

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 glucagon, GLP-1 and GIP 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 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: YX₂X₃GTX₆TSDYSIX₁₃LDKX₁₇AQX₂₀AFIEYLLEGGPSSGAPPPS, wherein:

X₂ is Aib,

X₃ is Q or H,

X₆ is αMeF or αMeF(2F),

X₁₃ is L or αMeL,

X₁₇ is amino acid K 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.

CLAIMS

The invention claimed is:

1. An incretin analog comprising:
YX₂X₃GTX₆TSDYSIX₁₃LDKX₁₇AQX₂₀AFIEYLLEGGPSSGAPPPS,
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 amino acid K 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 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.
3. The incretin analog of Claim 2, wherein the linker comprises one to four amino acids.
4. The incretin analog of Claim 3, wherein the amino acids are Glu or γ Glu.

5. The incretin analog of any one of Claims 2 to 4, 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.

6. The incretin analog of any one of Claims 2 to 5, wherein the linker further comprises one to four (2-[2-(2-amino-ethoxy)-ethoxy]-acetyl) moieties.

7. 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.

8. The incretin analog of Claim 7, wherein a is 1.

9. The incretin analog of Claim 7, wherein a is 2.

10. The incretin analog of any one of Claims 7 to 9, wherein b is 1.

11. The incretin analog of any one of Claims 7 to 9, wherein b is 2.

12. The incretin analog of any one of Claims 7 to 11, wherein c is 18.

13. The incretin analog of any one of Claims 1 to 12, wherein X_{13} is αMeL .

14. The incretin analog of any one of Claims 1 to 12, wherein X_{13} is L.

15. The incretin analog of any one of Claims 1 to 14, wherein X_3 is Q.

16. The incretin analog of any one of Claims 1 to 14, wherein X_3 is H.

17. The incretin analog of any one of Claims 1 to 16, wherein X_6 is αMeF .

18. The incretin analog of any one of Claims 1 to 16 wherein X₆ is αMeF(2F).
19. An incretin analog having a formula selected from the group consisting of SEQ ID NOS:5-11.
20. A pharmaceutical composition comprising:
an incretin analog of any one of Claims 1 to 19; and
a pharmaceutically acceptable carrier, diluent, or excipient.
21. An incretin analog of Claim 9, 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.
22. An incretin analog of Claim 9, for use in treating type II diabetes mellitus.
23. Use of an incretin analog of Claim 9, 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.
24. Use of an incretin analog of Claim 9, in the manufacture of a medicament for treating type II diabetes mellitus.
25. An incretin analog of Claim 9, for use in treating obesity.
26. Use of an incretin analog of Claim 9, in the manufacture of a medicament for treating obesity.