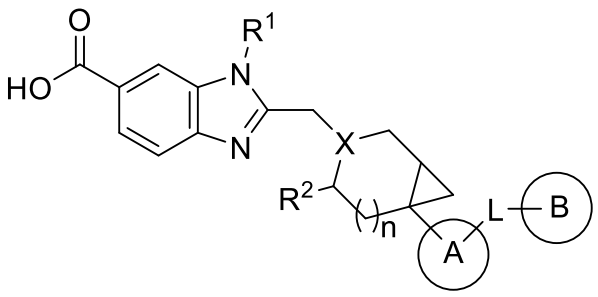
[0006] In a healthy individual, GLP-1 plays an important role regulating post-prandial blood glucose levels by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose output. In addition, GLP-1 delays gastric emptying and slows small bowel motility delaying food absorption. In people with T2DM, the normal post-prandial rise in GLP-1 is absent or reduced (Vilsboll T, et al. Diabetes. 2001. 50; 609-613).

[0007] Holst (Physiol. Rev. 2007, 87, 1409) and Meier (Nat. Rev. Endocrinol. 2012, 8, 728) describe that GLP-1 receptor agonists, such as liraglutide and exendin-4, have 3 major pharmacological activities to improve glycemic control in patients with T2DM by reducing fasting and postprandial glucose (FPG and PPG): (i) increased glucose-dependent insulin secretion (improved first- and second-phase), (ii) glucagon suppressing activity under hyperglycemic conditions, (iii) delay of gastric emptying rate resulting in retarded absorption of meal-derived glucose.

[0008] There remains a need of developing GLP-1 receptor agonists for an easily-administered prevention and/or treatment for cardiometabolic and associated diseases.

BRIEF SUMMARY

[0008a] In an aspect of the present disclosure, there is provided a compound of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

n is 0 or 1;

R^1 is -C_1-C_6 alkylene-R^5, wherein R^5 is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by C_1-C_6 alkyl;

R^2 is hydrogen, oxo, or C_1-C_6 alkyl;

Ring A is 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH;

L is a bond, -O-, C_1-C_6 alkylene, *-O-C_1-C_6 alkylene-**, *-C_1-C_6 alkylene-O-**, or *–NR^6-C_1-C_6 alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B,

when L is *-O-C_1-C_6 alkylene-**, the C_1-C_6 alkylene is optionally substituted by R^L, wherein:

each R^L is independently C_1-C_6 alkyl or halo, or

two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl;

when L is C_1-C_6 alkylene, the C_1-C_6 alkylene is optionally substituted by R^{L1}, wherein:

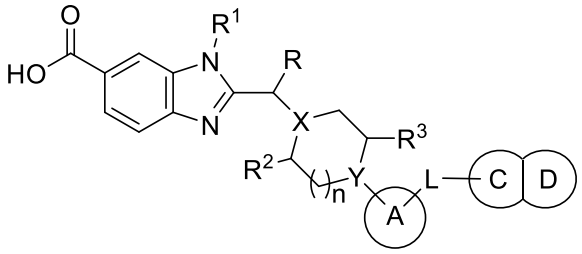
each R^{L1} is independently halo, OH, or C_1-C_6 alkyl; or

two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl, and

R^6 is hydrogen or C_1-C_6 alkyl; and

Ring B is C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$, and phenyl.

[0008b] In another aspect of the present disclosure, there is provided a compound of Formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein

X is N or CH;

n is 0 or 1;

R^1 is -C_1-C_6 alkylene-R^5, wherein R^5 is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by C_1-C_6 alkyl;

R^2 is hydrogen, oxo, or C_1-C_6 alkyl;

Ring A is 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH;

L is a bond, -O-, C_1-C_6 alkylene, *-O-C_1-C_6 alkylene-**, *-C_1-C_6 alkylene-O-**, or *–NR^6-C_1-C_6 alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to C D,

when L is *-O-C_1-C_6 alkylene-**, the C_1-C_6 alkylene is optionally substituted by R^L, wherein:

each R^L is independently C_1-C_6 alkyl or halo, or

two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl;

when L is C_1-C_6 alkylene, the C_1-C_6 alkylene is optionally substituted by R^{L1}, wherein:

each R^{L1} is independently halo, OH, or C_1-C_6 alkyl; or

two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl, and

R^6 is hydrogen or C_1-C_6 alkyl; and

 is a fused bicyclic ring system comprising fused rings Ring C and Ring D, wherein Ring C is C_5-C_6 cycloalkyl, 5- to 7-membered heterocyclyl, or 5- to 6-membered heteroaryl; and

Ring D is C_6 cycloalkyl, C_6 aryl or 6-membered heteroaryl;

wherein Ring C and Ring D are optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $–COCH_3$, $–CONH_2$, $–S(O)_2CH_3$, and phenyl.

[0008c] In a further aspect of the present disclosure, there is provided a compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of the compounds in Table 1.

[0008d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutical acceptable excipient.

[0008e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease mediated by glucagon-like peptide-1 receptor (GLP-1R) in an individual in need thereof.

[0008f] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

[0009] Disclosed are compounds that can be used as glucagon-like peptide-1 receptor (GLP-1R) agonists, compositions containing these compounds and methods for treating diseases and/or conditions mediated by GLP-1R.

[0010] In one ~~aspect~~example, provides is a compound of Formula (I), including compounds of Formulae (II)-(IV), or selected from the group consisting of a compound listed in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, as detailed herein.

[0011] Further provided is a pharmaceutical composition comprising is a compound of Formula (I), including compounds of Formulae (II)-(IV), or selected from the group consisting of a compound listed in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient.

[0012] In another ~~aspect~~example, provided is a method of treating a disease or a condition mediated by GLP-1R in a subject in need thereof comprises administering to the subject a therapeutically effective amount of a compound of Formula (I), including compounds of

Formulae (II)-(IV), or selected from the group consisting of compounds listed in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing. In some ~~embodiment~~example**s**, the disease or the condition is a cardiometabolic disease. In some ~~embodiment~~example**s**, the disease or the condition is diabetes. In some ~~embodiment~~example**s**, the disease or the condition is a liver disease.

[0013] Also provided is a compound of Formula (I), including compounds of Formulae (II)-(IV), or selected from the group consisting of a compound listed in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, as detailed herein, for the treatment.

[0014] Also provided is use of a compound of Formula (I), including compounds of Formulae (II)-(IV), or selected from the group consisting of a compound listed in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, as detailed herein, in the manufacture of a medicament for the treatment.

[0015] Further provided is a kit comprising a compound of Formula (I), including compounds of Formulae (II)-(IV), or selected from the group consisting of a compound listed in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing. In some ~~embodiment~~example**s**, the kit comprises instructions for use according to a method described herein.

[0016] In yet another ~~aspect~~example, provided is a method of making a compound of Formula (I), including compounds of Formulae (II)-(IV), or selected from the group consisting of a compound listed in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing. Also provided are compound intermediates useful in synthesis of a compound of Formula (I), including compounds of Formulae (II)-(IV), or selected from the group consisting of a compound listed in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing.

DETAILED DESCRIPTION

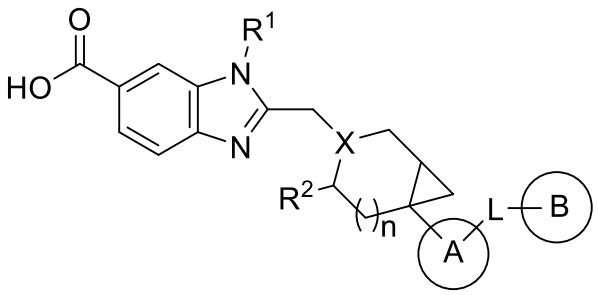
Definitions

[0017] As used herein, the following definitions shall apply unless otherwise indicated. Further, if any term or symbol used herein is not defined as set forth below, it shall have its ordinary meaning in the art.

[0018] As used herein and in the appended claims, the singular forms “a”, “an” and “the” include plural forms, unless the context clearly dictates otherwise.

CLAIMS

1. A compound of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

n is 0 or 1;

R^1 is -C_1-C_6 alkylene-R^5, wherein R^5 is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by C_1-C_6 alkyl;

R^2 is hydrogen, oxo, or C_1-C_6 alkyl;

Ring A is 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH;

L is a bond, -O-, C_1-C_6 alkylene, *-O-C_1-C_6 alkylene-**, *-C_1-C_6 alkylene-O-**, or *–NR^6-C_1-C_6 alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B,

when L is *-O-C_1-C_6 alkylene-**, the C_1-C_6 alkylene is optionally substituted by R^L, wherein:

each R^L is independently C_1-C_6 alkyl or halo, or

two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl;

when L is C_1-C_6 alkylene, the C_1-C_6 alkylene is optionally substituted by R^{L1}, wherein:

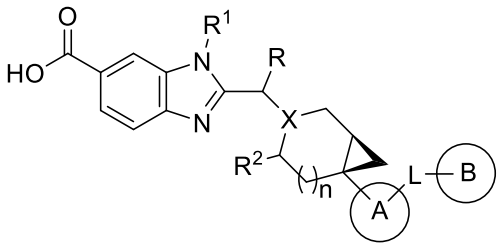
each R^{L1} is independently halo, OH, or C_1-C_6 alkyl; or

two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl, and

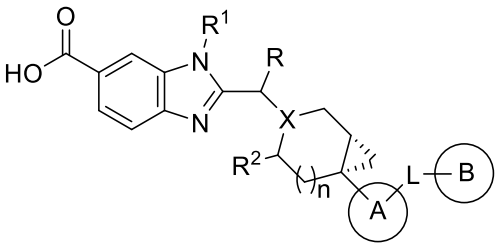
R^6 is hydrogen or C_1-C_6 alkyl; and

Ring B is C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $–COCH_3$, $–CONH_2$, $–S(O)_2CH_3$, and phenyl.

2. The compound of claim 1, wherein the compound is of formula (Va) or (Vb)



(Va)

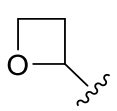


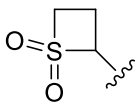
(Vb)

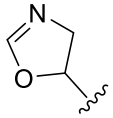
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is $–CH_2$-R^5.

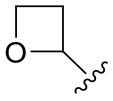
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^5 is 3- to 6-membered heterocyclyl, which is optionally substituted by C_1-C_6 alkyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^5 is 

, 

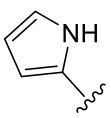
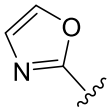
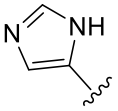
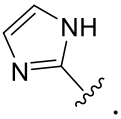
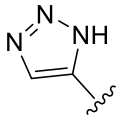
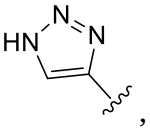
, or 

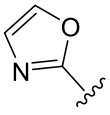
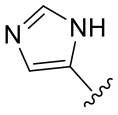
, each of which is independently optionally substituted by C_1-C_6 alkyl.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^5 is .

7. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^5 is 5- to 6-membered heteroaryl, which is optionally substituted by C_1-C_6 alkyl.

8. The compound of any one of claims 1-3 or 7, or a pharmaceutically acceptable salt thereof, wherein R^5 is 5-membered heteroaryl, which is optionally substituted by C_1-C_6 alkyl.

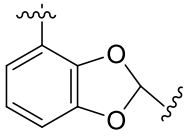
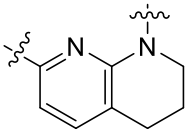
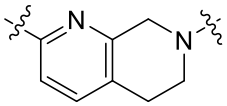
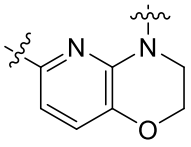
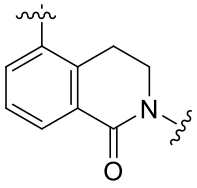
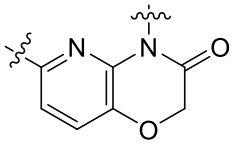
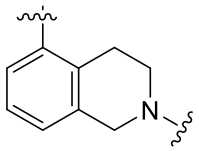
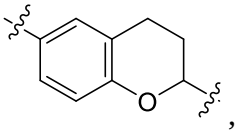
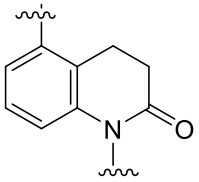
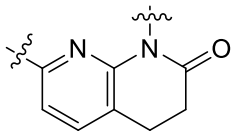
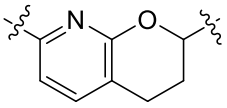
9. The compound of any one of claims 1-3 or 7-8, or a pharmaceutically acceptable salt thereof, wherein R^5 is , , , . , or , each of which is optionally substituted by C_1-C_6 alkyl.

10. The compound of any one of claims 1-3 or 7-9, or a pharmaceutically acceptable salt thereof, wherein R^5 is  or , each of which is optionally substituted by C_1-C_6 alkyl.

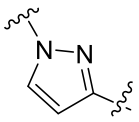
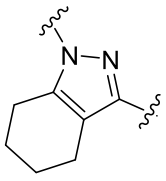
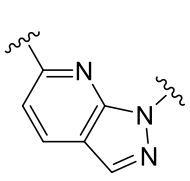
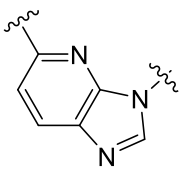
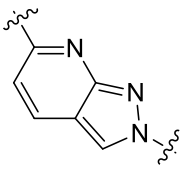
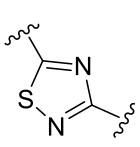
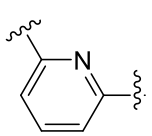
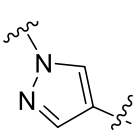
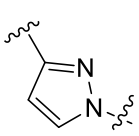
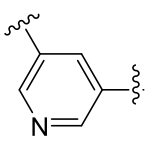
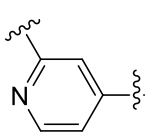
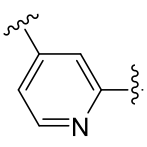
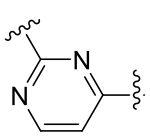
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein X is N.

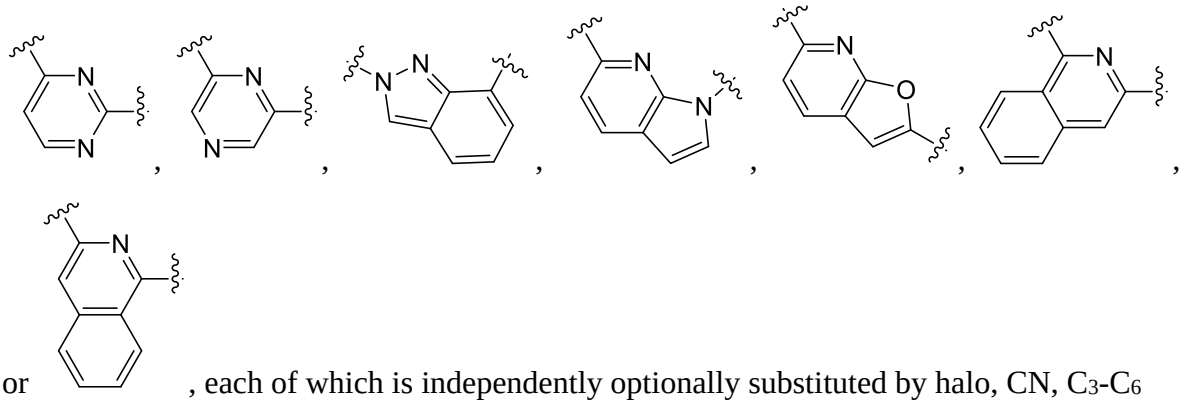
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein n is 1.

13. The compound of any of one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein Ring A is 5- to 12-membered heterocyclyl, which is optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

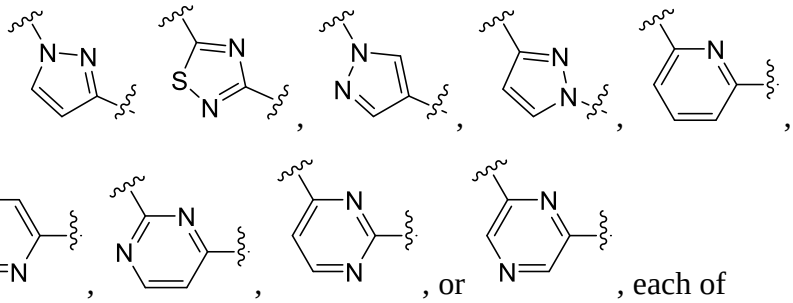
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein Ring A is Ring A is , , , , , , , , , , or , each of which is optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

15. The compound of any of one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein Ring A is 5- to 12-membered heteroaryl, which is optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

16. The compound of any one of claims 1-12 or 15, wherein Ring A is , , , , , , , , , , , , ,


or , each of which is independently optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

17. The compound of any of one of claims 1-12 or 15, or a pharmaceutically acceptable salt thereof, wherein Ring A is 5- to 6-membered heteroaryl, which is optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

18. The compound of any one of claims 1-12, 15, or 17, or a pharmaceutically acceptable salt thereof, wherein Ring A is 
, each of which is independently optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

20. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein L is -O-.

21. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein L is C_1-C_6 alkylene optionally substituted by R^{L1}.

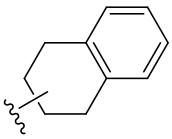
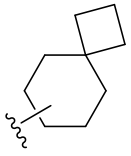
22. The compound of claim 21, or a pharmaceutically acceptable salt thereof, wherein L is C_2 alkylene optionally substituted by R^{L1}.

23. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein L is *-O-C_1-C_6 alkylene-** optionally substituted by R^L.

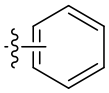
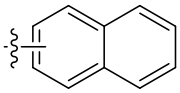
24. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein L is *-C_1-C_6 alkylene-O-**.

25. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein L is *–NR^6-C_1-C_6 alkylene-**.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Ring B is C_3-C_{10} cycloalkyl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$ and phenyl.

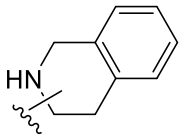
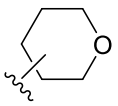
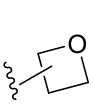
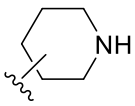
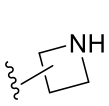
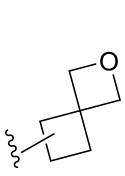
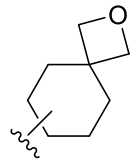
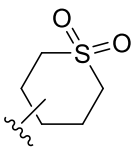
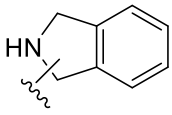
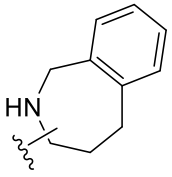
27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein Ring B is , , , or , each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$ and phenyl.

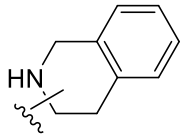
28. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Ring B is C_6-C_{14} aryl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$ and phenyl.

29. The compound of any one of claims 1-25 or 28, or a pharmaceutically acceptable salt thereof, wherein Ring B is  or , each of which is independently optionally substituted by one to three substituents each independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$ and phenyl.

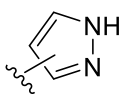
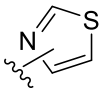
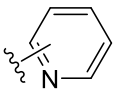
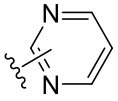
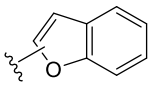
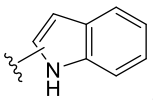
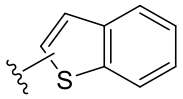
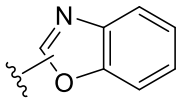
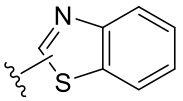
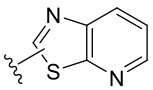
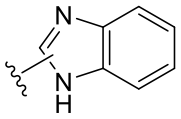
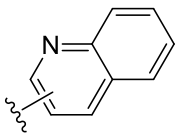
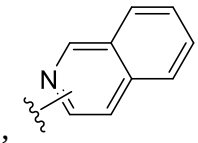
30. The compound of any one of claims 1-25 or 29, or a pharmaceutically acceptable salt thereof, wherein Ring B is phenyl substituted by one to three substituents independently selected from the group consisting of halo and CN.

31. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Ring B is 4- to 12-membered heterocyclyl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$ and phenyl.

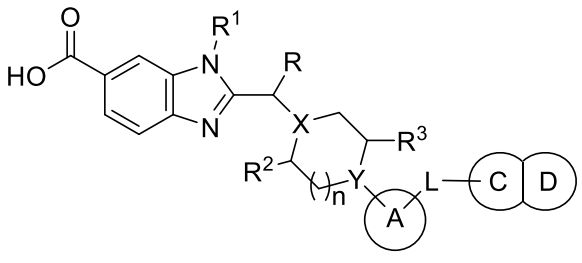
32. The compound of any one of claims 1-25 or 31, or a pharmaceutically acceptable salt thereof, wherein Ring B is , , , , , , , , , or , each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$ and phenyl.

33. The compound of any one of claims 1-25 or 31-32, or a pharmaceutically acceptable salt thereof, wherein Ring B is , which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$ and phenyl.

34. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Ring B is 5- to 12-membered heteroaryl, which is optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$ and phenyl.

35. The compound any one of claims 1-25 or 34, or a pharmaceutically acceptable salt thereof, wherein Ring B is , , , , , , , , , , , , , or, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, –$COCH_3$, –$CONH_2$, –$S(O)_2CH_3$ and phenyl.

36. A compound of Formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein

X is N or CH;

n is 0 or 1;

R^1 is -C_1-C_6 alkylene-R^5, wherein R^5 is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by C_1-C_6 alkyl;

R^2 is hydrogen, oxo, or C_1-C_6 alkyl;

Ring A is 5- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH;

L is a bond, -O-, C_1-C_6 alkylene, *-O-C_1-C_6 alkylene-**, *-C_1-C_6 alkylene-O-**, or *–NR^6-C_1-C_6 alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to 

,

when L is *-O-C_1-C_6 alkylene-**, the C_1-C_6 alkylene is optionally substituted by R^L, wherein:

each R^L is independently C_1-C_6 alkyl or halo, or

two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl;

when L is C_1-C_6 alkylene, the C_1-C_6 alkylene is optionally substituted by R^{L1}, wherein:

each R^{L1} is independently halo, OH, or C_1-C_6 alkyl; or

two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl, and

R^6 is hydrogen or C_1-C_6 alkyl; and



is a fused bicyclic ring system comprising fused rings Ring C and Ring D, wherein

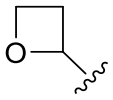
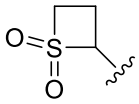
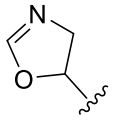
Ring C is C_5-C_6 cycloalkyl, 5- to 7-membered heterocyclyl, or 5- to 6-membered heteroaryl; and

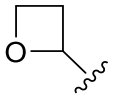
Ring D is C_6 cycloalkyl, C_6 aryl or 6-membered heteroaryl;

wherein Ring C and Ring D are optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $–COCH_3$, $–CONH_2$, $–S(O)_2CH_3$, and phenyl.

37. The compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein R^1 is $–CH_2$-R^5.

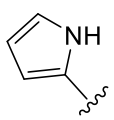
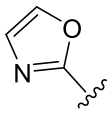
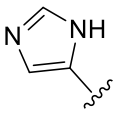
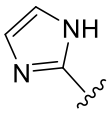
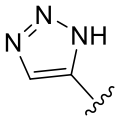
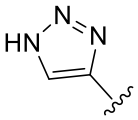
38. The compound of claim 36 or 37, or a pharmaceutically acceptable salt thereof, wherein R^5 is 3- to 6-membered heterocyclyl, which is optionally substituted by C_1-C_6 alkyl.

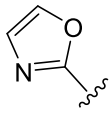
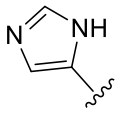
39. The compound of any one of claims 36-38, or a pharmaceutically acceptable salt thereof, wherein R^5 is , , or , each of which is independently optionally substituted by C_1-C_6 alkyl.

40. The compound of any one of claims 36-39, or a pharmaceutically acceptable salt thereof, wherein R^5 is .

41. The compound of claim 36 or 37, or a pharmaceutically acceptable salt thereof, wherein R^5 is 5- to 6-membered heteroaryl, which is optionally substituted by C_1-C_6 alkyl.

42. The compound of any one of claims 36-37 or 41, or a pharmaceutically acceptable salt thereof, wherein R^5 is 5-membered heteroaryl, which is optionally substituted by C_1-C_6 alkyl.

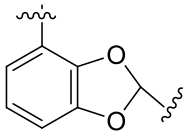
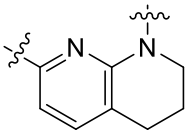
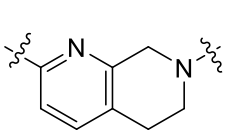
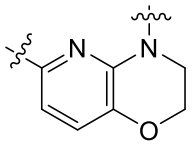
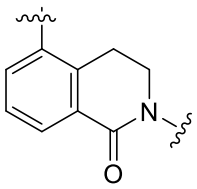
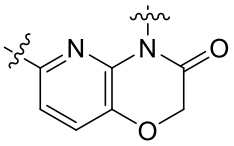
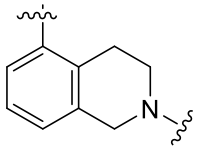
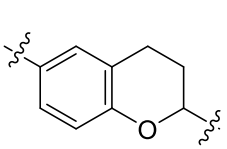
43. The compound of any one of claims 36-37 or 41-42, or a pharmaceutically acceptable salt thereof, wherein R^5 is , , , . , or , each of which is optionally substituted by C_1-C_6 alkyl.

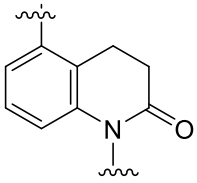
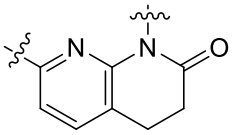
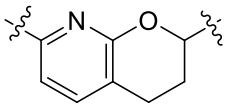
44. The compound of any one of claims 36-37 or 41-43, or a pharmaceutically acceptable salt thereof, wherein R^5 is  or , each of which is optionally substituted by C_1-C_6 alkyl.

45. The compound of any one of claims 36-44, or a pharmaceutically acceptable salt thereof, wherein X is N.

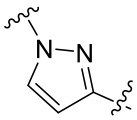
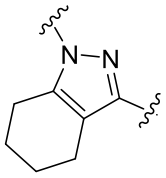
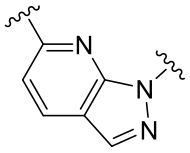
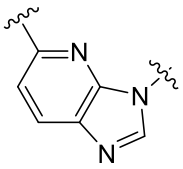
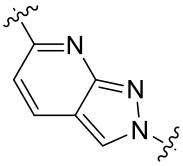
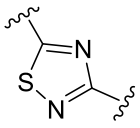
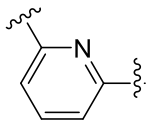
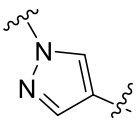
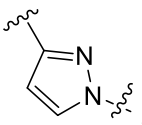
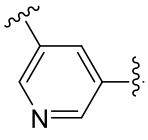
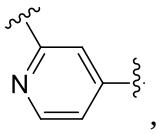
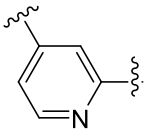
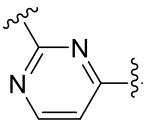
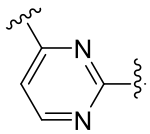
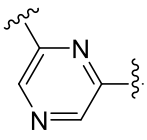
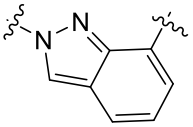
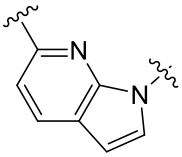
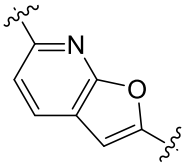
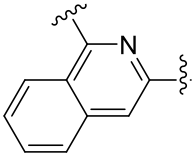
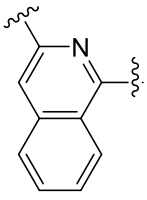
46. The compound of any one of claims 36-45, or a pharmaceutically acceptable salt thereof, wherein n is 1.

47. The compound of any of one of claims 36-46, or a pharmaceutically acceptable salt thereof, wherein Ring A is 5- to 12-membered heterocyclyl, which is optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

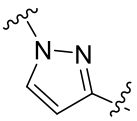
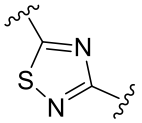
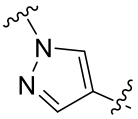
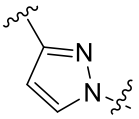
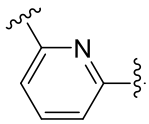
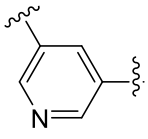
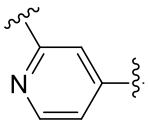
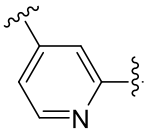
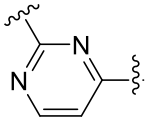
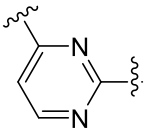
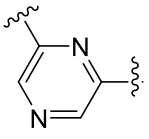
48. The compound of any one of claims 36-47, or a pharmaceutically acceptable salt thereof, wherein Ring A is Ring A is , , , , , , , ,



, or , each of which is optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

49. The compound of any of one of claims 36-46, or a pharmaceutically acceptable salt thereof, wherein Ring A is 5- to 12-membered heteroaryl, which is optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

50. The compound of any one of claims 36-46 or 49, wherein Ring A is ,
, , , , ,
, , , , , , ,
, , , , , ,
or , each of which is independently optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

51. The compound of any of one of claims 36-46 or 49, or a pharmaceutically acceptable salt thereof, wherein Ring A is 5- to 6-membered heteroaryl, which is optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

52. The compound of any one of claims 36-46, 49, or 51, or a pharmaceutically acceptable salt thereof, wherein Ring A is , , , , , , , , , , or , each of which is independently optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH.

53. The compound of any one of claims 36-52, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

54. The compound of any one of claims 36-52, or a pharmaceutically acceptable salt thereof, wherein L is -O-.

55. The compound of any one of claims 36-52, or a pharmaceutically acceptable salt thereof, wherein L is C_1-C_6 alkylene optionally substituted by R^{L1}.

56. The compound of claim 55, or a pharmaceutically acceptable salt thereof, wherein L is C_2 alkylene optionally substituted by R^{L1}.

57. The compound of any one of claims 36-52, or a pharmaceutically acceptable salt thereof, wherein L is *-O-C_1-C_6 alkylene-** optionally substituted by R^L.

58. The compound of any one of claims 36-52, or a pharmaceutically acceptable salt thereof, wherein L is *-C_1-C_6 alkylene-O-**.

59. The compound of any one of claims 36-52, or a pharmaceutically acceptable salt thereof, wherein L is *–NR^6-C_1-C_6 alkylene-**.

60. The compound of any one of claims 36-59, or a pharmaceutically acceptable salt thereof, wherein Ring D is C_6 aryl.

61. The compound of claim 60, wherein Ring C is C_5-C_6 cycloalkyl.

62. The compound of claim 60, wherein Ring C is 5- to 7-membered heterocyclyl.

63. The compound of claim 60, wherein Ring C is 5- to 6-membered heteroaryl.

64. The compound of any one of claims 36-59, or a pharmaceutically acceptable salt thereof, wherein Ring D is 6-membered heteroaryl.

65. The compound of claim 64, wherein Ring C is C_5-C_6 cycloalkyl.

66. The compound of claim 64, wherein Ring C is 5- to 7-membered heterocyclyl.

67. The compound of claim 64, wherein Ring C is 5- to 6-membered heteroaryl.

68. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of the compounds in Table 1.

69. A pharmaceutical composition comprising the compound of any one of claims 1-68, or a pharmaceutically acceptable salt thereof, and a pharmaceutical acceptable excipient.

70. ~~A method of treating a disease mediated by glucagon-like peptide-1 receptor (GLP-1R) in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the~~Use of a compound of any one of claims 1-68, or a

pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 69, in the manufacture of a medicament for treating a disease mediated by glucagon-like peptide-1 receptor (GLP-1R) in an individual in need thereof.

71. The ~~method~~ use of claim 70, wherein the disease is a liver disease.

72. The ~~method~~ use of claim 71, wherein the liver disease is primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), graft versus host disease, transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, or oti-antitrypsin deficiency.

73. The ~~method~~ use of claim 70, wherein the disease is diabetes.

74. The use ~~method~~ of claim 70, wherein the disease is a cardiometabolic disease.

75. The use ~~method~~ of claim 70, wherein the disease is obesity.

76. ~~Use of the~~A compound of any one of claims 1-68, or a pharmaceutically acceptable salt thereof, for use in therapy ~~in the manufacture of a medicament for treating a disease mediated by mediated by GLP-1R~~.