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~~embodiment, 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 embodiment, the 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 embodiment, 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 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

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.

In a first aspect, there is provided a compound having the formula:

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

or a pharmaceutically acceptable salt or solvate thereof.

For those peptide sequences X or X-Z composed exclusively of naturally-occurring amino acids, the 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~~ the first aspect. 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 seqeuence ~~X or X-Z~~according to the first aspect. The host cell is typically capable of expressing and optionally secreting the encoded peptide X or X-Z.

The compounds of the present disclosure are glucagon analogue peptides. References herein to a glucagon analogue peptide should be construed as references to a compound of the present disclosure or to a peptide X or X-Z as the context requires. Reference to a compound of the 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 present disclosure provides a composition comprising a compound of the 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~~ the first aspect 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 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 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 also provides a compound as disclosed ~~herein~~ the first aspect for use in a method of medical treatment, particularly for use in a method of treatment of a condition as described above.

The present disclosure also provides the use of a compound of the 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~~ the first aspect 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~~ the first aspect 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~~ the first aspect 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~~ the first aspect 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 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 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 further provides a composition or therapeutic kit comprising a compound of the present disclosure 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~~ the first aspect 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 may be made by synthetic chemistry. Accordingly, in an aspect, the present disclosure provides a method of synthesis of a compound as disclosed ~~herein~~ the first aspect.

As already described, the present disclosure 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.

In an aspect, the present disclosure provides a method of producing a compound as disclosed ~~herein~~ the first aspect, the method comprising culturing the host cells under conditions suitable for expressing the peptide sequence according to the first aspect ~~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 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 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 disclosed ~~herein~~ the first aspect, the method comprising expressing a peptide sequence containing one or more differences from the sequence according to the first aspect ~~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, 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.

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~~1. 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~~2. A composition comprising a compound according to ~~any one of~~ claims 1 ~~to 7~~ in admixture with a carrier.

~~93~~. A composition according to claim ~~8~~ 2 wherein the composition is a pharmaceutical composition, and the carrier is a pharmaceutically acceptable carrier.

~~104~~. A compound according to any one of claims 1 to ~~7~~ 3 for use in medical treatment.

~~115~~. Use of a compound according to any one of claims 1 to ~~7~~ 3 in the manufacture of a medicament for preventing weight gain or promoting weight loss.

~~126~~. Use of a compound according to any one of claims 1 to ~~7~~ 3 in the manufacture of a medicament for lowering circulating LDL levels, and/or increasing HDL/LDL ratio.

~~137~~. Use of a compound according to any one of claims 1 to ~~7~~ 3 in the manufacture of a medicament for treatment of a condition caused or characterised by excess body weight.

~~148~~. Use of a compound according to any one of claims 1 to ~~7~~ 3 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.

~~159~~. Use according to any one of claims ~~11~~ 5 to ~~14~~ 8 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.

~~1610~~. Use according to claim ~~15~~ 9 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.

~~1711~~. Use according to claim ~~15~~9, 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.

~~1812~~. Use according to claim ~~15~~ 9 wherein the agent for treatment of hypertension is an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, diuretic, beta-blocker, or calcium channel blocker.

~~1913~~. Use according to claim ~~15~~ 9 wherein the agent for treatment of dyslipidaemia is a statin, a fibrate, a niacin and/or a cholesterol absorbtion inhibitor.

~~20~~14. A nucleic acid encoding the amino acid sequence ~~X or X-Z~~ of a compound according to ~~any of~~ claims ~~1 to 7~~.

~~21~~15. An expression vector comprising the nucleic acid sequence of claim ~~20~~14.

~~22~~16. A host cell comprising the nucleic acid of claim ~~20~~14 or the expression vector of claim ~~21~~15 and capable of expressing and optionally secreting a compound having the amino acid seqeuence ~~X or X-Z~~ according to claim 1.

~~23~~17. A therapeutic kit comprising a compound according to ~~any of~~ claims ~~1 to 7~~ or a composition according to claim ~~8~~2 or claim ~~9~~3.

~~24~~18. A method of synthesis of a compound according to ~~any one of~~ claims ~~1 to 7~~.

~~25~~19. 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~~16 under conditions suitable for expressing the peptide sequence according to claim 1 ~~X or X-Z~~ and purifying the compound thus produced.

~~26~~20. 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 according to claim 1 ~~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~~21. A method according to claim ~~25~~19 or claim ~~26~~20 comprising modifying the sequence according to claim 1 ~~X or X-Z~~ to introduce one or more lipophilic moieties.