maintain long-term weight reduction. Available treatments for obesity are particularly unsatisfactory for patients with severe obesity. Successful treatment of obesity is associated with alleviation or prevention of T2D. There is a need for alternative treatment options to induce therapeutic weight loss in patients in need of such treatment. Compounds having a ratio that is about 2.5:1 to about 10:1 GIP receptor agonist potency to GLP-1 receptor agonist potency are useful for significantly improving weight management, and can prevent the manifestation of T2D in formerly obese patients susceptible to T2D.

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. US9474780 generally describes compositions containing a GIP/GLP1 co-agonist, administered by parenteral routes, and generally discloses a wide dosage range up to about 30 mg per person per week. US9474780 discloses the use of GIP/GLP1 co-agonists for treating diabetes, obesity, and other conditions. US9474780 describes and claims tirzepatide.

Summary

In an aspect of the present disclosure, there is provided a use of a compound of SEQ ID NO: 3:

$R_1X_1X_2X_3GTX_6TSDX_{10}X_{11}X_{12}X_{13}X_{14}DX_{16}X_{17}AX_{19}X_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}$
$X_{28}X_{29}X_{30}X_{31}$
or a pharmaceutically acceptable salt thereof,
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;
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, αMeP, A, P, and D-Ala;
or X_1 and X_2 combine to form desH-□[NHCO]-Aib;
X_3 is selected from the group consisting ofE, N, Aad, and cTA;
or X_1 and X_2 combine to form desH-□[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, αMeF, and αMeF(2F);
X_{10} 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-$(CH_2)qCO_2H$;
X_{11} is selected from the group consisting of S, αMeS, and D-Ser;
X_{12} is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;
X_{13} is selected from the group consisting of Nle, Aib, L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;
X_{14} is selected from the group consisting of L and K, wherein K is conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said K via a linker;
X_{16} 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-$(CH_2)qCO_2H$;
X_{17} is selected from the group consisting of K, Q, I, and an amino acid conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;

X_{19} is selected from the group consisting of Q, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{20} 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-$(CH_2)qCO_2H$;

X_{21} 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-$(CH_2)qCO_2H$;

X_{22} is selected from the group consisting of F and αMeF;

X_{23} 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-$(CH_2)qCO_2H$;

X_{24} 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-$(CH_2)qCO_2H$;

X_{25} is selected from the group consisting of Y and αMeY;

X_{26} is selected from the group consisting of L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{27} is selected from the group consisting of L, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{28} 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-$(CH_2)qCO_2H$;

X_{29} is selected from the group consisting of Aib, G, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{30} is selected from the group consisting of C, G, G-R_2 and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)q$-CO_2H;

X_{31} is absent or is selected from the group consisting of $PX_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:4), $PX_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:5), $PX_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:6), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)q$-CO_2H] $X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:7), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)q$-CO_2H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:8), and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)q$-CO_2H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:9);

wherein:

X_{32} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)q$-CO_2H];

X_{33} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)q$-CO_2H];

X_{34} is selected from the group consisting of G, C, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{35} is A or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{36} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{37} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{38} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{39} is selected from the group consisting of C, S, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{40} is selected from the group consisting of C and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
q is selected from the group consisting of 14, 15, 16, 17, 18, 19, and 20; and
R_2 is a modification of the C-terminal group, wherein the modification is NH_2 or absent;
or a pharmaceutically acceptable salt thereof;
wherein if X_{30} is G-R_2, then X_{31} is absent;
wherein no more than one of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} may be a substituent that contains a fatty acid; and
wherein no more than one of X_{30}, X_{34}, X_{39}, and X_{40} may be C; and
wherein if one of X_{30}, X_{34}, X_{39}, and X_{40} is C, then none of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} is a substituent that contains a fatty acid;
in the manufacture of a medicament for treating type 2 diabetes, NASH or obesity,
wherein the compound, or a pharmaceutically acceptable salt thereof, has a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5: 1 to about 10: 1,
wherein:

a) a titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter
b) a maintenance dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered;

wherein the titration dose is about 50% of the maintenance dose.

In another aspect of the present disclosure, there is provided a use of a compound of SEQ ID NO: 3:

$R_1X_1X_2X_3GTX_6TSDX_{10}X_{11}X_{12}X_{13}X_{14}DX_{16}X_{17}AX_{19}X_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}$

or a pharmaceutically acceptable salt thereof,

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;

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, αMeP, A, P, and D-Ala;

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

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

or X_1 and X_2 combine to form desH-□[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, αMeF, and αMeF(2F);

X_{10} 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-$(CH_2)qCO_2H$;

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

X_{12} is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{13} is selected from the group consisting of Nle, Aib, L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{14} is selected from the group consisting of L and K, wherein K is conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said K via a linker;

X_{16} 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-$(CH_2)qCO_2H$;

X_{17} is selected from the group consisting of K, Q, I, and an amino acid conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;

X_{19} is selected from the group consisting of Q, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO_2H;

X_{20} 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-(CH_2)qCO_2H;

X_{21} 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-(CH_2)qCO_2H;

X_{22} is selected from the group consisting of F and αMeF;

X_{23} 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-(CH_2)qCO_2H;

X_{24} 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-(CH_2)qCO_2H;

X_{25} is selected from the group consisting of Y and αMeY;

X_{26} is selected from the group consisting of L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO_2H;

X_{27} is selected from the group consisting of L, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO_2H;

X_{28} 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-(CH_2)qCO_2H;

X_{29} is selected from the group consisting of Aib, G, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO_2H;

X_{30} is selected from the group consisting of C, G, G-R_2 and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H;

X_{31} is absent or is selected from the group consisting of P$X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:4), P$X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:5), P$X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:6), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H] $X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:7), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:8), and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:9);

wherein:

X_{32} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{33} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{34} is selected from the group consisting of G, C, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{35} is A or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{36} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{37} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{38} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{39} is selected from the group consisting of C, S, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
X_{40} is selected from the group consisting of C and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];
q is selected from the group consisting of 14, 15, 16, 17, 18, 19, and 20; and
R_2 is a modification of the C-terminal group, wherein the modification is NH_2 or absent;
or a pharmaceutically acceptable salt thereof;
wherein if X_{30} is G-R_2, then X_{31} is absent;
wherein no more than one of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} may be a substituent that contains a fatty acid; and
wherein no more than one of X_{30}, X_{34}, X_{39}, and X_{40} may be C; and
wherein if one of X_{30}, X_{34}, X_{39}, and X_{40} is C, then none of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} is a substituent that contains a fatty acid;
in the manufacture of a medicament for treating type 2 diabetes, NASH or obesity,
wherein the compound, or a pharmaceutically acceptable salt thereof, has a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5: 1 to about 10: 1,
wherein:

a) a first titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter
b) a second titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

c) a third titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

d) a maintenance dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

In a further aspect of the present disclosure, there is provided a use of a compound of SEQ ID NO: 3:

$R_1X_1X_2X_3GTX_6TSDX_{10}X_{11}X_{12}X_{13}X_{14}DX_{16}X_{17}AX_{19}X_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}$
$X_{28}X_{29}X_{30}X_{31}$

or a pharmaceutically acceptable salt thereof,

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;

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, αMeP, A, P, and D-Ala;

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

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

or X_1 and X_2 combine to form desH-□[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, αMeF, and αMeF(2F);

X_{10} 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-(CH_2)qCO_2H;

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

X_{12} is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO_2H;

X_{13} is selected from the group consisting of Nle, Aib, L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO_2H;

X_{14} is selected from the group consisting of L and K, wherein K is conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said K via a linker;
X_{16} 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-$(CH_2)qCO_2H$;
X_{17} is selected from the group consisting of K, Q, I, and an amino acid conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;
X_{19} is selected from the group consisting of Q, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;
X_{20} 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-$(CH_2)qCO_2H$;
X_{21} 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-$(CH_2)qCO_2H$;
X_{22} is selected from the group consisting of F and αMeF;
X_{23} 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-$(CH_2)qCO_2H$;
X_{24} 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-$(CH_2)qCO_2H$;
X_{25} is selected from the group consisting of Y and αMeY;
X_{26} is selected from the group consisting of L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;
X_{27} is selected from the group consisting of L, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;
X_{28} 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-$(CH_2)qCO_2H$;
X_{29} is selected from the group consisting of Aib, G, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;
X_{30} is selected from the group consisting of C, G, G-R_2 and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)q$-CO_2H;
X_{31} is absent or is selected from the group consisting of $PX_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:4), $PX_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:5), $PX_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:6), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)q$-CO_2H]

$X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:7), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:8), and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:9);

wherein:

X_{32} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{33} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{34} is selected from the group consisting of G, C, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{35} is A or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{36} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{37} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{38} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{39} is selected from the group consisting of C, S, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

X_{40} is selected from the group consisting of C and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)q-CO_2H];

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

R_2 is a modification of the C-terminal group, wherein the modification is NH_2 or absent;

or a pharmaceutically acceptable salt thereof;

wherein if X_{30} is G-R_2, then X_{31} is absent;

wherein no more than one of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} may be a substituent that contains a fatty acid; and

wherein no more than one of X_{30}, X_{34}, X_{39}, and X_{40} may be C; and

wherein if one of X_{30}, X_{34}, X_{39}, and X_{40} is C, then none of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} is a substituent that contains a fatty acid;

in the manufacture of a medicament for treating type 2 diabetes, NASH or obesity,

wherein the compound, or a pharmaceutically acceptable salt thereof, has a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5: 1 to about 10: 1,:

a) a first titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter
b) a second titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter
c) a third titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter
d) a fourth titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter
e) a fifth titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter
f) a maintenance dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

Description

The present invention provides novel dosing regimens of a GIP:GLP-1 Peptide for use in the aforementioned therapies (glycemic control/diabetes, obesity) that include one or more titration doses and a maintenance dose. More specifically, the present invention provides novel dosing regimens that include a titration dose and a maintenance dose wherein the titration dose is about 50% of the maintenance dose and is administered about once weekly for a minimum of about 2 weeks before administration of the maintenance dose. In another aspect, the dosing regimen comprises three titration doses: the first being about 25% of the maintenance dose, the second being about 50% of the maintenance dose and the third being about 75% of the maintenance dose, and a maintenance dose wherein each titration dose is administered about once weekly for a minimum of about 2 weeks before the administration of the next higher dose. In yet a third embodiment, the dosing regimen comprises five titration doses: the first being about 17% of the maintenance dose, the second being about 33% of the maintenance dose, the third being about 50% of the maintenance dose, the fourth being about 66% of the maintenance dose and the fifth being about 83% of the maintenance dose wherein each titration dose is administered about once weekly for a minimum of about 2 weeks before the administration of the next higher dose. Further embodiments are dosing regimens as above where each titration

WE CLAIM:

1. Use of a compound of SEQ ID NO: 3:

$$R_1X_1X_2X_3GTX_6TSDX_{10}X_{11}X_{12}X_{13}X_{14}DX_{16}X_{17}AX_{19}X_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}$$

or a pharmaceutically acceptable salt thereof,

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;

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, αMeP, 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 ofE, N, Aad, and cTA;

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, αMeF, and αMeF(2F);

X_{10} 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-$(CH_2)qCO_2H$;

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

X_{12} is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{13} is selected from the group consisting of Nle, Aib, L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{14} is selected from the group consisting of L and K, wherein K is conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said K via a linker;

X_{16} 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-$(CH_2)qCO_2H$;

X_{17} is selected from the group consisting of K, Q, I, and an amino acid conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;

X_{19} is selected from the group consisting of Q, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{20} 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-(CH$_2$)qCO$_2$H;

X_{21} 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-(CH$_2$)qCO$_2$H;

X_{22} is selected from the group consisting of F and αMeF;

X_{23} 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-(CH$_2$)qCO$_2$H;

X_{24} 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-(CH$_2$)qCO$_2$H;

X_{25} is selected from the group consisting of Y and αMeY;

X_{26} is selected from the group consisting of L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)qCO$_2$H;

X_{27} is selected from the group consisting of L, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)qCO$_2$H;

X_{28} 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-(CH$_2$)qCO$_2$H;

X_{29} is selected from the group consisting of Aib, G, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)qCO$_2$H;

X_{30} is selected from the group consisting of C, G, G-R_2 and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_q$-CO$_2$H;

X_{31} is absent or is selected from the group consisting of P$X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:4), P$X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:5), P$X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:6), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_q$-CO$_2$H] $X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:7), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_q$-CO$_2$H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:8), and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_q$-CO$_2$H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:9);

wherein:

X_{32} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_q$-CO$_2$H];

X_{33} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_q$-CO$_2$H];

X_{34} is selected from the group consisting of G, C, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_q$-CO$_2$H];

X_{35} is A or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_q$-CO$_2$H];

X_{36} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{37} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{38} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{39} is selected from the group consisting of C, S, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

X_{40} is selected from the group consisting of C and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

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

R_2 is a modification of the C-terminal group, wherein the modification is NH_2 or absent;

or a pharmaceutically acceptable salt thereof;

wherein if X_{30} is G-R_2, then X_{31} is absent;

wherein no more than one of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} may be a substituent that contains a fatty acid; and

wherein no more than one of X_{30}, X_{34}, X_{39}, and X_{40} may be C; and

wherein if one of X_{30}, X_{34}, X_{39}, and X_{40} is C, then none of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} is a substituent that contains a fatty acid;

in the manufacture of a medicament for treating type 2 diabetes, NASH or obesity, wherein the compound, or a pharmaceutically acceptable salt thereof, has a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5: 1 to about 10: 1, wherein:

a) a titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

b) a maintenance dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered;

wherein the titration dose is about 50% of the maintenance dose.

2. Use of a compound of SEQ ID NO: 3:

$$R_1X_1X_2X_3GTX_6TSDX_{10}X_{11}X_{12}X_{13}X_{14}DX_{16}X_{17}AX_{19}X_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}$$
$$X_{28}X_{29}X_{30}X_{31}$$

or a pharmaceutically acceptable salt thereof,

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;

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, αMeP, 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 ofE, N, Aad, and cTA;

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, αMeF, and αMeF(2F);

X_{10} 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-$(CH_2)qCO_2H$;

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

X_{12} is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{13} is selected from the group consisting of Nle, Aib, L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{14} is selected from the group consisting of L and K, wherein K is conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said K via a linker;

X_{16} 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-$(CH_2)qCO_2H$;

X_{17} is selected from the group consisting of K, Q, I, and an amino acid conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;

X_{19} is selected from the group consisting of Q, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{20} 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-$(CH_2)qCO_2H$;

X_{21} 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-$(CH_2)qCO_2H$;

X_{22} is selected from the group consisting of F and αMeF;

X_{23} 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-$(CH_2)qCO_2H$;

X_{24} 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-(CH_2)qCO$_2$H;

X_{25} is selected from the group consisting of Y and αMeY;

X_{26} is selected from the group consisting of L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO$_2$H;

X_{27} is selected from the group consisting of L, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO$_2$H;

X_{28} 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-(CH_2)qCO$_2$H;

X_{29} is selected from the group consisting of Aib, G, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO$_2$H;

X_{30} is selected from the group consisting of C, G, G-R_2 and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H;

X_{31} is absent or is selected from the group consisting of P$X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:4), P$X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:5), P$X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:6), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H] $X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:7), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:8), and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:9);

wherein:

X_{32} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{33} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{34} is selected from the group consisting of G, C, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{35} is A or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{36} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{37} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{38} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{39} is selected from the group consisting of C, S, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{40} is selected from the group consisting of C and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

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

R_2 is a modification of the C-terminal group, wherein the modification is NH_2 or absent;

or a pharmaceutically acceptable salt thereof;

wherein if X_{30} is G-R_2, then X_{31} is absent;

wherein no more than one of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} may be a substituent that contains a fatty acid; and

wherein no more than one of X_{30}, X_{34}, X_{39}, and X_{40} may be C; and

wherein if one of X_{30}, X_{34}, X_{39}, and X_{40} is C, then none of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} is a substituent that contains a fatty acid;

in the manufacture of a medicament for treating type 2 diabetes, NASH or obesity, wherein the compound, or a pharmaceutically acceptable salt thereof, has a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5: 1 to about 10: 1, wherein:

a) a first titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

b) a second titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

c) a third titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

d) a maintenance dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered;

wherein the first titration dose is about 25% of the maintenance dose, the second titration dose is about 50% of the maintenance dose and the third titration dose is about 75% of the maintenance dose.

3. Use of a compound of SEQ ID NO: 3:

$$R_1X_1X_2X_3GTX_6TSDX_{10}X_{11}X_{12}X_{13}X_{14}DX_{16}X_{17}AX_{19}X_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}$$
$$X_{28}X_{29}X_{30}X_{31}$$

or a pharmaceutically acceptable salt thereof,

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;

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, αMeP, 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 ofE, N, Aad, and cTA;

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, αMeF, and αMeF(2F);

X_{10} 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-$(CH_2)qCO_2H$;

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

X_{12} is selected from the group consisting of I, S, D-Ile, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{13} is selected from the group consisting of Nle, Aib, L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{14} is selected from the group consisting of L and K, wherein K is conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said K via a linker;

X_{16} 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-$(CH_2)qCO_2H$;

X_{17} is selected from the group consisting of K, Q, I, and an amino acid conjugated to a C_{16}-C_{22} fatty acid wherein said fatty acid is optionally conjugated to said amino acid via a linker;

X_{19} is selected from the group consisting of Q, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)qCO_2H$;

X_{20} 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-$(CH_2)qCO_2H$;

X_{21} 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-$(CH_2)qCO_2H$;

X_{22} is selected from the group consisting of F and αMeF;

X_{23} 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-$(CH_2)qCO_2H$;

X_{24} 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-(CH_2)qCO$_2$H;

X_{25} is selected from the group consisting of Y and αMeY;

X_{26} is selected from the group consisting of L, αMeL, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO$_2$H;

X_{27} is selected from the group consisting of L, I, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO$_2$H;

X_{28} 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-(CH_2)qCO$_2$H;

X_{29} is selected from the group consisting of Aib, G, A, and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH_2)qCO$_2$H;

X_{30} is selected from the group consisting of C, G, G-R_2 and K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H;

X_{31} is absent or is selected from the group consisting of P$X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:4), P$X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:5), P$X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:6), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H] $X_{32}X_{33}X_{34}$-R_2 (SEQ ID NO:7), K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$-$R_2$ (SEQ ID NO:8), and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H] $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$-$R_2$ (SEQ ID NO:9);

wherein:

X_{32} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{33} is S or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{34} is selected from the group consisting of G, C, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{35} is A or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{36} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{37} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{38} is P or K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{39} is selected from the group consisting of C, S, and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO$_2$H];

X_{40} is selected from the group consisting of C and K[(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-$(CH_2)_q$-CO_2H];

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

R_2 is a modification of the C-terminal group, wherein the modification is NH_2 or absent;

or a pharmaceutically acceptable salt thereof;

wherein if X_{30} is G-R_2, then X_{31} is absent;

wherein no more than one of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} may be a substituent that contains a fatty acid; and

wherein no more than one of X_{30}, X_{34}, X_{39}, and X_{40} may be C; and

wherein if one of X_{30}, X_{34}, X_{39}, and X_{40} is C, then none of X_{10}, X_{12}, X_{13}, X_{14}, X_{16}, X_{17}, X_{19}, X_{20}, X_{21}, X_{23}, X_{24}, X_{26}, X_{27}, X_{28}, X_{29}, X_{30}, X_{31}, X_{32}, X_{33}, X_{34}, X_{35}, X_{36}, X_{37}, X_{38}, X_{39}, and X_{40} is a substituent that contains a fatty acid;

in the manufacture of a medicament for treating type 2 diabetes, NASH or obesity, wherein the compound, or a pharmaceutically acceptable salt thereof, has a GIP:GLP-1 receptor agonist potency ratio as measured after a 60 minute incubation using a casein cAMP assay normalized against GIP and GLP-1 that is about 2.5: 1 to about 10: 1,:

a) a first titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

b) a second titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

c) a third titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

d) a fourth titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

e) a fifth titration dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered for a minimum of about two weeks; and thereafter

f) a maintenance dose of said compound, or a pharmaceutically acceptable salt thereof, is to be administered;

wherein the first titration dose is about 17% of the maintenance dose, the second titration dose is about 33% of the maintenance dose, the third titration dose is about 50% of the maintenance dose, the fourth titration is about 66% of the maintenance dose and the fifth titration dose is about 83% of the maintenance dose.

4. The use according to any one of claims 1 to 3, wherein the titration doses are each to be administered for about four weeks before the administration of the next higher dose begins.