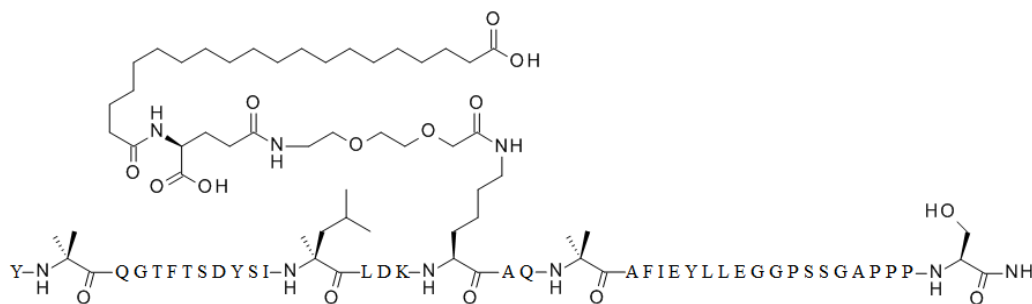


(SEQ ID NO:5), and

wherein the C-terminal amino acid is optionally amidated;
or a pharmaceutically acceptable salt thereof

In another aspect, the present disclosure refers to an incretin analog having a formula selected from the group consisting of SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided an incretin analog having a formula



or a pharmaceutically acceptable salt thereof.

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

CLAIMS

The invention claimed is:

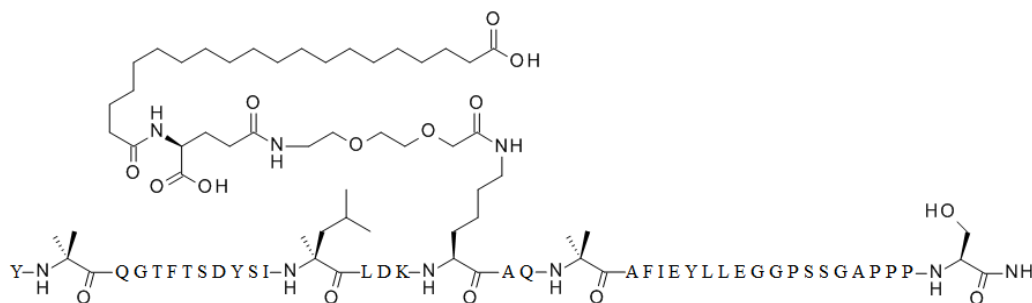
1. An incretin analog comprising:
 $\text{YX}_2\text{QGTFTSDYSIX}_{13}\text{LDKX}_{17}\text{AX}_{19}\text{X}_{20}\text{AFIEYLLX}_{28}\text{X}_{29}\text{GPSSX}_{34}\text{APPPS}$,
 wherein:
 X_2 is Aib,
 X_{13} is L or αMeL ,
 X_{17} is any amino acid with a functional group available for conjugation,
 and the functional group is conjugated to a $\text{C}_{16}\text{-C}_{22}$ fatty acid,
 X_{19} is Q or A,
 X_{20} is Aib, αMeK , Q or H,
 X_{28} is E or A,
 X_{29} is G or Aib,
 X_{34} is G or Aib,
 (SEQ ID NO:5), and
 wherein the C-terminal amino acid is optionally amidated;
 or a pharmaceutically acceptable salt thereof.
2. The incretin analog of any of Claim 1, wherein the amino acid with the functional group available for conjugation at position X_{17} is selected from the group consisting of K, C, E and D.
3. The incretin analog of Claim 1, wherein the amino acid with the functional group available for conjugation at position X_{17} 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 X_{17} and the $\text{C}_{16}\text{-C}_{22}$ 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 a structure of:

$$\text{H}-\{\text{NH}-\text{CH}_2-\text{CH}_2-[\text{O}-\text{CH}_2-\text{CH}_2]_m-\text{O}-(\text{CH}_2)_p-\text{CO}\}_n-\text{OH}$$
 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 a 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 α MeL.
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_{20} is Aib.
18. The incretin analog of any one of Claims 1 to 17, wherein X_{28} is E.

19. The incretin analog of any one of Claims 1 to 18, wherein X₂₉ is G.
20. The incretin analog of any one of Claims 1-19, wherein X₃₄ is G.
21. The incretin analog of any one of Claims 1-20, wherein X₁₉ is Q.
22. The incretin analog of Claim 9, wherein a is 1, b is 1, c is 18, X₁₃ is αMeL, X₁₉ is Q, X₂₀ is Aib, X₂₈ is E, X₂₉ is G and X₃₄ is G.
23. An incretin analog having a formula selected from the group consisting of SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25, or a pharmaceutically acceptable salt thereof.
24. The incretin analog of claim 23, having a formula of SEQ ID NO: 17, or a pharmaceutically acceptable salt thereof.
25. An incretin analog having a formula



or a pharmaceutically acceptable salt thereof.

26. A pharmaceutical composition comprising:
 - an incretin analog of any one of Claims 1 to 25; and
 - a pharmaceutically acceptable carrier, diluent or excipient.

27. An incretin analog of any one of Claims 1 to 25, 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.
28. An incretin analog of any one of Claims 1 to 25, for use in treating type II diabetes mellitus.
29. Use of an incretin analog of any one of Claims 1 to 25, 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.
30. Use of an incretin analog of any one of Claims 1 to 25, in the manufacture of a medicament for treating type II diabetes mellitus.
31. An incretin analog of any one of Claims 1 to 25, for use in treating obesity.
32. Use of an incretin analog of any one of Claims 1 to 25, in the manufacture of a medicament for treating obesity.