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: $YX_2X_3GTX_6TSDYSIX_{13}LDKX_{17}AQX_{20}AFIEYLLEGGPSSGAPPPS$,

wherein:

X_2 is Aib,

X_3 is Q or H,

X_6 is αMeF or αMeF(2F),

X_{13} is L or αMeL,

X_{17} is ~~any~~ amino acid K with a functional group available for conjugation, and the functional group is conjugated to a C_{16}-C_{22} fatty acid,

X_{20} 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:

$YX_2X_3GTX_6TSDYSIX_{13}LDKX_{17}AQX_{20}AFIEYLLEGGPSSGAPPPS$,

wherein:

X_2 is Aib,

X_3 is Q or H,

X_6 is αMeF or αMeF(2F),

X_{13} is L or αMeL,

X_{17} is ~~any~~ amino acid K with a functional group available for conjugation, and the functional group is conjugated to a C_{16}-C_{22} fatty acid,

X_{20} 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 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 a functional group available for conjugation at position X_{17} is K.~~

~~4~~2. The incretin analog of ~~any one of~~ Claim~~s~~ 1 ~~to 3~~, wherein the amino acid with the functional group available for conjugation at position X_{17} and the C_{16}-C_{22} fatty acid are conjugated by a linker between the amino acid and the fatty acid.

~~5~~3. The incretin analog of Claim ~~4~~2, wherein the linker comprises one to four amino acids.

~~6~~4. The incretin analog of Claim ~~5~~3, wherein the amino acids are Glu or γGlu.

~~7~~5. The incretin analog of any one of Claims ~~4~~2 to ~~6~~4, wherein the linker further comprises the following structure:

H-{NH-CH_2-CH_2-[O-CH_2-CH_2]$_m$-O-(CH_2)$_p$-CO}$_n$-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~~6. The incretin analog of any one of Claims ~~4~~2 to ~~7~~5, wherein the linker further comprises one to four (2-[2-(2-amino-ethoxy)-ethoxy]-acetyl) moieties.

~~9~~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-amino-ethoxy)-ethoxy]-acetyl)$_a$-(γGlu)$_b$-CO-(CH_2)$_c$-CO_2H, wherein $_a$ is 0, 1 or 2; $_b$ is 1 or 2; and $_c$ is an integer between 16 to 18.

~~10~~8. The incretin analog of Claim ~~9~~7, wherein a is 1.

~~11~~9. The incretin analog of Claim ~~9~~7, wherein a is 2.

~~12~~10. The incretin analog of any one of Claims ~~9~~7 to ~~11~~9, wherein b is 1.

~~13~~11. The incretin analog of any one of Claims ~~9~~7 to ~~11~~9, wherein b is 2.

~~14~~12. The incretin analog of any one of Claims ~~9~~7 to ~~13~~11, wherein c is 18.

~~15~~13. The incretin analog of any one of Claims 1 to ~~14~~12, wherein X_{13} is αMeL.

~~16~~14. The incretin analog of any one of Claims 1 to ~~14~~12, wherein X_{13} is L.

~~17~~15. The incretin analog of any one of Claims 1 to ~~16~~14, wherein X_3 is Q.

~~18~~16. The incretin analog of any one of Claims 1 to ~~16~~14, wherein X_3 is H.

~~19~~17. The incretin analog of any one of Claims 1 to ~~18~~16, wherein X_6 is αMeF.

~~20~~18. The incretin analog of any one of Claims 1 to ~~18~~16 wherein X_6 is αMeF(2F).

~~21~~19. An incretin analog having a formula selected from the group consisting of SEQ ID NOS:5-11.

~~22~~20. A pharmaceutical composition comprising:

an incretin analog of any one of Claims 1 to ~~21~~19; and

a pharmaceutically acceptable carrier, diluent, or excipient.

~~23~~21. An incretin analog of Claim 9~~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~~22. An incretin analog of Claim 9~~any one of Claims 1 to 21~~, for use in treating type II diabetes mellitus.

~~25~~23. Use of an incretin analog of Claim 9~~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~~24. Use of an incretin analog of Claim 9~~any one of Claims 1 to 21~~, in the manufacture of a medicament for treating type II diabetes mellitus.

~~27~~25. An incretin analog of Claim 9~~any one of Claims 1 to 21~~, for use in treating obesity.

~~28~~26. Use of an incretin analog of Claim 9~~any one of Claims 1 to 21~~, in the manufacture of a medicament for treating obesity.