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(57) **Abrégé/Abstract:**

The invention relates to the treatment of cardiac dysfunction. In particular, certain compounds, believed to be glucagon-GLP-1 dual agonist compounds, exert a positive inotropic effect while preserving the energy balance of the heart, and so may be superior to known inotropic agents such as dobutamine, norepinephrine and glucagon.



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(54) Title: TREATMENT OF CARDIAC CONDITIONS

(57) Abstract: The invention relates to the treatment of cardiac dysfunction. In particular, certain compounds, believed to be glucagon-GLP-1 dual agonist compounds, exert a positive inotropic effect while preserving the energy balance of the heart, and so may be superior to known inotropic agents such as dobutamine, norepinephrine and glucagon.



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TREATMENT OF CARDIAC CONDITIONS

FIELD OF THE INVENTION

The invention relates to the use of compounds, typically glucagon-GLP-1 dual agonist
5 compounds, as inotropic agents for the treatment of cardiac dysfunction.

BACKGROUND OF THE INVENTION

Positive inotropic agents are used to improve hemodynamic parameters and thereby relieve
symptoms and protect end-organs in patients with myocardial infarction, heart failure or
10 cardiogenic shock. The heart requires large amounts of chemical energy to support systolic and
diastolic work. Therefore, by increasing cardiac work, inotropic agents also increase cardiac
energy demand. However, the failing or diseased heart is usually energy starved (Ingwall, JS and
Weiss, RG. *Circ Res.* 2004; 95: 135-145), and the use of inotropic agents may therefore result in
energy depletion and ultimately increased mortality (Hamad, E et al. *American Journal of*
15 *Cardiovascular Drugs.* 2007; 7: 235-248; White, CM. *J Clin Pharmacol.* 1999; 39: 442-447).

Preproglucagon is a 158 amino acid precursor polypeptide that is differentially processed in the
tissues to form a number of structurally related proglucagon-derived peptides, including glucagon
(Glu), glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), and oxyntomodulin
20 (OXM). These molecules are involved in a wide variety of physiological functions, including
glucose homeostasis, insulin secretion, gastric emptying and intestinal growth, as well as
regulation of food intake.

A major biologically active fragment of GLP-1 is produced as a 30-amino acid, C-terminally
25 amidated peptide that corresponds to amino acids 98 to 127 of preproglucagon. GLP-1 is
produced in the intestinal epithelial endocrine L-cells by differential processing of proglucagon, a
hormone normally secreted by neuroendocrine cells of the gut in response to food. It increases
insulin release by the beta cells even in subjects with long-standing type 2 diabetes. GLP-1
treatment has an advantage over insulin therapy because GLP-1 stimulates endogenous insulin
secretion, which turns off when blood glucose levels drop. GLP-1 promotes euglycemia by
30 increasing insulin release and synthesis, inhibiting glucagon release, and decreasing gastric
emptying). GLP-1 (Holst, JJ. *Physiol Rev.* 2007; 87: 1409-1439), has been found to increase
myocardial glucose uptake in an insulin-independent manner in normal and post-ischemic rat
hearts (Zhao, T et al. *J Pharmacol Exp Ther.* 2006; 317: 1106-1113), isolated mouse hearts (Ban,
35 K et al. *Circulation.* 2008; 117: 2340-2350), as well as in conscious dogs with dilated
cardiomyopathy (Nikolaidis, LA et al. *Am J Physiol Heart Circ Physiol.* 2005; 289: H2401-H2408;
Nikolaidis, LA et al. *Circulation.* 2004; 110: 955-961).

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(Compound 1) Glucagon helps maintain the level of glucose in the blood by binding to glucagon receptors on hepatocytes, causing the liver to release glucose – stored in the form of glycogen – through glycogenolysis. As these stores become depleted, glucagon stimulates the liver to synthesize additional glucose by gluconeogenesis. This glucose is released into the bloodstream, preventing the development of hypoglycemia.

Glucagon has a well documented inotropic effect on the heart (Buse, MG et al. *J Biol Chem.* 1973; 248: 697-706; Farah, A and Tuttle, R. *J Pharmacol Exp Ther.* 1960; 129: 49-55; Levey, GS and Epstein, SE. *Circ Res.* 1969; 24: 151-156; Mayer, SE et al. *Circ Res.* 1970; 26: 225-233).

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 (Compound 2) 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) (Compound 3). OXM is released into the blood in response to food ingestion and in proportion to meal calorie content. OXM has been shown to suppress appetite and inhibit food intake in humans (Cohen et al, *Journal of Endocrinology and Metabolism*, 88, 4696-4701, 2003; WO 2003/022304). In addition to these anorectic effects, which are similar to those of GLP-1, OXM must also affect body weight by another mechanism, since rats treated with oxyntomodulin show less body weight gain than pair-fed rats (Bloom, *Endocrinology* 2004, 145, 2687).

OXM activates both the glucagon receptor and the GLP-1 receptor 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. 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 the glucagon receptor. The mechanism of action of oxyntomodulin is not well understood. In particular, it is not known whether the effects of the hormone are mediated exclusively through the glucagon receptor and the GLP-1 receptor, or through one or more as-yet unidentified receptors.

An eel analogue of oxyntomodulin appears to have an inotropic effect on eel heart (Uesaka et al, *J Experimental Biol.* 2001; 204, 3019-3026) and inotropic effects have also been documented for oxyntomodulin in mouse (Sowden et al. *Am J Phys Regul Integr Comp Physiol.* 2007; 292: R962-R970).

5

SUMMARY OF THE INVENTION

The present inventors have found that certain compounds can act as inotropic agents, more particularly positive inotropic agents, while having considerably less effect on the heart's energy status than known inotropic agents such as dobutamine, norepinephrine and glucagon. Consequently these compounds are more suitable for use as therapeutic agents than known inotropic agents.

10

Without wishing to be bound by any particular theory, the useful properties of these compounds may be due to their ability to activate both the glucagon receptor and the GLP-1 receptor. Thus, the compounds which can be used in the methods of the invention will be referred to as glucagon-GLP-1 dual agonists, or simply as "dual agonists".

15

Thus, the invention provides the use of a glucagon-GLP-1 dual agonist as a positive inotropic agent, in the treatment of heart disease or heart dysfunction.

20

The invention further provides a glucagon-GLP-1 dual agonist for use as a positive inotropic agent in the treatment of heart disease or heart dysfunction.

The invention further provides a glucagon-GLP-1 dual agonist for use in the preparation of a medicament for the treatment of heart disease or heart dysfunction, wherein the glucagon-GLP-1 dual agonist is to be administered for use as a positive inotropic agent.

25

The invention further provides the use of a glucagon-GLP-1 dual agonist in the preparation of a medicament for the treatment of heart disease or heart dysfunction, wherein the glucagon-GLP-1 dual agonist is to be administered for use as a positive inotropic agent.

30

The invention still further provides the use of a glucagon-GLP-1 agonists in the preparation of a medicament capable of improving cardiac contractility without causing concomitant increase in heart rate.

35

The invention further provides a method of treatment of heart disease or heart dysfunction in a subject, comprising administering a glucagon-GLP-1 dual agonist to the subject as a positive inotropic agent.

5 Glucagon-GLP-1 dual agonists are well known in the art.

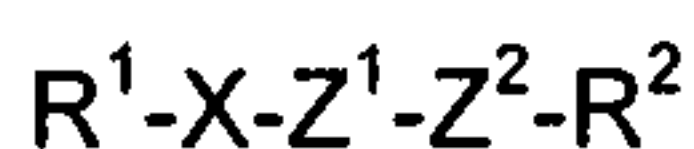
Oxyntomodulin is one example of a naturally-occurring dual agonist. Analogues of oxyntomodulin are described in WO2008/071972 and WO2007/100535.

10 Other dual agonists are described in WO2008/101017. The majority of those compounds are more similar in length to glucagon than OXM, being around 29 amino acids long, and so can be regarded as analogues of glucagon. However others are longer. Any of the dual agonists described in that document may be suitable for use as described herein. Further dual agonists are described in WO2009/155257 and WO2009/155258 and may also be suitable for use in the
15 methods of the invention.

Still further dual agonists are described in WO2008/152403, PCT/GB2008/004132, PCT/GB2008/004121, PCT/GB2008/004157, PCT/GB2008/004130 and European patent application no. 09251780.4, and may also be suitable for use in the methods of the invention.

20

The dual agonist may be a compound having the formula:



25 wherein:

R^1 is hydrogen, C_{1-4} alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl;

X has the Formula I:

30 X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-X10-Ser-X12-Tyr-Leu-X15-X16-X17-X18-Ala-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29

wherein

35 X1 is His, D-His, (Des-amino)His, hydroxyl-His, acetyl-His, homo-His, alpha,alpha-dimethyl imidazole acetic acid (DMIA), N-methyl His, alpha-methyl His or imidazole acetic acid;
X2 is Ser, Aib or D-Ser;

X3 is Gln, Glu, Orn or Nle;

X10 is Tyr or Trp;

X12 is Lys, Arg, His, Ala, Leu, Dpu, Dpr, Orn, Citrulline or Ornithine;

X15 is Asp, Glu, cysteic acid, homoglutamic acid or homocysteic acid;

5 X16 is Ser, Thr, Lys, Arg, His, Glu, Asp, Ala, Gly, Gln, homoglutamic acid or homocysteic acid;

X17 is Arg, Lys, His, Glu, Gln, Ala, Leu, Dpu, Dpr, Orn, Cys, homocysteine or acetyl
phenylalanine;

X18 is Arg, Lys, His, Tyr, Ala, Ser, Leu, Cys, Orn, homocysteine or acetyl phenylalanine;

X20 is Gln, Lys, Arg, His, Glu, Asp, Ala, Cys, Orn or Citrulline;

10 X21 is Asp, Glu, Gln, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val, Ile or Leu;

X24 is Gln, Lys, Arg, Glu, Asp, Ser, Ala, Leu, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Lys, Arg, Glu, Leu, Nle, Cys or absent;

X28 is Asn, Lys, Arg, Glu, Asp, Ser, Ala, Leu, Cys, Citrulline, Orn, or absent;

15 X29 is Thr, Lys, Arg, Glu, Ser, Ala, Gly, Cys, Orn, homocysteine, acetyl phenylalanine or absent;

R² is NH₂ or OH;

Z¹ is absent or has the sequence:

20 GlyProSerSerGlyAlaProProProSer;

GlyProSerSerGlyAlaProProProSerCys;

LysArgAsnArgAsnAsnIleAla; or

LysArgAsnArg;

25 Z² is absent or a peptide sequence of 1-20 amino acid units selected from the group consisting of
Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

wherein, if Z¹ is present, X27, X28 and X29 are also present; and

30 if Z¹ is absent, the compound has a substitution or deletion relative to human glucagon at one or
more of positions X1, X2, X3, X10, X12, X15, X16, X17, X18, X20, X21, X23, X24, X27, X28 and
X29;

or a pharmaceutically acceptable salt or derivative thereof;

35

wherein said compound has higher GLP-1 receptor selectivity than human glucagon.

Independently, where present, Z^2 may be or comprise one or more amino acid residues. For example, Z^2 may be a γ -Glu (also denoted isoGlu), Glu, β -Ala or ϵ -Lys residue, or a 4-aminobutanoyl, 8-aminooctanoyl or 8-amino-3,6-dioxaoctanoyl moiety.

5 The compound may have the formula $R^1-X-Z^2-R^2$

wherein

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

10 R^2 is OH or NH_2 ;

X is a peptide which has the Formula II

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Arg-Ala-Arg-Ala-Asp-Asp-Phe-
Val-Ala-Trp-Leu-Lys-Glu-Ala (Compound 4)

15

or differs from Formula II at up to 4 of the following positions whereby, if different from Formula I:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 16 is: Lys, Asp, Glu;

the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;

20

the residue at position 20 is selected from: Gln, His, Lys, Arg, Glu;

the residue at position 21 is: Glu;

the residue at position 24 is selected from: Gln, Leu, Glu, Lys, Arg, Asp;

the residue at position 27 is selected from: Met, Cys, Arg, Glu, Leu or is absent;

the residue at position 28 is selected from: Asn, Ser, Arg, Lys, Ala, Leu, Glu, Asp or is absent;

25

and

the residue at position 29 is selected from: Thr, Glu, Lys or is absent;

and Z^2 is absent or is a sequence of 1-20 amino acid units selected from the group consisting of
Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

30

or a pharmaceutically acceptable salt thereof,

In some embodiments, X may differ from Formula II at up to 4 of the following positions whereby,
if different from Formula II:

35

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;

the residue at position 20 is selected from: Gln, His, Lys, Arg, Glu;

the residue at position 24 is selected from: Gln, Leu, Glu, Lys, Arg;
the residue at position 27 is selected from: Met, Cys, Arg, Glu, Leu;
the residue at position 28 is selected from: Asn, Ser, Arg, Lys, Ala, Leu; and
the residue at position 29 is selected from: Thr, Glu, Lys.

5

In other embodiments, X comprises the residues 27-Lys and 28-Ser. In such cases, X may additionally differ from Formula II at one or two of the following positions whereby, if different from Formula II:

the residue at position 2 is selected from: Aib, D-Ser;

10

the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;

the residue at position 20 is selected from: Gln, His, Lys, Arg, Glu;

the residue at position 24 is selected from: Gln, Leu, Glu, Lys, Arg; and

the residue at position 29 is selected from: Thr, Glu, Lys.

15

In any of the embodiments described above, the residues at positions 16 and 20 may be capable of forming a salt bridge. Examples of suitable pairs of residues include:

16-Asp, 20-Lys;

16-Glu, 20-Lys;

16-Asp, 20-Arg;

20

16-Glu, 20-Arg;

16-Lys, 20-Asp;

16-Arg, 20-Asp;

16-Lys, 20-Glu; and

16-Arg, 20-Glu.

25

While maintaining consistency with the definitions above, it may be desirable that X comprises one or more of the following sets of residues:

16-Arg;

16-Arg, 20-Asp;

30

16-Arg, 20-Asp, 24-Ala;

16-Arg, 20-Asp, 27-Lys, 28-Ser;

16-Arg, 20-Asp, 29-Ala;

16-Arg, 27-Lys, 28-Ser;

16-Arg, 27-Lys, 28-Ser, 29-Ala;

35

24-Ala, 27-Lys, 28-Ser;

24-Ala, 27-Lys, 28-Ser, 29-Ala;

24-Ala;

27-Lys;
 28-Ser;
 20-Glu, 28-Ser, 29-Thr;
 24-Glu, 28-Ser, 29-Thr;
 5 27-Glu, 28-Arg;
 2-D-Ser, 28-Ser, 29-Thr; or
 20-His, 28-Ser, 29-Thr.

For example, X may have the sequence:

10 HSQGTFTSDYSKYLDRARADDFVAWLKSA; (Compound 5)
 HSQGTFTSDYSKYLDRARADDFVAWLKEA; (Compound 6)
 HSQGTFTSDYSKYLDRARAEDEFVAWLKST; (Compound 7)
 HSQGTFTSDYSKYLDRARADDFVEWLKST; (Compound 8)
 HSQGTFTSDYSKYLDRARADDFVAWLERA; (Compound 9)
 15 H-D-Ser-QGTFTSDYSKYLDRARADDFVAWLKST; (Compound 10)
 HSQGTFTSDYSKYLDRARAHDFVAWLKST; or (Compound 11)
 HSQGTFTSDYSKYLDRARADDFVAWLKST. (Compound 12)

20 The peptides defined by Formula II may carry one or more intramolecular bridge within the peptide sequence X. Each such bridge may suitably be formed between the side chains of two amino acid residues of X which are typically separated by three amino acids in the linear sequence of X (i.e. between amino acid A and amino acid A+4).

25 More particularly, the bridges may be formed between the side chains of residue pairs 12 and 16, 16 and 20, 17 and 21, 20 and 24, or 24 and 28. The two side chains can be linked to one another through ionic interactions or by covalent bonds. Thus these pairs of residues may comprise oppositely charged side chains in order to form a salt bridge by ionic interactions. For example, one of the residues may be Glu or Asp, while the other may be Lys or Arg. The pairings of Lys and Glu and Lys and Asp, may also be capable of reacting to form a lactam ring. Likewise, a Tyr and a Glu or a Tyr and an Asp are capable of forming a lactone ring.

30 In particular, residues at positions 16 and 20 may be capable of forming an intramolecular bridge. Examples of suitable pairs of residues at these positions include:

16-Asp, 20-Lys;
 35 16-Glu, 20-Lys;
 16-Asp, 20-Arg;
 16-Glu, 20-Arg;
 16-Lys, 20-Asp;

16-Arg, 20-Asp;
 16-Lys, 20-Glu; and
 16-Arg, 20-Glu.

5

The compound may have the formula $R^1-X-Z^2-R^2$

wherein

10 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 III:

15 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Leu-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Lys-Asp-Phe-
 Ile-Glu-Trp-Leu-Glu-Ser-Ala (Compound 13)

or differs from Formula III at up to 4 of the following positions whereby, if different from Formula III:

the residue at position 2 is selected from: Aib, D-Ser;

20 the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly, Asp;

the residue at position 17 is selected from: Lys, Leu;

the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;

the residue at position 20 is selected from: Gln, His, Arg, Glu, Asp;

the residue at position 21 is: Glu;

25 the residue at position 23 is selected from: Val, Leu;

the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg, Asp;

the residue at position 27 is selected from: Met, Cys, Lys, Arg, Leu or is absent;

the residue at position 28 is selected from: Asn, Arg, Lys, Glu, Ala, Leu, Asp or is absent; and

the residue at position 29 is selected from: Thr, Glu, Lys or is absent;

30

and Z^2 is absent or a peptide sequence of 1-20 amino acid units selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

or a pharmaceutically acceptable salt thereof.

35

In some embodiments, X differs from Formula III at up to 4 of the following positions whereby, if different from Formula III:

the residue at position 2 is selected from: Aib, D-Ser;
the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly;
the residue at position 17 is selected from: Lys, Leu;
the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;
5 the residue at position 23 is selected from: Val, Leu;
the residue at position 27 is selected from: Met, Cys, Lys, Arg, Leu;
the residue at position 28 is selected from: Asn, Arg, Lys, Glu, Ala, Leu; and
the residue at position 29 is selected from: Thr, Glu, Lys;

10 In some embodiments, X differs from Formula III at up to 4 of the following positions whereby, if different from Formula III:

the residue at position 2 is selected from: Aib, D-Ser;
the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly;
the residue at position 17 is selected from: Lys, Leu;
15 the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr; and
the residue at position 23 is selected from: Val, Leu.

In some embodiments, X differs from Formula III at up to 4 of the following positions whereby, if different from Formula III:

20 the residue at position 2 is selected from: Aib, D-Ser;
the residue at position 23 is selected from: Val, Leu;
the residue at position 27 is selected from: Met, Cys, Lys, Arg, Leu;
the residue at position 28 is selected from: Asn, Arg, Lys, Glu, Ala, Leu; and
the residue at position 29 is selected from: Thr, Glu, Lys.

25

While maintaining consistency with the definitions above, it may be desirable that X comprises one or more of the following sets of residues:

20-Lys, 24-Glu;

20-Lys, 24-Glu, 29-Ala;

30 20-Lys, 23-Ile, 24-Glu;

27-Glu, 28-Ser, 29-Ala;

29-Ala;

20-Gln;

23-Val;

35 24-Gln;

29-Thr;

27-Met, 28-Asn, 29-Thr;

20-Gln, 23-Val, 24-Gln;

20-Glu, 24-Lys; or

28-Arg.

5 For example, X may have the sequence:

HSQGTFTSDYSLYLDSTRRAQDFIEWLESA; (Compound 14)

HSQGTFTSDYSLYLDSTRRAKDFVEWLESA; (Compound 15)

HSQGTFTSDYSLYLDSTRRAKDFIQWLESA; (Compound 16)

HSQGTFTSDYSLYLDSTRRAKDFIEWLEST; (Compound 17)

10 HSQGTFTSDYSLYLDSTRRAKDFIEWLMNT; (Compound 18)

HSQGTFTSDYSLYLDSTRRAQDFVQWLESA; (Compound 19)

HSQGTFTSDYSLYLDSTRRAEDFIKWLESA; or (Compound 20)

HSQGTFTSDYSLYLDSTRRAKDFIEWLERA. (Compound 21)

15 The peptides defined by Formula III may carry one or more intramolecular bridges within the peptide sequence X. Each such bridge may suitably be formed between the side chains of two amino acid residues of X which are typically separated by three amino acids in the linear sequence of X (i.e. between amino acid A and amino acid A+4).

20 More particularly, the bridge may be formed between the side chains of residue pairs 16 and 20, 17 and 21, 20 and 24, or 24 and 28. The two side chains can be linked to one another through ionic interactions, or by covalent bonds. Thus these pairs of residues may comprise oppositely charged side chains in order to form a salt bridge by ionic interactions. For example, one of the residues may be Glu or Asp, while the other may be Lys or Arg. The pairings of Lys and Glu and
 25 Lys and Asp, may also be capable of reacting to form a lactam ring. Likewise, a Tyr and a Glu or a Tyr and a Asp are capable of forming a lactone ring.

In particular, the residues at positions 20 and 24 may be capable of forming an intramolecular bridge. Examples of suitable pairs of residues at these positions include:

30 20-Asp, 24-Lys;

20-Glu, 24-Lys;

20-Asp, 24-Arg;

20-Glu, 24-Arg;

20-Lys, 24-Asp;

35 20-Arg, 24-Asp;

20-Lys, 24-Glu; and

20-Arg, 24-Glu.

Without wishing to be bound by any particular theory, it is believed that such intramolecular bridges stabilise the alpha helical structure of the molecule and so increase potency and/or selectivity at the GLP-1 receptor and possibly also at the glucagon receptor.

5

The compound may have the formula $R^1-X-Z^2-R^2$ wherein

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

R^2 is OH or NH_2 ;

10

X is a peptide which has the Formula IV:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Leu-Ser-Ala (Compound 22)

15

or differs from Formula IV at up to 4 of the following positions whereby, if different from Formula IV:

the residue at position 2 is selected from: D-Ser, Aib;

the residue at position 16 is selected from: Ser, Asp, Lys, Arg;

the residue at position 18 is: Ala;

20

the residue at position 20 is selected from: Gln, Arg, Glu, Asp;

the residue at position 21 is: Glu;

the residue at position 23 is: Val;

the residue at position 24 is selected from: Gln, Asp, Lys, Arg, Ala;

the residue at position 27 is selected from: Met, Cys, Lys or is absent;

25

the residue at position 28 is selected from: Asn, Arg, Lys, Ala, Glu, Asp or is absent; and the

residue at position 29 is selected from: Thr, Arg or is absent;

and Z^2 is absent or a sequence of 1-20 amino acid units selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

30

or a pharmaceutically acceptable salt thereof.

In some embodiments, X differs from Formula IV at up to 4 of the following positions whereby, if different from Formula IV:

35

the residue at position 2 is selected from: D-Ser, Aib;

the residue at position 16 is selected from: Ser, Asp, Lys;

the residue at position 20 is selected from: Gln, Arg, Glu;

the residue at position 27 is selected from: Met, Cys, Lys; and
the residue at position 28 is selected from: Asn, Arg, Ala.

In some of those embodiments, X may differ from Formula IV at up to 3 of the following positions

5 whereby, if different from Formula IV:

the residue at position 2 is selected from: D-Ser, Aib;

the residue at position 16 is selected from: Ser, Asp, Lys; and

the residue at position 20 is selected from: Gln, Arg, Glu.

10 In alternative embodiments, X may differ from Formula IV at up to 4 of the following positions
whereby, if different from Formula IV:

the residue at position 2 is selected from: D-Ser, Aib;

the residue at position 16 is selected from: Ser, Asp, Lys;

the residue at position 18 is: Ala; and

15 the residue at position 20 is selected from: Gln, Arg, Glu.

In still further alternative embodiments, X may differ from Formula IV at up to 4 of the following
positions whereby, if different from Formula IV:

the residue at position 23 is: Val;

20 the residue at position 24 is selected from: Gln, Asp, Lys, Arg, Ala;

the residue at position 27 is selected from: Met, Cys, Lys; and

the residue at position 28 is selected from: Asn, Arg, Ala.

In any of the embodiments described above, the residues at positions 16 and 20 may be capable
25 of forming a salt bridge. Examples of suitable pairs of residues include:

16-Asp, 20-Lys;

16-Glu, 20-Lys;

16-Asp, 20-Arg;

16-Glu, 20-Arg;

30 16-Lys, 20-Asp;

16-Arg, 20-Asp;

16-Lys, 20-Glu;

16-Arg, 20-Glu.

35 Additionally or alternatively, the residues at positions 20 and 24 may be capable of forming a salt
bridge. Examples of suitable pairs of residues include:

20-Asp, 24-Lys;

20-Glu, 24-Lys;

20-Asp, 24-Arg;

20-Glu, 24-Arg;

20-Lys, 24-Asp;

5 20-Arg, 24-Asp;

20-Lys, 24-Glu;

20-Arg, 24-Glu.

While maintaining consistency with the definitions above, it may be desirable that X comprises

10 one or more of the following sets of residues:

20-Lys, 24-Glu;

20-Lys, 23-Ile, 24-Glu;

16-Glu, 20-Lys, 24-Glu;

16-Glu, 20-Lys;

15 16-Glu, 20-Lys, 29-Ala;

16-Glu, 20-Lys, 23-Ile, 24-Glu;

16-Glu, 20-Lys, 23-Ile, 24-Glu, 29-Ala;

16-Glu, 20-Lys, 24-Glu, 29-Ala;

20-Lys, 23-Ile, 24-Glu, 29-Ala;

20 27-Leu, 28-Ser, 29-Ala;

29-Ala;

16-Ser;

20-Gln;

23-Val;

25 24-Gln;

16-Ser, 20-Gln;

16-Asp, 20-Arg, 24-Asp;

16-Lys, 20-Glu;

24-Arg; or

30 28-Arg.

For example, X may have the sequence:

HSQGTFTSDYSKYLDERRAQDFIEWLLSA; (Compound 23)

HSQGTFTSDYSKYLDERRAKDFVEWLLSA; (Compound 24)

35 HSQGTFTSDYSKYLDERRAKDFIQWLLSA; (Compound 25)

HSQGTFTSDYSKYLDSRRAQDFIEWLLSA; (Compound 26)

HSQGTFTSDYSKYLDDRRARDFIDWLLSA; (Compound 27)

HSQGTFTSDYSKYLDKRRRAEDFIKWLLSA; (Compound 28)

HSQGTFTSDYSKYLDERRAKDFIRWLLSA; (Compound 29)

HSQGTFTSDYSKYLDERRAKDFIEWLLRA; (Compound 30)

HSQGTFTSDYSKYLDSRRRAKDFIEWLLSA; (Compound 31)

5 HSQGTFTSDYSKYLDERRAAKDFIEWLLSA; (Compound 32)

HSQGTFTSDYSKYLDERRAKDFIDWLLSA; (Compound 33)

HSQGTFTSDYSKYLDERRAKDFIEWLLAA; or (Compound 34)

HSQGTFTSDYSKYLDERRAKDFIEWLLSA. (Compound 35)

10 The peptides defined by Formula IV may carry one or more intramolecular bridge within the peptide sequence X. Each such bridge may suitably be formed between the side chains of two amino acid residues of X which are typically separated by three amino acids in the linear sequence of X (i.e. between amino acid A and amino acid A+4).

15 More particularly, the bridge may be formed between the side chains of residue pairs 12 and 16, 16 and 20, 17 and 21, 20 and 24, or 24 and 28. The two side chains can be linked to one another through ionic interactions, or by covalent bonds. Thus these pairs of residues may comprise oppositely charged side chains in order to form a salt bridge by ionic interactions. For example, one of the residues may be Glu or Asp, while the other may be Lys or Arg. The pairings of Lys
20 and Glu and Lys and Asp, may also be capable of reacting to form a lactam ring. Likewise, a Tyr and a Glu or a Tyr and a Asp are capable of forming a lactone ring.

In particular, the residues at positions 16 and 20, and/or 20 and 24 may be capable of forming an intramolecular bridge. Examples of suitable pairs of residues at these positions include:

25 16-Asp, 20-Lys;

16-Glu, 20-Lys;

16-Asp, 20-Arg;

16-Glu, 20-Arg;

16-Lys, 20-Asp;

30 16-Arg, 20-Asp;

16-Lys, 20-Glu;

16-Arg, 20-Glu; and/or

20-Asp, 24-Lys;

35 20-Glu, 24-Lys;

20-Asp, 24-Arg;

20-Glu, 24-Arg;

20-Lys, 24-Asp;
 20-Arg, 24-Asp;
 20-Lys, 24-Glu;
 20-Arg, 24-Glu.

5

Without wishing to be bound by any particular theory, it is believed that such intramolecular bridges stabilise the alpha helical structure of the molecule and so increase potency and/or selectivity at the GLP-1 receptor and possibly also the glucagon receptor.

10 The compound may have the formula $R^1-X-Z^2-R^2$

wherein

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

15 R^2 is OH or NH_2 ;

X is a peptide which has the Formula V:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Lys-Ala-Ala-His-Asp-Phe-
 Val-Glu-Trp-Leu-Leu-Arg-Ala (Compound 36)

20

or differs from Formula V at up to 4 of the following positions whereby, if different from Formula V:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 12 is selected from: Leu, Arg, Dpu, Dpr, Orn;

the residue at position 16 is selected from: Arg, His, Lys, Glu, Asp;

25 the residue at position 17 is selected from: Arg, Leu, Dpu, Dpr, Orn;

the residue at position 18 is selected from: Arg, Lys, His, Ser, Tyr;

the residue at position 20 is selected from: Gln, Lys, Arg, Glu, Asp;

the residue at position 21 is Glu;

the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg, Asp;

30 the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu or is absent;

the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu, Asp or is absent; and

the residue at position 29 is selected from: Thr, Glu, Lys or is absent;

and Z^2 is absent or a peptide sequence of 1-20 amino acid units selected from the group
 35 consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

or a pharmaceutically acceptable salt thereof.

In certain embodiments of this aspect, X may differ from Formula V at up to 4 of the following positions whereby, if different from Formula V:

the residue at position 2 is selected from: Aib, D-Ser;

5 the residue at position 16 is selected from: Arg, His, Lys, Glu;

the residue at position 17 is selected from: Arg, Leu;

the residue at position 18 is selected from: Arg, Lys, His, Ser, Tyr;

the residue at position 20 is selected from: Gln, Lys, Arg, Glu;

the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg;

10 the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu;

the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu; and

the residue at position 29 is selected from: Thr, Glu, Lys.

In certain embodiments of this aspect, X may differ from Formula V at up to 4 of the following positions whereby, if different from Formula V:

15 the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly;

the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg;

the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu;

20 the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu; and

the residue at position 29 is selected from: Thr, Glu, Lys.

While maintaining consistency with the definitions relating to Formula V above, it may be desirable that X comprises one or more of the following sets of residues:

25 17-Lys, 18-Ala;

17-Leu, 18-Ala;

17-Lys, 18-Ala, 20-His;

17-Leu, 18-Ala, 20-His;

17-Lys, 18-Ala, 24-Glu;

30 17-Leu, 18-Ala, 24-Glu;

17-Lys, 18-Ala, 27-Leu;

17-Leu, 18-Ala, 27-Leu;

17-Lys, 18-Ala, 29-Ala;

17-Leu, 18-Ala, 29-Ala;

35 17-Lys, 18-Ala, 27-Leu, 29-Ala;

17-Leu, 18-Ala, 27-Leu, 29-Ala;

17-Lys, 18-Ala, 27-Leu, 28-Arg, 29-Ala;

17-Leu, 18-Ala, 27-Leu, 28-Arg, 29-Ala;

24-Glu, 28-Arg;

24-Glu, 28-Arg, 27-Leu;

24-Glu, 28-Arg, 27-Leu, 29-Ala;

5 27-Leu, 28-Arg, 29-Ala;

29-Ala;

20-Arg, 24-Arg, 27-Lys, 28-Leu;

17-Arg;

18-Arg;

10 20-Gln;

24-Gln;

27-Met, 28-Asn, 29-Thr; or

24-Lys

and combinations thereof.

15

For example, X may have the sequence:

HSQGTFTSDYSKYLDSKAARDFVRWLKLA; (Compound 37)

HSQGTFTSDYSKYLDSRAAHDFVEWLLRA; (Compound 38)

HSQGTFTSDYSKYLDSKRAHDFVEWLLRA; (Compound 39)

20 HSQGTFTSDYSKYLDSKAAQDFVEWLLRA; (Compound 40)

HSQGTFTSDYSKYLDSKAAHDFVQWLLRA; (Compound 41)

HSQGTFTSDYSKYLDSKAAHDFVEWLMNT; (Compound 42)

HSQGTFTSDYSKYLDSKAAHDFVKWLLRA; (Compound 43)

H-DSer-QGTFTSDYSKYLDSKAAHDFVEWLLRA; (Compound 44)

25 H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLRA; (Compound 45)

HSQGTFTSDYSKYLDSKAAKDFVEWLLRA; (Compound 46)

HSQGTFTSDYSKYLDKKAHDFVEWLLRA or (Compound 47)

HSQGTFTSDYSKYLDSKAAHDFVEWLLRA. (Compound 48)

30 In an alternative aspect, the compound may have the formula $R^1-X-Z^2-R^2$

wherein

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

35 R^2 is OH or NH_2 ;

X is a peptide which has the Formula VI:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Lys-Ala-Ala-His-Asp-Phe-Val-Glu-Trp-Leu-Leu-Arg-Ala (Compound 49)

or differs from Formula VI at up to 5 of the following positions whereby, if different from Formula VI:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 16 is selected from: Arg, His, Lys, Glu;

the residue at position 17 is: Arg, Leu, Dpu, Dpr, Orn;

the residue at position 20 is selected from: Gln, Lys, Arg, Glu, Asp;

the residue at position 21 is Glu;

the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg, Asp;

the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu or is absent;

the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu, Asp or is absent; and

the residue at position 29 is selected from: Thr, Glu, Lys or is absent;

and Z^2 is absent or a peptide sequence of 1-20 amino acid units selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

or a pharmaceutically acceptable salt thereof.

In certain embodiments of this aspect, X may differ from Formula VI at up to 4 of the following positions whereby, if different from Formula VI:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly;

the residue at position 17 is selected from: Arg, Leu;

the residue at position 18 is selected from: Arg, Lys, His, Ser, Tyr;

the residue at position 20 is selected from: Gln, Lys, Arg, Glu;

the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg;

the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu;

the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu; and

the residue at position 29 is selected from: Thr, Glu, Lys.

While maintaining consistency with the definitions in relation to Formula VI above, it may be desirable that X comprises any of the sets of residues described above in relation to the first aspect, or one or more of the following sets of residues:

20-Gln, 24-Gln, 27-Met, 28-Asn, 29-Thr; or

17-Leu, 20-Gln, 24-Gln, 28-Asn, 29-Thr.

X may have the sequence:

HSQGTFTSDYSKYLD SKAAQDFVQWLMNT or (Compound 50)

HSQGTFTSDYSKYLD SLAAQDFVQWLLNT. (Compound 51)

5

The peptides defined by Formulae V and VI may carry one or more intramolecular bridge within the peptide sequence X. Each such bridge may suitably be formed between the side chains of two amino acid residues of X which are typically separated by three amino acids in the linear sequence of X (i.e. between amino acid A and amino acid A+4).

10

More particularly, the bridge may be formed between the side chains of residue pairs 12 and 16, 16 and 20, 17 and 21, 20 and 24, or 24 and 28. The two side chains can be linked to one another through ionic interactions or by covalent bonds. Thus these pairs of residues may comprise oppositely charged side chains in order to form a salt bridge by ionic interactions. For example, one of the residues may be Glu or Asp, while the other may be Lys or Arg. The pairings of Lys and Glu and Lys and Asp, may also be capable of reacting to form a lactam ring. Likewise, a Tyr and a Glu or a Tyr and a Asp are capable of forming a lactone ring.

15

In particular, residues at positions 16 and 20 may be capable of forming an intramolecular bridge.

20

Examples of suitable pairs of residues at these positions include:

16-Asp, 20-Lys;

16-Glu, 20-Lys;

16-Asp, 20-Arg;

16-Glu, 20-Arg;

25

16-Lys, 20-Asp;

16-Arg, 20-Asp;

16-Lys, 20-Glu; and

16-Arg, 20-Glu.

30

Without wishing to be bound by any particular theory, it is believed that such intramolecular bridges stabilise the alpha helical structure of the molecule and so increase potency and/or selectivity at the GLP-1 receptor and possibly also the glucagon receptor..

35

Without wishing to be bound by any particular theory, the arginine residues at positions 17 and 18 of native glucagon appear to provide significant selectivity for the glucagon receptor. A hydrophobic residue (e.g. Ala) at position 18 may also increase potency at both GLP-1 and glucagon receptors. It may also increase enzymatic stability compared to native glucagon.

Without wishing to be bound by any particular theory, the residues at positions 27, 28 and 29 of native glucagon appear to provide significant selectivity for the glucagon receptor. Substitutions at one, two, or all three of these positions with respect to the native glucagon sequence may increase potency at and/or selectivity for the GLP-1 receptor, potentially without significant reduction of potency at the glucagon receptor. Particular examples include Leu or Lys at position 27, Arg or Ser at position 28 and Ala at position 29.

Substitution of the naturally-occurring Met residue at position 27 (e.g. with Leu, Lys, Arg or Glu) also reduces the potential for oxidation, so increasing the chemical stability of the compounds.

Substitution of the naturally-occurring Asn residue at position 28 (e.g. by Glu, Ser, Arg, Lys, Ala or Leu) also reduces the potential for deamidation in acidic solution, so increasing the chemical stability of the compounds.

Potency and/or selectivity at the GLP-1 receptor may also be increased by introducing residues that are likely to form an amphipathic helical structure, potentially without significant loss of potency at the glucagon receptor. This may be achieved by introduction of charged residues at one or more of positions 16, 20, 24, and 28. Thus the residues of positions 16 and 20 may all be charged, the residues at positions 16, 20, and 28 may all be charged, or the residues at positions 16, 20, 24, and 28 may all be charged. The presence of charged residues at position 16 and 20 may be particularly desirable when they are capable of forming an intramolecular bridge, e.g. when they are oppositely charged amino acids, such as Arg at position 16 and Asp or Glu at position 20 or Glu at position 16 and His or Lys at position 20.

Substitution of one or both of the naturally-occurring Gln residues at positions 20 and 24 also reduces the potential for deamidation in acidic solution, so increasing the chemical stability of the compounds. For example, the compounds may have Asp or His at position 20 and Ala in position 24, optionally also with Ser, Glu or Arg at position 28.

The compound may have the formula $R^1-X-Z^1-Z^2-R^2$

wherein:

R^1 is hydrogen, C_{1-4} alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl;

wherein X has the Formula VII:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-X10-Ser-X12-Tyr-Leu-X15-X16-X17-X18-Ala-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29

wherein

5

X1 is His, D-His, (Des-amino)His, hydroxyl-His, acetyl-His, homo-His, alpha,alpha-dimethyl imidazole acetic acid (DMIA), N-methyl His, alpha-methyl His, or imidazole acetic acid;
X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, aminoisobutyric acid (Aib) or N-methyl Ala;
X3 is Gln, Glu, Orn or Nle;

10

X10 is Tyr or Trp;
X12 is Lys, Citrulline, Orn or Arg;
X15 is Asp, Glu, cysteic acid, homoglutamic acid or homocysteic acid;
X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;
X17 is Arg, Gln, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;
15 X18 is Arg, Ala, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;
X20 is Gln, Lys, Arg, Orn or Citrulline;
X21 is Gln, Glu, Asp, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;
X23 is Val or Ile;
X24 is Ala, Gln, Glu, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;
20 X27 is Met, Leu or Nle;
X28 is Asn, Arg, Citrulline, Orn, Lys or Asp;
X29 is Thr, Gly, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;

R² is NH₂ or OH;

25

Z¹ is absent or has the sequence:
GlyProSerSerGlyAlaProProProSer;
GlyProSerSerGlyAlaProProProSerCys;
LysArgAsnArgAsnAsnIleAla; or
30 LysArgAsnArg;

Z² is absent or a peptide sequence of 1-20 amino acid units selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Har, Dbu, Dpr and Orn;

35

wherein, if Z¹ is absent, the compound has a substitution or deletion relative to human glucagon at one or more of positions X1, X2, X3, X10, X12, X15, X16, X17, X18, X20, X21, X23, X24, X27, X28 and X29;

or a pharmaceutically acceptable salt or derivative thereof;

wherein said compound has higher GLP-1 receptor selectivity than human glucagon and/or

5 wherein the compound exhibits at least 20% of the activity of native GLP-1 at the GLP-1 receptor.

In addition, in certain embodiments, X may differ from Formula VII by 1 to 3 amino acid modifications at positions selected from 1, 2, 3, 5, 7, 10, 11, 13, 14, 17, 18, 19, 21, 24, 27, 28 and 29.

10

Compounds having sequences according to Formula VII are described in WO2008/101017.

X may have the Formula VII.2:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-X16-X17-Arg-Ala-Gln-Asp-Phe-
15 Val-Gln-Trp-Leu-X27-Asn-Thr (Compound 52)

wherein

X16 is Glu, Gln, homoglutamic acid or homocysteic acid;

X17 is Arg, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle

20

X may have the Formula VII.3:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-Gln-X21-Phe-
Val-Gln-Trp-Leu-X27- Asn-Thr (Compound 53)

wherein

25 X16 is Glu, Gln, homoglutamic acid or homocysteic acid;

X21 is Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle;

X may have the Formula VII.4:

30 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-Gln-X21-Phe-
Val-Gln-Trp-Leu-X27- Asn-Thr (Compound 54)

wherein

X16 is Glu, Gln, homoglutamic acid or homocysteic acid;

X24 is Gln, Cys, Orn, homocysteine or acetyl phenylalanine;

35 X27 is Met, Leu or Nle.

X may have the Formula VII.5:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-Gln-X21-Phe-Val-X24-Trp-Leu-X27- Asn-Thr (Compound 55)

wherein

X16 is Glu, Gln, homoglutamic acid or homocysteic acid;

5 X21 is Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X24 is Gln, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle.

X may have the Formula VII.6:

10 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Gln-X21-Phe-Val-Gln-Trp-Leu-X27- Asn-Thr (Compound 56)

wherein

X21 is Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle.

15

X may have the Formula VII.7:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-Val-X24-Trp-Leu-X27- Asn-Thr (Compound 57)

wherein

20 X24 is Gln, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle.

X may have the Formula VII.8:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met- Asn-Thr (Compound 58)

25

wherein

X16 is Glu, Gln, homoglutamic acid or homocysteic acid.

X may have the Formula VII.9:

30 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-X27- Asn-Thr (Compound 59)

wherein

X27 is Met, Leu or Nle.

35

X may have the Formula VII.19:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-Val-Glu-Trp-Leu-Met-Asn-Thr-X30 (Compound 60)

wherein

X30 is any suitable amino acid.

X may have the Formula VII.20:

5 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-X16-Arg-Arg- Ala-X20-Asp-Phe-Val-X24-Trp-Leu-Met-X28-X29 (Compound 61)

wherein

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln, Lys, Arg, Orn or Citrulline;

10 X24 is Gln or Glu;

X28 is Asn, Asp or Lys;

X29 is Thr or Gly.

X may have the Formula VII.21:

15 His-X2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg- Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr (Compound 62)

wherein

X2 is D-Ser, Ala, Gly, N-methyl Ser or aminoisobutyric acid.

20 X may have the Formula VII.22:

His-X2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg- Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr (Compound 63)

wherein

X2 is aminoisobutyric acid.

25

X may have the Formula VII.23:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Cys-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-X27- Asn-Thr (Compound 64)

wherein

30 the Cys at position 17 is PEGylated;

X27 is Met, Leu or Nle.

X may have the Formula VII.24:

35 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Cys-Phe-Val-Gln-Trp-Leu-X27- Asn-Thr (Compound 65)

wherein

the Cys at position 21 is PEGylated;

X27 is Met, Leu or Nle.

X may have the Formula VII.25:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-

5 Val-Cys-Trp-Leu-X27- Asn-Thr (Compound 66)

wherein

the Cys at position 24 is PEGylated;

X27 is Met, Leu or Nle.

10 X may have the Formula VII.30:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-

Val-Gln-Trp-Leu-X27- Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser (Compound 67)

wherein

X27 is Met, Leu or Nle.

15

X may have the Formula VII.31:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-

Val-Gln-Trp-Leu-X27- Asn-Thr-Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala (Compound 68)

wherein

20 X27 is Met, Leu or Nle.

X may have the Formula VII.32:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-

Val-Gln-Trp-Leu-X27- Asn-Thr-Lys-Arg-Asn-Arg (Compound 69)

25 wherein

X27 is Met, Leu or Nle.

X may have the Formula VII.33:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15- X16- Arg-Arg-Ala-X20-Asp-

30 Phe-Val-X24-Trp-Leu-Met-X28-X29 (Compound 70)

wherein

X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln or Lys;

35 X24 is Gln or Glu;

X28 is Asn, Lys or an acidic amino acid;

X29 is Thr, Gly or an acidic amino acid.

X may have the Formula VII.36:

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-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser. (Compound 71)

5

X may have the Formula VII.37:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Cys-Trp-Leu-Met-Asn-Thr (Compound 72)

wherein 24 2-butyrolactone is bound through thiol group of Cys.

10

X may have the Formula VII.38:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Cys-Trp-Leu-Met-Asn-Thr (Compound 73)

wherein a 24 carboxymethyl group is bound through thiol group of Cys.

15

X may have the Formula VII.39:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Arg-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-Met-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser. (Compound 74)

20

X may have the Formula VII.40:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Glu-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-Met-X28-Thr (Compound 75)

wherein

X15 is Glu or Asp;

25

X28 is Glu or Asp.

X may have the Formula VII.41:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Glu-Arg-Arg-Ala-Asp-Phe-Val-
Gln-Trp-Leu-Met-X28- Thr (Compound 76)

30

wherein

X15 is Glu or Asp;

X28 is Glu or Asp; and

a lactam ring is present between the side chains at positions 12 and 16.

35

X may have the Formula VII.42:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Glu-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Gln-Trp-Leu-Met-X28-Thr (Compound 77)

wherein

X15 is Glu or Asp;

X28 is Glu or Asp; and

a lactam ring is present between the side chains at positions 16 and 20.

5

X may have the Formula VII.43:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Ser-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Glu-Trp-Leu-Met-X28-Thr (Compound 78)

wherein

10

X15 is Glu or Asp;

X28 is Glu or Asp; and

a lactam ring is present between side chains at positions 20 and 24.

X may have the Formula VII.44:

15

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Glu-Trp-Leu-Met-Lys-X29 (Compound 79)

wherein

X15 is Glu or Asp;

X29 is Glu or Thr.

20

In the above Formulae Z1 and Z2 are typically absent. The C-terminus of the compound may be
amidated ($R^2 = NH_2$).

X may have the Formula VII.45:

25

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-X12-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-Asp-Phe-
Val-X24-Trp-Leu-Met-X28-X29 (Compound 80)

wherein

X12 is Lys or Glu;

X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;

30

X16 is Ser, Gln, Glu, Lys, homoglutamic acid, cysteic acid or homocysteic acid;

X20 is Gln, Glu or Lys;

X24 is Gln, Lys or Glu;

X28 is Asn, Lys or an acidic amino acid;

X29 is Thr, Gly or an acidic amino acid.

35

X may have the Formula VII.46:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-X20-Asp-Phe-
Val-X24-Trp-Leu-Met-Asn-Thr (Compound 81)

wherein

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

5 X20 is Gln or Lys;

X24 is Gln or Glu.

X may have the Formula VII.47:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-
10 Val-Gln-Trp-Leu-Met-Asn-Thr. (Compound 82)

X may have the Formula VII.48:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Glu-Trp-Leu-Met-Asn-Thr. (Compound 83)

15

X may have the Formula VII.49:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Glu-Trp-Leu-Met-Asn-Thr. (Compound 84)

20

X may have the Formula VII.50:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-
Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (Compound 85)

X may have the Formula VII.51:

25

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-X21-Phe-
Val-X24-Trp-Leu-Met-X28-X29 (Compound 86)

wherein

X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

30

X20 is Gln, Lys, Arg, Orn or Citrulline;

X21 is Asp, Glu, homoglutamic acid or homocysteic acid;

X24 is Gln or Glu;

X28 is Asn, Lys or an acidic amino acid;

X29 is Thr, Gly or an acidic amino acid.

35

X may have the Formula VII.52:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg. (Compound 87)

X may have the Formula VII.53:

5 His-Ser-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-Asp-Phe-Val-X24-Trp-Leu-Met-X28-X29 (Compound 88)

wherein

X3 is Glu, Orn or Nle;

X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;

10 X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln or Lys;

X24 is Gln or Glu;

X28 is Asn, Lys or an acidic amino acid;

X29 is Thr or an acidic amino acid.

15

X may have the Formula VII.54:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-X17-X18-Ala-Lys-X21-Phe-X23-X24-Trp-Leu-Met-Asn-Thr (Compound 89)

wherein

20 X17 is Arg or Gln;

X18 is Arg or Ala;

X21 is Asp or Glu;

X23 is Val or Ile;

X24 is Gln or Ala.

25

X may have the Formula VII.56:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29 (Compound 90)

wherein

30 X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle

X15 is Asp, Glu, cysteic acid, homoglutamic acid homocysteic acid;

35 X16 is Ser, Glu, Gln, homoglutamic acid, or homocysteic acid;

X20 is Gln, Lys, Arg, Orn or Citrulline;

X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

X24 is Ala, Gln, Glu, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle;

X28 is Asn, Lys or Asp;

5 X29 is Thr, Gly, Lys, Cys, Orn, homocysteine or acetyl phenylalanine.

X may have the Formula VII.57:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-Glu-Arg-Arg-Ala-X20-X21-Phe-
X23-X24-Trp-Leu-X27-X28-X29 (Compound 91)

10 wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle;

15 X15 is Asp, Glu, Cysteic acid, homoglutamic acid or homocysteic acid;

X20 is Gln, Lys, Arg, Orn, or Citrulline;

X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

X24 is Ala, Gln, Glu, Cys, Orn, homocysteine or acetyl phenylalanine;

20 X27 is Met, Leu or Nle;

X28 is Asn, Lys or Asp;

X29 is Thr, Gly, Cys, Orn, homocysteine or acetyl phenylalanine;

and wherein a lactam bridge is present between side chains at positions 12 and 16.

25 X may have the Formula VII.58:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-Glu-Arg-Arg-Ala-Lys-X21-Phe-
X23-X24-Trp-Leu-X27-X28-X29 (Compound 92)

wherein

30 X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle;

X15 is Asp, Glu, Cysteic acid, homoglutamic acid or homocysteic acid;

X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

35 X23 is Val or Ile;

X24 is Ala, Gln, Glu, Cys, Orn, homocysteine or acetyl phenylalanine,

X27 is Met, Leu or Nle;

X28 is Asn, Lys or Asp;

X29 is Thr, Gly, Cys, Orn, homocysteine or acetyl phenylalanine;

and wherein a lactam bridge is present between side chains at positions 16 and 20.

5 X may have the Formula VII.59:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-Lys-X21-Phe-
X23-Glu-Trp-Leu-X27-X28-X29 (Compound 93)

wherein

10 X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle;

X15 is Asp, Glu, Cysteic acid, homoglutamic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

15 X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

X27 is Met, Leu or Nle;

X28 is Asn, Lys or Asp;

X29 is Thr, Gly, Cys, Orn, homocysteine or acetyl phenylalanine;

20 and wherein a lactam bridge is present between side chains at positions 20 and 24.

X may have the Formula VII.60:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-X21-Phe-
X23-Glu-Trp-Leu-X27-Lys-X29 (Compound 94)

25 wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle;

30 X15 is Asp, Glu, Cysteic acid, homoglutamic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln, Lys, Arg, Orn or Citrulline

X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

35 X27 is Met, Leu or Nle;

X29 is Thr, Gly, Cys, Orn, homocysteine or acetyl phenylalanine;

and wherein a lactam bridge is present between side chains at positions 24 and 28

X-Z¹ may have the Formula VII.61:

X1-X2-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-X18-Ala-Lys-Asp-Phe-Val-X24-Trp-Leu-Met-Asn-X29-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Cys (Compound 95)

5 wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, acetyl-His, homo-His, DMIA, N-methyl His, alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, Val, Gly, N-methyl Ser, Aib, N-methyl Ala or D-Ala;

X18 is Ala or Arg;

10 X24 is Ala, Gln or Cys-PEG;

X29 is Thr-CONH₂, Cys-PEG, or Gly;

position 40 is Cys-PEG or not present;

provided that positions 30 to 40 (Z²) are present only if position 29 is Gly.

15 X-Z¹ may have the Formula VII.62:

X1-X2-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Gln-X18-Ala-Lys-Glu-Phe-Ile-X24-Trp-Leu-Met-Asn-X29-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Cys (Compound 96)

wherein

20 X1 is His, D-His, (Des-amino)His, hydroxyl-His, acetyl-His, homo-His, DMIA, N-methyl His, alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, Val, Gly, N-methyl Ser, Aib, N-methyl Ala or D-Ala;

X18 is Ala or Arg;

X24 is Ala, Gln or Cys-PEG;

X29 is Thr-CONH₂, Cys-PEG, or Gly;

25 position 40 is Cys-PEG or not present;

provided that positions 30 to 40 (Z²) are present only if position 29 is Gly

X may have the Formula VII.63:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-X20-X21-Phe-Val-X24-Trp-Leu-X27-Asp-Thr (Compound 97)

30 wherein

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln or Lys;

X21 is Asp, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;

35 X24 is Gln, Lys, Cys, Orn, homocysteine or acetylphenylalanine;

X27 is Met, Leu or Nle.

X-Z¹ may have the Formula VII.64:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-X16-Arg-Arg-Ala-X20-Asp-Phe-
Val-X24-Trp-Leu-Met-X28-Gly-Gly-Pro-Ser-Ser-Gly-Pro-Pro-Pro-Ser (Compound 98)

wherein

- 5 X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;
X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;
X20 is Gln or Lys;
X24) is Gln or Glu;
X28 is Asn, Lys or Asp.

10

X may have the Formula VII.66:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-Met-X28-X29 (Compound 99)

wherein

- 15 X28 is Asp or Asn;
X29 is Thr or Gly;
and wherein a lactam ring is present between side chains at positions 12 and 16.

X may have the Formula VII.67:

- 20 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Gln-Trp-Leu-Met-X28-X29 (Compound 100)

wherein

- X28 is Asp or Asn;
X29 is Thr or Gly;
25 and wherein a lactam ring is present between side chains at positions 16 and 20.

X may have the Formula VII.68:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Glu-Trp-Leu-Met-X28-X29 (Compound 101)

30 wherein

- X28 is Asp or Asn;
X29 is Thr or Gly;
and wherein a lactam ring is present between side chains at positions 20 and 24.

- 35 X may have the Formula VII.69:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Glu-Trp-Leu-Met-Lys-X29 (Compound 102)

wherein

X29 is Thr or Gly;

and wherein a lactam ring is present between side chains at positions 24 and 28.

- 5 Further specific compounds which may be useful in the methods of the invention are shown in Figure 3: Table 2 and Table 3

DESCRIPTION OF THE FIGURES

- 10 **Figure 1:** Effects of vehicle, glucagon, and a glucagon-GLP1 dual-agonist (Compound 12) on A: Heart rate in insulin-resistant (IR) JCR: LA rat hearts; B: Cardiac output in IR hearts; C: Cardiac power in IR hearts. Values are presented as mean + SEM. * P < 0.05; ** P < 0.01 compared to baseline.

- 15 **Figure 2:** Energy state in hearts from insulin-resistant (IR) JCR: LA rats after perfusion with increasing concentrations of vehicle (n=4), glucagon (n=6), and a glucagon-GLP1 dual-agonist (Compound 12) (n=5). A: Adenosine monophosphate (AMP) concentrations. B: Adenosine diphosphate (ADP) concentrations. C: Adenosine triphosphate (ATP) concentrations. D: ATP/AMP ratios. E: ATP/ADP ratios. Values are presented as mean + SEM. * P < 0.05; ** P < 0.01 compared to vehicle.

Figure 3: Shows a table (Table 2) of compounds by sequence which may be useful in accordance with the invention.

- 25 **Figure 4:** Strokework calculated from individual data for each compound infused with compound 1 or glucagon-GLP-1 dual agonists. Dose is given in nmol/kg/min and indicated on top of each figure. A maximum of 40% increase in strokework was set as end point, after which infusion was discontinued.

- 30 **Figure 5:** Heart rate calculated from individual data for each compound infused with compound 1 or glucagon-GLP-1 dual agonists. Dose is given in nmol/kg/min and indicated on top of each figure. A maximum of 40% increase in strokework (figure 4) was set as end point, after which infusion was discontinued.

- 35 **Figure 6:** Shows a table (Table 3) of compounds by sequence which may be useful in accordance with the invention.

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), Orn (ornithine), Dbu (2,4-diaminobutyric acid) and Dpr (2,3-diaminopropanoic acid), Cit (citrulline), 1Nal (1-naphthylalanine), Hph (homophenylalanine), Hse (homoserine) and Orn (ornithine).

In the context of the present invention, C₁₋₆ alkyl and C₁₋₄ alkyl include methyl, ethyl, 1-propyl and 2-propyl.

In the context of the present invention, the expression "positive inotropic" refers to agents that increase the force and velocity of myocardial contractility, i.e. improves myocardial contractility.

The term "native glucagon" 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.

The terms "oxyntomodulin" and "OXM" refer to native human oxyntomodulin 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-Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala-OH.

In certain embodiments of compounds of the invention wherein the amino acid residue X3 is 3-(heterocyclyl)alanyl [i.e. an amino acid residue deriving from a 3-(heterocyclyl)-substituted alanine], then X3 may be selected from the group consisting of 3-(2-furyl)alanyl, 3-(4-thiazolyl)alanyl, 3-(3-pyridyl)alanyl, 3-(4-pyridyl)alanyl, 3-(1-pyrazolyl)alanyl, 3-(2-thienyl)alanyl, 3-(3-thienyl)alanyl and 3-(1,2,4-triazol-1-yl)alanyl.

Peptide sequence X

For the avoidance of doubt, in the definitions above, it is generally intended that the sequence of X only differs from the formulae shown at those positions which are stated to allow variation. Amino acids within the sequences X described herein 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.

In any of the formulae provided herein, the residue at position X3 may alternatively be selected from acetamidomethyl-cysteine, acetyldiaminobutanoic acid, carbamoyldiaminopropanoic acid, methylglutamine and methionine sulfoxide.

- 5 Certain formulae presented above allow the residues at positions X27, X28 and/or X29 to be absent. Typically, if X28 is absent, then X29 is also absent. If X27 is absent, then X28 and X29 are both also absent. In other words, X28 will not be absent if X29 is present, and X27 will not be absent if either of X28 and X29 is present.
- 10 When Z¹ is absent, the peptide sequence X can be considered an analogue of glucagon. In such embodiments, the peptide sequence X differs from the sequence of native human glucagon at one or more of the 29 positions, for example at a minimum of 2 of 29 positions, e.g. at a minimum of 3, 4, 5, 6 of 29 positions.
- 15 In certain embodiments, when X differs from human glucagon at only one position, that position may be X12, X17 or X18.

The residue at X12 may be Ala or Arg.

The residue at X17 may be Glu or Lys.

- 20 The residue at X18 may be His, Ser, Ala or Tyr.

Thus the peptide X may have the sequence:

- HSQGTFTSDYSAYLDSRRAQDFVQWLMNT; (Compound 103)
- 25 HSQGTFTSDYSRYLDSRRAQDFVQWLMNT; (Compound 104)
- HSQGTFTSDYSKYLDSERAQDFVQWLMNT; (Compound 106)
- HSQGTFTSDYSKYLDSKRAQDFVQWLMNT; (Compound 107)
- HSQGTFTSDYSKYLDSRHAQDFVQWLMNT; (Compound 108)
- HSQGTFTSDYSKYLDSRSAQDFVQWLMNT; (Compound 109)
- 30 HSQGTFTSDYSKYLDSRAAQDFVQWLMNT; or (Compound 110)
- HSQGTFTSDYSKYLDSRYAQDFVQWLMNT. (Compound 111)

Sequences having 2 or 3 differences from human glucagon include:

- 35 HSQGTFTSDYSRYLDSRRAKDFVQWLLNT; (Compound 112)
- HSQGTFTSDYSRYLDSRRAQDFVQWLLNT; (Compound 113)
- HSQGTFTSDYSRYLDSRRAQDFVQWLLNK; (Compound 114)

HSQGTFTSDYSKYLDSALAQDFVQWLLNT; (Compound 115)
 HSQGTFTSDYSKYLDKRRRAEDFVQWLMNT; (Compound 116)
 HSQGTFTSDYSKYLDK()RRAE()DFVQWLMNT; (Compound 117)
 HSQGTFTSDYSRYLDERRAQDFVQWLMNT; (Compound 118)
 5 HSQGTFTSDYSK()YLDE()RRAQDFVQWLMNT; (Compound 119)
 HSQGTFTSDYSKYLDSRRAQDFIEWLMNT; and (Compound 120)
 HSQGTFTSDYSKYLDSKAAQDFVQWLMNT; (Compound 121)
 HSQGTFTSDYSKYLDSLAAQDFVQWLLNT. (Compound 122)

- 10 Whether Z^1 is present or absent, it may be desirable that the peptide sequence X differs from human glucagon at a maximum of 10 of 29 positions, e.g. at a maximum of 7, 8, 9 or 10 positions.

Z^1

Z^1 may have the sequence:

- 15 GlyProSerSerGlyAlaProProProSer, representing the C-terminal 10 amino acids of native Exendin-4;
 GlyProSerSerGlyAlaProProProSerCys, representing the C-terminal 10 amino acids of native Exendin-4 plus an additional C-terminal Cys residue;
 LysArgAsnArgAsnAsnIleAla, representing the C-terminal 8 amino acids of native oxyntomodulin;
 20 or
 LysArgAsnArg.

Z^2

- The compound may comprise a C-terminal peptide sequence Z^2 of 1-20 amino acids, for example
 25 to stabilise the conformation and/or secondary structure of the glucagon analogue peptide, and/or
 to make the glucagon analogue peptide more resistant to enzymatic hydrolysis, e.g. as described in WO99/46283.

- When present, Z^2 represents a peptide sequence of 1-20 amino acid residues, e.g. in the range of
 30 1-15, more preferably in the range of 1-10 in particular in the range of 1-7 amino acid residues,
 e.g., 1, 2, 3, 4, 5, 6 or 7 amino acid residues, such as 6 amino acid residues. Each of the amino acid residues in the peptide sequence Z^2 may independently be selected from Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu (2,4 diaminobutyric acid), Dpr (2,3-diaminopropanoic acid) and Orn (ornithine). Preferably, the amino acid residues are selected from Ser, Thr, Tyr, Cys, Glu, Lys,
 35 Arg, Dbu, Dpr and Orn, more preferably may be selected exclusively from Glu, Lys, and Cys, especially Lys. The above-mentioned amino acids may have either D- or L-configuration, but preferably have an L-configuration. Particularly preferred sequences for Z^2 are sequences of

four, five, six or seven consecutive lysine residues (i.e. Lys₃, Lys₄, Lys₅, Lys₆ or Lys₇), and particularly five or six consecutive lysine residues. Other exemplary sequences of Z are shown in WO 01/04156, the content of which is incorporated herein by reference. Alternatively the C-terminal residue of the sequence Z² may be a Cys residue. This may assist in modification of the compound, e.g. conjugation to a lipophilic substituent or polymeric moiety as described below. In such embodiments, the sequence Z² may, for example, be only one amino acid in length (i.e. Z² = Cys) or may be two, three, four, five, six or even more amino acids in length. The other amino acids therefore serve as a spacer between the peptide X and the terminal Cys residue. In such embodiments, Z¹ may be absent.

In some embodiments, the peptide sequence Z² has no more than 25% amino acid sequence identity with the corresponding sequence of the IP-1 portion of human OXM (which has the sequence Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala).

"Percent (%) amino acid sequence identity" of a given peptide or polypeptide sequence with respect to another polypeptide sequence (e.g. IP-1) is calculated as the percentage of amino acid residues in the given peptide sequence that are identical with corresponding amino acid residues in the corresponding sequence of that other polypeptide when the two are aligned with one another, introducing gaps for optimal alignment if necessary. % identity values may be determined by WU-BLAST-2 (Altschul et al., Methods in Enzymology, 266:460-480 (1996)). WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11. A % amino acid sequence identity value is determined by the number of matching identical residues as determined by WU-BLAST-2, divided by the total number of residues of the reference sequence (gaps introduced by WU-BLAST-2 into the reference sequence to maximize the alignment score being ignored), multiplied by 100.

Thus, when Z² is aligned optimally with the 8 amino acids of IP-1, it has no more than two amino acids which are identical with the corresponding amino acids of IP-1.

Amino acid modification

One or more of the amino acid side chains in any of the compounds suitable for use in the present invention may be conjugated to a lipophilic substituent. The lipophilic substituent may be covalently bonded to an atom in the amino acid side chain, or alternatively may be conjugated to the amino acid side chain by a spacer. The amino acid may be part of the peptide X, or part of the peptides Z¹ or Z². The spacer, when present, is used to provide a spacing between the rest of the compound and the lipophilic substituent.

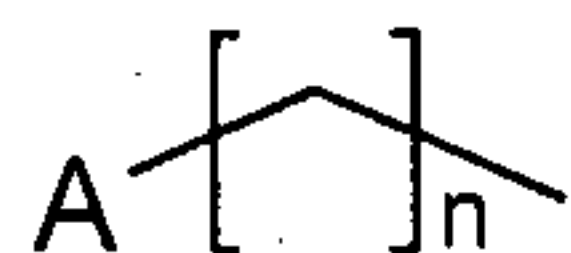
Without wishing to be bound by theory, it is thought that the lipophilic substituent binds albumin in the blood stream, thus shielding the compounds of the invention from enzymatic degradation which can enhance the half-life of the compounds. Thus compound modified in this way may be particularly suitable for chronic treatment.

The lipophilic substituent may be attached to the amino acid side chain or to the spacer via an ester, a sulphonyl ester, a thioester, an amide or a sulphonamide. Accordingly it will be understood that preferably the lipophilic substituent includes an acyl group, a sulphonyl group, an N atom, an O atom or an S atom which forms part of the ester, sulphonyl ester, thioester, amide or sulphonamide. Preferably, an acyl group in the lipophilic substituent forms part of an amide or ester with the amino acid side chain or the spacer.

The lipophilic substituent may include a hydrocarbon chain having 4 to 30 C atoms. Preferably it has at least 8 or 12 C atoms, and preferably it has 24 C atoms or fewer, or 20 C atoms or fewer. The hydrocarbon chain may be linear or branched and may be saturated or unsaturated. It will be understood that the hydrocarbon chain is preferably substituted with a moiety which forms part of the attachment to the amino acid side chain or the spacer, for example an acyl group, a sulphonyl group, an N atom, an O atom or an S atom. Most preferably the hydrocarbon chain is substituted with acyl, and accordingly the hydrocarbon chain may be part of an alkanoyl group, for example palmitoyl, caproyl, lauroyl, myristoyl or stearoyl.

In certain embodiments, the lipophilic substituent may include a hydrocarbon chain having 10 to 24 C atoms, e.g. 10 to 22 C atoms, e.g. 10 to 20 C atoms. Preferably it has at least 11 C atoms, and preferably it has 18 C atoms or fewer. For example, the hydrocarbon chain may contain 12, 13, 14, 15, 16, 17 or 18 carbon atoms. The hydrocarbon chain may be linear or branched and may be saturated or unsaturated. From the discussion above it will be understood that the hydrocarbon chain is preferably substituted with a moiety which forms part of the attachment to the amino acid side chain or the spacer, for example an acyl group, a sulphonyl group, an N atom, an O atom or an S atom. Most preferably the hydrocarbon chain is substituted with acyl, and accordingly the hydrocarbon chain may be part of an alkanoyl group, for example a dodecanoyl, 2-butyloctanoyl, tetradecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl or eicosanoyl group.

Accordingly, the lipophilic substituent may have the formula shown below:

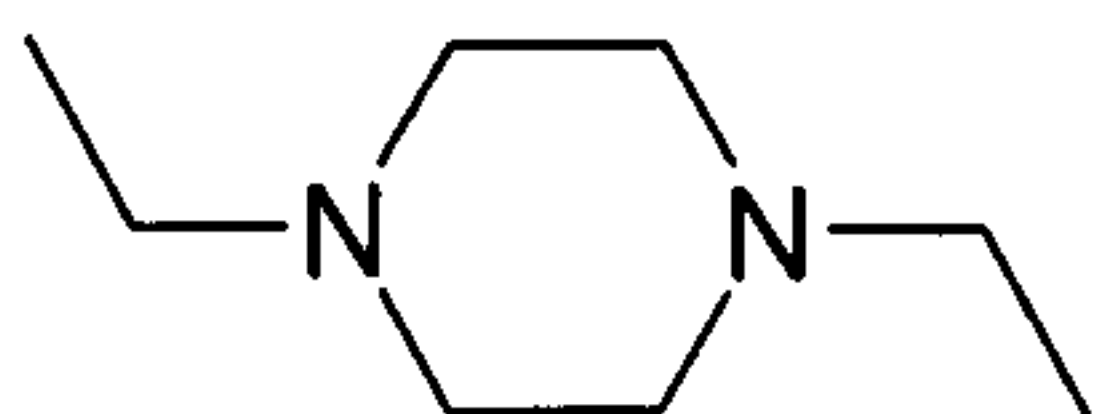


A may be, for example, an acyl group, a sulphonyl group, NH, N-alkyl, an O atom or an S atom, preferably acyl. n is an integer from 3 to 29, preferably at least 7 or at least 11, and preferably 23 or less, more preferably 19 or less.

5

The hydrocarbon chain may be further substituted. For example, it may be further substituted with up to three substituents selected from NH₂, OH and COOH. If the hydrocarbon chain is further substituted, preferably it is further substituted with only one substituent. Alternatively or additionally, the hydrocarbon chain may include a cycloalkane or heterocycloalkane, for example as shown below:

10



Preferably the cycloalkane or heterocycloalkane is a six-membered ring. Most preferably, it is piperidine.

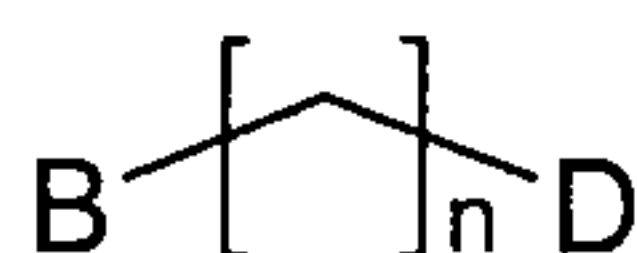
15

Alternatively, the lipophilic substituent may be based on a cyclopentanophenanthrene skeleton, which may be partially or fully unsaturated, or saturated. The carbon atoms in the skeleton each may be substituted with Me or OH. For example, the lipophilic substituent may be cholesteryl, deoxycholesteryl or lithocholesteryl.

20

As mentioned above, the lipophilic substituent may be conjugated to the amino acid side chain by a spacer. When present, the spacer is attached to the lipophilic substituent and to the amino acid side chain. The spacer may be attached to the lipophilic substituent and to the amino acid side chain independently by an ester, a sulphonyl ester, a thioester, an amide or a sulphonamide. Accordingly, it may include two moieties independently selected from acyl, sulphonyl, an N atom, an O atom or an S atom. The spacer may have the formula:

25



30

wherein B and D are each independently selected from acyl, sulphonyl, NH, N-alkyl, an O atom or an S atom, preferably from acyl and NH. Preferably, n is an integer from 1 to 10, preferably from

1 to 5. The spacer may be further substituted with one or more substituents selected from C₁₋₆ alkyl, amino-C₁₋₆ alkyl, hydroxy-C₁₋₆ alkyl and carboxy₁₋₆ alkyl.

Alternatively, the spacer may have two or more repeat units of the formula above. B, D and n are each selected independently for each repeat unit. Adjacent repeat units may be covalently attached to each other via their respective B and D moieties. For example, the B and D moieties of the adjacent repeat units may together form an ester, a sulphonyl ester, a thioester, an amide or a sulphonamide. The free B and D units at each end of the spacer are attached to the amino acid side chain and the lipophilic substituent as described above.

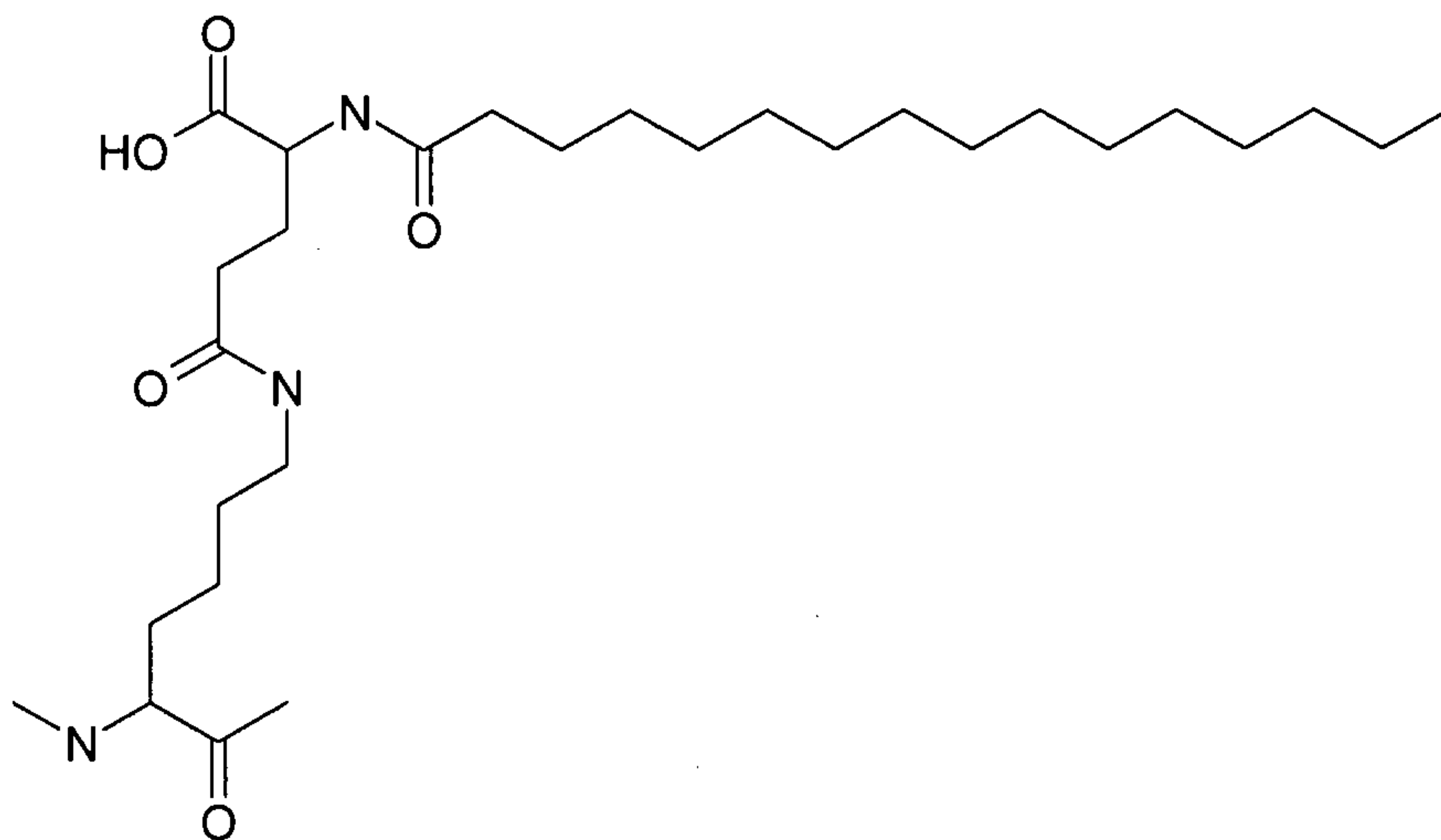
Preferably the spacer has five or fewer, four or fewer or three or fewer repeat units. Most preferably the spacer has two repeat units, or is a single unit.

The spacer (or one or more of the repeat units of the spacer, if it has repeat units) may be, for example, a natural or unnatural amino acid. It will be understood that for amino acids having functionalised side chains, B and/or D may be a moiety within the side chain of the amino acid. The spacer may be any naturally occurring or unnatural amino acid. For example, the spacer (or one or more of the repeat units of the spacer, if it has repeat units) may be Gly, Pro, Ala, Val, Leu, Ile, Met, Cys, Phe, Tyr, Trp, His, Lys, Arg, Gln, Asn, Glu, γ -Glu, ϵ -Lys, Asp, Ser, Thr, Gaba, Aib, β -Ala (i.e. 3-aminopropanoyl), 4-aminobutanoyl, 5-aminopentanoyl, 6-aminohexanoyl, 7-aminooctanoyl, 8-aminooctanoyl, 9-aminononanoyl, 10-aminodecanoyl or 8-amino-3,6-dioxaoctanoyl. In certain embodiments, the spacer is a residue of Glu, γ -Glu, ϵ -Lys, β -Ala (i.e. 3-aminopropanoyl), 4-aminobutanoyl, 8-aminooctanoyl or 8-amino-3,6-dioxaoctanoyl.

For example, the spacer may be a single amino acid selected from γ -Glu, Gaba, β -Ala and -Gly.

The lipophilic substituent may be conjugated to any amino acid side chain in the compound. Preferably, the amino acid side chain includes a carboxy, hydrox, thiol, amide or amine group, for forming an ester, a sulphonyl ester, a thioester, an amide or a sulphonamide with the spacer or lipophilic substituent. For example, the lipophilic substituent may be conjugated to a side chain of a Asn, Asp, Glu, Gln, His, Lys, Arg, Ser, Thr, Tyr, Trp, Cys or Dbu, Dpr or Orn residue, e.g. a side chain of a Glu, Lys, Ser, Cys, Dbu, Dpr or Orn residue. For example it may be a side chain of a Lys, Glu or Cys residue. Where two or more side chains carry a lipophilic substituent, they may be independently selected from these residues. Preferably, the lipophilic substituent is conjugated to Lys. However, any amino acid shown as Lys in the formulae provided herein may be replaced by Dbu, Dpr or Orn where a lipophilic substituent is added.

An example of a lipophilic substituent and spacer is shown in the formula below:



Here, the side chain of a Lys residue from the peptide X is covalently attached to a γ -Glu spacer via an amide linkage. A hexadecanoyl group is covalently attached to the γ -Glu spacer via an amide linkage. This combination of lipophilic moiety and spacer, conjugated to a Lys residue, may be referred to by the short-hand notation K(Hexadecanoyl- γ -Glu), e.g. when shown in formulae of specific compounds. γ -Glu can also be referred to as isoGlu, and a hexadecanoyl group as a palmitoyl group. Thus it will be apparent that the notation (Hexadecanoyl- γ -Glu) is equivalent to the notations (isoGlu(Palm)) or (isoGlu(Palmitoyl)) as used for example in PCT/GB2008/004121.

In certain embodiments, the side chain(s) of one or more of the residues at positions 16, 17, 18, 20, 24, 27, 28 or of Z^2 are conjugated to a lipophilic substituent. For example, one side chain of such a residue may be conjugated to a lipophilic substituent. Alternatively, two, or even more than two, side chains of such residues may be conjugated to a lipophilic substituent.

In some embodiments, Z^1 is absent and Z^2 consists of only one amino acid residue, which can then be regarded as position 30. It may be preferable that position 30 is Cys or Lys.

For example, at least one of positions 16, 17, 18, 20 and 28 may be conjugated to a lipophilic substituent. In such cases, position 30 may be absent. When position 30 is present, it is typically conjugated to a lipophilic substituent.

Thus the compound may have just one lipophilic substituent, at position 16, 17, 18, 20, 24, 27, 28 or 30, preferably at position 16, 17 or 20, particularly at position 17.

Alternatively, the compound may have precisely two lipophilic substituents, each at one of positions 16, 17, 18, 20, 24, 27, 28 or 30. Preferably one or both lipophilic substituents are present at one of positions 16, 17 or 20.

Thus, the compound may have lipophilic substituents at positions 16 and 17, 16 and 18, 16 and 20, 16 and 24, 16 and 27, 16 and 28 or 16 and 30; at 17 and 18, 17 and 20, 17 and 24, 17 and 27, 17 and 28 or 17 and 30; at 18 and 20, 18 and 24, 18 and 27, 18 and 28 or 18 and 30; at 20 and 24, 20 and 27, 20 and 28 or 20 and 30; at 24 and 27, 24 and 28 or 24 and 30; at 27 and 28 or 27 and 30; or at 28 and 30.

In yet further embodiments, the compound may have one or more further lipophilic substituents (giving three or more in total) at further positions selected from positions 16, 17, 18, 20, 24, 27, 28 or 30. However it may be desirable that a maximum of two positions are derivatised in this way.

Certain combinations of lipophilic moiety and spacer are dodecanoyl- γ -Glu, hexadecanoyl- γ -Glu, hexadecanoyl-Glu, hexadecanoyl-[3-aminopropanoyl], hexadecanoyl-[8-aminooctanoyl], hexadecanoyl- ϵ -Lys, 2-butyloctanoyl- γ -Glu, octadecanoyl- γ -Glu and hexadecanoyl-[4-aminobutanoyl].

In certain embodiments, the peptide X may have the sequence:

25 HSQGTFTSDYSKYLDKKAHDFVEWLLRA; (Compound 123)
 HSQGTFTSDYSKYLDSKAAKDFVEWLLRA; (Compound 124)
 HSQGTFTSDYSKYLDSKAAHDFVEWLKRA; (Compound 125)
 HSQGTFTSDYSKYLDSKAAHDFVEWLLKA; (Compound 126)
 HSQGTFTSDYSRYLDSKAAHDFVEWLLRA; (Compound 127)
 30 HSQGTFTSDYSLYLDSKAAHDFVEWLLRA; (Compound 128)
 HSQGTFTSDYSKYLDSKAAHDFVEWLLRAK; (Compound 129)
 HSQGTFTSDYSKYLDSKAAHDFVEWLLSAK (Compound 130)
 HSQGTFTSDYSKYLDSKAAHDFVEWLKSA; (Compound 131)
 HSQGTFTSDYSKYLDSKAAHDFVKWLLRA; (Compound 132)
 35 HSQGTFTSDYSKYLDSCAAHDFVEWLLRA; (Compound 133)
 HSQGTFTSDYSKYLDSCAAHDFVEWLLSA; (Compound 134)
 HSQGTFTSDYSKYLDSKAAACDFVEWLLRA; (Compound 135)

- HSQGTFTSDYSKYLDKSAAHDFVEWLLRA; (Compound 136)
 H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLSA; (Compound 137)
 H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLSAK; (Compound 138)
 H-Aib-QGTFTSDYSKYLDSKAAARDFVAWLLRA; (Compound 139)
 5 H-Aib-QGTFTSDYSKYLDSKAAKDFVAWLLRA; (Compound 140)
- H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLKA (Compound 141)
 H-Aib-QGTFTSDYSKYLDSKAAKDFVAWLLSA (Compound 142)
 H-Aib-QGTFTSDYSKYLDSKAAHDFVAWLLKA; (Compound 143)
 10 H-Aib-QGTFTSDYSKYLDKKAHDFVAWLLRA; (Compound 144)
 H-Aib-QGTFTSDYSRYLDSKAAHDFVEWLLSA; (Compound 145)
 H-Aib-QGTFTSDYSKYLDSKAAHDFVKWLLSA; (Compound 146)
 H-Aib-QGTFTSDYSLYLDSKAAHDFVEWLLSA; (Compound 147)
 H-Aib-QGTFTSDYSKYLDSCAAHDFVEWLLSA; (Compound 148)
 15 H-Aib-QGTFTSDYSKYLDSKAAACDFVEWLLRA; (Compound 149)
 H-Aib-QGTFTSDYSKYLDK()KAAE()DFVEWLLRA; (Compound 150)
 H-Aib-QGTFTSDYSKYLDSKAAHDFVE()WLLK()A (Compound 151)
 H-Aib-QGTFTSDYSKYLDSKAAK()DFVE()WLLRA; (Compound 152)
 H-Aib-QGTFTSDYSKYLDSK()AAHE()FVEWLLKA; or (Compound 153)
 20 H-Aib-QGTFTSDYSKYLDSK()AAKE()FVEWLLRA. (Compound 154)
 HSQGTFTSDYSKYLDRARADDFVAWLKSA; (Compound 155)
 HSQGTFTSDYSKYLDRARADDFVAWLKEA; (Compound 156)
 HSQGTFTSDYSKYLDRARAEDFVAWLKST; (Compound 157)
 HSQGTFTSDYSKYLDRARADDFVEWLKST; (Compound 158)
 25 H-DSer-QGTFTSDYSKYLDRARADDFVAWLKST; (Compound 159)
 HSQGTFTSDYSKYLDRARAHDFVAWLKST; (Compound 160)
 HSQGTFTSDYSKYLDKARADDFVAWLKST; (Compound 161)
 HSQGTFTSDYSKYLDRAKADDFVAWLKST; (Compound 162)
 HSQGTFTSDYSKYLDRARAKDFVAWLKST, or (Compound 163)
 30 HSQGTFTSDYSKYLDRARADDFVKWLKST (Compound 164)

In certain embodiments these peptides may carry a lipophilic substituent at the position marked "*" as follows:

- HSQGTFTSDYSKYLDS-K*-AAHDFVEWLLRA; (Compound 165)
 35 HSQGTFTSDYSKYLD-K*-KAAHDFVEWLLRA; (Compound 166)
 HSQGTFTSDYSKYLDSKAA-K*-DFVEWLLRA; (Compound 167)
 HSQGTFTSDYSKYLDSKAAHDFVEWL-K*-RA; (Compound 168)

- HSQGTFTSDYSKYLDSKAAHDFVEWLL-K*-A; (Compound 169)
 HSQGTFTSDYSRYLDS-K*-AAHDFVEWLLRA; (Compound 170)
 HSQGTFTSDYSLYLD-S-K*-AAHDFVEWLLRA; (Compound 171)
 HSQGTFTSDYSKYLDSKAAHDFVEWLLRA-K*; (Compound 172)
 5 HSQGTFTSDYSKYLDSKAAHDFVEWLLSA-K*; (Compound 173)
 HSQGTFTSDYSKYLDSKAAHDFVEWL-K*-SA; (Compound 174)
 HSQGTFTSDYSKYLDSKAAHDFV-K*-WLLRA; (Compound 175)
 HSQGTFTSDYSKYLDS-C*-AAHDFVEWLLRA; (Compound 176)
 HSQGTFTSDYSKYLDS-C*-AAHDFVEWLLSA; (Compound 177)
 10 HSQGTFTSDYSKYLDSKAA-C*-DFVEWLLRA; (Compound 178)
 HSQGTFTSDYSKYLD-K*-SAAHDFVEWLLRA; (Compound 179)
 H-Aib-QGTFTSDYSKYLDS-K*-AAHDFVEWLLSA; (Compound 180)
 H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLSA-K*; (Compound 181)
 H-Aib-QGTFTSDYSKYLDS-K*-AARDFVAWLLRA; (Compound 182)
 15 H-Aib-QGTFTSDYSKYLDSKAA-K*-DFVAWLLRA; (Compound 183)
 H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLL-K*-A; (Compound 184)
 H-Aib-QGTFTSDYSKYLDS-K*-AAHDFVEWLLKA; (Compound 185)
 H-Aib-QGTFTSDYSKYLDS-K*-AAHDFVEWLLRA; (Compound 186)
 H-Aib-QGTFTSDYSKYLDSKAA-K*-DFVAWLLSA; (Compound 187)
 20 H-Aib-QGTFTSDYSKYLDSKAAHDFVAWLL-K*-A; (Compound 188)
 H-Aib-QGTFTSDYSKYLD-K*-KAAHDFVAWLLRA; (Compound 189)
 H-Aib-QGTFTSDYSRYLDS-K*-AAHDFVEWLLSA; (Compound 190)
 H-Aib-QGTFTSDYSKYLDSKAAHDFV-K*-WLLSA; (Compound 191)
 H-Aib-QGTFTSDYSLYLD-S-K*-AAHDFVEWLLSA; (Compound 192)
 25 H-Aib-QGTFTSDYSKYLDS-C*-AAHDFVEWLLSA; (Compound 193)
 H-Aib-QGTFTSDYSKYLDSKAA-C*-DFVEWLLRA; (Compound 194)
 H-Aib-QGTFTSDYSKYLD-S*-KAAHDFVEWLLSA; (Compound 195)
 H-Aib-QGTFTSDYSKYLDK() $\text{K}^*\text{AAE}()$ DFVEWLLRA; (Compound 196)
 H-Aib-QGTFTSDYSKYLDSK $\text{AAHDFVE}()$ WLLK() A ; (Compound 197)
 30 H-Aib-QGTFTSDYSKYLDSK $\text{AAK}()$ DFVE() WLLRA ; (Compound 198)
 H-Aib-QGTFTSDYSKYLDSK() $\text{AAHE}()$ FVEWLLK A ; or (Compound 199)
 H-Aib-QGTFTSDYSKYLDSK() $\text{AAK}^*\text{E}()$ FVEWLLRA. (Compound 200)
 Residues marked "()" participate in an intramolecular bond, such as a lactam ring, as described above.

35

In particular embodiments, the derivatised peptide X has the formula:

HSQGTFTSDYSKYLDS-K(Hexadecanoyl- γ -Glu)-AAHDFVEWLLRA; (Compound 201)

- HSQGTFTSDYSKYLD-K(Hexadecanoyl- γ -Glu)-KAAHDFVEWLLRA; (Compound 202)
 HSQGTFTSDYSKYLDSKAAHDFVEWL-K(Hexadecanoyl- γ -Glu)-RA; (Compound 203)
 HSQGTFTSDYSKYLDSKAA-K(Hexadecanoyl- γ -Glu)-DFVEWLLRA; (Compound 204)
 HSQGTFTSDYSKYLDSKAAHDFVEWLL-K(Hexadecanoyl- γ -Glu)-A; (Compound 205)
 5 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl- γ -Glu)-AAHDFVEWLLRA; (Compound 206)
 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl- γ -Glu)-AARDFVAWLLRA; (Compound 207)
 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl- γ -Glu)-AAHDFVEWLLSA; (Compound 208)
 H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLL-K(Hexadecanoyl- γ -Glu)-A; (Compound 209)
 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl- γ -Glu)-AAHDFVE()WLLK()A; (Compound 210)
 10 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl- γ -Glu)-AAHDFVEWLLKA; (Compound 211)
 HSQGTFTSDYSKYLDS-K(Hexadecanoyl- γ -Glu)-AAHDFVEWLLRA; (Compound 212)
 H-Aib-QGTFTSDYSKYLDSKAA-K(Hexadecanoyl- γ -Glu)-DFVAWLLRA; (Compound 213)
 H-Aib-QGTFTSDYSKYLDS-K(Dodecanoyl- γ -Glu)-AAHDFVEWLLSA; (Compound 214)
 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-[3-aminopropanoyl])-AAHDFVEWLLSA;
 15 (Compound 215)
 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-[8-aminooctanoyl])-AAHDFVEWLLSA; (Compound 216)
 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl- ϵ -Lys)-AAHDFVEWLLSA; (Compound 217)
 HSQGTFTSDYSKYLDS-K(Hexadecanoyl)-AAHDFVEWLLSA; (Compound 218)
 20 HSQGTFTSDYSKYLDS-K(Octadecanoyl- γ -Glu)-AAHDFVEWLLSA; (Compound 219)
 HSQGTFTSDYSKYLDS-K([2-Butyloctanoyl]- γ -Glu)-AAHDFVEWLLSA; (Compound 220)
 HSQGTFTSDYSKYLDS-K(Hexadecanoyl-[4-Aminobutanoyl])-AAHDFVEWLLSA; (Compound 221)
 HSQGTFTSDYSKYLDS-K(Octadecanoyl- γ -Glu)-AAHDFVEWLLSA; (Compound 222)
 25 HSQGTFTSDYSKYLDS-K(Hexadecanoyl-E)-AAHDFVEWLLSA; (Compound 223)
 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl)-AAHDFVEWLLSA; (Compound 224)
 H-Aib-QGTFTSDYSKYLDS-K(Octadecanoyl- γ -Glu)-AAHDFVEWLLSA; (Compound 225)
 H-Aib-QGTFTSDYSKYLDS-K([2-Butyloctanoyl]- γ -Glu)-AAHDFVEWLLSA; (Compound 226)
 H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-[4-Aminobutanoyl])-AAHDFVEWLLSA; (Compound 227)
 30 HSQGTFTSDYSKYLDRARADDFVAWLK(Hexadecanoyl- γ -Glu)-SA; (Compound 228)
 HSQGTFTSDYSKYLDRARADDFVAWLK(Hexadecanoyl- γ -Glu)-EA; (Compound 229)
 HSQGTFTSDYSKYLDRARAEDFVAWLK(Hexadecanoyl- γ -Glu)-ST; (Compound 230)
 HSQGTFTSDYSKYLDRARADDFVEWLK(Hexadecanoyl- γ -Glu)-ST; (Compound 231)
 35 H-DSer-QGTFTSDYSKYLDRARADDFVAWLK(Hexadecanoyl- γ -Glu)-ST; (Compound 232)
 HSQGTFTSDYSKYLDRARAHDFVAWLK(Hexadecanoyl- γ -Glu)-ST; (Compound 233)
 HSQGTFTSDYSKYLDRARADDFVAWLK(Hexadecanoyl- γ -Glu)-ST; (Compound 234)

HSQGTFTSDYSKYLDK(Hexadecanoyl- γ -Glu)-ARADDFVAWLKST; (Compound 235)

HSQGTFTSDYSKYLDRAK(Hexadecanoyl- γ -Glu)-ADDFVAWLKST; (Compound 236)

HSQGTFTSDYSKYLDRARAK(Hexadecanoyl- γ -Glu)-DFVAWLKST; (Compound 237)

HSQGTFTSDYSKYLDRARADDFVK(Hexadecanoyl- γ -Glu)-WLKST; (Compound 238)

5 H-Aib-QGTFTSDYSKYLDS-K(Octadecanoyl- γ -Glu)-AAHDFVEWLLSA; or (Compound 239)

H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-E)-AAHDFVEWLLSA. (Compound 240)

Residues marked “()” participate in an intramolecular bond, such as a lactam ring.

10 Alternatively or additionally, one or more amino acid side chains in the compound of the invention may be conjugated to a polymeric moiety, for example, in order to increase solubility and/or half-life in vivo (e.g. in plasma) and/or bioavailability. Such modification is also known to reduce clearance (e.g. renal clearance) of therapeutic proteins and peptides.

15 The polymeric moiety is preferably water soluble (amphiphilic or hydrophilic), non-toxic, and pharmaceutically inert. Suitable polymeric moieties include polyethylene glycol (PEG), homo- or co-polymers of PEG, a monomethyl-substituted polymer of PEG (mPEG), or polyoxyethylene glycerol (POG). See, for example, *Int. J. Hematology* 68:1 (1998); *Bioconjugate Chem.* 6:150 (1995); and *Crit. Rev. Therap. Drug Carrier Sys.* 9:249 (1992).

20 Other suitable polymeric moieties include poly-amino acids such as poly-lysine, poly-aspartic acid and poly-glutamic acid (see for example Gombotz, et al. (1995) , *Bioconjugate Chem.* , vol. 6 : 332-351; Hudecz, et al. (1992) , *Bioconjugate Chem.* , vol. 3, 49-57; Tsukada, et al. (1984) , *J. Natl. Cancer Inst.* , vol 73, : 721-729; and Pratesi, et al. (1985), *Br. J. Cancer*, vol. 52: 841-848).

25 The polymeric moiety may be straight-chain or branched. It may have a molecular weight of 500-40,000 Da, for example 500-5,000 Da, 500-10,000 Da, 1000-5000 Da, 10,000-20,000 Da, or 20,000-40,000Da.

30 A compound may comprise two or more such moieties, in which case the total molecular weight of all such moieties will generally fall within the ranges provided above.

35 The polymeric moiety may be coupled (by covalent linkage) to an amino, carboxyl or thiol group of an amino acid side chain. Preferred examples are the thiol group of Cys residues and the epsilon amino group of Lys residues, and the carboxyl groups of Asp and Glu residues may also be used.

For example, the polymeric moiety may be coupled to the side chain of the residue at one or more of positions 16, 17 18, 20, 21, 24 or 29, or to the C-terminus of the peptide. For example, it may be coupled at one or more of positions 16, 17, 21 and 24.

- 5 The skilled reader will be well aware of suitable techniques which can be used to perform the coupling reaction. For example, a PEG moiety carrying a methoxy group can be coupled to a Cys thiol group by a maleimido linkage using reagents commercially available from Nektar Therapeutics AL. See also WO 2008/101017, and the references cited above for details of suitable chemistry.

10

Biological activity

- Binding of the relevant compounds to GLP-1 or glucagon (Glu) receptors may be used as an indication of agonist activity, but in general it is preferred to use a biological assay which measures intracellular signalling caused by binding of the compound to the relevant receptor. For
15 example, activation of the glucagon receptor by a glucagon agonist will stimulate cellular cyclic AMP (cAMP) formation. Similarly, activation of the GLP-1 receptor by a GLP-1 agonist will stimulate cellular cAMP formation. Thus, production of cAMP in suitable cells expressing one of these two receptors can be used to monitor the relevant receptor activity. Use of a suitable pair of cell types, each expressing one receptor but not the other, can hence be used to determine
20 agonist activity towards both types of receptor.

- The skilled person will be aware of suitable assay formats, and examples are provided below. The GLP-1 receptor and/or the glucagon receptor may have the sequence of the receptors as described in the examples. For example, the assays may make use of the human glucagon
25 receptor (Glucagon-R) having primary accession number GI:4503947 and/or the human glucagon-like peptide 1 receptor (GLP-1R) having primary accession number GI:166795283. (Where sequences of precursor proteins are referred to, it should of course be understood that assays may make use of the mature protein, lacking the signal sequence).

- 30 EC₅₀ values may be used as a numerical measure of agonist potency at a given receptor. An EC₅₀ value is a measure of the concentration of a compound required to achieve half of that compound's maximal activity in a particular assay. Thus, for example, a compound having EC₅₀[GLP-1] lower than the EC₅₀[GLP-1R] of glucagon in a particular assay may be considered to have higher potency at the GLP-1R than glucagon.

35

The compounds described in this specification are typically Glu-GLP-1 (glucagon-GLP-1) dual agonists, i.e. they are capable of stimulating cAMP formation at both the glucagon receptor and

the GLP-1 receptor. The stimulation of each receptor can be measured in independent assays and afterwards compared to each other.

By comparing the EC_{50} value for the glucagon receptor (EC_{50} [Glucagon-R]) with the EC_{50} value for the GLP-1 receptor, (EC_{50} [GLP-1R]) for a given compound the relative glucagon selectivity (%) of that compound can be found:

$$\text{Relative Glucagon-R selectivity [Compound]} = (1/EC_{50} [\text{Glucagon-R}]) \times 100 / (1/EC_{50} [\text{Glucagon-R}] + 1/EC_{50} [\text{GLP-1R}])$$

The relative GLP-1R selectivity can likewise be found:

$$\text{Relative GLP-1R selectivity [Compound]} = (1/EC_{50} [\text{GLP-1R}]) \times 100 / (1/EC_{50} [\text{Glucagon-R}] + 1/EC_{50} [\text{GLP-1R}])$$

A compound's relative selectivity allows its effect on the GLP-1 or glucagon receptor to be compared directly to its effect on the other receptor. For example, the higher a compound's relative GLP-1 selectivity is, the more effective that compound is on the GLP-1 receptor as compared to the glucagon receptor.

Using the assays described below, we have found the relative GLP-1 selectivity for human glucagon to be approximately 5%.

Compounds suitable for use in the methods of the invention typically have a higher relative GLP-1R selectivity than human glucagon. Thus, for a particular level of glucagon-R agonist activity, the compound will display a higher level of GLP-1R agonist activity (i.e. greater potency at the GLP-1 receptor) than glucagon. It will be understood that the absolute potency of a particular compound at the glucagon and GLP-1 receptors may be higher, lower or approximately equal to that of native human glucagon, as long as the appropriate relative GLP-1R selectivity is achieved.

Nevertheless, the compounds may have a lower EC_{50} [GLP-1R] than human glucagon. The compounds may have a lower EC_{50} [GLP-1-R] than glucagon while maintaining an EC_{50} [Glucagon-R] that is less than 10-fold higher than that of human glucagon, less than 5-fold higher than that of human glucagon, or less than 2-fold higher than that of human glucagon.

The compounds may have an EC_{50} [Glucagon-R] that is less than two-fold that of human glucagon. The compounds may have an EC_{50} [Glucagon-R] that is less than two-fold that of

human glucagon and have an EC_{50} [GLP-1R] that is less than half that of human glucagon, less than a fifth of that of human glucagon, or less than a tenth of that of human glucagon.

The relative GLP-1 selectivity of the compounds may be between 10% and 95%. For example, the compounds may have a relative selectivity of 10-20%, 10-30%, 20-50%, 30-70%, or 50-80%; or of 30-50%, 40-60%, 50-70% or 75-95%.

Therapeutic uses

The methods of the invention are applicable for conditions in which it is desirable to improve cardiac function directly, e.g. where there is a dysfunction of the cardiac muscle (myocardium) itself. Such conditions include myocardial infarction, heart failure and cardiogenic shock.

Positive inotropic agents increase the strength of myocardial contraction, and are used to improve hemodynamic parameters and thereby relieve symptoms and protect end-organs in patients with myocardial infarction, cardiogenic shock, or heart failure. Known inotropic agents such as dobutamine, norepinephrine and glucagon exert their effects (increase in cardiac work) at the expense of increased cardiac energy demand and can therefore have a severe depleting effect on the heart's energy reserves (as measured e.g. by total phosphocreatine (PCr), total ATP, or by PCr/ATP, ATP/ADP or ATP/AMP ratios). Since the failing or diseased heart is often energy-starved, the use of inotropic agents may therefore result in energy depletion and consequently in an increased incidence of arrhythmias as well as in increased short- and long-term mortality (Jessup M et al., Circulation 2009;119:1977-2016). Because of this, current guidelines for treatment of heart failure state that positive inotropic agents should only "be considered for palliation of symptoms in patients with refractory end-stage heart failure" (Dickstein K et al., Eur Heart J 2008;29:2388-2442), and that such agents should be "withdrawn as soon as adequate organ perfusion is restored and/or congestion reduced" (Jessup et al., op cit.). Typically, then, inotropic agents are administered only in order to stabilise a patient's condition, but withdrawn after a few hours or a few days.

Without wishing to be bound by any particular theory, it is believed that the compounds described above for use in the methods of the invention act as glucagon-GLP-1 dual agonists (although they may exert their beneficial cardiac effects by a different mechanism, e.g. via a distinct receptor). They have surprisingly been found to increase cardiac inotropy while simultaneously improving myocardial metabolism, in particular preserving the energetic state of the heart, or at least depleting the reserves of high energy phosphates to a lesser extent than the other inotropic agents discussed above. They are therefore particularly useful for treating an individual suffering from myocardial infarction, heart failure, cardiogenic shock or any other condition where increased cardiac inotropy is desired without compromising the energetic state of the heart, i.e.

any abnormality of cardiac function which results in the inability of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or allows it to do so only from an abnormally elevated ventricular diastolic volume. This includes, but is not restricted to; congestive heart failure, systolic dysfunction, diastolic dysfunction, myocardial infarction, ischemic heart disease, diabetic cardiomyopathy, or combinations thereof.

The myocardial energy status may be monitored by determining total phosphocreatine (PCr), total ATP, or PCr/ATP, ATP/ADP or ATP/AMP ratios. Such determinations may be made by biopsy (e.g. as described in Ally A and Park G. Rapid determination of creatine, phosphocreatine, purine bases and nucleotides (ATP, ADP, AMP, GTP, GDP) in heart biopsies by gradient ion-pair reversed-phase liquid chromatography. J Chromatogr 1992;575:19-27) or by magnetic resonance spectroscopy (Neubauer S et al., Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. Circulation 1997;96:2190-2196; Yabe T et al., Quantitative measurements of cardiac phosphorus metabolites in coronary artery disease by ³¹P magnetic resonance spectroscopy. Circulation 1995;92:15-23).

By improving myocardial metabolism simultaneously with having positive inotropic effects, the compounds for use in accordance with this invention may be associated with fewer arrhythmias and/or lower mortality than current positive inotropic agents. Consequently, the methods of the invention may be used for patients with less severe disease and/or for longer periods of time in those with severe heart failure, than is currently recommended.

For example, the subject may be treated with a suitable compound for a period greater than 12 hours, greater than 24 hours, greater than 36 hours or greater than 48 hours. For example, the subject may be treated for a period greater than 3 days, e.g. greater than 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days. The patient may be treated for a period greater than 2 weeks, greater than 3 weeks or greater than 4 weeks. The patient may be treated for a period greater than 1 month, 2 months, 3 months, 4 months, or 5 months, i.e. chronic/lifelong treatment.

The patient may be treated for a period between 1 week and 6 weeks, e.g. between 2 weeks and 6 weeks, between 3 weeks and 6 weeks, between 4 weeks and 6 weeks or between 5 weeks and 6 weeks.

The patient may be treated for a period between 1 week and 5 weeks, e.g. between 2 weeks and 5 weeks, between 3 weeks and 5 weeks, between 4 weeks and 5 weeks.

The patient may be treated for a period between 1 week and 4 weeks, e.g. between 2 weeks and 4 weeks, between 3 weeks and 4 weeks.

5 The patient may be treated for a period between 1 week and 3 weeks, e.g. between 2 weeks and 3 weeks.

10 For example, the patient may be treated for a period between 1 week and 6 months, e.g. between 1 week and 5 months, between 1 week and 4 months, between 1 week and 3 months, between 1 week and 2 months, or between 1 week and 1 month.

The patient may be treated for a period between 2 weeks and 6 months, e.g. between 2 weeks and 5 months, between 2 weeks and 4 months, between 2 weeks and 3 months, between 2 weeks and 2 months, or between 2 weeks and 1 month.

15 The patient may be treated for a period between 3 weeks and 6 months, e.g. between 3 weeks and 5 months, between 3 weeks and 4 months, between 3 weeks and 3 months, between 3 weeks and 2 months, or between 3 weeks and 1 month.

20 The patient may be treated for a period between 4 weeks and 6 months, e.g. between 4 weeks and 5 months, between 4 weeks and 4 months, between 4 weeks and 3 months, between 4 weeks and 2 months, or between 4 weeks and 1 month.

25 The patient may be treated for a period between 1 month and 6 months, e.g. between 2 months and 6 months, between 3 months and 6 months, between 4 months and 6 months, between 5 months and 6 months.

The patient may be treated for a period between 1 month and 5 months, e.g. between 2 months and 5 months, between 3 months and 5 months, between 4 months and 5 months.

30 The patient may be treated for a period between 1 month and 3 months, e.g. between 2 months and 3 months.

The patient may be treated for a period between 1 month and 2 months.

35 In some cases in accordance with the present invention treatment may comprise a dosage regime of continuous infusion, twice daily or once daily.

Other dosage regimes are contemplated, including a dosage regime that may be once daily, twice daily, once weekly, once bi-weekly or once monthly.

Pharmaceutical compositions

- 5 The compounds described for use in this invention, or salts thereof, may be formulated as pharmaceutical compositions prepared for storage or administration, which typically comprise a therapeutically effective amount of a compound or salt thereof in a pharmaceutically acceptable carrier.
- 10 The precise amount to be administered will depend on the route of administration, the type of mammal being treated, and the physical characteristics of the specific mammal under consideration. These factors and their relationship to determining this amount are well known to skilled practitioners in the medical arts. This amount and the method of administration can be tailored to achieve optimal efficacy, and may depend on such factors as weight, diet, concurrent
- 15 medication and other factors, well known to those skilled in the medical arts. The dosage levels and dosing regimen most appropriate for human use may be established on the basis of the results obtained by the present invention, and may be confirmed in properly designed clinical trials.
- 20 An effective dosage and treatment protocol may be determined by conventional means, starting with a low dose in laboratory animals and then increasing the dosage while monitoring the effects, and systematically varying the dosage regimen as well. Numerous factors may be taken into consideration by a clinician when determining an optimal dosage for a given subject. Such considerations are known to the skilled person.
- 25 The term "pharmaceutically acceptable carrier" includes any of the standard pharmaceutical carriers. Pharmaceutically acceptable carriers for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). For example, sterile saline and phosphate-buffered saline at slightly acidic or physiological pH may be used. pH buffering agents may be
- 30 phosphate, citrate, acetate, tris/hydroxymethyl)aminomethane (TRIS), N-Tris(hydroxymethyl)methyl -3- aminopropanesulphonic acid (TAPS), ammonium bicarbonate, diethanolamine, histidine, which is a preferred buffer, arginine, lysine, or acetate or mixtures thereof. The term further encompasses any agents listed in the US Pharmacopeia for use in
- 35 animals, including humans.

The term "pharmaceutically acceptable salt" refers to the salts of the dual agonist compounds. Pharmaceutically acceptable salts typically include acid addition salts and basic salts. Examples of pharmaceutically acceptable acid addition salts include hydrochloride salts, citrate salts and acetate salts. Examples of pharmaceutically acceptable basic salts include salts where the cation is selected from alkali metals, such as sodium and potassium, alkaline earth metals, such as calcium, and ammonium ions $^+N(R^3)_3(R^4)$, where R^3 and R^4 independently designates optionally substituted C_{1-6} -alkyl, optionally substituted C_{2-6} -alkenyl, optionally substituted aryl, or optionally substituted heteroaryl. Other examples of pharmaceutically acceptable salts are described in "Remington's Pharmaceutical Sciences", 17th edition. Ed. Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, U.S.A., 1985 and more recent editions, and in the Encyclopaedia of Pharmaceutical Technology.

"Treatment" is an approach for obtaining beneficial or desired clinical results. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

"Treatment" is an intervention performed with the intention of preventing the development of, or altering the pathology of, a disorder. Accordingly, "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented

The pharmaceutical compositions can be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms. It may be provided in single dose injectable form, for example in the form of a pen. Compositions may be formulated for any suitable route and means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and transdermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy.

Intravenous, subcutaneous or transdermal modes of administration may be particularly suitable for the compounds described herein.

Combination therapy

- 5 The compounds described above may be administered as part of a combination therapy with an agent for treatment of heart failure, diabetes, obesity, myocardial infarction, hypertension, or hypolipidemia.

- 10 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 (or salt thereof) can be used in combination with an anti-diabetic agent including but not limited to metformin, a sulfonylurea, a glinide, a DPP-IV inhibitor, a glitazone, or insulin. In a preferred embodiment the compound or salt thereof is used in combination with
15 insulin, DPP-IV inhibitor, sulfonylurea or metformin, particularly sulfonylurea or metformin, for achieving adequate glycemic control. In an even more preferred embodiment the compound or salt thereof is used in combination with insulin or an insulin analogue for achieving adequate glycemic control. Examples of insulin analogues include but are not limited to Lantus™, Novorapid™, Humalog™, Novomix™, and Actraphane HM™.

- 20 The compound or salt thereof 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.

- 25 The analogue compound or salt thereof can be used in combination with an anti-hypertension agent including but not limited to an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), diuretics, beta-blocker, or calcium channel blocker.

- 30 The analogue compound or salt thereof can in particular be used in combination with an agent for treatment of myocardial infarction, heart failure or cardiogenic shock including but not limited to diuretics, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), aldosterone antagonists, digitalis, acute ionotropes and inotropic dilators.

- 35 The analogue compound or salt thereof can in particular be used in combination with classes of hypolipidemic drugs such as cholesterol lowering agents including but not limited to statins (HMG-CoA reductase inhibitors), fibrates and niacin.

Recombinant expression

The compounds for use in the invention may be expressed by recombinant techniques, particularly when they consist entirely of naturally occurring amino acids. For recombinant
5 expression, nucleic acids encoding the relevant compounds will normally be inserted in suitable vectors to form cloning or expression vectors carrying the coding sequences. The vectors can, depending on purpose and type of application, be in the form of plasmids, phages, cosmids, mini-chromosomes, or virus, but also naked DNA which is only expressed transiently in certain cells is an important vector. Cloning and expression vectors (plasmid vectors) may be capable of
10 autonomous replication, thereby enabling high copy-numbers for the purposes of high-level expression or high-level replication for subsequent cloning.

In general outline, an expression vector comprises the following features in the 5'→3' direction and in operable linkage: a promoter for driving expression of the relevant coding nucleic acid,
15 optionally a nucleic acid sequence encoding a leader peptide enabling secretion (to the extracellular phase or, where applicable, into the periplasma), the nucleic acid fragment encoding the compound, and optionally a nucleic acid sequence encoding a terminator. They may comprise additional features such as selectable markers and origins of replication. When operating with expression vectors in producer strains or cell lines it may be preferred that the
20 vector is capable of integrating into the host cell genome. The skilled person is very familiar with suitable vectors and is able to design one according to their specific requirements.

The vectors of the invention are used to transform host cells to produce the compound. Such transformed cells can be cultured cells or cell lines used for propagation of the nucleic acid
25 fragments and vectors of the invention, or used for recombinant production of the peptides of the invention.

Preferred host cells are micro-organisms such as bacteria (such as the species *Escherichia* (e.g. *E. coli*), *Bacillus* (e.g. *Bacillus subtilis*), *Salmonella*, or *Mycobacterium* (preferably non-
30 pathogenic, e.g. *M. bovis* BCG), yeasts (such as *Saccharomyces cerevisiae*), and protozoans. Alternatively, the host cell may be derived from a multicellular organism, i.e. it may be fungal cell, an insect cell, a plant cell, or a mammalian cell. For the purposes of cloning and/or optimised expression it is preferred that the host cell is capable of replicating the nucleic acid fragment or
vector as applicable. Cells expressing the nucleic fragment are useful embodiments of the
35 invention; they can be used for small-scale or large-scale preparation of the compounds.

When producing the compound by means of transformed cells, it is convenient, although far from essential, that the expression product is secreted into the culture medium.

It will be understood that such nucleic acids, expression vectors and host cells may be used for treatment of any of the conditions described herein which may be treated with the compounds themselves. For example, nucleic acids encoding the compounds, particularly expression vectors containing such nucleic acids, may be suitable for direct administration to a subject so that the nucleic acid is taken up and the compound produced by the subject's own cells. The compound is preferably secreted by the cells containing the nucleic acid. Similarly, host cells capable of producing and secreting the compound may be administered to a subject so that the compound is produced in situ. The host cells may be treated (e.g. encapsulated) to inhibit or reduce their immunogenicity to the recipient subject. References to a therapeutic composition comprising a compound, administration of a compound, or any therapeutic use of such a compound, should therefore be construed to encompass the equivalent use of a nucleic acid, expression vector or host cell as described herein except where the context demands otherwise.

EXAMPLES

Example 1. Assessment of inotropic effect in working heart model

The effect of the inotropic compound glucagon and a glucagon-GLP-1 dual-agonist (Compound 12 having the sequence HSQGTFTSDYSKYLDRARADDFVAWLKST) on cardiac function, metabolism, and energy state was evaluated in isolated working hearts (Lopaschuk, GD and Barr, RL. Measurements of fatty acid and carbohydrate metabolism in the isolated working rat heart. *Molecular and Cellular Biochemistry*. 1997; 172: 137-147) from control and insulin-resistant JCR:LA-cp rats. Isolated working hearts were subjected to aerobic perfusion with Krebs-Henseleit solution (11 mM glucose, 2000 μ U/ml insulin, 1.25 mM free Ca^{2+} , 0.8 mM palmitate, and 3% BSA) and during perfusion increasing concentrations (10, 50, and 100 mM) of glucagon or Compound 12 was added to the perfusion buffer. Following perfusions, high energy phosphate nucleotide concentrations were measured by high performance liquid chromatography (HPLC) (Ally, A and Park, G. Rapid determination of creatine, phosphocreatine, purine bases and nucleotides (ATP, ADP, AMP, GTP, GDP) in heart biopsies by gradient ion-pair reversed-phase liquid chromatography. *Journal of Chromatography*. 1992; 575: 19-27).

Glucagon and Compound 12 had similar inotropic effects on cardiac function in both normal (data not shown) and insulin-resistant JCR-LA rats (Figure 1). Despite similar effects on cardiac function and thereby cardiac energy demand, glucagon and Compound 12 had statistically significant different effects on the energetic state of insulin resistant hearts (Figure 2). Specifically, treatment with glucagon caused statistically significant increases in AMP and ADP

levels and thereby decreased ATP/AMP and ATP/ADP ratios. However, following treatment with Compound 12 the energetic state of the hearts was not significantly different from vehicle perfused hearts. No effect was observed with the GLP-1 agonist exendin-4[1-39]-K₆ (H-HGEGTFTSDLSKQMEEEEAVRLFIEWLKNGGPSSGAS-K₆-NH₂) (Compound 241) (data not shown).

Example 2. Determination of efficacy at GLP-1 and glucagon receptors

HEK293 cells expressing the human glucagon receptor or human GLP-1R (see above for details) were seeded at 40,000 cells per well in 96-well microtiter plates coated with 0.01 % poly-L-lysine and grown for 1 day in culture in 100 µl growth medium. On the day of analysis, growth medium was removed and the cells washed once with 200 µl Tyrode buffer. Cells were incubated in 100 µl Tyrode buffer containing increasing concentrations of test peptides, 100 µM IBMX, and 6 mM glucose for 15 min at 37° C. The reaction was stopped by addition of 25 µl 0.5 M HCl and incubated on ice for 60 min. The cAMP content was estimated using the FlashPlate® cAMP kit from Perkin-Elmer. EC₅₀ values were estimated by computer aided curve fitting.

Table 1 shows results for sample compounds as EC₅₀ values.

Compound No	Test compound	EC ₅₀ (nM) GLP-1R	EC ₅₀ (nM) GluR
1	H-HSQGTFTSDYSKYLDSRRAQDFVWLMNT-OH (Human glucagon)	2,0	0,1
12	H-HSQGTFTSDYSKYLDRARADDFVAWLKST-NH ₂	0.23	0.50
242	H-HSQGTFTSDYSAYLDSRRAQDFVWLMNT-NH ₂	1,4	0,4
243	H-HSQGTFTSDYSKYLDSERAQDFVWLMNT-NH ₂	0,6	0,06
244	H-HSQGTFTSDYSKYLDSRHAQDFVWLMNT-NH ₂	0,5	0,05
245	H-HSQGTFTSDYSKYLDSRSAQDFVWLMNT-NH ₂	0,1	0,05
246	H-HSQGTFTSDYSKYLDSRAAQDFVWLMNT-NH ₂	0,3	0,05
247	H-HSQGTFTSDYSKYLDSRYAQDFVWLMNT-NH ₂	0,3	0,1
248	H-HSQGTFTSDYSKYLDSRRAQDFVWLESA-NH ₂	0,5	0,1
249	H-HSQGTFTSDYSKYLDSRRAQDFVWLKSA-NH ₂	0,1	0,1
250	H-HSQGTFTSDYSKYLDSRRAQDFVWLKRA-NH ₂	0,3	0,1
251	H-HSQGTFTSDYSKYLDSRRAQDFVWLERA-NH ₂	0,2	0,1
252	H-HSQGTFTSDYSRYLDSRRAKDFVWLLNT-NH ₂	0,5	0,3
253	H-HSQGTFTSDYSRYLDSRRAQDFVWLLNT-NH ₂	0,2	0,1
254	H-HSQGTFTSDYSRYLDSRRAQDFVWLLNK-NH ₂	0,2	0,2
255	H-HSQGTFTSDYSKYLDSALAQDFVWLLNT-NH ₂	0,24	0,1
256	H-HSQGTFTSDYSKYLDKRAEDFVWLMNT-NH ₂	0,2	0,07
257	H-HSQGTFTSDYSKYLDK()RRAE()DFVWLMNT-NH ₂	0,1	0,09
258	H-HSQGTFTSDYSRYLDERRAQDFVWLMNT-NH ₂	0,07	0,06
259	H-HSQGTFTSDYSK()YLDE()RRAQDFVWLMNT-NH ₂	0,04	0,03
120	H-HSQGTFTSDYSKYLDSRRAQDFIEWLMNT-NH ₂	0,2	0,2

Compound No	Test compound	EC ₅₀ (nM) GLP-1R	EC ₅₀ (nM) GluR
260	H-HSQTFTSDYSKYLDSKAAQDFVWLMNT-NH ₂	0,02	0,07
48	H-HSQTFTSDYSKYLDSKAAHDFVEWLLRA-NH ₂	0,06	0,06
44	H-H-DSer-QGTFTSDYSKYLDSKAAHDFVEWLLRA-NH ₂	0,09	0,11
45	H-H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLRA-NH ₂	0,08	0,06
261	H-HSQTFTSDYSKYLDSKAAHDFVE()WLLK()A-NH ₂	0,03	0,07
202	H-HSQTFTSDYSKYLD-K(Hexadecanoyl-γ-Glu)-KAAHDFVEWLLRA-NH ₂	0,20	0,13
262	H-HSQTFTSDYSKYLD-S-K(Hexadecanoyl-γ-Glu)-AAHDFVEWLLRA-NH ₂	0,11	0,12
204	H-HSQTFTSDYSKYLDSKAA-K(Hexadecanoyl-γ-Glu)-DFVEWLLRA-NH ₂	0,10	0,04
203	H-HSQTFTSDYSKYLDSKAAHDFVEWL-K(Hexadecanoyl-γ-Glu)-RA-NH ₂	0,57	0,22
205	H-HSQTFTSDYSKYLDSKAAHDFVEWLL-K(Hexadecanoyl-γ-Glu)-A-NH ₂	0,09	0,10
208	H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-γ-Glu)-AAHDFVEWLLSA-NH ₂	0,11	0,16
263	H-H-Aib-QGTFTSDYSKYLDE-K(Hexadecanoyl-γ-Glu)-RAKDFIEWLLSA-NH ₂	0,10	0,16
207	H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-γ-Glu)-AARDFVAWLLRA-NH ₂	0,12	0,17
213	H-H-Aib-QGTFTSDYSKYLDSKAA-K(Hexadecanoyl-γ-Glu)-DFVAWLLRA-NH ₂	0,15	0,63
206	H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-γ-Glu)-AAHDFVEWLLRA-NH ₂	0,09	0,16
209	H-H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLL-K(Hexadecanoyl-γ-Glu)-A-NH ₂	0,27	0,27
210	H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-γ-Glu)-AAHDFVE()WLLK()A-NH ₂	0,08	0,26
214	H-H-Aib-QGTFTSDYSKYLDS-K(Dodecanoyl-γ-Glu)-AAHDFVEWLLSA-NH ₂	0,14	0,78
215	H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-[3-Aminopropanoyl])-AAHDFVEWLLSA-NH ₂	0,23	1,87
216	H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-[8-Aminooctanoyl])-AAHDFVEWLLSA-NH ₂	0,24	0,46
217	H-H-Aib-QGTFTSDYSKYLDS-K(Hexadecanoyl-ε-Lys)-AAHDFVEWLLSA-NH ₂	0,09	0,39

Brackets () indicate intramolecular lactam rings.

Example 3. Assessment of inotropic effect *in vivo* in anaesthetized rats

- 5 The effect of the inotropic compound 1 and a glucagon-GLP-1 dual-agonist (Compound 12) on cardiac function, and heart rate was examined in anesthetized male Sprague-Dawley rats weighing approximately 300-400 g (Taconic)..

The rats were exposed to 5% isoflurane in 1:2 N₂O:O₂ until anesthesia were established. Body temperature was kept constant ($37.5 \pm 0.5^{\circ}\text{C}$) and the animals were artificially ventilated through an endotracheal cannula and anesthesia was maintained.

A catheter was inserted into the left femoral vein for drug administration and a pressure-volume catheter was inserted into the left ventricle via the right carotid artery. After instrumentation, isoflurane was delivered in pure O₂ during the experiment. After 20 min of stabilization, baseline data was recorded for 15 min while infusing vehicle (at 7 $\mu\text{L}/\text{min}$). Subsequently, compounds were infused After the infusion of the 2.5 nmol/kg/min dose (or a lower dose if heart rate or stroke work was increased more than 40%), vehicle was infused for 15 minutes after which animals were euthanized.

The impact of compound 1 and various dual glucagon-GLP-1 agonists (compounds 7, 9, 12, 35, 37, 206) on cardiac hemodynamic parameters was examined in the anaesthetized rats. Cardiac stroke work is descriptive of the work that the ventricle needs to perform in order to eject a volume of blood into the aorta, and thereby a good representative of the inotropic state of the heart. The measured strokework as a function of infusion dose for each compound is shown in the figure 4a-d. The horizontal line marks 40% increase in stroke work, which was defined as the maximal increase that should be obtained during the experiment. Compound 1 increase the strokework to approximately 40 % in respectively 0,1 and 0,2 nmol/kg/min infusion rates (figure 4b and 4c) after which infusion of this compound was stopped. Except from compound 12 and compound 7, all the dual glucagon-GLP-1 agonists increased the strokework to 40 % at a given infusion rate. The acylated, and thereby more stable, compound 206 showed a prolonged increase in strokework that outlasted the compound infusion and remained high throughout the final vehicle infusion.

In the same experiments, heart rate was calculated from the hemodynamic parameters and results are given in figure 5 showing the changes in heart rate for each infusion rate. Each bar represents different compound. At 0.1 nmol/kg/min and higher doses, compound 1 showed a significant increase in heart rate compared to control (figure 5b and c). None of the other compounds showed significant dose dependent changes in heart rate, although there was a tendency for both compounds 35 and 37 to increase heart rate at 0.2 and 0.5 nmol/kg/min (figure 5c and d).

In relation to the above results, while glucagon is known to increase cardiac contractility, the concomitant increase in heart rate results in increase in myocardial oxygen demand, which can precipitate angina in patients with coronary artery disease, and thereby pose a significant risk to the heart failure patient. The present experiments show that dual glucagon-GLP-1 agonists can

improve cardiac inotropic state to the same extent as glucagon. but the increase in inotropy seems not to be coupled to increase in heart rate as observed with infusions of glucagon. Taken together, the results presented above indicate that dual glucagon-GLP-1 agonists act by improving the cardiac contractility without causing the concomitant increase in heart rate
5 observed with glucagon.

Claims

1. A method of treatment of heart disease or heart dysfunction, such as congestive heart failure, systolic dysfunction, diastolic dysfunction, myocardial infarction, ischemic heart disease,
5 diabetic cardiomyopathy or a combination thereof, in a subject, comprising administering a glucagon-GLP-1 dual agonist to the subject as a positive inotropic agent.
2. A method according to claim 1 wherein the subject is treated with the glucagon-GLP-1 dual agonist for a period greater than 12 hours, greater than 24 hours, greater than 36 hours,
10 greater than 48 hours, greater than 3 days, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days, greater than 2 weeks, greater than 3 weeks, greater than 4 weeks, greater than 1 month, 2 months, 3 months, 4 months or greater than 5 months.
3. A method according to claim 1 or 2 wherein the subject is treated for a period:
15 between 1 week and 6 weeks, between 2 weeks and 6 weeks, between 3 weeks and 6 weeks, between 4 weeks and 6 weeks, between 5 weeks and 6 weeks, between 1 week and 5 weeks, between 2 weeks and 5 weeks, between 3 weeks and 5 weeks, between 4 weeks and 5 weeks; between 1 week and 4 weeks, between 2 weeks and 4 weeks, between 3 weeks and 4 weeks; between 1 week and 3 weeks, between 2 weeks and 3 weeks;
20 between 1 week and 6 months, between 1 week and 5 months, between 1 week and 4 months, between 1 week and 3 months, between 1 week and 2 months, between 1 week and 1 month; between 2 weeks and 6 months, between 2 weeks and 5 months, between 2 weeks and 4 months, between 2 weeks and 3 months, between 2 weeks and 2 months, between 2 weeks and 1 month;
25 between 3 weeks and 6 months, between 3 weeks and 5 months, between 3 weeks and 4 months, between 3 weeks and 3 months, between 3 weeks and 2 months, between 3 weeks and 1 month; between 4 weeks and 6 months, between 4 weeks and 5 months, between 4 weeks and 4 months, between 4 weeks and 3 months, between 4 weeks and 2 months, between 4 weeks and
30 1 month; between 1 month and 6 months, between 2 months and 6 months, between 3 months and 6 months, between 4 months and 6 months, between 5 months and 6 months; between 1 month and 5 months, between 2 months and 5 months, between 3 months and 5 months, between 4 months and 5 months;
35 between 1 month and 3 months, between 2 months and 3 months, or between 1 month and 2 months.

4. A method according to any one of the preceding claims wherein the glucagon-GLP-1 dual agonist is administered by an intravenous, subcutaneous or transdermal route.

5. A method according to any one of the preceding claims wherein the glucagon-GLP-1 dual agonist is administered in combination with an agent for treatment of heart failure, diabetes, obesity, myocardial infarction, hypolipidemia or hypertension.

6. A method according to any one of the preceding claims wherein the glucagon-GLP-1 dual agonist is a compound having the formula:

10 $R^1-X-Z^1-Z^2-R^2$

wherein:

R^1 is hydrogen, C_{1-4} alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl;

X has the Formula I:

15 X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-X10-Ser-X12-Tyr-Leu-X15-X16-X17-X18-Ala-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29

wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, acetyl-His, homo-His, alpha,alpha-dimethyl imidazole acetic acid (DMIA), N-methyl His, alpha-methyl His or imidazole acetic acid;

X2 is Ser, Aib or D-Ser;

20 X3 is Gln, Glu, Orn or Nle;

X10 is Tyr or Trp;

X12 is Lys, Arg, His, Ala, Leu, Dpu, Dpr, Orn, Citrulline or Ornithine;

X15 is Asp, Glu, cysteic acid, homoglutamic acid or homocysteic acid;

X16 is Ser, Thr, Lys, Arg, His, Glu, Asp, Ala, Gly, Gln, homoglutamic acid or homocysteic acid;

25 X17 is Arg, Lys, His, Glu, Gln, Ala, Leu, Dpu, Dpr, Orn, Cys, homocysteine or acetyl phenylalanine;

X18 is Arg, Lys, His, Tyr, Ala, Ser, Leu, Cys, Orn, homocysteine or acetyl phenylalanine;

X20 is Gln, Lys, Arg, His, Glu, Asp, Ala, Cys, Orn or Citrulline;

X21 is Asp, Glu, Gln, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;

30 X23 is Val, Ile or Leu;

X24 is Gln, Lys, Arg, Glu, Asp, Ser, Ala, Leu, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Lys, Arg, Glu, Leu, Nle, Cys or absent;

X28 is Asn, Lys, Arg, Glu, Asp, Ser, Ala, Leu, Cys, Citrulline, Orn, or absent;

X29 is Thr, Lys, Arg, Glu, Ser, Ala, Gly, Cys, Orn, homocysteine, acetyl phenylalanine or absent;

35 R^2 is NH_2 or OH;

Z^1 is absent or has the sequence:

Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser;

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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Cys;

Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala; or

Lys Arg Asn Arg;

Z² is absent or a peptide sequence of 1-20 amino acid units selected from the group consisting of

5 Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

wherein, if Z¹ is present, X27, X28 and X29 are also present; and

if Z¹ is absent, the compound has a substitution or deletion relative to human glucagon at one or more of positions X1, X2, X3, X10, X12, X15, X16, X17, X18, X20, X21, X23, X24, X27, X28 and X29;

10 or a pharmaceutically acceptable salt or derivative thereof;

wherein said compound has higher GLP-1 receptor selectivity than human glucagon.

7. A method according to any one of claims 1 to 6 wherein the glucagon-GLP-1 dual agonist has the formula R¹-X-Z²-R², wherein

15 R¹ is H, C₁₋₄ alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R² is OH or NH₂;

X is a peptide which has the Formula IV:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Leu-Ser-Ala

20 or differs from Formula IV at up to 4 of the following positions whereby, if different from Formula IV:

the residue at position 2 is selected from: D-Ser, Aib;

the residue at position 16 is selected from: Ser, Asp, Lys, Arg;

the residue at position 18 is: Ala;

25 the residue at position 20 is selected from: Gln, Arg, Glu, Asp;

the residue at position 21 is: Glu;

the residue at position 23 is: Val;

the residue at position 24 is selected from: Gln, Asp, Lys, Arg, Ala;

the residue at position 27 is selected from: Met, Cys, Lys or is absent;

30 the residue at position 28 is selected from: Asn, Arg, Lys, Ala, Glu, Asp or is absent; and the residue at position 29 is selected from: Thr, Arg or is absent;

and Z² is absent or a sequence of 1-20 amino acid units selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

or a pharmaceutically acceptable salt thereof.

35

8. A method according to claim 7 wherein X differs from Formula IV at up to 4 of the following positions whereby, if different from Formula IV:

the residue at position 2 is selected from: D-Ser, Aib;
the residue at position 16 is selected from: Ser, Asp, Lys;
the residue at position 20 is selected from: Gln, Arg, Glu;
the residue at position 27 is selected from: Met, Cys, Lys; and
5 the residue at position 28 is selected from: Asn, Arg, Ala.

9. A method according to claim 7 or claim 8 wherein X differs from Formula IV at up to 3 of the following positions whereby, if different from Formula IV:

the residue at position 2 is selected from: D-Ser, Aib;
10 the residue at position 16 is selected from: Ser, Asp, Lys; and
the residue at position 20 is selected from: Gln, Arg, Glu.

10. A method according to any one of claims 7 to 9 wherein X differs from Formula IV at up to 4 of the following positions whereby, if different from Formula IV:

15 the residue at position 2 is selected from: D-Ser, Aib;
the residue at position 16 is selected from: Ser, Asp, Lys;
the residue at position 18 is: Ala; and
the residue at position 20 is selected from: Gln, Arg, Glu.

20 11. A method according to any one of claims 7 to 10 wherein X differs from Formula IV at up to 4 of the following positions whereby, if different from Formula IV:

the residue at position 23 is: Val;
the residue at position 24 is selected from: Gln, Asp, Lys, Arg, Ala;
the residue at position 27 is selected from: Met, Cys, Lys; and
25 the residue at position 28 is selected from: Asn, Arg, Ala.

12. A method according to any one of claims 7 to 11 wherein one or more intramolecular bridges are formed within the peptide sequence X.

30 13. A method according to claim 12 wherein the or each bridge is formed between the side chains of two amino acid residues of X which are separated by three amino acids in the linear sequence of X.

14. A method according to claim 12 or claim 13 wherein the residues at positions 16 and 20
35 form a salt bridge.

15. A method according to claim 14 wherein the residues at positions 16 and 20 are selected from:

16-Asp, 20-Lys;

16-Glu, 20-Lys;

5 16-Asp, 20-Arg;

16-Glu, 20-Arg;

16-Lys, 20-Asp;

16-Arg, 20-Asp;

16-Lys, 20-Glu;

10 16-Arg, 20-Glu.

16. A method according to claim 12 or claim 13 wherein the residues at positions 20 and 24 form a salt bridge.

15 17. A method according to claim 16 wherein the residues at positions 20 and 24 are selected from:

20-Asp, 24-Lys;

20-Glu, 24-Lys;

20-Asp, 24-Arg;

20 20-Glu, 24-Arg;

20-Lys, 24-Asp;

20-Arg, 24-Asp;

20-Lys, 24-Glu;

20-Arg, 24-Glu;

25

18. A method according to any one of claims 7 to 17 wherein X comprises one or more of the following sets of residues:

20-Lys, 24-Glu;

20-Lys, 23-Ile, 24-Glu;

30 16-Glu, 20-Lys;

16-Glu, 20-Lys, 29-Ala;

16-Glu, 20-Lys, 23-Ile, 24-Glu;

16-Glu, 20-Lys, 23-Ile, 24-Glu, 29-Ala;

16-Glu, 20-Lys, 24-Glu, 29-Ala;

35 20-Lys, 23-Ile, 24-Glu, 29-Ala;

27-Leu, 28-Ser, 29-Ala;

29-Ala;

16-Ser;

20-Gln;

23-Val;

24-Gln;

5 16-Ser, 20-Gln;

16-Asp, 20-Arg, 24-Asp;

16-Lys, 20-Glu;

24-Arg; or

28-Arg.

10

19. A method according to any of the claims 7 to 18 wherein X has the sequence:

HSQGTFTSDYSKYLDERRAKDFIEWLLSA.;

HSQGTFTSDYSKYLDERRAQDFIEWLLSA;

HSQGTFTSDYSKYLDERRAKDFVEWLLSA;

15 HSQGTFTSDYSKYLDERRAKDFIQWLLSA;

HSQGTFTSDYSKYLDSRRAQDFIEWLLSA;

HSQGTFTSDYSKYLDERRARDFIDWLLSA;

HSQGTFTSDYSKYLDKRRRAEDFIKWLLSA;

HSQGTFTSDYSKYLDERRAKDFIRWLLSA;

20 HSQGTFTSDYSKYLDERRAKDFIEWLLRA;

HSQGTFTSDYSKYLDSRRAKDFIEWLLSA;

HSQGTFTSDYSKYLDERRAAKDFIEWLLSA;

HSQGTFTSDYSKYLDERRAKDFIDWLLSA; or

HSQGTFTSDYSKYLDERRAKDFIEWLLAA;

25

20. A method according to claim 6 wherein the glucagon-GLP-1 dual agonist has the formula
 $R^1-X-Z^2-R^2$

30

wherein

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

R^2 is OH or NH_2 ;

X is a peptide which has the Formula II

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Arg-Ala-Arg-Ala-Asp-Asp-Phe-

35

Val-Ala-Trp-Leu-Lys-Glu-Ala

or differs from Formula II at up to 4 of the following positions whereby, if different from Formula I:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 16 is: Lys, Asp, Glu;

the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;

the residue at position 20 is selected from: Gln, His, Lys, Arg, Glu;

the residue at position 21 is: Glu;

5 the residue at position 24 is selected from: Gln, Leu, Glu, Lys, Arg, Asp;

the residue at position 27 is selected from: Met, Cys, Arg, Glu, Leu or is absent;

the residue at position 28 is selected from: Asn, Ser, Arg, Lys, Ala, Leu, Glu, Asp or is absent;

and

the residue at position 29 is selected from: Thr, Glu, Lys or is absent;

10 and Z² is absent or a sequence of 1-20 amino acid units selected from the group consisting of
Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt thereof.

21. A method according to claim 20 wherein X differs from Formula II at up to 4 of the
15 following positions whereby, if different from Formula II:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;

the residue at position 20 is selected from: Gln, His, Lys, Arg, Glu;

the residue at position 24 is selected from: Gln, Leu, Glu, Lys, Arg;

20 the residue at position 27 is selected from: Met, Cys, Arg, Glu, Leu;

the residue at position 28 is selected from: Asn, Ser, Arg, Lys, Ala, Leu; and

the residue at position 29 is selected from: Thr, Glu, Lys.

22. A method according to claim 20 wherein X comprises the residues 27-Lys and 28-Ser.
25

23. A method according to claim 22 wherein X additionally differs from Formula II at one or
two of the following positions whereby, if different from Formula II:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;

30 the residue at position 20 is selected from: Gln, His, Lys, Arg, Glu;

the residue at position 24 is selected from: Gln, Leu, Glu, Lys, Arg; and

the residue at position 29 is selected from: Thr, Glu, Lys.

24. A method according to any one of claims 20 to 23 wherein one or more intramolecular
35 bridges are formed within the peptide sequence X.

25. A method according to claim 24 wherein the or each bridge is formed between the side chains of two amino acid residues of X which are separated by three amino acids in the linear sequence of X.

5 26. A method according to claim 24 or claim 25 wherein the residues at positions 16 and 20 form a salt bridge.

27. A method according to claim 26 wherein the salt bridge is formed between one of the following pairs of residues:

10 16-Asp, 20-Lys;
16-Glu, 20-Lys;
16-Asp, 20-Arg;
16-Glu, 20-Arg;
16-Lys, 20-Asp;
15 16-Arg, 20-Asp;
16-Lys, 20-Glu; and
16-Arg, 20-Glu.

28. A method according to any one of claims 20 to 27 wherein X comprises one or more of the following sets of residues:

20 16-Arg;
16-Arg, 20-Asp;
16-Arg, 20-Asp, 24-Ala;
16-Arg, 20-Asp, 27-Lys, 28-Ser;
25 16-Arg, 20-Asp, 29-Ala;
16-Arg, 27-Lys, 28-Ser;
16-Arg, 27-Lys, 28-Ser, 29-Ala;
24-Ala, 27-Lys, 28-Ser;
24-Ala, 27-Lys, 28-Ser, 29-Ala;
30 24-Ala;
27-Lys;
28-Ser;
20-Glu, 28-Ser, 29-Thr;
24-Glu, 28-Ser, 29-Thr;
35 27-Glu, 28-Arg;
2-D-Ser, 28-Ser, 29-Thr; or
20-His, 28-Ser, 29-Thr.

29. A method according to any one of claims 20 to 28 wherein X has the sequence:

HSQGTFTSDYSKYLDRARADDFVAWLKSA;

HSQGTFTSDYSKYLDRARADDFVAWLKEA;

5 HSQGTFTSDYSKYLDRARAEDEFVAWLKST;

HSQGTFTSDYSKYLDRARADDFVEWLKST;

HSQGTFTSDYSKYLDRARADDFVAWLERA;

H-DSer-QGTFTSDYSKYLDRARADDFVAWLKST;

HSQGTFTSDYSKYLDRARAHDFVAWLKST; or

10 HSQGTFTSDYSKYLDRARADDFVAWLKST.

30. A method according to any one of claims 1 to 6 wherein the glucagon-GLP-1 dual agonist has the formula $R^1-X-Z^2-R^2$

wherein

15 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 III:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Leu-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Glu-Ser-Ala

20 or differs from Formula III at up to 4 of the following positions whereby, if different from Formula III:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly, Asp;

the residue at position 17 is selected from: Lys, Leu;

25 the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;

the residue at position 20 is selected from: Gln, His, Arg, Glu, Asp;

the residue at position 21 is: Glu;

the residue at position 23 is selected from: Val, Leu;

the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg, Asp;

30 the residue at position 27 is selected from: Met, Cys, Lys, Arg, Leu or is absent;

the residue at position 28 is selected from: Asn, Arg, Lys, Glu, Ala, Leu, Asp or is absent; and

the residue at position 29 is selected from: Thr, Glu, Lys or is absent;

and Z^2 is absent or a peptide sequence of 1-20 amino acid units selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;

35 or a pharmaceutically acceptable salt thereof.

31 A method according to claim 30 wherein X differs from Formula III at up to 4 of the following positions whereby, if different from Formula III:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly;

5 the residue at position 17 is selected from: Lys, Leu;

the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr;

the residue at position 23 is selected from: Val, Leu;

the residue at position 27 is selected from: Met, Cys, Lys, Arg, Leu;

the residue at position 28 is selected from: Asn, Arg, Lys, Glu, Ala, Leu; and

10 the residue at position 29 is selected from: Thr, Glu, Lys.

32 A method according to claim 30 or claim 31 wherein, X differs from Formula III at up to 4 of the following positions whereby, if different from Formula III:

the residue at position 2 is selected from: Aib, D-Ser;

15 the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly;

the residue at position 17 is selected from: Lys, Leu;

the residue at position 18 is selected from: Lys, His, Ala, Ser, Tyr; and

the residue at position 23 is selected from: Val, Leu.

20 33. A method according to any one of claims 30 to 32 wherein X differs from Formula III at up to 4 of the following positions whereby, if different from Formula III:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 23 is selected from: Val, Leu;

the residue at position 27 is selected from: Met, Cys, Lys, Arg, Leu;

25 the residue at position 28 is selected from: Asn, Arg, Lys, Glu, Ala, Leu; and

the residue at position 29 is selected from: Thr, Glu, Lys.

34. A method according to any one of claims 30 to 33 wherein X comprises one or more of the following sets of residues:

30 20-Lys, 24-Glu;

20-Lys, 24-Glu, 29-Ala;

20-Lys, 23-Ile, 24-Glu;

27-Glu, 28-Ser, 29-Ala;

29-Ala;

35 20-Gln;

23-Val;

24-Gln;

29-Thr;
 27-Met, 28-Asn, 29-Thr;
 20-Gln, 23-Val, 24-Gln;
 20-Glu, 24-Lys; or
 28-Arg.

35. A method according to any one of claims 30 to 34 wherein one or more intramolecular bridges are formed within the peptide sequence X.

36. A method according to claim 35 wherein the or each bridge is formed between the side chains of two amino acid residues of X which are separated by three amino acids in the linear sequence of X.

37. A method according to claim 35 or claim 36 wherein the bridge is formed between the side chains of residue pairs 16 and 20, 17 and 21, 20 and 24, or 24 and 28.

38. A method according to claim 37 wherein the residues at positions 20 and 24 form an intramolecular bridge.

39. A method according to claim 38 wherein the residues at positions 20 and 24 are selected from:

20-Asp, 24-Lys;
 20-Glu, 24-Lys;
 20-Asp, 24-Arg;
 20-Glu, 24-Arg;
 20-Lys, 24-Asp;
 20-Arg, 24-Asp;
 20-Lys, 24-Glu; and
 20-Arg, 24-Glu.

40. A method according to any of claims 30 to 39 wherein X has the sequence:

HSQGTFTSDYSLYLDSRRAQDFIEWLESA;
 HSQGTFTSDYSLYLDSRRAKDFVEWLESA;
 HSQGTFTSDYSLYLDSRRAKDFIQWLESA;
 HSQGTFTSDYSLYLDSRRAKDFIEWLEST;
 HSQGTFTSDYSLYLDSRRAKDFIEWLMNT;
 HSQGTFTSDYSLYLDSRRAQDFVQWLESA;

HSQGTFTSDYSLYLDSSRAEDFIKWLESA; or
HSQGTFTSDYSLYLDSSRAKDFIEWLERA.

- 5 41. A method according to any one of claims 1 to 6 wherein the glucagon-GLP-1 dual agonist has the formula $R^1-X-Z^2-R^2$ wherein
- R^1 is H, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
 R^2 is OH or NH_2 ;
- 10 X is a peptide which has the Formula V:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Lys-Ala-Ala-His-Asp-Phe-Val-Glu-Trp-Leu-Leu-Arg-Ala
or differs from Formula V at up to 4 of the following positions whereby, if different from Formula V:
the residue at position 2 is selected from: Aib, D-Ser;
- 15 the residue at position 12 is selected from: Leu, Arg, Dpu, Dpr, Orn;
the residue at position 16 is selected from: Arg, His, Lys, Glu, Asp;
the residue at position 17 is selected from: Arg, Leu, Dpu, Dpr, Orn;
the residue at position 18 is selected from: Arg, Lys, His, Ser, Tyr;
the residue at position 20 is selected from: Gln, Lys, Arg, Glu, Asp;
- 20 the residue at position 21 is Glu;
the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg, Asp;
the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu or is absent;
the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu, Asp or is absent; and
the residue at position 29 is selected from: Thr, Glu, Lys or is absent;
- 25 and Z^2 is absent or a peptide sequence of 1-20 amino acid units selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
or a pharmaceutically acceptable salt thereof.
42. A method according to claim 41 wherein X differs from Formula V at up to 4 of the
- 30 following positions whereby, if different from Formula V:
the residue at position 2 is selected from: Aib, D-Ser;
the residue at position 16 is selected from: Arg, His, Lys, Glu;
the residue at position 17 is selected from: Arg, Leu;
the residue at position 18 is selected from: Arg, Lys, His, Ser, Tyr;
- 35 the residue at position 20 is selected from: Gln, Lys, Arg, Glu;
the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg;
the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu;

the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu; and
the residue at position 29 is selected from: Thr, Glu, Lys.

43. A method according to claim 41 or claim 42 wherein X differs from Formula V at up to 4 of
5 the following positions whereby, if different from Formula V:
the residue at position 2 is selected from: Aib, D-Ser;
the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly;
the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg;
the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu;
10 the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu; and
the residue at position 29 is selected from: Thr, Glu, Lys.

44. A method according to any one of claims 41 to 43 wherein X comprises one or more of
the following sets of residues:
15 17-Lys, 18-Ala;
17-Leu, 18-Ala;
17-Lys, 18-Ala, 20-His;
17-Leu, 18-Ala, 20-His;
17-Lys, 18-Ala, 24-Glu;
20 17-Leu, 18-Ala, 24-Glu;
17-Lys, 18-Ala, 27-Leu;
17-Leu, 18-Ala, 27-Leu;
17-Lys, 18-Ala, 29-Ala;
17-Leu, 18-Ala, 29-Ala;
25 17-Lys, 18-Ala, 27-Leu, 29-Ala;
17-Leu, 18-Ala, 27-Leu, 29-Ala;
17-Lys, 18-Ala, 27-Leu, 28-Arg, 29-Ala;
17-Leu, 18-Ala, 27-Leu, 28-Arg, 29-Ala;
24-Glu, 28-Arg;
30 24-Glu, 28-Arg, 27-Leu;
24-Glu, 28-Arg, 27-Leu, 29-Ala;
27-Leu, 28-Arg, 29-Ala;
29-Ala;
20-Arg, 24-Arg, 27-Lys, 28-Leu;
35 17-Arg;
18-Arg;
20-Gln;

24-Gln;
 27-Met, 28-Asn, 29-Thr; or
 24-Lys
 and combinations thereof.

5

45. A method according to any one of claims 41 to 45 wherein X has the sequence:

HSQGTFTSDYSKYLDSKAARDFVRWLKLA;
 HSQGTFTSDYSKYLDSRAAHDFVEWLLRA;
 HSQGTFTSDYSKYLDSKRAHDFVEWLLRA;
 10 HSQGTFTSDYSKYLDSKAAQDFVEWLLRA;
 HSQGTFTSDYSKYLDSKAAHDFVQWLLRA;
 HSQGTFTSDYSKYLDSKAAHDFVEWLMNT;
 HSQGTFTSDYSKYLDSKAAHDFVKWLLRA;
 H-DSer-QGTFTSDYSKYLDSKAAHDFVEWLLRA;
 15 H-Aib-QGTFTSDYSKYLDSKAAHDFVEWLLRA;
 HSQGTFTSDYSKYLDSKAAKDFVEWLLRA;
 HSQGTFTSDYSKYLDKKAHDFVEWLLRA or
 HSQGTFTSDYSKYLDSKAAHDFVEWLLRA.

20 46. A method according to any one of claims 1 to 6 wherein the glucagon-GLP-1 dual agonist has the formula $R^1-X-Z^2-R^2$ wherein

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

R^2 is OH or NH_2 ;

25 X is a peptide which has the Formula VI:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Lys-Ala-Ala-His-Asp-Phe-Val-Glu-Trp-Leu-Leu-Arg-Ala

or differs from Formula VI at up to 5 of the following positions whereby, if different from Formula VI:

30 the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 16 is selected from: Arg, His, Lys, Glu;

the residue at position 17 is: Arg, Leu, Dpu, Dpr, Orn;

the residue at position 20 is selected from: Gln, Lys, Arg, Glu, Asp;

the residue at position 21 is Glu;

35 the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg, Asp;

the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu or is absent;

the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu, Asp or is absent; and

the residue at position 29 is selected from: Thr, Glu, Lys or is absent;
 and Z² is absent or a peptide sequence of 1-20 amino acid units selected from the group
 consisting of Ala, Leu, Ser, Thr, Tyr, Cys, Glu, Lys, Arg, Dbu, Dpr and Orn;
 or a pharmaceutically acceptable salt thereof.

5

47. A method according to claim 46 wherein X differs from Formula VI at up to 4 of the
 following positions whereby, if different from Formula VI:

the residue at position 2 is selected from: Aib, D-Ser;

the residue at position 16 is selected from: Arg, His, Lys, Glu, Gly;

10 the residue at position 17 is selected from: Arg, Leu;

the residue at position 18 is selected from: Arg, Lys, His, Ser, Tyr;

the residue at position 20 is selected from: Gln, Lys, Arg, Glu;

the residue at position 24 is selected from: Gln, Leu, Ala, Lys, Arg;

the residue at position 27 is selected from: Met, Cys, Lys, Arg, Glu;

15 the residue at position 28 is selected from: Asn, Ser, Lys, Glu, Ala, Leu; and

the residue at position 29 is selected from: Thr, Glu, Lys.

48. A method according to claim 46 or claim 47 wherein X comprises any of the sets of
 residues:

20 17-Lys, 18-Ala;

17-Leu, 18-Ala;

17-Lys, 18-Ala, 20-His;

17-Leu, 18-Ala, 20-His;

17-Lys, 18-Ala, 24-Glu;

25 17-Leu, 18-Ala, 24-Glu;

17-Lys, 18-Ala, 27-Leu;

17-Leu, 18-Ala, 27-Leu;

17-Lys, 18-Ala, 29-Ala;

17-Leu, 18-Ala, 29-Ala;

30 17-Lys, 18-Ala, 27-Leu, 29-Ala;

17-Leu, 18-Ala, 27-Leu, 29-Ala;

17-Lys, 18-Ala, 27-Leu, 28-Arg, 29-Ala;

17-Leu, 18-Ala, 27-Leu, 28-Arg, 29-Ala;

24-Glu, 28-Arg;

35 24-Glu, 28-Arg, 27-Leu;

24-Glu, 28-Arg, 27-Leu, 29-Ala;

27-Leu, 28-Arg, 29-Ala;

29-Ala;

20-Arg, 24-Arg, 27-Lys, 28-Leu;

17-Arg;

18-Arg;

5 20-Gln;

24-Gln;

27-Met, 28-Asn, 29-Thr;

24-Lys; or

20-Gln, 24-Gln, 27-Met, 28-Asn, 29-Thr; or

10 17-Leu, 20-Gln, 24-Gln, 28-Asn, 29-Thr.

49. A method according to any one of claims 46 to 48 wherein X has the sequence:

HSQGTFTSDYSKYLD SKAAQDFVQWLMNT or

HSQGTFTSDYSKYLD SLAAQDFVQWLLNT.

15

50. A method according to any one of claims 41 to 49 wherein the peptide X has one or more intramolecular bridges.

51. A method according to claim 50 wherein the or each bridge is formed between the side chains of two amino acid residues of X which are separated by three amino acids in the linear sequence of X.

20

52. A method according to claim 50 or claim 51 wherein the bridge is formed between the side chains of residue pairs 12 and 16, 16 and 20, 17 and 21, 20 and 24, or 24 and 28.

25

53. A method according to claim 52 wherein the residues at positions 16 and 20 are selected from:

16-Glu, 20-Lys;

30 16-Asp, 20-Arg;

16-Glu, 20-Arg;

16-Lys, 20-Asp;

16-Arg, 20-Asp;

16-Lys, 20-Glu; and

35 16-Arg, 20-Glu.

54. A method according to any one of claims 1 to 6 wherein the glucagon-GLP-1 dual agonist the formula $R^1-X-Z^1-Z^2-R^2$

wherein:

R^1 is hydrogen, C_{1-4} alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl;

wherein X has the Formula VII:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-X10-Ser-X12-Tyr-Leu-X15-X16-X17-X18-Ala-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29

wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, acetyl-His, homo-His, alpha,alpha-dimethyl

imidazole acetic acid (DMIA), N-methyl His, alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, aminoisobutyric acid (Aib) or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle;

X10 is Tyr or Trp;

X12 is Lys, Citrulline, Orn or Arg;

X15 is Asp, Glu, cysteic acid, homoglutamic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X17 is Arg, Gln, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;

X18 is Arg, Ala, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;

X20 is Gln, Lys, Arg, Orn or Citrulline;

X21 is Gln, Glu, Asp, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

X24 is Ala, Gln, Glu, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle;

X28 is Asn, Arg, Citrulline, Orn, Lys or Asp;

X29 is Thr, Gly, Lys, Cys, Orn, homocysteine or acetyl phenylalanine;

R^2 is NH_2 or OH;

Z^1 is absent or has the sequence:

Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser;

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Cys;

Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala; or

Lys Arg Asn Arg;

Z^2 is absent or a peptide sequence of 1-20 amino acid units selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Har, Dbu, Dpr and Orn;

wherein, if Z^1 is absent, the compound has a substitution or deletion relative to human glucagon

at one or more of positions X1, X2, X3, X10, X12, X15, X16, X17, X18, X20, X21, X23, X24, X27, X28 and X29;

or a pharmaceutically acceptable salt or derivative thereof;

wherein said compound has higher GLP-1 receptor selectivity than human glucagon and/or wherein the compound exhibits at least 20% of the activity of native GLP-1 at the GLP-1 receptor.

55. A method according to any one of claims 1 to 6 or 54 wherein X differs from Formula VII by 1 to 3 amino acid modifications at positions selected from 1, 2, 3, 5, 7, 10, 11, 13, 14, 17, 18, 19, 21, 24, 27, 28 and 29.

56. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.2:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-X16-X17-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-X27-Asn-Thr
wherein

X16 is Glu, Gln, homoglutamic acid or homocysteic acid;

X17 is Arg, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle

57. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.3:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-Gln-X21-Phe-
Val-Gln-Trp-Leu-X27- Asn-Thr
wherein

X16 is Glu, Gln, homoglutamic acid or homocysteic acid;

X21 is Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle;

58. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.4:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-Gln-X21-Phe-
Val-Gln-Trp-Leu-X27- Asn-Thr
wherein

X16 is Glu, Gln, homoglutamic acid or homocysteic acid;

X24 is Gln, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle.

59. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.5:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-Gln-X21-Phe-
Val-X24-Trp-Leu-X27- Asn-Thr
wherein

X16 is Glu, Gln, homoglutamic acid or homocysteic acid;

X21 is Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X24 is Gln, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle.

60. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.6:

5 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Gln-X21-Phe-Val-Gln-Trp-Leu-X27- Asn-Thr

wherein

X21 is Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle.

10

61. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.7:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-Val-X24-Trp-Leu-X27- Asn-Thr

wherein

15 X24 is Gln, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle.

62. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.8:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met- Asn-Thr

20

wherein

X16 is Glu, Gln, homoglutamic acid or homocysteic acid.

63. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.9:

25 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-X27- Asn-Thr

wherein

X27 is Met, Leu or Nle.

64. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.19:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-Val-Glu-Trp-Leu-Met-Asn-Thr-X30

30

wherein

X30 is any suitable amino acid.

35

65. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.20:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-X16-Arg-Arg- Ala-X20-Asp-Phe-
Val-X24-Trp-Leu-Met-X28-X29

wherein

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

5 X20 is Gln, Lys, Arg, Orn or Citrulline;

X24 is Gln or Glu;

X28 is Asn, Asp or Lys;

X29 is Thr or Gly.

10 66. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.21:
His-X2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg- Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-Met-Asn-Thr

wherein

X2 is D-Ser, Ala, Gly, N-methyl Ser or aminoisobutyric acid.

15

67. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.22:
His-X2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg- Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-Met-Asn-Thr

wherein

20 X2 is aminoisobutyric acid.

68. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.23:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Cys-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-X27- Asn-Thr

25 wherein

the Cys at position 17 is PEGylated;

X27 is Met, Leu or Nle.

69. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.24:
30 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Cys-Phe-
Val-Gln-Trp-Leu-X27- Asn-Thr

wherein

the Cys at position 21 is PEGylated;

X27 is Met, Leu or Nle.

35

70. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.25:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Cys-Trp-Leu-X27- Asn-Thr

wherein

the Cys at position 24 is PEGylated;

5 X27 is Met, Leu or Nle.

71. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.30:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-X27- Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser

10 wherein

X27 is Met, Leu or Nle.

72. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.31:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-
15 Val-Gln-Trp-Leu-X27- Asn-Thr-Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala

wherein

X27 is Met, Leu or Nle.

73. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.32:
20 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-X27- Asn-Thr-Lys-Arg-Asn-Arg

wherein

X27 is Met, Leu or Nle.

74. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.33:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15- X16- Arg-Arg-Ala-X20-Asp-
Phe-Val-X24-Trp-Leu-Met-X28-X29

wherein

X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;

30 X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln or Lys;

X24 is Gln or Glu;

X28 is Asn, Lys or an acidic amino acid;

X29 is Thr, Gly or an acidic amino acid.

35

75. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.36:

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-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser.

76. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.37:
5 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Cys-Trp-Leu-Met-Asn-Thr
wherein 24 2-butyrolactone is bound through thiol group of Cys.

77. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.38:
10 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Cys-Trp-Leu-Met-Asn-Thr
wherein a 24 carboxymethyl group is bound through thiol group of Cys.

78. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.39:
15 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Arg-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-Met-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser.

79. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.40:
20 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Glu-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-Met-X28-Thr
wherein
X15 is Glu or Asp;
X28 is Glu or Asp.

80. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.41:
25 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Glu-Arg-Arg-Ala-Asp-Phe-Val-
Gln-Trp-Leu-Met-X28- Thr
wherein
X15 is Glu or Asp;
30 X28 is Glu or Asp; and
a lactam ring is present between the side chains at positions 12 and 16.

81. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.42:
35 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Glu-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Gln-Trp-Leu-Met-X28-Thr
wherein
X15 is Glu or Asp;

X28 is Glu or Asp; and

a lactam ring is present between the side chains at positions 16 and 20.

82. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.43:

5 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Ser-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Glu-Trp-Leu-Met-X28-Thr

wherein

X15 is Glu or Asp;

X28 is Glu or Asp; and

10 a lactam ring is present between side chains at positions 20 and 24.

83. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.44:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Glu-Trp-Leu-Met-Lys-X29

15 wherein

X15 is Glu or Asp;

X29 is Glu or Thr.

84. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.45:

20 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-X12-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-Asp-Phe-
Val-X24-Trp-Leu-Met-X28-X29

wherein

X12 is Lys or Glu;

X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;

25 X16 is Ser, Gln, Glu, Lys, homoglutamic acid, cysteic acid or homocysteic acid;

X20 is Gln, Glu or Lys;

X24 is Gln, Lys or Glu;

X28 is Asn, Lys or an acidic amino acid;

X29 is Thr, Gly or an acidic amino acid.

30

85. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.46:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-X20-Asp-Phe-
Val-X24-Trp-Leu-Met-Asn-Thr

wherein

35 X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln or Lys;

X24 is Gln or Glu.

86. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.47:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Gln-Trp-Leu-Met-Asn-Thr.

5

87. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.48:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Glu-Trp-Leu-Met-Asn-Thr.

10

88. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.49:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Glu-Trp-Leu-Met-Asn-Thr.

15

89. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.50:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-
Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly

20

90. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.51:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-X21-Phe-
Val-X24-Trp-Leu-Met-X28-X29

wherein

X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln, Lys, Arg, Orn or Citrulline;

25

X21 is Asp, Glu, homoglutamic acid or homocysteic acid;

X24 is Gln or Glu;

X28 is Asn, Lys or an acidic amino acid;

X29 is Thr, Gly or an acidic amino acid.

30

91. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.52:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-
Ala-Trp-Leu-Val-Lys-Gly-Arg.

35

92. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.53:
His-Ser-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-Asp-Phe-
Val-X24-Trp-Leu-Met-X28-X29

wherein

X3 is Glu, Orn or Nle;

X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln or Lys;

5 X24 is Gln or Glu;

X28 is Asn, Lys or an acidic amino acid;

X29 is Thr or an acidic amino acid.

93. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.54:

10 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-X17-X18-Ala-Lys-X21-Phe-X23-X24-Trp-Leu-Met-Asn-Thr

wherein

X17 is Arg or Gln;

X18 is Arg or Ala;

15 X21 is Asp or Glu;

X23 is Val or Ile;

X24 is Gln or Ala.

94. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.56:

20 X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29

wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

25 X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle

X15 is Asp, Glu, cysteic acid, homoglutamic acid homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid, or homocysteic acid;

X20 is Gln, Lys, Arg, Orn or Citrulline;

30 X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

X24 is Ala, Gln, Glu, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle;

X28 is Asn, Lys or Asp;

35 X29 is Thr, Gly Lys, Cys, Orn, homocysteine or acetyl phenylalanine.

95. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.57:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-Glu-Arg-Arg-Ala-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29

wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle;

X15 is Asp, Glu, Cysteic acid, homoglutamic acid or homocysteic acid;

X20 is Gln, Lys, Arg, Orn, or Citrulline;

X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

X24 is Ala, Gln, Glu, Cys, Orn, homocysteine or acetyl phenylalanine;

X27 is Met, Leu or Nle;

X28 is Asn, Lys or Asp;

X29 is Thr, Gly, Cys, Orn, homocysteine or acetyl phenylalanine;

and wherein a lactam bridge is present between side chains at positions 12 and 16.

96. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.58:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-Glu-Arg-Arg-Ala-Lys-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29

wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle;

X15 is Asp, Glu, Cysteic acid, homoglutamic acid or homocysteic acid;

X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

X24 is Ala, Gln, Glu, Cys, Orn, homocysteine or acetyl phenylalanine,

X27 is Met, Leu or Nle;

X28 is Asn, Lys or Asp;

X29 is Thr, Gly, Cys, Orn, homocysteine or acetyl phenylalanine;

and wherein a lactam bridge is present between side chains at positions 16 and 20.

97. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.59:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-Lys-X21-Phe-X23-Glu-Trp-Leu-X27-X28-X29

wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

5 X3 is Gln, Glu, Orn or Nle;

X15 is Asp, Glu, Cysteic acid, homoglutamic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

10 X27 is Met, Leu or Nle;

X28 is Asn, Lys or Asp;

X29 is Thr, Gly, Cys, Orn, homocysteine or acetyl phenylalanine;

and wherein a lactam bridge is present between side chains at positions 20 and 24.

15 98. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.60:

X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-X15-X16-Arg-Arg-Ala-X20-X21-Phe-X23-Glu-Trp-Leu-X27-Lys-X29

wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, Acetyl-His, homo-His, DMIA, N-methyl His, Alpha-methyl His, or imidazole acetic acid;

20 X2 is Ser, D-Ser, Ala, D-Ala, Val, Gly, N-methyl Ser, Aib or N-methyl Ala;

X3 is Gln, Glu, Orn or Nle;

X15 is Asp, Glu, Cysteic acid, homoglutamic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

25 X20 is Gln, Lys, Arg, Orn or Citrulline

X21 is Gln, Glu, Asp, Cys, Orn, homocysteine or acetyl phenylalanine;

X23 is Val or Ile;

X27 is Met, Leu or Nle;

X29 is Thr, Gly, Cys, Orn, homocysteine or acetyl phenylalanine;

30 and wherein a lactam bridge is present between side chains at positions 24 and 28

99. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.63:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-X16-Arg-Arg-Ala-X20-X21-Phe-Val-X24-Trp-Leu-X27-Asp-Thr

35 wherein

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln or Lys;

X21 is Asp, Lys, Cys, Orn, homocysteine or acetyl phenyalanine;

X24 is Gln, Lys, Cys, Orn, homocysteine or acetylphenyalanine;

X27 is Met, Leu or Nle.

5 100. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.66:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Gln-Trp-Leu-Met-X28-X29

wherein

X28 is Asp or Asn;

10 X29 is Thr or Gly;

and wherein a lactam ring is present between side chains at positions 12 and 16.

101. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.67:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-

15 Val-Gln-Trp-Leu-Met-X28-X29

wherein

X28 is Asp or Asn;

X29 is Thr or Gly;

and wherein a lactam ring is present between side chains at positions 16 and 20.

20

102. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.68:
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Lys-Asp-Phe-
Val-Glu-Trp-Leu-Met-X28-X29

wherein

25 X28 is Asp or Asn;

X29 is Thr or Gly;

and wherein a lactam ring is present between side chains at positions 20 and 24.

103. A method according to any one of claims 1 to 6 or 54 wherein X has the Formula VII.69:
30 His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
Val-Glu-Trp-Leu-Met-Lys-X29

wherein

X29 is Thr or Gly;

and wherein a lactam ring is present between side chains at positions 24 and 28.

35

104. A method according to any one of claims 1 to 6 or 54 wherein X has a sequence set out
in Figure 3: Table 2.

105. A method according to any one of claims 1 to 6 or 54 wherein X-Z¹ has the Formula VII.61:

X1-X2-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Arg-X18-Ala-Lys-Asp-Phe-
5 Val-X24-Trp-Leu-Met-Asn-X29-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Cys
wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, acetyl-His, homo-His, DMIA, N-methyl His, alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, Val, Gly, N-methyl Ser, Aib, N-methyl Ala or D-Ala;

10 X18 is Ala or Arg;

X24 is Ala, Gln or Cys-PEG;

X29 is Thr-CONH₂, Cys-PEG, or Gly;

position 40 is Cys-PEG or not present;

provided that positions 30 to 40 (Z²) are present only if position 29 is Gly.

15

106. A method according to any one of claims 1 to 6 or 54 wherein X-Z¹ has the Formula VII.62:

X1-X2-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Gln-X18-Ala-Lys-Glu-Phe-Ile-
X24-Trp-Leu-Met-Asn-X29-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Cys

20 wherein

X1 is His, D-His, (Des-amino)His, hydroxyl-His, acetyl-His, homo-His, DMIA, N-methyl His, alpha-methyl His, or imidazole acetic acid;

X2 is Ser, D-Ser, Ala, Val, Gly, N-methyl Ser, Aib, N-methyl Ala or D-Ala;

X18 is Ala or Arg;

25 X24 is Ala, Gln or Cys-PEG;

X29 is Thr-CONH₂, Cys-PEG, or Gly;

position 40 is Cys-PEG or not present;

provided that positions 30 to 40 (Z²) are present only if position 29 is Gly

30 107. A method according to any one of claims 1 to 6 or 54 wherein X-Z¹ has the Formula VII.64:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- X15-X16-Arg-Arg-Ala-X20-Asp-Phe-
Val-X24-Trp-Leu-Met-X28-Gly-Gly-Pro-Ser-Ser-Gly-Pro-Pro-Pro-Ser

wherein

35 X15 is Asp, Glu, homoglutamic acid, cysteic acid or homocysteic acid;

X16 is Ser, Glu, Gln, homoglutamic acid or homocysteic acid;

X20 is Gln or Lys;

X24) is Gln or Glu;

X28 is Asn, Lys or Asp.

108. A method according to any one of claims 1 to 107 wherein the peptide sequence X differs
5 from the sequence of native human glucagon at a minimum of 2 positions, e.g. at a minimum of 3, 4, 5, 6 of 29 positions.

109. A method according to any one of claims 1 to 6 wherein X differs from human glucagon
10 at only position X12, X17 or X18.

110. A method according to claim 109 wherein the residue at X12 is Ala or Arg.

111. A method according to claim 109 wherein the residue at X17 is Glu or Lys.

112. A method according to claim 109 wherein the residue at X18 is His, Ser, Ala or Tyr.
15

113. A method according to claim 109 wherein X has the sequence:

HSQGTFTSDYSAYLDSRRAQDFVQWLMNT;

HSQGTFTSDYSRYLDSRRAQDFVQWLMNT;

20 HSQGTFTSDYSKYLDSERAQDFVQWLMNT;

HSQGTFTSDYSKYLDSKRAQDFVQWLMNT;

HSQGTFTSDYSKYLDSRHAQDFVQWLMNT;

HSQGTFTSDYSKYLDSRSAQDFVQWLMNT;

HSQGTFTSDYSKYLDSRAAQDFVQWLMNT; or

25 HSQGTFTSDYSKYLDSRYAQDFVQWLMNT.

114. A method according to claim 108 wherein X has the sequence:

HSQGTFTSDYSRYLDSRRAKDFVQWLLNT;

HSQGTFTSDYSRYLDSRRAQDFVQWLLNT;

30 HSQGTFTSDYSRYLDSRRAQDFVQWLLNK;

HSQGTFTSDYSKYLDSALAQDFVQWLLNT;

HSQGTFTSDYSKYLDKRRRAEDFVQWLMNT;

HSQGTFTSDYSKYLDK()RRAE()DFVQWLMNT;

HSQGTFTSDYSRYLDERRAQDFVQWLMNT;

35 HSQGTFTSDYSK()YLDE()RRAQDFVQWLMNT;

HSQGTFTSDYSKYLDSRRAQDFIEWLMNT;

HSQGTFTSDYSKYLDSKAAQDFVQWLMNT; or

HSQGTFTSDYSKYLDLAAQDFVQWLMNT.

115. A method according to any one of claims 1 to 108 wherein X differs from human glucagon at a maximum of 10 positions, e.g. at a maximum of 7, 8, 9 or 10 positions.

5

116. A method according to any one of claims 6 to 115 wherein Z^2 represents a peptide sequence of 1-15, 1-10 or 1-7 amino acid residues, e.g., 1, 2, 3, 4, 5, 6 or 7 amino acid residues, such as 6 amino acid residues.

10

117. A method according to claim 116 wherein each of the amino acid residues in Z^2 is independently selected from Glu, Lys, and Cys

118. A method according to claim 117 wherein Z^2 is selected from Lys₃, Lys₄, Lys₅, Lys₆ or Lys₇.

15

119. A method according to any one of claims 6 to 115 wherein Z^2 is absent.

120. A method according to any one of claims 6 to 104 or 108 to 119 wherein Z^1 is absent.

20

121. A method according to any one of claims 6 to 120 wherein the C-terminus of the glucagon-GLP-1 dual agonist is amidated.

122. A method according to any one of claims 6 to 121 wherein the residue at position X3 is alternatively selected from acetamidomethyl-cysteine, cetyldiaminobutanoic acid, carbamoyldiaminopropanoic acid, methylglutamine and methionine sulfoxide.

25

123. A method according to any one of claims 6 to 122 wherein one or more of the amino acid side chains of the glucagon-GLP-1 agonist is conjugated to a lipophilic substituent.

30

124. A method according to claim 123 wherein the lipophilic substituent is covalently bonded directly to an atom in the amino acid side chain.

125. A method according to claim 123 or claim 124 wherein the side chain(s) of one or more of the residues at positions 16, 17, 20, 24, 27, 28 or one of the residues of Z^2 is conjugated to a lipophilic substituent.

35

126. A method according to claim 125 wherein at least one of positions 16, 17, 20 and 28 is conjugated to a lipophilic substituent.

127. A method according to any one of claims 122 to 126 wherein Z¹ is absent and Z² consists
5 of only one amino acid residue X30.

128. A method according to claim 127 wherein X30 is Cys or Lys.

129. A method according to 127 or claim 128 wherein X30 is conjugated to a lipophilic
10 substituent.

130. A method according to any one of claims 123 to 129 wherein only one side chain is conjugated to a lipophilic substituent.

15 131. A method according to claim 130 wherein said one side chain is at position 16, 17, 18, 20, 24, 27, 28 or 30, e.g. at position 16, 17 or 20, e.g. at position 17.

132. A method according to any one of claims 123 to 129 wherein precisely two side chains are conjugated to lipophilic substituents.
20

133. A method according to claim 132 wherein each substituent is at one of positions 16, 17, 18, 20, 24, 27, 28 or 30, e.g. at one of positions 16, 17 or 20.

134. A method according to any one of claims 123 to 133 wherein each lipophilic substituent
25 comprises a lipophilic moiety conjugated to the amino acid side chain by a spacer.

135. A method according to claim 134 wherein the combination of lipophilic moiety and spacer is selected from dodecanoyl-γ-Glu, hexadecanoyl-γ-Glu, hexadecanoyl-Glu, hexadecanoyl-[3-aminopropanoyl], hexadecanoyl-[8-aminooctanoyl], hexadecanoyl-ε-Lys, 2-butyloctanoyl-γ-Glu,
30 octadecanoyl-γ-Glu and hexadecanoyl-[4-aminobutanoyl].

136. A method according to any one of claims 6 to 135 wherein one or more amino acid side chains of the glucagon-GLP-1 dual agonist is conjugated to a polymeric moiety.

35 137. A method according to claim 136 wherein the polymeric moiety is water soluble (amphiphilic or hydrophilic), non-toxic, and pharmaceutically inert.

138. A method according to claim 136 or claim 137 wherein the polymeric moiety is selected from polyethylene glycols (PEG), homo- or co-polymers of PEG, monomethyl-substituted polymers of PEG (mPEG), polyoxyethylene glycerols (POG), and poly-amino acids.

5 139. A method according to claim 138 wherein the poly-amino acid is selected from poly-lysine, poly-aspartic acid and poly-glutamic acid.

140. A method according to any one of claims 136 to 139 wherein the polymeric moiety is straight-chain.

10

141. A method according to any one of claims 136 to 139 wherein the polymeric moiety is branched.

15

142. A method according to any one of claims 136 to 139 wherein the polymeric moiety has a molecular weight of 500-40,000 Da, 500-5,000 Da, 500-10,000 Da, 1000-5000 Da, 10,000-20,000 Da, or 20,000-40,000Da.

143. A method according to any one of claims 136 to 142 wherein the glucagon-GLP-1 dual agonist comprises two or more polymeric moieties.

20

144. A method according to claim 143 wherein the total molecular weight of all polymeric moieties is 500-40,000 Da, 500-5,000 Da, 500-10,000 Da, 1000-5000 Da, 10,000-20,000 Da, or 20,000-40,000Da.

25

145. A method according to any one of claims 136 to 144 wherein the polymeric moiety is covalently coupled to an amino, carboxyl or thiol group of an amino acid side chain.

30

146. A method according to claim 145 wherein the polymeric moiety is covalently coupled to the thiol group of a Cys residue, the epsilon amino group of a Lys residue, or the carboxyl groups of an Asp or Glu residue.

35

147. A method according to any one of claims 136 to 146 wherein the polymeric moiety is coupled to the side chain of the residue at one or more of positions 16, 17, 20, 21, 24 or 29, or to the C-terminus of the peptide.

148. A method according to claim 147 wherein the polymeric moiety is coupled at one or more of positions 16, 17, 21 and 24.

149. Use of a glucagon-GLP-1 dual agonist as an inotropic agent in the treatment of heart disease or heart dysfunction.

5 150. Use of a glucagon-GLP-1 dual agonist in the preparation of a medicament for the treatment of heart disease or heart dysfunction, wherein the glucagon-GLP-1 dual agonist is to be administered for use as an inotropic agent.

10 151. Use of a glucagon-GLP-1 dual agonists in the preparation of a medicament capable of improving cardiac contractility without causing concomitant increase in heart rate.

152. A glucagon-GLP-1 dual agonist for use as an inotropic agent in the treatment of heart disease or heart dysfunction.

15 153. A glucagon-GLP-1 dual agonist for use in the preparation of a medicament for the treatment of heart disease or heart dysfunction, wherein the glucagon-GLP-1 dual agonist is to be administered for use as an inotropic agent.

20 154. A glucagon-GLP-1 dual agonist for use according to any one of claims 149 to 153 wherein the glucagon-GLP-1 dual agonist is as defined in any one of claims 6 to 148.

Figure 1

5

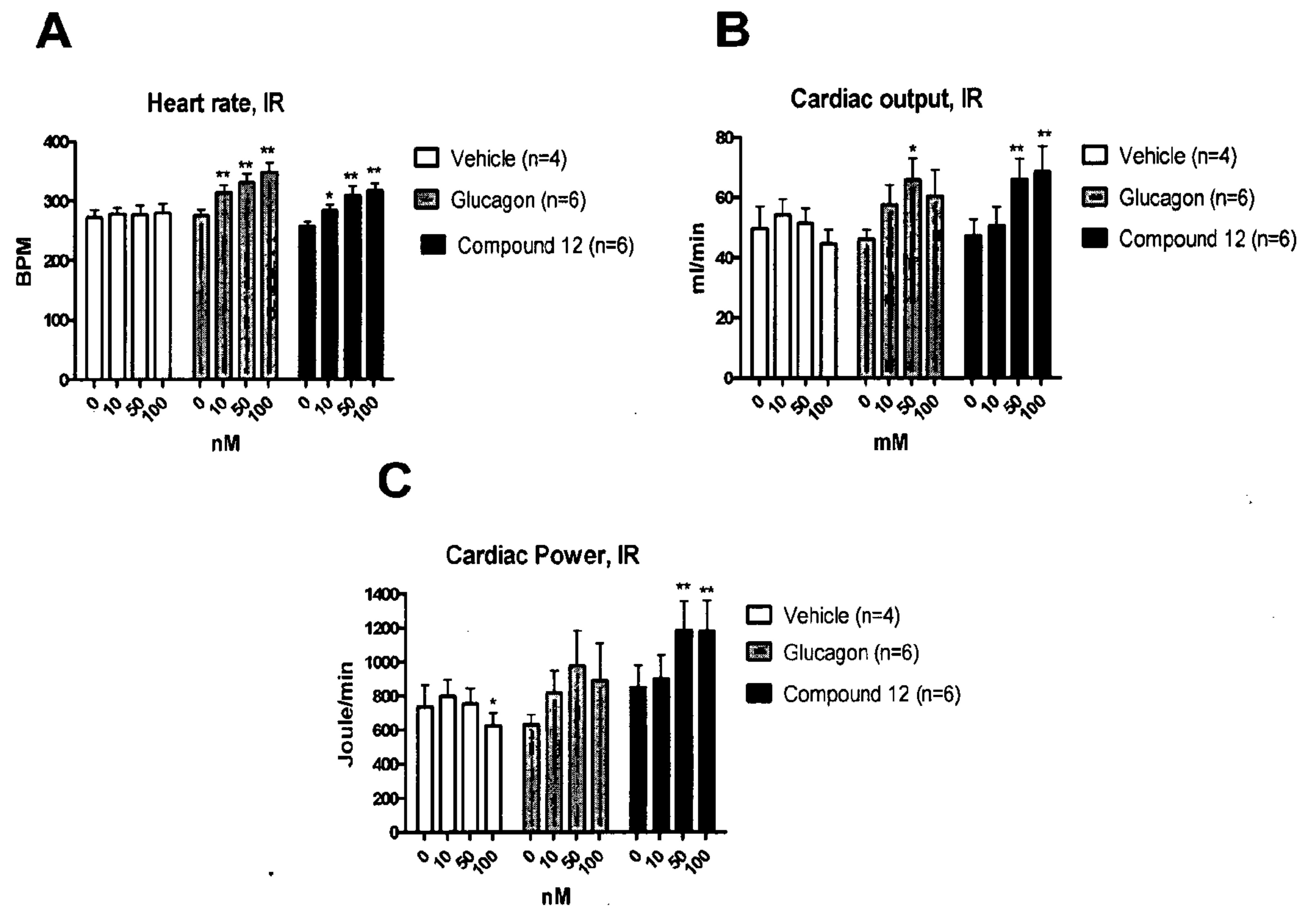


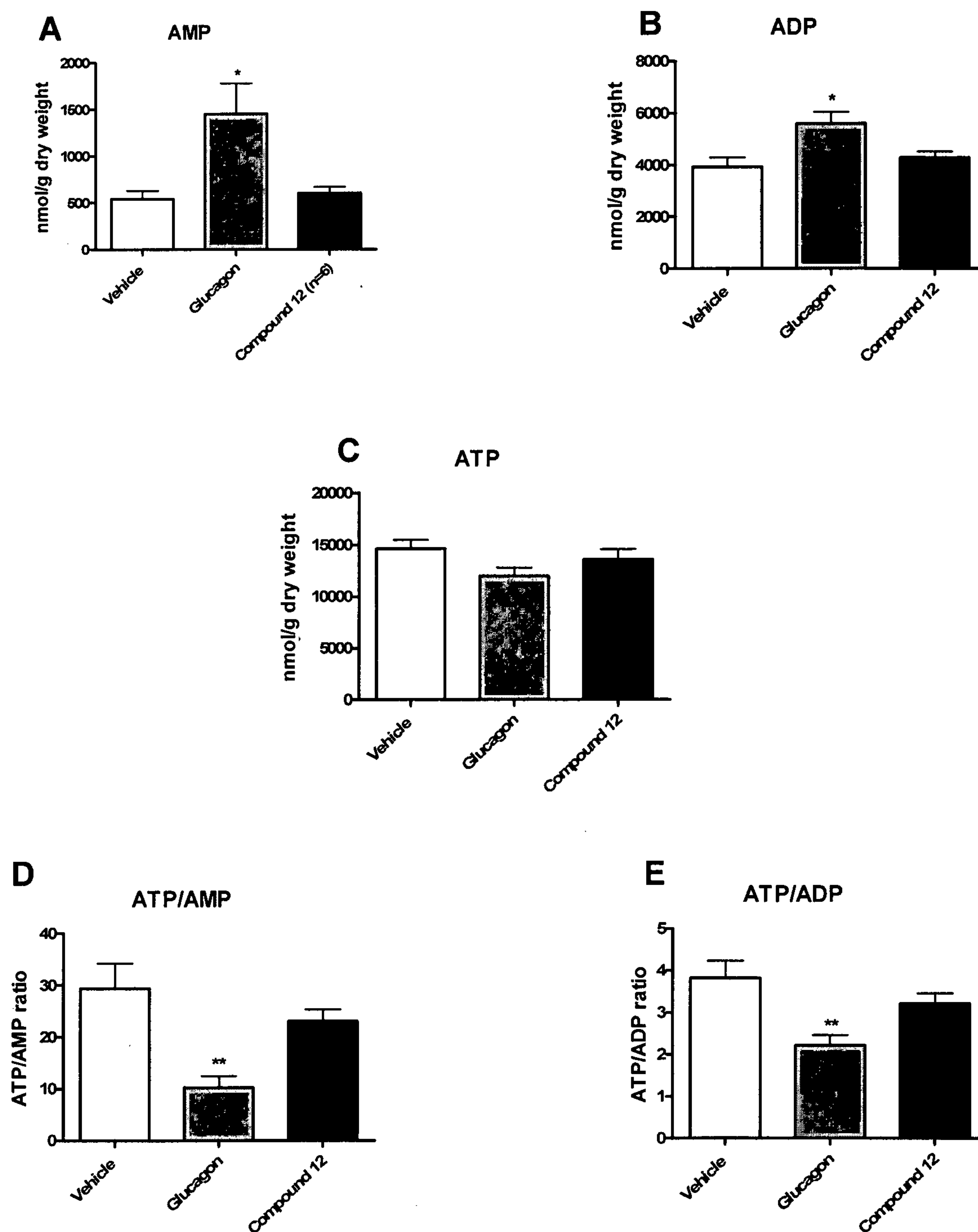
Figure 2

Figure 3

Table 2

DAH = (Des-amino)His

Residues marked “()” participate in a lactam ring or other intramolecular bond.

Residues marked “*” are derivatised, e.g. with PEG.

The compound numbers (D# 10, 11, 12 etc.) in the following, separate list of compounds apply only to the compounds in question

D#	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
10	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
11	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
12	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
13	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	N	T	NH2
14	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	R	R	A	K()	D	F	V	E()	W	L	M	N	T	NH2
15	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	R	R	A	Q	D	F	V	E()	W	L	M	K()	T	NH2
16	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	E()	W	L	M	N()	T	NH2
17	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	D()	D	F	V	E()	W	L	M	K()	T	NH2
18	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	E()	W	L	M	K()	T	NH2
70	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
71	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
72	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	N	T	NH2
73	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
74	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
75	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	Q	W	L	M	N	T	NH2
76	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
77	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	N	T	NH2
78	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	N	T	NH2
79	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
80	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	N	T	NH2
81	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
82	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
83	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	N	T	NH2
84	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2

85	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
86	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	V	K	G	NH2
87	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
88	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
89	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	N	T	NH2
90	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
91	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
92	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	Q	W	L	M	N	T	NH2
93	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
94	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	N	T	NH2
95	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	N	T	NH2
96	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
97	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	N	T	NH2
98	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
99	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
100	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	N	T	NH2
101	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
102	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
103	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	V	K	G	NH2
104	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
105	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
106	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	N	T	NH2
107	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
108	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
109	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	Q	W	L	M	N	T	NH2
110	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
111	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	N	T	NH2
112	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	N	T	NH2
113	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
114	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	N	T	NH2
115	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
116	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
117	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	N	T	NH2
118	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
119	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2

120	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	V	K	G	NH2
121	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
122	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
123	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	N	T	NH2
124	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
125	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
126	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	Q	W	L	M	N	T	NH2
127	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
128	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	N	T	NH2
129	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	N	T	NH2
130	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
131	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	N	T	NH2
132	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
133	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
134	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	N	T	NH2
135	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
136	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
137	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	V	K	G	NH2
138	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
139	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
140	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	N	T	NH2
141	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
142	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
143	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	Q	W	L	M	N	T	NH2
144	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
145	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	N	T	NH2
146	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	N	T	NH2
147	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
148	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	N	T	NH2
149	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
150	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
151	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	N	T	NH2
152	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
153	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
154	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	V	K	G	NH2

155	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
156	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
157	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	N	T	NH2
158	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
159	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
160	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	Q	W	L	M	N	T	NH2
161	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
162	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	N	T	NH2
163	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	N	T	NH2
164	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
165	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	N	T	NH2
166	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
167	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
168	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	N	T	NH2
169	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
170	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
171	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	V	K	G	NH2
172	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
173	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
174	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	N	T	NH2
175	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
176	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
177	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	E()	D	F	V	Q	W	L	M	N	T	NH2
178	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
179	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
180	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	N	T	NH2
181	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
182	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
183	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	N	T	NH2
184	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
185	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
186	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	N	T	NH2
187	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
188	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
189	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2

190	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
191	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	N	T	NH2
192	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	N	T	NH2
193	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
194	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	Q	W	L	M	N	T	NH2
195	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
196	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	N	T	NH2
197	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	N	T	NH2
198	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
199	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	E()	D	F	V	Q	W	L	M	N	T	NH2
200	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
201	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
202	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	N	T	NH2
203	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
204	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
205	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	V	K	G	NH2
206	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
207	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
208	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	C*	W	L	M	N	T	NH2
209	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
210	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
211	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2
212	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
213	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	C*	W	L	M	N	T	NH2
214	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	C*	W	L	M	N	T	NH2
215	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
216	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	C*	W	L	M	N	T	NH2
217	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
218	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
219	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	M	N	T	NH2
220	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	V	K	G	NH2
221	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	V	K	G	NH2
222	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	V	K	G	NH2
223	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
224	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	C*	W	L	M	N	T	NH2

225	DAH	S	Q	G	T	F	T	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	C*	W	L	M	N	T	NH2
226	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
227	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
228	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2
229	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
230	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	C*	W	L	M	N	T	NH2
231	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	C*	W	L	M	N	T	NH2
232	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
233	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	R	A	A	E()	D	F	V	C*	W	L	M	N	T	NH2
234	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
235	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
236	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	M	N	T	NH2
237	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
238	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	V	K	G	NH2
239	DAH	S	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	V	K	G	NH2
240	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
241	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
242	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	C*	W	L	M	N	T	NH2
243	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
244	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
245	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2
246	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
247	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
248	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	R	A	A	K()	D	F	V	C*	W	L	M	N	T	NH2
249	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
250	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	C*	W	L	M	N	T	NH2
251	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
252	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
253	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	M	N	T	NH2
254	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	V	K	G	NH2
255	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	V	K	G	NH2
256	H	Aib	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	V	K	G	NH2
257	H	D-Ala	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
258	H	D-Ala	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
259	H	D-Ala	Q	G	T	F	T	S	D	Y	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	C*	W	L	M	N	T	NH2

260	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K()	Y	L	D	E()	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
261	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K()	Y	L	D	E()	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
262	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K	Y	L	D	K()	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2
263	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K	Y	L	D	E	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
264	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K	Y	L	D	E()	R	A	K()	D	F	V	C*	W	L	M	N	T	NH2
265	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K()	Y	L	D	E()	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
266	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K()	Y	L	D	E()	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
267	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K	Y	L	D	K()	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2
268	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K	Y	L	D	E	Q	A	K	E	F	I	C*	W	L	M	N	T	NH2
269	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K()	Y	L	D	E()	Q	A	K	E	F	I	C*	W	L	M	N	T	NH2
270	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K	Y	L	D	E()	Q	A	K()	E	F	I	C*	W	L	M	N	T	NH2
271	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K	Y	L	D	E	Q	A	K	E	F	I	C*	W	L	V	K	G	NH2
272	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K()	Y	L	D	E()	Q	A	K	E	F	I	C*	W	L	V	K	G	NH2
273	H	D-Ala	Q	G	T	G	T	F	T	S	D	Y	S	S	K	Y	L	D	E()	Q	A	K()	E	F	I	C*	W	L	V	K	G	NH2
274	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
275	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
276	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	K()	D	F	V	C*	W	L	M	N	T	NH2
277	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
278	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	K	E	F	V	C*	W	L	M	N	T	NH2
279	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2
280	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
281	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	K()	D	F	V	C*	W	L	M	N	T	NH2
282	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
283	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
284	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2
285	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	K	E	F	I	C*	W	L	M	N	T	NH2
286	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	K	E	F	I	C*	W	L	M	N	T	NH2
287	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	K()	E	F	I	C*	W	L	M	N	T	NH2
288	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	K	E	F	I	C*	W	L	V	K	G	NH2
289	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	K	E	F	I	C*	W	L	V	K	G	NH2
290	H	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	K()	E	F	I	C*	W	L	V	K	G	NH2
291	DAH	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	Q	D	F	V	C*	W	L	M	N	T	NH2
292	DAH	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
293	DAH	S	E	G	T	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	K()	D	F	V	C*	W	L	M	N	T	NH2
294	DAH	S	E	G	T	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2

295	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	K	D	F	V	C*	W	L	M	N	T	NH2	
296	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2	
297	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
298	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	C*	W	L	M	N	T	NH2
299	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	C*	W	L	M	N	T	NH2
300	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
301	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	C*	W	L	M	N	T	NH2
302	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
303	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
304	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	M	N	T	NH2
305	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	V	K	G	NH2
306	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	V	K	G	NH2
307	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	V	K	G	NH2
308	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	Q	D	F	V	C*	W	L	M	N	T	NH2
309	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
310	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	C*	W	L	M	N	T	NH2
311	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	C*	W	L	M	N	T	NH2
312	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
313	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	C*	W	L	M	N	T	NH2
314	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
315	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	C*	W	L	M	N	T	NH2
316	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	C*	W	L	M	N	T	NH2
317	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
318	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	C*	W	L	M	N	T	NH2
319	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
320	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	M	N	T	NH2
321	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	M	N	T	NH2
322	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	C*	W	L	V	K	G	NH2
323	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	C*	W	L	V	K	G	NH2
324	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	C*	W	L	V	K	G	NH2
325	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	Q	D	F	V	C*	W	L	M	N	T	NH2
326	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2
327	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	C*	W	L	M	N	T	NH2
328	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	C*	W	L	M	N	T	NH2
329	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	C*	W	L	M	N	T	NH2

330	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2
331	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
332	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	K()	D	F	V	C*	W	L	M	N	T	NH2
333	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	Q	D	F	V	C*	W	L	M	N	T	NH2
334	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	K	D	F	V	C*	W	L	M	N	T	NH2
335	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	E()	D	F	V	C*	W	L	M	N	T	NH2
336	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	K	E	F	I	C*	W	L	M	N	T	NH2
337	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	K	E	F	I	C*	W	L	M	N	T	NH2
338	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	K()	E	F	I	C*	W	L	M	N	T	NH2
339	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	K	E	F	I	C*	W	L	V	K	G	NH2
340	H	D-Ala	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	K	E	F	I	C*	W	L	V	K	G	NH2
341	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	K()	E	F	I	C*	W	L	V	K	G	NH2
342	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
343	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
344	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	M	N	T	NH2
345	H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	V	K	G	NH2
346	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
347	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
348	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	M	N	T	NH2
349	DAH	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	V	K	G	NH2
350	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
351	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
352	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	M	N	T	NH2
353	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	V	K	G	NH2
354	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
355	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
356	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	M	N	T	NH2
357	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	V	K	G	NH2
358	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
359	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
360	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	M	N	T	NH2
361	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	V	K	G	NH2
362	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
363	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
364	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	K	E	F	I	A	W	L	M	N	T	NH2

365	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
366	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
367	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
368	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
369	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	A	K	E	F	I	A	W	L	V	K	G	NH2
370	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	R	A	K	D	F	V	Q	W	L	M	N	T	NH2
371	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	R	A	A	K	D	F	V	Q	W	L	M	N	T	NH2
372	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
373	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	C*	Q	A	A	K	E	F	I	A	W	L	M	N	T	NH2
374	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
375	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	D	T	NH2
376	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	D	T	NH2
377	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
378	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	D	T	NH2
379	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	E()	D	F	V	Q	W	L	M	D	T	NH2
380	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
381	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	D	T	NH2
382	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
383	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
384	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	E()	D	F	V	Q	W	L	M	D	T	NH2
385	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
386	H	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
387	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
388	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	D	T	NH2
389	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
390	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	D	T	NH2
391	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	D	T	NH2
392	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
393	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	R	A	E()	D	F	V	Q	W	L	M	D	T	NH2
394	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
395	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	D	T	NH2
396	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
397	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
398	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	D	T	NH2
399	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2

400	DAH	S	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
401	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	D	T	NH2
402	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
403	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	D	T	NH2
404	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	D	T	NH2
405	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
406	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	D	T	NH2
407	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	E()	D	F	V	Q	W	L	M	D	T	NH2
408	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
409	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	D	T	NH2
410	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
411	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
412	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	E()	D	F	V	Q	W	L	M	D	T	NH2
413	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
414	H	Aib	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
415	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	D	T	NH2
416	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
417	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	D	T	NH2
418	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	D	T	NH2
419	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
420	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	D	T	NH2
421	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	E()	D	F	V	Q	W	L	M	D	T	NH2
422	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
423	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
424	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
425	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
426	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	E()	D	F	V	Q	W	L	M	D	T	NH2
427	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
428	H	D-Ala	Q	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
429	H	D-Ala	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	D	T	NH2
430	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
431	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	W	L	M	D	T	NH2
432	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	R	A	K()	D	F	V	Q	W	L	M	D	T	NH2
433	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	Q	D	F	V	Q	W	L	M	D	T	NH2
434	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	R	A	K	D	F	V	Q	W	L	M	D	T	NH2

435	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	D	T	NH2
436	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
437	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	D	T	NH2
438	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
439	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
440	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	D	T	NH2
441	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
442	H	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
443	H	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	D	T	NH2
444	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
445	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
446	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	D	T	NH2
447	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
448	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
449	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
450	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
451	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	D	T	NH2
452	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
453	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
454	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	D	T	NH2
455	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
456	DAH	S	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2
457	DAH	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	Q	A	A	K()	E	F	I	A	W	L	M	D	T	NH2
458	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
459	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
460	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	D	T	NH2
461	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
462	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
463	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	D	T	NH2
464	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
465	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E()	R	A	A	K()	D	F	V	Q	W	L	M	D	T	NH2
466	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	Q	D	F	V	Q	W	L	M	D	T	NH2
467	H	Aib	E	G	T	F	T	S	D	Y	S	K()	Y	L	D	E()	R	A	A	K	D	F	V	Q	W	L	M	D	T	NH2
468	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	K()	R	A	A	E()	D	F	V	Q	W	L	M	D	T	NH2
469	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	K	E	F	I	A	W	L	M	D	T	NH2

470	H	Aib	E G T F T S D Y S K()	Y L D E()	Q A A K	E F I A W L M D	T NH2
471	H	Aib	E G T F T S D Y S K	Y L D E()	Q A A K()	E F I A W L M D	NH2
472	H	D-Ala	E G T F T S D Y S K	Y L D E	R R A	D F V Q W L M D	NH2
473	H	D-Ala	E G T F T S D Y S K	Y L D E	R R A K	D F V Q W L M D	NH2
474	H	D-Ala	E G T F T S D Y S K	Y L D E()	R R A K()	D F V Q W L M D	NH2
475	H	D-Ala	E G T F T S D Y S K()	Y L D E()	R R A	D F V Q W L M D	NH2
476	H	D-Ala	E G T F T S D Y S K()	Y L D E()	R R A K	D F V Q W L M D	NH2
477	H	D-Ala	E G T F T S D Y S K	Y L D K()	R R A E()	D F V Q W L M D	NH2
478	H	D-Ala	E G T F T S D Y S K	Y L D E	R A A K	D F V Q W L M D	NH2
479	H	D-Ala	E G T F T S D Y S K	Y L D E()	R A A K()	D F V Q W L M D	NH2
480	H	D-Ala	E G T F T S D Y S K()	Y L D E()	R A A	D F V Q W L M D	NH2
481	H	D-Ala	E G T F T S D Y S K()	Y L D E()	R A A K	D F V Q W L M D	NH2
482	H	D-Ala	E G T F T S D Y S K	Y L D K()	R A A E()	D F V Q W L M D	NH2
483	H	D-Ala	E G T F T S D Y S K	Y L D E	Q A A K	E F I A W L M D	NH2
484	H	D-Ala	E G T F T S D Y S K()	Y L D E()	Q A A K	E F I A W L M D	NH2
485	H	D-Ala	E G T F T S D Y S K	Y L D E()	Q A A K()	E F I A W L M D	NH2
486	H	Aib	E G T F T S D Y S K	Y L D E	Q A A K	E F I C* W L M N	NH2
487	H	Aib	E G T F T S D Y S K	Y L D E	Q A A K	E F I A W L M N	C* NH2
488	H	Aib	E G T F T S D Y S K Y L D E	Q A A K E F I A W L M N G	G P S S G A P P P S	S S G A P P P S C*	NH2
				E(K(			
489	H	Aib	E G T F T S D Y S K Y L D)	Q A A)	E F I A W L M N G	G P S S G A P P P S	C* NH2
					C		
490	H	Aib	E G T F T S D Y S K Y L D E	Q A A K E F I *	W L M N G	G P S S G A P P P S	NH2
				E(K(			
491	H	Aib	E G T F T S D Y S K Y L D)	Q A A)	E F I * W L M N G	G P S S G A P P P S	NH2
					C		
492	H	Aib	E G T F T S D Y S K Y L D E	R A A K D F V *	W L M N T 2		
					C		
493	H	Aib	E G T F T S D Y S K Y L D E	R A A K D F V Q	W L M N * 2		
494	H	Aib	E G T F T S D Y S K Y L D E	R A A K D F V Q	W L M N G	G P S S G A P P P S	C* NH2
				E(K(			
495	H	Aib	E G T F T S D Y S K Y L D)	R A A)	D F V Q W L M N G	G P S S G A P P P S	C* NH2
					C		
496	H	Aib	E G T F T S D Y S K Y L D E	R A A K D F V *	W L M N G	G P S S G A P P P S	NH2
497	H	Aib	E G T F T S D Y S K Y L D E(	R A A K(	D F V C W L M N G	G P S S G A P P P S	NH2

498	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	*	C	NH
499	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
500	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
501	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
502	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
503	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
504	H	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
505	DM	IA	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
506	DM	IA	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
507	DM	IA	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
508	DM	IA	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
509	DM	IA	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
510	DM	IA	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
511	H	X2	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
512	DM	IA	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
513	DM	IA	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH
514	Optio nal lacta	S	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	D	F	V	Q	*	NH

Figure 4

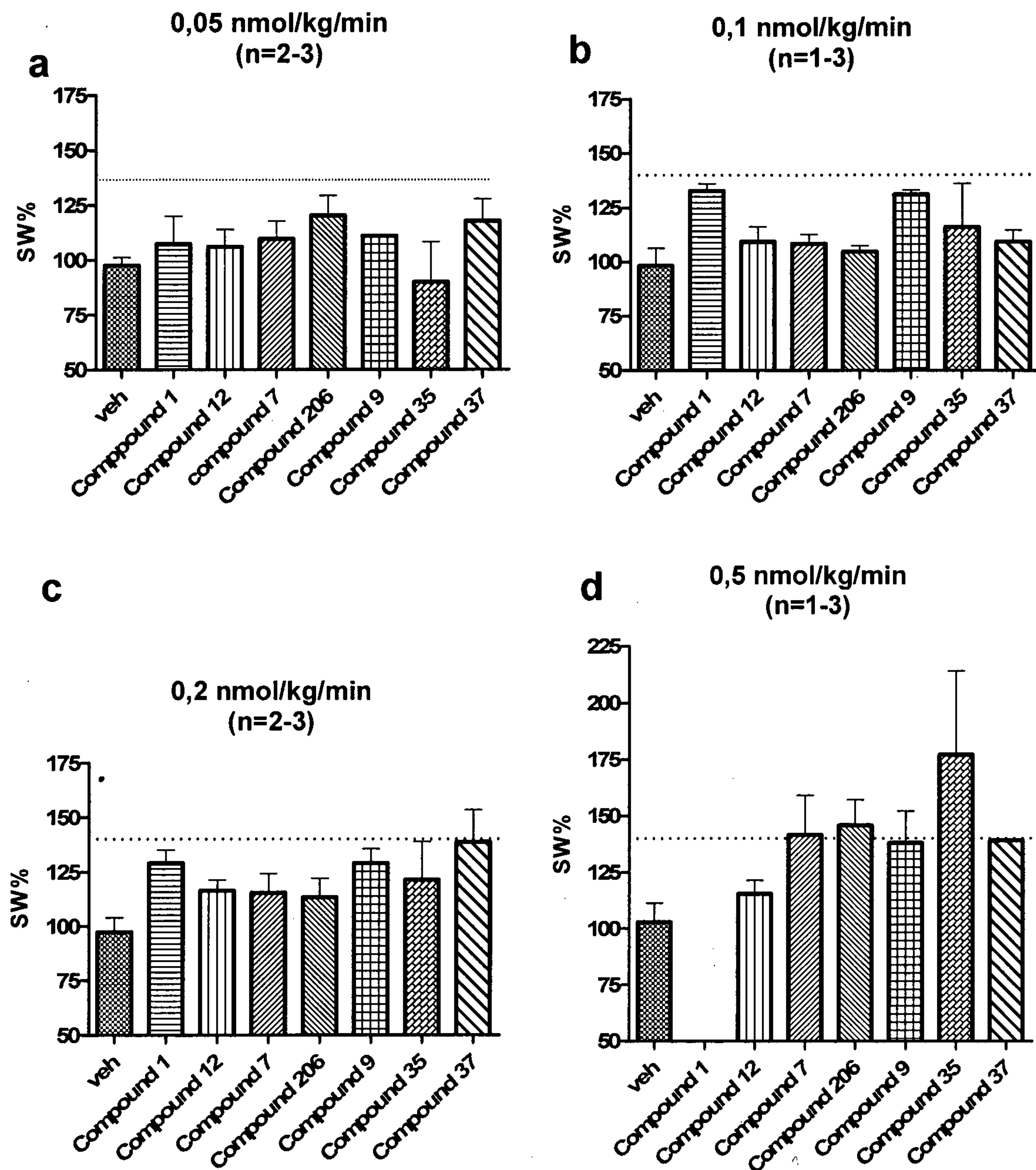


Figure 5

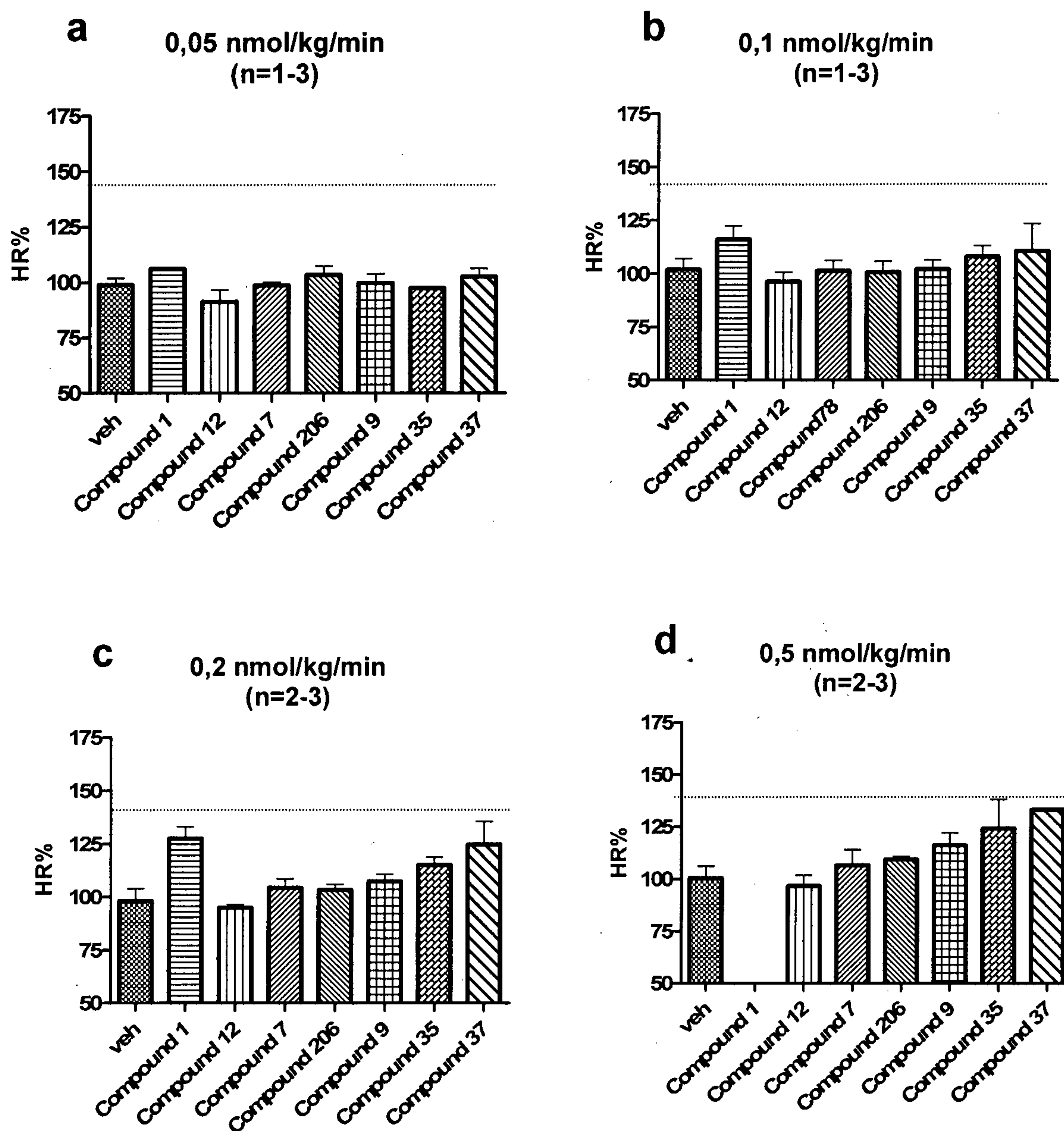


Figure 6

Table 3.

Compound No.	Sequence
264	H-HSQGTFTSDYSKY-Nle-DSKAAHDFVEWLLRA-NH2
265	H-HSQGT-Hph-TSDYSKYLDSKAAHDFVEWLLRA-NH2
266	H-HSQGTFTSDYSKY-Cha-DSKAAHDFVEWLLRA-NH2
267	H-HSQGTFTSDYSKYLDSKAAHDFVEWL-C({PEG12}3PEG4-Mal)-RA-NH2
268	H-H-Aib-QGT-Hph-TSDYSKY-Nle-DS-K(isoGlu(Palm))-AAHDFVEWLLRA-NH2
269	H-H-Aib-QGT-Hph-TSDYSKY-Nle-DSK()AAHE()FVAWLLRA-NH2
270	H-H-Aib-QGTFTSDYSKYLDS-K(isoGlu)-AAHDFVEWLLSA-NH2
271	H-H-Aib-QGTFTSEYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
272	H-H-Aib-QGTFTSDYSKYLE-S-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
273	H-HSQGTFTSDYSKYLDERRAKDFIEWLLSAKKKKKK-NH2
274	H-HGQGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
275	H-H-Aib-QGTFTSSYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
276	H-H-Aib-QGTFTSDYSKYLSS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
277	H()H-Aib-E()GTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2 (Cyclic)
278	H-H-Aib-[3-(4-Thiazolyl)-alanyl]-GTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)- AAHDFVEWLLSA-NH2
279	H-HGQ-Aib-TFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
280	H-HGEGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
281	H-HSQ-Aib-TFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
282	H-H-Aib-QLTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
283	H-H-Aib-QPTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
284	H-H-Aib-QETFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
285	H-H-Aib-Q-Aib-TFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
286	H-H-Aib-QFTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
287	H-H-Aib-FGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
288	H-H-Aib-Q-DPhe-TFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA- NH2
289	H-H-Aib-QRTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
290	H-H-Aib-LGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
291	H-H-Aib-Hph-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
292	H-H-Aib-WGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
293	H-H-Aib-YGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
294	H-H-Aib-VGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
295	H-H-Aib-QKTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
296	H-H-Aib-RGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
297	H-H-Aib-AGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
298	H-H-Aib-SGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
299	H-H-Aib-IGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
300	H-H-Aib-GGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2
301	H-H-Aib-PGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH2

- 302 H-H-Aib-HGTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHEFVEWLLEA-NH₂
- 303 H-H-Aib-Cit-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 304 H-H-Aib-Q-DAla-TFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 305 H-H-Aib-Hse-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 306 H-H-Aib-Q-DLeu-TFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 307 H-H-Aib-HGTFTSDYSKYLESK(hexadecanoyl-isoGlu)-AAEEFVEWLLEA-NH₂
- 308 H-H-Aib-1Nal-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 309 H-H-Aib-[3-(2-furyl)alanyl]-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 310 H-H-Aib-[3-(4-thiazolyl)alanyl]-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 311 H-H-Aib-[3-(3-pyridyl)alanyl]-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 312 H-H-Aib-[3-(4-pyridyl)alanyl]-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 313 H-H-Aib-[3-(2-thienyl)alanyl]-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 314 H-H-Aib-[3-(3-thienyl)alanyl]-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 315 H-H-Aib-[3-(1-pyrazolyl)alanyl]-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 316 H-H-Aib-[3-(1,2,4-triazol-1-yl)alanyl]-GTFTSDYSKYLDSK(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 317 H-H-Aib-HGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 318 H-H-Aib-Q-DPhe-TFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 319 H-H-Aib-YGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 320 H-H-Aib-PGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 321 H-H-Aib-HGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHEFVEWLLEA-NH₂
- 322 H-H-Aib-Q-DAla-TFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 323 H-H-Aib-EGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 324 H-H-Aib-QATFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 325 H-HSQ-Aib-TFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 326 H-H-Aib-QETFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 327 H-H-Aib-Q-Aib-TFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 328 H-H-Aib-QFTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 329 H-H-Aib-LGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 330 H-H-Aib-Hph-GTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 331 H-H-Aib-WGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂

- 332 H-H-Aib-VGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 333 H-H-Aib-AGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 334 H-H-Aib-SGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 335 H-H-Aib-IGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 336 H-H-Aib-GGTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 337 H-H-Aib-Cit-GTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH₂
- 338 H-H-Aib-[3-(2-furyl)alanyl]-GTFTSDYSKYLDS-K(hexadecanoyl-isoGlu)-
AAHDFVEWLLSA-NH₂