

[0005] 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 GCG receptors. In fact, certain compounds already have been described as having triple receptor agonist activity (*i.e.*, activity at each of the GIP, GLP-1 and GCG receptors). For example, Intl. Patent Application Publication No. WO 2015/067716 describes GCG analogs having triple receptor agonist activity. Similarly, Intl. Patent Application Publication No. WO 2016/198624 describes exendin-4 analogs having triple receptor agonist activity. Likewise, Intl. Patent Application Publication Nos. WO 2014/049610 and WO 2017/116204 each describe a variety of compounds having triple receptor agonist activity. Moreover, Intl. Patent Application Publication No. WO 2017/153575 describes GCG and GLP-1 co-agonists that also are stated to have GIP receptor agonist activity.

[0006] Although typically used for treating T2DM, incretins and analogs thereof having activity at one or more of the GIP, GLP-1 and/or GCG receptors also have been described as having a potential for therapeutic value in a number of other conditions, diseases or disorders, including, for example, Alzheimer's disease, bone-related disorders, dyslipidemia, metabolic syndrome, NAFLD and NASH, obesity and Parkinson's disease. *See, e.g.*, Jall *et al.* (2017) *Mol. Metab.* 6:440-446; Carbone *et al.* (2016) *J. Gastroenterol. Hepatol.* 31:23-31; Finan *et al.* (2016) *Trends Mol. Med.* 22:359-376; Choi *et al.* (2017) *Potent body weight loss and efficacy in a NASH animal model by a novel long-acting GLP-1/Glucagon/GIP triple-agonist (HM15211)*, ADA Poster 1139-P; Ding (2008) *J. Bone Miner. Res.* 23:536-543; Tai *et al.* (2018) *Brain Res.* 1678:64-74; Müller *et al.* (2017) *Physiol. Rev.* 97:721-766; Finan *et al.* (2013) *Sci. Transl. Med.* 5:209; Hölscher (2014) *Biochem. Soc. Trans.* 42:593-600.

[0007] Nevertheless, a need remains for treatments for such conditions, diseases and disorders, especially T2DM, that are capable of providing effective glucose control, with weight loss benefits and/or 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.

[0007a] Summary

[0007b] In one aspect of the present disclosure, there is provided a compound comprising:

YX₂QGTX₆TSDX₁₀SIX₁₃LDX₁₆X₁₇AQX₂₀X₂₁FIX₂₄X₂₅LLEGGPSSGEPPPX₃₉,

wherein X₂ is Aib,

X₆ is αMeF(2F),

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X₁₀ can be Y or 4Pal,

X₁₃ can be L or α MeL,

X₁₆ is Orn,

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

X₂₀ can be 4Pal, Iva or α MeL,

X₂₁ can be A or Aib,

X₂₄ can be E or e,

X₂₅ can be Y or α MeY, and

X₃₉ can be E or S

(SEQ ID NO:5), and

wherein a carboxy-terminal (C-terminal) amino acid optionally is amidated;

or a pharmaceutically acceptable salt thereof.

[0007c] In another aspect of the present disclosure, there is provided a compound having a formula selected from the group consisting of SEQ ID NOS:6-11, or a pharmaceutically acceptable salt thereof.

[0007d] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

compound disclosed herein; and

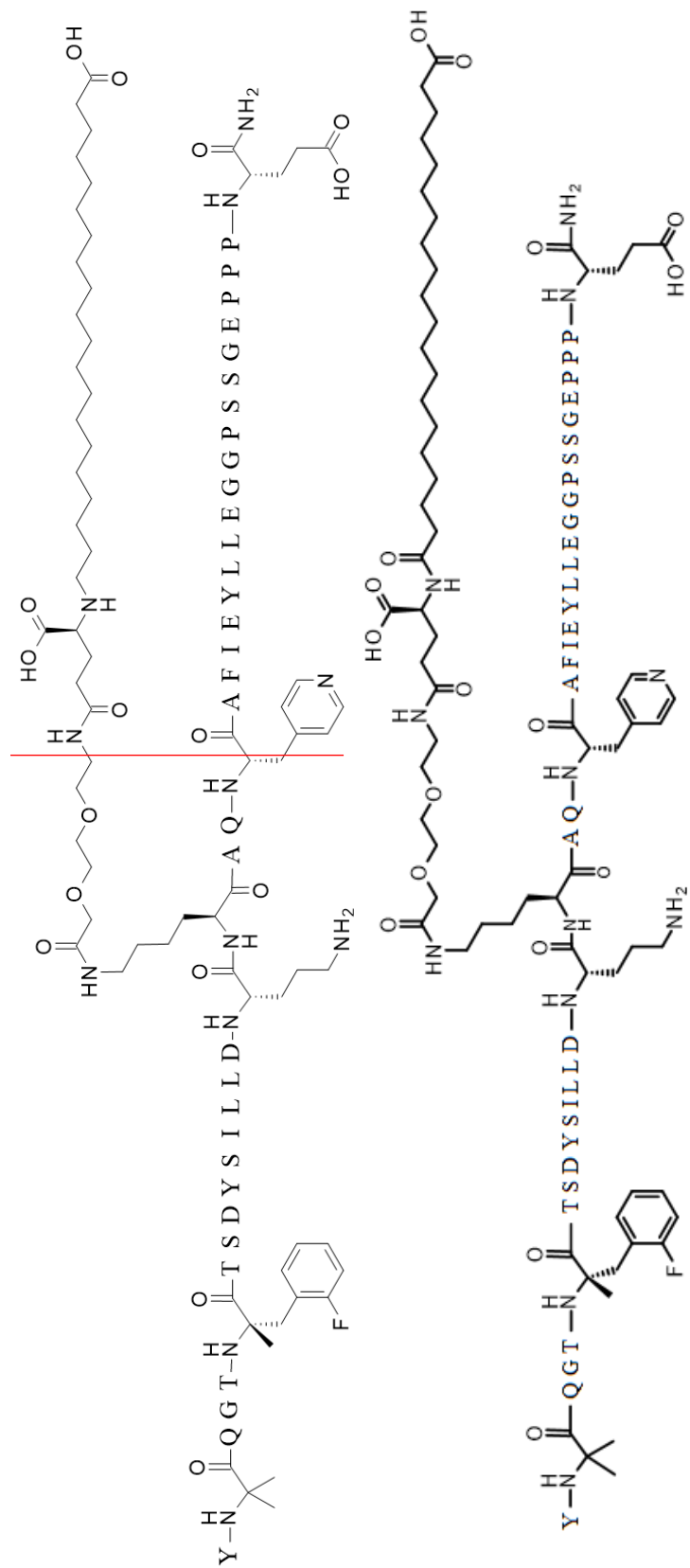
a pharmaceutically acceptable carrier, diluent, or excipient.

[0007e] In another aspect of the present disclosure, there is provided a compound disclosed herein for use in treating a disease selected from the group consisting of type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and obesity.

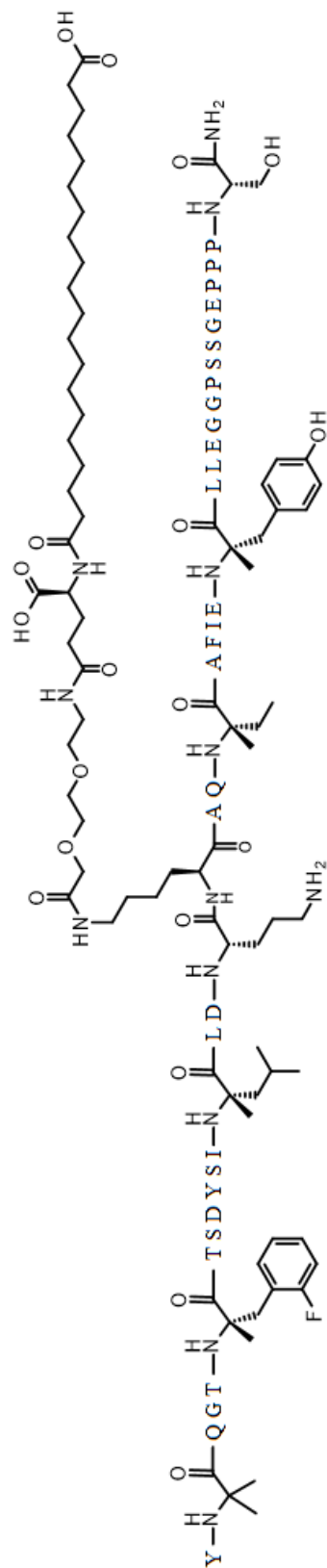
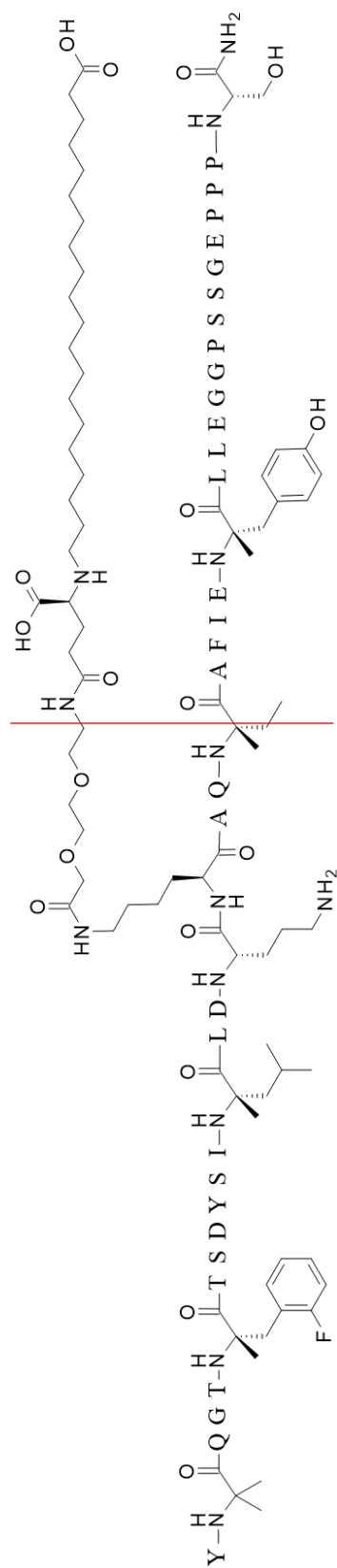
[0007f] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating a disease selected from the group consisting of type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and obesity.

[0007h] Description

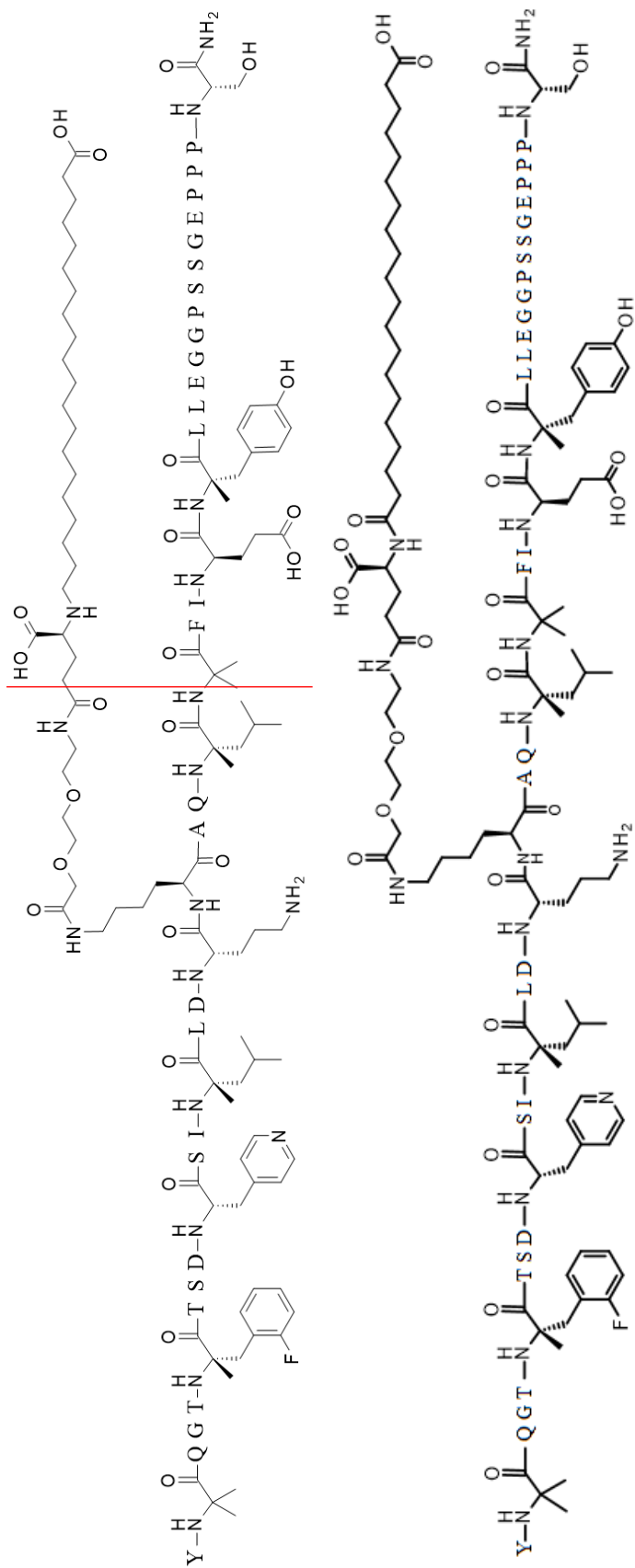
[0008] The incretin analogs herein seek to meet the needs above. Accordingly, the disclosure describes incretin analogs with activity at each of the GIP, GLP-1 and GCG receptors. Advantageously, the incretin analogs herein have balanced activity at these



(SEQ ID NO:9),



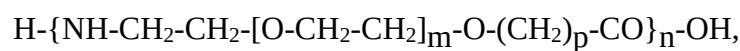
(SEQ ID NO:10), or



(SEQ ID NO:11).

[0059] In certain instances, the C₁₆-C₂₂ fatty acid can be a saturated C₂₀ monoacid, a saturated C₂₀ diacid, and branched and substituted derivatives thereof. In more particular instances, the C₁₆-C₂₂ fatty acid can be eicosanedioic acid.

[0060] In some instances, the linker can have from one to four amino acids, an amino polyethylene glycol carboxylate or mixtures thereof. In certain instances, the amino polyethylene glycol carboxylate has the following structure:

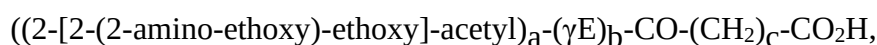


where m is any integer from 1 to 12, n is any integer from 1 to 12, and p is 1 or 2.

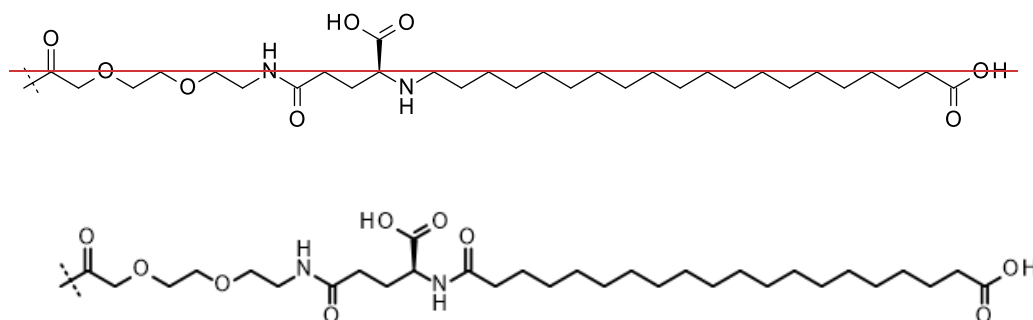
[0061] In certain instances, the linker can have one or more AEEA moieties, optionally in combination with one to four amino acids.

[0062] In instances in which the linker includes at least one amino acid, the amino acid can be one to four E or γ E amino acid residues. In some instances, the linker can include one or two E or γ E amino acid residues, including the D-forms thereof. For example, the linker can include either one or two γ E amino acid residues. Alternatively, the linker can include one to four amino acid residues (such as, for example, E or γ E amino acids) used in combination with up to thirty-six AEEA moieties. Specifically, the linker can be combinations of one to four E or γ E amino acids and one to four AEEA moieties. In other instances, the linker can be combinations of one or two γ E amino acids and one or two AEEA moieties.

[0063] In a specific instance, the incretin analogs herein have a linker-fatty acid moiety having the following structure:



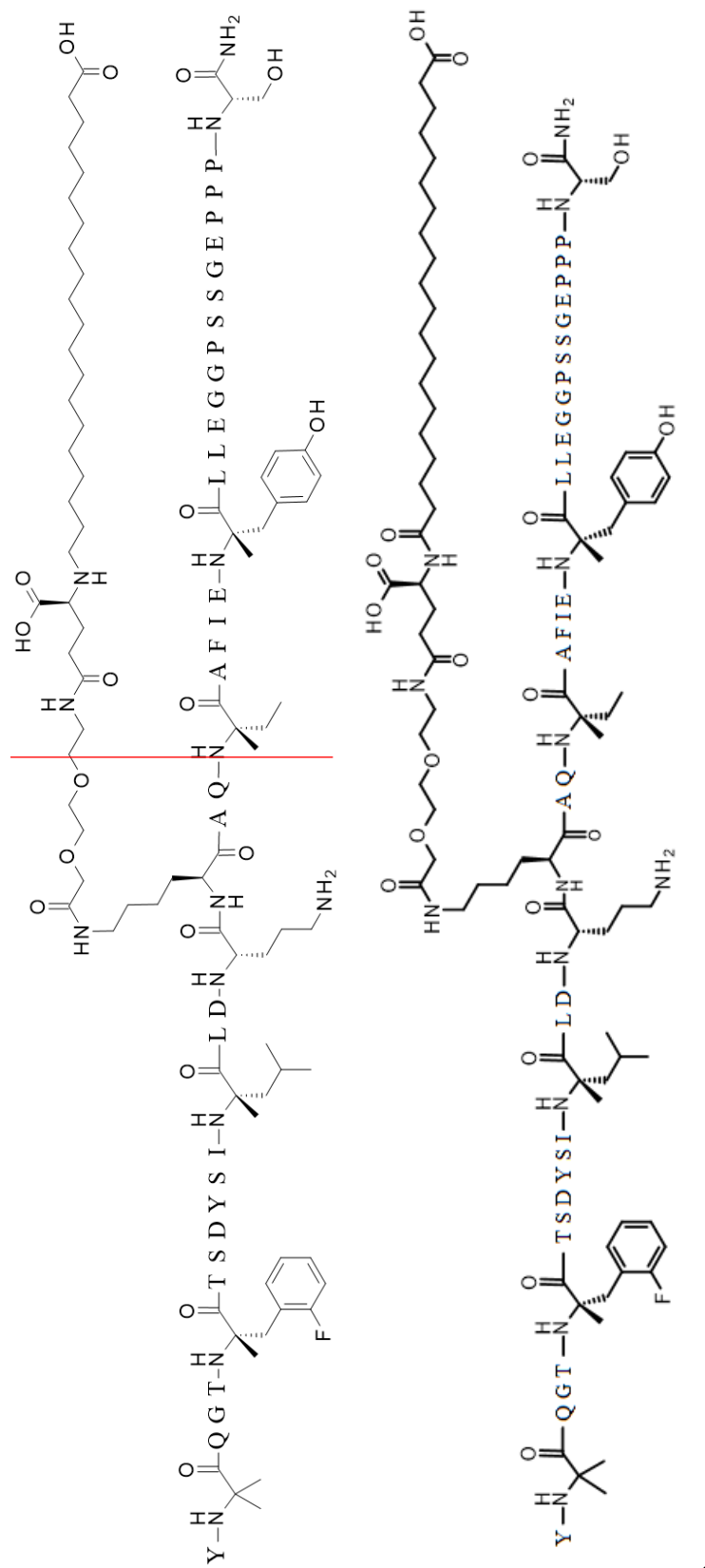
where a is 0, 1 or 2, b is 1 or 2, and c is 16 or 18. In a particular instance, a is 1, b is 1 and c is ~~20~~18, having the following structure:

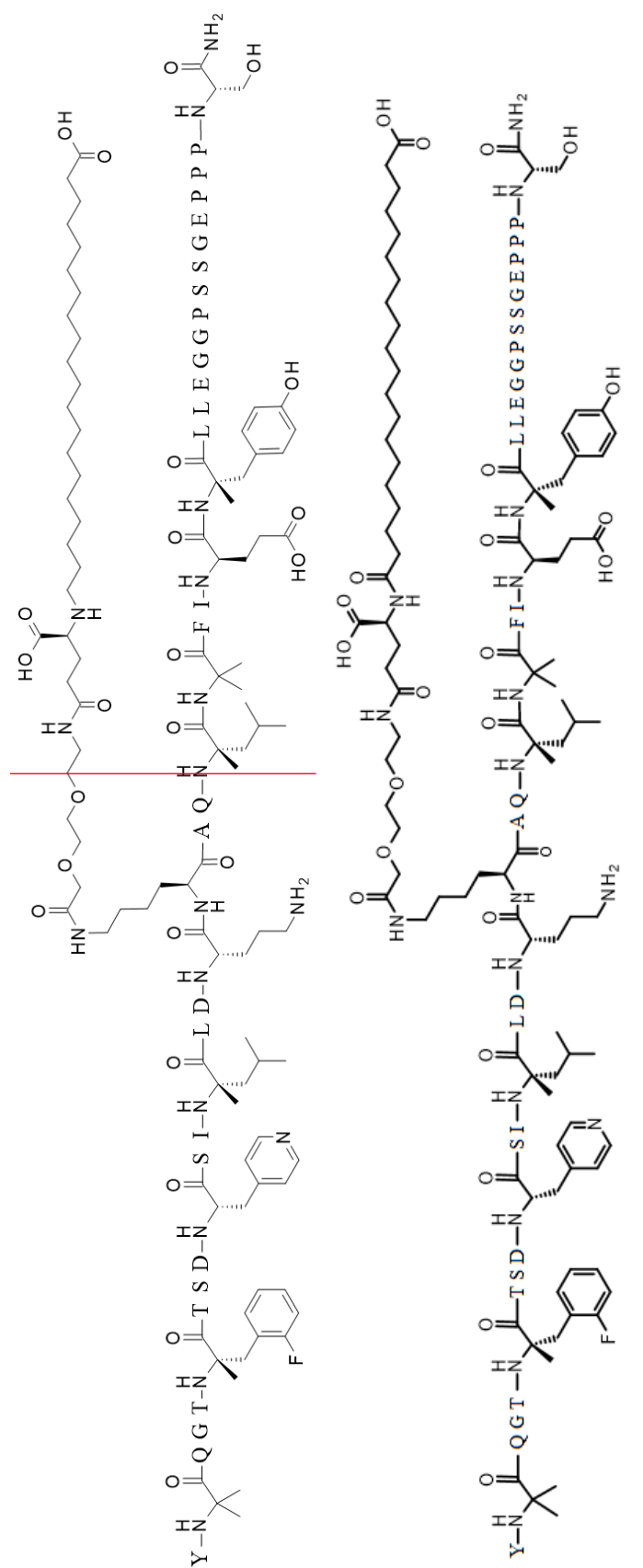


[0064] As shown in the chemical structures of Examples 1-3 below, the linker-fatty acid moiety described above can be linked to the epsilon (ϵ)-amino group of the K side-chain.

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[0065] The affinity of the incretin analogs herein for each of the GIP, GLP-1 and GCG receptors may be measured using techniques known in the art for measuring receptor binding levels, including, for example, those described in the examples below, and is





CLAIMS

The invention claimed is:

1. A compound comprising:
 $YX_2QGT X_6TSD X_{10}SIX_{13}LDX_{16}X_{17}AQX_{20}X_{21}FIX_{24}X_{25}LLEG GPSSGEPPP X_{39}$,
 wherein X_2 is Aib,
 X_6 is α MeF(2F),
 X_{10} can be Y or 4Pal,
 X_{13} can be L or α MeL,
 X_{16} is Orn,
 X_{17} is any amino acid with a functional group available for conjugation and
 the functional group is conjugated to a C₁₆-C₂₂ fatty acid moiety,
 X_{20} can be 4Pal, Iva or α MeL,
 X_{21} can be A or Aib,
 X_{24} can be E or e,
 X_{25} can be Y or α MeY, and
 X_{39} can be E or S
 (SEQ ID NO:5), and
 wherein a carboxy-terminal (C-terminal) amino acid optionally is amidated;
 or a pharmaceutically acceptable salt thereof.
2. The compound 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 C, D, E, K and Q.
3. The compound of Claim 1, wherein the amino acid with a functional group available
 for conjugation at position X_{17} is K.
4. The compound 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 C₁₆-C₂₂ fatty acid moiety
 are conjugated by a linker between the amino acid and the fatty acid moiety.
5. The compound of Claim 4, wherein the linker comprises one to four amino acids.

6. The compound of Claim 5, wherein the amino acids are E or γ E.
7. The compound 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 compound 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 compound 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:

$$(2-[2-(2\text{-amino-ethoxy})\text{-ethoxy}]\text{-acetyl})_a-(\gamma\text{E})_b-\text{CO}-(\text{CH}_2)_c-\text{CO}_2\text{H},$$
 wherein a is 0, 1 or 2; b is 1 or 2; and c is an integer between 16 to 20.
10. The compound of Claim 9, wherein a is 1.
11. The compound of Claim 9, wherein a is 2.
12. The compound of any one of Claims 9 to 11, wherein b is 1.
13. The compound of any one of Claims 9 to 11, wherein b is 2.
14. The compound of any one of Claims 9 to 13, wherein c is ~~20~~18.
15. The compound of any one of Claims 1-14, wherein X_{10} is Y.
16. The compound of any one of Claims 1-14, wherein X_{10} is 4Pal.
17. The compound of any one of Claims 1-16, wherein X_{13} is L.
18. The compound of any one of Claims 1-16, wherein X_{13} is α MeL.

19. The compound of any one of Claims 1-18, wherein X₂₀ is 4Pal.
20. The compound of any one of Claims 1-18, wherein X₂₀ is Iva.
21. The compound of any one of Claims 1-18, wherein X₂₀ is αMeL.
22. The compound of any one of Claims 1-21, wherein X₂₁ is A.
23. The compound of any one of Claims 1-21, wherein X₂₁ is Aib.
24. The compound of any one of Claims 1-23, wherein X₂₄ is E.
25. The compound of any one of Claims 1-23, wherein X₂₄ is e.
26. The compound of any one of Claims 1-25, wherein X₂₅ is Y.
27. The compound of any one of Claims 1-25, wherein X₂₅ is αMeY.
28. The compound of any one of Claims 1-27, wherein X₃₉ is E.
29. The compound of any one of Claims 1-27, wherein X₃₉ is S.
30. A compound having a formula selected from the group consisting of SEQ ID NOS:6-11, or a pharmaceutically acceptable salt thereof.
- ~~31. A method of treating a disease selected from the group consisting of type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and obesity, the method comprising the step of:
administering to an individual in need thereof an effective amount of a compound of any one of Claims 1 to 30.~~

~~32. A method of treating type 2 diabetes mellitus, the method comprising the step of:
administering to an individual in need thereof an effective amount of compound of
any one of Claims 1 to 30.~~

~~33.~~31. A pharmaceutical composition comprising:
compound of any one of Claims 1 to 30; and
a pharmaceutically acceptable carrier, diluent, or excipient.

~~34.~~32. A compound of any one of Claims 1 to 30 for use in treating a disease selected from
the group consisting of type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, non-
alcoholic fatty liver disease, non-alcoholic steatohepatitis and obesity.

~~35.~~33. The compound of Claim ~~34~~32, wherein the disease is type 2 diabetes mellitus or
obesity.

~~36.~~34. Use of a compound of any one of Claims 1 to 30 in the manufacture of a medicament
for treating a disease selected from the group consisting of type 2 diabetes mellitus,
dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease, non-alcoholic
steatohepatitis and obesity.

~~37.~~35. Use of the compound of Claim ~~36~~34, wherein the disease is type 2 diabetes mellitus
or obesity.

~~38. A compound comprising SEQ ID NO:6, or a pharmaceutically acceptable salt
thereof.~~

~~39. A compound comprising SEQ ID NO:7, or a pharmaceutically acceptable salt
thereof.~~

~~40. A compound comprising SEQ ID NO:8, or a pharmaceutically acceptable salt
thereof.~~

~~41. A compound comprising SEQ ID NO:9, or a pharmaceutically acceptable salt thereof.~~

~~42. A compound comprising SEQ ID NO:10, or a pharmaceutically acceptable salt thereof.~~

~~43. A compound comprising SEQ ID NO:11, or a pharmaceutically acceptable salt thereof.~~