

WO2016/111971 describes peptides stated to have GLP-1 and GIP activity.

WO2013/164483 also discloses compounds stated to have GLP-1 and GIP activity.

There is a need for T2DM treatments capable of providing effective glucose control for a larger portion of the patients in need of such treatment. There is a further need for T2D
5 treatments capable of providing effective glucose control and with a favorable side effect profile. There is a need for alternate treatment options to provide therapeutic weight loss in a patient in need of such treatment. There is a need for an alternate treatment option for a patient in need of treatment for severe obesity.

There is a desire for compounds having agonist activity at the GIP and GLP-1
10 receptors that are suitable for oral administration. Compounds with extended duration of action at each of the GIP and GLP-1 receptors are desirable to allow for less frequent dosing of the compound.

Summary

15 In an aspect of the present disclosure, there is provided a compound of the formula:

$R_1X_1X_2X_3GTX_6TSDX_{10}X_{11}X_{12}X_{13}X_{14}DX_{16}X_{17}AX_{19}X_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}$
 $X_{28}X_{29}X_{30}X_{31}$ (SEQ ID NO:3) wherein:

R_1 is a modification of the N-terminal amino group wherein the modification is selected from the group consisting of Ac and absent;

20 X_1 is selected from the group consisting of Y, H, D-Tyr, F, desH, and desY;

X_2 is selected from the group consisting of Aib, α MeP, A, P, and D-Ala;

or X_1 and X_2 combine to form desH- ψ [NHCO]-Aib;

X_3 is selected from the group consisting of E, N, Aad, and cTA;

X_6 is selected from the group consisting of F, α MeF, and α MeF(2F);

25 X_{10} is selected from the group consisting of A, L, H, 3Pal, 4Pal, V, Y, E, α MeF, α MeF(2F), I, α MeY, Q, D-His, D-Tyr, cTA, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ -Glu)-CO-(CH₂)_qCO₂H;

X_{11} is selected from the group consisting of S, α MeS, and D-Ser;

X₁₂ is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₃ is selected from the group consisting of Nle, Aib, L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₄ is selected from the group consisting of L and K, wherein K is conjugated to a C₁₆-C₂₂ fatty acid wherein said fatty acid is optionally conjugated to said K via a linker;

X₁₆ is selected from the group consisting of K, E, Orn, Dab, Dap, S, T, H, Aib, αMeK, R, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₇ is selected from the group consisting of K, Q, I, and an amino acid conjugated to a C₁₆-C₂₂ fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;

X₁₉ is selected from the group consisting of Q, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₀ is selected from the group consisting of Aib, Q, H, R, K, αMeK, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₁ is selected from the group consisting of H, Aad, D, Aib, T, A, E, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₂ is selected from the group consisting of F and αMeF;

X₂₃ is selected from the group consisting of I, L, A, G, F, H, E, V, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₄ is selected from the group consisting of S, Aad, D-Glu, E, Aib, H, V, A, Q, D, P, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₅ is selected from the group consisting of Y and αMeY;

X₂₆ is selected from the group consisting of L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₇ is selected from the group consisting of L, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₈ is selected from the group consisting of E, A, S, D-Glu, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₉ is selected from the group consisting of Aib, G, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₃₀ is selected from the group consisting of C, G, G-R₂ and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H;

X₃₁ is absent or is selected from the group consisting of PX₃₂X₃₃X₃₄-R₂ (SEQ ID NO:4), PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ (SEQ ID NO:5),

PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉X₄₀-R₂ (SEQ ID NO:6), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H] X₃₂X₃₃X₃₄-R₂ (SEQ ID NO:7), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H]

X₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ (SEQ ID NO:8), and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H] X₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉X₄₀-R₂ (SEQ ID NO:9); wherein:

X₃₂ is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₃ is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₄ is selected from the group consisting of G, C, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₅ is A or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₆ is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₇ is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₈ is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₉ is selected from the group consisting of C, S, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₄₀ is selected from the group consisting of C and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

q is selected from the group consisting of 14, 15, 16, 17, 18, 19, and 20; and

R₂ is a modification of the C-terminal group, wherein the modification is NH₂ or absent;

or a pharmaceutically acceptable salt thereof;

wherein if X₃₀ is G-R₂, then X₃₁ is absent;

wherein no more than one of X₁₀, X₁₂, X₁₃, X₁₄, X₁₆, X₁₇, X₁₉, X₂₀, X₂₁, X₂₃, X₂₄, X₂₆, X₂₇, X₂₈, X₂₉, X₃₀, X₃₁, X₃₂, X₃₃, X₃₄, X₃₅, X₃₆, X₃₇, X₃₈, X₃₉, and X₄₀ may be a substituent that contains a fatty acid; and

wherein no more than one of X₃₀, X₃₄, X₃₉, and X₄₀ may be C; and

wherein if one of X₃₀, X₃₄, X₃₉, and X₄₀ is C, then none of X₁₀, X₁₂, X₁₃, X₁₄, X₁₆, X₁₇, X₁₉, X₂₀, X₂₁, X₂₃, X₂₄, X₂₆, X₂₇, X₂₈, X₂₉, X₃₀, X₃₁, X₃₂, X₃₃, X₃₄, X₃₅, X₃₆, X₃₇, X₃₈, X₃₉, and X₄₀ is a substituent that contains a fatty acid.

In another aspect of the present disclosure, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof disclosed herein, in the manufacture of a medicament for treating a condition selected from the group consisting of type 2 diabetes mellitus, obesity, NAFLD, nonalcoholic steatohepatitis, dyslipidemia, and metabolic syndrome.

In a further aspect of the present disclosure, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof disclosed herein, in the manufacture of a medicament for treating obesity.

In another aspect of the present disclosure, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof disclosed herein, in the manufacture of a medicament for providing therapeutic weight loss.

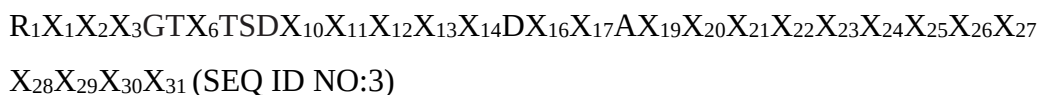
In a further aspect of the present disclosure, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof disclosed herein, in the manufacture of a medicament for treating type 2 diabetes mellitus.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound, or a pharmaceutically acceptable salt thereof disclosed herein, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

In a further aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof disclosed herein, for use as a medicament.

Description

Accordingly, the present invention provides a compound of Formula I:



wherein:

R₁ is a modification of the N-terminal amino group wherein the modification is selected from the group consisting of Ac and absent;

X₁ is selected from the group consisting of Y, H, D-Tyr, F, desH, and desY,

X₂ is selected from the group consisting of Aib, αMeP, A, P, and D-Ala;

or X₁ and X₂ combine to form desH-ψ[NHCO]-Aib;

X₃ is selected from the group consisting of E, N, Aad, and cTA;

X₆ is selected from the group consisting of F, αMeF, and αMeF(2F);

X₁₀ is selected from the group consisting of A, L, H, 3Pal, 4Pal, V, Y, E, αMeF, αMeF(2F), I, αMeY, Q, D-His, D-Tyr, cTA, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₁ is selected from the group consisting of S, αMeS, and D-Ser;

X₁₂ is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

WE CLAIM:

1. A compound of the formula:

R₁X₁X₂X₃GTX₆TSDX₁₀X₁₁X₁₂X₁₃X₁₄DX₁₆X₁₇AX₁₉X₂₀X₂₁X₂₂X₂₃X₂₄X₂₅X₂₆X₂₇
X₂₈X₂₉X₃₀X₃₁ (SEQ ID NO:3) wherein:

R₁ is a modification of the N-terminal amino group wherein the modification is selected from the group consisting of Ac and absent;

X₁ is selected from the group consisting of Y, H, D-Tyr, F, desH, and desY;

X₂ is selected from the group consisting of Aib, αMeP, A, P, and D-Ala;

or X₁ and X₂ combine to form desH-ψ[NHCO]-Aib;

X₃ is selected from the group consisting of E, N, Aad, and cTA;

X₆ is selected from the group consisting of F, αMeF, and αMeF(2F);

X₁₀ is selected from the group consisting of A, L, H, 3Pal, 4Pal, V, Y, E, αMeF, αMeF(2F), I, αMeY, Q, D-His, D-Tyr, cTA, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₁ is selected from the group consisting of S, αMeS, and D-Ser;

X₁₂ is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₃ is selected from the group consisting of Nle, Aib, L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₄ is selected from the group consisting of L and K, wherein K is conjugated to a C₁₆-C₂₂ fatty acid wherein said fatty acid is optionally conjugated to said K via a linker;

X₁₆ is selected from the group consisting of K, E, Orn, Dab, Dap, S, T, H, Aib, αMeK, R, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₇ is selected from the group consisting of K, Q, I, and an amino acid conjugated to a C₁₆-C₂₂ fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;

X₁₉ is selected from the group consisting of Q, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₀ is selected from the group consisting of Aib, Q, H, R, K, αMeK, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₁ is selected from the group consisting of H, Aad, D, Aib, T, A, E, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

5 X₂₂ is selected from the group consisting of F and αMeF;

X₂₃ is selected from the group consisting of I, L, A, G, F, H, E, V, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₄ is selected from the group consisting of S, Aad, D-Glu, E, Aib, H, V, A, Q, D, P, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

10 X₂₅ is selected from the group consisting of Y and αMeY;

X₂₆ is selected from the group consisting of L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₇ is selected from the group consisting of L, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

15 X₂₈ is selected from the group consisting of E, A, S, D-Glu, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₉ is selected from the group consisting of Aib, G, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

20 X₃₀ is selected from the group consisting of C, G, G-R₂ and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H;

X₃₁ is absent or is selected from the group consisting of PX₃₂X₃₃X₃₄-R₂ (SEQ ID NO:4), PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ (SEQ ID NO:5),

PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉X₄₀-R₂ (SEQ ID NO:6), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H] X₃₂X₃₃X₃₄-R₂ (SEQ ID NO:7), K[(2-

25 [2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H]

X₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ (SEQ ID NO:8), and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H] X₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉X₄₀-R₂

(SEQ ID NO:9); wherein:

X₃₂ is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

30

X₃₃ is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₄ is selected from the group consisting of G, C, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

5 X₃₅ is A or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₆ is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

10 X₃₇ is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₈ is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

X₃₉ is selected from the group consisting of C, S, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

15 X₄₀ is selected from the group consisting of C and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H];

q is selected from the group consisting of 14, 15, 16, 17, 18, 19, and 20; and

R₂ is a modification of the C-terminal group, wherein the modification is NH₂ or absent;

20 or a pharmaceutically acceptable salt thereof;

wherein if X₃₀ is G-R₂, then X₃₁ is absent;

wherein no more than one of X₁₀, X₁₂, X₁₃, X₁₄, X₁₆, X₁₇, X₁₉, X₂₀, X₂₁, X₂₃, X₂₄, X₂₆, X₂₇, X₂₈, X₂₉, X₃₀, X₃₁, X₃₂, X₃₃, X₃₄, X₃₅, X₃₆, X₃₇, X₃₈, X₃₉, and X₄₀ may be a substituent that contains a fatty acid; and

25 wherein no more than one of X₃₀, X₃₄, X₃₉, and X₄₀ may be C; and

wherein if one of X₃₀, X₃₄, X₃₉, and X₄₀ is C, then none of X₁₀, X₁₂, X₁₃, X₁₄, X₁₆, X₁₇, X₁₉, X₂₀, X₂₁, X₂₃, X₂₄, X₂₆, X₂₇, X₂₈, X₂₉, X₃₀, X₃₁, X₃₂, X₃₃, X₃₄, X₃₅, X₃₆, X₃₇, X₃₈, X₃₉, and X₄₀ is a substituent that contains a fatty acid.

2. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein X_1 and X_2 do not combine to form desH- ψ [NHCO]-Aib.
3. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 2 wherein X_{17} is an amino acid conjugated to a C_{16} - C_{22} fatty acid.
- 5 4. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein:
 X_1 is Y;
 X_2 is Aib;
 X_3 is E;
10 X_{10} is selected from the group consisting of A, L, H, 3Pal, 4Pal, V, and Y;
 X_{11} is S;
 X_{12} is I;
 X_{14} is L;
 X_{16} is selected from the group consisting of K, E, Orn, Dab, and Dap;
15 X_{17} is K conjugated to a C_{16} - C_{22} fatty acid wherein said fatty acid is conjugated to K via a linker;
 X_{19} is Q;
 X_{20} is Aib;
 X_{21} is selected from the group consisting of H, Aad, D, Aib, T, A, and E;
20 X_{22} is F;
 X_{23} is I;
 X_{24} is selected from the group consisting of S, Aad, D-Glu, and E;
 X_{26} is L;
 X_{27} is selected from the group consisting of L and I; and
25 X_{28} is selected from the group consisting of E and A.
5. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein:
 X_{30} is G and X_{31} is $PX_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}-R_2$ (SEQ ID NO:5), wherein X_{32} is S, X_{33} is S, X_{34} is G, X_{35} is A, X_{36} is P, X_{37} is P, X_{38} is P and X_{39} is S (SEQ ID
30 NO:298).
6. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein X_{17} is K.

7. The compound, or a pharmaceutically acceptable salt thereof, as claimed by claim 4 wherein the linker comprises one to two amino acids.
8. The compound, or a pharmaceutically acceptable salt thereof, as claimed by claim 7 wherein the linker comprises from one to two (2-[2-(2-Amino-ethoxy)-ethoxy]-
5 acetyl) moieties.
9. The compound, or a pharmaceutically acceptable salt thereof, as claimed by claim 8 wherein the linker comprises one to two amino acids independently selected from the group consisting of Glu and γ -Glu.
10. The compound, or a pharmaceutically acceptable salt thereof, as claimed by claim 9 wherein the linker has the following formula:
10 $\{(2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)_a-(\gamma-Glu)_b\}$, wherein a is 1 or 2; and b is 1 or 2.
11. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein X_{17} is $K(2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)_a-(\gamma-Glu)_b-CO-(CH_2)_q-$
15 CO_2H , wherein: a is 1 or 2; b is 1 or 2; and q is selected from the group consisting of 14 to 20.
12. The compound, or a pharmaceutically acceptable salt thereof, as claimed by claim 11 wherein a is 1.
13. The compound, or a pharmaceutically acceptable salt thereof, as claimed by claim
20 11 wherein a is 2.
14. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 11 wherein b is 1.
15. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 11 wherein b is 2.
- 25 16. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 11 wherein q is 18.
17. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 11 wherein q is 16.
18. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1
30 wherein X_{17} is $K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)_2-(\gamma-Glu)-CO-(CH_2)_q-$
 CO_2H .

19. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 18 wherein X₂₇ is I.
20. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 18 wherein X₂₇ is L.
- 5 21. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 19 wherein:
- R₁ is absent;
- X₁ is Y;
- X₂ is Aib;
- 10 X₃ is E;
- X₆ is α MeF(2F);
- X₁₀ is selected from the group consisting of Y, 4-PaI, and V;
- X₁₁ is S;
- X₁₂ is I;
- 15 X₁₃ is selected from the group consisting of L, Aib, and α MeL;
- X₁₄ is L;
- X₁₆ is selected from the group consisting of E, K, and Orn;
- X₁₇ is K;
- X₁₉ is Q;
- 20 X₂₀ is Aib
- X₂₁ is selected from the group consisting of E, A, and T;
- X₂₂ is F;
- X₂₃ is I;
- X₂₄ is D-Glu;
- 25 X₂₆ is L;
- X₂₇ is I;
- X₂₈ is E;
- X₂₉ is G;
- X₃₀ is G; and
- 30 X₃₁ is PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ (SEQ ID NO:5), wherein X₃₂ is S, X₃₃ is S,
- X₃₄ is G, X₃₅ is A, X₃₆ is P, X₃₇ is P, X₃₈ is P and X₃₉ is S (SEQ ID NO:298).

22. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 21 wherein X_{25} is Y.
23. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 22 wherein X_{13} is α MeL.
- 5 24. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 23 wherein X_{16} is Orn.
25. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 23 wherein X_{16} is E.
26. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 10 25 wherein X_{10} is Y.
27. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 25 wherein X_{10} is V.
28. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 25 wherein X_{10} is 4Pal.
- 15 29. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 11 wherein X_{13} is α MeL; a is 2; b is 1; q is 16; and X_{25} is Y.
30. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 11 wherein X_{13} is α MeL; a is 2; b is 1; q is 18; and X_{25} is Y.
31. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 20 11 wherein X_{13} is α MeL; a is 2; b is 1; q is 14; and X_{25} is Y.
32. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein X_{10} is Y; and X_{16} is Orn.
33. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein X_{10} is Y; and X_{16} is E.
- 25 34. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein X_{10} is 4Pal; and X_{16} is Orn.
35. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein X_{10} is V; and X_{16} is Orn.
36. The compound as claimed by Claim 1 wherein the compound is selected from the 30 group consisting of SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, and SEQ ID NO:14, or a pharmaceutically acceptable salt thereof.

37. The compound as claimed by Claim 36 wherein the compound is SEQ ID NO:13, or a pharmaceutically acceptable salt thereof.
38. The compound as claimed by Claim 36 wherein the compound is SEQ ID NO:11, or a pharmaceutically acceptable salt thereof.
- 5 39. The compound, or a pharmaceutically acceptable salt thereof as claimed by Claim 1 wherein:
- X₁₀ is selected from the group consisting of A, L, H, 3Pal, 4Pal, V, Y, αMeF, αMeF(2F), I, αMeY, Q, D-His, E, cTA, and D-Tyr;
- X₁₂ is selected from the group consisting of I, D-Ile, and S;
- 10 X₁₃ is selected from the group consisting of Nle, Aib, L, and αMeL;
- X₁₄ is L;
- X₁₆ is selected from the group consisting of K, E, Orn, Dab, Dap, S, T, H, Aib, αMeK, and R;
- X₁₇ is selected from the group consisting of K, Q, and I;
- 15 X₁₉ is selected from the group consisting of Q and A;
- X₂₀ is selected from the group consisting of Aib, Q, H, R, K, and αMeK;
- X₂₁ is selected from the group consisting of H, Aad, D, Aib, T, A, E, and I;
- X₂₃ is selected from the group consisting of I, L, A, G, F, H, E, and V;
- X₂₄ is selected from the group consisting of S, Aad, D-Glu, E, Aib, H, V, A, Q, D, and P;
- 20 X₂₆ is selected from the group consisting of L and αMeL;
- X₂₇ is selected from the group consisting of L and I;
- X₂₈ is selected from the group consisting of E, A, S, and D-Glu; and
- X₂₉ is selected from the group consisting of Aib, G, and A.
- 25 40. The compound, or a pharmaceutically acceptable salt thereof as claimed by Claim 39 wherein:
- X₁ is Y;
- X₂ is Aib;
- X₃ is E;
- 30 X₁₀ is selected from the group consisting of A, L, H, 3Pal, 4Pal, V, and Y;
- X₁₁ is S;
- X₁₂ is I;

X₁₆ is selected from the group consisting of K, E, Orn, Dab, and Dap;

X₁₉ is Q;

X₂₀ is selected from the group consisting of Aib and K;

X₂₁ is selected from the group consisting of H, Aad, D, Aib, T, A, and E;

5 X₂₂ is F;

X₂₃ is I;

X₂₄ is selected from the group consisting of S, Aad, D-Glu, and E;

X₂₆ is L; and

X₂₈ is selected from the group consisting of E and A.

10 41. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 40 wherein one of X₃₀, X₃₄, and X₃₉ is C.

42. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 41 wherein the compound is modified using time-extension technology.

15 43. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 39 wherein q is 18.

44. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 39 wherein q is 16.

45. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 40 wherein X₂₇ is L.

20 46. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 39 wherein X₃₁ is PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂.

47. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 39 wherein X₃₁ is absent.

25 48. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 47 wherein R₂ is NH₂.

49. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1

wherein:

X₁₄ is L;

30 X₁₇ is selected from the group consisting of K, Q, and I;

X₃₀ is selected from the group consisting of G-R₂ and G; and

q is selected from the group consisting of 16, 18, and 20;

wherein if X₃₀ is G, then X₃₁ is selected from the group consisting of:

PX₃₂X₃₃X₃₄-R₂ (SEQ ID NO:4), wherein:

X₃₂ is S, X₃₃ is S, X₃₄ is G and R₂ is absent (SEQ ID NO:299) or

X₃₂ is S, X₃₃ is S, X₃₄ is G and R₂ is NH₂ (SEQ ID NO:300);

and

PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ (SEQ ID NO:5), wherein:

X₃₂ is S, X₃₃ is S, X₃₄ is G, X₃₅ is A, X₃₆ is P, X₃₇ is P, X₃₈ is P, X₃₉ is S
and R₂ is absent (SEQ ID NO:301) or

X₃₂ is S, X₃₃ is S, X₃₄ is G, X₃₅ is A, X₃₆ is P, X₃₇ is P, X₃₈ is P, X₃₉ is S
and R₂ is NH₂ (SEQ ID NO:302); and

wherein one of X₁₀, X₁₂, X₁₃, X₁₄, X₁₆, X₁₉, X₂₀, X₂₁, X₂₃, X₂₄, X₂₆, X₂₇, X₂₈, and
X₂₉ is K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-γGlu-CO-(CH₂)_qCO₂H.

50. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim
49 wherein:

X₁ is Y;

X₂ is Aib;

X₃ is E;

X₁₀ is selected from the group consisting of A, L, H, 3Pal, 4Pal, V, Y, E, cTA, and
K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₁ is S;

X₁₂ is selected from the group consisting of I, D-Ile, and K(2-[2-(2-amino-
ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₄ is selected from the group consisting of L and K(2-[2-(2-amino-ethoxy)-
ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₆ is selected from the group consisting of K, E, Orn, Dab, Dap, and K(2-[2-(2-
amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₁₇ is selected from the group consisting of K and I;

X₁₉ is selected from the group consisting of Q and K(2-[2-(2-amino-ethoxy)-
ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₀ is selected from the group consisting of Aib and K(2-[2-(2-amino-ethoxy)-
ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₁ is selected from the group consisting of H, Aad, D, Aib, T, A, E, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₂ is F;

X₂₃ is I;

5 X₂₄ is selected from the group consisting of S, Aad, D--Glu, E, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₆ is selected from the group consisting of L, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₂₇ is selected from the group consisting of L and I;

10 X₂₈ is selected from the group consisting of E, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_qCO₂H;

X₃₀ is G; and

X₃₁ is selected from the group consisting of PX₃₂X₃₃X₃₄-R₂ (SEQ ID NO:4),

PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ (SEQ ID NO:5),

15 X₃₂ is S;

X₃₃ is S;

X₃₄ is G;

X₃₅ is A;

X₃₆ is P;

20 X₃₇ is P;

X₃₈ is P; and

X₃₉ is S.

51. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 50 wherein X₂₀ is K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-
25 CO₂H.

52. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 51 wherein PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ is selected from the group consisting of PSSGAPPPS (SEQ ID NO:301) and PSSGAPPPS-NH₂ (SEQ ID NO:302).

53. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 30 51 wherein q is 18.

54. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 51 wherein q is 16.
55. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1
5 wherein:
X₁ is selected from the group consisting of Y, F, D-Tyr, and desY,
X₆ is F; and
X₁₃ is selected from the group consisting of Aib, L, and αMeL.
- 10 56. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 55 wherein
R₁ is absent;
X₂ is Aib;
X₃ is E;
X₁₀ is Y;
15 X₁₁ is S;
X₁₂ is I;
X₁₄ is L;
X₁₆ is selected from the group consisting of K, E, Orn, Dab, Dap, S, T, H, Aib, αMeK, and R
20 X₁₇ is an amino acid conjugated to a C₁₆-C₂₂ fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;
X₁₉ is Q;
X₂₀ is selected from the group consisting of Aib, Q, H, and K;
X₂₁ is selected from the group consisting of H, D, T, A, and E;
25 X₂₂ is F;
X₂₃ is I;
X₂₄ is selected from the group consisting of D-Glu and E;
X₂₆ is L;
X₂₇ is I;
30 X₂₈ is selected from the group consisting of E, A, S, and D-Glu;
X₂₉ is selected from the group consisting of Aib, G, and A;
X₃₀ is selected from the group consisting of C, G, and G-R₂;

X₃₁ is absent or is selected from the group consisting of PX₃₂X₃₃X₃₄-R₂ (SEQ ID NO:4), PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ (SEQ ID NO:5), and PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉X₄₀-R₂ (SEQ ID NO:6); wherein:

X₃₂ is S;

5 X₃₃ is S;

X₃₄ is selected from the group consisting of G and C;

X₃₅ is A;

X₃₆ is P;

X₃₇ is P;

10 X₃₈ is P;

X₃₉ is selected from the group consisting of C and S; and

X₄₀ is C.

57. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 56 wherein X₁₇ is K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ-Glu)-CO-(CH₂)_q-CO₂H.

15

58. The compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 57 wherein PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ is selected from the group consisting of PSSGAPPPS (SEQ ID NO:301) and PSSGAPPPS-NH₂ (SEQ ID NO:302).

59. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 57 wherein

20

X₂₈ is A;

X₂₉ G;

X₃₀ is G;

X₃₁ is PX₃₂X₃₃X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉-R₂ (SEQ ID NO:5)

25

X₃₄ is G; and

X₃₉ is S.

60. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 55 wherein

X₁ is selected from the group consisting of Y and D-Tyr; and X₁₃ is αMeL.

30

61. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 55 wherein q is 16.

62. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 55 wherein q is 18.
63. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 1 wherein the compound is selected from the group consisting of SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, and SEQ ID NO:392.
64. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 63 wherein the compound is SEQ ID NO:305.
65. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 63 wherein the compound is SEQ ID NO:307.
66. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 63 wherein the compound is SEQ ID NO:308.
67. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 63 wherein the compound is SEQ ID NO:392.
68. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 55 wherein the compound is a partial agonist on the GLP-1R.
69. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 68 wherein the compound stimulates GLP-1R induced activation of $G\alpha_s$ in the GIPR and GLP-1R HEK293 Cell Membrane Guanosine 5'-(gamma-thio) Triphosphate- $[^{35}S]$ (GTP γ S) Binding Assay.
70. The compound, or pharmaceutically acceptable salt thereof, as claimed by Claim 69 wherein the compound is a partial agonist on the GLP-1R with respect to the β -arrestin-2 recruitment assay.
71. Use of a compound, or a pharmaceutically acceptable salt thereof as claimed by Claim 1, in the manufacture of a medicament for treating a condition selected from the group consisting of type 2 diabetes mellitus, obesity, NAFLD, nonalcoholic steatohepatitis, dyslipidemia, and metabolic syndrome.
72. Use of a compound, or a pharmaceutically acceptable salt thereof as claimed by Claim 1, in the manufacture of a medicament for treating obesity.
73. Use of a compound, or a pharmaceutically acceptable salt thereof as claimed by Claim 1, in the manufacture of a medicament for providing therapeutic weight loss.

74. Use of a compound, or a pharmaceutically acceptable salt thereof as claimed by Claim 1, in the manufacture of a medicament for treating type 2 diabetes mellitus.
75. A pharmaceutical composition comprising the compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 and at least one pharmaceutically acceptable carrier, diluent, or excipient.
76. The pharmaceutical composition as claimed by Claim 75 wherein the composition is to be administered as a subcutaneous injection.
77. The pharmaceutical composition as claimed by Claim 75 wherein the composition is to be administered orally.
78. The pharmaceutical composition as claimed by Claim 77 wherein the composition comprises a permeation enhancer and at least one pharmaceutically acceptable carrier, diluent, or excipient.
79. The pharmaceutical composition as claimed by Claim 78 wherein the permeation enhancer is selected from the group consisting of sodium decanoate ("C10"), sodium taurodeoxycholate ("NaTDC"), lauroyl carnitine ("LC"), dodecyl maltoside ("C12-maltoside"), dodecyl phosphatidylcholine ("DPC"), sodium taurodeoxycholate ("NaTDC"), and a Rhamnolipid.
80. The pharmaceutical composition as claimed by Claim 79 wherein the permeation enhancer is selected from the group consisting of C10 and LC.
81. The pharmaceutical composition as claimed by Claim 80 wherein the permeation enhancer is C10.
82. The pharmaceutical composition as claimed by Claim 81 wherein the composition comprises a permeation enhancer and a protease inhibitor, and at least one pharmaceutically acceptable carrier, diluent, or excipient.
83. The pharmaceutical composition as claimed by Claim 82 wherein the protease inhibitor is selected from the group consisting of soybean trypsin inhibitor ("SBTI"), soybean trypsin-chymotrypsin inhibitor ("SBTICI"), ecotin, sunflower trypsin inhibitor ("SFTI"), leupeptin, citric acid, ethylenediaminetetraacetic acid ("EDTA"), sodium glycocholate and 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride ("AEBSF").
84. The pharmaceutical composition as claimed by Claim 83 wherein the protease inhibitor is selected from the group consisting of SBTI, SBTICI, and SFTI.

85. The pharmaceutical composition as claimed by Claim 84 wherein the protease inhibitor is SBTI.
86. The pharmaceutical composition as claimed by Claim 78 wherein the composition is a monolithic formulation.
- 5 87. The pharmaceutical composition as claimed by Claim 78 wherein the composition is a multiparticulate formulation.
88. The pharmaceutical composition as claimed by Claim 78 wherein the composition is a capsule or tablet.
89. The pharmaceutical composition as claimed by Claim 86 wherein the composition
10 is an enteric capsule or tablet.
90. A compound, or a pharmaceutically acceptable salt thereof, as claimed by Claim 1 for use as a medicament.