

response to ingestion of food. GLP-1 has been shown to stimulate insulin secretion in a physiological and glucose-dependent manner, decrease glucagon secretion, inhibit gastric emptying, decrease appetite, and stimulate proliferation of beta-cells. In non-clinical experiments GLP-1 promotes continued beta-cell competence by stimulating transcription of genes important for glucose-dependent insulin secretion and by promoting beta-cell neogenesis (Meier *et al.*, *Biodrugs*. 17(2): 93-102, 2013).

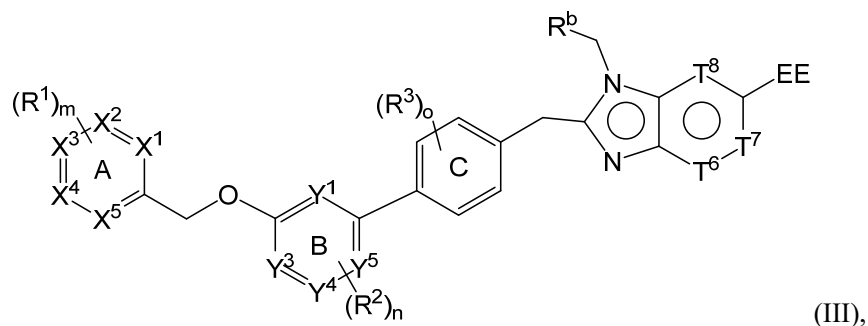
In a healthy individual, GLP-1 plays an important role regulating post-prandial blood glucose levels by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose 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 *et al.*, *Diabetes*. 50:609-613, 2001).

Hoist (*Physiol. Rev.* 87:1409, 2007) and Meier (*Nat. Rev. Endocrinol.* 8:728, 2012) describe that GLP-1 receptor agonists, such as GLP-1, 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.

There remains a need for an easily-administered prevention and/or treatment for cardiometabolic and associated diseases.

SUMMARY

In one aspect of the present disclosure, there is provided a compound represented by structural formula (III):



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

X^1 , X^2 , X^3 , X^4 , and X^5 are each independently selected from N and CH; wherein no more than three of X^1 , X^2 , X^3 , X^4 , and X^5 are N and wherein ring A does not contain 3 nitrogen ring atoms at 3 contiguous positions;

ring B is 6-membered heteroaryl or phenyl, wherein Y^1 , Y^3 , Y^4 , and Y^5 are each independently

selected from N or CH; wherein there are no more than 3 nitrogen ring atoms in ring B and ring B does not contain 3 nitrogen ring atoms at 3 contiguous positions;

T⁶, T⁷, and T⁸ are each independently selected from N and CR⁴;

EE is -COOH;

R^b is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR^{5'}R^{6'}, 6-10 membered aryl, 5-6 membered heteroaryl, 3-6 membered saturated or partially saturated cycloalkyl and 3-7 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆ alkyl or C₁-C₆ alkoxy represented by R^b is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, and C₃-C₆ saturated or partially saturated cycloalkyl; and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R^b or in the group represented by R^b is optionally substituted with one or more groups selected from halogen, oxo (when R^b is non-aromatic), CN, OH, C₁-C₃ alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and C₁-C₃ alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and NR^{5'}R^{6'};

each R¹ is independently selected from H, halogen, -CN, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NR^{5'}R^{6'}, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, or C₂-C₆ alkynyl represented by R¹ is optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃, and saturated or partially saturated C₃-C₆ cycloalkyl (optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃); and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R¹ or in the group represented by R¹ is optionally substituted with one or more groups selected from halogen, oxo (as appropriate), CN, OH, C₁-C₃ alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and C₁-C₃ alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and NR^{5'}R^{6'}.

each R² is independently selected from halogen, -CN, OH, C₁-C₂ alkyl, C₁-C₂ haloalkyl, and C₁-C₂ alkoxy;

each R³ is independently selected from halogen, CN, OH, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, and NR^{5'}R^{6'};

each R⁴ is independently selected from H, F, Cl, methyl, and methoxy;

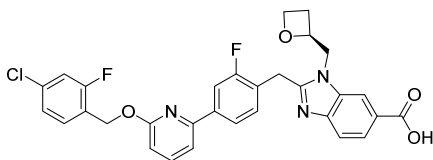
R^{5'} and R^{6'} are each independently selected from hydrogen and C₁-C₆ alkyl;

m is an integer selected from 0, 1, 2, 3, and 4;

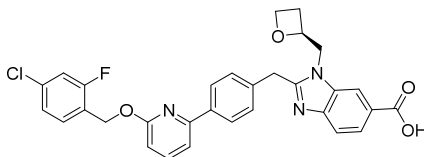
n is an integer selected from 0, 1, 2, 3, and 4

o is an integer selected from 0, 1, 2, 3, and 4.

In another aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structure:



In a further aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structure:



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 pharmaceutically acceptable excipient.

In a further aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutically acceptable salt thereof, for use in treating cardiometabolic and associated diseases, wherein the disease is type 1 diabetes, type 2 diabetes mellitus, obesity, hyperglycemia, non-alcoholic steatohepatitis, Alzheimer's Disease, Parkinson's Disease, ulcerative colitis, or nonalcoholic fatty liver disease.

In another aspect of the present disclosure, there is provided a use of a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for of treating a subject in need of with cardiometabolic and associated diseases, wherein the disease is type 1 diabetes, type 2 diabetes mellitus, obesity, hyperglycemia, non-alcoholic steatohepatitis, Alzheimer's Disease, Parkinson's Disease, ulcerative colitis, or nonalcoholic fatty liver disease.

In one example, the present disclosure provides a compound of any one of the formulae described herein (*e.g.*, Structural Formula (I), (I-1), (I-2), (II), (III), (I-A), (I-B), (I-C), (I-D), (II-A), (II-B), (II-B'), (II-C), or (II-D)), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof.

In one example, the present disclosure provides a pharmaceutical composition comprising a compound of any one of the formulae described herein (*e.g.*, Structural Formula (I), (I-1), (I-2), (II), (III), (I-A), (I-B), (I-C), (I-D), (II-A), (II-B), (II-B'), (II-C), or (II-D)), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, as defined in any one of the examples

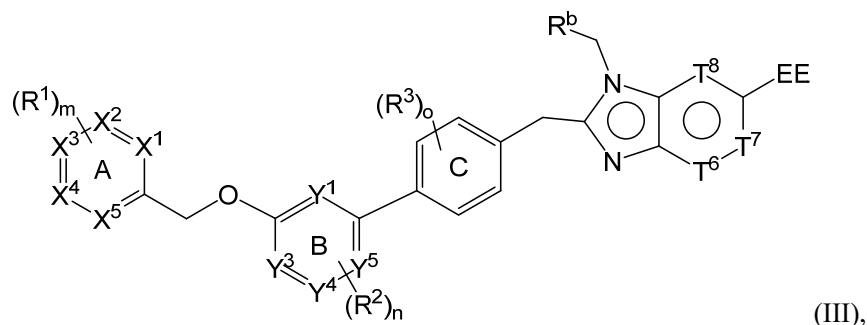
described herein, in a mixture with at least one pharmaceutically acceptable excipient.

In another example, the present disclosure provides a compound of any one of the formulae described herein (*e.g.*, Structural Formula (I), (I-1), (I-2), (II), (III), (I-A), (I-B), (I-C), (I-D), (II-A), (II-B), (II-B'), (II-C), or (II-D)), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, as defined in any one of the examples described herein, for use as a medicament.

In another example, the present disclosure provides a compound of any one of the formulae

CLAIMS

1. A compound represented by structural formula (III):



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

- 5 X^1 , X^2 , X^3 , X^4 , and X^5 are each independently selected from N and CH; wherein no more than three of X^1 , X^2 , X^3 , X^4 , and X^5 are N and wherein ring A does not contain 3 nitrogen ring atoms at 3 contiguous positions;
- ring B is 6-membered heteroaryl or phenyl, wherein Y^1 , Y^3 , Y^4 , and Y^5 are each independently selected from N or CH; wherein there are no more than 3 nitrogen ring atoms in ring B and ring B does not contain 3 nitrogen ring atoms at 3 contiguous positions;
- 10 T^6 , T^7 , and T^8 are each independently selected from N and CR^4 ;
- EE is $-COOH$;
- R^b is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $NR^{5'}R^{6'}$, 6-10 membered aryl, 5-6 membered heteroaryl, 3-6 membered saturated or partially saturated cycloalkyl and 3-7 membered saturated or partially saturated heterocyclyl, wherein the C_1 - C_6 alkyl or C_1 - C_6 alkoxy represented by R^b is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, and C_3 - C_6 saturated or partially saturated cycloalkyl; and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R^b or in the group represented by R^b is optionally substituted with one or more groups selected from halogen, oxo (when R^b is non-aromatic), CN, OH, C_1 - C_3 alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH_3), and C_1 - C_3 alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH_3), and $NR^{5'}R^{6'}$;
- 25 each R^1 is independently selected from H, halogen, $-CN$, OH, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $NR^{5'}R^{6'}$, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl represented by R^1 is optionally substituted with one or more groups selected from halogen, oxo, CN, CF_3 , OH, OCH_3 , OCH_2CH_3 , and saturated or partially saturated C_3 - C_6
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cycloalkyl (optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃); and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R¹ or in the group represented by R¹ is optionally substituted with one or more groups selected from halogen, oxo (as appropriate), CN, OH, C₁-C₃ alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and C₁-C₃ alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and NR^{5'}R^{6'}.

each R² is independently selected from halogen, -CN, OH, C₁-C₂ alkyl, C₁-C₂ haloalkyl, and C₁-C₂ alkoxy;

each R³ is independently selected from halogen, CN, OH, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, and NR^{5'}R^{6'};

each R⁴ is independently selected from H, F, Cl, methyl, and methoxy;

R^{5'} and R^{6'} are each independently selected from hydrogen and C₁-C₆ alkyl;

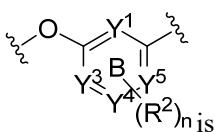
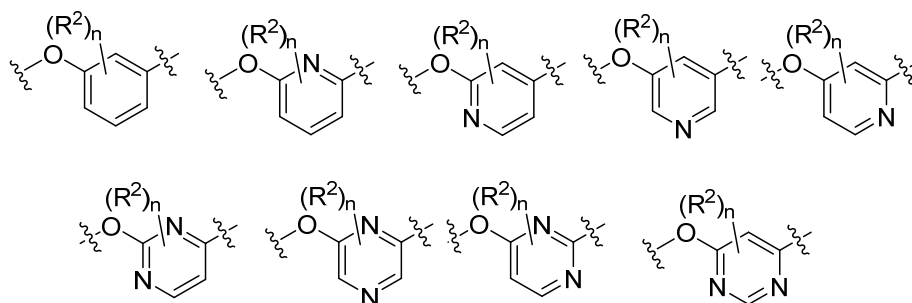
m is an integer selected from 0, 1, 2, 3, and 4;

n is an integer selected from 0, 1, 2, 3, and 4

o is an integer selected from 0, 1, 2, 3, and 4.

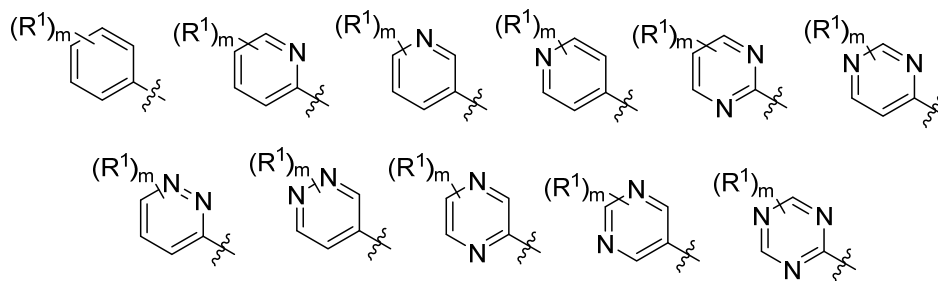
2. The compound according to claim 1, or a pharmaceutically acceptable salt, or stereoisomer

thereof, wherein

wherein n is an integer selected from 0, 1, 2, and 3 as appropriate.

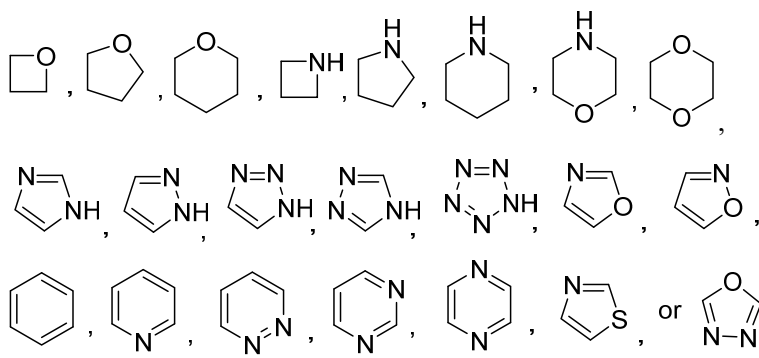
3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein ring A is



each R^1 is independently selected from halogen, OH, CN, CF_3 , C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, C_1 - C_2 alkoxy, $-NH_2$, $-NHC_1$ - C_2 alkyl, $-N(C_1$ - C_2 alkyl) $_2$, and C_2 - C_4 alkynyl optionally substituted with cyclopropane; and m is an integer selected from 0, 1, and 2.

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4. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^b is

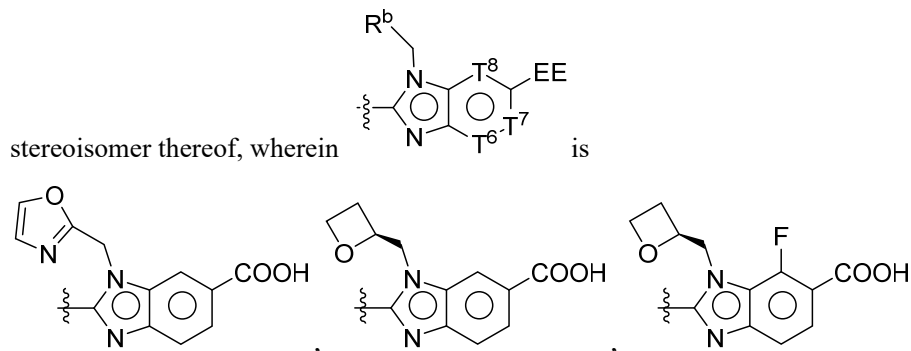


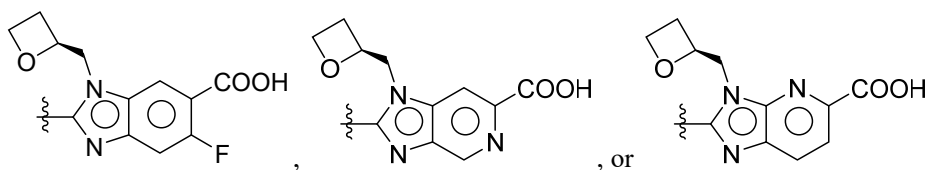
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each of which is optionally substituted with 1 or 2 groups selected from F, Cl, oxo (when R^b is non-aromatic), C_1 - C_3 alkyl, and C_1 - C_3 alkoxy, wherein the C_1 - C_3 alkyl or C_1 - C_3 alkoxy in the group represented by R^b is optionally substituted with 1 or 2 groups selected from F, OH, and OCH_3 .

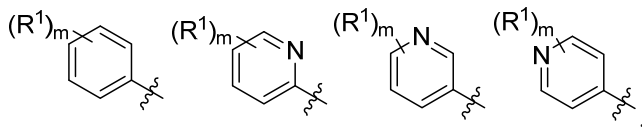
15 5.

- The compound according to any one of claims 2-4, or a pharmaceutically acceptable salt, or



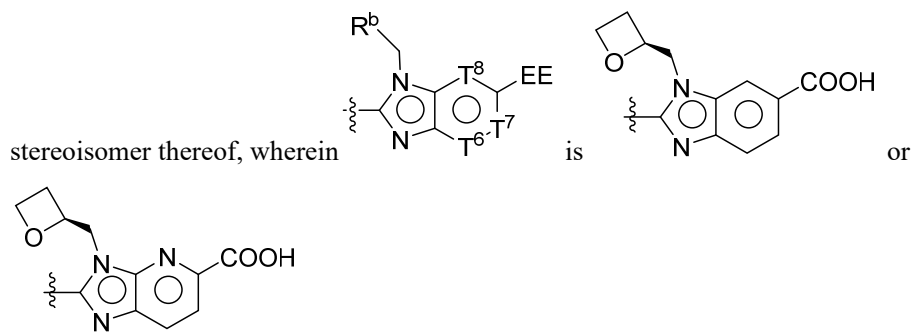


6. The compound according to any one of claims 1-5, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein ring A is



each R^1 is independently selected from halogen, OH, CN, C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, C_1 - C_2 alkoxy, and C_2 - C_4 alkynyl; and m is an integer selected from 0, 1, and 2.

7. The compound according to any one of claims 2-6, or a pharmaceutically acceptable salt, or



stereoisomer thereof, wherein

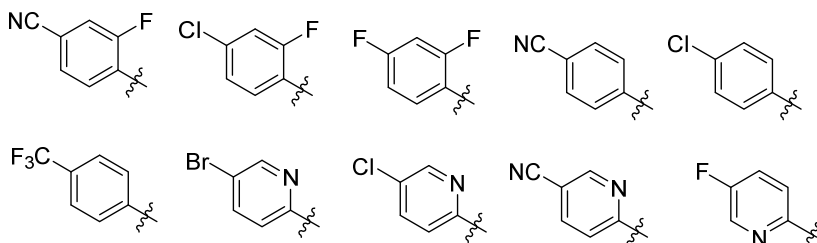
is

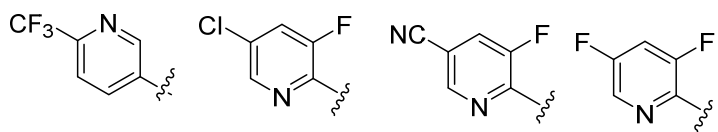
or

8. The compound according to any one of claims 1-7, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^2 is independently selected from halogen (e.g., F); and n is an integer selected from 0, 1, and 2.

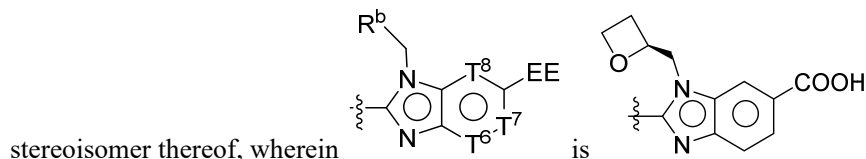
9. The compound according to any one of claims 1-8, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^3 is F, Cl or CH_3 ; and o is 0, 1, or 2.

10. The compound according to any one of claims 1-9, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein ring A is



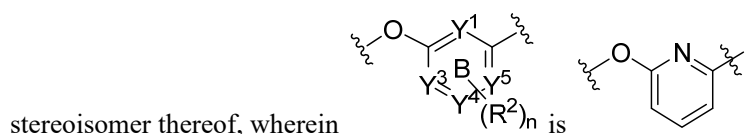


11. The compound according to any one of claims 1-10, or a pharmaceutically acceptable salt or

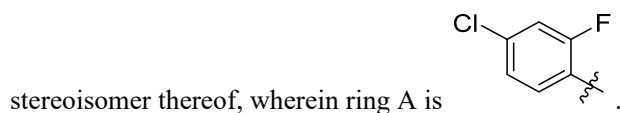


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12. The compound according to any one of claims 1-11, or a pharmaceutically acceptable salt or

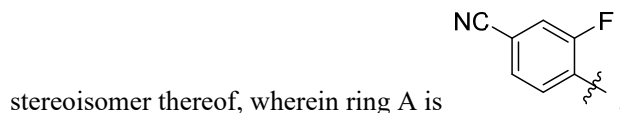


13. The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt or



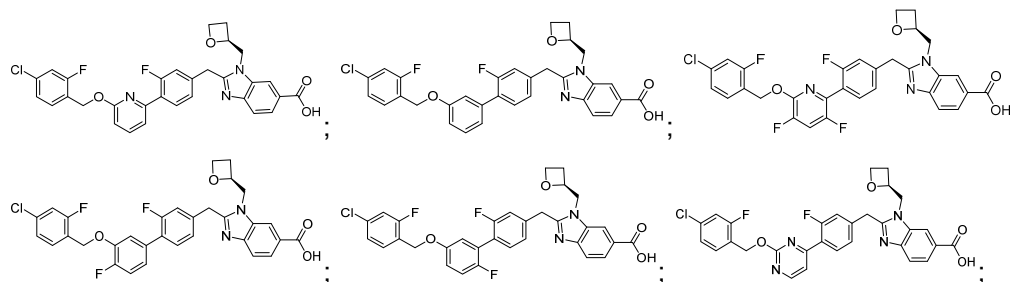
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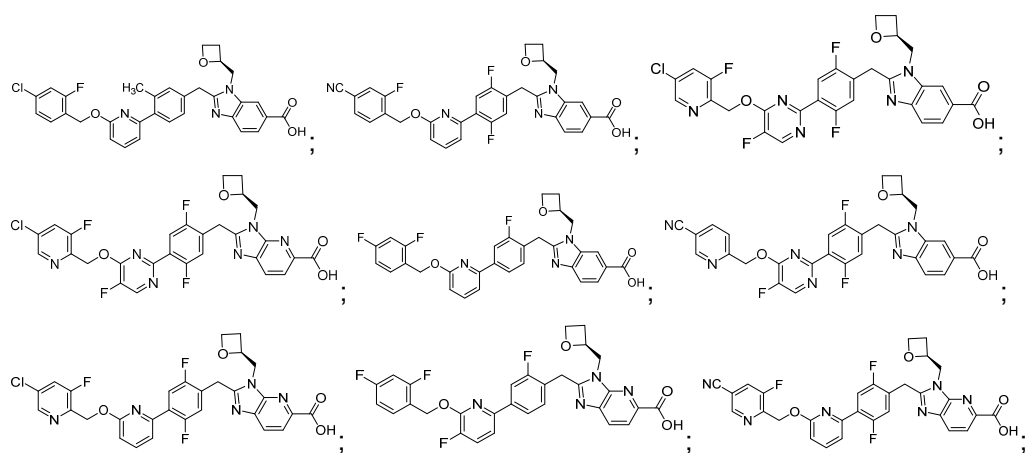
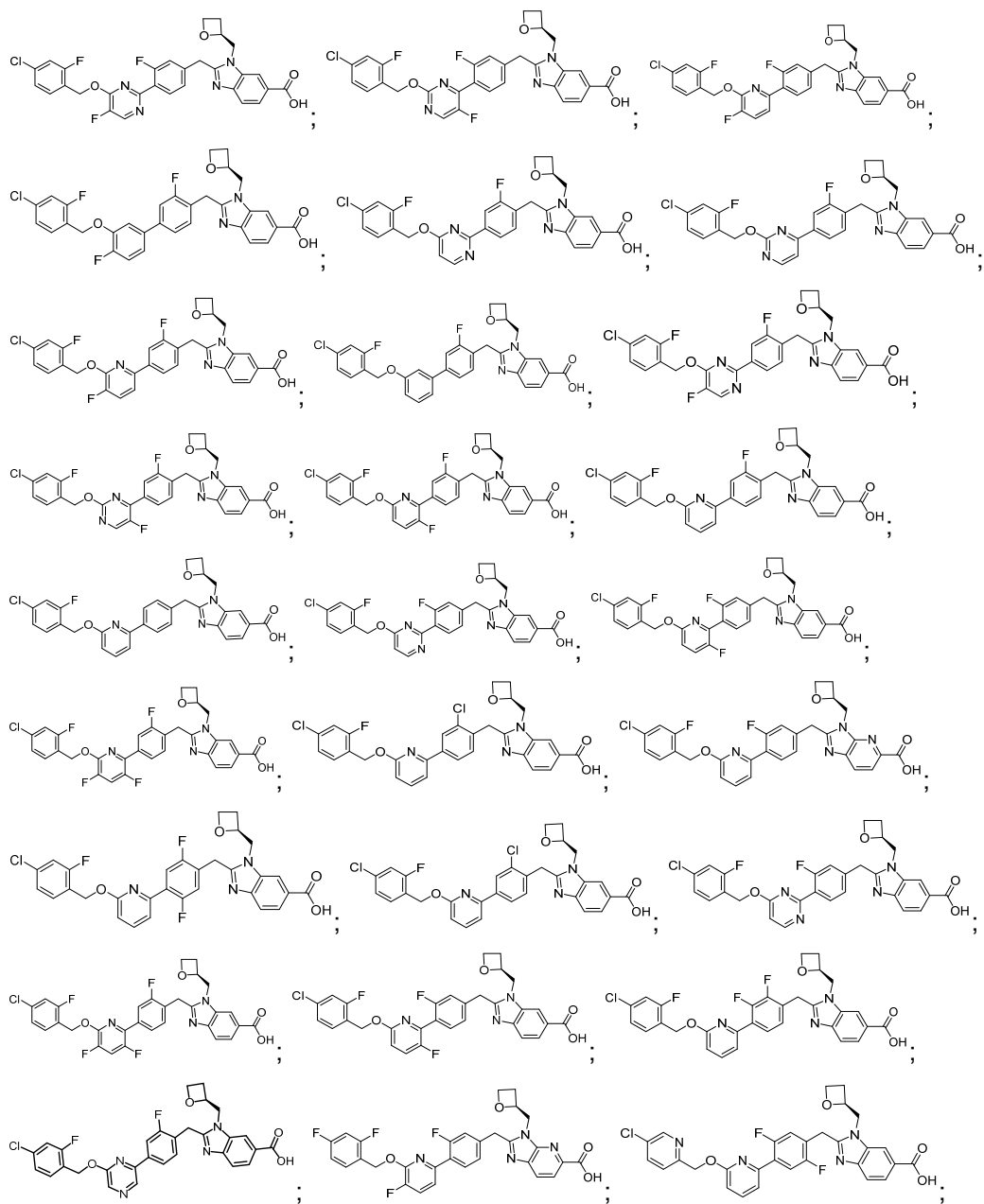
14. The compound according to any one of claims 1-13, or a pharmaceutically acceptable salt, or

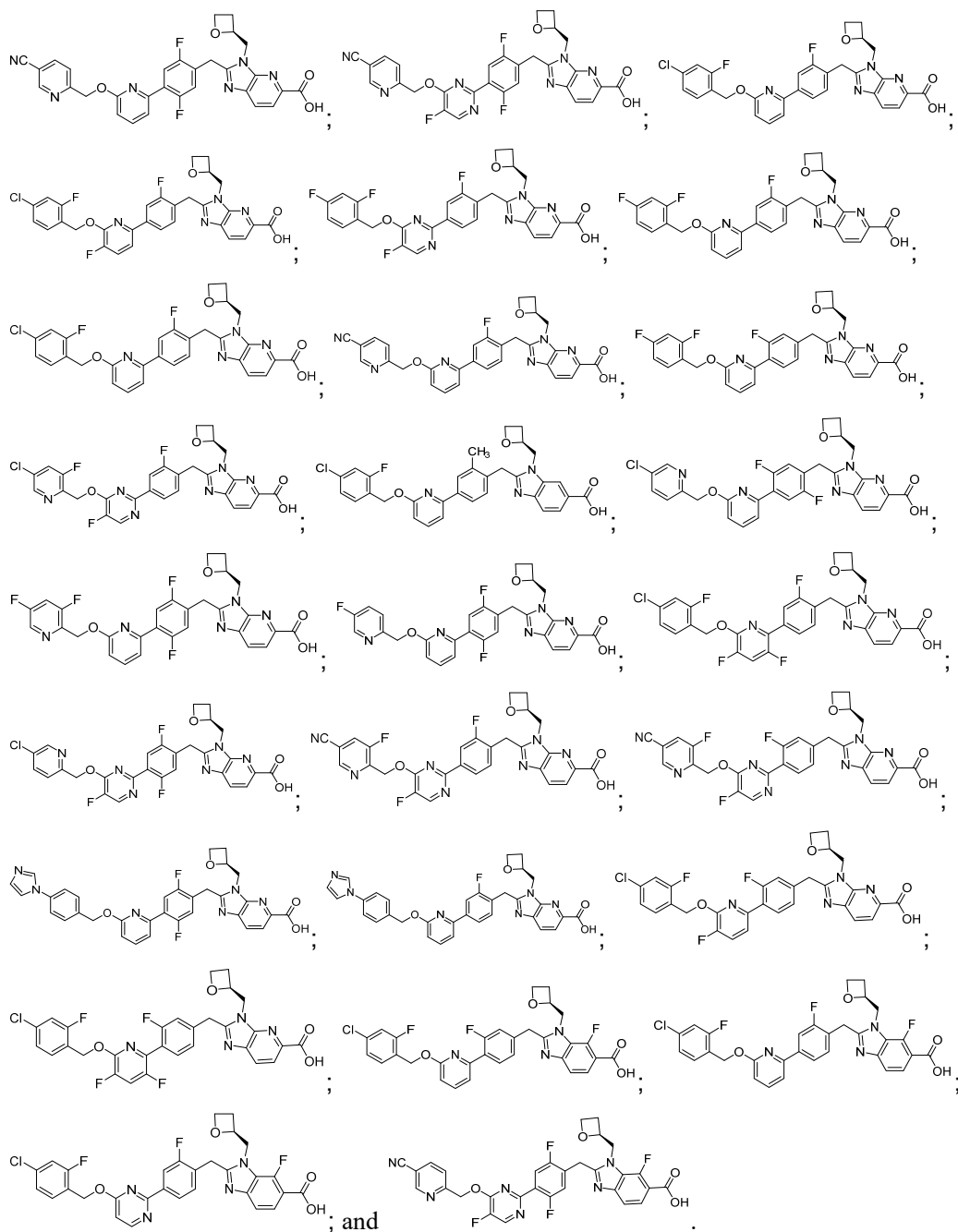


15. The compound according to any one of claims 1-14, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R³ is F or CH₃; and o is 2.

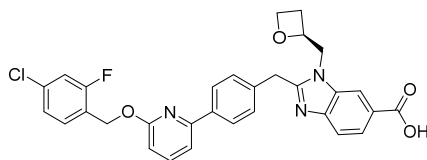
16. The compound according to claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is selected from the group consisting of







18. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structure:



- 5 19. A pharmaceutical composition comprising the compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
20. A compound of any one of claims 1-18 or a pharmaceutically acceptable salt thereof, for use in treating cardiometabolic and associated diseases, wherein the disease is type 1 diabetes, type 2 diabetes mellitus, obesity, hyperglycemia, non-alcoholic steatohepatitis, Alzheimer's Disease, Parkinson's Disease, ulcerative colitis, or nonalcoholic fatty liver disease.
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21. Use of a therapeutically effective amount of a compound of any one of claims 1-18 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for of treating a subject in need of with cardiometabolic and associated diseases, wherein the disease is type 1 diabetes, type 2 diabetes mellitus, obesity, hyperglycemia, non-alcoholic steatohepatitis, Alzheimer's Disease, Parkinson's Disease, ulcerative colitis, or nonalcoholic fatty liver disease.
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