OXM activates both the glucagon and the GLP-1 receptors with a two-fold higher potency for the glucagon receptor over the GLP-1 receptor, but is less potent than native glucagon and GLP-1 on their respective receptors. Human glucagon is also capable of activating both receptors, though with a strong preference for the glucagon receptor over the GLP-1 receptor. GLP-1 on the other hand is not capable of activating glucagon receptors. The mechanism of action of oxyntomodulin is not well understood. In particular, it is not known whether some of the extrahepatic effects of the hormone are mediated through the GLP-1 and glucagon receptors, or through one or more unidentified receptors.

Other peptides have been shown to bind and activate both the glucagon and the GLP-1 receptor (Hjort et al, Journal of Biological Chemistry, 269, 30121-30124, 1994) and to suppress body weight gain and reduce food intake (see, for example, WO 2006/134340, WO 2007/100535, WO 2008/10101, WO 2008/152403, WO 2009/155257, WO 2009/155258, WO2010/070252, WO2010/070253, WO2010/070255, WO2010/070251, WO2011/006497, WO2011/160630, WO2011/160633).

Obesity is a globally increasing health problem is associated with various diseases, particularly cardiovascular disease (CVD), type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis. As a result, obesity has been found to reduce life expectancy. According to 2005 projections by the World Health Organization there are 400 million adults (age > 15) classified as obese worldwide. In the US, obesity is now believed to be the second-leading cause of preventable death after smoking.

The rise in obesity drives an increase in diabetes, and approximately 90% of people with type 2 diabetes may be classified as obese. There are 246 million people worldwide with diabetes, and by 2025 it is estimated that 380 million will have diabetes. Many have additional cardiovascular risk factors, including high/aberrant LDL and triglycerides and low HDL.

SUMMARY ~~OF THE INVENTION~~

In a first ~~aspect~~embodiment, the ~~invention~~ present disclosure provides a compound having the formula:

R^1-X-Z-R^2

wherein

R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2;

X is a peptide which has the formula:

H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLS (SEQ ID NO: 1)

HSQGTFTSDYSKYLDSKAAHDFVEWLLSA (SEQ ID NO: 2)

H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLLSA (SEQ ID NO: 4)

H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLESA (SEQ ID NO: 5)

HSQGTFTSDYSRYLDSKAAEDFVEWLLRA (SEQ ID NO: 6)

HSQGTFTSDYSKYLDSKAAEDFVEWLLRA (SEQ ID NO: 7)
HSQGTFTSDYSKYLDSKAAHDFVEWLLS (SEQ ID NO: 8)
HSQGTFTSDYSKYLDSKAAHDFVEWLLR (SEQ ID NO: 9)
HSQGTFTSDYSKYLDEKAAHEFVEWLESA (SEQ ID NO: 10)
H-Aib-QGTFTSDYSKYLDEKRAKDFIEWLLS (SEQ ID NO: 11)
HSQGTFTSDYSRYLDSKAAHDFVEWLLSA (SEQ ID NO: 12)
H-Aib-HGTFTSDYSKYLESKAAEEFIEWLESA (SEQ ID NO: 17)
HSHGTFTSDYSKYLEEKAAHEFIEWLESA (SEQ ID NO: 18)
H-Aib-HGTFTSDYSKYLEEKAAHEFVEWLESA (SEQ ID NO: 19)

and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

In an aspect, the present disclosure provides a compound having the formula:
R^1-X-Z-R^2
wherein
R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2;
X is a peptide which has the formula:
HSQGTFTSDYSKYLDSKAAEDFVEWLLRA (SEQ ID NO: 7)
and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

In a second ~~aspect~~embodiment, the ~~invention~~ present disclosure provides a compound of the formula:
R^1-X-OH
wherein
R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
and X is a peptide of SEQ ID NO: 3, 13 or 14:
HSQGTFTSDYSKYLDSKAAHDFVEWLLRA (SEQ ID NO: 3)
H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLSA (SEQ ID NO: 13)
H-Aib-QGTFTSDYSKYLDEKRAKDFIEWLLSA (SEQ ID NO: 14)
or a pharmaceutically acceptable salt or solvate thereof.

In a third ~~aspect~~embodiment, the ~~invention~~ present disclosure provides a compound having the formula:
R^1-X-Z-R^2
wherein
R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2;
X is a peptide of SEQ ID NO: 15:
H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLESA (SEQ ID NO: 15)
or which differs from SEQ ID NO: 15 at up to three of the following positions whereby, if different from SEQ ID NO: 15:
the residue at position 2 is selected from Ser and D-Ser
the residue at position 3 is selected from His and Hse
the residue at position 12 is Arg
the residue at position 15 is Glu
the residue at position 16 is Ser
the residue at position 18 is Arg
the residue at position 20 is selected from His and Glu

the residue at position 21 is Glu
the residue at position 23 is Val
the residue at position 28 is selected from Arg and Glu
the residue at position 29 is absent;
and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

In certain embodiments, the residue at position 20 is not variable and is His.

The compound may have the formula:
R^1-X-Z-R^2
wherein
R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2;
X is a peptide of SEQ ID NO: 15:
H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLESA (SEQ ID NO: 15)
or which differs from SEQ ID NO: 15 at one or both of the following positions whereby, if different from SEQ ID NO: 15:
the residue at position 21 is Glu
the residue at position 23 is Val
and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

In a fourth ~~aspect~~embodiment, the ~~invention~~ present disclosure provides a compound having the formula:
R^1-X-Z-R^2
wherein
R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2;
X is a peptide of SEQ ID NO: 16:
H-Aib-QGTFTSDYSKYLDSKAAEDFVEWLESA (SEQ ID NO: 16)
or which differs from SEQ ID NO: 16 at up to three of the following positions whereby, if different from SEQ ID NO: 16:
the residue at position 2 is selected from Ser and D-Ser
the residue at position 3 is selected from His and Hse
the residue at position 12 is Arg
the residue at position 15 is Glu
the residue at position 16 is Glu
the residue at position 18 is Arg

the residue at position 20 is selected from Lys and His
the residue at position 21 is Glu
the residue at position 23 is Ile
the residue at position 28 is selected from Arg and Glu
the residue at position 29 is absent
and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

The compound may have the formula:
R^1-X-Z-R^2
wherein
R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2;
X is a peptide of SEQ ID NO: 16:
H-Aib-QGTFTSDYSKYLDSKAAEDFVEWLESA (SEQ ID NO: 16)
or which differs from SEQ ID NO: 16 at one or both of the following positions whereby, if different from SEQ ID NO: 16:
the residue at position 21 is Glu
the residue at position 23 is Ile
and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

A compound of the third or fourth ~~aspects~~ embodiments of the ~~invention~~ present disclosure may comprise a peptide X having the sequence:
H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLESA (SEQ ID NO: 15)
H-Aib-QGTFTSDYSKYLDSKAAEDFVEWLESA (SEQ ID NO: 16)
H-Aib-QGTFTSDYSKYLEEKAAKDFIEWLESA (SEQ ID NO: 20)
H-Aib-QGTFTSDYSKYLESKAAEDFIEWLESA (SEQ ID NO: 21)
HSQGTFTSDYSKYLEEKAAKDFIEWLESA (SEQ ID NO: 22)
H-Aib-QGTFTSDYSKYLESKAAHDFVEWLESA (SEQ ID NO: 23)
H-Aib-QGTFTSDYSKYLESKAAEDFVEWLESA (SEQ ID NO: 24) or
H-DSer-QGTFTSDYSKYLDEKAAKDFIEWLESA (SEQ ID NO: 25).

~~A~~In any ~~aspect~~embodiment, the compound of the ~~invention~~ present disclosure may have the formula:
H-H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLS-OH
H-HSQGTFTSDYSKYLDSKAAHDFVEWLLSA-OH
H-H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLLSA-NH_2

H-H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLESA-NH_2

H-HSQGTFTSDYSRYLDSKAAEDFVEWLLRA-NH_2

H-HSQGTFTSDYSKYLDSKAAEDFVEWLLRA-NH_2

H-HSQGTFTSDYSKYLDSKAAHDFVEWLLS-NH_2

H-HSQGTFTSDYSKYLDSKAAHDFVEWLLR-OH

H-HSQGTFTSDYSKYLDEKAAHEFVEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLDEKRAKDFIEWLLS-OH

H-HSQGTFTSDYSRYLDSKAAHDFVEWLLSA-NH_2

H-HSQGTFTSDYSKYLDSKAAHDFVEWLLRA-OH

H-H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLSA-OH

H-H-Aib-QGTFTSDYSKYLDEKRAKDFIEWLLSA-OH

H-H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLDSKAAEDFVEWLESA-NH_2

H-Aib-HGTFTSDYSKYLESKAAEEFIEWLESA-OH

H-HSHGTFTSDYSKYLEEKAAHEFIEWLESA-OH

H-H-Aib-HGTFTSDYSKYLEEKAAHEFVEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLEEKAAKDFIEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLESKAAEDFIEWLESA-NH_2

H-HSQGTFTSDYSKYLEEKAAKDFIEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLESKAAHDFVEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLESKAAEDFVEWLESA-NH_2

H-H-DSer-QGTFTSDYSKYLDEKAAKDFIEWLESA-NH_2

or may be a pharmaceutically acceptable salt or solvate thereof.

For the avoidance of doubt, in compounds of the third and fourth ~~aspects~~ embodiments of the ~~invention~~present disclosure, those positions which are not expressly stated to permit variability are intended to be fixed and thus only include the stated residue at those positions.

In all ~~aspects~~ embodiments of the ~~invention~~present disclosure, one or more of the amino acid side chains in the peptide X or Z (where present) may be conjugated to a lipophilic substituent.

Preferably, one or more of the amino acid side chains in the peptide X is conjugated to the lipophilic substituent.

A lipophilic substituent may have the formula Z^1 wherein Z^1 is a lipophilic moiety conjugated (covalently linked) directly to the side chain of the relevant residue of X or Z, or Z^1Z^2 where Z^1 is a lipophilic moiety, Z^2 is a spacer, and Z^1 is conjugated to the side chain of the residue of X or Z via Z^2.

Additionally or alternatively, one or more of the amino acid side chains in peptide X or Z (where present) is conjugated to a polymeric substituent.

In certain embodiments, the peptide X or X-Z carries only one lipophilic substituent and/or only one polymeric substituent.

Lipophilic and polymeric substituents are described in more detail below.

The lipophilic moiety and/or polymeric substituent may be conjugated to the side chain of any suitable residue. A lysine residue may be particularly suitable, e.g. a lysine residue at position 12 (if present) or 17.

Thus peptide X may have the formula:

H-Aib-QGTFTSDYSKYLDSK*AAHDFVEWLLS

HSQGTFTSDYSKYLDSK*AAHDFVEWLLSA

H-Aib-QGTFTSDYSKYLDEK*AAKDFIEWLLSA

H-Aib-QGTFTSDYSKYLDSK*AAHDFVEWLESA

HSQGTFTSDYSRYLDSK*AAEDFVEWLLRA

HSQGTFTSDYSKYLDSK*AAEDFVEWLLRA

HSQGTFTSDYSKYLDSK*AAHDFVEWLLS

HSQGTFTSDYSKYLDSK*AAHDFVEWLLR

HSQGTFTSDYSKYLDEK*AAHEFVEWLESA

H-Aib-QGTFTSDYSKYLDEK*RAKDFIEWLLS

HSQGTFTSDYSRYLDSK*AAHDFVEWLLSA

HSQGTFTSDYSKYLDSK*AAHDFVEWLLRA

H-Aib-QGTFTSDYSKYLDSK*AAHDFVEWLLSA

H-Aib-QGTFTSDYSKYLDEK*RAKDFIEWLLSA

H-Aib-QGTFTSDYSKYLDEK*AAKDFIEWLESA

H-Aib-QGTFTSDYSKYLDSK*AAEDFVEWLESA

H-Aib-HGTFTSDYSKYLESK*AAEEFIEWLESA

HSHGTFTSDYSKYLEEK*AAHEFIEWLESA

H-Aib-HGTFTSDYSKYLEEK*AAHEFVEWLESA

H-Aib-QGTFTSDYSKYLEEK*AAKDFIEWLESA

H-Aib-QGTFTSDYSKYLESK*AAEDFIEWLESA

HSQGTFTSDYSKYLEEK*AAKDFIEWLESA

H-Aib-QGTFTSDYSKYLESK*AAHDFVEWLESA

H-Aib-QGTFTSDYSKYLESK*AAEDFVEWLESA

H-DSer-QGTFTSDYSKYLDEK*AAKDFIEWLESA

where "*" indicates the position of a lipohilic or polymeric substituent, particularly a lipophilic substituent.

The compound of the ~~invention~~ present disclosure may have the formula:

H-H-Aib-QGTFTSDYSKYLDSK*AAHDFVEWLLS-OH

H-HSQGTFTSDYSKYLDSK*AAHDFVEWLLSA-OH

H-H-Aib-QGTFTSDYSKYLDEK*AAKDFIEWLLSA-NH_2

H-H-Aib-QGTFTSDYSKYLDSK*AAHDFVEWLESA-NH_2

H-HSQGTFTSDYSRYLDSK*AAEDFVEWLLRA-NH_2

H-HSQGTFTSDYSKYLDSK*AAEDFVEWLLRA-NH_2

H-HSQGTFTSDYSKYLDSK*AAHDFVEWLLS-NH_2

H-HSQGTFTSDYSKYLDSK*AAHDFVEWLLR-OH

H-HSQGTFTSDYSKYLDEK*AAHEFVEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLDEK*RAKDFIEWLLS-OH

H-HSQGTFTSDYSRYLDSK*AAHDFVEWLLSA-NH_2

H-HSQGTFTSDYSKYLDSK*AAHDFVEWLLRA-OH

H-H-Aib-QGTFTSDYSKYLDSK*AAHDFVEWLLSA-OH

H-H-Aib-QGTFTSDYSKYLDEK*RAKDFIEWLLSA-OH

H-H-Aib-QGTFTSDYSKYLDEK*AAKDFIEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLDSK*AAEDFVEWLESA-NH_2

H-H-Aib-HGTFTSDYSKYLESK*AAEEFIEWLESA-OH

H-HSHGTFTSDYSKYLEEK*AAHEFIEWLESA-OH

H-H-Aib-HGTFTSDYSKYLEEK*AAHEFVEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLEEK*AAKDFIEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLESK*AAEDFIEWLESA-NH_2

H-HSQGTFTSDYSKYLEEK*AAKDFIEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLESK*AAHDFVEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLESK*AAEDFVEWLESA-NH_2

H-H-DSer-QGTFTSDYSKYLDEK*AAKDFIEWLESA-NH_2

or may be a pharmaceutically acceptable salt or solvate thereof.

In certain embodiments, X has the formula:

H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLS

HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA

H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLLSA

H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLESA

HSQGTFTSDYSRYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA

HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA

HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLS

HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLR

HSQGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAHEFVEWLESA

H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-RAKDFIEWLLS

HSQGTFTSDYSRYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA

HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA

H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA

H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-RAKDFIEWLLSA

H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA

H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLESA

H-Aib-HGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEEFIEWLESA

HSHGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAHEFIEWLESA

H-Aib-HGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAHEFVEWLESA

H-Aib-QGTFTSDYSKYLEEK-(Hexadecanoyl-isoGlu)-AAKDFIEWLESA

H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEDFIEWLESA

HSQGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA

H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAHDFVEWLESA

H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEDFVEWLESA

H-DSer-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA

The compound of the ~~invention~~ present disclosure may be:

H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLS-OH (Compound 1)

H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-OH (Compound 2)

H-H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLLSA-NH_2 (Compound 4)

H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLESA-NH_2 (Compound 5)

H-HSQGTFTSDYSRYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA-NH_2 (Compound 6)

H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA-NH_2 (Compound 7)

H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLS-NH_2 (Compound 8)

H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLR-OH (Compound 9)

H-HSQGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAHEFVEWLESA-NH_2 (Compound 10)

H-H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-RAKDFIEWLLS-OH (Compound 11)

H-HSQGTFTSDYSRYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2 (Compound 12)

H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-OH (Compound 3)

H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-OH (Compound 13)

H-H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-RAKDFIEWLLSA-OH (Compound 14)

H-H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2 (Compound 15)

H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLESA-NH_2 (Compound 16)
H-Aib-HGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEEFIEWLESA-OH (Compound 17)
H-HSHGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAHEFIEWLESA-OH (Compound 18)
H-H-Aib-HGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAHEFVEWLESA-NH_2 (Compound 19)
H-H-Aib-QGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2 (Compound 20)
H-H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEDFIEWLESA-NH_2 (Compound 21)
H-HSQGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2 (Compound 22)
H-H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAHDFVEWLESA-NH_2 (Compound 23)
H-H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEDFVEWLESA-NH_2 (Compound 24)
H-H-DSer-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2 (Compound 25)

or may be a pharmaceutically acceptable salt or solvate thereof.

For those peptide sequences X or X-Z composed exclusively of naturally-occurring amino acids, the ~~invention~~ present disclosure further provides a nucleic acid (which may be DNA or RNA) encoding a peptide X or X-Z as defined herein. In an aspect, the present disclosure provides a nucleic acid encoding the amino acid sequence X or X-Z of a compound as disclosed herein. Also provided is an expression vector comprising such a nucleic acid in an aspect, and a host cell containing such a nucleic acid or expression vector. In another aspect, the present disclosure provides a host cell comprising such a nucleic acid or expression vector and capable of expressing and optionally secreting a compound having the amino acid sequence X or X-Z. The host cell is typically capable of expressing and optionally secreting the encoded peptide X or X-Z.

The compounds of the ~~invention~~ present disclosure are glucagon analogue peptides. References herein to a glucagon analogue peptide should be construed as references to a compound of the ~~invention~~ present disclosure or to a peptide X or X-Z as the context requires. Reference to a compound of the ~~invention~~ present disclosure should be taken to include any pharmaceutically acceptable salt (e.g. an acetate or chloride salt) or solvate thereof, unless otherwise stated or excluded by context.

The ~~invention~~ present disclosure provides a composition comprising a compound of the ~~invention~~ present disclosure as defined herein (including pharmaceutically acceptable salts or solvates thereof, as already described), a nucleic acid encoding a peptide X or X-Z, an expression vector comprising such a nucleic acid, or a host cell containing such a nucleic acid or expression vector, in admixture with a carrier. In an aspect, the present disclosure provides a composition comprising a compound as defined herein in admixture with a carrier. In preferred embodiments, the composition is a pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier. The glucagon analogue peptide may be in the form of a pharmaceutically acceptable salt of the glucagon analogue.

The compounds described herein find use, *inter alia*, in preventing weight gain or promoting weight loss. By "preventing" is meant inhibiting or reducing when compared to the absence of treatment, and is not necessarily meant to imply complete cessation of weight gain. The peptides may cause a decrease in food intake and/or increased energy expenditure, resulting in the observed effect on body weight. Independently of their effect on body weight, the compounds of the ~~invention~~ present disclosure may have a beneficial effect on glucose control and/or on circulating cholesterol levels, being capable of lowering circulating LDL levels and increasing HDL/LDL ratio. Thus the compounds of the present disclosure ~~invention~~ can be used for direct or indirect therapy of any condition caused or characterised by excess body weight, such as the treatment and/or prevention of obesity, morbid obesity, obesity linked inflammation, obesity linked gallbladder disease, obesity induced sleep apnea. They may also be used for the prevention of conditions caused or characterised by inadequate glucose control or dyslipidaemia (e.g. elevated LDL levels or reduced HDL/LDL ratio), diabetes (especially Type 2 diabetes), metabolic syndrome, hypertension, atherogenic dyslipidemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke or microvascular disease. Their effects in these conditions may be as a result of or associated with their effect on body weight, or may be independent thereof.

In an aspect, the present disclosure ~~The invention~~ also provides a compound as disclosed herein ~~of the invention~~ for use in a method of medical treatment, particularly for use in a method of treatment of a condition as described above.

The ~~invention~~ present disclosure also provides the use of a compound of the ~~invention~~ present disclosure in the preparation of a medicament for the treatment of a condition as described above. In an aspect, the present disclosure provides use of a compound as disclosed herein in the manufacture of a medicament for preventing weight gain or promoting weight loss. In another aspect, the present disclosure provides use of a compound as disclosed herein in the manufacture of a medicament for lowering circulating LDL levels, and/or increasing HDL/LDL ratio. In another aspect, the present disclosure provides use of a compound as disclosed herein in the manufacture of a medicament for treatment of a condition caused or characterised by excess body weight. In another aspect, the present disclosure provides use of a compound as disclosed herein in the manufacture of a medicament for prevention or treatment of obesity, morbid obesity, morbid obesity prior to surgery, obesity linked inflammation, obesity linked gallbladder disease, obesity induced sleep apnea, diabetes, metabolic syndrome, hypertension, atherogenic dyslipidimia, atherosclerois, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke or microvascular disease.

The compound of the present disclosure ~~invention~~ may be administered as part of a combination therapy with an agent for treatment of diabetes, obesity, dyslipidaemia or hypertension.

In such cases, the two active agents may be given together or separately, and as part of the same pharmaceutical formulation or as separate formulations.

Thus the compound of the present disclosure ~~invention~~ can be used in combination with an anti-diabetic agent including but not limited to a biguanide (e.g. metformin), a sulfonylurea, a meglitinide or glinide (e.g. nateglinide), a DPP-IV inhibitor, a glitazone, an insulin, or an insulin analogue. Examples of insulin analogues include but are not limited to Lantus™, Novorapid™, Humalog™, Novomix™, Actraphane HM™, Levemir™ and Apidra™.

The compound can further be used in combination with an anti-obesity agent including but not limited to a glucagon-like peptide receptor 1 agonist, peptide YY or analogue thereof,

cannabinoid receptor 1 antagonist, lipase inhibitor, melanocortin receptor 4 agonist, or melanin concentrating hormone receptor 1 antagonist.

The compound can further be used in combination with an anti-hypertension agent including but not limited to an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, diuretic, beta-blocker, or calcium channel blocker.

The compound can be used in combination with an anti-dyslipidaemia agent including but not limited to a statin, a fibrate, a niacin or a cholesterol absorbtion inhibitor.

Thus the present disclosure ~~invention~~ further provides a composition or therapeutic kit comprising a compound of the present disclosure ~~invention~~ and for example an anti-diabetic agent, anti-obesity agent, anti-hypertension agent or anti-dyslipidaemia agent as described above. In an aspect, the present disclosure provides a therapeutic kit comprising a compound as disclosed herein or a composition as disclosed herein. Also provided is such a composition or therapeutic kit for use in a method of medical treatment, especially for treament of a condition as described above.

The compound of the present disclosure ~~invention~~ may be made by synthetic chemistry. Accordingly, in an aspect, the ~~invention~~ present disclosure provides a method of synthesis of a compound as disclosed herein~~of the invention~~.

As already described, the present disclosure ~~invention~~ extends to nucleic acids encoding the peptide sequence X or X-Z, as well as expression vectors comprising the above-described nucleic acid sequence (optionally operably linked to sequences to direct its expression) and host cells containing the nucleic acids or expression vectors. Preferably the host cells are capable of expressing and optionally secreting the compound of the present disclosure~~invention~~.

In an aspect, ~~T~~the present ~~invention~~ disclosure provides a method of producing a compound as disclosed herein~~of the invention~~, the method comprising culturing the host cells under conditions suitable for expressing the peptide sequence X or X-Z and purifying the compound thus produced. This is particularly useful where the peptide contains only naturally-occurring amino acids.

Where the compound of the present disclosure ~~invention~~ contains one or more non-naturally-occurring amino acids, the method may comprise expressing a peptide sequence containing one or more differences from the sequence X or X-Z, optionally purifying the compund thus produced, and adding or modifying one or more amino acids to produce a compound of the present disclosure ~~invention~~ or a compound comprising the amino acid sequence X or X-Z. In an aspect, the present disclosure provides a method of producing a compound as discloed herein, the method comprising expressing a peptide sequence containing one or more differences from the sequence X or X-Z in a host cell, optionally purifying the compund thus produced, and adding or modifying one or more amino acids to produce the compound.

Whichever method is used to produce the compound of the present disclosure~~invention~~, it may comprise one or more further steps of modifying the sequence X or X-Z, especially to introduce one or more lipophilic and/or polymeric moieties as defined elsewhere in this specification.

The present disclosure ~~invention~~ further provides a nucleic acid of the present disclosure~~invention~~, an expression vector of the present disclosure~~invention~~, or a host cell capable of expressing and optionally secreting a compound of the invention, for use in a method of medical treatment. It will be understood that the nucleic acid, expression vector and host cells may be used for treatment of any of the disorders described herein which may be treated with the compounds of the present disclosure ~~invention~~ themselves. References to a therapeutic composition comprising a compound of the invention, administration of a compound of the present disclosure~~invention~~, or any therapeutic use thereof, should therefore be construed to encompass the equivalent use of a nucleic acid, expression vector or host cell of the present disclosure~~invention~~, except where the context demands otherwise.

DETAILED DESCRIPTION OF THE INVENTION

Throughout this specification, the conventional one letter and three letter codes for naturally occurring amino acids are used, as well as generally accepted three letter codes for other amino acids, such as Aib (α-aminoisobutyric acid), Hse (homoserine), Orn (ornithine), Dbu (2,4-diaminobutyric acid), Dpr (2,3-diaminopropanoic acid).

Glucagon is a 29-amino acid peptide that corresponds to amino acids 53 to 81 of pre-proglucagon and has the sequence His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr (SEQ ID NO: 26). Oxyntomodulin (OXM) is a 37 amino acid peptide which includes the complete 29 amino acid sequence of glucagon with an octapeptide carboxyterminal extension (amino acids 82 to 89 of pre-proglucagon, having the sequence Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala (SEQ ID NO: 27) and termed "intervening peptide 1" or IP-1; the full sequence of human oxyntomodulin is thus His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala) (SEQ ID NO: 28). The major biologically active fragment of GLP-1 is produced as a 30-amino acid, C-terminally amidated peptide that corresponds to amino acids 98 to 127 of pre-proglucagon.

The term "native glucagon" thus refers to native human glucagon having the sequence H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-OH (SEQ ID NO: 26).

Amino acids within the sequence X of the compounds of the invention can be considered to be numbered consecutively from 1 to 29 in the conventional N-terminal to C-terminal direction. Reference to a "position" within X should be construed accordingly, as should reference to positions within native human glucagon and other molecules.

A compound of the invention may comprise a C-terminal peptide sequence Z of 1-20 amino acids, for example to stabilise the conformation and/or secondary structure of the glucagon

CLAIMS

1. A compound having the formula:

R^1-X-Z-R^2

wherein

R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2;

X is a peptide which has the formula:

HSQGTFTSDYSKYLDSKAAEDFVEWLLRA (SEQ ID NO: 7)

and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 having the formula:

H-HSQGTFTSDYSKYLDSKAAEDFVEWLLRA-NH_2

or a pharmaceutically acceptable salt or solvate thereof.

3. A compound according to claim 1 or claim 2 wherein one or more of the amino acid side chains in the peptide X or Z is conjugated to a lipophilic substituent.

4. A compound according to claim 3 wherein peptide X has the formula:

HSQGTFTSDYSKYLDSK*AAEDFVEWLLRA

where "*" indicates the position of a lipophilic substituent.

5. A compound according to claim 4 having the formula:

H-HSQGTFTSDYSKYLDSK*AAEDFVEWLLRA-NH_2

or a pharmaceutically acceptable salt or solvate thereof,

where "*" indicates the position of a lipophilic substituent.

6. A compound according to claim 4 wherein peptide X has the formula:

HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA.

7. A compound according to claim 6 having the formula:

H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA-NH_2 (Compound 7)

or a pharmaceutically acceptable salt or solvate thereof.

8. A composition comprising a compound according to any one of claims 1 to 7 in admixture with a carrier.

9. A composition according to claim 8 wherein the composition is a pharmaceutical composition, and the carrier is a pharmaceutically acceptable carrier.

10. A compound according to any one of claims 1 to 7 for use in medical treatment.

11. Use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for preventing weight gain or promoting weight loss.

12. Use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for lowering circulating LDL levels, and/or increasing HDL/LDL ratio.

13. Use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for treatment of a condition caused or characterised by excess body weight.

14. Use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for prevention or treatment of obesity, morbid obesity, morbid obesity prior to surgery, obesity linked inflammation, obesity linked gallbladder disease, obesity induced sleep apnea, diabetes, metabolic syndrome, hypertension, atherogenic dyslipidimia, atherosclerois, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke or microvascular disease.

15. Use according to any one of claims 11 to 14 wherein the compound is to be administered as part of a combination therapy together with an agent for treatment of diabetes, obesity, dyslipidemia or hypertension.

16. Use according to claim 15 wherein the agent for treatment of diabetes is a biguanide (e.g. metformin), a sulfonylurea, a meglitinide or glinide (e.g. nateglinide), a DPP-IV inhibitor, a glitazone, a different GLP-1 agonist, an insulin or an insulin analogue.

17. Use according to claim 15, wherein the agent for treatment of obesity is a glucagon-like peptide receptor 1 agonist, peptide YY receptor agonist or analogue thereof, cannabinoid receptor 1 antagonist, lipase inhibitor, melanocortin receptor 4 agonist, or melanin concentrating hormone receptor 1 antagonist.

18. Use according to claim 15 wherein the agent for treatment of hypertension is an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, diuretic, beta-blocker, or calcium channel blocker.

19. Use according to claim 15 wherein the agent for treatment of dyslipidaemia is a statin, a fibrate, a niacin and/or a cholesterol absorbtion inhibitor.

20. A nucleic acid encoding the amino acid sequence X or X-Z of a compound according to any of claims 1 to 7.

21. An expression vector comprising the nucleic acid sequence of claim 20.

22. A host cell comprising the nucleic acid of claim 20 or the expression vector of claim 21 and capable of expressing and optionally secreting a compound having the amino acid seqeuence X or X-Z.

23. A therapeutic kit comprising a compound according to any of claims 1 to 7 or a composition according to claim 8 or claim 9.

24. A method of synthesis of a compound according to any one of claims 1 to 7.

25. A method of producing a compound according to any one of claims 1 to 7, the method comprising culturing a host cell according to claim 22 under conditions suitable for expressing the peptide sequence X or X-Z and purifying the compound thus produced.

26. A method of producing a compound according to any one of claims 1 to 7, the method comprising expressing a peptide sequence containing one or more differences from the sequence X or X-Z in a host cell, optionally purifying the compund thus produced, and adding or modifying one or more amino acids to produce the compound.

27. A method according to claim 25 or claim 26 comprising modifying the sequence X or X-Z to introduce one or more lipophilic moieties.

CLAIMS

1. A compound having the formula.

R^1-X-Z-R^2

wherein

R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2;

X is a peptide which consists of the sequence:

H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLLSA (SEQ ID NO: 4)

H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLESA (SEQ ID NO: 5)

HSQGTFTSDYSRYLDSKAAEDFVEWLLRA (SEQ ID NO: 6)

HSQGTFTSDYSKYLDSKAAEDFVEWLLRA (SEQ ID NO: 7)

HSQGTFTSDYSKYLDSKAAHDFVEWLLS (SEQ ID NO: 8)

HSQGTFTSDYSKYLDSKAAHDFVEWLLR (SEQ ID NO: 9)

HSQGTFTSDYSKYLDEKAAHEFVEWLESA (SEQ ID NO: 10)

H-Aib-QGTFTSDYSKYLDEKRAKDFIEWLLS (SEQ ID NO: 11) or

HSQGTFTSDYSRYLDSKAAHDFVEWLLSA (SEQ ID NO. 12)

H-Aib-HGTFTSDYSKYLESKAAEEFIEWLESA (SEQ ID NO: 17)

HSHGTFTSDYSKYLEEKAAHEFIEWLESA (SEQ ID NO: 18)

H-Aib-HGTFTSDYSKYLEEKAAHEFVEWLESA (SEQ ID NO: 19)

and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound which consists of the formula:

H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-OH (SEQ ID NO. 2)

H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-OH (SEQ ID NO: 3)

H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-OH (SEQ ID NO: 13)

or a pharmaceutically acceptable salt or solvate thereof.

3. A compound having the formula:

R^1-X-Z-R^2

wherein

R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2;

X is a peptide of SEQ ID NO: 15:

H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLESA (SEQ ID NO: 15)

or which differs from SEQ ID NO: 15 at up to three of the following positions whereby, if different from SEQ ID NO: 15:

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the residue at position 2 is selected from Ser and D-Ser
the residue at position 3 is selected from His and Hse
the residue at position 12 is Arg
the residue at position 15 is Glu
the residue at position 16 is Ser
the residue at position 18 is Arg
the residue at position 20 is selected from His and Glu
the residue at position 21 is Glu
the residue at position 23 is Val
the residue at position 28 is selected from Arg and Glu
the residue at position 29 is absent;
and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

4. A compound according to claim 3 wherein the residue at position 20 is His.

5. A compound according to claim 3 having the formula:
R^1-X-Z-R^2
wherein
R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2;
X is a peptide of SEQ ID NO: 15:
H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLESA (SEQ ID NO: 15)
or which differs from SEQ ID NO: 15 at one or both of the following positions whereby, if different from SEQ ID NO: 15:
the residue at position 21 is Glu
the residue at position 23 is Val
and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

6. A compound having the formula:
R^1-X-Z-R^2
wherein
R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2;
X is a peptide of SEQ ID NO: 16:
H-Aib-QGTFTSDYSKYLDSKAAEDFVEWLESA (SEQ ID NO: 16)

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or which differs from SEQ ID NO: 16 at up to three of the following positions whereby, if different from SEQ ID NO: 16:
the residue at position 2 is selected from Ser and D-Ser
the residue at position 3 is selected from His and Hse
the residue at position 12 is Arg
the residue at position 15 is Glu
the residue at position 16 is Glu
the residue at position 18 is Arg
the residue at position 20 is selected from Lys and His
the residue at position 21 is Glu
the residue at position 23 is Ile
the residue at position 28 is selected from Arg and Glu
the residue at position 29 is absent
and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

7. A compound according to claim 6 having the formula:
R^1-X-Z-R^2
wherein
R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2;
X is a peptide of SEQ ID NO: 16:
H-Aib-QGTFTSDYSKYLDSKAAEDFVEWLESA (SEQ ID NO: 16)
or which differs from SEQ ID NO: 16 at one or both of the following positions whereby, if different from SEQ ID NO: 16:
the residue at position 21 is Glu
the residue at position 23 is Ile
and Z is absent or is a sequence of 1-20 amino acid units independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt or solvate thereof.

8. A compound according to any of claims 3 to 7 wherein X is a peptide which consists of the sequence:
H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLESA (SEQ ID NO: 15)
H-Aib-QGTFTSDYSKYLDSKAAEDFVEWLESA (SEQ ID NO: 16)
H-Aib-QGTFTSDYSKYLEEKAAKDFIEWLESA (SEQ ID NO: 20)
H-Aib-QGTFTSDYSKYLESKAAEDFIEWLESA (SEQ ID NO: 21)

HSQGTFTSDYSKYLEEKAAKDFIEWLESA (SEQ ID NO: 22)

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H-Aib-QGTFTSDYSKYLESKAAHDFVEWLESA (SEQ ID NO: 23)

H-Aib-QGTFTSDYSKYLESKAAEDFVEWLESA (SEQ ID NO: 24) or
H-DSer-QGTFTSDYSKYLDEKAAKDFIEWLESA (SEQ ID NO: 25).

9. A compound according to any one of claims 1 to 8 having the formula:

H-H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLLSA-NH_2
H-H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLESA-NH_2
H-HSQGTFTSDYSRYLDSKAAEDFVEWLLRA-NH_2
H-HSQGTFTSDYSKYLDSKAAEDFVEWLLRA-NH_2
H-HSQGTFTSDYSKYLDSKAAHDFVEWLLS-NH_2
H-HSQGTFTSDYSKYLDSKAAHDFVEWLLR-OH
H-HSQGTFTSDYSKYLDEKAAHEFVEWLESA-NH_2
H-H-Aib-QGTFTSDYSKYLDEKRAKDFIEWLLS-OH
H-HSQGTFTSDYSRYLDSKAAHDFVEWLLSA-NH_2
H-H-Aib-QGTFTSDYSKYLDEKAAKDFIEWLESA-NH_2
H-H-Aib-QGTFTSDYSKYLDSKAAEDFVEWLESA-NH_2
H-H-Aib-HGTFTSDYSKYLESKAAEEFIEWLESA-OH
H-HSHGTFTSDYSKYLEEKAAHEFIEWLESA-OH
H-H-Aib-HGTFTSDYSKYLEEKAAHEFVEWLESA-NH_2
H-H-Aib-QGTFTSDYSKYLEEKAAKDFIEWLESA-NH_2
H-H-Aib-QGTFTSDYSKYLESKAAEDFIEWLESA-NH_2

H-HSQGTFTSDYSKYLEEKAAKDFIEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLESKAAHDFVEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLESKAAEDFVEWLESA-NH_2
H-H-DSer-QGTFTSDYSKYLDEKAAKDFIEWLESA-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

10. A compound according to any one of claims 1 to 8 wherein one or more of the amino acid side chains in the peptide X or Z is conjugated to a lipophilic substituent.

11. A compound according to any one of claims 1 to 8 or claim 10 wherein one or more of the amino acid side chains in the peptide X or Z is conjugated to a polymeric substituent.

12. A compound according to claim 10 or claim 11 wherein peptide X consists of the sequence:
H-Aib-QGTFTSDYSKYLDEK*AAKDFIEWLLSA
H-Aib-QGTFTSDYSKYLDSK*AAHDFVEWLESA

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HSQGTFTSDYSRYLDSK*AAEDFVEWLLRA
HSQGTFTSDYSKYLDSK*AAEDFVEWLLRA
HSQGTFTSDYSKYLDSK*AAHDFVEWLLS
HSQGTFTSDYSKYLDSK*AAHDFVEWLLR
HSQGTFTSDYSKYLDEK*AAHEFVEWLESA
H-Aib-QGTFTSDYSKYLDEK*RAKDFIEWLLS
HSQGTFTSDYSRYLDSK*AAHDFVEWLLSA
H-Aib-QGTFTSDYSKYLDEK*AAKDFIEWLESA
H-Aib-QGTFTSDYSKYLDSK*AAEDFVEWLESA
H-Aib-HGTFTSDYSKYLESKAAEEFIEWLESA
HSHGTFTSDYSKYLEEKAAHEFIEWLESA
H-Aib-HGTFTSDYSKYLEEKAAHEFVEWLESA
H-Aib-QGTFTSDYSKYLEEK*AAKDFIEWLESA
H-Aib-QGTFTSDYSKYLESK*AAEDFIEWLESA

HSQGTFTSDYSKYLEEK*AAKDFIEWLESA

H-Aib-QGTFTSDYSKYLESK*AAHDFVEWLESA

H-Aib-QGTFTSDYSKYLESK*AAEDFVEWLESA
H-DSer-QGTFTSDYSKYLDEK*AAKDFIEWLESA
where "*" indicates the position of a lipophilic or polymeric substituent.

13. A compound according to claim 12 having the formula:
H-H-Aib-QGTFTSDYSKYLDEK*AAKDFIEWLLSA-NH_2
H-H-Aib-QGTFTSDYSKYLDSK*AAHDFVEWLESA-NH_2
H-HSQGTFTSDYSRYLDSK*AAEDFVEWLLRA-NH_2
H-HSQGTFTSDYSKYLDSK*AAEDFVEWLLRA-NH_2
H-HSQGTFTSDYSKYLDSK*AAHDFVEWLLS-NH_2
H-HSQGTFTSDYSKYLDSK*AAHDFVEWLLR-OH
H-HSQGTFTSDYSKYLDEK*AAHEFVEWLESA-NH_2
H-H-Aib-QGTFTSDYSKYLDEK*RAKDFIEWLLS-OH
H-HSQGTFTSDYSRYLDSK*AAHDFVEWLLSA-NH_2
H-H-Aib-QGTFTSDYSKYLDEK*AAKDFIEWLESA-NH_2
H-H-Aib-QGTFTSDYSKYLDSK*AAEDFVEWLESA-NH_2
H-H-Aib-HGTFTSDYSKYLESK*AAEEFIEWLESA-OH
H-HSHGTFTSDYSKYLEEK*AAHEFIEWLESA-OH
H-H-Aib-HGTFTSDYSKYLEEK*AAHEFVEWLESA-NH_2
H-H-Aib-QGTFTSDYSKYLEEK*AAKDFIEWLESA-NH_2
H-H-Aib-QGTFTSDYSKYLESK*AAEDFIEWLESA-NH_2

H-HSQGTFTSDYSKYLEEK*AAKDFIEWLESA-NH_2

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H-H-Aib-QGTFTSDYSKYLESK*AAHDFVEWLESA-NH_2

H-H-Aib-QGTFTSDYSKYLESK*AAEDFVEWLESA-NH_2
H-H-DSer-QGTFTSDYSKYLDEK*AAKDFIEWLESA-NH_2
or a pharmaceutically acceptable salt or solvate thereof,
where "*" indicates the position of a lipophilic or polymeric substituent.

14. A compound according to claim 12 wherein peptide X consists of the formula:
H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLLSA
H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLESA
HSQGTFTSDYSRYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA
HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA
HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLS
HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLR
HSQGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAHEFVEWLESA
H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-RAKDFIEWLLS
HSQGTFTSDYSRYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA

H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA
H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLESA
H-Aib-HGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEEFIEWLESA
HSHGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAHEFIEWLESA
H-Aib-HGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAHEFVEWLESA
H-Aib-QGTFTSDYSKYLEEK-(Hexadecanoyl-isoGlu)-AAKDFIEWLESA
H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEDFIEWLESA

HSQGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA

H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAHDFVEWLESA

H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEDFVEWLESA
H-DSer-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA

15. A compound according to claim 14 having the formula:
H-H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLLSA-NH_2 (Compound 4)
H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLESA-NH_2 (Compound 5)
H-HSQGTFTSDYSRYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA-NH_2 (Compound 6)
H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLLRA-NH_2 (Compound 7)
H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLS-NH_2 (Compound 8)
H-HSQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLR-OH (Compound 9)
H-HSQGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAHEFVEWLESA-NH_2 (Compound 10)

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H-H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-RAKDFIEWLLS-OH (Compound 11)
H-HSQGTFTSDYSRYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2 (Compound 12)
H-H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2 (Compound 15)
H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAEDFVEWLESA-NH_2 (Compound 16)
H-H-Aib-HGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEEFIEWLESA-OH (Compound 17)
H-HSHGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAHEFIEWLESA-OH (Compound 18)
H-H-Aib-HGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAHEFVEWLESA-NH_2 (Compound 19)
H-H-Aib-QGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2 (Compound 20)
H-H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEDFIEWLESA-NH_2 (Compound 21)
H-HSQGTFTSDYSKYLEE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2 (Compound 22)
H-H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAHDFVEWLESA-NH_2 (Compound 23)
H-H-Aib-QGTFTSDYSKYLES-K(Hexadecanoyl-isoGlu)-AAEDFVEWLESA-NH_2 (Compound 24)
H-H-DSer-QGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2 (Compound 25)
or a pharmaceutically acceptable salt or solvate thereof.

16. A composition comprising a compound according to any one of claims 1 to 15 in admixture with a carrier.

17. A composition according to claim 16 wherein the composition is a pharmaceutical composition, and the carrier is a pharmaceutically acceptable carrier.

18. A compound according to any one of claims 1 to 15 for use in a method of medical treatment.

19. A compound according to any one of claims 1 to 15 for use in a method of preventing weight gain or promoting weight loss in an individual in need thereof.

20. A compound according to any one of claims 1 to 15 for use in a method of lowering circulating LDL levels, and/or increasing HDL/LDL ratio in an individual in need thereof.

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21. A compound according to any one of claims 1 to 15 for use in a method of treatment of a condition caused or characterised by excess body weight.

22. A compound according to any one of claims 1 to 15 for use in a method of prevention or treatment of obesity, morbid obesity, morbid obesity prior to surgery, obesity linked inflammation, obesity linked gallbladder disease, obesity induced sleep apnea, diabetes, metabolic syndrome, hypertension, atherogenic dyslipidimia, atherosclerois, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke or microvascular disease.

23. A compound for use according to any one of claims 18 to 22 wherein the compound is administered as part of a combination therapy together with an agent for treatment of diabetes, obesity, dyslipidemia or hypertension.

24. A compound for use according to claim 23 wherein the agent for treatment of diabetes is a biguanide (e.g. metformin), a sulfonylurea, a meglitinide or glinide (e.g. nateglinide), a DPP-IV inhibitor, a glitazone, a different GLP-1 agonist, an insulin or an insulin analogue.

25. A compound for use according to claim 23, wherein the agent for treatment of obesity is a glucagon-like peptide receptor 1 agonist, peptide YY receptor agonist or analogue thereof, cannabinoid receptor 1 antagonist, lipase inhibitor, melanocortin receptor 4 agonist, or melanin concentrating hormone receptor 1 antagonist

26. A compound for according to claim 23 wherein the agent for treatment of hypertension is an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, diuretic, beta-blocker, or calcium channel blocker.

27. A compound for use according to claim 23 wherein the agent for treatment of dyslipidaemia is a statin, a fibrate, a niacin and/or a cholesterol absorbtion inhibitor.

28. A nucleic acid encoding the amino acid sequence X or X-Z of a compound according to any of claims 1 to 15.

29. An expression vector comprising the nucleic acid sequence of claim 28.

30. A host cell comprising the nucleic acid of claim 28 or the expression vector of claim 29 and capable of expressing and optionally secreting a compound having the amino acid seqeuence X or X-Z.

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31. A therapeutic kit comprising a compound according to any of claims 1 to 15 or a composition according to claims 14 or 15.

32. A method of synthesis of a compound according to any one of claims 1 to 15.

33. A method of producing a compound according to any one of claims 1 to 15, the method comprising culturing a host cell according to claim 30 under conditions suitable for expressing the peptide sequence X or X-Z and purifying the compound thus produced.

34. A method of producing a compound according to any one of claims 1 to 15, the method comprising expressing a peptide sequence containing one or more differences from the sequence X or X-Z in a host cell, optionally purifying the compund thus produced, and adding or modifying one or more amino acids to produce the compound.

35. A method according to claim 33 or claim 34 comprising modifying the sequence X or X-Z to introduce one or more lipophilic and/or polymeric moieties.

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