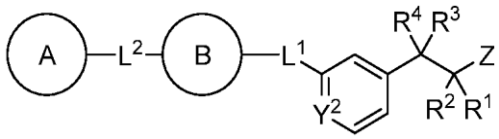
GPR40 AGONISTS

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

[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-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_6 alkyl, or C_1-C_6 fluoroalkyl;

each L^A 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 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.

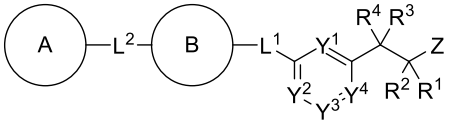
[0001b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[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 examples, are free fatty acid receptor 1 (GPR40) agonists useful for the treatment of conditions or disorders involving the gut-brain axis. In some examples, the GPR40 agonists are gut-restricted or selectively modulate GPR40 located in the gut. In some 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 examples, is a compound of Formula (I):



Formula (I)

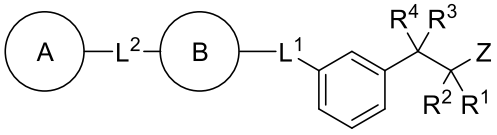
consisting of halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 hydroxyalkyl, –O–(C_1-C_6 alkyl), and –O–(C_1-C_6 fluoroalkyl); and

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.

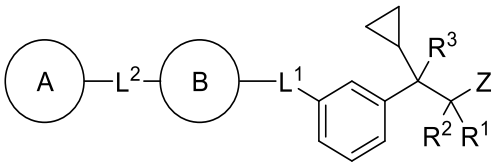
[0005] In some examples, the compound is a compound of Formula (II):



Formula (II)

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

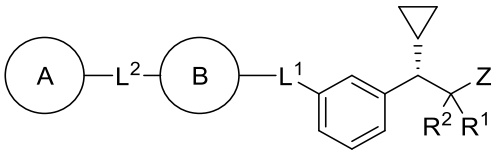
[0006] In some examples, the compound is a compound of Formula (III):



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.

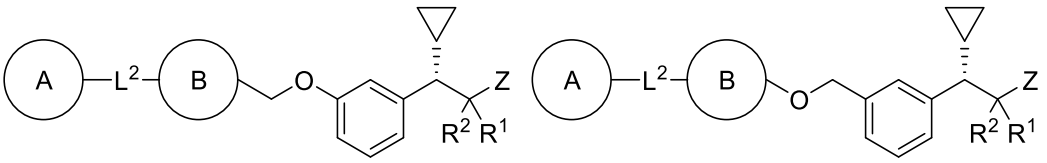
[0007] In some examples, the compound is a compound of Formula (IV):



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.

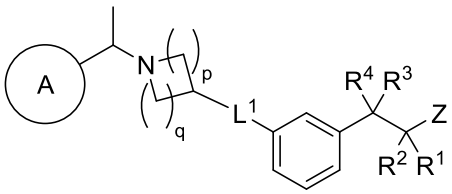
[0008] In some examples, the compound is a compound of Formula (IVa) or Formula (IVb):



Formula (IVa) Formula (IVb)

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

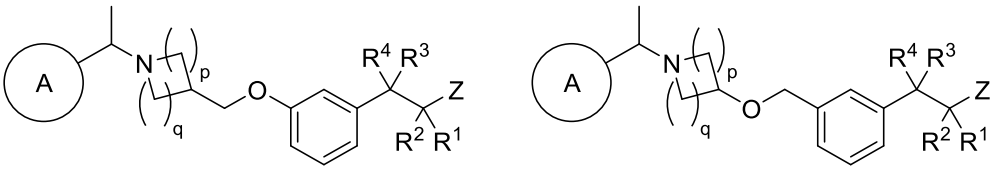
[0009] In some examples, the compound is a compound of Formula (V):



Formula (V)

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

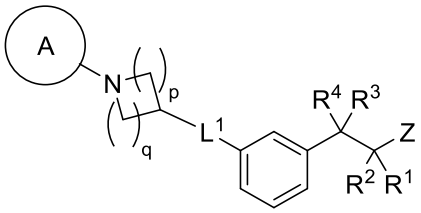
[0010] In some examples, the compound is a compound of Formula (Va) or Formula (Vb):



Formula (Va) Formula (Vb)

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

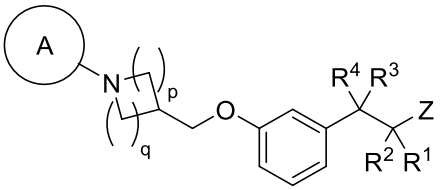
[0011] In some examples, the compound is a compound of Formula (VI):



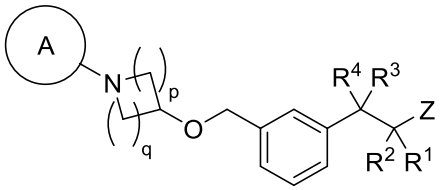
Formula (VI)

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

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



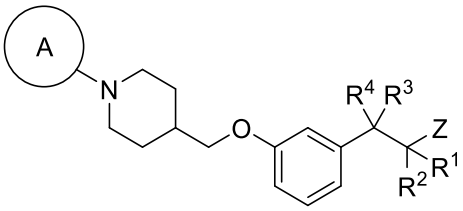
Formula (VIa)



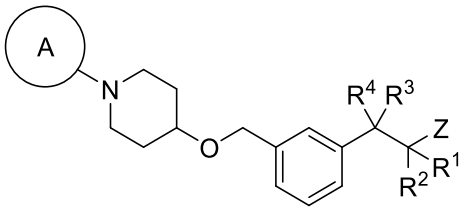
Formula (VIb)

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

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



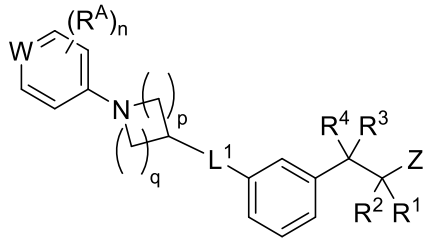
Formula (VIa-i)



Formula (VIb-i)

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

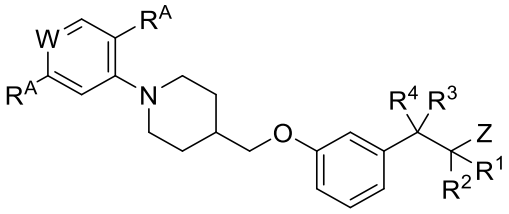
[0014] In some examples, the compound is a compound of Formula (XV):



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.

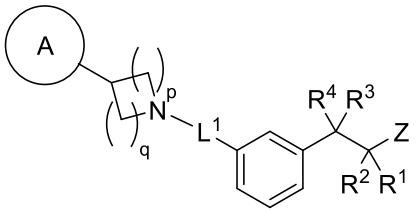
[0015] In some examples, the compound is a compound of Formula (XVa-i):



Formula (XVa-i)

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

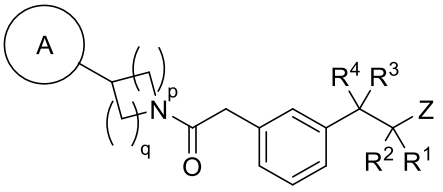
[0016] In some examples, the compound is a compound of Formula (VII):



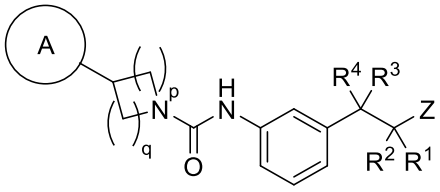
Formula (VII)

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

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



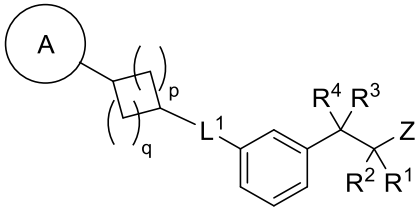
Formula (VIIa)



Formula (VIIb)

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

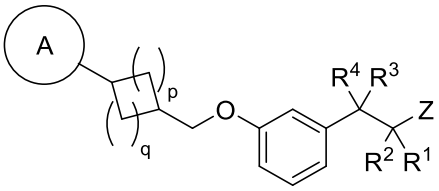
[0018] In some examples, the compound is a compound of Formula (VIII):



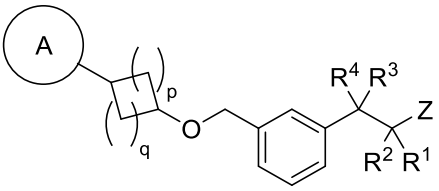
Formula (VIII)

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

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



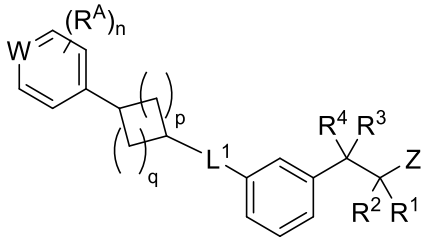
Formula (VIIIa)



Formula (VIIIb)

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

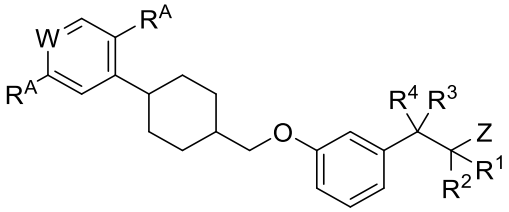
[0020] In some examples, the compound is a compound of Formula (XIV):



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 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 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 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 examples, the condition or disorder is associated with GPR40 activity. In some examples, the condition or disorder is a metabolic disorder. In some examples, the condition or disorder is type 2 diabetes, hyperglycemia, metabolic syndrome, obesity, hypercholesterolemia, nonalcoholic steatohepatitis, or hypertension. In some examples, the condition or disorder is a nutritional disorder. In some examples, the condition or disorder is short bowel syndrome, intestinal failure, or intestinal insufficiency. In some examples, the compound disclosed herein is gut-restricted. In some examples, the compound disclosed herein has low systemic exposure.

[0024] In some examples, the methods disclosed herein further comprise administering one or more additional therapeutic agents to the subject. In some 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 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:

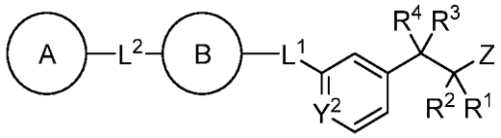
[0030] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. By way of example only, a group designated as "C_1-C_4" indicates that there are one to four carbon atoms in the moiety, i.e., groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example 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):



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-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_6 alkyl, or C_1-C_6 fluoroalkyl;

each L^A 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 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;

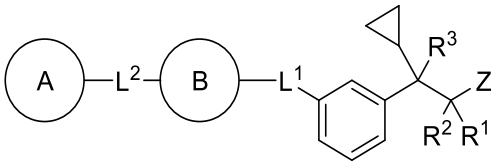
or two R^{11} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6-membered *N*-heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen, –OH,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

2. The compound of claim 1, 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.

3. The compound of claim 1 or 2, 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.

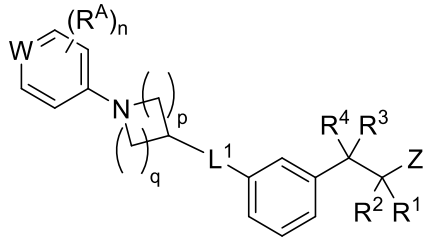
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

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

5. The compound of any one of claims 1-4, 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.

6. The compound of any one of claims 1-5, having the structure of Formula (XV):



Formula (XV)

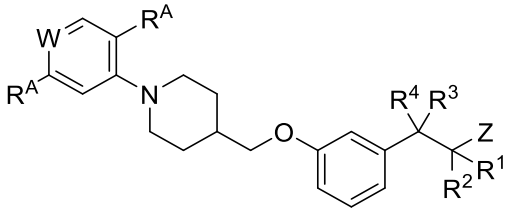
or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein:

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.

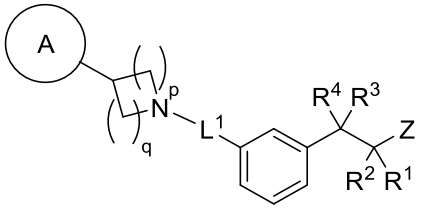
7. The compound of claim 6, having the structure of Formula (XVa-i)



Formula (XVa-i)

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

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

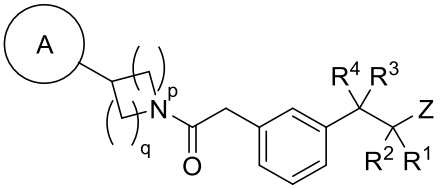


Formula (VII)

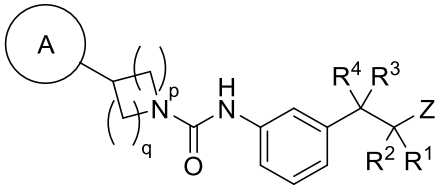
or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein:

p and q are each independently 1 or 2.

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



Formula (VIIa)



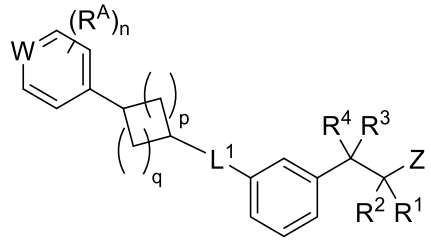
Formula (VIIb)

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

10. The compound of any one of claims 1-4, 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.

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



Formula (XIV)

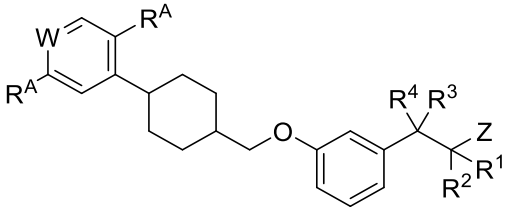
or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof; wherein:

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.

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



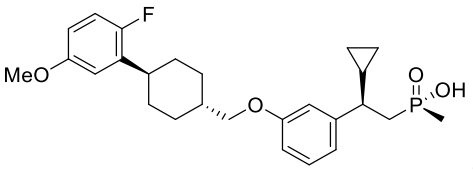
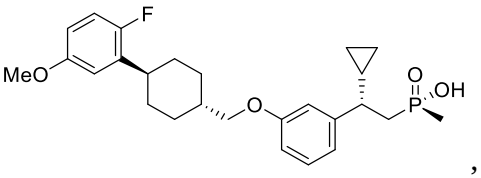
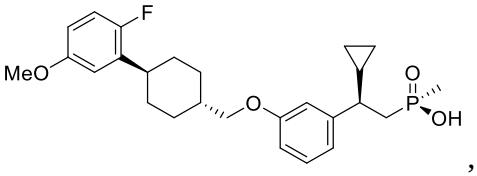
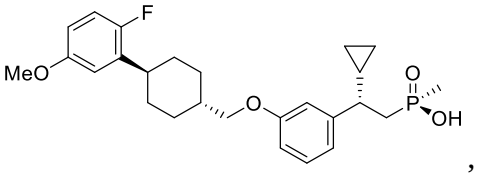
Formula (XIVa-i)

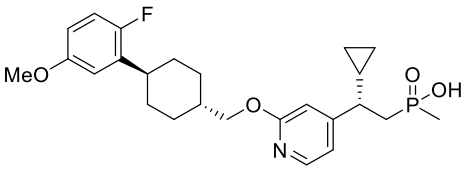
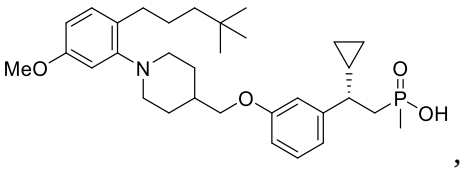
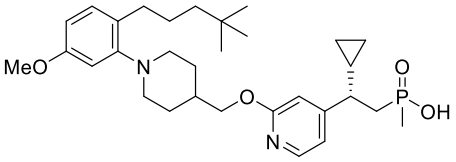
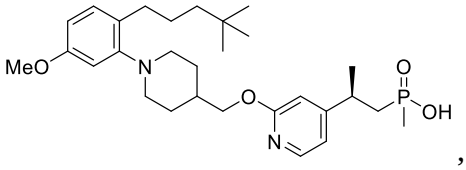
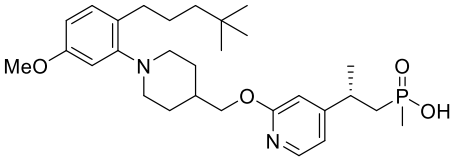
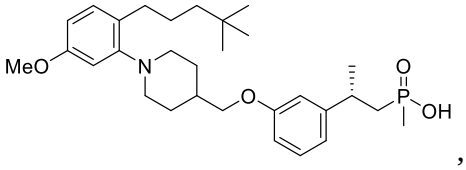
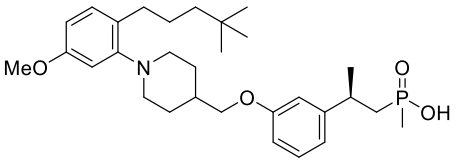
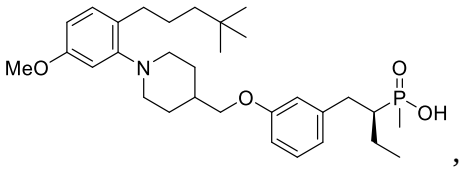
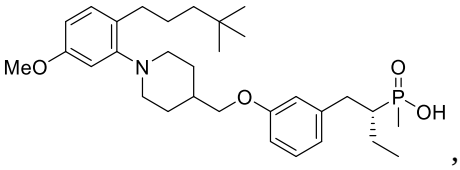
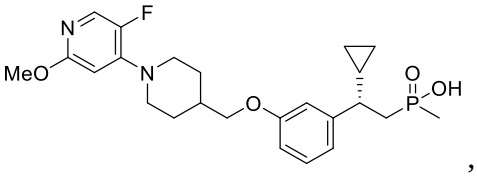
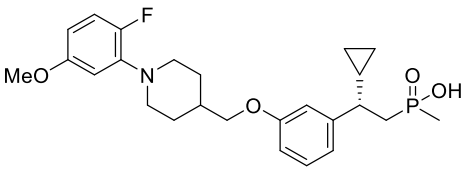
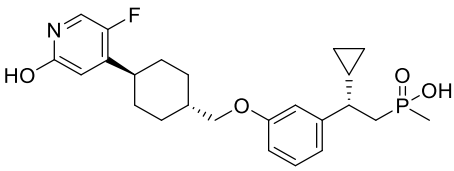
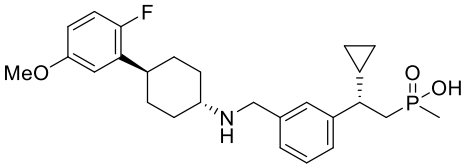
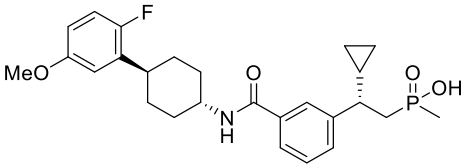
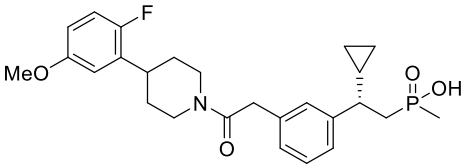
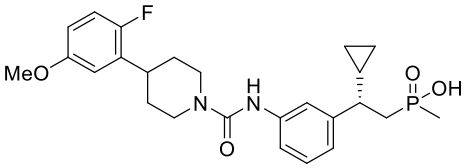
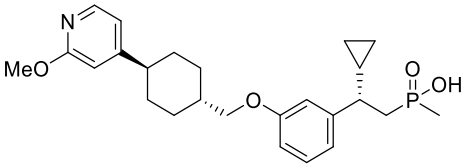
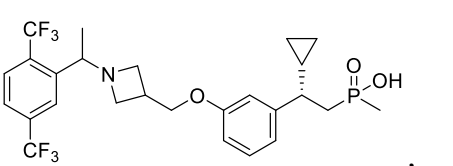
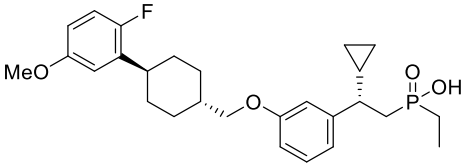
or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

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

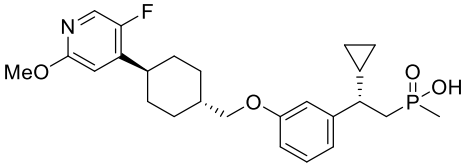
Z is –P(=O)(CH_3)OH.

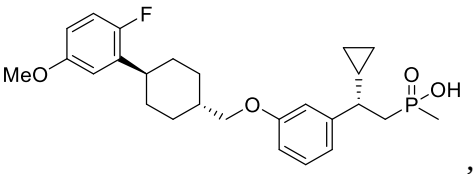
14. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, selected from:

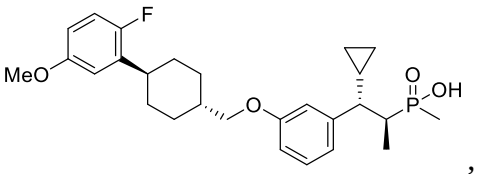

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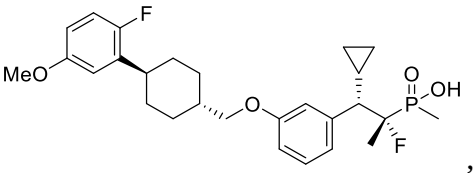

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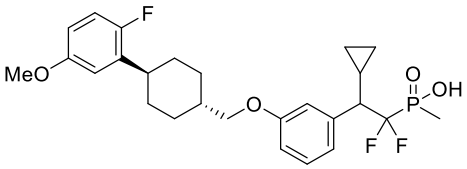
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or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

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

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 treating a condition or disorder involving the gut-brain axis; wherein the condition or disorder is associated with GPR40 activity.

17. The use of claim 16, wherein the condition or disorder is a metabolic disorder.

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

19. The use of claim 16, wherein the condition or disorder is a nutritional disorder.

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

21. The use of any one of claims 16-20, wherein the compound, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, is to be administered to a subject, and wherein 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.

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