

effective in glucose control and weight reduction are needed for better disease management.

In view thereof, new therapies being studied include compounds having not only activity at a GLP-1 receptor but also activity at one or more other receptors, such as the GIP and/or glucagon receptors. In fact, certain compounds have been described as having triple agonist activity (*i.e.*, activity at each of the GIP, GLP-1 and glucagon receptors). For example, Int'l Patent Application Publication No. WO 2015/067716 describes glucagon analogs having triple agonist activity. Similarly, Int'l Patent Application No. WO 2016/198624 describes analogs of exendin-4, itself a GLP-1 analog, having triple agonist activity. Likewise, Int'l Patent Application Nos. WO 2014/049610 and WO 2017/116204 each describe a variety of analogs having triple agonist activity. Moreover, Int'l Patent Application No. WO 2017/153375 describes glucagon and GLP-1 co-agonists that also are stated to have GIP activity.

Nevertheless, a need remains for treatments, especially for T2DM, that are capable of providing effective glucose control, with weight loss benefits and a favorable side effect profile. There also is a need for therapeutic agents available for use with sufficiently extended duration of action to allow for dosing as infrequently as once a day, thrice-weekly, twice-weekly or once a week.

Summary

In one aspect, the present disclosure refers to an incretin analog comprising:
 YX₂QGTFTSDYSIX₁₃LDKX₁₇AX₁₉X₂₀AFIEYLLX₂₈X₂₉GPSSX₃₄APPPS,
 wherein:

X₂ is Aib,

X₁₃ is L or αMeL,

X₁₇ is any amino acid with a functional group available for conjugation, and the functional group is conjugated to a C₁₆-C₂₂ fatty acid,

X₁₉ is Q or A,

X₂₀ is Aib, αMeK, Q or H,

X₂₈ is E or A,

X₂₉ is G or Aib,

X₃₄ is G or Aib,

(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:8, SEQ ID NO:9, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:21 and SEQ ID NO:23.

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 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 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.

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:

YX₂QGTFTSDYSIX₁₃LDKX₁₇AX₁₉X₂₀AFIEYLLX₂₈X₂₉GPSSX₃₄APPPS,

wherein:

X₂ is Aib,

X₁₃ is L or αMeL,

X₁₇ is any amino acid with a functional group available for conjugation,
and the functional group is conjugated to a C₁₆-C₂₂ fatty acid,

X₁₉ is Q or A,

X₂₀ is Aib, αMeK, Q or H,

X₂₈ is E or A,

X₂₉ is G or Aib,

X₃₄ 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 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 the 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 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 A.
22. The incretin analog of Claim 9, wherein a is 1, b is 1, c is 18, X₁₃ is α MeL, X₁₉ is A, 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:8, SEQ ID NO:9, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:21 and SEQ ID NO:23.
24. A pharmaceutical composition comprising:
 - an incretin analog of any one of Claims 1 to 23; and
 - a pharmaceutically acceptable carrier, diluent or excipient.
25. An incretin analog of any one of Claims 1 to 23, for use in treating a disease selected from the group consisting of diabetes mellitus, dyslipidemia, fatty liver disease, metabolic syndrome, non-alcoholic steatohepatitis and obesity.

26. An incretin analog of any one of Claims 1 to 23, for use in treating type II diabetes mellitus.

27. Use of an incretin analog of any one of Claims 1 to 23, in the manufacture of a medicament for treating a disease selected from the group consisting of diabetes mellitus, dyslipidemia, fatty liver disease, metabolic syndrome, non-alcoholic steatohepatitis and obesity.

28. Use of an incretin analog of any one of Claims 1 to 23, in the manufacture of a medicament for treating type II diabetes mellitus.