These data suggest that OXM has the potential of being a well-tolerated anti-diabetes/obesity agent. OXM, however, presents several challenges for development into a commercially-viable therapeutic agent. Endogenous OXM is quickly degraded *in vivo* by dipeptidyl peptidase IV and other peptidases as well as being subject to rapid renal clearance due to its small size. It is therefore desirable to identify peptides that activate the Gcg and GLP-1 receptors with improved metabolic stability and reduced rate of clearance.

OXM peptides with amino acid substitutions to improve stability and with additional modifications to slow clearance, such as PEGylation or lipidation are disclosed in the art. Other peptides have been stated to bind to and activate both the Gcg receptor and the GLP-1 receptor and to suppress body weight gain (see for example, WO 2011/075393 A2 and WO 2012/177444 A2).

Despite the availability of various peptides that agonize both the Gcg and GLP-1 receptors, there remains a need for more potent, stable, long-acting, and/or well-tolerated compounds having a ratio of Gcg receptor (Gcg-R)/GLP-1 receptor (GLP-1-R) activity that has been optimized such that the potency and insulinotropic activity of the compounds provides effective treatments for diabetes, preferably T2D, and related disorders. In particular, there remains a need for compounds with a balanced ratio of Gcg-R/GLP-1-R coagonist activity that reduce body weight. Also, there remains a need to provide compounds with a balanced ratio of Gcg-R/GLP-1-R co-agonist activity that supports potential daily, bi-weekly, once-weekly or monthly dosing in humans. Accordingly, the present invention seeks to provide effective treatments for diabetes, obesity, nonalcoholic fatty liver disease (NAFLD) and/or nonalcoholic steatohepatitis (NASH).

## SUMMARY

In one aspect of the present disclosure, there is provided a compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser;

Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with a C14-C24 fatty acid *via* a linker between the Lys at position 20 and the C14-C24 fatty acid, wherein the linker is $([2-(2-aminoethoxy)-ethoxy]-acetyl)_2-(\gamma-Glu)_t$, wherein t is 1 or 2; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 2);

or a pharmaceutically acceptable salt thereof.

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

In yet another aspect of the present disclosure, there is provided a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating type 2 diabetes in a subject in need thereof.

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

In another aspect of the present disclosure, there is provided a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating nonalcoholic fatty liver disease (NAFLD) in a subject in need thereof.

In yet another aspect of the present disclosure, there is provided a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH) in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inducing non-therapeutic weight-loss in a subject.

In another aspect of the present disclosure, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In yet another aspect of the present disclosure, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of type 2 diabetes.

In a further aspect of the present disclosure, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of obesity.

In another aspect of the present disclosure, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of nonalcoholic fatty liver disease (NAFLD).

In yet another aspect of the present disclosure, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of nonalcoholic steatohepatitis (NASH).

In a further aspect of the present disclosure, there is provided an intermediate compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 9),

or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a process for the manufacture of a compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser;

Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with a C14-C24 fatty acid *via* a linker between the Lys at position 20 and the C14-C24 fatty acid, wherein the linker is ([2-(2-aminoethoxy)-ethoxy]-acetyl)$_2$-($\gamma$-Glu)$_t$, wherein t is 1 or 2; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 2), said process comprising the step of:

(i) modifying an intermediate compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 9)

by conjugating the epsilon-amino group of the Lys side chain at position 20 of the intermediate compound with a C14-C24 fatty acid *via* a linker, wherein the linker is ([2-(2-aminoethoxy)-ethoxy]-acetyl)$_2$-($\gamma$-Glu)$_t$, wherein t is 1 or 2.

## DESCRIPTION

In one aspect, the present invention provides a compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

WE CLAIM:

1. A compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser;

Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with a C14-C24 fatty acid *via* a linker between the Lys at position 20 and the C14-C24 fatty acid, wherein the linker is ([2-(2-aminoethoxy)-ethoxy]-acetyl)$_2$-($\gamma$-Glu)$_t$, wherein t is 1 or 2; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 2);

or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Xaa28 is Glu.

3. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Xaa28 is Ser.

4. The compound according to any one of Claims 1-3, or a pharmaceutically acceptable salt thereof, wherein t is 1.

5. The compound according to any one of Claims 1-3, or a pharmaceutically acceptable salt thereof, wherein t is 2.

6. The compound according to any one of Claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the C14-C24 fatty acid is a saturated monoacid or a saturated diacid.

7. The compound according to Claim 6, or a pharmaceutically acceptable salt thereof, wherein the fatty acid is a saturated monoacid or saturated diacid selected from the group consisting of myristic acid (tetradecanoic acid)(C14 monoacid), tetradecanedioic acid (C14 diacid), palmitic acid (hexadecanoic acid)(C16 monoacid), hexadecanedioic acid (C16 diacid), margaric acid (heptadecanoic acid)(C17 monoacid), heptadecanedioic acid (C17 diacid), stearic acid (octadecanoic acid)(C18 monoacid), octadecanedioic acid (C18 diacid), nonadecylic acid (nonadecanoic acid)(C19 monoacid), nonadecanedioic acid (C19 diacid), arachadic acid (eicosanoic acid)(C20 monoacid), eicosanedioic acid (C20 diacid), heneicosylic acid (heneicosanoic acid)(C21 monoacid), heneicosanedioic

acid (C21 diacid), behenic acid (docosanoic acid)(C22), docosanedioic acid (C22 diacid), lignoceric acid (tetracosanoic acid)(C24 monoacid) and tetracosanedioic acid (C24 diacid).

8. The compound according to Claim 6 or 7, or a pharmaceutically acceptable salt thereof, wherein the C14-C24 fatty acid is octadecanedioic acid.

9. The compound according to Claim 6 or 7, or a pharmaceutically acceptable salt thereof, wherein the C14-C24 fatty acid is eicosanedioic acid.

10. The compound according to any preceding claim, or a pharmaceutically acceptable salt thereof, wherein the C-terminal amino acid is amidated.

11. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

12. Use of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating type 2 diabetes in a subject in need thereof.

13. Use of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obesity in a subject in need thereof.

14. Use of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating nonalcoholic fatty liver disease (NAFLD) in a subject in need thereof.

15. Use of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH) in a subject in need thereof.

16. Use of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inducing non-therapeutic weight-loss in a subject.

17. A compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in therapy.

18. A compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the treatment of type 2 diabetes.

19. A compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the treatment of obesity.

20. A compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the treatment of nonalcoholic fatty liver disease (NAFLD).

21. A compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the treatment of nonalcoholic steatohepatitis (NASH).

22. An intermediate compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 9),

or a pharmaceutically acceptable salt thereof.

23. The intermediate compound according to Claim 22, wherein Xaa28 is Glu.

24 The intermediate compound according to Claim 22, wherein Xaa28 is Ser.

25. A process for the manufacture of a compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser;

Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with a C14-C24 fatty acid *via* a linker between the Lys at position 20 and the C14-C24 fatty acid, wherein the linker is ([2-(2-aminoethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)$_t$, wherein t is 1 or 2; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 2), said process comprising the step of:

(i) modifying an intermediate compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 9)

by conjugating the epsilon-amino group of the Lys side chain at position 20 of the intermediate compound with a C14-C24 fatty acid *via* a linker, wherein the linker is ([2-(2-aminoethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)$_t$, wherein t is 1 or 2.