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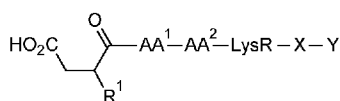
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(54) Title: GLP-1 RECEPTOR ANTAGONISTS

(57) Abstract: The disclosures herein relate to novel compounds of formula (1): and salts thereof, wherein R¹, AA¹, AA², LysR, X and Y are defined herein, and their use in treating, preventing, ameliorating, controlling or reducing the risk of disorders associated with Glucagon-like peptide-1 (GLP-1) receptors.



(1)



GLP-1 Receptor Antagonists

This invention relates to a class of novel peptide compounds, their salts, pharmaceutical compositions containing them and their use in therapy of the human body. In particular, the invention is directed to a class of compounds which are antagonists of Glucagon-like peptide (GLP) receptors. More particularly, the invention is directed to compounds that are antagonists of the Glucagon-like peptide-1 (GLP-1) receptor. The invention also relates to the manufacture and use of these compounds and compositions in the prevention or treatment of such diseases in which GLP receptors are involved.

Background of the Invention

The gastrointestinal hormone, glucagon-like peptide-1 (GLP-1) is released post-prandially (after a meal) from the L-cells of the gut and exerts a direct and potent glucose-dependent insulinotropic effect on the pancreatic b-cell.

GLP-1 is synthesised by posttranslational processing of proglucagon in the intestine. Cleavage of proglucagon by prohormone convertase 1/3 expressed only in the intestinal L-cells releases the incretin peptides GLP-1 and GLP-2. Secreted GLP-1 is rapidly degraded by the ubiquitous enzyme dipeptidyl peptides IV, resulting in an extremely short half-life for GLP-1 of ~2min.

GLP-1 acts via a specific receptor, glucagon-like peptide-1 receptor (GLP-1R), which belongs to the ClassB G protein-coupled receptor family. The GLP-1 receptor is widely distributed in pancreatic islets, brain, heart, kidney and the gastrointestinal tract. Binding of GLP-1 to its cognate receptor causes activation via the stimulatory G-protein Gas to activate adenylate cyclase resulting in the formation of intracellular cAMP levels, membrane depolarisation, elevation of intracellular calcium concentrations and enhanced exocytosis of insulin-containing granules located in the pancreatic b-cell. GLP-1 mediated sustained elevation of cAMP concentrations also stimulates pancreatic b-cell proliferation and enhances the differentiation of new beta cells from progenitor cells in the pancreatic duct epithelium.

GLP-1 also directly influences secretion of other hormones critical for control of plasma glucose. The pancreatic a-cell is under tonic inhibitory control of GLP-1 which strongly suppresses glucagon secretion through a paracrine action of somatostatin. Inhibition of glucagon via GLP-1 activity results in reduced hepatic production of glucose contributing to the overall GLP-1 effects on controlling postprandial glucose excursions.

In summary GLP-1 has been demonstrated to have profound antidiabetic effects through increased pancreatic glucose-stimulated insulin secretion resulting in increased glucose uptake in peripheral tissues. GLP-1 also plays key roles in inhibition of gastric emptying and antroduodenal motility, decrease satiety and food intake and weight loss.

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The significant effects of GLP-1 described above have led to the hypothesis that clinical indications associated with exaggerated plasma concentrations of GLP-1, increased GLP-1 signalling and/or increased GLP-1R levels would result in hyperinsulinemia (excessive glucose-dependent insulin secretion) resulting on hypoglycaemia and evidence of
10 gastrointestinal dysfunction. Therefore conditions such as hyperinsulinemia and hypoglycaemia could be treated by blocking/antagonising activation of the GLP-1R.

The specific GLP-1 receptor antagonist exendin(9-39)amide [Ex(9-39)] was initially isolated from the venom of the lizard *Heloderma suspectum* and shares a degree of sequence
15 homology with GLP-1. Ex(9-39) is a selective, competitive peptide antagonist of the GLP-1 receptor that blocks GLP-1 mediated insulin secretion in vitro and in vivo and impairs glucose tolerance in response to endogenous and exogenous administration of GLP-1 in humans and rodent models. Ex(9-39) also inhibits insulin secretion in the absence of increased GLP-1 levels suggesting that Ex(9-39) is an inverse agonist of the GLP-1
20 receptor. These data suggest that the presence of the GLP-1 receptor alone is important for maintaining the glucose-competent status of pancreatic β -cells.

The influences of GLP-1 on islet β -cells are profound. GLP-1 promotes insulin release, the expression of proinsulin, insulin biosynthesis and mRNA stability. GLP-1 will also trigger
25 somatostatin secretion from islet δ -cells and suppress glucagon secretion from islet α -cells. Glucagons' effects oppose that of insulin raising the concentration of glucose in the bloodstream via effects directly on the liver increasing glycogenolysis and gluconeogenesis. This suggests that blocking the GLP-1 system will not only have direct effects on insulin secretion but will also release the suppression on glucagon secretion driving increased
30 glucose production by the liver.

Under healthy conditions the insulin-secreting actions of GLP-1 are normally highly glucose-dependent such that excessive GLP-1 secretion or sensitivity will not lead to hypoglycaemia. However clinical studies using administration of GLP-1 in the presence of a non glucose-
35 dependent insulin secretagogue (e.g. a sulphonylurea that acts on the KATP channel) or even directly infusing supraphysiological levels of GLP-1 into normal subjects is associated with an increased risk of hypoglycaemia.

Hypoglycemia not associated with diabetes is an uncommon clinical disorder. It is usually diagnosed when venous plasma glucose is < 55mg/ml and supported by the presence of Whipple's triad. The subject of this application, a GLP-1R antagonists would have potential to treat a range of conditions associated with exaggerated plasma concentrations of GLP-1, increased GLP-1 signalling and/or increased GLP-1R levels resulting in hyperinsulinemia and/or hypoglycaemia and/or evidence of gastrointestinal dysfunction. These conditions would include both symptomatic treatment of hypoglycaemia, and, based on effects of GLP-1 on cell growth and differentiation, include the potential to influence the course of disease progression.

No new medicines have gained regulatory approval for the treatment of hyperinsulinemia hypoglycaemia (HH) in more than 20 years and there are significant short-comings associated with all current treatments. This has created a significant unmet medical need that spans from rare disease indications, to short-term requirements in approximately 10% of term admissions to neonatal units through to 0.2-1% of adults undergoing gastric bypass surgery. The validity of specifically targeting this mechanism has recently been clinically validated using the GLP-1 receptor antagonist peptide Ex9-39 in two distinct clinical populations.

Congenital hyperinsulinism (CHI) represents the most frequent cause of severe, persistent HH in newborn babies and children occurring in the UK in approximately 1/40,000 live births. The potential benefits of GLP-1R antagonists in CHI were demonstrated in rodent models of hyperinsulinism. These findings have been extended to testing Ex9-39 in human adult subjects with CHI owing to inactivating mutations in the KATP channel. The introduction of GLP-1 receptor antagonist treatment is predicted to relieve the pressure to perform irreversible pancreatectomy for many CHI patients. This will include patients with CHI in which there is growing evidence that GLP-1 hypersecretion is the underlying cause of inappropriate insulin release. GLP-1 antagonist treatment is predicted to have a sustained response profile, be effective in all patients and could be continued in adults without the need for dose titration or the adjustment for drug interactions resulting from the introduction of other pharmacological treatments.

Post bariatric surgery hypoglycaemia (PBHS). Gastric bypass surgery is being used increasingly in the treatment of morbidly obese type 2 diabetics and has been demonstrated to profoundly increase the levels of GLP-1 secretion. In a relatively small but clinically important number of patients this treatment can lead to a profound post-prandial hyperinsulinaemic hypoglycaemic state that can emerge after surgery with glucose

concentrations low enough (20-40 mg/dL) to cause seizures, altered mental status, loss of consciousness, cognitive dysfunction, disability, and death. There is no effective treatment for those patients exhibiting severe symptoms. The present invention provides a therapeutic intervention opportunity that can largely protect them should they suffer from post-bariatric hyperinsulinemia. Recently Salehi and colleagues have reported that this severe post-prandial hypoglycaemia in gastric bypass patients can be corrected by infusion of the GLP-1 antagonist Ex(9-39) consistent with a fundamental role for GLP-1 and its receptor in this mechanism.

The unmet medical need for the symptomatic treatment of hypoglycaemia extends beyond CHI and PBSH. Hyperinsulinism-induced hypoglycaemia encompasses a number of heterogeneous disorders principally characterised by the dysregulation of insulin secretion and resulting hypoglycaemia from pancreatic β -cells that may be effectively treated with a GLP1-R antagonist. These include but are not limited to indications of hypoglycaemia in children (e.g. neonatal hypoglycaemia, hypoglycaemia secondary to gastrostomy insertion, post prandial hypoglycaemia of uncertain aetiology) and adults (e.g. insulinomas, gastric bypass surgery-induced hypoglycaemia).

Transient unexplained hypoglycemia is one of the most common and important healthcare problems encountered in neonatology. In the UK, internal audits in our treatment centers suggest that approximately 10% of term baby admissions to neonatal units are solely due to hypoglycaemia with unknown causes. Given a live birth number of 800,000 in 2012, this suggests an incidence of ~8,000 new cases per year. A similar figure can also be derived from a USA-based study of neonatal hypoglycaemia in babies with extreme weights. A safe and effective treatment such as described in this invention would provide potential therapeutic benefit in this patient population.

Hyperinsulinemia and/or hypoglycaemia is observed in a subset of 'dumping syndrome' patients (e.g. as a complication of gastric bypass surgery and surgical procedures such as gastric/oesophageal surgery) that exhibit a very rapid gastric emptying and an exaggerated release of insulin and current hypotheses suggest a link between the rapid post-prandial glucose flux, GLP-1 secretion and hyperinsulinemia.

Tumour induced hypoglycaemia (TH) is a rare clinical condition that may occur as a result of eutopic insulin secretion by a pancreatic islet b-cell tumour (insulinoma) or ectopic tumour insulin secretion by a non-islet-cell tumour (examples include, but are not limited to, bronchial carcinoids and gastrointestinal stroma tumours). Insulinoma is a rare tumour with

an incidence of ~0.4/100,000 person-years and are usually small, sporadic intrapancreatic benign tumours.

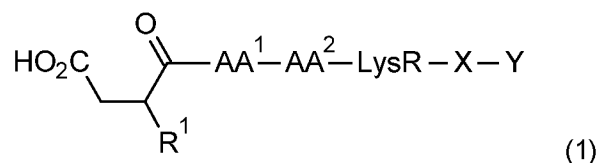
Finally clinical data using the antagonist Ex(9-39) has consistently demonstrated the ability to block the consequences of raised GLP-1 levels and insulin levels. Other embodiments of this invention include the treatment of unexplained symptomatic hyperinsulinemia and/or associated hypoglycaemia in a range of conditions such as hypoglycemia due to hyperinsulinism associated with leucine sensitivity, hypoglycemia due to hyperinsulinism associated with non-malignant insulinomas, inoperable islet cell adenoma or carcinoma, or extrapancreatic malignancy, hyperinsulinmia and hypoglycaemia in polycystic ovary syndrome, sulphonylurea-induced toxicity in T2DM, Prader-Willi syndrome, Adrenal Insufficiency and Addison's Disease, Beckwith-Wiedemann syndrome, Soto's Syndrome, Costello Syndrome, Timothy Syndrome, Kabuki Syndrome, Congenital Disorders of Glycosylation, Late dumping syndrome, Reactive hypoglycaemia infants of diabetic mothers, Trisomy 13, Central hypoventilation syndrome, Leprechaunism (insulin resistance syndrome), Mosaic Turner Syndrome, Usher Syndrome, Non-insulinoma pancreatogenous hypoglycaemia, Factitious hypoglycaemia, Insulin gene receptor mutations, Insulin autoimmune syndrome, Non-islet cells tumor hypoglycemia (NICTH) and withdrawal from alcoholic and other addictive substances.

Summary of the Invention

The present invention relates to novel compounds with antagonist activity at the GLP-1 receptor, pharmaceutical compositions comprising these, and use of the compounds for the manufacture of medicaments for treatment of diseases.

Accordingly, in one embodiment the invention provides a compound of the formula (1):

A compound comprising a sequence of formula (1):



wherein;

R^1 is H, NHR^2 or CH_2R^2 ; where R^2 is selected from: H, C_{1-6} alkyl, $(\text{CH}_2)_n\text{aryl}$ and $(\text{CH}_2)_n\text{heteroaryl}$; where n is 1 to 6;

AA¹ is -Leu- or -Nle-;

AA² is -NHCR^{3a}R^{3b}CO-; wherein R^{3a} is hydrogen or a C₁₋₃ alkyl group, or is joined to R^{3b} to form a 3-6 membered ring optionally containing one or more heteroatoms selected from N and O; and R^{3b} is C₁₋₆ alkyl, (CH₂)_naryl, (CH₂)_nOH or (CH₂)_nOR⁴, or is joined to R^{3a} to form a 3-6 membered ring optionally containing one or more heteroatoms selected from N and O; where R⁴ is C₁₋₆ alkyl and n is 1 to 6;

LysR is an optionally N-substituted substituted Lysine residue;

X is a sequence -Gln-AA³-Glu-AA⁴-Glu-AA⁵-Val-AA⁶-Leu-Phe-AA⁷-Glu-Trp-Leu-Lys-Asn-AA⁸-;

wherein AA³ is -Met- or -Nle-; where when AA³ is -Met-, LysR is an N-substituted lysine residue;

AA⁴ is -Glu- or -Gln-;

AA⁵ is -Ser- or -Ala-;

AA⁶ is -Arg- or -DArg-;

AA⁷ is a group -NHCHR⁵CO-; where R⁵ is a C₁₋₆ alkyl group;

AA⁸ is -Gly-, -Ser-, -DAla- or -βAla-;

Y is absent or is a sequence -AA⁹-AA¹⁰-AA¹¹-AA¹²-AA¹³-AA¹⁴-AA¹⁵-AA¹⁶-AA¹⁷-AA¹⁸-AA¹⁹-

wherein AA⁹ is -Gly- or -Ser-;

AA¹⁰ is -Pro- or -Ser-;

AA¹¹ is -Ser-, -DSer- or -Lys-;

AA¹² is -Ser-, -DSer-, -Lys- or -Phe-;

AA¹³ is absent or is -Ser-, -DSer-, -Gly-, -Glu- or -Lys-;

AA¹⁴ is absent or is -Ser-, -DSer-, -Ala-, -Lys- or -Tyr-;

AA¹⁵ is absent or is -Ser-, -DSer-, -Pro-, -Glu- or -Lys-;

AA¹⁶ is absent or is -Ser-, -DSer-, -Pro-, -Lys- or -LysR-;

AA¹⁷ is absent or is -Pro- or -Glu-;

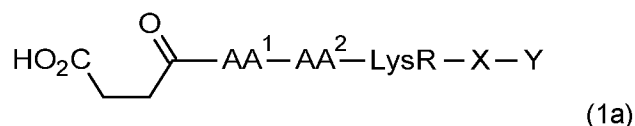
AA¹⁸ is absent or is -Ser- or -Tyr-;

AA¹⁹ is absent or is -Glu-;

wherein the X or Y C-terminus is a carboxyl group or a carboxamide group, or is adjoined to any natural or non-natural amino acid sequence or any other moiety, functional group or groups;

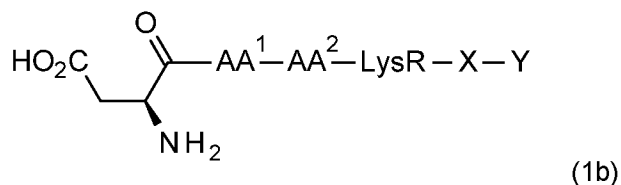
- 5 or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

Particular compounds also include compounds of formula (1a):



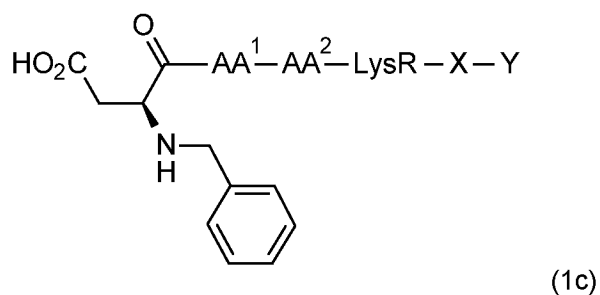
- 10 or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA^1 , AA^2 , LysR, X and Y are as defined above.

Particular compounds also include compounds of formula (1b):



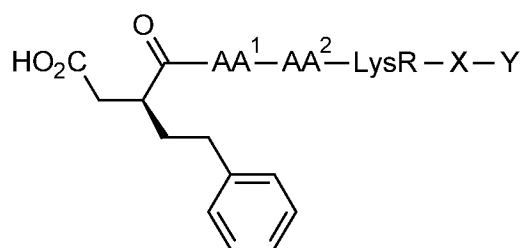
- 15 or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA^1 , AA^2 , LysR, X and Y are as defined above.

Particular compounds also include compounds of formula (1c):



- 20 or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA^1 , AA^2 , LysR, X and Y are as defined above.

Particular compounds also include compounds of formula (1d):



(1d)

or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA¹, AA², LysR, X and Y are as defined above.

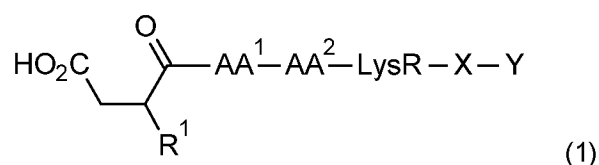
- 5 The compounds herein may be used as antagonists of the Glucagon-like peptide-1 (GLP-1) receptor. The compounds may be used in the manufacture of medicaments. The compounds or medicaments may be for use in treating, preventing, ameliorating, controlling or reducing the risk of disorders associated with GLP-1 receptors including unexplained symptomatic hyperinsulinemia and/or associated hypoglycaemia in a range of conditions such as
- 10 hypoglycemia due to hyperinsulinism associated with leucine sensitivity, hypoglycemia due to hyperinsulinism associated with non-malignant insulinomas, inoperable islet cell adenoma or carcinoma, or extrapancreatic malignancy, hyperinsulinmia and hypoglycaemia in polycystic ovary syndrome, sulphonylurea-induced toxicity in T2DM, Prader-Willi syndrome, Adrenal Insufficiency and Addison's Disease, Beckwith-Wiedemann syndrome, Soto's
- 15 Syndrome, Costello Syndrome, Timothy Syndrome, Kabuki Syndrome, Congenital Disorders of Glycosylation, Late dumping syndrome, Reactive hypoglycaemia infants of diabetic mothers, Trisomy 13, Central hypoventilation syndrome, Leprechaunism (insulin resistance syndrome), Mosaic Turner Syndrome, Usher Syndrome, Non-insulinoma pancreatogenous hypoglycaemia, Factitious hypoglycaemia, Insulin gene receptor mutations, Insulin
- 20 autoimmune syndrome, Non-islet cells tumor hypoglycemia (NICTH) and withdrawal from alcoholic and other addictive substances.

Detailed Description of the Invention

- This invention relates to novel compounds. The invention also relates to the use of novel
- 25 compounds as antagonists of GLP-1 receptors. The invention further relates to the use of novel compounds in the manufacture of medicaments for use as GLP-1 receptor antagonists or for the treatment of disorders associated with GLP-1 receptors. The invention further relates to compounds, compositions and medicaments which are selective antagonists of the GLP-1 receptor with respect to other GLP receptor sub-types.

The invention further relates to compounds, compositions and medicaments useful for the treatment of unexplained symptomatic hyperinsulinemia conditions and/or associated hypoglycaemia conditions such as hypoglycemia due to hyperinsulinism associated with leucine sensitivity, hypoglycemia due to hyperinsulinism associated with non-malignant insulinomas, inoperable islet cell adenoma or carcinoma, or extrapancreatic malignancy, hyperinsulinemia and hypoglycaemia in polycystic ovary syndrome, sulphonylurea-induced toxicity in T2DM, Prader-Willi syndrome, Adrenal Insufficiency and Addison's Disease, Beckwith-Wiedemann syndrome, Soto's Syndrome, Costello Syndrome, Timothy Syndrome, Kabuki Syndrome, Congenital Disorders of Glycosylation, Late dumping syndrome, Reactive hypoglycaemia infants of diabetic mothers, Trisomy 13, Central hypoventilation syndrome, Leprechaunism (insulin resistance syndrome), Mosaic Turner Syndrome, Usher Syndrome, Non-insulinoma pancreatogenous hypoglycaemia, Factitious hypoglycaemia, Insulin gene receptor mutations, Insulin autoimmune syndrome, Non-islet cells tumor hypoglycemia (NICTH) and withdrawal from alcoholic and other addictive substances.

Accordingly, in one embodiment the invention provides a compound comprising a sequence of formula (1):



wherein;

R^1 is H, NHR^2 or CH_2R^2 ; where R^2 is selected from: H, C_{1-6} alkyl, $(\text{CH}_2)_n\text{aryl}$ and $(\text{CH}_2)_n\text{heteroaryl}$; where n is 1 to 6;

AA^1 is -Leu- or -Nle-;

AA^2 is $-\text{NHCR}^{3a}\text{R}^{3b}\text{CO}-$; wherein R^{3a} is hydrogen or a C_{1-3} alkyl group, or is joined to R^{3b} to form a 3-6 membered ring optionally containing one or more heteroatoms selected from N and O; and R^{3b} is C_{1-6} alkyl, $(\text{CH}_2)_n\text{aryl}$, $(\text{CH}_2)_n\text{OH}$ or $(\text{CH}_2)_n\text{OR}^4$, or is joined to R^{3a} to form a 3-6 membered ring optionally containing one or more heteroatoms selected from N and O; where R^4 is C_{1-6} alkyl and n is 1 to 6;

LysR is an optionally N-substituted substituted Lysine residue;

X is a sequence -Gln-AA³-Glu-AA⁴-Glu-AA⁵-Val-AA⁶-Leu-Phe-AA⁷-Glu-Trp-Leu-Lys-Asn-AA⁸-;

wherein AA³ is -Met- or -Nle-; where when AA³ is -Met-, LysR is an N-substituted lysine residue;

AA⁴ is -Glu- or -Gln-;

AA⁵ is -Ser- or -Ala-;

AA⁶ is -Arg- or -DArg-;

AA⁷ is a group -NHCHR⁵CO-; where R⁵ is a C₁₋₈ alkyl group;

AA⁸ is -Gly-, -Ser-, -DAla- or -βAla-;

Y is absent or is a sequence -AA⁹-AA¹⁰-AA¹¹-AA¹²-AA¹³-AA¹⁴-AA¹⁵-AA¹⁶-AA¹⁷-AA¹⁸-AA¹⁹-

wherein AA⁹ is -Gly- or -Ser-;

AA¹⁰ is -Pro- or -Ser-;

AA¹¹ is -Ser-, -DSer- or -Lys-;

AA¹² is -Ser-, -DSer-, -Lys- or -Phe-;

AA¹³ is absent or is -Ser-, -DSer-, -Gly-, -Glu- or -Lys-;

AA¹⁴ is absent or is -Ser-, -DSer-, -Ala-, -Lys- or -Tyr-;

AA¹⁵ is absent or is -Ser-, -DSer-, -Pro-, -Glu- or -Lys-;

AA¹⁶ is absent or is -Ser-, -DSer-, -Pro-, -Lys- or -LysR-;

AA¹⁷ is absent or is -Pro- or -Glu-;

AA¹⁸ is absent or is -Ser- or -Tyr-;

AA¹⁹ is absent or is -Glu-;

wherein the X or Y C-terminus is a carboxyl group or a carboxamide group, or is adjoined to any natural or non-natural amino acid sequence or any other moiety, functional group or groups;

or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

R¹ can be H, NH₂, NHBn or CH₂Bn. R¹ can be H. R¹ can be hydrogen. R¹ can be NH₂. R¹ can be NHBn. R¹ can be CH₂Bn. R¹ can be NH-benzyl. R¹ can be CH₂-benzyl.

R² can be H. R² can be hydrogen. R² can be Bn. R² can be benzyl.

AA¹ can be -Leu-. AA¹ can be -Nle-.

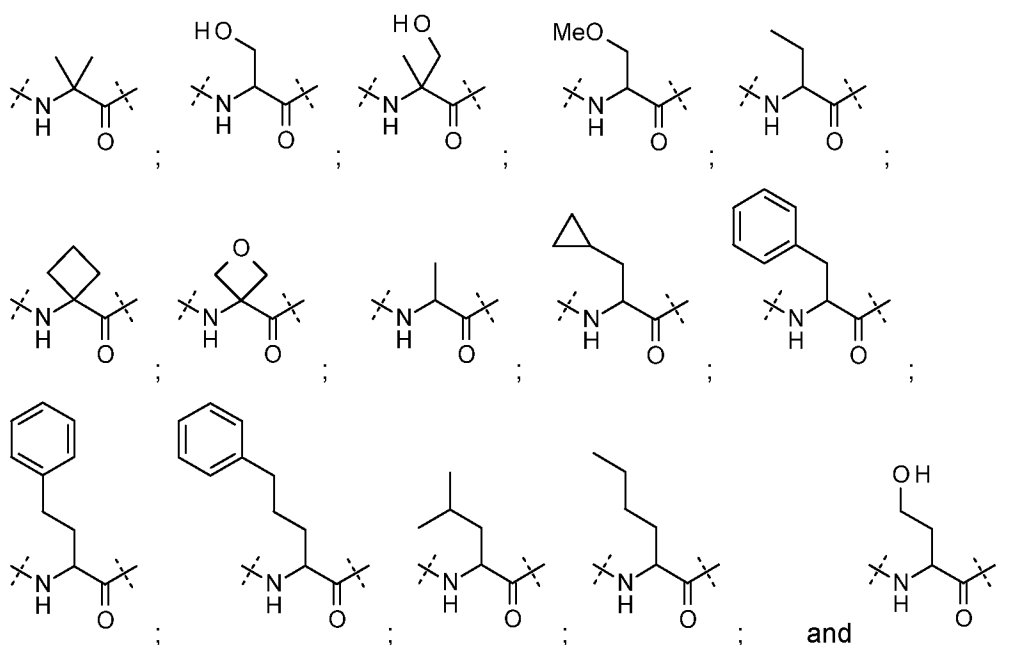
AA² can be -NHCR^{3a}R^{3b}CO-; wherein R^{3a} is hydrogen or methyl, and R^{3b} is selected from methyl, ethyl, isobutyl, *n*-butyl, CH₂OH, CH₂CH₂OH, CH₂OCH₃, CH₂-cyclopropyl, Bn, CH₂Bn or CH₂CH₂Bn.

R^{3a} can be hydrogen or methyl. R^{3a} can be hydrogen. R^{3a} can be methyl.

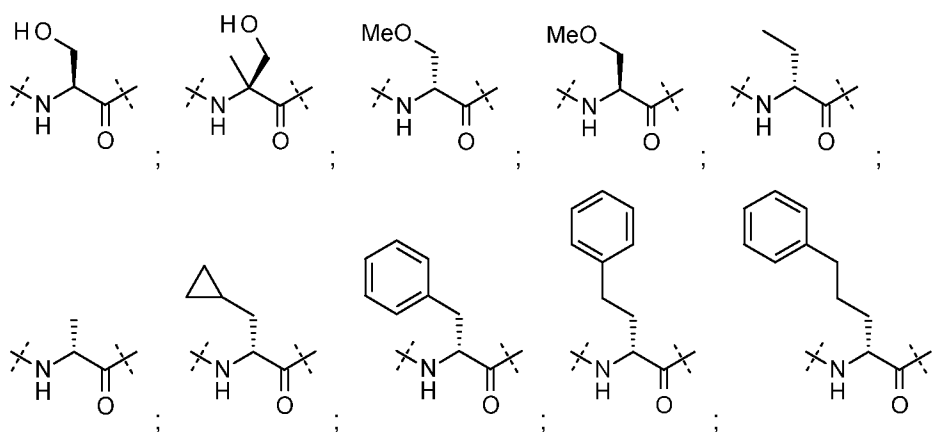
R^{3b} can be selected from methyl, ethyl, isobutyl, *n*-butyl, CH₂OH, CH₂CH₂OH, CH₂OCH₃, CH₂-cyclopropyl, Bn, CH₂Bn or CH₂CH₂Bn.

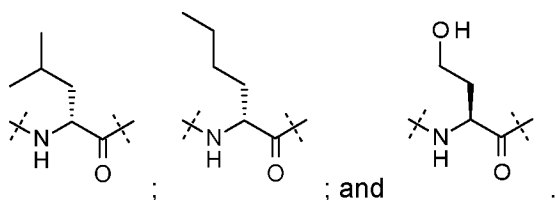
R^{3a} and R^{3b} can be joined to form a ring. R^{3a} and R^{3b} can be joined to form a cyclobutyl or an oxetanyl ring.

AA² can be selected from:



AA² can be selected from:





LysR can be an unsubstituted lysine residue.

LysR can be an N-substituted Lysine residue, wherein the N-substituent is selected from: -

- 5 $\text{CO}(\text{CH}_2)_q\text{CH}_3$; $-\text{CO}(\text{CH}_2)_q\text{CO}_2\text{H}$; $-\text{CO}(\text{CH}_2)_q\text{CHCH}_2$; $-\text{COO}(\text{CH}_2)_q\text{CH}_3$; $-\text{COO}(\text{CH}_2)_q\text{CO}_2\text{H}$ and $-\text{COO}(\text{CH}_2)_q\text{CHCH}_2$; where q is 1 to 22.

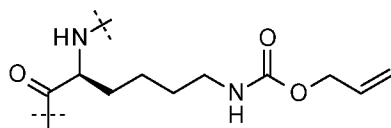
LysR can be an N-substituted Lysine residue, wherein the N-substituent is - $\text{COO}(\text{CH}_2)_q\text{CHCH}_2$; where q is 1 to 22.

LysR can be an N-substituted Lysine residue, wherein the N-substituent is -

- 10 $\text{COO}(\text{CH}_2)_q\text{CHCH}_2$; where q is 1.

LysR can be an N-substituted Lysine residue, wherein the N-substituent is $-\text{COOCH}_2\text{CHCH}_2$.

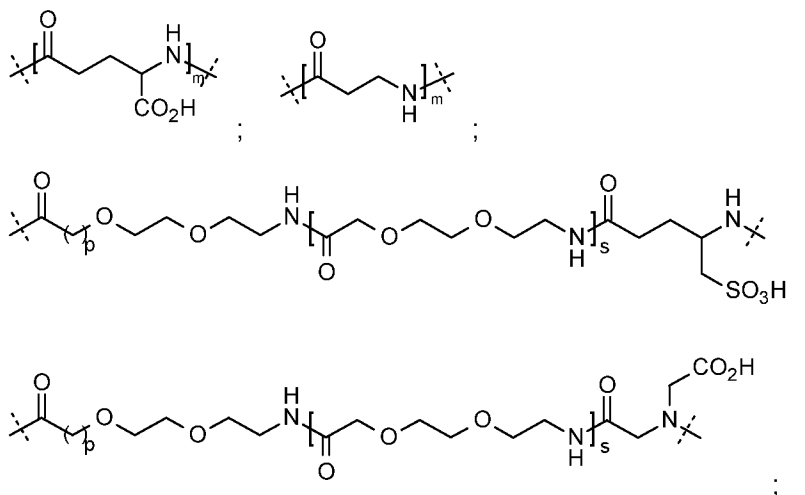
Lys R can be



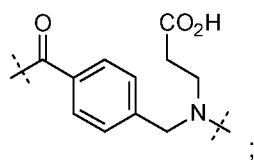
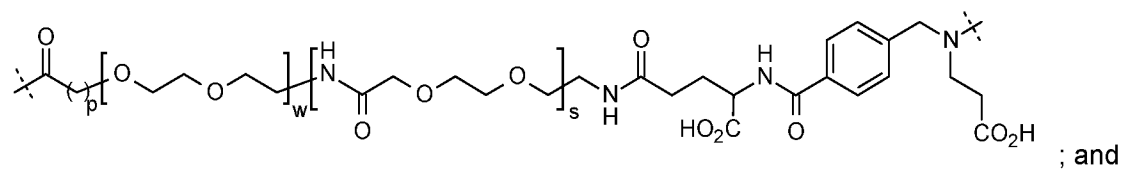
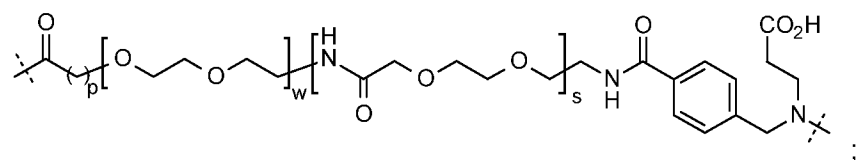
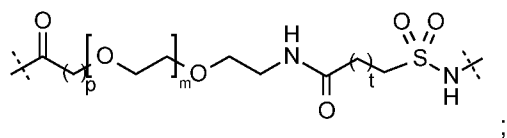
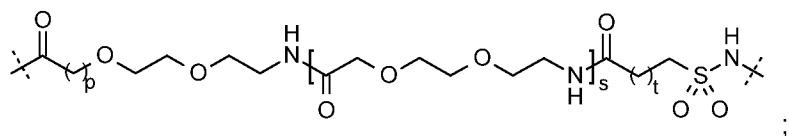
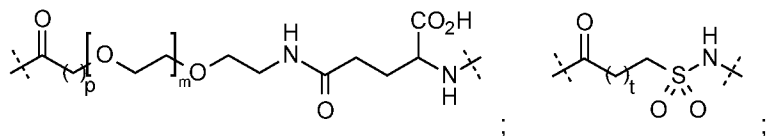
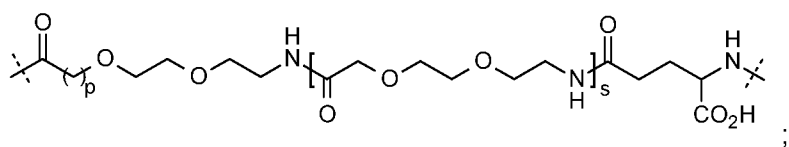
15

LysR can be an N-substituted Lysine residue, wherein the N-substituent is a group -L-G;

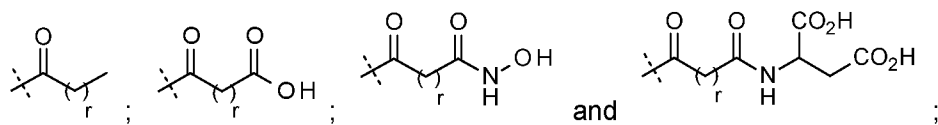
wherein L is selected from the group consisting of:



20



and G is selected from the group consisting of:



where m is 1 to 23;

p is 1 to 3;

```
15    r is 1 to 20;
```

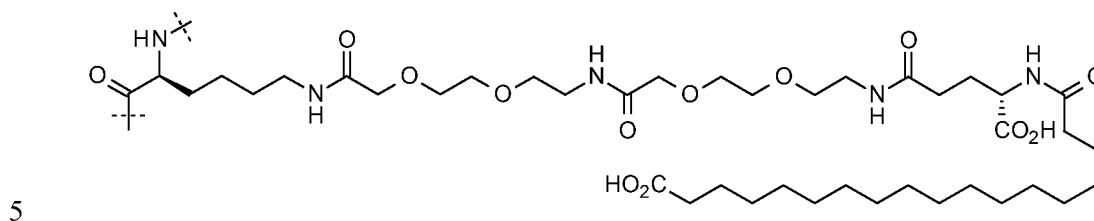
s is 0 to 3;

14

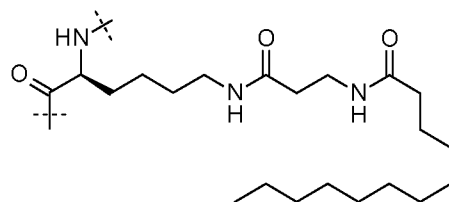
t is 0 to 4;

and w is 0 to 4.

LysR can be



LysR can be



- 10 AA³ can be -Met-. AA³ can be -Nle-. When AA³ is -Met-, LysR is an N-substituted lysine residue.
- AA⁴ can be -Glu-. AA⁴ can be -Gln-.
- AA⁵ can be -Ser-. AA⁵ can be -Ala-.
- AA⁶ can be -Arg-. AA⁶ can be -DArg-.
- 15 AA⁷ can be a group -NHCHR⁵CO-; where R⁵ is selected from isopropyl, *sec*-butyl and neopentyl. R⁵ can be isopropyl. R⁵ can be *sec*-butyl. R⁵ can be neopentyl.
- AA⁷ can be -Ile-. AA⁷ can be -Val-. AA⁷ can be a *tert*-butyl alanine residue.
- AA⁸ can be -Gly-. AA⁸ can be -Ser-. AA⁸ can be -DAla-. AA⁸ can be -βAla-.
- 20 Y can be absent or present. Y can be absent. Y can be present.
- AA⁹ can be -Gly-. AA⁹ can be -Ser-.
- AA¹⁰ can be -Pro-. AA¹⁰ can be -Ser-.
- AA¹¹ can be -Ser-. AA¹¹ can be -DSer-. AA¹¹ can be -Lys-.
- 25 AA¹² can be -Ser-. AA¹² can be -DSer-. AA¹² can be -Lys-. AA¹² can be -Phe-.
- AA¹³ can be absent. AA¹³ can be -Ser-. AA¹³ can be -DSer-. AA¹³ can be -Gly-. AA¹³ can be -Glu-. AA¹³ can be -Lys-.
- AA¹⁴ can be absent. AA¹⁴ can be -Ser-. AA¹⁴ can be -DSer-. AA¹⁴ can be -Ala-. AA¹⁴ can be -Lys-. AA¹⁴ can be -Tyr-.

AA¹⁵ can be absent. AA¹⁵ can be -Ser-. AA¹⁵ can be -DSer-. AA¹⁵ can be -Pro-. AA¹⁵ can be -Glu-. AA¹⁵ can be -Lys-.

AA¹⁶ can be absent. AA¹⁶ can be -Ser-. AA¹⁶ can be -DSer-. AA¹⁶ can be -Pro-. AA¹⁶ can be -Lys-. AA¹⁶ can be -LysR-.

5 AA¹⁷ can be absent. AA¹⁷ can be -Pro-. AA¹⁷ can be -Glu-.

AA¹⁸ can be absent. AA¹⁸ can be -Ser-. AA¹⁸ can be -Tyr-.

AA¹⁹ can be absent. AA¹⁹ can be -Glu-.

10 When Y is absent, the X C-terminus can be a carboxamide group. When Y is absent, the X C-terminus can be a carboxyl group. When Y is absent, the X C-terminus can be adjoined to any natural or non-natural amino acid sequence or any other moiety, functional group or groups.

15 The Y C-terminus can be a carboxamide group. The Y C-terminus can be a carboxyl group. the Y C-terminus can be adjoined to any natural or non-natural amino acid sequence or any other moiety, functional group or groups.

20 The compound can be a compound wherein R¹ is NHBn, AA¹ is -Leu-, AA² is -D-HomoPhe-, LysR is -Lys-, AA³ is -Nle-, AA⁴ is -Glu-, AA⁵ is -Ala-, AA⁶ is -Arg-, AA⁷ is -Ile- and AA⁸ is -DAla-, where Y is absent and the X C-terminus is a carboxamide group.

The compound can be a compound wherein R¹ is NHBn, AA¹ is -Leu-, AA² is -DAla-, LysR is -Lys-, AA³ is -Nle-, AA⁴ is -Glu-, AA⁵ is -Ala-, AA⁶ is -DArg-, AA⁷ is -Ile- and AA⁸ is -DAla-, where Y is absent and the X C-terminus is a carboxamide group.

25 The compound can be a compound wherein R¹ is H, AA¹ is -Leu-, AA² is -D-CyclopropylAla-, LysR is -Lys-, AA³ is -Nle-, AA⁴ is -Glu-, AA⁵ is -Ala-, AA⁶ is -DArg-, AA⁷ is -Ile- and AA⁸ is -DAla-, where Y is absent and the X C-terminus is a carboxamide group.

30 The compound can be a compound wherein R¹ is NHBn, AA¹ is -Leu-, AA² is -Aib-, LysR is -Lys-, AA³ is -Nle-, AA⁴ is -Glu-, AA⁵ is -Ala-, AA⁶ is -DArg-, AA⁷ is -Ile- and AA⁸ is -DAla-, where Y is absent and the X C-terminus is a carboxamide group.

The compound can be a compound wherein R¹ is NHBn, AA¹ is -Nle-, AA² is -Aib-, LysR is -Lys-, AA³ is -Nle-, AA⁴ is -Glu-, AA⁵ is -Ala-, AA⁶ is -DArg-, AA⁷ is -Ile- and AA⁸ is -DAla-, where Y is absent and the X C-terminus is a carboxamide group.

35

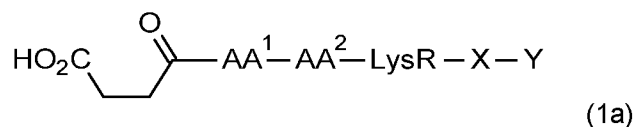
The compound can be a compound wherein R¹ is NHBn, AA¹ is -Leu-, AA² is -D-HomoPhe-, LysR is -Lys-, AA³ is -Nle-, AA⁴ is -Glu-, AA⁵ is -Ala-, AA⁶ is -Arg-, AA⁷ is -Ile-, AA⁸ is -DAla-,

AA⁹ is -Gly-, AA¹⁰ is -Pro-, AA¹¹ is -Ser-, AA¹² is -Ser-, AA¹³ is -Ser-, AA¹⁴ is -Ser-, AA¹⁵ is -Ser- and AA¹⁶ is -Ser-, where AA¹⁷, AA¹⁸ and AA¹⁹ are absent and the Y C-terminus is a carboxamide group.

- 5 The compound can be a compound wherein R¹ is NHBn, AA¹ is -Nle-, AA² is -Aib-, LysR is -Lys-, AA³ is -Nle-, AA⁴ is -Glu-, AA⁵ is -Ala-, AA⁶ is -DArg-, AA⁷ is -Ile-, AA⁸ is -DAla-, AA⁹ is -Gly-, AA¹⁰ is -Pro-, AA¹¹ is -DSer-, AA¹² is -DSer-, AA¹³ is -DSer-, AA¹⁴ is -DSer-, AA¹⁵ is -DSer- and AA¹⁶ is -DSer-, where AA¹⁷, AA¹⁸ and AA¹⁹ are absent and the Y C-terminus is a carboxamide group.

10

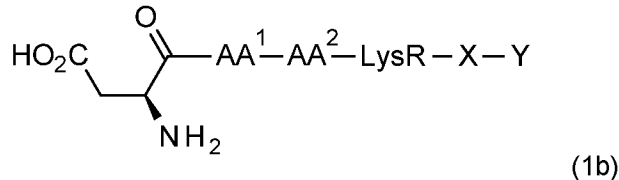
The compound can be a compound of formula (1a):



or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA¹, AA², LysR, X and Y are as defined above.

15

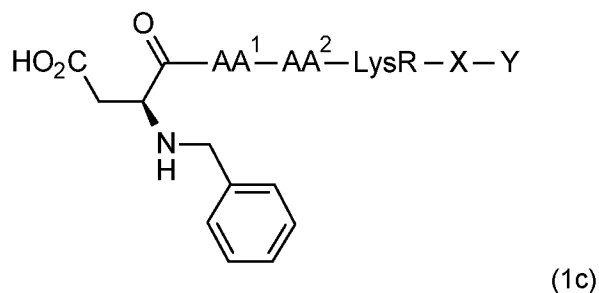
The compound can be a compound of formula (1b):



or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA¹, AA², LysR, X and Y are as defined above.

20

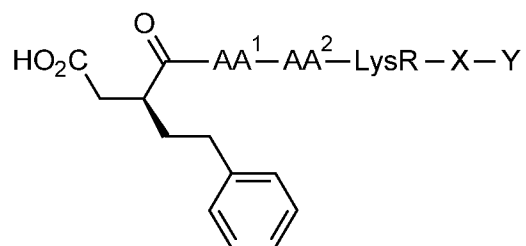
The compound can be a compound of formula (1c):



or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA¹, AA², LysR, X and Y are as defined above.

25

The compound can be a compound of formula (1d):

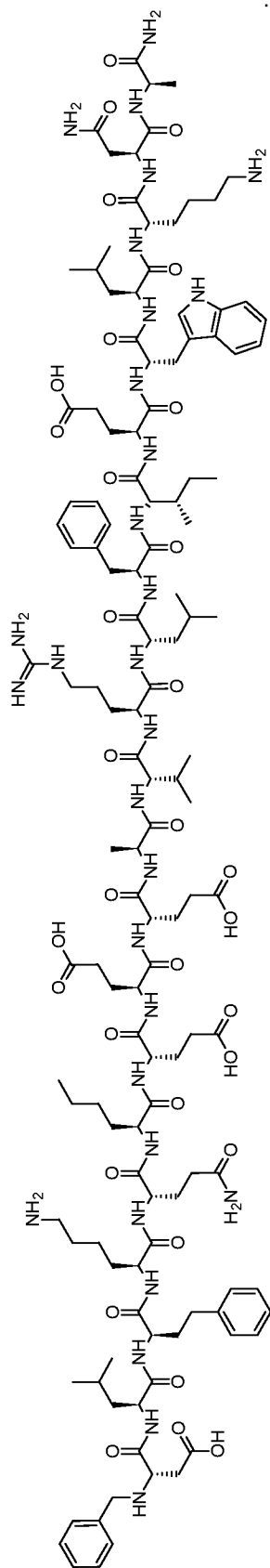


(1d)

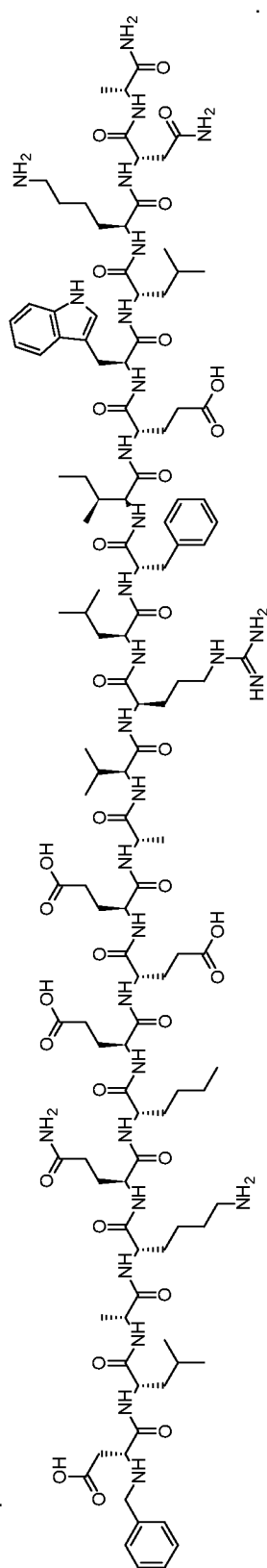
or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA¹, AA², LysR, X and Y are as defined above.

The compound can be a compound selected from any one of the group consisting of:

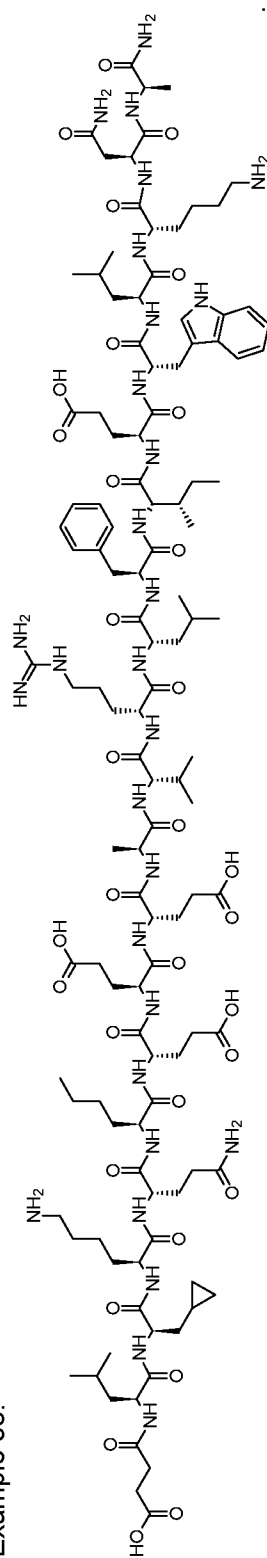
Example 24:



5 Example 34:



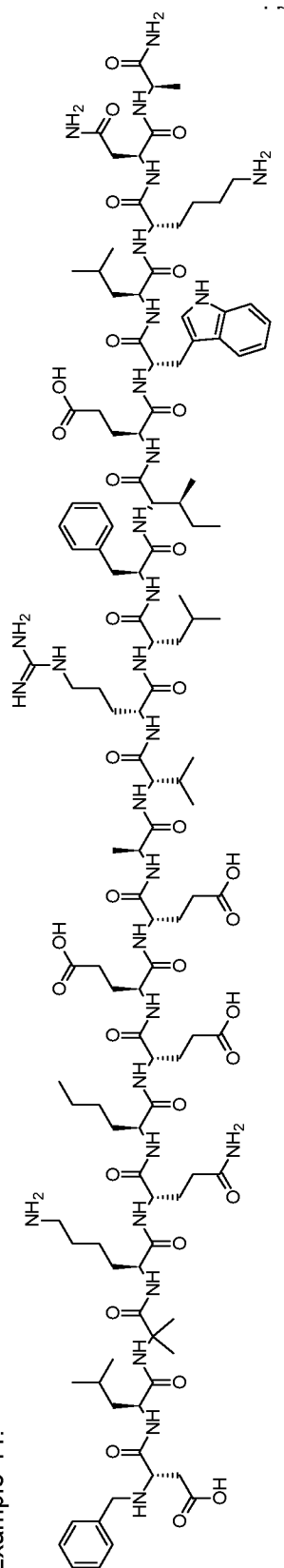
Example 38:



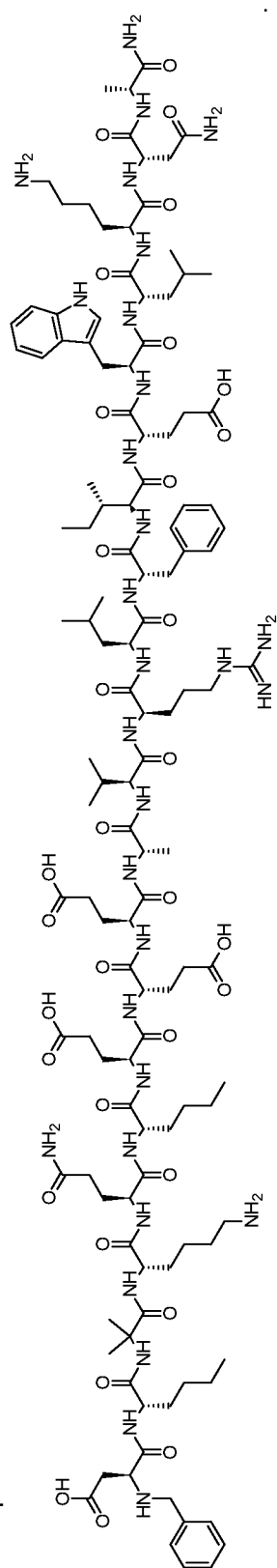
19

P30670WO1

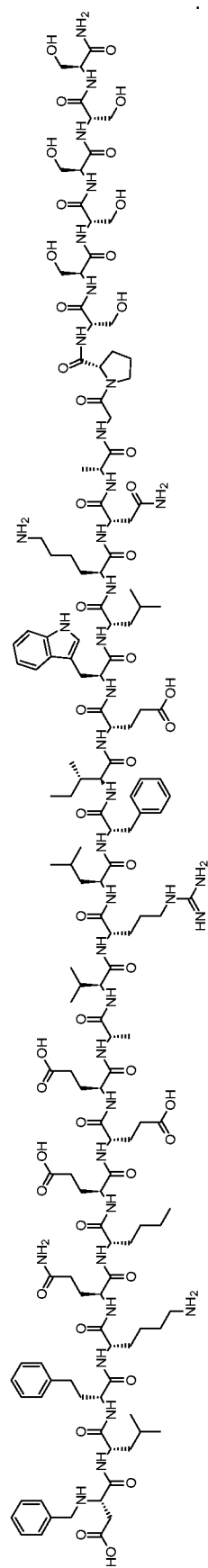
Example 44:



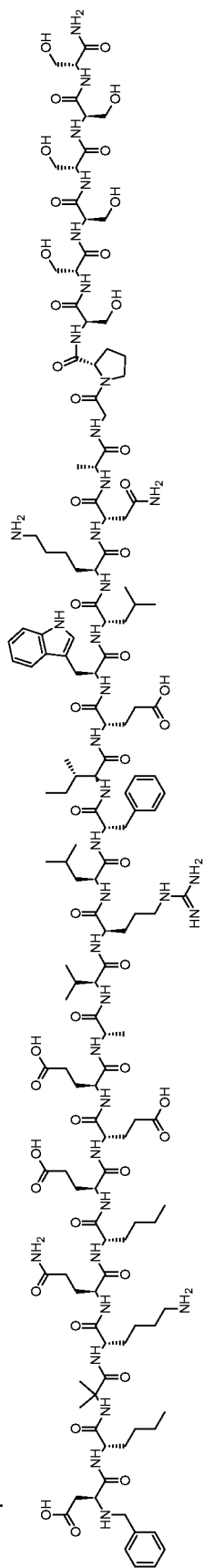
5 Example 53:



Example 63:



Example 85:



5 or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

The compound can be selected from any one of Examples 1 to 85 shown in Table 1:

Table 1

[illegible]

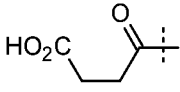
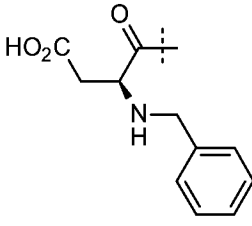
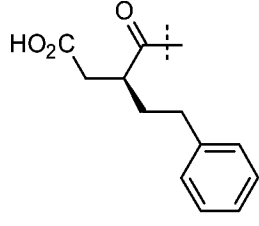
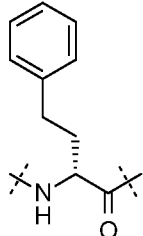
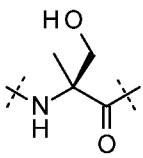
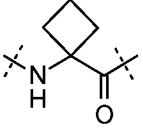
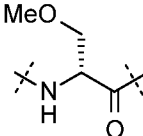
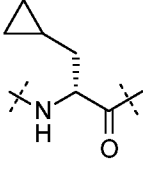
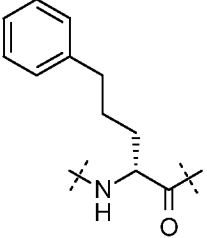
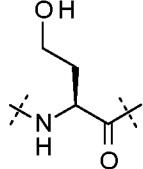
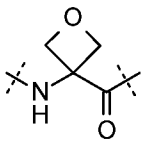
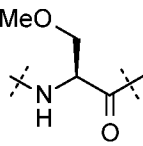
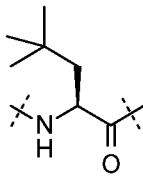
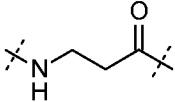
[illegible]

[illegible]

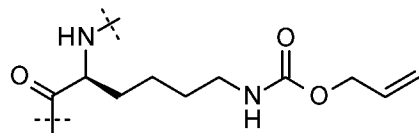
[illegible]

Exam ple 77	Bn-ASP	LE U	D-ALA	LVS	G L N	G L N	G L U	G L U	G A V	D- AR E H	P H E	P H E	I L E	G L U	T P U	L E Y S N	A	D- ALA	G LY	PR O R	SE R R	GL Y A	AL O	PR O	N H2	
Exam ple 78	Bn-ASP	LE U	D-ALA	LVS	G N L L	G G A V	G L L A	G L L A	G A V	D- AR E H	P H E	P H E	I L E	G T L	T L L	E Y S N	A	D- ALA	G LY	PR O R	D- SE SE R R	D- SE SE R R	D- SE SE R R	D-SER	N H2	
Exam ple 79	Bn-ASP	LE U	D-ABU	LVS	G N L L	G G A V	G L L A	G L L A	G A V	D- AR E H	P H E	P H E	I L E	G T L	T L L	E Y S N	A	D- ALA	G LY	PR O R	D- SE SE R R	D- SE SE R R	D- SE SE R R	D-SER	N H2	
Exam ple 80	Bn-ASP	LE U	D-ALA	LVS	G N L L	G G A V	G L L A	G L L A	G A V	D- AR E H	P H E	P H E	I L E	G T L	T L L	E Y S N	A	D- ALA	G LY	PR O R	LY LY	LY LY	LY LY	LVS	N H2	
Exam ple 81	Bn-ASP	LE U	D-ALA	LVS	G N L L	G G A V	G L L A	G L L A	G A V	D- AR E H	P H E	P H E	I L E	G T L	T L L	E Y S N	A	D- ALA	G LY	PR O R	SE R R	GL U R	GL U R	LVS+GLU- 2xOEG C18 diacid	GL U R	N H 2
Exam ple 82	Bn-ASP	LE U	SER	LVS	G N L L	G G A V	G L L A	G L L A	G A V	D- AR E H	P H E	P H E	I L E	G T L	T L L	E Y S N	A	D- ALA	G LY	PR O R	SE R R	GL U R	GL U R	LVS+GLU- 2xOEG C18 diacid	GL U R	N H 2
Exam ple 83	Bn-ASP	LE U	AIB	LVS	G N L L	G G A V	G L L A	G L L A	G A V	D- AR E H	P H E	P H E	I L E	G T L	T L L	E Y S N	A	D- ALA	G LY	PR O R	SE R R	SE R R	SE R R	SER	N H2	
Exam ple 84	Bn-ASP	LE U	AIB	LVS	G N L L	G G A V	G L L A	G L L A	G A V	D- AR E H	P H E	P H E	I L E	G T L	T L L	E Y S N	A	D- ALA	G LY	PR O R	D- SE SE R R	D- SE SE R R	D- SE SE R R	D-SER	N H2	
Exam ple 85	Bn-ASP	N LE	AIB	LVS	G N L L	G G A V	G L L A	G L L A	G A V	D- AR E H	P H E	P H E	I L E	G T L	T L L	E Y S N	A	D- ALA	G LY	PR O R	D- SE SE R R	D- SE SE R R	D- SE SE R R	D-SER	N H2	

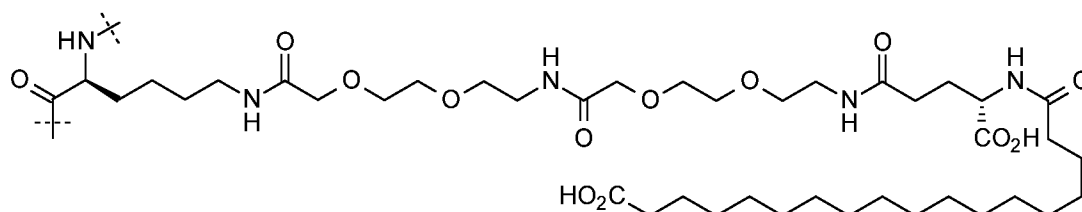
Standard amino acid symbols are used in Table 1 where appropriate. In cases where a standard symbol is not available, the following representations are used:

 Succinate	 Bn-ASP	 2-(S)-phenethylbutanate
 D-HomoPHE	 a-MeSER	 Cyclobutyl
 D-Ser(Me)-OH	 D-CyclopropylALA	 D-homohomoPHE
 HomoSER	 Oxetane	 Ser(Me)-OH
 tBuALA	 betaALA	

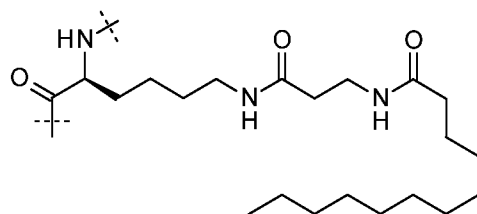
allocLys:



LYS-γGlu-2xOEG C18 diacid:



5 LYS-β-ALA-C12:



Specific examples of compounds include compounds having GLP-1 receptor antagonist activity.

- 10 The compounds of the invention may be used in a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable excipient.

The compounds of the invention may be used in medicine.

- 15 The compounds of the invention may be used in the treatment of disorders associated with GLP-1 receptors.

- 20 The compounds of the invention may be used in the treatment of unexplained symptomatic hyperinsulinemia conditions and/or associated hypoglycaemia conditions such as hypoglycemia due to hyperinsulinism associated with leucine sensitivity, hypoglycemia due to hyperinsulinism associated with non-malignant insulinomas, inoperable islet cell adenoma or carcinoma, or extrapancreatic malignancy, hyperinsulinemia and hypoglycaemia in polycystic ovary syndrome, sulphonylurea-induced toxicity in T2DM, Prader-Willi syndrome, Adrenal Insufficiency and

Addison's Disease, Beckwith-Wiedemann syndrome, Soto's Syndrome, Costello Syndrome, Timothy Syndrome, Kabuki Syndrome, Congenital Disorders of Glycosylation, Late dumping syndrome, Reactive hypoglycaemia infants of diabetic mothers, Trisomy 13, Central hypoventilation syndrome, Leprechaunism (insulin resistance syndrome), Mosaic Turner Syndrome, Usher Syndrome, Non-insulinoma pancreatogenous hypoglycaemia, Factitious hypoglycaemia, Insulin gene receptor mutations, Insulin autoimmune syndrome, Non-islet cells tumor hypoglycemia (NICTH) and withdrawal from alcoholic and other addictive substances,

Definitions

In this application, the following definitions apply, unless indicated otherwise.

The term “alkyl”, “aryl”, and “heteroaryl” are used in their conventional sense (e.g. as defined in the IUPAC Gold Book) unless indicated otherwise.

The term “treatment”, in relation to the uses of any of the compounds described herein, including those of the formula (1), is used to describe any form of intervention where a compound is administered to a subject suffering from, or at risk of suffering from, or potentially at risk of suffering from the disease or disorder in question. Thus, the term “treatment” covers both preventative (prophylactic) treatment and treatment where measurable or detectable symptoms of the disease or disorder are being displayed.

The term “effective therapeutic amount” as used herein (for example in relation to methods of treatment of a disorder, disease or condition) refers to an amount of the compound which is effective to produce a desired therapeutic effect. For example, if the condition is pain, then the effective therapeutic amount is an amount sufficient to provide a desired level of pain relief. The desired level of pain relief may be, for example, complete removal of the pain or a reduction in the severity of the pain.

To the extent that any of the compounds described have chiral centres, the present invention extends to all optical isomers of such compounds, whether in the form of racemates or resolved enantiomers. The invention described herein relates to all crystal forms, solvates and hydrates of any of the disclosed compounds however so prepared. To the extent that any of the compounds disclosed herein have acid or basic centres such as carboxylates or amino groups, then all salt forms of said compounds are included herein. In the case of pharmaceutical uses, the salt should be seen as being a pharmaceutically acceptable salt.

Salts or pharmaceutically acceptable salts that may be mentioned include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Examples of pharmaceutically acceptable salts include acid addition salts derived from mineral acids and organic acids, and salts derived from metals such as sodium, magnesium, potassium and calcium.

Examples of acid addition salts include acid addition salts formed with acetic, 2,2-dichloroacetic, adipic, alginic, aryl sulfonic acids (e.g. benzenesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic and p-toluenesulfonic), ascorbic (e.g. L-ascorbic), L-aspartic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, gluconic (e.g. D-gluconic), glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α -oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic and ($\pm$)-DL-lactic), lactobionic, maleic, malic (e.g. (-)-L-malic), malonic, ($\pm$)-DL-mandelic, metaphosphoric, methanesulfonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, tartaric (e.g. (+)-L-tartaric), thiocyanic, undecylenic and valeric acids.

Also encompassed are any solvates of the compounds and their salts. Preferred solvates are solvates formed by the incorporation into the solid state structure (e.g. crystal structure) of the compounds of the invention of molecules of a non-toxic pharmaceutically acceptable solvent (referred to below as the solvating solvent). Examples of such solvents include water, alcohols (such as ethanol, isopropanol and butanol) and dimethylsulfoxide. Solvates can be prepared by recrystallising the compounds of the invention with a solvent or mixture of solvents containing the solvating solvent. Whether or not a solvate has been formed in any given instance can be determined by subjecting crystals of the compound to analysis using well known and standard

techniques such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and X-ray crystallography.

The solvates can be stoichiometric or non-stoichiometric solvates. Particular solvates may be hydrates, and examples of hydrates include hemihydrates, monohydrates and dihydrates. For a more detailed discussion of solvates and the methods used to make and characterise them, see Bryn *et al*, Solid-State Chemistry of Drugs, Second Edition, published by SSCI, Inc of West Lafayette, IN, USA, 1999, ISBN 0-967-06710-3.

The term “pharmaceutical composition” in the context of this invention means a composition comprising an active agent and comprising additionally one or more pharmaceutically acceptable carriers. The composition may further contain ingredients selected from, for example, diluents, adjuvants, excipients, vehicles, preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavouring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispersing agents, depending on the nature of the mode of administration and dosage forms. The compositions may take the form, for example, of tablets, dragees, powders, elixirs, syrups, liquid preparations including suspensions, sprays, inhalants, tablets, lozenges, emulsions, solutions, cachets, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations.

The compounds of the invention may contain one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope ^1H , ^2H (D), and ^3H (T). Similarly, references to carbon and oxygen include within their scope respectively ^{12}C , ^{13}C and ^{14}C and ^{16}O and ^{18}O . In an analogous manner, a reference to a particular functional group also includes within its scope isotopic variations, unless the context indicates otherwise. For example, a reference to an alkyl group such as an ethyl group or an alkoxy group such as a methoxy group also covers variations in which one or more of the hydrogen atoms in the group is in the form of a deuterium or tritium isotope, e.g. as in an ethyl group in which all five hydrogen atoms are in the deuterium isotopic form (a perdeuteroethyl group) or a methoxy group in which all three hydrogen atoms are in the deuterium isotopic form (a trideuteromethoxy group). The isotopes may be radioactive or non-radioactive.

Therapeutic dosages may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with the smaller dosages which are less than the optimum dose of the compound.

5 Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

10 The magnitude of an effective dose of a compound will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound and its route of administration. The selection of appropriate dosages is within the ability of one of ordinary skill in this art, without undue burden. In general, the daily dose range may be from about 10 μg to about 30 mg per kg body weight of a human and non-human animal, preferably from about 50 μg to about 30 mg per kg of body weight of a human and non-human animal, for example from
15 about 50 μg to about 10 mg per kg of body weight of a human and non-human animal, for example from about 100 μg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 100 μg to about 10 mg per kg of body weight of a human and non-human animal and most preferably from about 100 μg to about 1 mg per kg of body weight of a human and non-human animal.

20

Pharmaceutical Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation).

25 Accordingly, in another embodiment of the invention, there is provided a pharmaceutical composition comprising at least one compound of the formula (1) as defined above together with at least one pharmaceutically acceptable excipient.

The composition may be a composition suitable for injection. The injection may be intra-venous (IV) or subcutaneous. The composition may be supplied in a sterile buffer solution or as a solid
30 which can be suspended or dissolved in sterile buffer for injection.

The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents (e.g. solid diluents such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), granulating agents, binders, flow

aids, coating agents, release-controlling agents (e.g. release retarding or delaying polymers or waxes), binding agents, disintegrants, buffering agents, lubricants, preservatives, anti-fungal and antibacterial agents, antioxidants, buffering agents, tonicity-adjusting agents, thickening agents, flavouring agents, sweeteners, pigments, plasticizers, taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions.

The term "pharmaceutically acceptable" as used herein means compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. a human subject) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each excipient must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Pharmaceutical compositions containing compounds of the formula (1) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Suitable formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

The compounds of the formula (1) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within these ranges, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect (effective amount). The precise amounts of compound administered may be determined by a supervising physician in accordance with standard procedures.

EXAMPLES

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

5 **EXAMPLES 1 TO 85**

The compounds of Examples 1 to 85 shown in Table 1 above have been prepared. Their LCMS properties and the methods used to prepare them are set out in Table 2. The starting materials for each of the Examples are commercial unless indicated otherwise.

10 **General procedures**

Where no preparative routes are included, the relevant intermediate is commercially available. Commercial reagents were utilized without further purification. Room temperature (rt) refers to approximately 20-27°C.

15 **Analytical Methods**

LCMS analysis of compounds was performed under electrospray conditions.

Analytical Method A

MS ion determined using LCMS method below under electrospray conditions, HPLC retention
20 time (R_T) determined using HPLC method below, purity > 95% by HPLC unless indicated.
LCMS: Agilent 1200 HPLC&6410B Triple Quad, Column: Xbridge C18 3.5µm 2.1*30mm.
Gradient [time (min)/solvent B(%)]:0.0/10,0.9/80,1.5/90,8.5/5,1.51/10. (Solvent A=1mL of TFA in
1000 mL Water; Solvent B=1mL of TFA in 1000 mL of MeCN); Injection volume 5 µL (may
vary); UV detection 220 nm 254 nm 210 nm; Column temperature 25°C; 1.0 mL/min.
25 HPLC: Agilent Technologies 1200, Column: Gemini-NX C18 5µm 110A 150*4.6mm. Gradient
[time (min)/solvent B(%)]:0.0/30,20/60,20.1/90,23/90. (Solvent A=1mL of TFA in 1000 mL
Water; Solvent B=1mL of TFA in 1000 mL of MeCN); Injection volume 5 µL (may vary); UV
detection 220 nm 254 nm; Column temperature 25°C; 1.0 mL/min

30 **Analytical Method B1**

Instrument: Thermo Scientific Orbitrap Fusion; Column: Phenomenex Kinetex Biphenyl 100 Å,
2.6 µm, 2.1 x 50 mm; Gradient [time (min)/solvent B in A (%)]: 0.00/10, 0.30/10, 0.40/60,
1.10/90, 1.70/90, 1.75/10, 1.99/10, 2.00/10; Solvents: Solvent A = 0.1% formic acid in water;
Solvent B = 0.1% formic acid in acetonitrile; Injection volume 5 µL; Column temperature 25 °C;
35 Flow rate 0.8 mL/min.

Analytical Method B2

Instrument: Thermo Scientific Orbitrap Fusion; Column: Phenomenex Luna Omega C18 100 Å, 1.6 µm, 2.1 x 50 mm; Gradient [time (min)/solvent B in A (%): 0.00/10, 0.30/10, 0.40/60, 1.10/90, 1.70/90, 1.75/10, 1.99/10, 2.00/10; Solvents: Solvent A = 0.1% formic acid in water; Solvent B = 0.1% formic acid in acetonitrile; Injection volume 5 µL; Column temperature 25 °C; Flow rate 0.8 mL/min.

Synthesis of Intermediates and Compounds

The following examples are provided to illustrate preferred aspects of the invention and are not intended to limit the scope of the invention. All Fmoc-amino acids are commercially available

Synthesis of Examples 1-85

Standard Fmoc solid phase peptide synthesis (SPPS) was used to synthesize the linear peptides which were then cleaved from the resin and purified.

General method for Peptide Synthesis: The peptide was synthesized using standard Fmoc chemistry.

Method a - Exemplified by the Synthesis of Example 24

- 1) Add DCM to the vessel containing Rink amide MBHA Resin (sub: 0.35 mmol/g, 1.0 mmol, 2.86 g) and swell for 2 hours.
- 2) Drain and then wash with DMF (5 times, drain between each wash).
- 3) A solution of 20% piperidine in DMF was added agitate with N₂ bubbling for 30 min.
- 4) Drain and wash with DMF (5 times, drain between each wash).
- 5) Add Fmoc-amino acid solution (3.0 equivalents in DMF) and mix for 30 seconds, then add activation buffer (HBTU (2.85 equivalents) and DIEA (6 equivalents) in DMF), agitate with N₂ bubbling for 1 hour.
- 6) The coupling reaction was monitored by ninhydrin test
- 7) If required repeat steps 4 to 6 for same amino acid coupling if inefficient coupling occurs
- 8) Repeat steps 2 to 6 for next amino acid coupling.

Peptide Cleavage and Purification:

- 1) Add cleavage buffer (92.5%TFA/2.5%EDT/2.5%TIS/2.5%H₂O) to the flask containing the side chain protected peptide at room temperature and stir for 3 hours.

- 2) The peptide is precipitated with cold tert-butyl methyl ether and centrifuged (3 min at 3000 rpm).
- 3) Reaction mixture was filtered and filtrate collected.
- 4) Residue washed with tert-butyl methyl ether (2 times).
- 5) Crude peptide was dried under vacuum for 2 hours.
- 6) The crude peptide was purified by prep-HPLC. Prep-HPLC Conditions: Instrument: Gilson 281. Solvent: A - 0.1% TFA in H₂O, B - acetonitrile, Column: Luna C18 (200×25 mm; 10 µm) and Gemini C18 (150×30 mm; 5 µm) in series. Gradient [time (min)/solvent B (%)]:0.0/25, 60.0/55, 60.1/90, 70/90, 70.1/10., at 20 mL/min with UV detection (wave length = 215/254 nm). Residue was re-purified by prep-HPLC. Prep-HPLC Conditions: Instrument: Gilson 281. Solvent: A - 0.5% AcOH in H₂O, B - acetonitrile, Column: Luna C18 (200×25 mm; 10 µm) and Gemini C18 (150×30 mm; 5 µm) in series. Gradient [time (min)/solvent B (%)]:0.0/20, 60.0/50, 60.1/90, 70/90, 70.1/10., at 20 mL/min with UV detection (wave length = 215/254 nm) and then lyophilized to give Example 24 (377.6 mg, 14.0% yield).

Method b – Pseudoprolines method, Exemplified by the Synthesis of Example 63

- 1) Add DCM to the vessel containing Rink amide MBHA Resin (sub: 0.69 mmol/g, 20 mmol, 29.0 g) and swell for 2 hours.
- 2) Drain and then wash with DMF (5 times, drain between each wash).
- 3) A solution of 20% piperidine in DMF was added agitate with N₂ bubbling for 30 min.
- 4) Drain and wash with DMF (5 times, drain between each wash).
- 5) Add Fmoc-amino acid solution (3.0 equivalents in DMF) and mix for 30 seconds, then add activation buffer (HBTU (2.85 equivalents) and DIEA (6 equivalents) in DMF), agitate with N₂ bubbling for 1 hour.
- 6) The coupling reaction was monitored by ninhydrin test
- 7) If required repeat steps 2 to 5 for same amino acid coupling if inefficient coupling occurs
- 8) Repeat steps 2 to 5 for next amino acid coupling.

Note: for the amino acids in the table below different equivalents and coupling agents were used.

Step	Materials	Coupling reagents
5 and 6	Fmoc-Ser(tBu)-Ser(Psi(Me,Me) Pro)-OH (2.0 eq)	HATU (1.9 eq) and DIEA (4.0 eq)
27	Fmoc-D-HomePhe-OH (2.0 eq)	HATU (1.9 eq) and DIEA (4.0 eq)
29	(S)-2-(benzylamino)-4-(tert-butoxy)-4-oxobutanoic acid (2.0 eq)	DIC (2.0 eq) and HOAt (2.0 eq)

Peptide Cleavage and Purification:

- 1) Add cleavage buffer (92.5%TFA/2.5%EDT/2.5%TIS/2.5%H₂O) to the flask containing the side chain protected peptide at room temperature and stir for 3 hours.
- 5 2) Reaction mixture was filtered and filtrate collected.
- 3) The peptide is precipitated with cold isopropyl ether and centrifuged (3 min at 3000 rpm).
- 4) Residue washed with isopropyl ether (2 times).
- 5) Crude peptide dried *in vacuo* for 2 hours.
- 6) The crude peptide was purified by prep-HPLC (A: 0.01 M NH₄HCO₃, B: MeCN). Prep-HPLC Conditions: Agilent SD-1. Solvent: A- 0.01 M NH₄HCO₃ in H₂O, B- acetonitrile, Column: Luna 80*250mm, C18*10µm, 110A. Gradient [time (min)/solvent B (%]): 0.0/30, 60.0/60, 60.1/90, 70/90, 70.1/10. Then re-purified by prep-HPLC (A: 0.075% TFA in H₂O, B: MeCN), Prep-HPLC Conditions: Instrument: Agilent SD-1. Solvent: A- 0.075% TFA in H₂O, B- acetonitrile, Column: Luna 80*250mm, C18*10µm, 110A. Gradient [time (min)/solvent B (%)]: 0.0/30, 60.0/60, 60.1/90, 70/90, 70.1/10. Then used the prep-HPLC (A: 0.5% Acetic Acid in H₂O, B: MeCN) to give Example 63 (11.3 g, 16.7% yield).
- 10
- 15

Method c – Exemplified by the Synthesis of Example 85

- 1) Add DCM to the vessel containing Rink amide MBHA Resin (sub: 0.69 mmol/g, 20 mmol, 20 29.0 g) and swell for 2 hours.
- 2) Drain and then wash with DMF (5 times, drain between each wash).
- 3) A solution of 20% piperidine in DMF was added agitate with N₂ bubbling for 30 min.
- 4) Drain and wash with DMF (5 times, drain between each wash).
- 5) Add Fmoc-amino acid solution (3.0 equivalents in DMF) and mix for 30 seconds, then add 25 activation buffer (HBTU (2.85 equivalents) and DIEA (6 equivalents) in DMF), agitate with N₂ bubbling for 1 hour.
- 6) The coupling reaction was monitored by ninhydrin test
- 7) If required repeat steps 2 to 5 for same amino acid coupling if inefficient coupling occurs
- 8) Repeat steps 2 to 5 for next amino acid coupling.
- 30 Note: for the amino acids in the table below different protecting groups, equivalents and / or coupling agents were used

Step	Materials	Coupling reagents
3	Fmoc-D-Ser(Trt)-OH (3.0 eq)	HBTU (2.85 eq) and DIEA (6.0 eq)
6	Fmoc-D-Ser(Trt)-OH (3.0 eq)	HBTU (2.85 eq) and DIEA (6.0 eq)
29	(S)-2-(benzylamino)-4-(tert-butoxy)-4-oxobutanoic acid (2.0 eq)	DIC (2.0 eq) and HOAt (2.0 eq)

Peptide Cleavage and Purification:

- 1) Add cleavage buffer (92.5%TFA/2.5%EDT/2.5%TIS/2.5%H₂O) to the flask containing the side chain protected peptide at room temperature and stir for 3 hours.
- 2) Reaction mixture was filtered and filtrate collected.
- 3) The peptide is precipitated with cold isopropyl ether and centrifuged (3 min at 3000 rpm).
- 4) Residue washed with isopropyl ether (2 times).
- 5) Crude peptide dried *in vacuo* for 2 hours.
- 6) The crude peptide was purified by prep-HPLC (A: 0.01 M NH₄HCO₃, B: MeCN). Prep-HPLC Conditions: Agilent SD-1. Solvent: A- 0.01 M NH₄HCO₃ in H₂O, B- acetonitrile, Column: Luna 80*250mm, C18*10μm, 110A. Gradient [time (min)/solvent B (%): 0.0/30, 60.0/60, 60.1/90, 70/90, 70.1/10. Then re-purified by prep-HPLC (A: 0.075% TFA in H₂O, B: MeCN), Prep-HPLC Conditions: Instrument: Agilent SD-1. Solvent: A- 0.075% TFA in H₂O, B- acetonitrile, Column: Luna 80*250mm, C18*10μm, 110A. Gradient [time (min)/solvent B (%): 0.0/30, 60.0/60, 60.1/90, 70/90, 70.1/10. Then used the prep-HPLC (A: 0.5% Acetic Acid in H₂O, B: MeCN) to give Example 85 (15.6 g, 9.45% yield).

Table 2 - HRMS and LCMS properties of purified peptides represented by Examples 1-85

Example	Synthetic Method	HRMS	HRMS Method	LCMS / HPLC (Method A)
1	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₁₂₀ H ₁₈₉ N ₃₀ O ₃₃ 2575.3799; Found 859.4693	B1	m/z 859.8 [M+3H] ³⁺ , R _T = 12.21 min
2	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₁₂₁ H ₁₉₁ N ₃₀ O ₃₃ 2589.3955; Found 864.1394	B1	m/z 864.3 [M+3H] ³⁺ , R _T = 12.55 min
3	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₁₂₁ H ₁₉₁ N ₃₀ O ₃₃ 2589.3955; Found 864.1402	B1	m/z 864.2 [M+3H] ³⁺ , R _T = 12.71 min
4	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₁₂₇ H ₁₉₅ N ₃₀ O ₃₃ 2665.4268; Found 889.4853	B1	m/z 889.6 [M+3H] ³⁺ , R _T = 12.49 min
5	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₁₂₂ H ₁₉₂ N ₂₉ O ₃₃ 2588.4001; Found 863.8101	B1	m/z 864.1 [M+3H] ³⁺ , R _T = 11.42 min
6	a	HRMS (HESI/FT) m/z: [M+2H] ²⁺ Calcd for C ₁₂₇ H ₁₉₇ N ₂₉ O ₃₅ 2686.437; Found 1344.2273	B1	m/z 896.8 [M+3H] ³⁺ , R _T = 11.53 min
7	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₁₂₁ H ₁₉₀ N ₂₉ O ₃₃ 2574.3845; Found 859.1348	B1	m/z 859.3 [M+3H] ³⁺ , R _T = 11.09 min

8	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C158H255N32O45 3317.8416; Found 1106.9577	B1	m/z 1107.5 [M+3H] ³⁺ , R _T = 14.92 min
9	a	ND		m/z 894.4 [M+3H] ³⁺ , R _T = 9.60 min
10	a	HRMS (HESI/FT) m/z: [M+2H] ²⁺ Calcd for C127H198N29O35 2686.437; Found 1344.2269	B1	m/z 896.8 [M+3H] ³⁺ , R _T = 11.74 min
11	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C158H255N32O45 3317.8416; Found 1106.9618	B1	m/z 1107.7 [M+3H] ³⁺ , R _T = 10.89 min
12	a	ND		m/z 859.4 [M+3H] ³⁺ , R _T = 7.59 min
13	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H192N29O33 2588.4001; Found 863.8097	B1	m/z 864.2 [M+3H] ³⁺ , R _T = 13.93 min
14	a	ND		m/z 859.5 [M+3H] ³⁺ , R _T = 11.04 min
15	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C156H251N32O45 3289.8101; Found 1097.6165	B1	m/z 1097.9 [M+3H] ³⁺ , R _T = 9.12 min
16	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C156H251N32O45 3289.8101; Found 1097.6158	B1	m/z 1097.9 [M+3H] ³⁺ , R _T = 12.52 min
17	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H193N30O335 2603.4111; Found 868.8140	B1	m/z 869.0 [M+3H] ³⁺ , R _T = 13.04 min
18	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H192N29O33 2588.4001; Found 863.8103	B1	m/z 864.2 [M+3H] ³⁺ , R _T = 11.74 min
19	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C157H253N32O45 3303.8257; Found 1102.2851	B1	m/z 1102.7 [M+3H] ³⁺ , R _T = 12.46 min
20	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H193N30O33 2603.4111; Found 868.8129	B1	m/z 869.1 [M+3H] ³⁺ , R _T = 9.41 min
21	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C157H251N33O44 3302.8418; Found 1101.9560	B1	m/z 1102.1 [M+3H] ³⁺ , R _T = 9.16 min
22	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H193N30O32 2587.4163; Found 863.4864	B2	m/z 863.6 [M+3H] ³⁺ , R _T = 11.38 min
23	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C129H198N29O33 2678.4473; Found 893.8291	B2	m/z 894.6 [M+3H] ³⁺ , R _T = 9.59 min
24	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C129H199N30O33 2693.458; Found 898.8311	B2	m/z 898.9 [M+3H] ³⁺ , R _T = 8.39 min
25	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C129H199N30O33 2693.458; Found 898.8269	B1	m/z 899.2 [M+3H] ³⁺ , R _T = 14.14 min
26	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C163H259N34O44 3393.884; Found 1132.6339	B1	m/z 1133.1 [M+3H] ³⁺ , R _T = 9.78 min
27	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C118H193N30O33 2555.4111; Found 852.8142	B1	m/z 853.1 [M+3H] ³⁺ , R _T = 12.73 min
28	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H193N30O34 2619.406; Found 874.1465	B1	m/z 874.5 [M+3H] ³⁺ , R _T = 12.74 min
29	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C129H199N30O33 2693.458; Found 898.8323	B2	m/z 898.8 [M+3H] ³⁺ , R _T = 13.33 min
30	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C129H199N30O33 2693.458; Found 898.8303	B1	m/z 899.0 [M+3H] ³⁺ , R _T = 10.15 min
31	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H193N30O34 2619.406; Found 874.1415	B1	m/z 874.6 [M+3H] ³⁺ , R _T = 12.31 min
32	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C125H199N30O33 2645.458; Found 882.8307	B1	m/z 883.1 [M+3H] ³⁺ , R _T = 9.66 min
33	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C164H260N33O45 3408.8836; Found 1137.3051	B1	m/z 1137.9 [M+3H] ³⁺ , R _T = 12.91 min
34	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H193N30O33 2603.4111; Found 868.8139	B1	m/z 868.9 [M+3H] ³⁺ , R _T = 10.36 min
35	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for	B1	m/z 883.2 [M+3H] ³⁺ ,

		C125H199N30O33 2645.458; Found 882.8299		R _T = 12.39 min
36	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C118H192N29O33 2540.4001; Found 847.8078	B1	m/z 848.2 [M+3H] ³⁺ , R _T = 11.14 min
37	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C125H197N30O33 2643.4424; Found 882.1548	B1	m/z 882.5 [M+3H] ³⁺ , R _T = 8.68 min
38	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C118H190N29O33 2538.3845; Found 847.1428	B2	m/z 847.3 [M+3H] ³⁺ , R _T = 13.49 min
39	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C126H197N30O33 2657.458; Found 886.8297	B1	m/z 887.1 [M+3H] ³⁺ , R _T = 12.23 min
40	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C119H192N29O33 2552.4001; Found 851.8097	B1	m/z 852.1 [M+3H] ³⁺ , R _T = 10.71 min
41	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H192N29O34 2604.3953; Found 869.1420	B1	m/z 869.3 [M+3H] ³⁺ , R _T = 14.00 min
42	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H192N29O34 2604.3953; Found 869.1414	B1	m/z 869.3 [M+3H] ³⁺ , R _T = 12.25 min
43	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C123H192N30O33 2617.4268; Found 873.4864	B1	m/z 873.4 [M+3H] ³⁺ , R _T = 14.31 min
44	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C123H195N30O33 2617.4268; Found 873.8203	B2	m/z 873.7 [M+3H] ³⁺ , R _T = 10.84 min
45	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C123H195N30O34 2633.4216; Found 878.8171	B1	m/z 878.8 [M+3H] ³⁺ , R _T = 12.40 min
46	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C123H195N30O34 2633.4216; Found 878.8177	B1	m/z 879.0 [M+3H] ³⁺ , R _T = 13.31 min
47	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C123H195N30O34 2633.4216; Found 878.8211	B2	m/z 878.8 [M+3H] ³⁺ , R _T = 13.06 min
48	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C122H193N30O33 2603.4111; Found 868.8184	B2	m/z 868.9 [M+3H] ³⁺ , R _T = 10.34 min
49	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C123H195N30O33 2617.4268; Found 873.4885	B2	m/z 873.6 [M+3H] ³⁺ , R _T = 10.92 min
50	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C121H191N30O33 2589.3955; Found 864.1454	B2	m/z 864.2 [M+3H] ³⁺ , R _T = 13.68 min
51	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C123H195N30O34 2633.4216; Found 878.8212	B2	m/z 878.9 [M+3H] ³⁺ , R _T = 13.72 min
52	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C124H195N30O33 2629.4268; Found 877.4890	B2	m/z 877.5 [M+3H] ³⁺ , R _T = 12.20 min
53	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C123H195N30O33 2617.4268; Found 873.4894	B2	m/z 873.7 [M+3H] ³⁺ , R _T = 11.77 min
54	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C123H193N30O34 2631.406; Found 878.1494	B2	m/z 878.0 [M+3H] ³⁺ , R _T = 13.91 min
55	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C133H209N34O39 2903.5181; Found 968.8527	B2	m/z 969.1 [M+3H] ³⁺ , R _T = 10.39 min
56	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C134H211N34O39 2917.5337; Found 973.5199	B1	m/z 973.5 [M+3H] ³⁺ , R _T = 13.96 min
57	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C133H208N33O39 2888.5073; Found 963.8461	B1	m/z 963.9 [M+3H] ³⁺ , R _T = 12.24 min
58	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C139H212N33O38 2948.5437; Found 983.8103	B2	m/z 984.0 [M+3H] ³⁺ , R _T = 13.83 min
59	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C133H209N34O39 2903.5181; Found 968.8477	B1	m/z 969.2 [M+3H] ³⁺ , R _T = 13.81 min
60	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C134H211N34O39 2917.5337; Found 973.5238	B1	m/z 973.8 [M+3H] ³⁺ , R _T = 10.44 min
61	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C140H217N34O41 3027.5706; Found 1010.2023	B2	m/z 1010.5 [M+3H] ³⁺ , R _T = 9.25 min
62	a	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C202H307N43O58 4259.208; Found 1065.8148	B1	m/z 1421.2 [M+3H] ³⁺ , R _T = 11.74 min

63	b	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C154H239N38O47 3369.7246; Found 1124.2550	B2	m/z 1124.4 [M+3H] ³⁺ , R _T = 9.77 min
64	b	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C147H232N37O47 3264.6667; Found 1089.2328	B1	m/z 1089.0 [M+3H] ³⁺ , R _T = 14.42 min
65	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C134H212N33O41 2936.5283; Found 979.8584	B2	m/z 980.1 [M+3H] ³⁺ , R _T = 12.15 min
66	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C195H299N42O58 4154.1504; Found 1385.7322	B1	m/z 1386.5 [M+3H] ³⁺ , R _T = 12.77 min
67	a	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C195H297N43O59 4185.1563; Found 1047.3042	B1	m/z 1269.5 [M+3H] ³⁺ , R _T = 12.88 min
68	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C147H233N38O47 3279.6775; Found 1094.2364	B1	m/z 1094.3 [M+3H] ³⁺ , R _T = 10.81 min
69	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C184H298N43O59S 4083.1125; Found 1362.0493	B1	m/z 1362.5 [M+3H] ³⁺ , R _T = 13.81 min
70	a	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C158H248N40O47 3453.7932; Found 864.4594	B1	m/z 1152.5 [M+3H] ³⁺ , R _T = 12.86 min
71	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C193H308N43O59 4169.2188; Found 1390.7396	B2	m/z 1391.1 [M+3H] ³⁺ , R _T = 11.68 min
72	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C148H235N38O47 3293.6931; Found 1098.9091	B1	m/z 1099.1 [M+3H] ³⁺ , R _T = 11.32 min
73	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C147H233N38O47 3279.6775; Found 1094.2365	B1	m/z 1094.7 [M+3H] ³⁺ , R _T = 10.78 min
74	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C148H232N38O47 3293.6931; Found 1098.9095	B1	m/z 1099.7 [M+3H] ³⁺ , R _T = 10.81 min
75	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C147H233N38O47 3279.6775; Found 1094.2397	B2	m/z 1094.3 [M+3H] ³⁺ , R _T = 10.88 min
76	a	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C148H235N38O47 3293.6931; Found 1098.9059	B1	m/z 1099.1 [M+3H] ³⁺ , R _T = 10.85 min
77	a	ND		m/z 1085.8 [M+3H] ³⁺ , R _T = 10.62 min
78	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C147H233N38O47 3279.6775; Found 1094.2395	B2	m/z 1094.6 [M+3H] ³⁺ , R _T = 10.30 min
79	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C148H235N38O47 3293.6931; Found 1098.9121	B2	m/z 1099.1 [M+3H] ³⁺ , R _T = 10.86 min
80	a	ND		m/z 882.8 [M+4H] ⁴⁺ , R _T = 9.70 min
81	a	ND		m/z 1155.5 [M+4H] ⁴⁺ , R _T = 11.46 min
82	a	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C214H333N45O69 4633.3618; Found 1159.6092	B2	m/z 1160.0 [M+4H] ⁴⁺ , R _T = 13.56 min
83	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C148H235N38O47 3293.6931; Found 1098.9110	B2	m/z 1098.9 [M+3H] ³⁺ , R _T = 11.90 min
84	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C148H235N38O47 3293.6931; Found 1098.9110	B2	m/z 1099.2 [M+3H] ³⁺ , R _T = 11.79 min
85	c	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C148H235N38O47 3293.6931; Found 1098.9111	B2	m/z 1099.1 [M+3H] ³⁺ , R _T = 12.30 min

ND – Not determined

Biological Activity

The following examples are provided to illustrate preferred aspects of the invention and are not intended to limit the scope of the invention.

Example A. In vitro pharmacological characterization of GLP-1 peptides - Functional antagonism of human GLP1 receptors, cAMP accumulation assay

Antagonist inhibition of cAMP production upon stimulation of GLP-1R with agonist ligand (GLP-1(7-36) amide peptide, Tocris) was assessed using HiRange cAMP kit (Cisbio). The method followed a two-step protocol provided in the kit. In brief, HEK cells infected with 1% v/v GLP-1R Bacmam for 24h were harvested using cell dissociation solution (Gibco), centrifuged and resuspended in the assay buffer (HBSS (Lonza) supplemented with 0.5 mM IBMX (Tocris)). DMSO stock of test compounds were serially diluted in the assay buffer and added to 96-well half area white plates (Costar). Final DMSO concentration in the assay was 0.3%. 20K cells per well were added to plates followed by 30 min incubation (humidified air (5% CO₂), 37°C). Then, cells were stimulated for further 30 min (humidified air (5% CO₂), 37°C) by addition of an equivalent to EC₈₀ concentration of GLP-1(7-36) peptide. Intracellular accumulation of cAMP was stopped by addition of the HTRF detection reagents in lysis buffer, provided in the kit. Following 1-hour incubation at RT, plates were read on Pherastar FS (BMG Labtech, Inc.) Dotmatics Studies software was used for fitting data to a four-parameter concentration response curve. Calculated IC₅₀ values were corrected for the agonist concentration using an adaptation of the Cheng-Prusoff equation to generate functional pK_b values: $fpKb = -\log_{10}\left(\frac{IC_{50}}{[A]}\right) + 1$.

Example	Human GLP-1R antagonist cAMP fpKb	Example	Human GLP-1R antagonist cAMP fpKb
Ex 9-39	7.8	43	8.5
1	8.2	44	8.7
2	8.4	45	8.4
3	8.3	46	8.4
4	8.3	47	8.4
5	8.3	48	8.5
6	8.3	49	8.4
7	8.3	50	8.3
8	8.3	51	8.3
9	8.6	52	8.3
10	8.2	53	8.8
11	8.2	54	8.4
12	8.2	55	8.3
13	8.4	56	8.2
14	8.4	57	8.2
15	8.3	58	8.2
16	8.3	59	8.3
17	8.2	60	8.3
18	8.5	61	8.7
19	8.3	62	8.5
20	8.4	63	9.0
21	8.2	64	8.6

22	8.3	65	8.5
23	8.6	66	8.2
24	8.6	67	8.2
25	8.2	68	8.5
26	8.2	69	8.4
27	8.3	70	8.3
28	8.2	71	8.8
29	8.4	72	8.5
30	8.2	73	8.6
31	8.2	74	8.5
32	8.5	75	8.6
33	8.3	76	8.4
34	8.3	77	8.5
35	8.3	78	8.4
36	8.3	79	8.4
37	8.5	80	8.3
38	8.5	81	8.3
39	8.3	82	8.3
40	8.2	83	8.5
41	8.3	84	8.4
42	8.5	85	9.1

Example B. In vitro pharmacological characterization of GLP-1 peptides – Functional antagonism of mouse GLP1 receptors, cAMP accumulation assay:

Antagonist inhibition of cAMP production upon stimulation of GLP-1R with agonist ligand was assessed using HitHunter cAMP assay (DiscoverX). The method followed antagonist procedure steps provided in the kit. In brief, CHO-K1 cells stably expressing mouse GLP-1R were thawed and plated at 10K cells per well in CP05 reagent in the total volume of 20 µl into white walled, 384-well plates and incubated overnight at 37°C in Cytomat. On the day of the assay, the media was replaced with 15µl of HBSS/10mM HEPES. DMSO stock of test compounds were serially diluted in DMSO and then further diluted in the HBSS/10mM HEPES, 5 µl of each concentration were added to the plate followed by 30 min incubation at 37°C. Final DMSO concentration in the assay was 1%. Cells were stimulated for further 30 min at 37°C by addition of an equivalent to EC₈₀ concentration of Exendin-4. Intracellular accumulation of cAMP was stopped by addition of the HitHunter detection reagents in lysis buffer, provided in the kit. Following 1-hour incubation at RT in the dark, plates were read on Envision (Perkin Elmer). Dotmatics Studies software was used for fitting data to a four-parameter concentration response curve. Calculated IC50 values were corrected for the agonist concentration using an adaptation of the Cheng-Prusoff equation to generate functional pKb values: $fpKb = -\log_{10}\left(\frac{IC_{50}}{\frac{[A]}{[EC_{50}] + 1}}\right)$.

Example	Mouse GLP-1R antagonist cAMP	Example	Mouse GLP-1R antagonist cAMP
	fpKb		fpKb
Ex 9-39	7.2	55	7.9
2	7.0	56	8.0
3	7.4	57	8.1
10	7.7	58	8.1
24	8.0	59	8.1
25	7.8	62	7.9
29	7.7	64	8.3
30	7.9	65	8.4
32	7.8	69	7.8
35	7.4	70	7.5
36	7.4	71	7.3
38	7.6	72	7.9
39	7.2	73	7.7
44	7.1	74	7.7
45	7.5	75	7.5
46	7.2	76	7.6
47	7.0	77	7.7
48	7.1	78	7.5
49	7.0	79	7.6
50	7.0	80	7.5
52	7.8	84	8.3
53	7.8	85	8.0
54	7.6		

Example C: Mouse intraperitoneal glucose tolerance test (ipGTT)

5 The aim of this study is to evaluate the effects of intravenous administration of a lead GLP1 antagonist peptide on blocking/reducing/antagonising exendin-4-induced (GLP-1 receptor agonist) improvements in glucose tolerance in lean male C57BL/6J mice. Glucose was administered by the intraperitoneal route.

MATERIALS AND METHODS

10 Lean, male C57BL/6J JAX mice were singly housed upon arrival and throughout the study in polypropylene cages on a normal phase 12 h light-dark cycle (lights on 07:00). Relative humidity will typically be 55±15% with prolonged periods below 40%RH or above 70%RH avoided. Animals had free access to standard maintenance diet and tap water *ad libitum* for the duration of the study unless otherwise stated.

EXEPRIMENTAL PROCEDURE

Animals were habituated to the animal unit and diet for approximately 2 weeks with daily handling for the 5 days prior to the study in order to familiarise the animals to the dosing protocol. Animals were randomised on the basis of body weight and ensured that groups were
5 balanced as closely as possible for mean body weight.

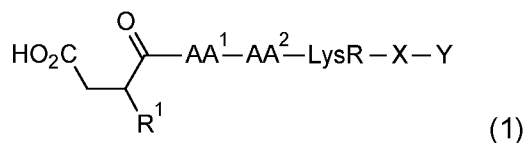
The day prior to the ipGTT, all animals were fasted (free access to water maintained) to ensure. The day of the experiment the animals were moved to a separate room. A baseline blood sample was taken from all animals prior to Treatment 1 (20 minutes pre-glucose). Five minutes
10 later, mice were dosed with Treatment 1 by the intravenous route (15 minutes pre-glucose). Treatment 2 (Exendin-4 or vehicle) was administered 10 minutes prior to the glucose load (all groups). Ten minutes after dosing with Treatment 2 animals were administered a glucose load of D-glucose by the intraperitoneal route (2.0 g/kg at a volume of 5 ml/kg at a concentration of 400 mg/ml). Blood samples were taken 3 minutes before glucose administration and 10, 30, 60,
15 90 and 120 minutes post glucose administration. Plasma samples were subsequently assayed for glucose and insulin at the 10 minute time as single replicates and data analysed by robust regression and AUC 0 to 120 minutes calculated for the glucose data (as total AUC and AUC from baseline) by trapezoidal rule and analysed by the same methodology.

20 Figure 1 shows the results for Examples 24, 31, 34, 38, 44, 68 and 85. Glucose AUC over the 0-120min time period post-glucose administration. Example compound effects compared to Exendin-4 by Williams' test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 2 shows the results for Examples 24, 31, 34, 38, 44, 68 and 85. Plasma insulin (ng/ml) at
25 10 minutes post-glucose administration. Example compound effects compared to Exendin-4 by Williams' test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Claims

1. A compound comprising a sequence of formula (1):



5 wherein;

R^1 is H, NHR^2 or CH_2R^2 ; where R^2 is selected from: H, C_{1-6} alkyl, $(\text{CH}_2)_n\text{aryl}$ and $(\text{CH}_2)_n\text{heteroaryl}$; where n is 1 to 6;

10 AA^1 is -Leu- or -Nle-;

AA^2 is $-\text{NHCR}^{3a}\text{R}^{3b}\text{CO}-$; wherein R^{3a} is hydrogen or a C_{1-3} alkyl group, or is joined to R^{3b} to form a 3-6 membered ring optionally containing one or more heteroatoms selected from N and O; and R^{3b} is C_{1-6} alkyl, $(\text{CH}_2)_n\text{aryl}$, $(\text{CH}_2)_n\text{OH}$ or $(\text{CH}_2)_n\text{OR}^4$, or is joined to R^{3a} to form a 3-6 membered ring optionally containing one or more heteroatoms selected from N and O; where R^4 is C_{1-6} alkyl and n is 1 to 6;

LysR is an optionally N-substituted substituted Lysine residue;

20 X is a sequence $-\text{Gln}-\text{AA}^3-\text{Glu}-\text{AA}^4-\text{Glu}-\text{AA}^5-\text{Val}-\text{AA}^6-\text{Leu}-\text{Phe}-\text{AA}^7-\text{Gln}-\text{Trp}-\text{Leu}-\text{Lys}-\text{Asn}-\text{AA}^8-$

wherein AA^3 is -Met- or -Nle-; where when AA^3 is -Met-, LysR is an N-substituted lysine residue;

25 AA^4 is -Glu- or -Gln-;

AA^5 is -Ser- or -Ala-;

AA^6 is -Arg- or -DArg-;

AA^7 is a group $-\text{NHCHR}^5\text{CO}-$; where R^5 is a C_{1-6} alkyl group;

AA^8 is -Gly-, -Ser-, -DAla- or - β Ala-;

30

Y is absent or is a sequence $-\text{AA}^9-\text{AA}^{10}-\text{AA}^{11}-\text{AA}^{12}-\text{AA}^{13}-\text{AA}^{14}-\text{AA}^{15}-\text{AA}^{16}-\text{AA}^{17}-\text{AA}^{18}-\text{AA}^{19}-$

wherein AA⁹ is -Gly- or -Ser-;

AA¹⁰ is -Pro- or -Ser-;

AA¹¹ is -Ser-, -DSer- or -Lys-;

AA¹² is -Ser-, -DSer-, -Lys- or -Phe-;

5 AA¹³ is absent or is -Ser-, -DSer-, -Gly-, -Glu- or -Lys-;

AA¹⁴ is absent or is -Ser-, -DSer-, -Ala-, -Lys- or -Tyr-;

AA¹⁵ is absent or is -Ser-, -DSer-, -Pro-, -Glu- or -Lys-;

AA¹⁶ is absent or is -Ser-, -DSer-, -Pro-, -Lys- or -LysR-;

AA¹⁷ is absent or is -Pro- or -Glu-;

10 AA¹⁸ is absent or is -Ser- or -Tyr-;

AA¹⁹ is absent or is -Glu-;

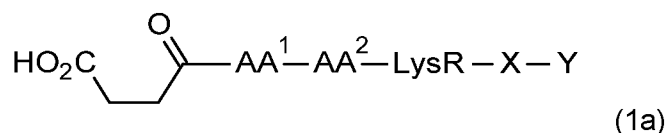
wherein the X or Y C-terminus is a carboxyl group or a carboxamide group, or is
adjoined to any natural or non-natural amino acid sequence or any other moiety,
15 functional group or groups;

or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion
thereof.

20 2. The compound according to claim 1, wherein R¹ is selected from H, NH₂, NHBn and
CH₂Bn.

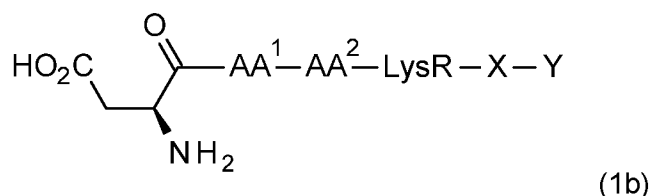
3. The compound according to claim 2, wherein R¹ is NHBn.

25 4. The compound according to claim 1 which is a compound of formula (1a):



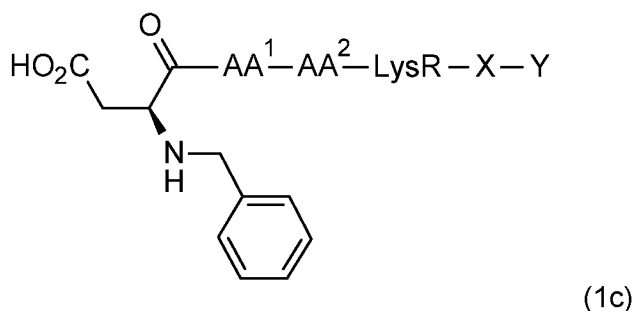
or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or
zwitterion thereof, wherein AA¹, AA², LysR, X and Y are as defined in claim 1.

30 5. The compound according to claim 1 which is a compound of formula (1b):



or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA¹, AA², LysR, X and Y are as defined in claim 1.

- 5 6. The compound according to claim 1 which is a compound of formula (1c):



or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof, wherein AA¹, AA², LysR, X and Y are as defined in claim 1.

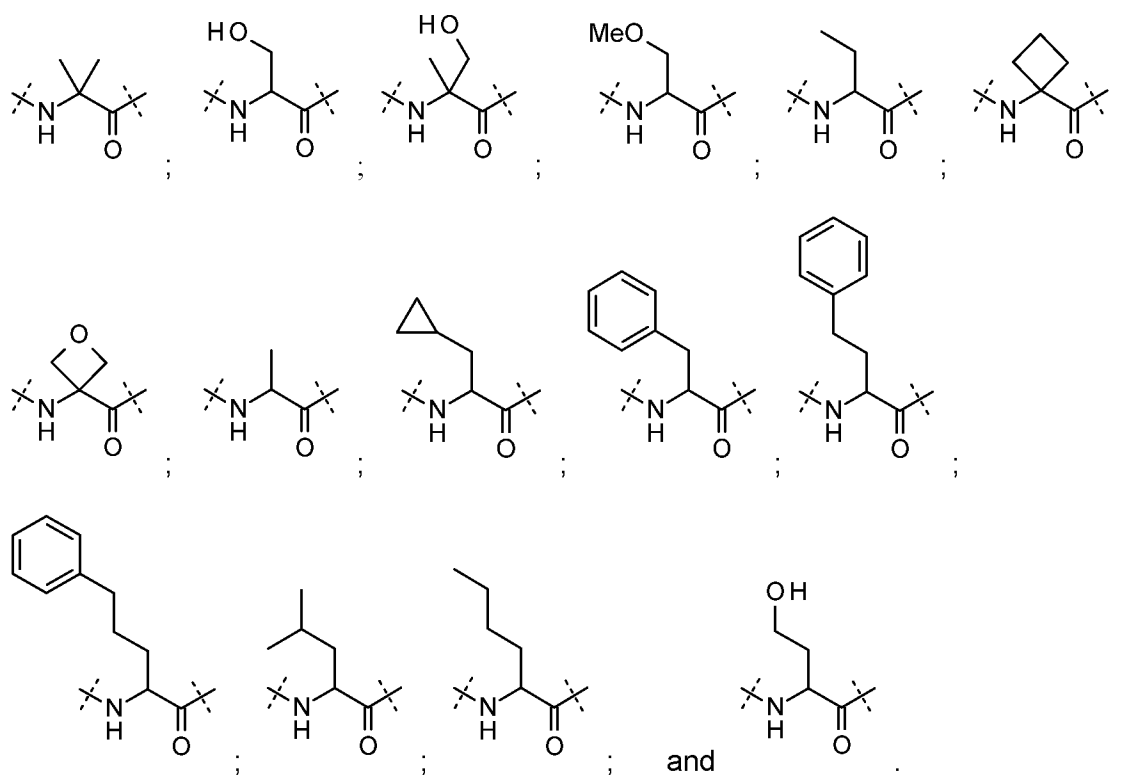
- 10 7. The compound according to any one of claims 1 to 6, wherein AA¹ is -Leu-.

8. The compound according to any one of claims 1 to 6, wherein AA¹ is -Ile-.

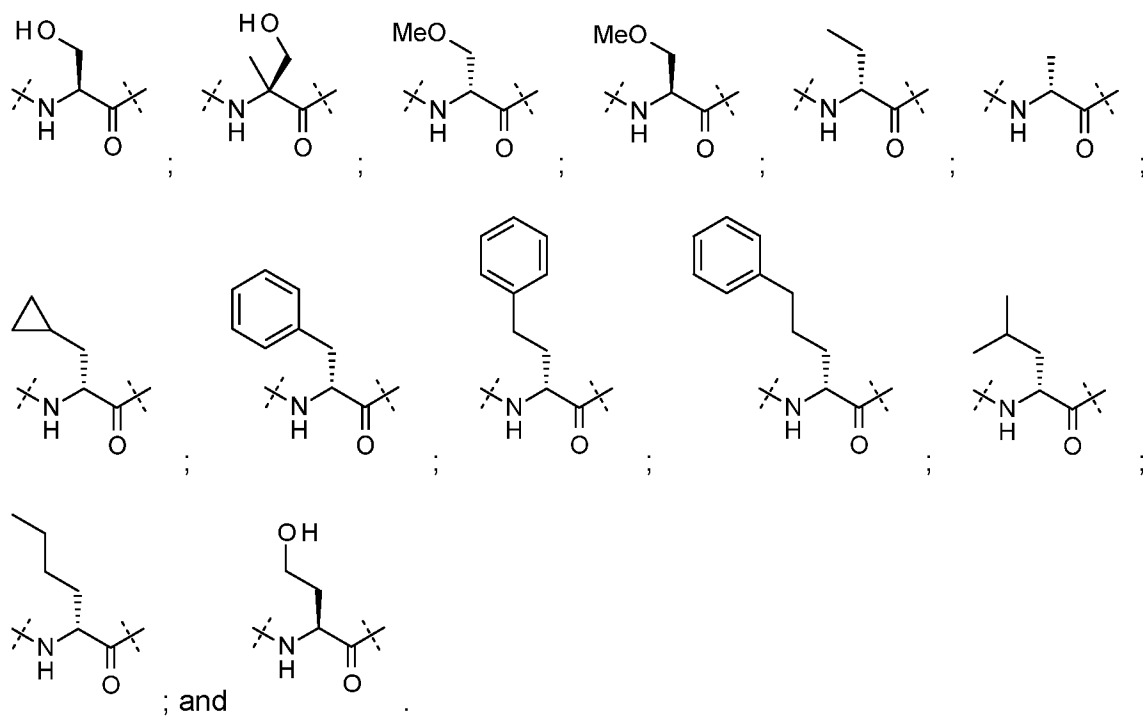
- 15 9. The compound according to any one of claims 1 to 8, wherein R^{3a} is hydrogen or methyl and R^{3b} is selected from methyl, ethyl, isobutyl, *n*-butyl, CH₂OH, CH₂CH₂OH, CH₂OCH₃, CH₂-cyclopropyl, Bn, CH₂Bn or CH₂CH₂Bn.

10. The compound according to any one of claims 1 to 8, wherein R^{3a} and R^{3b} form a cyclobutyl or an oxetanyl ring.

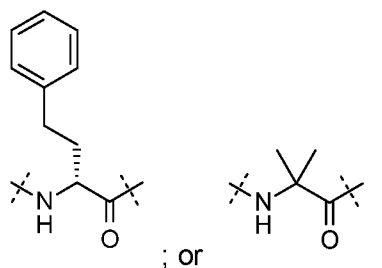
- 20 11. The compound according to any one of claims 1 to 8, wherein AA² is selected from:



5 12. The compound according to claim 11, wherein AA² is selected from



10 13. The compound according to claim 11, wherein AA² is:

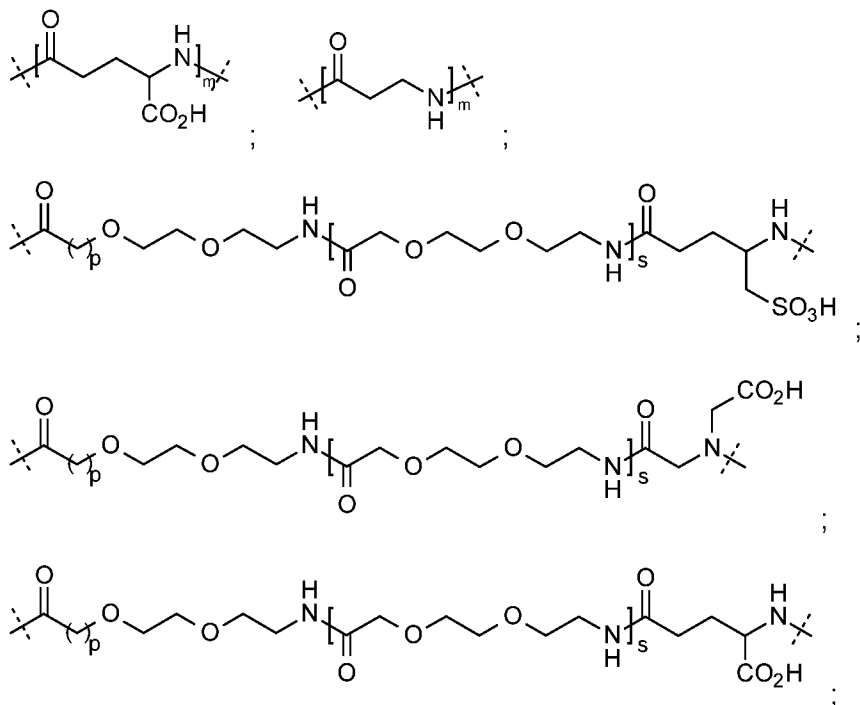


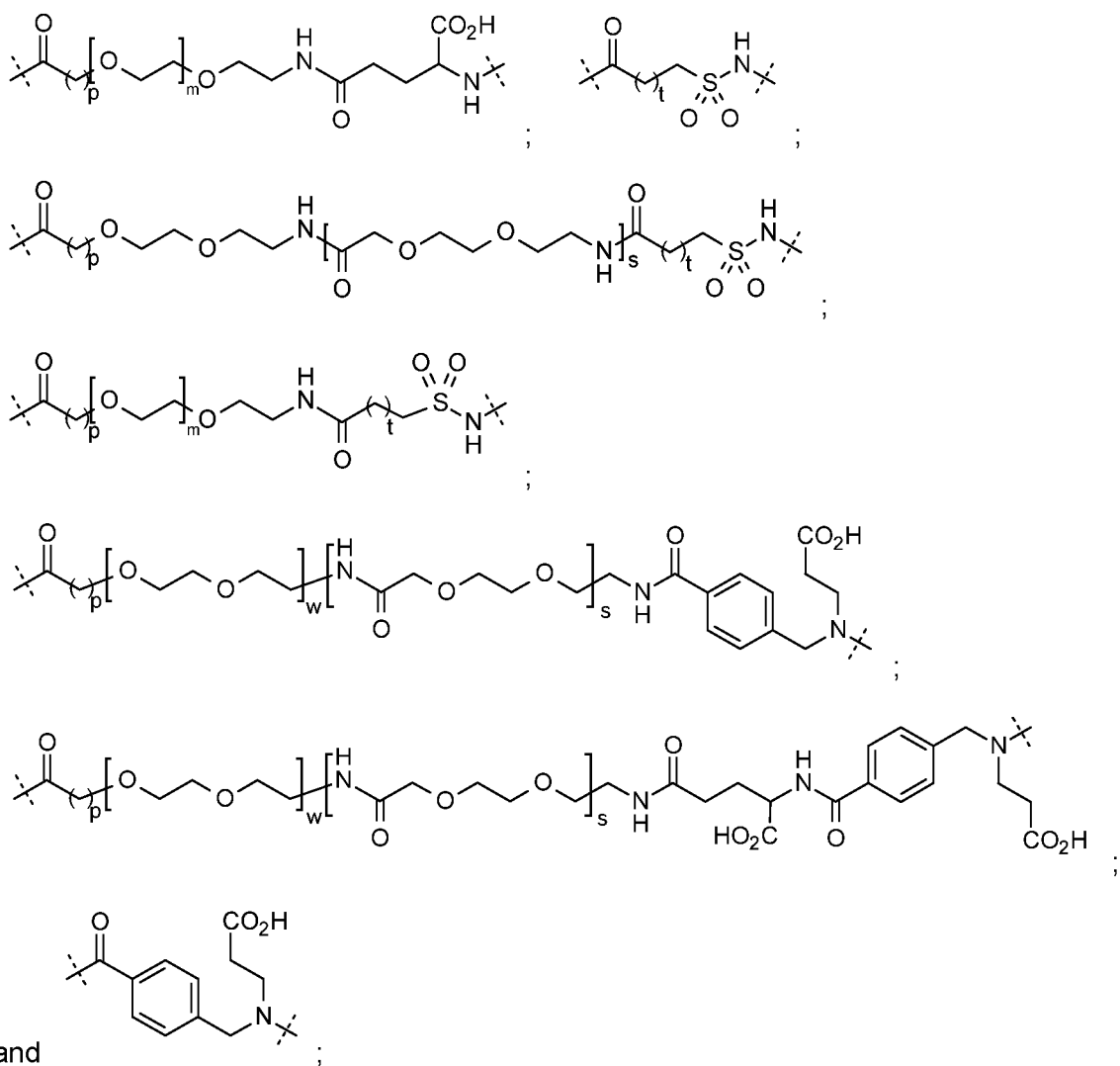
14. The compound according to any one of claims 1 to 13, wherein the group LysR is an unsubstituted lysine residue.

15. The compound according to any one of claims 1 to 13, wherein LysR is an N-substituted Lysine residue, wherein the N-substituent is selected from: $-\text{CO}(\text{CH}_2)_q\text{CH}_3$; $-\text{CO}(\text{CH}_2)_q\text{CO}_2\text{H}$; $-\text{CO}(\text{CH}_2)_q\text{CHCH}_2$; $-\text{COO}(\text{CH}_2)_q\text{CH}_3$; $-\text{COO}(\text{CH}_2)_q\text{CO}_2\text{H}$ and $-\text{COO}(\text{CH}_2)_q\text{CHCH}_2$; where q is 1 to 22.

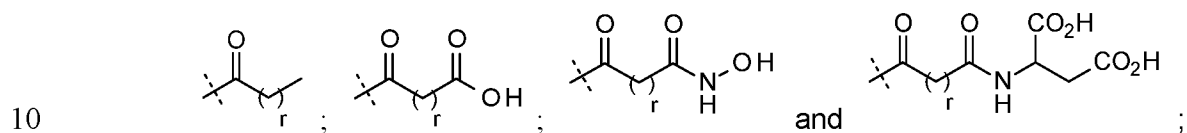
16. The compound according to any one of claims 1 to 13, wherein LysR is an N-substituted Lysine residue, wherein the N-substituent is a group -L-G;

wherein L is selected from the group consisting of:





and G is selected from the group consisting of:



where m is 1 to 23;

p is 1 to 3;

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r is 1 to 20;

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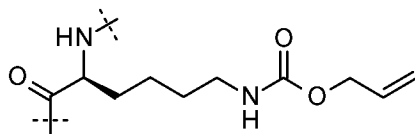
s is 0 to 3;

t is 0 to 4;

15

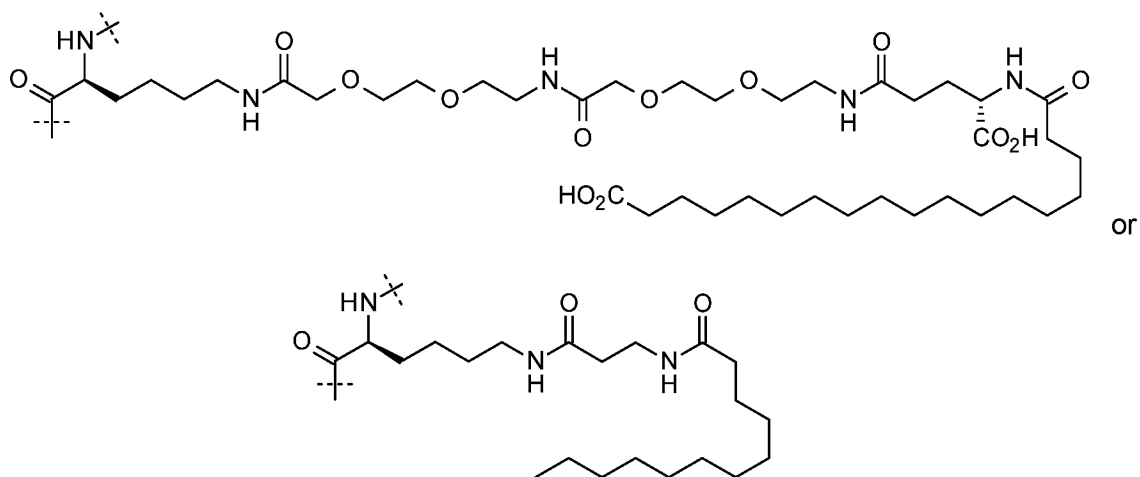
and w is 0 to 4.

17. The compound according to claim 15, wherein the group LysR is:



5

18. The compound according to claim 16, wherein the group LysR is selected from:

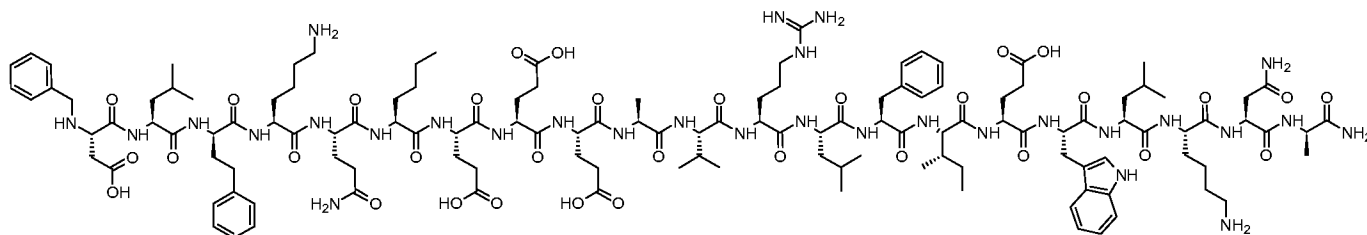


10 19. The compound according to any one of claims 1 to 18, wherein the X C-terminus is a carboxamide group.

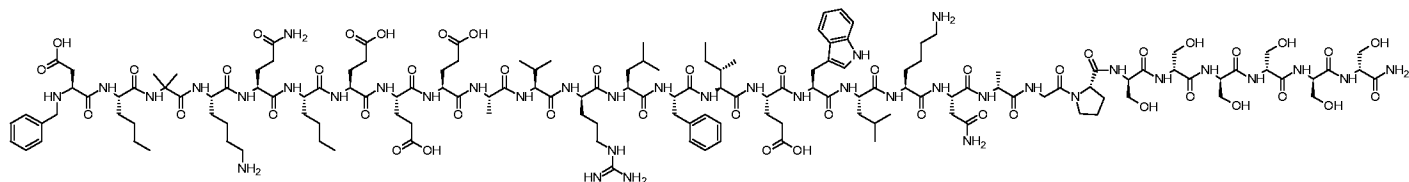
20. The compound according to claim 1 which is selected from any one of Examples 1 to 85.

15 21. The compound according to claim 1 which is selected from the group consisting of:

Example 24:



Example 85:



or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

22. The compound according to any one of claims 1 to 21 having GLP-1 receptor antagonist activity.

23. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 24 and a pharmaceutically acceptable excipient.

24. The compound or composition according to any one of claims 1 to 23 for use in the treatment of unexplained symptomatic hyperinsulinemia conditions and/or associated hypoglycaemia conditions.

25. The compound according to claim 24, wherein the condition is selected from unexplained symptomatic hyperinsulinemia and/or associated hypoglycaemia in a range of conditions such as hypoglycemia due to hyperinsulinism associated with leucine sensitivity, hypoglycemia due to hyperinsulinism associated with non-malignant insulinomas, inoperable islet cell adenoma or carcinoma, or extrapancreatic malignancy, hyperinsulinemia and hypoglycaemia in polycystic ovary syndrome, sulphonylurea-induced toxicity in T2DM, Prader-Willi syndrome, Adrenal Insufficiency and Addison's Disease, Beckwith-Wiedemann syndrome, Soto's Syndrome, Costello Syndrome, Timothy Syndrome, Kabuki Syndrome, Congenital Disorders of Glycosylation, Late dumping syndrome, Reactive hypoglycaemia infants of diabetic mothers, Trisomy 13, Central hypoventilation syndrome, Leprechaunism (insulin resistance syndrome), Mosaic Turner Syndrome, Usher Syndrome, Non-insulinoma pancreatogenous hypoglycaemia, Factitious hypoglycaemia, Insulin gene receptor mutations, Insulin autoimmune

syndrome, Non-islet cells tumor hypoglycemia (NICTH) and withdrawal from alcoholic and other addictive substances.

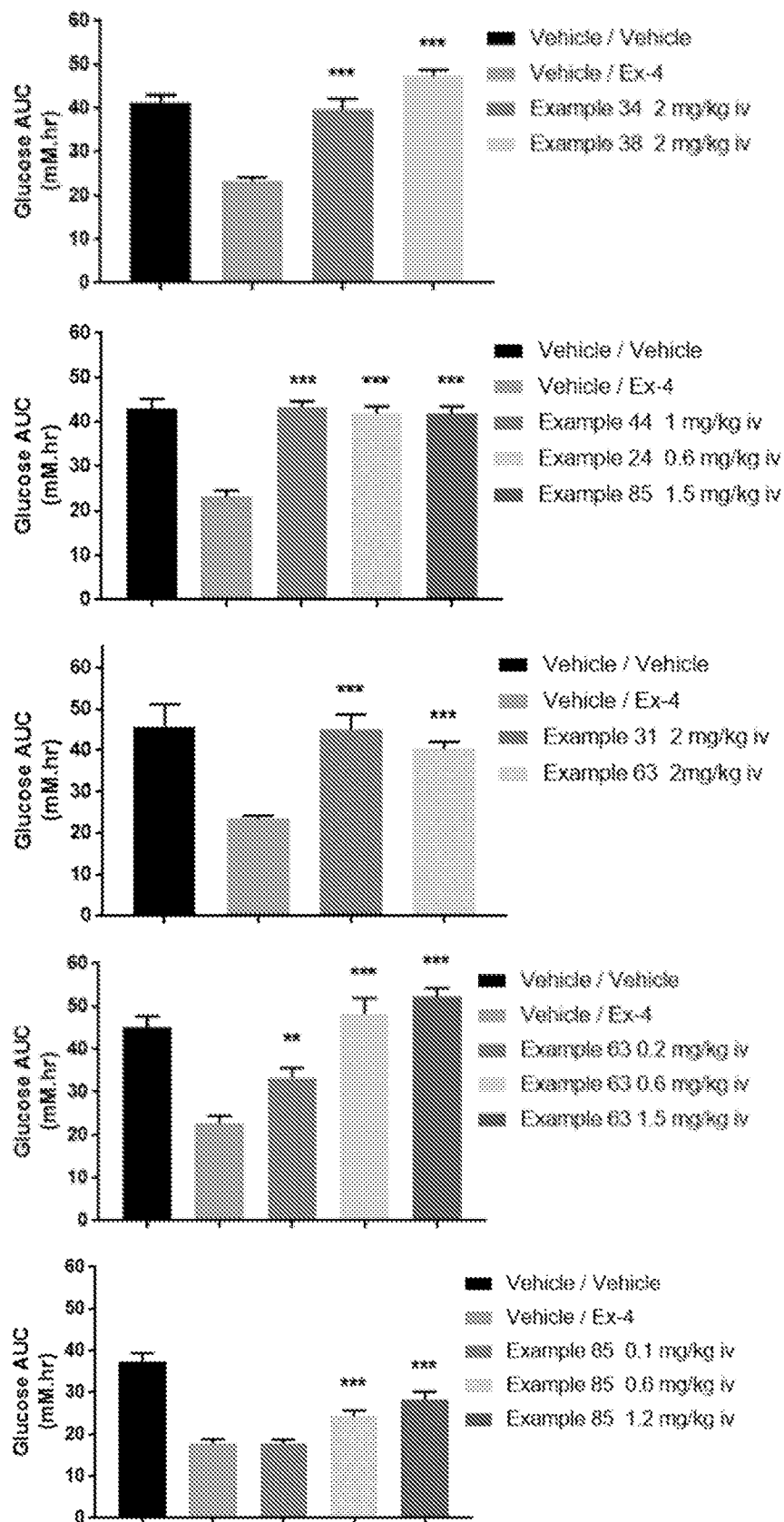
Figure 1

Figure 2