

Z is $–P(=O)(R^5)OR^6$;

R^5 is C_1-C_6 alkyl;

R^6 is hydrogen or C_1-C_6 alkyl;

R^1, R^2, and R^3 are each independently hydrogen, halogen, or C_1-C_6 alkyl;

R^4 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

Y^2 is N or CH;

L^1 is *-O-CH_2-, *-CH_2-O-, *-NR^7-CH_2-, *-NR^7-C(O)-, *-C(O)-NR^7-, or *-C(O)-CH_2-;

wherein * represents the connection to Ring B;

R^7 is hydrogen or C_1-C_6 alkyl;

Ring B is 3- to 6-membered heterocycloalkylene; wherein the heterocycloalkylene is unsubstituted or substituted with 1, 2, 3, or 4 R^B substituents; or

Ring B is C_3-C_6 cycloalkylene; wherein the cycloalkylene is unsubstituted or substituted with 1, 2, 3, or 4 R^B substituents;

Ring A is aryl or heteroaryl; wherein the aryl or heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^A substituents;

L^2 is a bond or C_1-C_6 alkylene; wherein the alkylene is unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of –OH, C_1-C_6 alkyl, and –O–(C_1-C_6 alkyl);

each R^A is independently halogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} fluoroalkyl, $–L^A–CN$, $–L^A–OH$, $–L^A–OR^{10}$, $–L^A–NR^{11}R^{11}$, $–L^A–C(=O)R^{10}$, $–L^A–$

$C(=O)OR^{11}$, $–L^A–OC(=O)R^{11}$, $–L^A–C(=O)NR^{11}R^{11}$, $–L^A–NR^{11}C(=O)R^{11}$, $–L^A–NR^{11}C(=O)NR^{11}R^{11}$, $–L^A–OC(=O)NR^{11}R^{11}$, $–L^A–NR^{11}C(=O)OR^{10}$, $–L^A–OC(=O)OR^{10}$, $–L^A–$aryl, $–L^A–$heteroaryl, $–L^A–(C_3\text{-}C_{10}$ cycloalkyl), or $–L^A–$(3- to 10-membered heterocycloalkyl); wherein each alkyl, alkenyl, alkynyl, fluoroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –CN, –OH, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ fluoroalkyl, $C_1\text{-}C_6$ hydroxyalkyl, $–O–(C_1\text{-}C_6$ alkyl), and $–O–(C_1\text{-}C_6$ fluoroalkyl);

each R^B is independently halogen, $C_1\text{-}C_6$ alkyl, or $C_1\text{-}C_6$ fluoroalkyl;

each L^A is independently a bond or $C_1\text{-}C_6$ alkylene; wherein the alkylene is unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, –CN, –OH, $–O–(C_1\text{-}C_6$ alkyl), and $C_1\text{-}C_6$ alkyl;

each R^{10} is independently $C_1\text{-}C_6$ alkyl; wherein each alkyl is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –OH, $C_1\text{-}C_6$ alkyl, and $C_1\text{-}C_6$ hydroxyalkyl; and

each R^{11} is independently hydrogen, $C_1\text{-}C_6$ alkyl, or monocyclic heteroaryl; wherein each alkyl and heteroaryl is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –OH, $C_1\text{-}C_6$ alkyl, and $C_1\text{-}C_6$ hydroxyalkyl;

or two R^{11} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6-membered *N*-heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –OH, $C_1\text{-}C_6$ alkyl, and $C_1\text{-}C_6$ hydroxyalkyl.

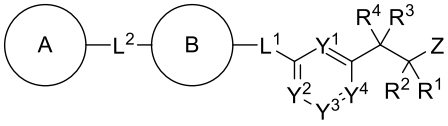
[0001b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[0001c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, in the manufacture of a medicament for treating a condition or disorder involving the gut-brain axis; wherein the condition or disorder is associated with GPR40 activity.

[0001d] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for use in therapy.

[0002] Disclosed herein, in certain ~~embodiment~~examples, are free fatty acid receptor 1 (GPR40) agonists useful for the treatment of conditions or disorders involving the gut-brain axis. In some ~~embodiment~~examples, the GPR40 agonists are gut-restricted or selectively modulate GPR40 located in the gut. In some ~~embodiment~~examples, the condition is selected from the group consisting of: central nervous system (CNS) disorders including mood disorders, anxiety, depression, affective disorders, schizophrenia, malaise, cognition disorders, addiction, autism, epilepsy, neurodegenerative disorders, Alzheimer's disease, and Parkinson's disease, Lewy Body dementia, episodic cluster headache, migraine, pain; metabolic conditions including diabetes and its complications such as chronic kidney disease/diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, and cardiovascular disease, metabolic syndrome, obesity, dyslipidemia, and nonalcoholic steatohepatitis (NASH); eating and nutritional disorders including hyperphagia, cachexia, anorexia nervosa, short bowel syndrome, intestinal failure, intestinal insufficiency and other eating disorders; inflammatory disorders and autoimmune diseases such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis and celiac disease; necrotizing enterocolitis; gastrointestinal injury resulting from toxic insults such as radiation or chemotherapy; diseases/disorders of gastrointestinal barrier dysfunction including environmental enteric dysfunction, spontaneous bacterial peritonitis; functional gastrointestinal disorders such as irritable bowel syndrome, functional dyspepsia, functional abdominal bloating/distension, functional diarrhea, functional constipation, and opioid-induced constipation; gastroparesis; nausea and vomiting; disorders related to microbiome dysbiosis, and other conditions involving the gut-brain axis.

[0003] Disclosed herein, in certain ~~embodiment~~examples, is a compound of Formula (I):



Formula (I)

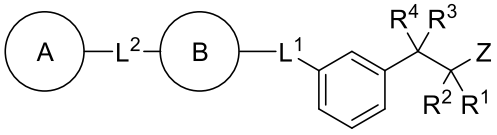
consisting of halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 hydroxyalkyl, –O–(C_1-C_6 alkyl), and –O–(C_1-C_6 fluoroalkyl); and

each R^{11} is independently hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl; wherein each alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 hydroxyalkyl, –O–(C_1-C_6 alkyl), and –O–(C_1-C_6 fluoroalkyl);

or two R^{11} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 10-membered *N*-heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 hydroxyalkyl, –O–(C_1-C_6 alkyl), and –O–(C_1-C_6 fluoroalkyl).

[0004] Any combination of the groups described above or below for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

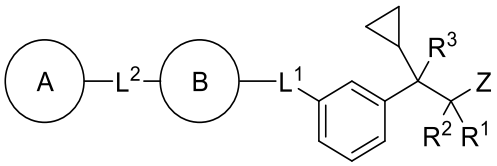
[0005] In some ~~embodiment~~examples, the compound is a compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

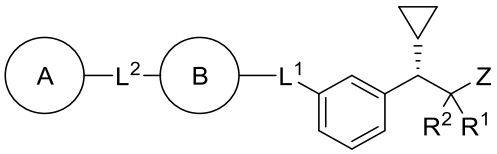
[0006] In some ~~embodiment~~examples, the compound is a compound of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein R^1, R^2, and R^3 are each independently hydrogen, -F, -Cl, or C_1-C_4 alkyl.

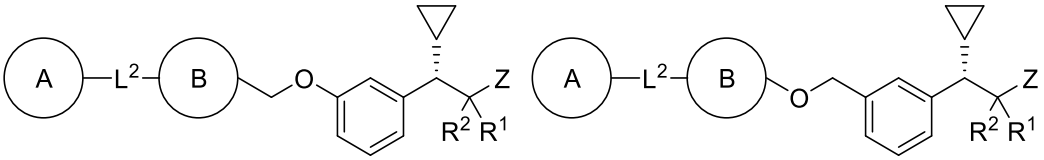
[0007] In some ~~embodiment~~examples, the compound is a compound of Formula (IV):



Formula (IV)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein R^1 and R^2 are each independently hydrogen, -F, or methyl.

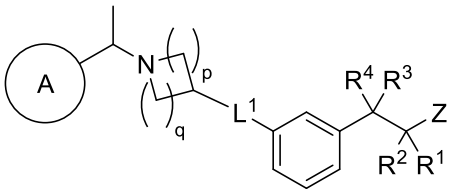
[0008] In some ~~embodiment~~examples, the compound is a compound of Formula (IVa) or Formula (IVb):



Formula (IVa) Formula (IVb)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

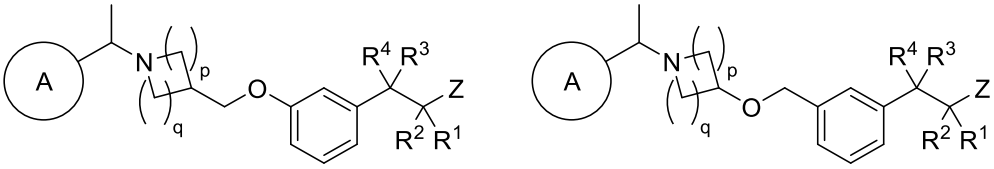
[0009] In some ~~embodiment~~examples, the compound is a compound of Formula (V):



Formula (V)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein p and q are each independently 1 or 2.

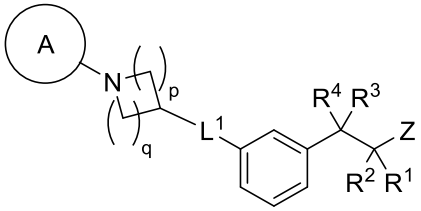
[0010] In some ~~embodiment~~examples, the compound is a compound of Formula (Va) or Formula (Vb):



Formula (Va) Formula (Vb)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

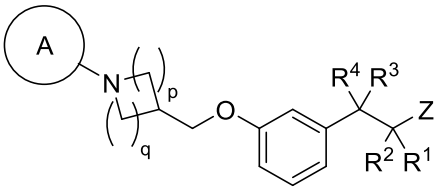
[0011] In some ~~embodiment~~examples, the compound is a compound of Formula (VI):



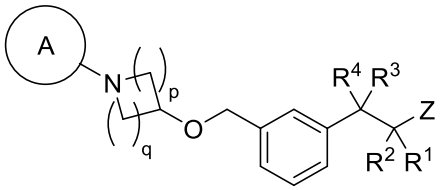
Formula (VI)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein p and q are each independently 1 or 2.

[0012] In some ~~embodiment~~examples, the compound is a compound of Formula (VIa) or Formula (VIb):



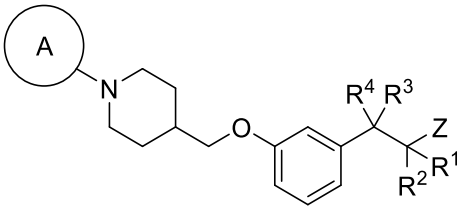
Formula (VIa)



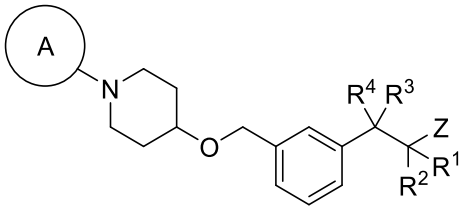
Formula (VIb)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

[0013] In some ~~embodiment~~examples, the compound is a compound of Formula (VIa-i) or Formula (VIb-i):



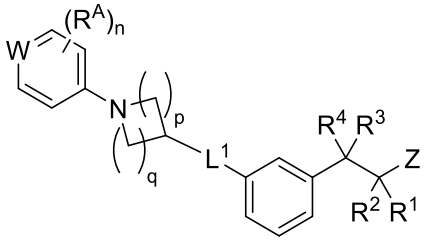
Formula (VIa-i)



Formula (VIb-i)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

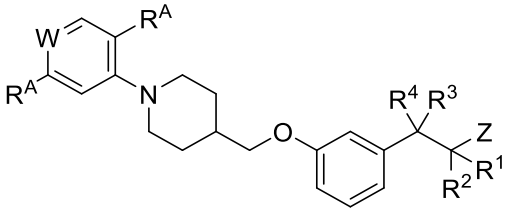
[0014] In some ~~embodiment~~examples, the compound is a compound of Formula (XV):



Formula (XV)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein: W is N, CH, or CR^A; each R^A is independently -F, -Cl, C_1-C_7 alkyl, C_1-C_4 fluoroalkyl, -OH, or $-OR^{10}$; and n is 0, 1, or 2.

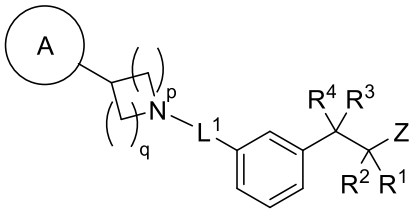
[0015] In some ~~embodiment~~examples, the compound is a compound of Formula (XVa-i):



Formula (XVa-i)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

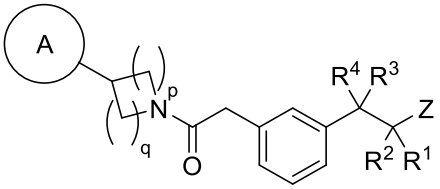
[0016] In some ~~embodiment~~examples, the compound is a compound of Formula (VII):



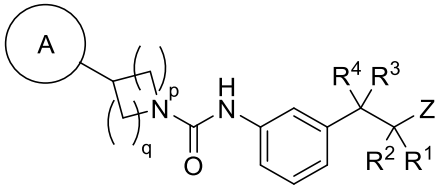
Formula (VII)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein p and q are each independently 1 or 2.

[0017] In some ~~embodiment~~examples, the compound is a compound of Formula (VIIa) or Formula (VIIb):



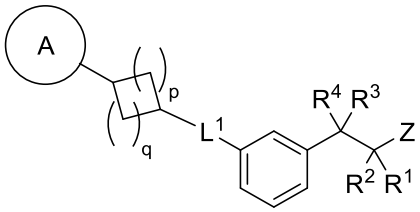
Formula (VIIa)



Formula (VIIb)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

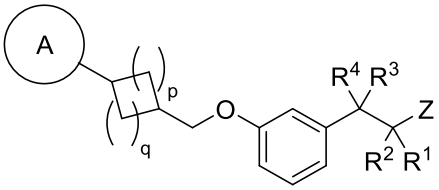
[0018] In some ~~embodiment~~examples, the compound is a compound of Formula (VIII):



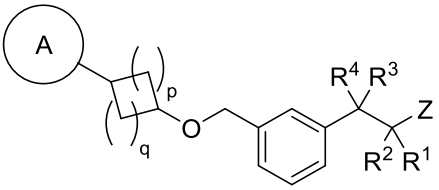
Formula (VIII)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein p and q are each independently 1 or 2.

[0019] In some ~~embodiment~~examples, the compound is a compound of Formula (VIIIa) or Formula (VIIIb):



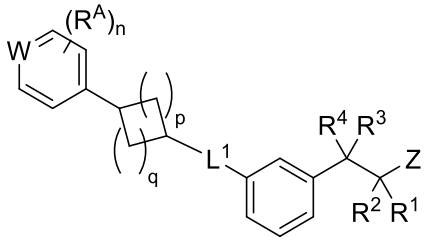
Formula (VIIIa)



Formula (VIIIb)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

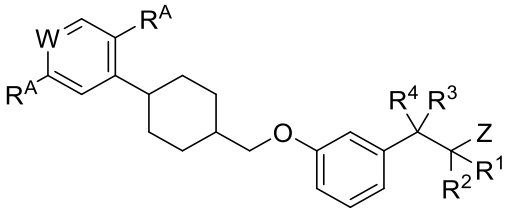
[0020] In some ~~embodiment~~examples, the compound is a compound of Formula (XIV):



Formula (XIV)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein: W is N, CH, or CR^A; each R^A is independently -F, -Cl, C_1-C_7 alkyl, C_1-C_4 fluoroalkyl, -OH, or $-OR^{10}$; and n is 0, 1, or 2.

[0021] In some ~~embodiment~~examples, the compound is a compound of Formula (XIVa-i):



Formula (XIVa-i)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

[0022] Disclosed herein, in certain ~~embodiment~~examples, are pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[0023] Disclosed herein, in certain ~~embodiment~~examples, are methods of treating a condition or disorder involving the gut-brain axis in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof. In some ~~embodiment~~examples, the condition or disorder is associated with GPR40 activity. In some ~~embodiment~~examples, the condition or disorder is a metabolic disorder. In some ~~embodiment~~examples, the condition or disorder is type 2 diabetes, hyperglycemia, metabolic syndrome, obesity, hypercholesterolemia, nonalcoholic steatohepatitis, or hypertension. In some ~~embodiment~~examples, the condition or disorder is a nutritional disorder. In some ~~embodiment~~examples, the condition or disorder is short bowel syndrome, intestinal failure, or intestinal insufficiency. In some ~~embodiment~~examples, the compound disclosed herein is gut-restricted. In some ~~embodiment~~examples, the compound disclosed herein has low systemic exposure.

[0024] In some ~~embodiment~~examples, the methods disclosed herein further comprise administering one or more additional therapeutic agents to the subject. In some ~~embodiment~~examples, the one or more additional therapeutic agents are selected from a TGR5 agonist, a GPR119 agonist, an SSTR5 antagonist, an SSTR5 inverse agonist, a CCK1 agonist, a PDE4 inhibitor, a DPP-4 inhibitor, a

GLP-1 receptor agonist, a GOAT inhibitor, metformin, or combinations thereof. In some ~~embodiment~~examples, the TGR5 agonist, GPR119 agonist, SSTR5 antagonist, SSTR5 inverse agonist or CCK1 agonist is gut-restricted.

DETAILED DESCRIPTION OF THE INVENTION

[0025] This disclosure is directed, at least in part, to GPR40 agonists useful for the treatment of conditions or disorders involving the gut-brain axis. In some embodiments, the GPR40 agonists are gut-restricted compounds. In some embodiments, the GPR40 agonists are full agonists or partial agonists.

Definitions

[0026] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulas, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included.

[0027] The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range.

[0028] The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

[0029] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below:

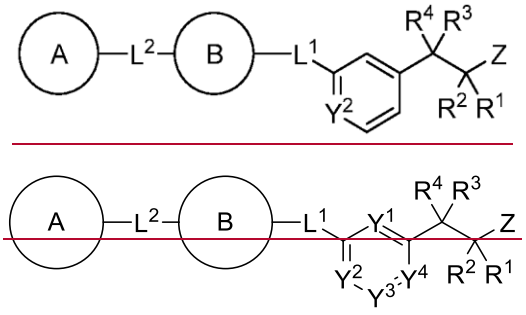
[0030] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. By way of example only, a group designated as "C_1-C_4" indicates that there are one to four carbon atoms in the moiety, i.e., groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, i.e., the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[0031] "Alkyl" refers to an optionally substituted straight-chain, or optionally substituted branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms,

CLAIMS

We Claim:

1. A compound of Formula (2~~I~~):



Formula (2~~I~~)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

Z is ~~–P(=O)(H)OR^6,~~ –P(=O)(R^5)OR^6, ~~–P(=O)(OR^6)$_2$, –S(=O)(OR^6), –SO$_2$OR^6, –C(=O)NHSO$_2$R^5, –C(=O)NHSO$_2$N(R^6)$_2$, –N(R^6)SO$_2$N(R^6)$_2$, –N(R^6)C(=O)NHSO$_2$(R^5), –N(R^6)C(=O)NHSO$_2$N(R^6)$_2$, –N(R^6)C(=NH)NH$_2$, –C(=O)NHNHC(=O)N(R^6)$_2$, or –B(OR^6)$_2$~~;

R^5 is C$_1$-C$_6$ alkyl~~, C$_3$-C$_6$ cycloalkyl, phenyl, or –(C$_1$-C$_6$ alkyl)–phenyl; wherein each alkyl, cycloalkyl, and phenyl is independently unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, –CN, –OH, –O–(C$_1$-C$_6$ alkyl), C$_1$-C$_6$ alkyl, C$_1$-C$_6$ fluoroalkyl, C$_1$-C$_6$ hydroxyalkyl, –O–(C$_1$-C$_6$ fluoroalkyl), C$_3$-C$_6$ cycloalkyl, and 3- to 6-membered heterocycloalkyl~~;

~~each~~ R^6 is ~~independently~~ hydrogen~~,~~ or C$_1$-C$_6$ alkyl~~, C$_3$-C$_6$ cycloalkyl, phenyl, or –(C$_1$-C$_6$ alkyl)–phenyl; wherein each alkyl, cycloalkyl, and phenyl is independently unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, –CN, –OH, –O–(C$_1$-C$_6$ alkyl), C$_1$-C$_6$ alkyl, C$_1$-C$_6$ fluoroalkyl, C$_1$-C$_6$ hydroxyalkyl, –O–(C$_1$-C$_6$ fluoroalkyl), C$_3$-C$_6$ cycloalkyl, and 3- to 6-membered heterocycloalkyl~~;

R^1, R^2, and R^3 are each independently hydrogen, halogen, or ~~–OH, –O–(C$_1$-C$_6$ alkyl), C$_1$-C$_6$ alkyl, C$_3$-C$_6$ cycloalkyl, or 3- to 6-membered heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, –CN, –OH, –O–(C$_1$-C$_6$ alkyl), and~~ C$_1$-C$_6$ alkyl;

R^4 is C$_1$-C$_6$ alkyl~~,~~ or C$_3$-C$_6$ cycloalkyl~~, or 3- to 6-membered heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, –CN, –OH, –O–(C$_1$-C$_6$ alkyl), and C$_1$-C$_6$ alkyl~~;

Y^1, Y^2, Y^3, and Y^4 are each independently is N, or CH, or C–R^Y;

each R^Y is independently halogen, –CN, –OH, –O–(C_1-C_6 alkyl), –NH_2, –NH–(C_1-C_6 alkyl), –N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or 3- to 6-membered heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, –CN, –OH, –O–(C_1-C_6 alkyl), and C_1-C_6 alkyl;

L^1 is –O–, –NR^7–, *-O-CH_2-, *-CH_2-O-, *-NR^7-CH_2-, *-CH_2-NR^7-, *-NR^7-C(O)-, *-C(O)-NR^7-, or *-C(O)-CH_2-; wherein * represents the connection to Ring B;

R^7 is hydrogen or, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

Ring B is 3- to 6-membered cycloalkylene or heterocycloalkylene; wherein the cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1, 2, 3, or 4 R^B substituents; or

Ring B is C_3-C_6 cycloalkylene; wherein the cycloalkylene is unsubstituted or substituted with 1, 2, 3, or 4 R^B substituents;

Ring A is carbocycle aryl or heterocycleheteroaryl; wherein the aryl or heteroarylcarbocycle or heterocycle is unsubstituted or substituted with 1, 2, or 3, 4, or 5 R^A substituents;

L^2 is a bond or, C_1-C_6 alkylene, or –(C_1-C_6 alkylene)–O–; wherein the alkylene is unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, –CN, –OH, C_1-C_6 alkyl, and –O–(C_1-C_6 alkyl);

each R^A is independently halogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} fluoroalkyl, –L^A–CN, –L^A–OH, –L^A–OR^{10}, –L^A–$NR^{11}R^{11}$, –L^A–C(=O)R^{10}, –L^A–C(=O)OR^{11}, –L^A–OC(=O)R^{11}, –L^A–C(=O)$NR^{11}R^{11}$, –L^A–NR^{11}C(=O)R^{11}, –L^A–NR^{11}C(=O)$NR^{11}R^{11}$, –L^A–OC(=O)$NR^{11}R^{11}$, –L^A–NR^{11}C(=O)OR^{10}, –L^A–OC(=O)OR^{10}, –L^A–aryl, –L^A–heteroaryl, –L^A–(C_3-C_{10} cycloalkyl), or –L^A–(3- to 10-membered heterocycloalkyl); wherein each alkyl, alkenyl, alkynyl, fluoroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 hydroxyalkyl, –O–(C_1-C_6 alkyl), and –O–(C_1-C_6 fluoroalkyl);

each R^B is independently halogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, or C_1-C_{10} fluoroalkyl, –L^B–CN, –L^B–OH, –L^B–OR^{10}, –L^B–$NR^{11}R^{11}$, –L^B–C(=O)R^{10}, –L^B–C(=O)OR^{11}, –L^B–OC(=O)R^{11}, –L^B–C(=O)$NR^{11}R^{11}$, –L^B–NR^{11}C(=O)R^{11}, –L^B–NR^{11}C(=O)$NR^{11}R^{11}$, –L^B–OC(=O)$NR^{11}R^{11}$, –L^B–NR^{11}C(=O)OR^{10}, –L^B–

~~$OC(=O)OR^{10}$, L^B-aryl, L^B-heteroaryl, L^B-(C_3-C_{10} cycloalkyl), or L^B-(3- to 10-membered heterocycloalkyl); wherein each alkyl, alkenyl, alkynyl, fluoroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 hydroxyalkyl, –O–(C_1-C_6 alkyl), and –O–(C_1-C_6 fluoroalkyl)~~;

each L^A ~~and L^B~~ is independently a bond or C_1-C_6 alkylene; wherein the alkylene is unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, –CN, –OH, –O–(C_1-C_6 alkyl), and C_1-C_6 alkyl;

each R^{10} is independently C_1-C_6~~C_{10}~~ alkyl~~, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl~~; wherein each alkyl~~, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, and heterocycloalkyl~~ is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, and C_1-C_6 hydroxyalkyl~~, –O–(C_1-C_6 alkyl), and –O–(C_1-C_6 fluoroalkyl)~~; and

each R^{11} is independently hydrogen, C_1-C_{10}~~$_6$~~ alkyl, ~~C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, phenyl,~~ or monocyclic heteroaryl; wherein each alkyl~~, alkenyl, alkynyl, phenyl,~~ and heteroaryl~~, cycloalkyl, and heterocycloalkyl~~ is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, ~~–CN,~~ –OH, C_1-C_6 alkyl, and ~~C_1-C_6 fluoroalkyl,~~ C_1-C_6 hydroxyalkyl~~, –O–(C_1-C_6 alkyl), and –O–(C_1-C_6 fluoroalkyl)~~;

or two R^{11} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6~~10~~-membered *N*-heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, ~~–CN,~~ –OH, C_1-C_6 alkyl, ~~C_1-C_6 fluoroalkyl,~~ and C_1-C_6 hydroxyalkyl~~, –O–(C_1-C_6 alkyl), and –O–(C_1-C_6 fluoroalkyl)~~.

~~2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:~~

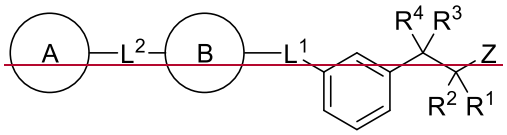
~~Y^1, Y^2, Y^3, and Y^4 are each independently N, CH, or C–R^Y; and~~

~~each R^Y is independently F, Cl, Br, –CN, –OH, –O–(C_1-C_6 alkyl), or C_1-C_6 alkyl.~~

~~3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:~~

~~Y^1, Y^2, Y^3, and Y^4 are each independently N or CH.~~

~~4. The compound of any one of claims 1-3, having the structure of Formula (II):~~



~~Formula (II)~~

~~or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.~~

~~5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:~~

~~R^1, R^2, and R^3 are each independently hydrogen, halogen, or C_1-C_6 alkyl; and~~

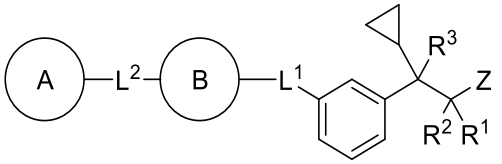
~~R^4 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl.~~

~~6.~~2. The compound of ~~any one of~~ claim~~s~~ 1~~-5~~, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

R^1, R^2, and R^3 are each independently hydrogen, halogen, or C_1-C_4 alkyl; and

R^4 is unsubstituted C_3-C_6 cycloalkyl.

~~7.~~3. The compound of claim~~any one of claims~~ 1 or 2~~-6~~, having the structure of Formula (III):



Formula (III)

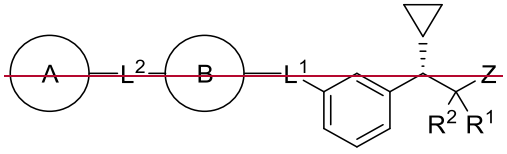
or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

R^1, R^2, and R^3 are each independently hydrogen, -F, -Cl, or C_1-C_4 alkyl.

~~8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:~~

~~R^1, R^2, and R^3 are each independently hydrogen, -F, or methyl.~~

~~9. The compound of any one of claims 1-8, having the structure of Formula (IV):~~



~~Formula (IV)~~

~~or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:~~

~~R^1 and R^2 are each independently hydrogen, -F, or methyl.~~

~~10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:~~

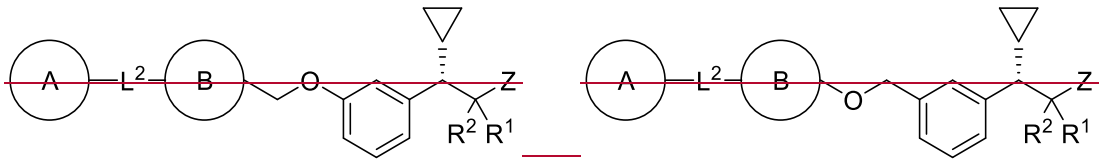
~~L^1 is * $-O-CH_2-$, * $-CH_2-O-$, * $-NR^7-CH_2-$, * $-NR^7-C(O)-$, * $-C(O)-NR^7-$, or * $-C(O)-CH_2-$;~~

~~wherein * represents the connection to Ring B.~~

~~11.~~4. The compound of any one of claims 1-~~3~~10, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

L^1 is *-O-CH_2- or *-CH_2-O-; wherein * represents the connection to Ring B.

~~12. The compound of any one of claims 1-11, having the structure of Formula (IVa) or Formula (IVb):~~



~~Formula (IVa) Formula (IVb)~~

~~or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.~~

~~13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:~~

~~Ring B is C_3-C_{10} cycloalkylene or 3- to 10-membered heterocycloalkylene; wherein the cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1, 2, 3, or 4 R^B substituents; and~~

~~Ring A is aryl, heteroaryl, C_3-C_{10} cycloalkyl, or 3- to 10-membered heterocycloalkyl; wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 R^A substituents.~~

~~14.~~5. The compound of any one of claims 1-~~4~~13, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

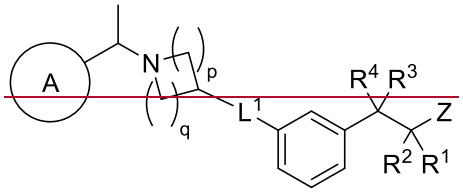
Ring B is 3- to 6-membered heterocycloalkylene; wherein the heterocycloalkylene is unsubstituted or substituted with 1, 2, 3, or 4 R^B substituents~~;~~

~~each R^B is independently halogen, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;~~

~~L^2 is a bond or C_1-C_6 alkylene; wherein the alkylene is unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of –OH, C_1-C_6 alkyl, and –O–(C_1-C_6 alkyl); and~~

~~Ring A is aryl or heteroaryl; wherein the aryl or heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^A substituents~~.

~~15. The compound of any one of claims 1-9, having the structure of Formula (V):~~

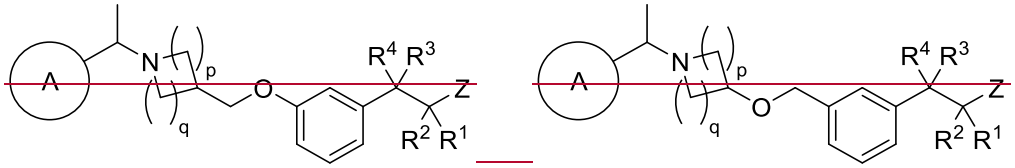


~~Formula (V)~~

~~or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein:~~

p and q are each independently 1 or 2.

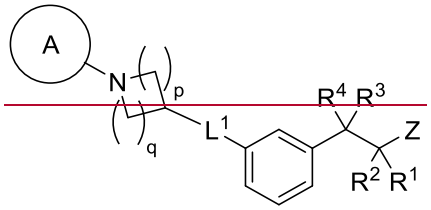
16. The compound of claim 15, having the structure of Formula (Va) or Formula (Vb):



Formula (Va) Formula (Vb)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

17. The compound of any one of claims 1-9, having the structure of Formula (VI):

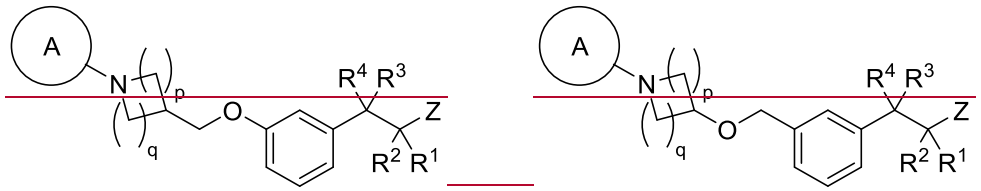


Formula (VI)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein:

p and q are each independently 1 or 2.

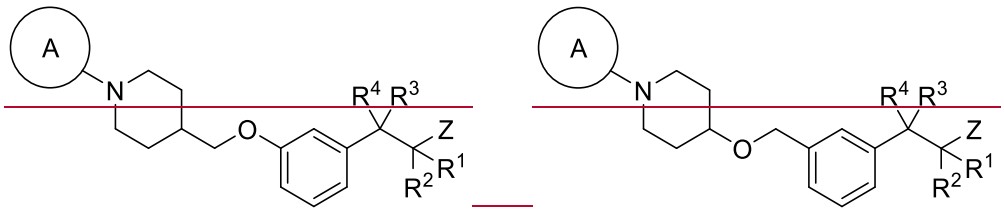
18. The compound of claim 17, having the structure of Formula (VIa) or Formula (VIb):



Formula (VIa) Formula (VIb)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

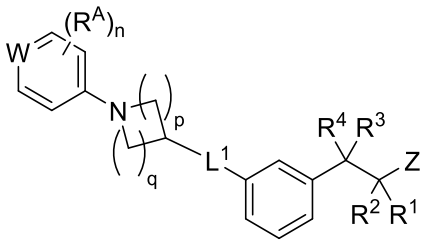
19. The compound of claim 17 or claim 18, having the structure of Formula (VIa-i) or Formula (VIb-i):



Formula (VIa-i) Formula (VIb-i)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

20.6. The compound of any one of claims 1-517, having the structure of Formula (XV):



Formula (XV)

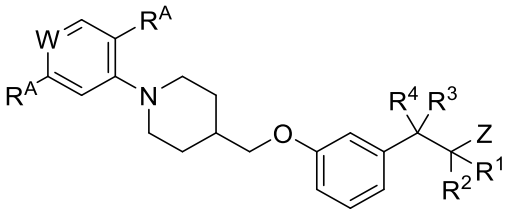
or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein:

W is N, CH, or CR^A;

each R^A is independently -F, -Cl, C_1-C_7 alkyl, C_1-C_4 fluoroalkyl, -OH, or $-OR^{10}$; and

n is 0, 1, or 2.

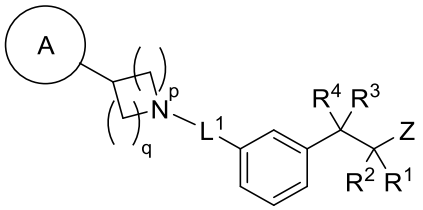
~~21.~~7. The compound of claim ~~6~~20, having the structure of Formula (XVa-i)



Formula (XVa-i)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

~~22.~~8. The compound of any one of claims 1-~~5~~9, having the structure of Formula (VII):

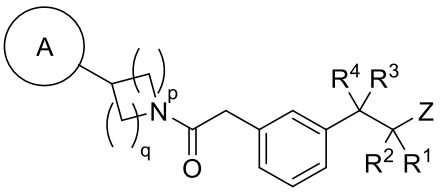


Formula (VII)

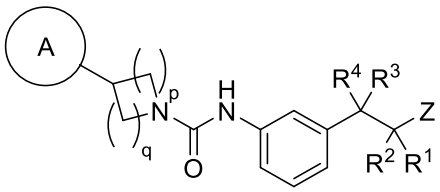
or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein:

p and q are each independently 1 or 2.

~~23.~~9. The compound of claim ~~8~~22, having the structure of Formula (VIIa) or Formula (VIIb):



Formula (VIIa)



Formula (VIIb)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

~~24.~~10. The compound of any one of claims 1-~~4~~13, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

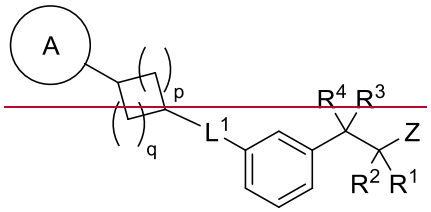
Ring B is C_3-C_6 cycloalkylene; wherein the cycloalkylene is unsubstituted or substituted with 1, 2, 3, or 4 R^B substituents~~;~~

~~each R^B is independently halogen, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;~~

~~L^2 is a bond or C_1-C_6 alkylene; wherein the alkylene is unsubstituted or substituted with 1, 2, or 3 substituents selected from the group consisting of –OH, C_1-C_6 alkyl, and –O–(C_1-C_6 alkyl); and~~

~~Ring A is aryl or heteroaryl; wherein the aryl or heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^A substituents~~.

~~25. The compound of any one of claims 1-9, having the structure of Formula (VIII):~~

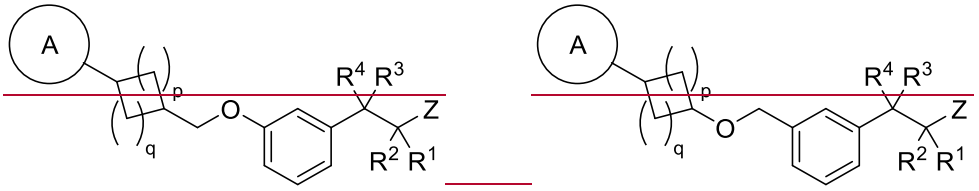


~~Formula (VIII)~~

~~or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein:~~

~~p and q are each independently 1 or 2.~~

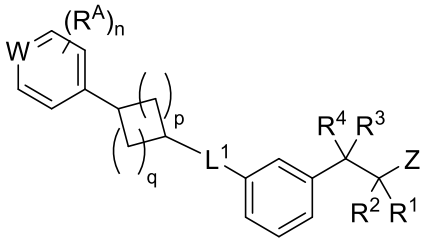
~~26. The compound of claim 25, having the structure of Formula (VIIIa) or Formula (VIIIb):~~



~~Formula (VIIIa)~~ ~~Formula (VIIIb)~~

~~or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.~~

~~27.~~11. The compound of any one of claims 1-3~~25~~, having the structure of Formula (XIV)



Formula (XIV)

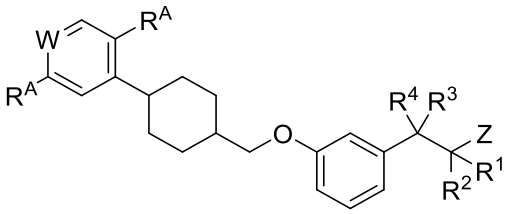
or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein:

W is N, CH, or CR^A;

each R^A is independently -F, -Cl, C_1-C_7 alkyl, C_1-C_4 fluoroalkyl, -OH, or $-OR^{10}$; and

n is 0, 1, or 2.

~~28.~~12. The compound of claim 11~~27~~, having the structure of Formula (XIVa-i)



Formula (XIVa-i)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

Z is $P(=O)(H)OR^6$, $P(=O)(R^5)OR^6$, $P(=O)(OR^6)_2$, $S(=O)(OR^6)$, SO_2OR^6, or $C(=O)NHSO_2R^5$;

R^5 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, or $(C_1$-C_6 alkyl)-phenyl; wherein each alkyl, cycloalkyl, and phenyl is independently unsubstituted or substituted with one, two, or three substituents selected from -F, -Cl, -OH, -O-(C_1-C_6 alkyl), C_1-C_6 alkyl, and C_1-C_6 hydroxyalkyl; and

each R^6 is independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, or $(C_1$-C_6 alkyl)-phenyl; wherein each alkyl, cycloalkyl, and phenyl is independently unsubstituted or substituted with one, two, or three substituents selected from -F, -Cl, -OH, -O-(C_1-C_6 alkyl), C_1-C_6 alkyl, and C_1-C_6 hydroxyalkyl.

30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

Z is $P(=O)(H)OR^6$, $P(=O)(R^5)OR^6$, $P(=O)(OR^6)_2$, $S(=O)(OR^6)$, or SO_2OR^6;

R^5 is C_1-C_6 alkyl; and

each R^6 is independently hydrogen or C_1-C_6 alkyl.

31. The compound of any one of claims 1-30, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

Z is $P(=O)(H)OR^6$, $P(=O)(R^5)OR^6$, $P(=O)(OR^6)_2$, or SO_2OR^6;

R^5 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-CH(CH_3)(CH_2CH_3)$; and

each R^6 is independently hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-CH(CH_3)(CH_2CH_3)$.

32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

Z is $P(=O)(H)OH$, $P(=O)(CH_3)OH$, $P(=O)(CH_2CH_3)OH$, PO_3H_2, $P(=O)(OCH_3)(OH)$, $S(=O)OH$, SO_2OH, or $C(=O)NHSO_2CH_3$.

~~33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:~~

~~Z is –P(=O)(CH_3)OH, or –SO_2OH.~~

~~34.~~13. The compound of any one of claims 1-12~~33~~, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

Z is –P(=O)(CH_3)OH.

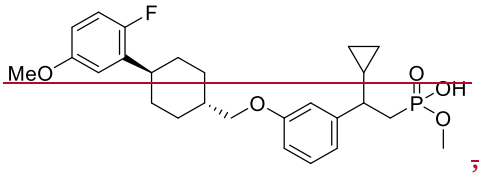
~~35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:~~

~~each R^{10} is independently C_1-C_6 alkyl; wherein each alkyl is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –OH, C_1-C_6 alkyl and C_1-C_6 hydroxyalkyl; and~~

~~each R^{11} is independently hydrogen, C_1-C_6 alkyl, or monocyclic heteroaryl; wherein each alkyl and heteroaryl is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –OH, C_1-C_6 alkyl and C_1-C_6 hydroxyalkyl;~~

~~or two R^{11} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6-membered *N*-heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –OH, C_1-C_6 alkyl, and C_1-C_6 hydroxyalkyl.~~

~~36.~~14. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, selected from:



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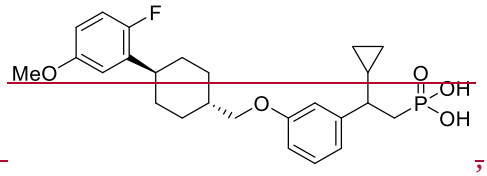

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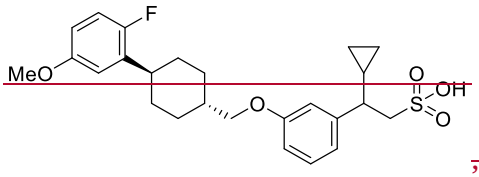

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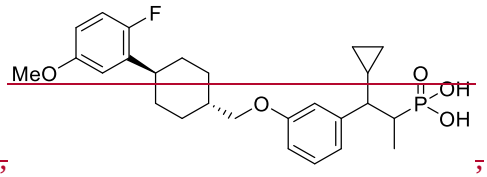

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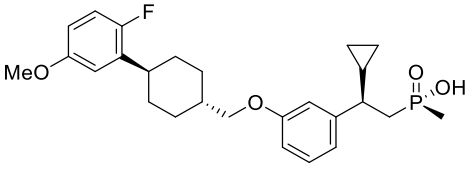

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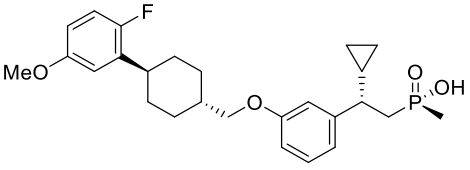

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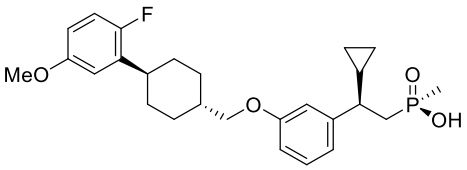
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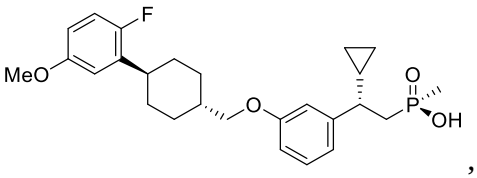
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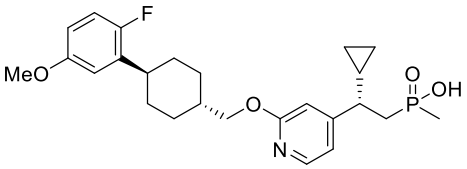
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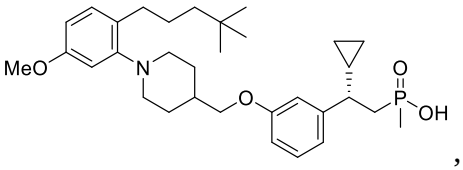
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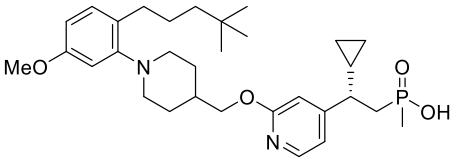
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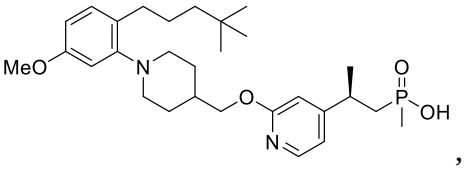
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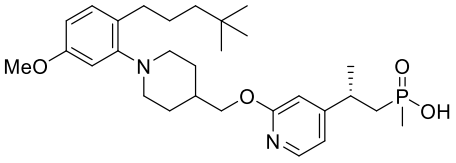
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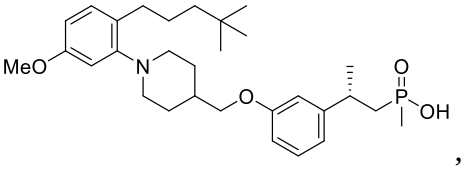
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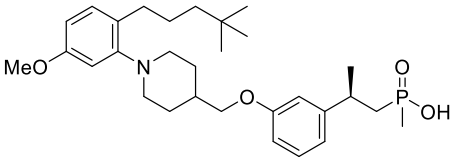
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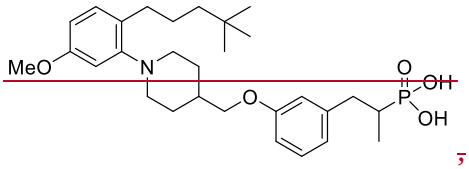
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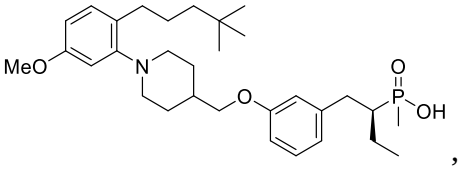
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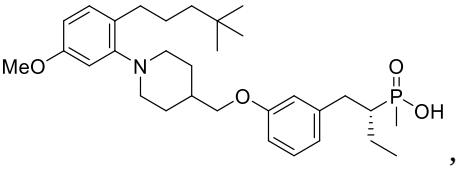
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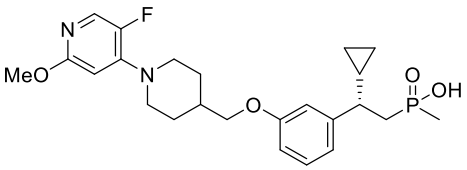
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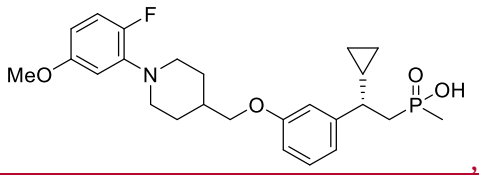
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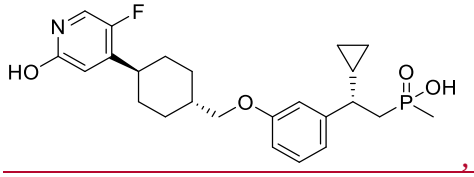
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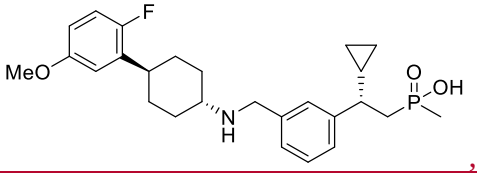
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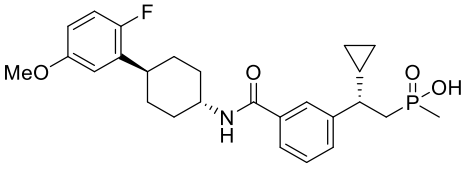
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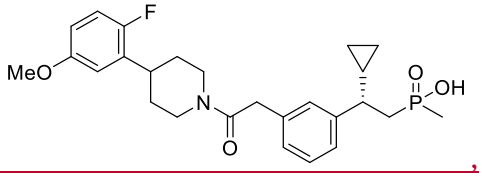
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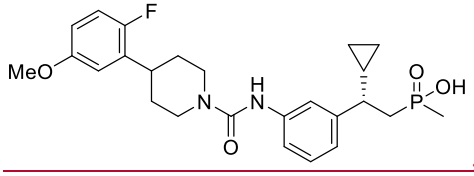
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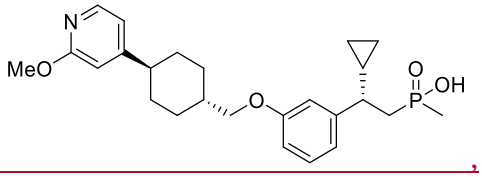
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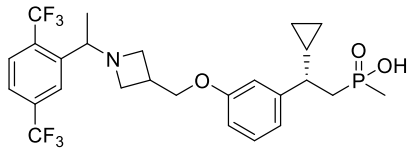
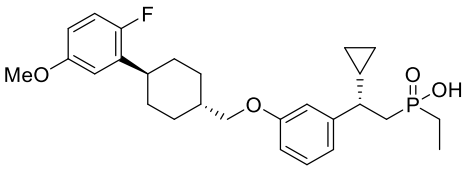
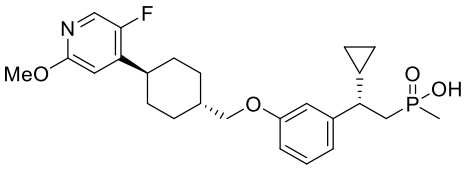
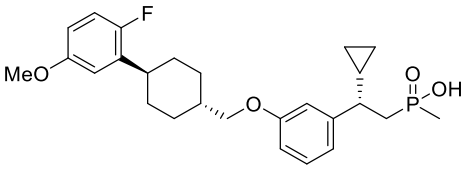
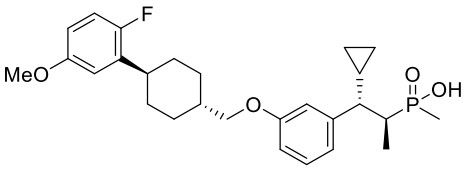
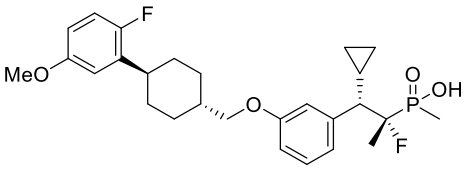
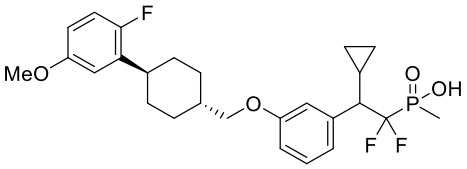
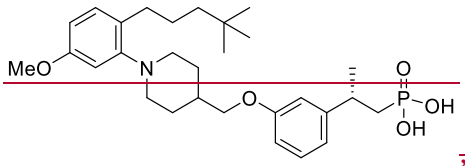
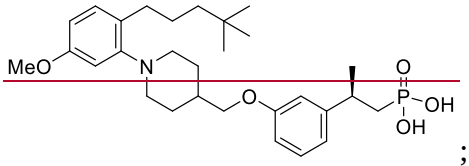
 ,  ,

 ,  ,

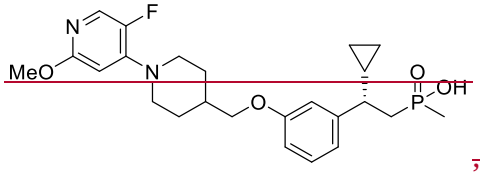
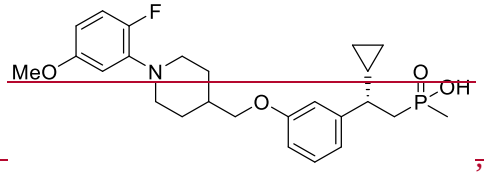
 ,  , and

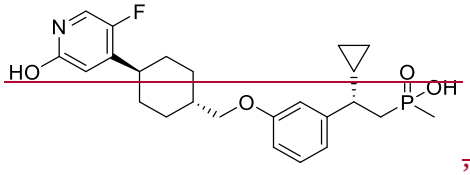
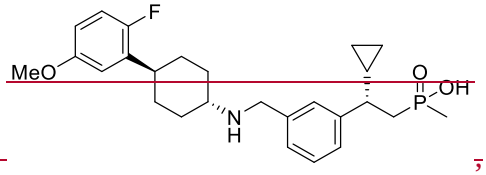
  , and

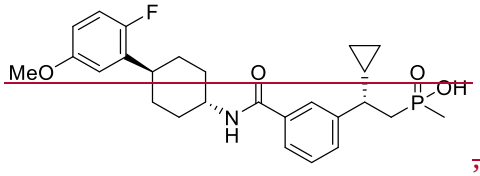
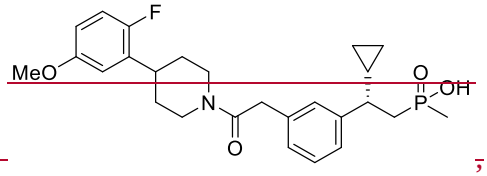
 ;

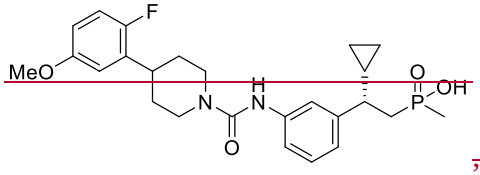
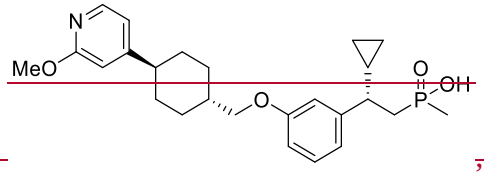
or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

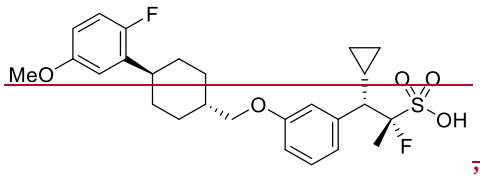
37. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, selected from:

 ,  ,

 ,  ,

 ,  ,

 ,  ,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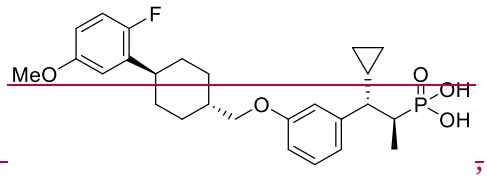
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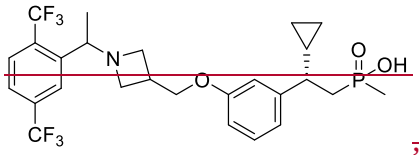
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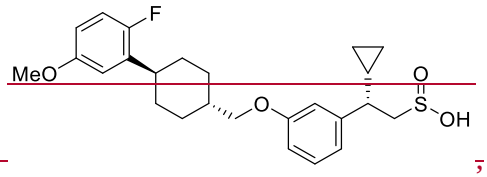
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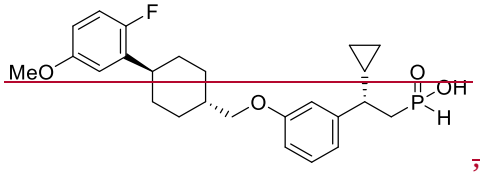
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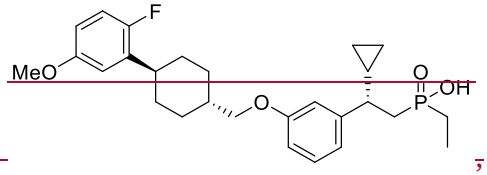
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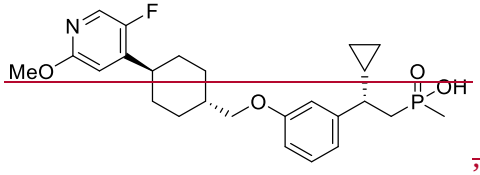
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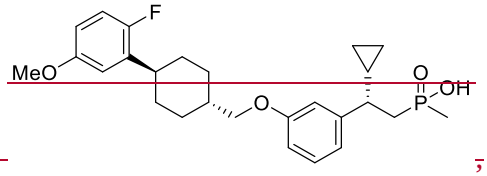
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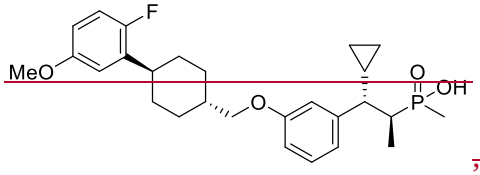
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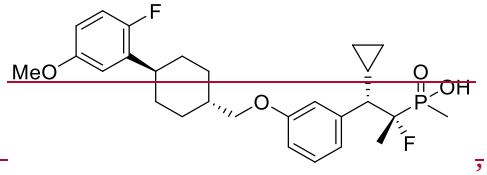
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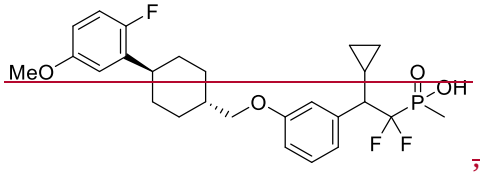
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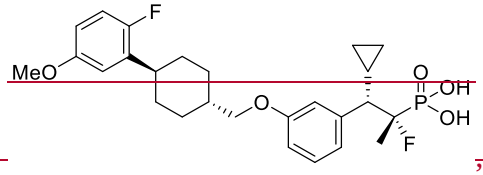
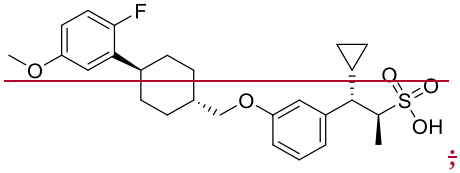

~~, and~~

;

~~or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.~~

~~38.~~15. A pharmaceutical composition comprising a compound of any one of claims 1-14~~37~~, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

~~39.~~16. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, in the manufacture of a medicament for ~~A method of~~ treating a condition or disorder involving the gut-brain axis; wherein the condition or disorder is associated with GPR40 activity ~~in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a~~

~~compound of any one of claims 1-37, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof~~.

~~40. The method of claim 39, wherein the condition or disorder is associated with GPR40 activity.~~

~~41.~~17. The use~~method~~ of claim 16~~39 or claim 40~~, wherein the condition or disorder is a metabolic disorder.

~~42.~~18. The use~~method~~ of claim 16 or 17~~41~~, wherein the condition or disorder is type 2 diabetes, hyperglycemia, metabolic syndrome, obesity, hypercholesterolemia, nonalcoholic steatohepatitis, or hypertension.

~~43.~~19. The use~~method~~ of claim 16~~39 or claim 40~~, wherein the condition or disorder is a nutritional disorder.

~~44.~~20. The use~~method~~ of claim 16 or 19~~43~~, wherein the condition or disorder is short bowel syndrome, intestinal failure, or intestinal insufficiency.

~~45. The method of any one of claims 39-44, wherein the compound is gut-restricted.~~

~~46. The method of claim 45, wherein the compound has low systemic exposure.~~

~~47.~~21. The ~~method~~ use of any one of claims ~~39~~16-~~46~~20, wherein the compound, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, is to be administered to a subject, and wherein ~~further comprising administering~~ one or more additional therapeutic agents for the treatment of the condition or disorder are to be further administered to the subject; wherein the one or more additional therapeutic agents are selected from a TGR5 agonist, a GPR119 agonist, an SSTR5 antagonist, an SSTR5 inverse agonist, a CCK1 agonist, a PDE4 inhibitor, a DPP-4 inhibitor, a GLP-1 receptor agonist, a GOAT inhibitor, metformin, or combinations thereof~~to the subject~~.

~~48. The method of claim 47, wherein the one or more additional therapeutic agents are selected from a TGR5 agonist, a GPR119 agonist, an SSTR5 antagonist, an SSTR5 inverse agonist, a CCK1 agonist, a PDE4 inhibitor, a DPP-4 inhibitor, a GLP-1 receptor agonist, a GOAT inhibitor, metformin, or combinations thereof.~~

~~49. The method of claim 48, wherein the TGR5 agonist, GPR119 agonist, SSTR5 antagonist, SSTR5 inverse agonist or CCK1 agonist is gut-restricted.~~

22. A compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for use in therapy.