

In another aspect, the present disclosure refers to an incretin analog having a formula selected from the group consisting of SEQ ID NOS:5-11.

In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising:

- an incretin analog disclosed herein; and
- a pharmaceutically acceptable carrier, diluent, or excipient.

In a further aspect, the present disclosure refers to an incretin analog disclosed herein, for use in treating a disease selected from the group consisting of type II diabetes mellitus, dyslipidemia, fatty liver disease, metabolic syndrome, non-alcoholic steatohepatitis and obesity.

In another aspect, the present disclosure refers to an incretin analog disclosed herein, for use in treating type II diabetes mellitus.

In yet another aspect, the present disclosure refers to a use of an incretin analog disclosed herein, in the manufacture of a medicament for treating a disease selected from the group consisting of type II diabetes mellitus, dyslipidemia, fatty liver disease, metabolic syndrome, non-alcoholic steatohepatitis and obesity.

In a further aspect, the present disclosure refers to a use of an incretin analog disclosed herein, in the manufacture of a medicament for treating type II diabetes mellitus.

In another aspect of the present disclosure, there is provided an incretin analog disclosed herein, for use in treating obesity.

In a further aspect of the present disclosure, there is provided a use of an incretin analog disclosed herein, in the manufacture of a medicament for treating obesity.

Description

The incretin analogs described herein seek to meet the needs above. Accordingly, this disclosure describes incretin analogs with activity at each of the GIP, GLP-1 and glucagon receptors. Advantageously, the incretin analogs described herein have balanced activity allowing for administration of doses that provide sufficient activity at each receptor to provide the benefits of agonism of that receptor while avoiding unwanted side effects associated with too much activity. Moreover, the incretin analogs described herein have extended duration of action at each of the GIP, GLP-1 and glucagon receptors allowing for dosing as infrequently as once-a-day, thrice-weekly, twice-weekly or once-a-week. In this manner, the incretin analogs result in enhanced glucose control, metabolic benefits such as

body weight lowering and/or improved body composition, lipid benefits such as proprotein convertase subtilisin/kexin type 9 (PCSK9) lowering, and/or other benefits such as an increase in bone mass or bone formation or a decrease in bone resorption. This disclosure also describes effective treatments for other disorders or conditions, including obesity, NAFLD, NASH, dyslipidemia, and/or metabolic disorder.

CLAIMS

The invention claimed is:

1. An incretin analog comprising:
YX₂X₃GTX₆TSYX₁₃LDKX₁₇AQX₂₀AFIEYLLEGGPSSGAPPPS,
wherein:
X₂ is Aib,
X₃ is Q or H,
X₆ is α MeF or α MeF(2F),
X₁₃ is L or α MeL,
X₁₇ is any amino acid with a functional group available for conjugation,
and the functional group is conjugated to a C₁₆-C₂₂ fatty acid,
X₂₀ is Aib, Q or H,
(SEQ ID NO:5), and the C-terminal amino acid is optionally amidated;
or a pharmaceutically acceptable salt thereof.
2. The incretin analog of Claim 1, wherein the amino acid with a functional group available for conjugation at position X₁₇ is selected from the group consisting of K, C, E and D.
3. The incretin analog of Claim 1, wherein the amino acid with a functional group available for conjugation at position X₁₇ is K.
4. The incretin analog of any one of Claims 1 to 3, wherein the amino acid with the functional group available for conjugation at position X₁₇ and the C₁₆-C₂₂ fatty acid are conjugated by a linker between the amino acid and the fatty acid.
5. The incretin analog of Claim 4, wherein the linker comprises one to four amino acids.
6. The incretin analog of Claim 5, wherein the amino acids are Glu or γ Glu.

7. The incretin analog of any one of Claims 4 to 6, wherein the linker further comprises the following structure:

$$\text{H}-\{\text{NH}-\text{CH}_2-\text{CH}_2-[\text{O}-\text{CH}_2-\text{CH}_2]_m-\text{O}-(\text{CH}_2)_p-\text{CO}\}_n-\text{OH}$$
, wherein m is any integer from 1 to 12, n is any integer from 1 to 12, and p is 1 or 2.

8. The incretin analog of any one of Claims 4 to 7, wherein the linker further comprises one to four (2-[2-(2-amino-ethoxy)-ethoxy]-acetyl) moieties.

9. The incretin analog of Claim 1, wherein X_{17} is K chemically modified through conjugation to an epsilon-amino group of a K side-chain with the following structure:

$$(2-[2-(2\text{-amino-ethoxy})\text{-ethoxy}]\text{-acetyl})_a-(\gamma\text{Glu})_b-\text{CO}-(\text{CH}_2)_c-\text{CO}_2\text{H}$$
, wherein a is 0, 1 or 2; b is 1 or 2; and c is an integer between 16 to 18.

10. The incretin analog of Claim 9, wherein a is 1.

11. The incretin analog of Claim 9, wherein a is 2.

12. The incretin analog of any one of Claims 9 to 11, wherein b is 1.

13. The incretin analog of any one of Claims 9 to 11, wherein b is 2.

14. The incretin analog of any one of Claims 9 to 13, wherein c is 18.

15. The incretin analog of any one of Claims 1 to 14, wherein X_{13} is αMeL .

16. The incretin analog of any one of Claims 1 to 14, wherein X_{13} is L.

17. The incretin analog of any one of Claims 1 to 16, wherein X_3 is Q.

18. The incretin analog of any one of Claims 1 to 16, wherein X_3 is H.

19. The incretin analog of any one of Claims 1 to 18, wherein X_6 is αMeF .

20. The incretin analog of any one of Claims 1 to 18 wherein X₆ is αMeF(2F).
21. An incretin analog having a formula selected from the group consisting of SEQ ID NOS:5-11.
22. A pharmaceutical composition comprising:
an incretin analog of any one of Claims 1 to 21; and
a pharmaceutically acceptable carrier, diluent, or excipient.
23. An incretin analog of any one of Claims 1 to 21, for use in treating a disease selected from the group consisting of type II diabetes mellitus, dyslipidemia, fatty liver disease, metabolic syndrome, non-alcoholic steatohepatitis and obesity.
24. An incretin analog of any one of Claims 1 to 21, for use in treating type II diabetes mellitus.
25. Use of an incretin analog of any one of Claims 1 to 21, in the manufacture of a medicament for treating a disease selected from the group consisting of type II diabetes mellitus, dyslipidemia, fatty liver disease, metabolic syndrome, non-alcoholic steatohepatitis and obesity.
26. Use of an incretin analog of any one of Claims 1 to 21, in the manufacture of a medicament for treating type II diabetes mellitus.
27. An incretin analog of any one of Claims 1 to 21, for use in treating obesity.
28. Use of an incretin analog of any one of Claims 1 to 21, in the manufacture of a medicament for treating obesity.