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(54) Title: SELECTIVE VPAC2 RECEPTOR PEPTIDE AGONISTS

(57) Abstract: The present invention encompasses peptides that selectively activate the VPAC2 receptor and are useful in the treatment of diabetes.



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SELECTIVE VPAC2 RECEPTOR PEPTIDE AGONISTS

The present invention relates to selective VPAC2 receptor peptide agonists.

In particular, the present invention relates to selective VPAC2 receptor peptide
5 agonists which are covalently attached to one or more molecules of polyethylene glycol
or a derivative thereof.

Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), is the most
common form of diabetes, affecting 90% of people with diabetes. With NIDDM, patients
have impaired β -cell function resulting in insufficient insulin production and/or decreased
10 insulin sensitivity. If NIDDM is not controlled, excess glucose accumulates in the blood,
resulting in hyperglycemia. Over time, more serious complications may arise including
renal dysfunction, cardiovascular problems, visual loss, lower limb ulceration,
neuropathy, and ischemia. Treatments for NIDDM include improving diet, exercise, and
weight control as well as using a variety of oral medications. Individuals with NIDDM
15 can initially control their blood glucose levels by taking such oral medications. These
medications, however, do not slow the progressive loss of β -cell function that occurs in
type 2 diabetes patients and, thus, are not sufficient to control blood glucose levels in the
later stages of the disease. Also, treatment with currently available medications exposes
NIDDM patients to potential side effects such as hypoglycemia, gastrointestinal
20 problems, fluid retention, oedema, and/or weight gain.

Compounds, such as peptides that are selective for a particular G-protein coupled
receptor known as the VPAC2 receptor, were initially identified by modifying vasoactive
intestinal peptide (VIP) and/or pituitary adenylate cyclase-activating polypeptide
(PACAP). (See, for example, Xia *et al.*, *J Pharmacol Exp Ther.*, 281:629-633 (1997);
25 Tsutsumi *et al.*, *Diabetes*, 51:1453-1460 (2002), WO 01/23420, WO 2004/006839.)

PACAP belongs to the secretin / glucagon / vasoactive intestinal peptide (VIP)
family of peptides and works through three G-protein-coupled receptors that exert their
action through the cAMP-mediated and other Ca^{2+} -mediated signal transduction
pathways. These receptors are known as the PACAP-preferring type 1 (PAC1) receptor
30 (Isobe, *et al.*, *Regul. Pept.*, 110:213-217 (2003); Ogi, *et al.*, *Biochem. Biophys. Res.*
Commun., 196:1511-1521 (1993)) and the two VIP-shared type 2 receptors (VPAC1 and
VPAC2) (Sherwood *et al.*, *Endocr. Rev.*, 21:619-670 (2000); Hammar *et al.*, *Pharmacol*

Rev, 50:265-270 (1998); Couvineau, *et al.*, *J. Biol. Chem.*, 278:24759-24766 (2003); Sreedharan, *et al.*, *Biochem. Biophys. Res. Commun.*, 193:546-553 (1993); Lutz, *et al.*, *FEBS Lett.*, 458: 197-203 (1999); Adamou, *et al.*, *Biochem. Biophys. Res. Commun.*, 209: 385-392 (1995)).

5 PACAP has comparable activities towards all three receptors, whilst VIP selectively activates the two VPAC receptors (Tsutsumi *et al.*, *Diabetes*, 51:1453-1460 (2002)). Both VIP (Eriksson *et al.*, *Peptides*, 10: 481-484 (1989)) and PACAP (Filipsson *et al.*, *JCEM*, 82:3093-3098 (1997)) have been shown to not only stimulate insulin secretion in man when given intravenously but also increase glucagon secretion and
10 hepatic glucose output. As a consequence, PACAP or VIP stimulation generally does not result in a net improvement of glycemia. Activation of multiple receptors by PACAP or VIP also has broad physiological effects on nervous, endocrine, cardiovascular, reproductive, muscular, and immune systems (Gozes *et al.*, *Curr. Med. Chem.*, 6:1019-1034 (1999)). Furthermore, it appears that VIP-induced watery diarrhoea in rats is
15 mediated by only one of the VPAC receptors, VPAC1 (Ito *et al.*, *Peptides*, 22:1139-1151 (2001); Tsutsumi *et al.*, *Diabetes*, 51:1453-1460 (2002)). In addition, the VPAC1 and PAC1 receptors are expressed on α -cells and hepatocytes and, thus, are most likely involved in the effects on hepatic glucose output.

 Exendin-4 is found in the salivary excretions from the Gila Monster, *Heloderma*
20 *suspectum*, (Eng *et al.*, *J. Biol. Chem.*, 267(11):7402-7405 (1992)). It is a 39 amino acid peptide, which has glucose dependent insulin secretagogue activity. Particular PEGylated exendin and exendin agonist peptides are described in WO 2000/66629.

 Recent studies have shown that peptides selective for the VPAC2 receptor are able to stimulate insulin secretion from the pancreas without gastrointestinal (GI) side effects
25 and without enhancing glucagon release and hepatic glucose output (Tsutsumi *et al.*, *Diabetes*, 51:1453-1460 (2002)).

 Many of the VPAC2 receptor peptide agonists reported to date have, however, less than desirable potency, selectivity, and stability profiles, which could impede their clinical viability. In addition, many of these peptides are not suitable for commercial
30 candidates as a result of stability issues associated with the polypeptides in formulation, as well as issues with the short half-life of these polypeptides *in vivo*. It has, furthermore, been identified that some VPAC2 receptor peptide agonists are inactivated by dipeptidyl-

-3-

peptidase (DPP-IV). A short serum half-life could hinder the use of these agonists as therapeutic agents. There is, therefore, a need for new therapies, which overcome the problems associated with current medications for NIDDM.

The present invention seeks to provide improved compounds that are selective for the VPAC2 receptor and which induce insulin secretion from the pancreas only in the presence of high blood glucose levels. The compounds of the present invention are peptides, which are believed to also improve beta cell function. These peptides can have the physiological effect of inducing insulin secretion without GI side effects or a corresponding increase in hepatic glucose output and also generally have enhanced selectivity, potency, and/or *in vivo* stability of the peptide compared to known VPAC2 receptor peptide agonists.

The present invention also seeks to provide selective VPAC2 receptor peptide agonists, which have reduced clearance and improved *in vivo* stability. It is desirable that the agonists of the present invention be administered a minimum number of times during a prolonged period of time.

According to a first aspect of the present invention, there is provided a PEGylated VPAC2 receptor peptide agonist comprising a sequence of the formula:

Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Thr-Xaa₈-Xaa₉-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃-
Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Xaa₂₃-Xaa₂₄-
Xaa₂₅-Xaa₂₆-Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁-Xaa₃₂-Xaa₃₃-Xaa₃₄-Xaa₃₅-
Xaa₃₆-Xaa₃₇-Xaa₃₈-Xaa₃₉-Xaa₄₀

Formula 10 (SEQ ID NO:18)

wherein:

- Xaa₁ is: His, dH, or is absent;
- Xaa₂ is: dA, Ser, Val, Gly, Thr, Leu, dS, Pro, or Aib;
- Xaa₃ is: Asp or Glu;
- Xaa₄ is: Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, Gly, dA, Aib, or NMeA;
- Xaa₅ is: Val, Leu, Phe, Ile, Thr, Trp, Tyr, dV, Aib, or NMeV;
- Xaa₆ is: Phe, Ile, Leu, Thr, Val, Trp, or Tyr;
- Xaa₈ is: Asp, Glu, Ala, Lys, Leu, Arg, or Tyr;
- Xaa₉ is: Asn, Gln, Asp, Glu, Ser, Cys, Lys, or K(CO(CH₂)₂SH);
- Xaa₁₀ is: Tyr, Trp, Tyr(OMe), Ser, Cys, or Lys;

- Xaa₁₂ is: Arg, Lys, Glu, hR, Orn, Lys (isopropyl), Aib, Cit, Ala, Leu, Gln, Phe, Ser, or Cys;
- Xaa₁₃ is: Leu, Phe, Glu, Ala, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH);
- Xaa₁₄ is: Arg, Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, Cit, Ser, or Cys;
- 5 Xaa₁₅ is: Lys, Ala, Arg, Glu, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit, Ser, Cys, K(W), or K(CO(CH₂)₂SH);
- Xaa₁₆ is: Gln, Lys, Glu, Ala, hR, Orn, Lys (isopropyl), Cit, Ser, Cys, K(CO(CH₂)₂SH), or K(W);
- Xaa₁₇ is: Val, Ala, Leu, Ile, Met, Nle, Lys, Aib, Ser, Cys, K(CO(CH₂)₂SH), or K(W);
- 10 Xaa₁₈ is: Ala, Ser, Cys, Lys, K(CO(CH₂)₂SH), or K(W);
- Xaa₁₉ is: Val, Ala, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Trp, Tyr, Cys, Asp, K(CO(CH₂)₂SH), or K(W);
- Xaa₂₀ is: Lys, Gln, hR, Arg, Ser, His, Orn, Lys (isopropyl), Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, Cys, K(CO(CH₂)₂SH), or K(W);
- 15 Xaa₂₁ is: Lys, His, Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, Cys, Val, Tyr, Ile, Thr, Trp, K(W), or K(CO(CH₂)₂SH);
- Xaa₂₂ is: Tyr, Trp, Phe, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, Cys, Lys, K(W), or K(CO(CH₂)₂SH);
- Xaa₂₃ is: Leu, Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, Cys, Lys, K(W), or K(CO(CH₂)₂SH);
- 20 Xaa₂₄ is: Gln, Glu, Asn, Ser, Cys, Lys, K(CO(CH₂)₂SH), or K(W);
- Xaa₂₅ is: Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, Lys, K(CO(CH₂)₂SH), or K(W);
- Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, Phe, Aib, Ser, Cys, Lys, K(CO(CH₂)₂SH), or K(W);
- Xaa₂₇ is: Lys, hR, Arg, Gln, Ala, Asp, Glu, Phe, Gly, His, Ile, Met, Asn, Pro, Ser, Thr, Val, Trp, Tyr, Lys (isopropyl), Cys, Leu, Orn, dK, K(W), or K(CO(CH₂)₂SH);
- 25 Xaa₂₈ is: Asn, Asp, Gln, Lys, Arg, Aib, Orn, hR, Cit, Pro, dK, Ser, Cys, K(CO(CH₂)₂SH), or K(W);
- Xaa₂₉ is: Lys, Ser, Arg, Asn, hR, Ala, Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Gln, Thr, Val, Trp, Tyr, Cys, Orn, Cit, Aib, K(W), K(CO(CH₂)₂SH), or is absent;
- 30 Xaa₃₀ is: Arg, Lys, Ile, Ala, Asp, Glu, Phe, Gly, His, Leu, Met, Asn, Pro, Gln, Ser, Thr, Val, Trp, Tyr, Cys, hR, Cit, Aib, Orn, K(W), K(CO(CH₂)₂SH), or is absent;
- Xaa₃₁ is: Tyr, His, Phe, Thr, Cys, Ser, Lys, Gln, K(W), K(CO(CH₂)₂SH), or is absent;

Xaa₃₂ is: Ser, Cys, Lys, or is absent;

Xaa₃₃ is: Trp, or is absent;

Xaa₃₄ is: Cys or is absent;

Xaa₃₅ is: Glu or is absent;

5 Xaa₃₆ is: Pro or is absent;

Xaa₃₇ is: Gly or is absent;

Xaa₃₈ is: Trp or is absent;

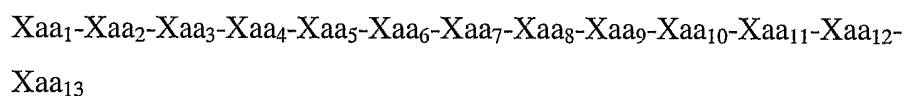
Xaa₃₉ is: Cys or is absent; and

Xaa₄₀ is: Arg or is absent

10 provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆, Xaa₃₇, Xaa₃₈, or Xaa₃₉ is absent, the next amino acid present downstream is the next amino acid in the peptide agonist sequence,

and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the peptide of Formula 10 and wherein the C-terminal

15 extension comprises an amino acid sequence of the formula:



Formula 17 (SEQ ID NO: 29)

wherein:

20 Xaa₁ is: Gly, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₂ is: Gly, Arg, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₃ is: Pro, Thr, Ser, Ala, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₄ is: Ser, Pro, His, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₅ is: Ser, Arg, Thr, Trp, Lys, Cys, K(W), K(CO(CH₂)₂SH), or absent;

25 Xaa₆ is: Gly, Ser, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₇ is: Ala, Asp, Arg, Glu, Lys, Gly, Cys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₈ is: Pro, Ser, Ala, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₉ is: Pro, Ser, Ala, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₁₀ is: Pro, Ser, Ala, Arg, Lys, His, Cys, K(W), K(CO(CH₂)₂SH), or absent;

30 Xaa₁₁ is: Ser, Cys, His, Pro, Lys, Arg, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₁₂ is: His, Ser, Arg, Lys, Cys, K(W), K(CO(CH₂)₂SH), or absent; and

Xaa₁₃ is: His, Ser, Arg, Lys, Cys, K(W), K(CO(CH₂)₂SH), or absent;

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provided that at least five of Xaa₁ to Xaa₁₃ of the C-terminal extension are present and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, or Xaa₁₂ is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated,

5 and wherein;

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

10 at least one of the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to a PEG molecule, or

15 the carboxy-terminal amino acid of the peptide agonist is covalently attached to a PEG molecule, or a combination thereof.

Preferably, at least six of Xaa₁ to Xaa₁₃ of the C-terminal extension are present. More preferably at least seven, eight, nine, ten, eleven, twelve or all of Xaa₁ to Xaa₁₃ of the C-terminal extension are present.

20 It is preferable that the C-terminal extension has no more than three of any one of the following; Cys, Lys, K(W) or K(CO(CH₂)₂SH). It is more preferable that the C-terminal extension has no more than two of any of these residues. It is even more preferable that the C-terminal extension has no more than one of any of these residues. If there is only one Cys residue in the C-terminal extension, it is preferred that the Cys residue is at the C-terminus.

25 Preferably, the VPAC2 receptor peptide agonist comprises a sequence of the formula:

Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Thr-Xaa₈-Xaa₉-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃-
Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Xaa₂₃-Xaa₂₄-
Xaa₂₅-Xaa₂₆-Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁-Xaa₃₂

30 Formula 12 (SEQ ID NO: 20)

wherein:

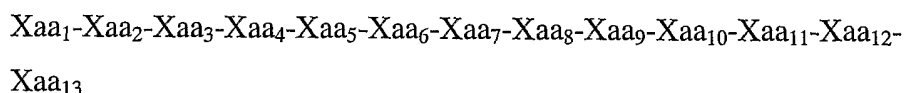
Xaa₁ is: His, dH, or is absent;

- Xaa₂ is: dA, Ser, Val, Gly, Thr, Leu, dS, Pro, or Aib;
Xaa₃ is: Asp or Glu;
Xaa₄ is: Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, Gly, dA, Aib, or NMeA;
Xaa₅ is: Val, Leu, Phe, Ile, Thr, Trp, Tyr, dV, Aib, or NMeV;
5 Xaa₆ is: Phe, Ile, Leu, Thr, Val, Trp, or Tyr;
Xaa₈ is: Asp, Glu, Ala, Lys, Leu, Arg, or Tyr;
Xaa₉ is: Asn, Gln, Glu, Ser, Cys, or Lys;
Xaa₁₀ is: Tyr, Trp, Tyr(OMe), Ser, Cys, or Lys;
Xaa₁₂ is: Arg, Lys, hR, Orn, Aib, Cit, Ala, Leu, Gln, Phe, Ser, or Cys;
10 Xaa₁₃ is: Leu, Phe, Glu, Ala, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH);
Xaa₁₄ is: Arg, Leu, Lys, Ala, hR, Orn, Phe, Gln, Aib, Cit, Ser, or Cys;
Xaa₁₅ is: Lys, Ala, Arg, Glu, Leu, hR, Orn, Phe, Gln, Aib, K(Ac), Cit, Ser, Cys, or K(W);
Xaa₁₆ is: Gln, Lys, Ala, hR, Orn, Cit, Ser, Cys, or K(CO(CH₂)₂SH);
Xaa₁₇ is: Val, Ala, Leu, Ile, Met, Nle, Lys, Aib, Ser, Cys, or K(CO(CH₂)₂SH);
15 Xaa₁₈ is: Ala, Ser, Cys, or Lys;
Xaa₁₉ is: Ala, Gly, Leu, Ser, Cys, Lys, or K(CO(CH₂)₂SH);
Xaa₂₀ is: Lys, Gln, hR, Arg, Ser, Orn, Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac),
Cit, or Cys;
Xaa₂₁ is: Lys, Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, or Cys;
20 Xaa₂₂ is: Tyr, Trp, Phe, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, Cys, or Lys;
Xaa₂₃ is: Leu, Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, Cys, or Lys;
Xaa₂₄ is: Gln, Asn, Ser, Cys, Lys, or K(CO(CH₂)₂SH);
Xaa₂₅ is: Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, Lys, or
K(CO(CH₂)₂SH);
25 Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, Phe, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH);
Xaa₂₇ is: Lys, hR, Arg, Gln, Orn, dK, Ser, or Cys;
Xaa₂₈ is: Asn, Gln, Lys, Arg, Aib, Orn, hR, Cit, Pro, dK, Ser, Cys, or K(CO(CH₂)₂SH);
Xaa₂₉ is: Lys, Ser, Arg, Asn, hR, Orn, Cit, Aib, Cys, or is absent;
Xaa₃₀ is: Arg, Lys, Ile, hR, Cit, Aib, Orn, Ser, Cys, or is absent;
30 Xaa₃₁ is: Tyr, His, Phe, Lys, Ser, Cys, Gln, or is absent; and
Xaa₃₂ is: Cys, Ser, Lys, or is absent;

provided that if Xaa₂₉, Xaa₃₀, or Xaa₃₁ is absent, the next amino acid present downstream is the next amino acid in the peptide agonist sequence,

and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the peptide of Formula 12 and wherein the C-terminal

5 extension comprises an amino acid sequence of the formula:



Formula 11 (SEQ ID NO: 19)

wherein:

- 10 Xaa₁ is: Gly, Cys, Lys, or absent;
Xaa₂ is: Gly, Arg, Cys, Lys, or absent;
Xaa₃ is: Pro, Thr, Ser, Ala, Cys, Lys, or absent;
Xaa₄ is: Ser, Pro, His, Cys, Lys, or absent;
Xaa₅ is: Ser, Arg, Thr, Trp, Lys, Cys, or absent;
15 Xaa₆ is: Gly, Ser, Cys, Lys, or absent;
Xaa₇ is: Ala, Asp, Arg, Glu, Lys, Gly, Cys, or absent;
Xaa₈ is: Pro, Ser, Ala, Cys, Lys, or absent;
Xaa₉ is: Pro, Ser, Ala, Cys, Lys, or absent;
Xaa₁₀ is: Pro, Ser, Ala, Arg, Lys, His, Cys, or absent;
20 Xaa₁₁ is: Ser, Cys, His, Pro, Lys, Arg, or absent;
Xaa₁₂ is: His, Ser, Arg, Lys, Cys, or absent; and
Xaa₁₃ is: His, Ser, Arg, Lys, Cys, or absent;

provided that at least five of Xaa₁ to Xaa₁₃ of the C-terminal extension are present and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁,
25 or Xaa₁₂ is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated,

and wherein:

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

30 at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the $K(CO(CH_2)_2SH)$ in the peptide agonist is covalently attached to a PEG molecule, or

the $K(W)$ in the peptide agonist is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid of the peptide agonist is covalently attached to a PEG molecule, or a combination thereof.

Preferably, at least six of Xaa_1 to Xaa_{13} of the C-terminal extension are present. More preferably at least seven, eight, nine, ten, eleven, twelve or all of Xaa_1 to Xaa_{13} of the C-terminal extension are present.

The VPAC2 receptor peptide agonist preferably comprises a sequence of the formula:

His- Xaa_2 - Xaa_3 - Xaa_4 - Xaa_5 -Phe-Thr- Xaa_8 - Xaa_9 - Xaa_{10} -Thr- Xaa_{12} - Xaa_{13} -
 Xaa_{14} - Xaa_{15} - Xaa_{16} - Xaa_{17} - Xaa_{18} - Xaa_{19} - Xaa_{20} - Xaa_{21} - Xaa_{22} - Xaa_{23} - Xaa_{24} -
 Xaa_{25} - Xaa_{26} - Xaa_{27} - Xaa_{28} - Xaa_{29} - Xaa_{30} - Xaa_{31}

Formula 13 (SEQ ID NO: 21)

wherein:

Xaa_2 is: dA, Ser, Val, dS, or Aib;

Xaa_3 is: Asp or Glu;

Xaa_4 is: Ala, dA, or Aib;

Xaa_5 is: Val, Leu, dV, or Aib;

Xaa_6 is: Asp, Glu, or Ala;

Xaa_9 is: Asn, Gln, Glu, Ser, Cys, or Lys;

Xaa_{10} is: Tyr, or Tyr(OMe);

Xaa_{12} is: Ala, Arg, Lys, hR, Orn, Ser, or Cys;

Xaa_{13} is: Leu, Ser, Cys, Lys, or $K(CO(CH_2)_2SH)$;

Xaa_{14} is: Arg, Leu, Lys, Ala, hR, Orn, Phe, Gln, Aib, Cit, Ser, or Cys;

Xaa_{15} is: Lys, Ala, Arg, Leu, Orn, Phe, Gln, Aib, K(Ac), Ser, Cys, or $K(W)$;

Xaa_{16} is: Gln, Lys, Ser, Cys, or $K(CO(CH_2)_2SH)$;

Xaa_{17} is: Val, Ala, Leu, Ile, Met, Nle, Lys, Ser, Cys, or $K(CO(CH_2)_2SH)$;

Xaa_{18} is: Ala, Ser, Cys, or Lys;

Xaa_{19} is: Ala, Leu, Ser, Cys, Lys, or $K(CO(CH_2)_2SH)$;

Xaa_{20} is: Lys, Gln, hR, Arg, Ser, Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), or Cys;

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Xaa₂₁ is: Lys, Arg, Ala, Phe, Aib, Leu, Gln, K(Ac), Orn, Ser, or Cys;

Xaa₂₂ is: Tyr, Trp, Phe, Leu, Ile, Val, Ser, Cys, Lys, or Tyr(OMe);

Xaa₂₃ is: Leu, Ser, Cys, or Lys;

Xaa₂₄ is: Gln, Asn, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

5 Xaa₂₅ is: Ser, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, Phe, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₂₇ is: Lys, hR, Arg, dK, Orn, Ser, or Cys;

Xaa₂₈ is: Asn, Gln, Lys, hR, Aib, Orn, dK, Pro, Ser, Cys, or K(CO(CH₂)₂SH);

10 Xaa₂₉ is: Lys, Ser, Arg, hR, Orn, Cys, or is absent;

Xaa₃₀ is: Arg, Lys, hR, Ser, Cys, or is absent;

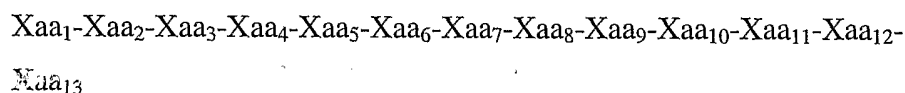
Xaa₃₁ is: Tyr, Phe, Lys, Ser, Cys, or is absent; and

Xaa₃₂ is: Cys, Ser, Lys, or is absent;

provided that if Xaa₂₉, Xaa₃₀, or Xaa₃₁ is absent, the next amino acid present

15 downstream is the next amino acid in the peptide agonist sequence,

and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the peptide of Formula 13 and wherein the C-terminal extension comprises an amino acid sequence of the formula:



Formula 11 (SEQ ID NO: 19)

wherein:

Xaa₁ is: Gly, Cys, Lys, or absent;

Xaa₂ is: Gly, Arg, Cys, Lys, or absent;

25 Xaa₃ is: Pro, Thr, Ser, Ala, Cys, Lys, or absent;

Xaa₄ is: Ser, Pro, His, Cys, Lys, or absent;

Xaa₅ is: Ser, Arg, Thr, Trp, Lys, Cys, or absent;

Xaa₆ is: Gly, Ser, Cys, Lys, or absent;

Xaa₇ is: Ala, Asp, Arg, Glu, Lys, Gly, Cys, or absent;

30 Xaa₈ is: Pro, Ser, Ala, Cys, Lys, or absent;

Xaa₉ is: Pro, Ser, Ala, Cys, Lys, or absent;

Xaa₁₀ is: Pro, Ser, Ala, Arg, Lys, His, Cys, or absent;

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Xaa₁₁ is: Ser, Cys, His, Pro, Lys, Arg, or absent;

Xaa₁₂ is: His, Ser, Arg, Lys, Cys, or absent; and

Xaa₁₃ is: His, Ser, Arg, Lys, Cys, or absent;

provided that at least five of Xaa₁ to Xaa₁₃ of the C-terminal extension are present
 5 and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁,
 or Xaa₁₂ is absent, the next amino acid present downstream is the next amino acid in the
 C-terminal extension and wherein the C-terminal amino acid may be amidated,

and wherein:

at least one of the Cys residues in the peptide agonist is covalently attached to a
 10 PEG molecule, or

at least one of the Lys residues in the peptide agonist is covalently attached to a
 PEG molecule, or

at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to
 a PEG molecule, or

15 the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid of the peptide agonist is covalently attached to a
 PEG molecule, or a combination thereof.

Preferably, the VPAC2 receptor peptide agonist of the present invention
 comprises a sequence of the Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20)
 20 or Formula 13 (SEQ ID NO: 21) wherein Xaa₂ is Asp or Glu, Xaa₃ is Asp or Glu, Xaa₄ is
 Arg, hR, Lys, or Orn, Xaa₁₄ is Arg, Gln, Aib, hR, Orn, Cit, Lys, Ala, or Leu, Xaa₁₅ is Lys,
 Aib, Orn, or Arg, Xaa₁₆ is Gln or Lys, Xaa₁₇ is Val, Leu, Ala, Ile, Lys, or Nle, Xaa₂₀ is
 Lys, Val, Leu, Aib, Ala, Gln, or Arg, Xaa₂₁ is Lys, Aib, Orn, Ala, Gln, or Arg, Xaa₂₇ is
 Lys, Orn, hR, or Arg, Xaa₂₈ is Asn, Gln, Lys, hR, Aib, Orn, or Pro and Xaa₂₉ is Lys, Orn,
 25 hR, or is absent.

More preferably, the VPAC2 receptor peptide agonist of the present invention
 comprises a sequence of the Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20)
 or Formula 13 (SEQ ID NO: 21) wherein Xaa₁₂ is Arg, hR, or Orn, Xaa₁₄ is Arg, Aib,
 Gln, Ala, Leu, Lys, or Orn, Xaa₁₅ is Lys or Aib, Xaa₁₇ is Val or Leu, Xaa₂₀ is Lys or Aib,
 30 Xaa₂₁ is Lys, Aib, or Gln and Xaa₂₈ is Asn or Gln.

Preferably, the VPAC2 receptor peptide agonist of the present invention
 comprises a sequence of the Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20)

or Formula 13 (SEQ ID NO: 21) wherein Xaa₃₀ and/or Xaa₃₁ are absent. Alternatively, Xaa₂₉, Xaa₃₀ and Xaa₃₁ are all absent.

Preferably, the VPAC2 receptor peptide agonist of the present invention comprises a sequence of the Formula 10 (SEQ ID NO:18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein either Xaa₁₄ or Xaa₁₅ is Aib.

Also preferably, the VPAC2 receptor peptide agonist of the present invention comprises a sequence of the Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein either Xaa₂₀ or Xaa₂₁ is Aib.

More preferably, either Xaa₁₄ or Xaa₁₅ is Aib and either Xaa₂₀ or Xaa₂₁ is Aib. It is especially preferred that Xaa₁₅ is Aib and Xaa₂₀ is Aib.

Preferably, the VPAC2 receptor peptide agonist of the present invention comprises a sequence of the Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein Xaa₂₈ is Gln and Xaa₂₉ is Lys or is absent.

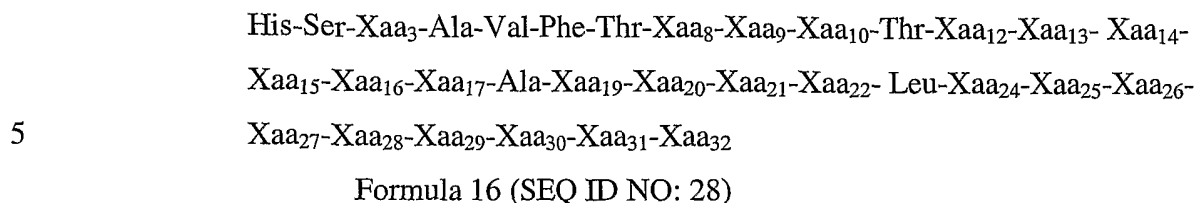
More preferably, Xaa₂₈ is Gln and Xaa₂₉ is Lys or is absent, and either Xaa₁₄ or Xaa₁₅ is Aib and either Xaa₂₀ or Xaa₂₁ is Aib.

Preferably, the VPAC2 receptor peptide agonist of the present invention comprises a sequence of the Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein Xaa₁₂ is hR or Orn, Xaa₂₇ is hR or Orn and Xaa₂₉ is hR or Orn. Alternatively, any one of Xaa₁₂, Xaa₂₇ and Xaa₂₉ may be a PEGylated Lys, Cys, K(CO(CH₂)₂SH) or K(W), whilst all the other two positions have the preferred amino acid substitutions as described.

More preferably, Xaa₁₂ is hR or Orn, Xaa₂₇ is hR or Orn and Xaa₂₉ is hR or Orn, and either Xaa₁₄ or Xaa₁₅ is Aib and either Xaa₂₀ or Xaa₂₁ is Aib.

Preferably, the VPAC2 receptor peptide agonist of the present invention comprises a sequence of the Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein Xaa₁₅ is Aib, Xaa₂₀ is Aib, and Xaa₁₂, Xaa₂₁, Xaa₂₇ and Xaa₂₈ are all Orn. More preferably, Xaa₁₅ is Aib, Xaa₂₀ is Aib, Xaa₁₂, Xaa₂₁, Xaa₂₇ and Xaa₂₈ are all Orn, Xaa₈ is Glu, Xaa₉ is Gln and Xaa₁₀ is Tyr(OMe). Alternatively, any one or more of Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₂, Xaa₁₅, Xaa₂₀, Xaa₂₁, Xaa₂₇ and Xaa₂₈ may be a PEGylated Lys, Cys, K(CO(CH₂)₂SH) or K(W), whilst all the other positions have the preferred amino acid substitutions as described.

The PEGylated VPAC2 receptor peptide agonist of the invention more preferably comprises a sequence of the formula:



Xaa₃ is: Asp, or Glu;

Xaa₈ is: Asp, or Glu;

10 Xaa₉ is: Asn, Gln, or Cys;

Xaa₁₀ is: Tyr, or Tyr(OMe);

Xaa₁₂ is: Arg, Orn, or hR;

Xaa₁₃ is: Leu, Cys, or K(CO(CH₂)₂SH);

Xaa₁₄ is: Arg, Leu, or Aib;

15 Xaa₁₅ is: Lys, Ala, Arg, Aib, or K(W);

Xaa₁₆ is: Gln, Lys, or K(CO(CH₂)₂SH);

Xaa₁₇ is: Val, Leu, Cys, or K(CO(CH₂)₂SH);

Xaa₁₉ is: Ala, Leu, Cys, or K(CO(CH₂)₂SH);

Xaa₂₀ is: Lys, Gln, Arg, Aib, or Cys;

20 Xaa₂₁ is: Lys, Arg, Aib, or Orn;

Xaa₂₂ is: Tyr, or Tyr(OMe);

Xaa₂₄ is: Gln, Cys, or K(CO(CH₂)₂SH);

Xaa₂₅ is: Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₆ is: Ile, Cys, or K(CO(CH₂)₂SH);

25 Xaa₂₇ is: Lys, Arg, Orn, or hR;

Xaa₂₈ is: Asn, hR, Orn, Cys, or K(CO(CH₂)₂SH);

Xaa₂₉ is: Orn, Lys, hR, or is absent;

Xaa₃₀ is: Arg, hR, or is absent; and

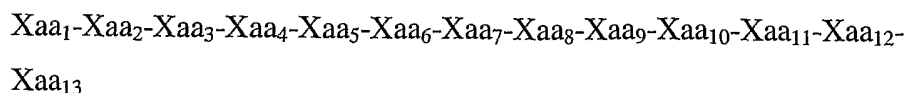
Xaa₃₁ is: Tyr, or is absent; and

30 Xaa₃₂ is: Cys, or is absent

provided that if Xaa₂₉, Xaa₃₀, or Xaa₃₁ is absent, the next amino acid present downstream is the next amino acid in the peptide agonist sequence,

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and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the peptide of Formula 16 and wherein the C-terminal extension comprises an amino acid sequence of the formula:



5

Formula 11 (SEQ ID NO: 19)

wherein:

Xaa₁ is: Gly, Cys, Lys, or absent;

Xaa₂ is: Gly, Arg, Cys, Lys, or absent;

10 Xaa₃ is: Pro, Thr, Ser, Ala, Cys, Lys, or absent;

Xaa₄ is: Ser, Pro, His, Cys, Lys, or absent;

Xaa₅ is: Ser, Arg, Thr, Trp, Lys, Cys, or absent;

Xaa₆ is: Gly, Ser, Cys, Lys, or absent;

Xaa₇ is: Ala, Asp, Arg, Glu, Lys, Gly, Cys, or absent;

15 Xaa₈ is: Pro, Ser, Ala, Cys, Lys, or absent;

Xaa₉ is: Pro, Ser, Ala, Cys, Lys, or absent;

Xaa₁₀ is: Pro, Ser, Ala, Arg, Lys, His, Cys, or absent;

Xaa₁₁ is: Ser, Cys, His, Pro, Lys, Arg, or absent;

Xaa₁₂ is: His, Ser, Arg, Lys, Cys, or absent; and

20 Xaa₁₃ is: His, Ser, Arg, Lys, Cys, or absent;

provided that at least five of Xaa₁ to Xaa₁₃ of the C-terminal extension are present and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, or Xaa₁₂ is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated,

25

and wherein:

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

30

at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to a PEG molecule, or

the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

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the carboxy-terminal amino acid of the peptide agonist is covalently attached to a PEG molecule, or a combination thereof.

Preferably, the C-terminal extension of the VPAC2 receptor peptide agonist comprises an amino acid sequence of the formula:

5 Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Xaa₇-Xaa₈-Xaa₉-Xaa₁₀-Xaa₁₁

Formula 7 (SEQ ID NO:15)

wherein:

Xaa₁ is: Gly, Cys, or absent;

Xaa₂ is: Gly, Arg, or absent;

10 Xaa₃ is: Pro, Thr, or absent;

Xaa₄ is: Ser, or absent;

Xaa₅ is: Ser, or absent;

Xaa₆ is: Gly, or absent;

Xaa₇ is: Ala, or absent;

15 Xaa₈ is: Pro, or absent;

Xaa₉ is: Pro, or absent;

Xaa₁₀ is: Pro, or absent; and

Xaa₁₁ is: Ser, Cys, or absent;

provided that at least five of Xaa₁ to Xaa₁₁ of the C-terminal extension are present
 20 and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated.

Preferably, at least six of Xaa₁ to Xaa₁₁ of the C-terminal extension are present.
 More preferably at least seven, eight, nine, ten, or all of Xaa₁ to Xaa₁₁ of the C-terminal
 25 extension are present.

More preferably, the C-terminal extension of the VPAC2 receptor peptide agonist is selected from:

SEQ ID NO: 10	GGPSSGAPPPS
SEQ ID NO: 11	GGPSSGAPPPS-NH ₂
SEQ ID NO: 22	GGPSSGAPPPC
SEQ ID NO: 23	GGPSSGAPPPC-NH ₂

SEQ ID NO: 16	GRPSSGAPPPS
SEQ ID NO: 17	GRPSSGAPPPS-NH ₂

It is especially preferred that the C-terminal extension is GGPSSGAPPPS (SEQ ID NO: 10) or GGPSSGAPPPS-NH₂ (SEQ ID NO: 11).

The PEG molecule(s) may be covalently attached to any Lys, Cys, K(W), or K(CO(CH₂)₂SH) residues at any position in the peptide agonist. In particular, the PEG molecule(s) may be covalently attached to any Lys, Cys, K(W), or K(CO(CH₂)₂SH) residue at positions 9, 13, 15, 16, 17, 18, 19, 20, 21, 24, 25, 26 and/or 28 of Formula 10, 12, 13, or 16. Alternatively, the PEG molecule(s) may be covalently attached to a residue in the C-terminal extension.

Preferably, there is at least one PEG molecule covalently attached to Xaa₂₅ or any subsequent residue in Formula 10, 12, 13, or 16.

Preferably, there is at least one PEG molecule covalently attached to a residue in the C-terminal extension of the VPAC2 receptor peptide agonist.

Any Lys residue in the VPAC2 receptor peptide agonist may be substituted for a K(W) or a K(CO(CH₂)₂SH), which may be PEGylated. In addition, any Cys residue in the peptide agonist may be substituted for a modified cysteine residue, for example, hC. The modified Cys residue may be covalently attached to a PEG molecule.

It is preferred that two of the Cys residues are each covalently attached to a PEG molecule or two of the Lys residues are each covalently attached to a PEG molecule. Alternatively, one of the Cys residues may be covalently attached to a PEG molecule or one of the Lys residues may be covalently attached to a PEG molecule.

It is preferred that there is a K(CO(CH₂)₂SH) is the VPAC2 receptor peptide agonist and that this is PEGylated.

Where there is more than one PEG molecule, there may be a combination of Lys, Cys, K(CO(CH₂)₂SH), K(W) and carboxy-terminal amino acid PEGylation. For example, if there are two PEG molecules, one may be attached to a Lys residue and one may be attached to a Cys residue.

Preferably, the PEG molecule is branched. Alternatively, the PEG molecule may be linear.

Preferably, the PEG molecule is between 1,000 daltons and 100,000 daltons in molecular weight. More preferably the PEG molecule is selected from 10,000, 20,000, 30,000, 40,000, 50,000 and 60,000 daltons. Even more preferably, it is selected from 20,000, 40,000, or 60,000. Where there are two PEG molecules covalently attached to the peptide agonist of the present invention, each is 1,000 to 40,000 daltons and preferably, they have molecular weights of 20,000 and 20,000 daltons, 10,000 and 30,000 daltons, 30,000 and 30,000 daltons, or 20,000 and 40,000 daltons.

Preferably, the VPAC2 receptor peptide agonist sequence further comprises a histidine residue at the N-terminal extension region of the peptide sequence before Xaa₁.

Preferably, the VPAC2 receptor peptide agonist of the present invention further comprises a N-terminal modification at the N-terminus of the peptide agonist wherein the N-terminal modification is selected from:

- (a) addition of D-histidine, isoleucine, methionine, or norleucine;
- (b) addition of a peptide comprising the sequence Ser-Trp-Cys-Glu-Pro-Gly-Trp-Cys-Arg (SEQ ID NO:14) wherein the Arg is linked to the N-terminus of the peptide agonist;
- (c) addition of C₁-C₁₆ alkyl optionally substituted with one or more substituents independently selected from aryl, C₁-C₆ alkoxy, -NH₂, -OH, halogen and -CF₃;
- (d) addition of -C(O)R¹ wherein R¹ is a C₁-C₁₆ alkyl optionally substituted with one or more substituents independently selected from aryl, C₁-C₆ alkoxy, -NH₂, -OH, halogen, -SH and -CF₃; an aryl or aryl C₁-C₄ alkyl optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, -NH₂, -OH, halogen and -CF₃; -NR²R³ wherein R² and R³ are independently hydrogen, C₁-C₆ alkyl, aryl or aryl C₁-C₄ alkyl; -OR⁴ wherein R⁴ is C₁-C₁₆ alkyl optionally substituted with one or more substituents independently selected from aryl, C₁-C₆ alkoxy, -NH₂, -OH, halogen and -CF₃, aryl or aryl C₁-C₄ alkyl optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, -NH₂, -OH, halogen and -CF₃; or 5-pyrrolidin-2-one;
- (e) addition of -SO₂R⁵ wherein R⁵ is aryl, aryl C₁-C₄ alkyl or C₁-C₁₆ alkyl;
- (f) formation of a succinimide group optionally substituted with C₁-C₆ alkyl or -SR⁶, wherein R⁶ is hydrogen or C₁-C₆ alkyl;

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- (g) addition of methionine sulfoxide;
- (h) addition of biotinyl-6-aminohexanoic acid (b-aminocaproic acid); and
- (i) addition of $-C(=NH)-NH_2$.

5 Preferably, the N-terminal modification is the addition of a group selected from: acetyl, propionyl, butyryl, pentanoyl, hexanoyl, methionine, methionine sulfoxide, 3-phenylpropionyl, phenylacetyl, benzoyl, norleucine, D-histidine, isoleucine, γ -mercaptopropionyl, biotinyl-6-aminohexanoic acid, and $-C(=NH)-NH_2$, and more preferably is the addition of acetyl or hexanoyl. It is especially preferred that the N-
10 terminal modification is the addition of hexanoyl.

It will be appreciated by the person skilled in the art that PEGylated VPAC2 receptor peptide agonists comprising various combinations of peptide sequence according to Formula 10, 12, 13 or 16, C-terminal extensions and N-terminal modifications as described herein, may be made based on the above disclosure.

15 The following VPAC2 receptor peptide agonists may be PEGylated:

Agonist #	SEQ ID NO	Sequence
P6	30	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P7	31	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRGGT
P8	32	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRGGT
P9	33	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKKGGPSSGAPP PS
P18	34	HSDAVFTDNYTRLRKQVAAhRKYLQSIKNKRYGGPSSGA PPPS
P19	35	HSDAVFTDNYTRLRKQVAAIKYLQSIKNKRYGGPSSGAP PPS
P20	36	HSDAVFTDNYTRLRKQVAARKYLQSIKNKRYGGPSSGA PPPS
P21	37	HSDAVFTDNYTRLRKQVAASKYLQSIKNKRYGGPSSGAP PPS
P22	38	HSDAVFTDNYTRLRKQVAAKKYLQSIhRNKRYGGPSSGA PPPS
P23	39	HSDAVFTDNYTRLRKQVAAKKYLQSIrNKRYGGPSSGA PPPS
P24	40	HSDAVFTDNYTRLRKQVAAKKYLQSIKNhRRYGGPSSGA PPPS

P25	41	HSDAVFTDNYTRLRKQVAAKKYLQSIKNRRYGGPSSGA PPPS
P26	42	HSDAVFTDNYTRFRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P27	43	HSDAVFTDNWTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P28	44	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRHGGPSSGA PPPS
P29	45	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRQGGPSSGA PPPS
P31	46	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P33	47	Ac- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P34	48	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRF
P37	49	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYC
P43	50	HGDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P44	51	HVDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P45	52	HTDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P46	53	HLDVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P47	54	HdADAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P48	55	HdSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P49	56	HPDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P50	57	HSDIVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P51	58	HSDYVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P52	59	HSDFVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P53	60	HSDVVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P54	61	HSDTVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P55	62	HSDLVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P56	63	HSDWVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS

P58	64	HSDAFFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P60	65	HSDAIFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P61	66	HSDALFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P62	67	HSDATFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P63	68	HSDAVITDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P64	69	HSDAVLTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P65	70	HSDAVTTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P66	71	HSDAVVTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P67	72	HSDAVWTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P68	73	HSDAVYTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P69	74	HSDAWFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P70	75	HSDAYFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P71	76	HSDAVFTDNYTRLRRQVAARRYLQSIRNRRYGGPSSGAP PPS
P72	77	HSDAVFTDNYTRLRRQVAAKKYLQSIKNKRYGGPSSGA PPPS
P73	78	HSDAVFTDNYTRLRKQVAARKYLOSIKNKRYGGPSSGA PPPS
P74	79	HSDAVFTDNYTRLRKQVAAKKYLQSIQNKRYGGPSSGA PPPS
P75	80	HSDAVFTDNYTRLRKQVAAKKYLQSIKNNRYGGPSSGA PPPS
P76	81	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKIYGGPSSGAP PPS
P82	82	HSDAVFTDNYTRLRKQVAAKKYLQSIKRGGPSSGAPPPS
P83	83	HSDAVFTDNYTRLRKQVAAKKYLQSIKNGGPSSGAPPPS
P84	84	dHSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P85	85	HSDAVFTDNYTRLRKQVAAKKYLQSIKKGPSSGAPPPS
P87	86	HSDAVFTDNYTREKEKVAKKYLQSIKNKRYGGPSSGA PPPS
P88	87	HSDAVFTDNYTRAAKVAKKYLQSIKNKRYGGPSSGA PPPS
P89	88	HSDAVFTDNYTRLLAKVAKKYLQSIKNKRYGGPSSGA PPPS

P92	89	HSDAVFTDNYTRLRKQVAAKKYLQSIKNGRPSSGAPPPS
P93	90	HSDAVFTDNYTRLLKVAACKYLQSIKNKRYGGPSSGAPPPS
P94	91	HSDAVFTDNYTRAKAKVAAKKYLQSIKNKRYGGPSSGAPPPS
P98	92	C6- HSDAVFTDNYTRLRRQVAARRYLSIRNRRYGGPSSGAPPPS
P99	93	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPS
P100	94	M- HSDAVFTDQYTRLRKQVAAKKYLQSIKQKRYGGPSSGAPPPS
P101	95	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPS
P102	96	HSDGVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPS
P103	97	C6- HSDAVFTDNYTKLKKQVAAKKYLQSIKNKRYGGPSSGAPPPS
P104	98	M- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPS
P105	99	I- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPS
P106	100	C6- HSDAVFTDNYTRLRKQVAAKKYLQSFKNKRYGGPSSGAPPPS
P107	101	C6- HSDAVFTDNYTRLRKQVAAKKYLQSLKNKRYGGPSSGAPPPS
P108	102	C6- HSDAVFTDNYTRLRKQVAAKKYLQSTKNKRYGGPSSGAPPPS
P109	103	C6- HSDAVFTDNYTRLRKQVAAKKYLQSVKNKRYGGPSSGAPPPS
P110	104	C6- HSDAVFTDNYTRLRKQVAAKKYLQSWKNKRYGGPSSGAPPPS
P111	105	C6- HSDAVFTDNYTRLRKQVAAKKYLQSYKNKRYGGPSSGAPPPS

P112	106	C6- HSDAVFTDNYTRLRKQVAAKKYLQFIKNKRYGGPSSGA PPPS
P113	107	C6- HSDAVFTDNYTRLRKQVAAKKYLQIIKNKRYGGPSSGAP PPS
P114	108	C6- HSDAVFTDNYTRLRKQVAAKKYLQLIKNKRYGGPSSGA PPPS
P115	109	C6- HSDAVFTDNYTRLRKQVAAKKYLQTIKNKRYGGPSSGA PPPS
P116	110	C6- HSDAVFTDNYTRLRKQVAAKKYLQVIKNKRYGGPSSGA PPPS
P117	111	C6- HSDAVFTDNYTRLRKQVAAKKYLQWIKNKRYGGPSSGA PPPS
P119	112	C6- HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAP PPS
P120	113	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPC
P121	114	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKKGGPSSGAPP PS
P122	115	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNSROGPSSGAPP PS
P123	116	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRGGPSSGAPP PS
P124	117	C6- HSDAVFTDNYTRLRKQVAAKKYLQQIKNKRYGGPSSGA PPPS
P125	118	C6- HSDAVFTDNYTRLRKQVAAKKYLQNIKNKRYGGPSSGA PPPS
P126	119	HSDAVFTDNYTRLRKQVAAKKYLQSIKRGPSSGAPPPS
P127	120	C6- HSDAVFTDNYTRLRKQVAAKKYLQYIKNKRYGGPSSGA PPPS
P129	121	C6- HSDAVFTDNYTRLRKQVAAKKWLQSIKNKRYGGPSSGA PPPS

P130	122	C6- HSDAVFTDNYTRLRKQVAAKKFLQSIKNKRYGGPSSGAP PPS
P131	123	C6- HSDAVFTDNYTRLRKQVAAKKTLQSIKNKRYGGPSSGAP PPS
P132	124	C6- HSDAVFTDNYTRLRKQVAAKKLLQSIKNKRYGGPSSGAP PPS
P133	125	C6- HSDAVFTDNYTRLRKQVAAKKILQSIKNKRYGGPSSGAP PPS
P134	126	C6- HSDAVFTDNYTRLRKQVAAKKVLQSIKNKRYGGPSSGA PPPS
P135	127	C6- HSDAVFTDNYTRLLAKVAAKKYLQSIKNKRYGGPSSGA PPPS
P138	128	C6- HSDAVFTDNYTRLRAQVAAQKYLQSIKNKRYGGPSSGA PPPS
P139	129	C6- HSDAVFTDNYTRLRAQVAAKKYLQSIKNKRYGGPSSGA PPPS
P140	130	M- HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAP PPS
P141	131	C6- HSDAVFTDNYTRLKAQVAAKKYLOSINKKRYGGPSSGA PPPS
P142	132	C6- HSDAVFTDNYTRLRAQLAAQKYLQSIKNKRYGGPSSGAP PPS
P143	133	C6- HSDAVFTDNYTRLRKQMAAQKYLNQLKKGGPSSGAPPP S
P144	134	C6- HSDAVFTDNYTRLRKQVAAQKYLNQLKKGGPSSGAPPP S
P146	135	C6- HSDAVFTDNYTRLRKQVAAVKYLQSIKNKRYGGPSSGA PPPS
P147	136	C6- HSDAVFTDNYTRLRKQVAAKYQYLQSIKNKRYGGPSSGA PPPS

P148	137	C6- HSDAVFTDNYTRLRKQVA AFKYLQSIKNKRYGGPSSGAP PPS
P149	138	C6- HSDAVFTDNYTRLRKQVA AIKYLQSIKNKRYGGPSSGAP PPS
P150	139	C6- HSDAVFTDNYTRLRKQVA AQKYLQSIKNKRYGGPSSGA PPPS
P151	140	C6- HSDAVFTDNYTRLRKQVA ALKYLQSIKNKRYGGPSSGAP PPS
P152	141	C6- HSDAVFTDNYTRLRKQVA ATKYLQSIKNKRYGGPSSGAP PPS
P153	142	C6- HSDAVFTDNYTRLRKQVA AWKYLQSIKNKRYGGPSSGA PPPS
P154	143	C6- HSDAVFTDNYTRLRKQVA AKKYLQSIKNGGPSSGAPPPS
P155	144	C6- HSDAVFTDNYTRLRKQVA LKKYLQSIKNKRYGGPSSGAP PPS
P158	145	C6- HSDAVFTANYTRLRKQVA AKKYLQSIKNKRYGGPSSGA PPPS
P159	146	C6- HSDAVFTENYTRLRKQVA AKKYLQSIKNKRYGGPSSGAP PPS
P160	147	C6- HSDAVFTKNYTRLRKQVA AKKYLQSIKNKRYGGPSSGA PPPS
P161	148	C6- HSDAVFTLNYTRLRKQVA AKKYLQSIKNKRYGGPSSGAP PPS
P162	149	C6- HSDAVFTRNYTRLRKQVA AKKYLQSIKNKRYGGPSSGA PPPS
P163	150	C6- HSDAVFTYNYTRLRKQVA AKKYLQSIKNKRYGGPSSGA PPPS
P164	151	C6- HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAP PPC
P165	152	C6- HSDAVFTEEYTRLQKQVA AKQYLQSIKNKRYGGPSSGAP PPS

P166	153	C6- HAibDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P167	154	C6- HSDAVFTDNYTRLAibKQVAAKKYLQSIKNKRYGGPSSG APPPS
P168	155	C6- HSDAVFTDNYTRLRAibQVAAKKYLQSIKNKRYGGPSSG APPPS
P169	156	C6- HSDAVFTDNYTRLRKQVAAaibKYLQSIKNKRYGGPSSG APPPS
P170	157	C6- HSDAVFTDNYTRLRKQVAAKAibYLQSIKNKRYGGPSSG APPPS
P171	158	C6- HSDAVFTDNYTRLKKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P172	159	C6- HSDAVFTDNYTRLQKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P173	160	C6- HSDAVFTDNYTRLAKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P174	161	C6- HSDAVFTDNYTRLLKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P175	162	C6- HSDAVFTDNYTRLFKQVAAKKYLQSIKNKRYGGPSSGAP PPPS
P176	163	C6- HSDAVFTDNYTRLRRQVAAKKYLQSIKNKRYGGPSSGA PPPS
P177	164	C6- HSDAVFTDNYTRLRQQVAAKKYLQSIKNKRYGGPSSGA PPPS
P179	165	C6- HSDAVFTDNYTRLRLQVAAKKYLQSIKNKRYGGPSSGAP PPS
P180	166	C6- HSDAVFTDNYTRLRFQVAAKKYLQSIKNKRYGGPSSGAP PPS
P181	167	C6- HSDAVFTDNYTRLRKQVAAAKYLQSIKNKRYGGPSSGA PPPS

P182	168	C6- HSDAVFTDNYTRLRKQVAAKRYLQSIKNKRYGGPSSGA PPPS
P183	169	C6- HSDAVFTDNYTRLRKQVAAKQYLQSIKNKRYGGPSSGA PPPS
P184	170	C6- HSDAVFTDNYTRLRKQVAAKAYLQSIKNKRYGGPSSGA PPPS
P185	171	C6- HSDAVFTDNYTRLRKQVAAKLYLQSIKNKRYGGPSSGAP PPS
P186	172	C6- HSDAVFTDNYTRLRKQVAAKFYLQSIKNKRYGGPSSGAP PPS
P187	173	C6- HSDAVFTDNYTRLRKQVAAKKYLQAibIKNKRYGGPSSG APPPS
P188	174	C6- HSDAVFTDNYTRLRKQVAAKKYLQSAibKNKRYGGPSSG APPPS
P189	175	C6- HSDAVFTDNYTRLRKQAibAAKKYLQSIKNKRYGGPSSG APPPS
P191	176	C6- HHSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGA PPPS
P192	177	C6- HSDAVFTDQYTRLLAKLALQKYLQSIKNKRYGGPSSGAP PPS
P193	178	C6- HSDAVFTDNYTRLRK(Ac)QVAAK(Ac)KYLQSIKNKRYG GPSSGAPPPS
P194	179	C6- HSDAVFTDNYTRLRK(Ac)QVAAK(Ac)YLQSIKNKRYG GPSSGAPPPS
P195	180	C6- HSDAVFTDNYTRLLAQLALQKYLQSIKNKRYGGPSSGAP PPS
P196	181	C6- HSDAVFTDNYTRLLAKVALQKYLQSIKNKRYGGPSSGAP PPS
P197	182	C6- HSDAVFTDNYTRLLAKLAAQKYLQSIKNKRYGGPSSGAP PPS

P198	183	C6- HSDAVFTDNYTRLAKLALQKYLQSIKNKGGPSSGAPPP C
P199	184	Met(O)- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P203	185	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRFGGPSSGAP PPS
P205	186	HS(CH ₂) ₂ CO- HSDAVFTDNYTRLAKLALQKYLQSIKNKRYGGPSSGAP PPS
P206	187	HS(CH ₂) ₂ CO- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P207	188	C6- HSDdAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P208	189	C6- HSDNMeAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPS SGAPPPS
P209	190	C6- HSDAibVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P210	191	C6- HSDAdVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P211	192	C6- HSDANMeVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPS SGAPPPS
P212	193	C6- HSDAAibFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P213	194	C6- HSDAVFTDNYTRLRKQVAAKRYLQSIRNGGPSSGAPPPS
P214	195	C6- HSDAVFTDNYTRLRKQVAARRYLQSIRNGGPSSGAPPPS
P215	196	C6- HSDAVFTDNYTRLRRQVAAKRYLQSIRNGGPSSGAPPPS
P216	197	C6- HSDAVFTDNYTRLRRQVAARKYLQSIRNGGPSSGAPPPS
P220	198	C6- HSDAVFTDQYTRLRRQVAARKYLQSIRQGGPSSGAPPPS
P221	199	C6- HSDIVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS

P222	200	C6- HGEFTFDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P223	201	C6- HSDLVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P224	202	C6- HSEAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P226	203	C6- HSDAVFTDNY(OMe)TRLRKQVAAKKYLQSIKNKRYGGP SSGAPPPS
P227	204	C6- HSDAVFTDNYTRLRKQVAAKKY(OMe)LQSIKNKRYGGP SSGAPPPS
P228	205	C6- HSDAVFTDNYTRLRKQVAAKKAibLQSIKNKRYGGPSSG APPPS
P229	206	C6- HSDAVFTDNYTRLRKQVAAKKALQSIKNKRYGGPSSGA PPPS
P230	207	C6- HSDAVFTDNYTRLRKQVAAKKYWQSIKNKRYGGPSSGA PPPS
P231	208	C6- HSDAVFTDNYTRLRKQVAAKKYFQSIKNKRYGGPSSGA PPPS
P232	209	C6- HSDAVFTDNYTRLRKQVAAKKYTQSIKNKRYGGPSSGA PPPS
P233	210	C6- HSDAVFTDNYTRLRKQVAAKKYIQSIKNKRYGGPSSGAP PPS
P234	211	C6- HSDAVFTDNYTRLRKQVAAKKYVQSIKNKRYGGPSSGA PPPS
P235	212	C6- HSDAVFTDNYTRLRKQVAAKKYAQSIKNKRYGGPSSGA PPPS
P236	213	C6- HSDAVFTDNYTRLRKQVAAKKYAibQSIKNKRYGGPSSG APPPS
P240	214	C6- HSDAVFTDNYTRLAibKQLAAaibKYLQSIKNKRYGGPSS GAPPPS

P241	215	C6- HSDAVFTDNYTRLAibKQLAAKAibYLQSIKNKRYGGPSS GAPPPS
P242	216	C6- HSDAVFTDNYTRLAibKQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P243	217	C6- HSDAVFTDNYTRLAibKQVAAQKYLQSIKNKRYGGPSSG APPPS
P244	218	C6- HSDAVFTDNYTRLAibKQVAAKAibYLQSIKNKRYGGPSS GAPPPS
P249	219	C6- HSDAVFTDNYTRLAibKQVAAKQYLQSIKNKRYGGPSSG APPPS
P250	220	C6- HSDAVFTDNYTRLQKQVAAAibKYLQSIKNKRYGGPSSG APPPS
P251	221	C6- HSDAVFTDNYTRLQKQVAAKAibYLQSIKNKRYGGPSSG APPPS
P252	222	C6- HSDAVFTDNYTRLQKQVAAQKYLQSIKNKRYGGPSSGA PPPS
P253	223	C6- HSDAVFTDNYTRLQKQVAAKQYLQSIKNKRYGGPSSGA PPPS
P258	224	C6- HSDAVFTDNYTRLQAibQVAAKKYLQSIKNKRYGGPSSG APPPS
P259	225	C6- HSDAVFTDNYTRLAibKQVAALKYLQSIKNKRYGGPSSG APPPS
P260	226	C6- HSDAVFTDNYTRLAibKQVAAAKYLQSIKNKRYGGPSSG APPPS
P261	227	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P262	228	C6- HSDAVFTDNYTRLRAibQVAAVKYLQSIKNKRYGGPSSG APPPS
P263	229	C6- HSDAVFTDNYTRLRAibQVAAAKYLQSIKNKRYGGPSSG APPPS

P264	230	C6- HSDAVFTDNYTRLRAibQVAAKAibYLQSIKNKRYGGPSS GAPPPS
P265	231	C6- HSDAVFTDNYTRLRAibQVAALKYLQSIKNKRYGGPSSG APPPS
P269	232	C6- HSDAVFTDNYTRLAibKQVAAVKYLQSIKNKRYGGPSSG APPPS
P270	233	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKQKGGPSSGAPPP S
P271	234	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNGRPSSGAPPPS
P275	235	C6- HSDAVFTDNYTRLRKQVAGKKYLQSIKNKRYGGPSSGA PPPS
P282	236	C6- HSDAVFTDNYTRLAibKQVAAAibKYLQSIKNKRYGGPSS GAPPPC-NH ₂
P284	237	C6- HSDAVFTDNYTRLRAibQLAAKAibYLQSIKNKRYGGPSS GAPPPS
P285	238	C6- HSDAVFTDNYTRLRAibQVAAKAibYLQSIKNKRYGGPSS GAPPPC-NH ₂
P289	239	C6- HSDALFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P290	240	C6- HSDAVFTDNYTRLRKQLAAKKYLQSIKNKRYGGPSSGAP PPS
P291	241	C6- HSDAVFTDNYTRLRAibQLAAAibKYLQSIKNKRYGGPSS GAPPPS
P292	242	C6- HSDAVFTDNYTRLRAibQLAAAibKYLQSIKNKGGPSSGA PPPS
P293	243	C6- HSDAVFTDNYTRLAibKQVAAAibKYLQSIKQKGGPSSGA PPPS
P294	244	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKQKGGPSSGA PPPS
P295	245	C6- HSDAVFTDNYTRLRAibQVAAKAibYLQSIKQKGGPSSGA PPPS

P296	246	C6- HSDAVFTDNYTRLAibKQVAAAibKYLQSIKQGGPSSGAP PPS
P297	247	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKQGGPSSGAP PPS
P298	248	C6- HSDAVFTDNYTRLRAibQVAAKAibYLQSIKQGGPSSGAP PPS
P299	249	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKNKRYGGPSS GAPPPC-NH ₂
P301	250	C6- HSDAVFTDNYTRLAAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P302	251	C6- HSDAVFTDNYTRLQAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P305	252	C6- HSDAVFTDNYTRLhRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P307	253	C6- HSDAVFTDNYTRLROmQVAAKKYLQSIKNKRYGGPSSG APPPS
P308	254	C6- HSDAVFTDNYTRLhROmQVAAKKYLQSIKNKRYGGPSS GAPPPS
P314	255	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P315	256	C6- HSDAVFTDQYTRLRAibQVAAAibKYLQSIKQKRYGGPSS GAPPPS
P316	257	C6- HSDAVFTDNYTRLhRAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P317	258	C6- HSDAVFTDNYTRLAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P318	259	C6- HSDAVFTDNYTRLKAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P319	260	C6- HSDAVFTDNYTRLomAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS

P320	261	C6- HSDAVFTDNYTRLCitAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P321	262	C6- HSDAVFTDNYTRLRAibKVAAAibKYLQSIKNKRYGGPSS GAPPPS
P322	263	C6- HSDAVFTDNYTRLRAibQIAAAibKYLQSIKNKRYGGPSSG APPPS
P323	264	C6- HSDAVFTDNYTRLRAibQKAAAibKYLQSIKNKRYGGPSS GAPPPS
P324	265	C6- HSDAVFTDNYTRLRAibQAAAAibKYLQSIKNKRYGGPSS GAPPPS
P325	266	C6- HSDAVFTDNYTRLRAibQNleAAAibKYLQSIKNKRYGGPS SGAPPPS
P326	267	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSIOrnNOmGGP SSGAPPPS
P327	268	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSIOrnNOmGGP SSGAPPPC-NH ₂
P329	269	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRGGPSS GAPPPS
P330	270	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRGGPSS GAPPPC-NH ₂
P332	271	HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRhRGGPSSG APPPS
P333	272	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRhRGGPSSG APPPC-NH ₂
P335	273	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSIhRhRGGPSS GAPPPS
P336	274	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSIhRhRGGPSS GAPPPC-NH ₂
P338	275	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRhRYGG PSSGAPPPS
P339	276	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRhRYGG PSSGAPPPC-NH ₂

P341	277	C6- HSDAVFTDNYTRLRAibQVAAAibAYLQSIKNKRYGGPSS GAPPPS
P342	278	C6- HSDAVFTDNYTRLRAibQVAAAibOmYLQSIKNKRYGGPS SGAPPPS
P343	279	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P344	280	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P345	281	C6- HSDAVFTDNYTAibLRAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P346	282	C6- HSDAVFTDNYTRAibRAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P349	283	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKAibKGGPSSG APPPS
P350	284	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKPKGGPSSGA PPPS
P351	285	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKKGGPSSGAP PPS
P352	286	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIOMOmGGPSSG APPPS
P353	287	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIIdKdKGGPSSGA PPPS
P354	288	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKhRGGPSSGAP PPS
P355	289	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKAibGGPSSGA PPPS
P356	290	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIOMQOmGGPSS GAPPPS
P357	291	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKAibOmGGPSS GAPPPS

P358	292	C6- HSDAVFTDNY(OMe)TRLRAibQVAAAibKYLQSIKNKRYG GPSSGAPPPS
P362	293	C6- HSEAVFTENYTOmLRAibQVAAAibKYLQSIOrnNOmGGP SSGAPPPS
P363	294	C6- HSDAVFTDQYTOmLRAibQVAAAibKYLQSIOrnQOmGGP SSGAPPPS
P364	295	C6- HSDAVFTDNYTOmLRAibQLAAAibKYLQSIOrnNOmGGP SSGAPPPS
P365	296	C6- HSDAVFTDNYTOmLRAibQIAAAibKYLQSIOrnNOmGGPS SGAPPPS
P366	297	C6- HSDAVFTDNYTALRAibQVAAAibKYLQSIOrnNOmGGPSS GAPPPS
P367	298	C6- HSDAVFTDNYTLLRAibQVAAAibKYLQSIOrnNOmGGPSS GAPPPS
P368	299	C6- HSDAVFTDNYTQLRAibQVAAAibKYLQSIOrnNOmGGPSS GAPPPS
P369	300	C6- HSDAVFTDNYTFLRAibQVAAAibKYLQSIOrnNOmGGPSS GAPPPS
P370	301	C6- HSDAVFTDNYTRLAKLALQKYLQSIOrnNOmGGPSSGA PPPS
P371	302	C6- HSDAVFTDNYTOmLLAKLALQKYLQSIOrnNOmGGPSSG APPPS
P372	303	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQCIOrnNOmGGP SSGAPPPS
P377	304	C6- HSDAVFTDNYTOmLRAibQVAACOrnYLQSIOrnNOmGGP SSGAPPPS-NH ₂
P379	305	C6- HSEAVFTEQYTOmLRAibQVAAAibOrnYLQSIOrnOrnGGP SSGAPPPC-NH ₂
P382	306	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSSOrnNOmGGP SSGAPPPS

P383	307	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLSSIOmNOmGGP SSGAPPPS
P384	308	C6- HSDAVFTDNYTOmLRAibQVAAAibKYSQSIOrnNOmGGP SSGAPPPS
P385	309	C6- HSDAVFTDNYTOmLRAibQVAAAibKSLQSIOrnNOmGGP SSGAPPPS
P386	310	C6- HSDAVFTDNYTOmLRAibQVAAAibSYLQSIOrnNOmGGP SSGAPPPS
P387	311	C6- HSDAVFTDNYTOmLRAibQVASAibKYLQSIOrnNOmGGP SSGAPPPS
P388	312	C6- HSDAVFTDNYTOmLRAibQVSAAibKYLQSIOrnNOmGGP SSGAPPPS
P389	313	C6- HSDAVFTDNYTOmLRAibQSAAAibKYLQSIOrnNOmGGP SSGAPPPS
P390	314	C6- HSDAVFTDNYTOmLRAibSVAAAibKYLQSIOrnNOmGGP SSGAPPPS
P391	315	C6- HSDAVFTDNYTOmSRAibQVAAAibKYLQSIOrnNOmGGP SSGAPPPS
P392	316	C6- HSDAVFTDSYTOmLRAibQVAAAibKYLQSIOrnNOmGGP SSGAPPPS
P393	317	C6- HSEAVFTEQY(OMe)TOmLRAibQLAAAibOmYLQSIOrnOr nGGPSSGAPPPS
P394	318	C6- HSDAVFTDQY(OMe)TOmLRAibQLAAAibOmYLQSIOrnOr nGGPSSGAPPPS
P395	319	C6- HSDAVFTDQYTOmLRAibQLAAAibOmYLQSIOrnOmGGP SSGAPPPS
P396	320	C6- HSDAVFTDQYTOmLRAibQVAAAibOmYLQSIOrnOmGGP SSGAPPPS
P397	321	C6- HSDAVFTDNYTOmLRAibQVAAAibOmYLQSIOrnOmGGP SSGAPPPS

P398	322	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSIOr nGGPSSGAPPPC-NH ₂
P405	323	C6- HSDAVFTDNYTRAibRAibQVAAAibKYLQSIKAibKGGPSS GAPPPS
P406	324	C6- HSDAVFTDQYTRAibRAibQVAAAibKYLQSIKAibKGGPSS GAPPPS
P407	325	C6- HSDAVFTDQYTRAibRAibQLAAAibKYLQSIKAibKGGPSS GAPPPS
P408	326	C6- HSDAVFTDQY(OMe)TRAibRAibQLAAAibKYLQSIKAibK GGPSSGAPPPS
P409	327	C6- HSEAVFTEQY(OMe)TRAibRAibQLAAAibKYLQSIKAibKG GPSSGAPPPS
P412	328	C6- HSDAVFTDNYTOmLRK(W)QVAAAibKYLQSIOrnNOmGG PSSGAPPPS
P414	329	C6- HSDAVFTEQY(OMe)TOmLRAibQLAAAibOmY(OMe)LQSI OrnOrnGGPSSGAPPPC-NH ₂
P418	330	C6- HSDAVFTEQY(OMe)TOmLRAibQLAAAibOmY(OMe)LQSI OrnOrnGGPSSGAPPPS
P419	331	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSCOrnO rnGGPSSGAPPPS-NH ₂
P425	332	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLCsIOmOr nGGPSSGAPPPS-NH ₂
P427	333	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLK(CO(CH 2) ₂ SH)SIOrnOrnGGPSSGAPPPS-NH ₂
P429	334	C6- HSDAVFTEQY(OMe)TOmLRAibQVACAibOmYLQSIOrnOr nGGPSSGAPPPS-NH ₂
P431	335	C6- HSDAVFTEQY(OMe)TOmLRAibQVAK(CO(CH ₂) ₂ SH)AibOr nYLQSIOrnOrnGGPSSGAPPPS-NH ₂
P433	336	C6- HSDAVFTEQY(OMe)TOmLRAibQCAAAibOmYLQSIOrnOr nGGPSSGAPPPS-NH ₂

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P437	337	C6- HSDAVFTEQY(OMe)TOmLRAibCVAAAibOrnYLQSIOrnOr nGGPSSGAPPPS-NH ₂
P442	338	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQSIOrnC OrnGGPSSGAPPPS-NH ₂
P446	339	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQCIOrnO rnGGPSSGAPPPC-NH ₂
P448	340	C6- HSDAVFTECY(OMe)TOmLRAibQVAAAibOrnYLQSIOrnOr nGGPSSGAPPPS-NH ₂
P455	341	C6- HSDAVFTEQY(OMe)TOmCRAibQVAAAibOrnYLQSIOrnOr nGGPSSGAPPPS-NH ₂
P421	722	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQSK(CO(CH ₂) ₂ SH)OrnOrnGGPSSGAPPPS-NH ₂
P423	723	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQK(CO(C H ₂) ₂ SH)IOrnOrnGGPSSGAPPPS-NH ₂
P435	724	C6- HSDAVFTEQY(OMe)TOmLRAibQK(CO(CH ₂) ₂ SH)AAAib OrnYLQSIOrnOrnGGPSSGAPPPS-NH ₂
P439	725	C6- HSDAVFTEQY(OMe)TOmLRAibK(CO(CH ₂) ₂ SH)VAAAib OrnYLQSIOrnOrnGGPSSGAPPPS-NH ₂
P444	726	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQSIOrnK(CO(CH ₂) ₂ SH)OrnGGPSSGAPPPS-NH ₂
P457	727	C6- HSDAVFTEQY(OMe)TOmK(CO(CH ₂) ₂ SH)RAibQVAAAib OrnYLQSIOrnOrnGGPSSGAPPPS-NH ₂

Preferably, the following VPAC2 receptor peptide agonists may be PEGylated:

Agonist #	SEQ ID NO:	Sequence
P18	34	HSDAVFTDNYTRLRKQVAAhRKYLQSIKNKRYGGPSSGA PPPS
P20	36	HSDAVFTDNYTRLRKQVAARKYLQSIKNKRYGGPSSGA PPPS
P21	37	HSDAVFTDNYTRLRKQVAASKYLQSIKNKRYGGPSSGA PPS

P22	38	HSDAVFTDNYTRLRKQVAAKKYLQSIhRNKRYGGPS SGAPPPS
P23	39	HSDAVFTDNYTRLRKQVAAKKYLQSI RNKRYGGPSS GAPPPS
P31	46	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSS GAPPPS
P33	47	Ac- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSS GAPPPS
P34	48	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRF
P44	51	HVDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSS GAPPPS
P47	54	HdADAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPS SGAPPPS
P48	55	HdSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P61	66	HSDALFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P72	77	HSDAVFTDNYTRLRRQVAAKKYLQSIKNKRYGGPSSGA PPPS
P89	88	HSDAVFTDNYTRLLAKVAAKKYLQSIKNKRYGGPSS GAPPPS
P98	92	C6- HSDAVFTDNYTRLRRQVAARRYLSIRNRRYGGPSS GAPPPS
P99	93	C6- HVDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSS GAPPPS
P100	94	M- HSDAVFTDQYTRLRKQVAAKKYLQSIKQKRYGGPSS GAPPPS
P101	95	C6- HdADAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P103	97	C6- HSDAVFTDNYTKLKKQVAAKKYLQSIKNKKYGGPSS GAPPPS
P104	98	M- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSS GAPPPS
P106	100	C6- HSDAVFTDNYTRLRKQVAAKKYLQSFKNKRYGGPSSGA PPPS
P107	101	C6- HSDAVFTDNYTRLRKQVAAKKYLQSLKNKRYGGPSS GAPPPS

P108	102	C6- HSDAVFTDNYTRLRKQVAAKKYLQSTKNKRYGGPSS GAPPPS
P109	103	C6- HSDAVFTDNYTRLRKQVAAKKYLQSVKNKRYGGPSS GAPPPS
P110	104	C6- HSDAVFTDNYTRLRKQVAAKKYLQSWKNKRYGGPS SGAPPPS
P111	105	C6- HSDAVFTDNYTRLRKQVAAKKYLQSYKNKRYGGPSS GAPPPS
P112	106	C6- HSDAVFTDNYTRLRKQVAAKKYLQFIKNKRYGGPSS GAPPPS
P113	107	C6- HSDAVFTDNYTRLRKQVAAKKYLQIIKNKRYGGPSS GAPPPS
P114	108	C6- HSDAVFTDNYTRLRKQVAAKKYLQLIKNKRYGGPSS GAPPPS
P115	109	C6- HSDAVFTDNYTRLRKQVAAKKYLQTIKNKRYGGPSS GAPPPS
P116	110	C6- HSDAVFTDNYTRLRKQVAAKKYLQVIKNKRYGGPSS GAPPPS
P117	111	C6- HSDAVFTDNYTRLRKQVAAKKYLQWIKNKRYGGPSS GAPPPS
P119	112	C6- HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSS GAPPPS
P120	113	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSS GAPPPC
P121	114	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKKGGPSSG APPPS
P122	115	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNSRGGPSSG APPPS
P123	116	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRGGPSSG APPPS

P124	117	C6- HSDAVFTDNYTRLRKQVAAKKYLQQIKNKRYGGPSS GAPPPS
P125	118	C6- HSDAVFTDNYTRLRKQVAAKKYLQNIKNKRYGGPSS GAPPPS
P127	120	C6- HSDAVFTDNYTRLRKQVAAKKYLQYIKNKRYGGPSS GAPPPS
P129	121	C6- HSDAVFTDNYTRLRKQVAAKKWLQSIKNKRYGGPSSGA PPPS
P130	122	C6- HSDAVFTDNYTRLRKQVAAKKFLQSIKNKRYGGPSSGAP PPS
P132	124	C6- HSDAVFTDNYTRLRKQVAAKKLLQSIKNKRYGGPSSGAP PPS
P133	125	C6- HSDAVFTDNYTRLRKQVAAKKILQSIKNKRYGGPSSGAP PPS
P134	126	C6- HSDAVFTDNYTRLRKQVAAKKVLQSIKNKRYGGPSSGA PPPS
P135	127	C6- HSDAVFTDNYTRLLAKVAAKKYLQSIKNKRYGGPSSGA PPPS
P138	128	C6- HSDAVFTDNYTRLRAQVAAQKYLSIKNKRYGGPSSGA PPPS
P139	129	C6- HSDAVFTDNYTRLRAQVAAKKYLQSIKNKRYGGPSSGA PPPS
P142	132	C6- HSDAVFTDNYTRLRAQLAAQKYLSIKNKRYGGPSSGAP PPS
P143	133	C6- HSDAVFTDNYTRLRKQMAAQKYLNQLKKGGPSSGAPPP S
P144	134	C6- HSDAVFTDNYTRLRKQVAAQKYLNQLKKGGPSSGAPPP S
P146	135	C6- HSDAVFTDNYTRLRKQVAAVKYLQSIKNKRYGGPSSGA PPPS

P147	136	C6- HSDAVFTDNYTRLRKQVAAYKYLQSIKNKRYGGPSSGA PPPS
P148	137	C6- HSDAVFTDNYTRLRKQVAAFKYLQSIKNKRYGGPSSGAP PPS
P149	138	C6- HSDAVFTDNYTRLRKQVAAIKYLQSIKNKRYGGPSSGAP PPS
P150	139	C6- HSDAVFTDNYTRLRKQVAAQKYLQSIKNKRYGGPSSGA PPPS
P151	140	C6- HSDAVFTDNYTRLRKQVAALKYLQSIKNKRYGGPSSGAP PPS
P152	141	C6- HSDAVFTDNYTRLRKQVAATKYLQSIKNKRYGGPSSGAP PPS
P153	142	C6- HSDAVFTDNYTRLRKQVAAWKYLQSIKNKRYGGPSSGA PPPS
P154	143	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNGGPSSGAPPPS
P155	144	C6- HSDAVFTDNYTRLRKQVALKKYLQSIKNKRYGGPSSGAP PPS
P158	145	C6- HSDAVFTANYTRLRKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P159	146	C6- HSDAVFTENYTRLRKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P164	151	C6- HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAP PPC
P165	152	C6- HSDAVFTEEYTRLQKQVAAKQYLQSIKNKRYGGPSSGAP PPS
P166	153	C6- HAibDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P167	154	C6- HSDAVFTDNYTRLAibKQVAAKKYLQSIKNKRYGGPSSG APPPS
P168	155	C6- HSDAVFTDNYTRLRAibQVAAKKYLQSIKNKRYGGPSSG APPPS

P169	156	C6- HSDAVFTDNYTRLRKQVAAAibKYLQSIKNKRYGGPSSG APPPS
P170	157	C6- HSDAVFTDNYTRLRKQVAAKAibYLQSIKNKRYGGPSSG APPPS
P171	158	C6- HSDAVFTDNYTRLKKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P172	159	C6- HSDAVFTDNYTRLQKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P173	160	C6- HSDAVFTDNYTRLAKQVAAKKYLQSIKNKRYGGPSSGA PPPS
P175	162	C6- HSDAVFTDNYTRLFKQVAAKKYLQSIKNKRYGGPSSGAP PPS
P176	163	C6- HSDAVFTDNYTRLRRQVAAKKYLQSIKNKRYGGPSSGA PPPS
P177	164	C6- HSDAVFTDNYTRLRQQVAAKKYLQSIKNKRYGGPSSGA PPPS
P179	165	C6- HSDAVFTDNYTRLRLQVAAKKYLQSIKNKRYGGPSSGAP PPS
P180	166	C6- HSDAVFTDNYTRLRFQVAAKKYLQSIKNKRYGGPSSGAI PPS
P181	167	C6- HSDAVFTDNYTRLRKQVAAAKYLQSIKNKRYGGPSSGA PPPS
P182	168	C6- HSDAVFTDNYTRLRKQVAAKRYLQSIKNKRYGGPSSGA PPPS
P183	169	C6- HSDAVFTDNYTRLRKQVAAKQYLQSIKNKRYGGPSSGA PPPS
P184	170	C6- HSDAVFTDNYTRLRKQVAAKAYLQSIKNKRYGGPSSGA PPPS
P185	171	C6- HSDAVFTDNYTRLRKQVAAKLYLQSIKNKRYGGPSSGAP PPS

P186	172	C6- HSDAVFTDNYTRLRKQVAAKFYLSIKNKRYGGPSSGAP PPS
P187	173	C6- HSDAVFTDNYTRLRKQVAAKKYLQAibIKNKRYGGPSSG APPPS
P188	174	C6- HSDAVFTDNYTRLRKQVAAKKYLSAibIKNKRYGGPSSG APPPS
P192	177	C6- HSDAVFTDQYTRLLAKLALQKYLSIKQKRYGGPSSGAP PPS
P193	178	C6- HSDAVFTDNYTRLRK(Ac)QVAAK(Ac)KYLQSIKNKRYG GPSSGAPPPS
P194	179	C6- HSDAVFTDNYTRLRK(Ac)QVAAK(Ac)YLQSIKNKRYG GPSSGAPPPS
P195	180	C6- HSDAVFTDNYTRLLAQLALQKYLSIKNKRYGGPSSGAP PPS
P196	181	C6- HSDAVFTDNYTRLLAKVALQKYLSIKNKRYGGPSSGAP PPS
P197	182	C6- HSDAVFTDNYTRLLAKLAAQKYLSIKNKRYGGPSSGAP PPS
P207	188	C6- HSDdAVFTDNYTRLRKQVAAKKYLSIKNKRYGGPSSG APPPS
P209	190	C6- HSDAibVFTDNYTRLRKQVAAKKYLSIKNKRYGGPSSG APPPS
P210	191	C6- HSDAdVFTDNYTRLRKQVAAKKYLSIKNKRYGGPSSG APPPS
P212	193	C6- HSDAAibFTDNYTRLRKQVAAKKYLSIKNKRYGGPSSG APPPS
P213	194	C6- HSDAVFTDNYTRLRKQVAAKRYLSIRNGGPSSGAPPPS
P214	195	C6- HSDAVFTDNYTRLRKQVAARRYLSIRNGGPSSGAPPPS
P215	196	C6- HSDAVFTDNYTRLRRQVAAKRYLSIRNGGPSSGAPPPS
P216	197	C6- HSDAVFTDNYTRLRRQVAARKYLSIRNGGPSSGAPPPS

P240	214	C6- HSDAVFTDNYTRLAibKQLAAaibKYLQSIKNKRYGGPSS GAPPPS
P241	215	C6- HSDAVFTDNYTRLAibKQLAAKaibYLQSIKNKRYGGPSS GAPPPS
P242	216	C6- HSDAVFTDNYTRLAibKQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P243	217	C6- HSDAVFTDNYTRLAibKQVAAQKYLQSIKNKRYGGPSSG APPPS
P244	218	C6- HSDAVFTDNYTRLAibKQVAAKaibYLQSIKNKRYGGPSS GAPPPS
P249	219	C6- HSDAVFTDNYTRLAibKQVAAKQYLQSIKNKRYGGPSSG APPPS
P250	220	C6- HSDAVFTDNYTRLQKQVAAAibKYLQSIKNKRYGGPSSG APPPS
P251	221	C6- HSDAVFTDNYTRLQKQVAAKaibYLQSIKNKRYGGPSSG APPPS
P258	224	C6- HSDAVFTDNYTRLQAibQVAAKKYLQSIKNKRYGGPSSG APPPS
P259	225	C6- HSDAVFTDNYTRLAibKQVAAALKYLQSIKNKRYGGPSSG APPPS
P260	226	C6- HSDAVFTDNYTRLAibKQVAAAKYLQSIKNKRYGGPSSG APPPS
P261	227	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P262	228	C6- HSDAVFTDNYTRLRAibQVAAVKYLQSIKNKRYGGPSSG APPPS
P263	229	C6- HSDAVFTDNYTRLRAibQVAAAKYLQSIKNKRYGGPSSG APPPS
P264	230	C6- HSDAVFTDNYTRLRAibQVAAKaibYLQSIKNKRYGGPSS GAPPPS

P265	231	C6- HSDAVFTDNYTRLRAibQVAALKYLQSIKNKRYGGPSSG APPPS
P269	232	C6- HSDAVFTDNYTRLAibKQVAAVKYLQSIKNKRYGGPSSG APPPS
P284	237	C6- HSDAVFTDNYTRLRAibQLAAKAibYLQSIKNKRYGGPSS GAPPPS
P291	241	C6- HSDAVFTDNYTRLRAibQLAAAibKYLQSIKNKRYGGPSS GAPPPS
P292	242	C6- HSDAVFTDNYTRLRAibQLAAAibKYLQSIKNKGGPSSGA PPPS
P293	243	C6- HSDAVFTDNYTRLAibKQVAAAibKYLQSIKQKGGPSSGA PPPS
P294	244	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKQKGGPSSGA PPPS
P295	245	C6- HSDAVFTDNYTRLRAibQVAAKAibYLQSIKQKGGPSSGA PPPS
P296	246	C6- HSDAVFTDNYTRLAibKQVAAAibKYLQSIKQGGPSSGAP PPS
P297	247	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKQGGPSSGAP PPS
P298	248	C6- HSDAVFTDNYTRLRAibQVAAKAibYLQSIKQGGPSSGAP PPS
P301	250	C6- HSDAVFTDNYTRLAAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P302	251	C6- HSDAVFTDNYTRLQAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P305	252	C6- HSDAVFTDNYTRLhRKQVAAKKYLQSIKNKRYGGPSSG APPPS
P307	253	C6- HSDAVFTDNYTRLROmQVAAKKYLQSIKNKRYGGPSSG APPPS

P314	255	C6- HSEAVFTENYTRLRAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P317	258	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P318	259	C6- HSDAVFTDNYTRLKAibQVAAAibKYLQSIKNKRYGGPSS GAPPPS
P319	260	C6- HSDAVFTDNYTRLORmAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P321	262	C6- HSDAVFTDNYTRLRAibKVAAAibKYLQSIKNKRYGGPSS GAPPPS
P322	263	C6- HSDAVFTDNYTRLRAibQIAAAibKYLQSIKNKRYGGPSSG APPPS
P323	264	C6- HSDAVFTDNYTRLRAibQKAAAibKYLQSIKNKRYGGPSS GAPPPS
P324	265	C6- HSDAVFTDNYTRLRAibQAAAAibKYLQSIKNKRYGGPSS GAPPPS
P325	266	C6- HSDAVFTDNYTRLRAibQNleAAAibKYLQSIKNKRYGGPS SGAPPPS
P326	267	C6- HSDAVFTDNYTOrnLRAibQVAAAibKYLQSIOrnOrnGGP SSGAPPPS
P329	269	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRGGPSS GAPPPS
P343	279	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P344	280	C6- HSDAVFTDNYTOrnLRAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P346	282	C6- HSDAVFTDNYTRAibRAibQVAAAibKYLQSIKNKRYGGPS SGAPPPS
P349	283	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKAibKGGPSSG APPPS

P350	284	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKPKGGPSSGA PPPS
P351	285	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKKGGPSSGAP PPS
P353	287	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIIdKdKGGPSSGA PPPS
P354	288	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKhRGGPSSGAP PPS
P355	289	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKAibGGPSSGA PPPS
P357	291	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKAibOmGGPSS GAPPPS
P358	292	C6- HSDAVFTDNY(OMe)TRLRAibQVAAAibKYLQSIKNKRYG GPSSGAPPPS
P362	293	C6- HSEAVFTENYTOmLRAibQVAAAibKYLQSIOMNOmGGP SSGAPPPS
P363	294	C6- HSDAVFTDQYTOmLRAibQVAAAibKYLQSIOMQOmGGP SSGAPPPS
P364	295	C6- HSDAVFTDNYTOmLRAibQLAAAibKYLQSIOMNOmGGP SSGAPPPS
P365	296	C6- HSDAVFTDNYTOmLRAibQIAAAibKYLQSIOMNOmGGPS SGAPPPS
P372	303	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQCIOMNOmGGP SSGAPPPS
P379	305	C6- HSEAVFTEQYTOmLRAibQVAAAibOmYLQSIOMOmGGP SSGAPPPC-NH ₂
P393	317	C6- HSEAVFTEQY(OMe)TOmLRAibQLAAAibOmYLQSIOMOr nGGPSSGAPPPS
P394	318	C6- HSDAVFTDQY(OMe)TOmLRAibQLAAAibOmYLQSIOMOr nGGPSSGAPPPS

P395	319	C6- HSDAVFTDQYTOmLRAibQLAAibOmYLQSIOrnOmGGP SSGAPPPS
P396	320	C6- HSDAVFTDQYTOmLRAibQVAAibOmYLQSIOrnOmGGP SSGAPPPS
P397	321	C6- HSDAVFTDNYTOmLRAibQVAAibOmYLQSIOrnOmGGP SSGAPPPS
P398	322	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAibOmYLQSIOrnOr nGGPSSGAPPPC-NH ₂

According to a second aspect of the present invention, the preferred PEGylated VPAC2 receptor peptide agonists comprise an amino acid sequence selected from:

Agonist #	SEQ ID NO:	Sequence
P41	342	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYC(PEG40K)
P137	343	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPP PC(PEG40K)
P190	344	C6- HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAPP PC(PEG40K)
P202	345	C6- HSDAVFTDNYTRLLAKLALQKYLQSIKNKGGPSSGAPPPC(PEG40K)
P217	346	C6- HSDAVFTDNYTRLRK(PEG20K)QVAAK(PEG20K)RYLQSIR NGGPSSGAPPPS
P219	347	C6- HSDAVFTDNYTRLRRQVAAK(PEG20K)RYLQSIRNGGPSS GAPPPS
P245	348	C6- HSDAVFTDNYTRLRK(PEG40K)QVAARRYLSIRNGGPSS GAPPPS
P246	349	C6- HSDAVFTDNYTRLRRQVAAK(PEG40K)RYLQSIRNGGPSS GAPPPS
P247	350	C6- HSDAVFTDNYTRLRRQVAARK(PEG40K)YLQSIRNGGPSS GAPPPS

P283	351	C6- HSDAVFTDNYTRLAibKQVAAAibKYLQSIKNKRYGGPSSG APPPC(PEG40K)-NH ₂
P286	352	C6- HSDAVFTDNYTRLAibQVAAKAibYLQSIKNKRYGGPSSG APPPC(PEG40K)-NH ₂
P300	353	C6- HSDAVFTDNYTRLAibQVAAAibKYLQSIKNKRYGGPSSG APPPC(PEG40K)-NH ₂
P328	354	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSIOrnNOmGGPS SGAPPPC(PEG40K)-NH ₂
P331	355	C6- HSDAVFTDNYThRLAibQVAAAibKYLQSIhRNhRGGPSSG APPPC(PEG40K)-NH ₂
P337	356	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSIhRhRGGPSSGA PPPC(PEG40K)-NH ₂
P340	357	C6- HSDAVFTDNYThRLAibQVAAAibKYLQSIhRNhRhRYGGP SSGAPPPC(PEG40K)-NH ₂
P373	358	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQC(PEG40K)IOmN OrnGGPSSGAPPPS
P380	359	C6- HSEAVFTEQYTOmLRAibQVAAAibOrnYLQSIOrnOrnGGPSS GAPPPC(PEG40K)-NH ₂
P378	360	C6- HSDAVFTDNYTOmLRAibQVAAC(PEG40K)OrnYLQSIOrnN OrnGGPSSGAPPPS-NH ₂
P272	361	Biotin-Acp- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPP PC(PEG40K)
P399	362	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQSIOrnOrn GGPSSGAPPPC(PEG40K)-NH ₂
P404	363	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQSIOrnOrn GGPSSGAPPPC(PEG60K)-NH ₂
P411	364	C6- HSDAVFTDNYTOmLRAibQVAAC(PEG20K)OrnYLQSIOrnN OrnGGPSSGAPPPS-NH ₂
P413	365	C6- HSDAVFTDNYTOmLRK(WPEG40K)QVAAAibKYLQSIOrnN OrnGGPSS GAPPPS

P415	366	C6-HSDAVFTEQY(OMe)TOmLRAibQLAAaibOmY(OMe)LQSIOrnOmGGPSSGAPPPC(PEG40K)-NH ₂
P420	367	C6-HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSC(PEG40K)OrnOmGGPSSGAPPPS-NH ₂
P426	368	C6-HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLC(PEG40K)SIOrnOmGGPSSGAPPPS-NH ₂
P428	369	C6-HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLK(CO(CH ₂) ₂ SPEG40K)SIOrnOmGGPSSGAPPPS-NH ₂
P430	370	C6-HSDAVFTEQY(OMe)TOmLRAibQVAC(PEG40K)AibOmYLQSIOrnOmGGPSSGAPPPS-NH ₂
P432	371	C6-HSDAVFTEQY(OMe)TOmLRAibQVAK(CO(CH ₂) ₂ SPEG40K)AibOmYLQSIOrnOmGGPSSGAPPPS-NH ₂
P434	372	C6-HSDAVFTEQY(OMe)TOmLRAibQC(PEG40K)AAAibOmYLQSIOrnOmGGPSSGAPPPS-NH ₂
P438	373	C6-HSDAVFTEQY(OMe)TOmLRAibC(PEG40K)VAAAibOmYLQSIOrnOmGGPSSGAPPPS-NH ₂
P443	374	C6-HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSIOrnC(PEG40K)OrnGGPSSGAPPPS-NH ₂
P447	375	C6-HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLOC(PEG20K)OrnOmGGPSSGAPPPC(PEG20K)-NH ₂
P449	376	C6-HSDAVFTEC(PEG40K)Y(OMe)TOmLRAibQVAAAibOmYLQSIOrnOmGGPSSGAPPPS-NH ₂
P452	377	C6-HSDAVFTEQY(OMe)TOmLRAibC(PEG20K)VAAAibOmYLQSIOrnOmGGPSSGAPPPS-NH ₂
P456	378	C6-HSDAVFTEQY(OMe)TOmC(PEG40K)RAibQVAAAibOmYLQSIOrnOmGGPSSGAPPPS-NH ₂
P461	379	C6-HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLK(CO(CH ₂) ₂ SPEG20K)SIOrnOmGGPSSGAPPPS-NH ₂
P462	380	C6-HSDAVFTEQY(OMe)TOmLRAibQVAK(CO(CH ₂) ₂ SPEG20K)AibOmYLQSIOrnOmGGPSSGAPPPS-NH ₂
P422	728	C6-HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSK(CO(CH ₂) ₂ SPEG40K)OrnOmGGPSSGAPPPS-NH ₂

P424	729	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAaibOmYLQK(CO(CH ₂) ₂ SPEG40K)IOmOmGGPSSGAPPPS-NH ₂
P436	730	C6- HSDAVFTEQY(OMe)TOmLRAibQK(CO(CH ₂) ₂ SPEG40K)AA AibOmYLQSIOMOmGGPSSGAPPPS-NH ₂
P440	731	C6- HSDAVFTEQY(OMe)TOmLRAibK(CO(CH ₂) ₂ SPEG40K)VAA AibOmYLQSIOMOmGGPSSGAPPPS-NH ₂
P445	732	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAaibOmYLQSIOMK(C O(CH ₂) ₂ SPEG40K)OmGGPSSGAPPPS-NH ₂
P458	733	C6- HSDAVFTEQY(OMe)TOmK(CO(CH ₂) ₂ SPEG40K)RAibQVAA AibOmYLQSIOMOmGGPSSGAPPPS-NH ₂
P464	734	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAaibOmYLQSK(CO(C H ₂) ₂ SPEG20K)OmOmGGPSSGAPPPS-NH ₂
P465	735	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAaibOmYLQK(CO(CH ₂) ₂ SPEG20K)IOmOmGGPSSGAPPPS-NH ₂
P466	736	C6- HSDAVFTEQY(OMe)TOmLRAibQK(CO(CH ₂) ₂ SPEG20K)AA AibOmYLQSIOMOmGGPSSGAPPPS-NH ₂
P467	737	C6- HSDAVFTEQY(OMe)TOmLRAibK(CO(CH ₂) ₂ SPEG20K)VAA AibOmYLQSIOMOmGGPSSGAPPPS-NH ₂
P468	738	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAaibOmYLQSIOMK(C O(CH ₂) ₂ SPEG20K)OmGGPSSGAPPPS-NH ₂

More preferred PEGylated VPAC2 receptor peptide agonists according to the second aspect of the present invention comprise an amino acid sequence selected from:

Agonist #	SEQ ID NO:	Sequence
P137	343	C6- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPP PC(PEG40K)
P190	344	C6- HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAPP PC(PEG40K)

P217	346	C6- HSDAVFTDNYTRLRK(PEG20K)QVAAK(PEG20K)RYLQSIR NGGPSSGAPPPS
P219	347	C6- HSDAVFTDNYTRLRRQVAAK(PEG20K)RYLQSIRNGGPSS GAPPPS
P245	348	C6- HSDAVFTDNYTRLRK(PEG40K)QVAARRYLSIRNGGPSS GAPPPS
P246	349	C6- HSDAVFTDNYTRLRRQVAAK(PEG40K)RYLQSIRNGGPSS GAPPPS
P247	350	C6- HSDAVFTDNYTRLRRQVAARK(PEG40K)YLQSIRNGGPSS GAPPPS
P283	351	C6- HSDAVFTDNYTRLAibKQVAAAibKYLQSIKNKRYGGPSSG APPPC(PEG40K)-NH ₂
P286	352	C6- HSDAVFTDNYTRLRAibQVAAKAibYLQSIKNKRYGGPSSG APPPC(PEG40K)-NH ₂
P300	353	C6- HSDAVFTDNYTRLRAibQVAAAibKYLQSIKNKRYGGPSSG APPPC(PEG40K)-NH ₂
P328	354	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSIOnNOmGGPS SGAPPPC(PEG40K)-NH ₂
P331	355	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIbRNhRGPPSSG APPPC (PEG40K)-NH ₂
P337	356	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQSIhRhRGGPSSGA PPPC(PEG40K)-NH ₂
P340	357	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRhRYGGP SSGAPPPC(PEG40K)-NH ₂
P373	358	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQC(PEG40K)IOmN OmGGPSSGAPPPS
P380	359	C6- HSEAVFTEQYTOMLRAibQVAAAibOmYLQSIOMOmGGPSS GAPPPC(PEG40K)-NH ₂
P378	360	C6- HSDAVFTDNYTOmLRAibQVAAC(PEG40K)OmYLQSIOMN OmGGPSSGAPPPS-NH ₂

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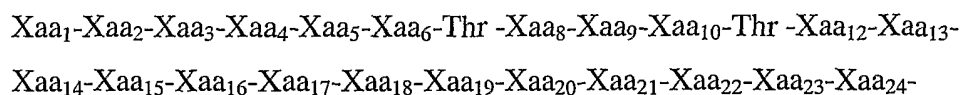
P272	361	Biotin-Acp- HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPP PC(PEG40K)
P399	362	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQSIOrnOrn GGPSSGAPPPC(PEG40K)-NH ₂
P404	363	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQSIOrnOrn GGPSSGAPPPC(PEG60K)-NH ₂
P432	371	C6- HSDAVFTEQY(OMe)TOmLRAibQVAK(CO(CH ₂) ₂ SPEG40K) AibOrnYLQSIOrnOrnGGPSSGAPPPS-NH ₂

Even more preferred PEGylated VPAC2 receptor peptide agonists according to the second aspect of the present invention comprise an amino acid sequence selected from:

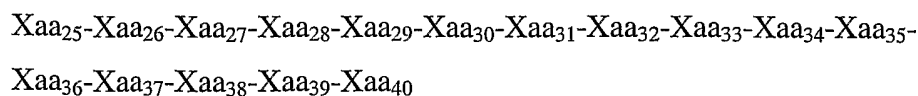
5

Agonist #	SEQ ID NO:	Sequence
P190	344	C6- HSDAVFTDNYTRLAKLALQKYLQSIKNKRYGGPSS GAPPPC(PEG40K)
P286	352	C6- HSDAVFTDNYTRLRAibQVAAKAibYLQSIKNKRYGG PSSGAPPPC(PEG40K)-NH ₂
P340	357	C6- HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRhRY GGPSSGAPPPC(PEG40K)-NH ₂
P373	358	C6- HSDAVFTDNYTOmLRAibQVAAAibKYLQC(PEG40K)IOm NOmGGPSSGAPPPS
P404	363	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOrnYLQSIOr nOrnGGPSSGAPPPC(PEG60K)-NH ₂
P432	371	C6- HSDAVFTEQY(OMe)TOmLRAibQVAK(CO(CH ₂) ₂ SPEG40K))AibOrnYLQSIOrnOrnGGPSSGAPPPS-NH ₂

According to a third aspect of the present invention, there is provided a PEGylated VPAC2 receptor peptide agonist comprising a sequence of the formula:



10



Formula 14 (SEQ ID NO: 26)

wherein:

- 5 Xaa₁ is: any naturally occurring amino acid, dH, or is absent;
 Xaa₂ is: any naturally occurring amino acid, dA, dS, or Aib;
 Xaa₃ is: Asp or Glu;
 Xaa₄ is: any naturally occurring amino acid, dA, Aib, or NMeA;
 Xaa₅ is: any naturally occurring amino acid, dV, or Aib;
- 10 Xaa₆ is: any naturally occurring amino acid;
 Xaa₈ is: Asp, Glu, Ala, Lys, Leu, Arg, or Tyr;
 Xaa₉ is: Asn, Gln, Asp, Glu, Ser, or Cys;
 Xaa₁₀ is: any naturally occurring aromatic amino acid, or Tyr (OMe);
 Xaa₁₂ is: hR, Orn, Lys (isopropyl), Aib, Cit, or any naturally occurring amino acid except
- 15 Pro;
 Xaa₁₃ is: Aib, K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;
 Xaa₁₄ is: hR, Orn, Lys (isopropyl), Aib, Cit, or any naturally occurring amino acid except Pro;
 Xaa₁₅ is: hR, Orn, Lys (isopropyl), Aib, K (Ac), Cit, K(W), or any naturally occurring
- 20 amino acid except Pro;
 Xaa₁₆ is: hR, Orn, Lys (isopropyl), Cit, K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;
 Xaa₁₇ is: Nle, Aib, K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;
 Xaa₁₈ is: any naturally occurring amino acid;
- 25 Xaa₁₉ is: K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;
 Xaa₂₀ is: hR, Orn, Lys (isopropyl), Aib, K(Ac), Cit, or any naturally occurring amino acid except Pro;
 Xaa₂₁ is: hR, Orn, Aib, K(Ac), Cit, or any naturally occurring amino acid except Pro;
 Xaa₂₂ is: Aib, Tyr (OMe), or any naturally occurring amino acid except Pro;
- 30 Xaa₂₃ is: Aib or any naturally occurring amino acid except Pro;
 Xaa₂₄ is: K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;
 Xaa₂₅ is: Aib, K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;

- Xaa₂₆ is: K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;
- Xaa₂₇ is: hR, Lys (isopropyl), Orn, dK, or any naturally occurring amino acid except Pro;
- Xaa₂₈ is: any naturally occurring amino acid, Aib, hR, Cit, Orn, dK, or K(CO(CH₂)₂SH);
- Xaa₂₉ is: any naturally occurring amino acid, hR, Orn, Cit, Aib, or is absent;
- 5 Xaa₃₀ is: any naturally occurring amino acid, hR, Orn, Cit, Aib, or is absent; and
- Xaa₃₁ to Xaa₄₀ are any naturally occurring amino acid or are absent;
- provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆, Xaa₃₇, Xaa₃₈ or Xaa₃₉ is absent, the next amino acid present downstream is the next amino acid in the peptide agonist sequence and that the peptide agonist comprises at least one amino
- 10 acid substitution selected from:
- Xaa₂ is: dA, Val, Gly, Leu, dS, or Aib;
- Xaa₄ is: Ile, Tyr, Phe, Val, Thr, Leu, Trp, dA, Aib, or NMeA;
- Xaa₅ is: Leu, Phe, Thr, Trp, Tyr, dV, or Aib;
- Xaa₈ is: Leu, Arg, or Tyr;
- 15 Xaa₉ is: Glu, Ser, or Cys;
- Xaa₁₀ is: Trp;
- Xaa₁₂ is: Ala, hR, Aib, Lys (isopropyl), Cit, Gln, or Phe;
- Xaa₁₃ is: Phe, Glu, Ala, Aib, Ser, Cys, or K(CO(CH₂)₂SH);
- Xaa₁₄ is: Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, or Cit;
- 20 Xaa₁₅ is: Ala, Arg, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit, or K(W);
- Xaa₁₆ is: Lys, Lys (isopropyl), hR, Orn, Cit, Ser, Cys, or K(CO(CH₂)₂SH);
- Xaa₁₇ is: Lys, Aib, Ser, Cys, or K(CO(CH₂)₂SH);
- Xaa₁₈ is: Ser, or Cys;
- Xaa₁₉ is: K(CO(CH₂)₂SH);
- 25 Xaa₂₀ is: Gln, hR, Arg, Ser, Orn, Lys(isopropyl), Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, or Cys;
- Xaa₂₁ is: Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, or Cys;
- Xaa₂₂ is: Trp, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, or Cys;
- Xaa₂₃ is: Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, or Cys;
- 30 Xaa₂₄ is: Ser, Cys, or K(CO(CH₂)₂SH);
- Xaa₂₅ is: Phe, Ile, Leu, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, or K(CO(CH₂)₂SH);
- Xaa₂₆ is: Thr, Trp, Tyr, Phe, Ser, Cys, or K(CO(CH₂)₂SH);

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Xaa₂₇ is: hR, Orn, or dK;

Xaa₂₈ is: Pro, Arg, Aib, Orn, hR, Cit, dK, Cys, or K(CO(CH₂)₂SH);

Xaa₂₉ is: hR, Cys, Orn, Cit, or Aib;

Xaa₃₀ is: hR, Cit, Aib, or Orn; and

5 Xaa₃₁ is: His, or Phe,

and wherein:

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

10 at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to a PEG molecule, or

the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

15 the carboxy-terminal amino acid of the peptide agonist is covalently attached to a PEG molecule, or

any combination thereof.

Preferably, the PEGylated VPAC2 receptor peptide agonist according to the third aspect of the present invention comprises a sequence of the formula:

His-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Phe-Thr-Xaa₈-Xaa₉-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃-
 20 Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Xaa₂₃-Xaa₂₄-
 Xaa₂₅-Xaa₂₆-Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁-Xaa₃₂-Xaa₃₃-Xaa₃₄-Xaa₃₅-
 Xaa₃₆-Xaa₃₇-Xaa₃₈-Xaa₃₉-Xaa₄₀

Formula 15 (SEQ ID NO: 27)

wherein:

25 Xaa₂ is: dA, Ser, Val, Gly, Thr, Leu, dS, Pro, or Aib;

Xaa₃ is: Asp or Glu;

Xaa₄ is: Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, Gly, dA, Aib, or NMeA;

Xaa₅ is: Val, Leu, Phe, Ile, Thr, Trp, Tyr, dV, or Aib;

Xaa₈ is: Asp, Glu, Ala, Lys, Leu, Arg, or Tyr;

30 Xaa₉ is: Asn, Gln, Asp, Glu, Ser, or Cys;

Xaa₁₀ is: Tyr, Trp, or Tyr(OMe);

Xaa₁₂ is: Arg, Lys, Glu, hR, Orn, Lys (isopropyl), Aib, Cit, Ala, Leu, Gln, or Phe;

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- Xaa₁₃ is: Leu, Phe, Glu, Ala, Aib, Ser, Cys, or K(CO(CH₂)₂SH);
- Xaa₁₄ is: Arg, Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, or Cit;
- Xaa₁₅ is: Lys, Ala, Arg, Glu, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit, or K(W);
- 5 Xaa₁₆ is: Gln, Lys, Glu, Ala, hR, Orn, Lys (isopropyl), Cit, Ser, Cys, or K(CO(CH₂)₂SH);
- Xaa₁₇ is: Val, Ala, Leu, Ile, Met, Nle, Lys, Aib, Ser, Cys, or K(CO(CH₂)₂SH);
- Xaa₁₈ is: Ala, Ser, or Cys;
- Xaa₁₉ is: Val, Ala, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Trp, Tyr, Cys, Asp, or K(CO(CH₂)₂SH);
- 10 Xaa₂₀ is: Lys, Gln, hR, Arg, Ser, His, Orn, Lys (isopropyl), Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, or Cys;
- Xaa₂₁ is: Lys, His, Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, or Cys;
- Xaa₂₂ is: Tyr, Trp, Phe, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, or Cys;
- Xaa₂₃ is: Leu, Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, or Cys;
- 15 Xaa₂₄ is: Gln, Glu, Asn, Ser, Cys, or K(CO(CH₂)₂SH);
- Xaa₂₅ is: Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, or K(CO(CH₂)₂SH);
- Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, Phe, Ser, Cys, or K(CO(CH₂)₂SH);
- Xaa₂₇ is: Lys, hR, Arg, Gln, Ala, Asp, Glu, Phe, Gly, His, Ile, Met, Asn, Ser, Thr, Val, Trp, Tyr, Lys (isopropyl), Cys, Leu, Orn, or dK;
- 20 Xaa₂₈ is: Asn, Asp, Gln, Lys, Arg, Aib, Orn, hR, Cit, Pro, dK, Cys, or K(CO(CH₂)₂SH);
- Xaa₂₉ is: Lys, Ser, Arg, Asn, hR, Ala, Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Gln, Thr, Val, Trp, Tyr, Cys, Orn, Cit, Aib or is absent;
- Xaa₃₀ is: Arg, Lys, Ile, Ala, Asp, Glu, Phe, Gly, His, Leu, Met, Asn, Pro, Gln, Ser, Thr, Val, Trp, Tyr, Cys, hR, Cit, Aib, Orn, or is absent;
- 25 Xaa₃₁ is: Tyr, His, Phe, Thr, Cys, or is absent;
- Xaa₃₂ is: Ser, Cys, or is absent;
- Xaa₃₃ is: Trp or is absent;
- Xaa₃₄ is: Cys or is absent;
- 30 Xaa₃₅ is: Glu or is absent;
- Xaa₃₆ is: Pro or is absent;
- Xaa₃₇ is: Gly or is absent;

Xaa₃₈ is: Trp or is absent;

Xaa₃₉ is: Cys or is absent; and

Xaa₄₀ is: Arg or is absent

provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆, Xaa₃₇,

- 5 Xaa₃₈, or Xaa₃₉ is absent, the next amino acid present downstream is the next amino acid in the peptide agonist sequence,

and that the peptide agonist comprises at least one amino acid substitution selected from:

Xaa₂ is: dA, Val, Gly, Leu, dS, or Aib;

- 10 Xaa₄ is: Ile, Tyr, Phe, Val, Thr, Leu, Trp, dA, Aib, or NMeA;

Xaa₅ is: Leu, Phe, Thr, Trp, Tyr, dV, or Aib;

Xaa₈ is: Leu, Arg, or Tyr;

Xaa₉ is: Glu, Ser, or Cys;

Xaa₁₀ is: Trp;

- 15 Xaa₁₂ is: Ala, hR, Aib, Lys (isopropyl), Cit, Gln, or Phe;

Xaa₁₃ is: Phe, Glu, Ala, Aib, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₄ is: Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, or Cit;

Xaa₁₅ is: Ala, Arg, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit, or K(W);

Xaa₁₆ is: Lys, Lys (isopropyl), hR, Orn, Cit, Ser, Cys, or K(CO(CH₂)₂SH);

- 20 Xaa₁₇ is: Lys, Aib, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₈ is: Ser, or Cys;

Xaa₁₉ is: K(CO(CH₂)₂SH);

Xaa₂₀ is: Gln, hR, Arg, Ser, Orn, Lys(isopropyl), Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, or Cys;

- 25 Xaa₂₁ is: Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K (Ac), Cit, Ser, or Cys;

Xaa₂₂ is: Trp, Thr, Leu, Ile, Val, Tyr (OMe), Ala, Aib, Ser, or Cys;

Xaa₂₃ is: Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, or Cys;

Xaa₂₄ is: Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₅ is: Phe, Ile, Leu, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, or K(CO(CH₂)₂SH);

- 30 Xaa₂₆ is: Thr, Trp, Tyr, Phe, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₇ is: hR, Orn, or dK;

Xaa₂₈ is: Pro, Arg, Aib, Orn, hR, Cit, dK, Cys, or K(CO(CH₂)₂SH);

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Xaa₂₉ is: hR, Cys, Orn, Cit, or Aib;

Xaa₃₀ is: hR, Cit, Aib, or Orn; and

Xaa₃₁ is: His, or Phe,

and wherein:

5 at least one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

10 at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to a PEG molecule, or

the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid of the peptide agonist is covalently attached to the PEG molecule, or

any combination thereof.

15 According to a fourth aspect of the present invention, there is provided a PEGylated VPAC2 receptor peptide agonist of the present invention for use as a medicament.

According to a further aspect of the present invention, there is provided the use of a PEGylated VPAC2 receptor peptide agonist of the present invention for the

20 manufacture of a medicament for the treatment non-insulin-dependent diabetes.

According to yet a further aspect of the present invention, there is provided the use of a PEGylated VPAC2 receptor peptide agonist of the present invention for the manufacture of a medicament for the treatment of insulin-dependent diabetes.

Alternative embodiments of the present invention are described below.

25 A first alternative embodiment of the present invention is a PEGylated VPAC2 receptor peptide agonist comprising a sequence of the formula:

Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Thr-Xaa₈-Xaa₉-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃-
 Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Ala-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Leu-Xaa₂₄-Xaa₂₅-
 Xaa₂₆-Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁-Xaa₃₂-Xaa₃₃-Xaa₃₄-Xaa₃₅-Xaa₃₆-
 30 Xaa₃₇-Xaa₃₈-Xaa₃₉-Xaa₄₀

Formula 4 (SEQ ID NO: 7)

wherein:

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- Xaa₁ is: His or is absent;
Xaa₂ is: dA, Ser, Val, Gly, Thr, Leu, dS, or Pro;
Xaa₃ is: Asp, or Glu;
Xaa₄ is: Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, or Gly;
5 Xaa₅ is: Val, Leu, Phe, Ile, Thr, Trp, or Tyr;
Xaa₆ is: Phe, Ile, Leu, Thr, Val, Trp, or Tyr;
Xaa₈ is: Asp or Glu;
Xaa₉ is: Asn, Gln, or Asp;
Xaa₁₀ is: Tyr or Trp;
10 Xaa₁₂ is: Arg, Lys, Glu, hR, Orn, or Lys (isopropyl);
Xaa₁₃ is: Leu, Phe, Glu, or Ala;
Xaa₁₄ is: Arg, Leu, Lys, Ala, hR, Orn, or Lys (isopropyl);
Xaa₁₅ is: Lys, Ala, Arg, Glu, Leu, hR, Orn, or Lys (isopropyl);
Xaa₁₆ is: Gln, Lys, Glu, Ala, hR, Orn, or Lys (isopropyl);
15 Xaa₁₇ is: Val, Ala, Leu, Ile, or Met;
Xaa₁₉ is: Val, Ala, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr,
Trp, Tyr, Cys, or Asp;
Xaa₂₀ is: Lys, Gln, hR, Arg, Ser, His, Orn, or Lys (isopropyl);
Xaa₂₁ is: Lys, His, or Arg;
20 Xaa₂₂ is: Tyr, Trp, Phe, Thr, Leu, Ile, or Val;
Xaa₂₄ is: Gln, Glu, or Asn;
Xaa₂₅ is: Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, or Tyr;
Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, or Phe;
Xaa₂₇ is: Lys, hR, Arg, Gln, Ala, Asp, Glu, Phe, Gly, His, Ile, Met, Asn, Pro, Ser, Thr,
25 Val, Trp, Tyr, Lys (isopropyl), Cys, or Leu;
Xaa₂₈ is: Asn, Asp, Gln, Lys, or Arg;
Xaa₂₉ is: Lys, Ser, Arg, Asn, hR, Gly, Ala, Asp, Glu, Phe, His, Ile, Leu, Met, Pro, Gln,
Thr, Val, Trp, Tyr, Cys, or is absent;
Xaa₃₀ is: Arg, Lys, Ile, Gly, Ala, Asp, Glu, Phe, His, Leu, Met, Asn, Pro, Gln, Ser, Thr,
30 Val, Trp, Tyr, Cys, or is absent;
Xaa₃₁ is: Tyr, His, Phe, Thr, Cys, or is absent;
Xaa₃₂ is: Ser, Cys, or is absent;

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Xaa₃₃ is: Trp or is absent;

Xaa₃₄ is: Cys or is absent;

Xaa₃₅ is: Glu or is absent;

Xaa₃₆ is: Pro or is absent;

5 Xaa₃₇ is: Gly or is absent;

Xaa₃₈ is: Trp or is absent;

Xaa₃₉ is: Cys or is absent; and

Xaa₄₀ is: Arg or is absent

provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆, Xaa₃₇,

10 Xaa₃₈, or Xaa₃₉ is absent, the next amino acid present downstream is the next amino acid in the sequence;

and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the sequence and wherein the C-terminal extension comprises an amino acid sequence selected from the group consisting of:

15 a) Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Xaa₇-Xaa₈-Xaa₉-Xaa₁₀-Xaa₁₁

Formula 7 (SEQ ID NO: 15)

wherein:

Xaa₁ is: Gly, Cys, or absent;

Xaa₂ is: Gly, Arg, or absent;

20 Xaa₃ is: Pro, Thr, or absent;

Xaa₄ is: Ser or absent;

Xaa₅ is: Ser or absent;

Xaa₆ is: Gly or absent;

Xaa₇ is: Ala or absent;

25 Xaa₈ is: Pro, or absent;

Xaa₉ is: Pro, or absent;

Xaa₁₀ is: Pro or absent; and

Xaa₁₁ is: Ser, Cys, or absent;

provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ is

30 absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated;

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b) Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Xaa₇-Xaa₈-Xaa₉-Xaa₁₀-Xaa₁₁-Xaa₁₂-
Xaa₁₃

Formula 5 (SEQ ID NO: 8)

wherein:

- 5 Xaa₁ is: Gly or absent;
Xaa₂ is: Gly or absent;
Xaa₃ is: Pro, Ser, Ala, or absent;
Xaa₄ is: Ser, Pro, His, or absent;
Xaa₅ is: Ser, Arg, Thr, Trp, Lys, or absent;
10 Xaa₆ is: Gly, Ser, or absent;
Xaa₇ is: Ala, Asp, Arg, Glu, Lys, Gly, or absent;
Xaa₈ is: Pro, Ser, Ala, or absent;
Xaa₉ is: Pro, Ser, Ala, or absent;
Xaa₁₀ is: Pro, Ser, Ala, Arg, Lys, His, or absent;
15 Xaa₁₁ is: Ser, His, Pro, Lys, Arg, or absent;
Xaa₁₂ is: His, Ser, Arg, Lys, or absent; and
Xaa₁₃ is: His, Ser, Arg, Lys, or absent;

provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀,
Xaa₁₁, or Xaa₁₂ is absent, the next amino acid present downstream is the next amino acid
20 in the C-terminal extension and wherein the C-terminal amino acid may be amidated; and

c) Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Xaa₇-Xaa₈-Xaa₉-Xaa₁₀-Xaa₁₁

Formula 6 (SEQ ID NO: 9)

wherein:

- Xaa₁ is: Gly or absent;
25 Xaa₂ is: Gly or absent;
Xaa₃ is: Pro, Ser, Ala, or absent;
Xaa₄ is: Ser or absent;
Xaa₅ is: Ser or absent;
Xaa₆ is: Gly or absent;
30 Xaa₇ is: Ala or absent;
Xaa₈ is: Pro, Ser, Ala, or absent;
Xaa₉ is: Pro, Ser, Ala, or absent;

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Xaa₁₀ is: Pro, Ser, Ala, or absent; and

Xaa₁₁ is: Ser or absent;

provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ is absent, the next amino acid present downstream is the next amino acid in the sequence

5 and wherein the C-terminal amino acid may be amidated,

and wherein:

at least one of the Cys residues is covalently attached to a PEG molecule, or

at least one of the Lys residues is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid is covalently attached to a PEG molecule, or any

10 combination thereof.

Preferably, an alternative selective VPAC2 receptor peptide agonist of the present invention has the amino acid sequence of Formula 4 (SEQ ID NO: 7), modified so that from one, two, three, four, five, six, seven, eight, nine, or ten amino acids differ from the amino acid in the corresponding position of SEQ ID NO: 1.

15 Another alternative embodiment of the present invention is a PEGylated VPAC2 receptor peptide agonist comprising a sequence of the formula:

Xaa₁-Xaa₂-Asp-Xaa₄-Xaa₅-Xaa₆-Thr-Xaa₈-Asn-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃-
Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Ala-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Leu-Xaa₂₄-Xaa₂₅-
Xaa₂₆-Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁

20 **Formula 2 (SEQ ID NO: 5)**

wherein:

Xaa₁ is: His or is absent;

Xaa₂ is: dA, Ser, Val, Gly, Thr, Leu, dS, or Pro;

Xaa₄ is: Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, or Gly;

25 Xaa₅ is: Val, Leu, Phe, Ile, Thr, Trp, or Tyr;

Xaa₆ is: Phe, Ile, Leu, Thr, Val, Trp, or Tyr;

Xaa₈ is: Asp;

Xaa₁₀ is: Tyr or Trp;

Xaa₁₂ is: Arg or Lys;

30 Xaa₁₃ is: Leu, Phe, Glu, or Ala;

Xaa₁₄ is: Arg, Leu, Lys or Ala;

Xaa₁₅ is: Lys, Ala, Arg, Glu, or Leu;

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Xaa₁₆ is: Gln, Lys, or Ala;

Xaa₁₇ is: Val, Ala, Leu, or Met;

Xaa₁₉ is: Ala or Leu;

Xaa₂₀ is: Lys, Gln, hR, Arg, or Ser;

5 Xaa₂₁ is: Lys or Arg;

Xaa₂₂ is: Tyr, Trp, Phe, Thr, Leu, Ile, or Val;

Xaa₂₄ is: Gln or Asn;

Xaa₂₅ is: Ser, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, or Tyr;

Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, or Phe;

10 Xaa₂₇ is: Lys, hR, Arg, Gln, or Leu;

Xaa₂₈ is: Asn, Lys, or Arg;

Xaa₂₉ is: Lys, Ser, Arg, Asn, hR, or is absent;

Xaa₃₀ is: Arg, Lys, Ile, or is absent; and

Xaa₃₁ is: Tyr, His, Phe, or is absent,

15 provided that if Xaa₂₉ is absent then Xaa₃₀ and Xaa₃₁ are also absent and if Xaa₃₀ is absent then Xaa₃₁ is absent;

and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the sequence and wherein the C-terminal extension comprises an amino acid sequence of the Formula 7 (SEQ ID NO: 15);

20 provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ of Formula 7 is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated,

and wherein:

at least one of the Cys residues is covalently attached to a PEG molecule, or

25 at least one of the Lys residues is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid is covalently attached to a PEG molecule, or any combination thereof.

Preferably, an alternative selective VPAC2 receptor peptide agonist of the present invention has the amino acid sequence of Formula 2 (SEQ ID NO: 5), modified so that
30 from one, two, three, four, five, six, seven, eight, nine, or ten amino acids differ from the amino acid in the corresponding position of SEQ ID NO: 1.

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Yet another alternative embodiment of the present invention is a PEGylated VPAC2 receptor peptide agonist comprising a sequence of the formula:

His-Xaa₂-Xaa₃-Ala-Val-Phe-Thr-Xaa₈-Xaa₉-Tyr-Thr-Xaa₁₂-Leu-Arg-
 Xaa₁₅-Xaa₁₆-Xaa₁₇-Ala-Xaa₁₉-Xaa₂₀-Xaa₂₁-Tyr-Leu-Xaa₂₄-Xaa₂₅-Xaa₂₆-
 5 Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁-Xaa₃₂-Xaa₃₃-Xaa₃₄-Xaa₃₅-Xaa₃₆-Xaa₃₇-
 Xaa₃₈-Xaa₃₉-Xaa₄₀

Formula 3 (SEQ ID NO: 6)

wherein:

- Xaa₂ is: Ser or Thr;
- 10 Xaa₃ is: Asp or Glu;
- Xaa₈ is: Asp or Glu;
- Xaa₉ is: Asn, Gln, or Asp;
- Xaa₁₂ is: Arg, Lys, or Glu;
- Xaa₁₅ is: Lys or Glu;
- 15 Xaa₁₆ is: Gln or Glu;
- Xaa₁₇ is: Met, Leu, Ile, or Val;
- Xaa₁₉ is: Val, Ala, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr,
 Trp, Tyr, Cys, or Asp;
- Xaa₂₀ is: Lys or His;
- 20 Xaa₂₁ is: Lys or His;
- Xaa₂₄ is: Asn, Gln, or Glu;
- Xaa₂₅ is: Ser, Asp, or Thr;
- Xaa₂₆ is: Ile or Leu;
- Xaa₂₇ is: Leu, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Met, Asn, Pro, Gln, Arg, Ser, Thr,
 25 Val, Trp, Tyr, or Cys;
- Xaa₂₈ is: Asn, Asp, Gln, or Lys;
- Xaa₂₉ is: Gly, Lys, Ala, Asp, Glu, Phe, His, Ile, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr,
 Val, Trp, Tyr, Cys, or is absent;
- Xaa₃₀ is: Gly, Arg, Ala, Asp, Glu, Phe, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Ser, Thr,
 30 Val, Trp, Tyr, Cys, or is absent;
- Xaa₃₁ is: Thr, Tyr, Cys, or is absent;
- Xaa₃₂ is: Ser, Cys, or is absent;

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Xaa₃₃ is: Trp or is absent;

Xaa₃₄ is: Cys or is absent;

Xaa₃₅ is: Glu or is absent;

Xaa₃₆ is: Pro or is absent;

5 Xaa₃₇ is: Gly or is absent;

Xaa₃₈ is: Trp or is absent;

Xaa₃₉ is: Cys or is absent;

Xaa₄₀ is: Arg or is absent;

provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆, Xaa₃₇,

10 Xaa₃₈, or Xaa₃₉ is absent, the next amino acid present downstream is the next amino acid in the sequence;

and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the sequence and wherein the C-terminal extension comprises an amino acid sequence selected from the group consisting of:

15 a) Formula 7 (SEQ ID NO: 15);

provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ of Formula 7 is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated;

b) Formula 5 (SEQ ID NO: 8);

20 provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, or Xaa₁₂ of Formula 5 is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated; and

c) Formula 6 (SEQ ID NO: 9);

25 provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ of Formula 6 is absent, the next amino acid present downstream is the next amino acid in the sequence and wherein the C-terminal amino acid may be amidated,

and wherein:

at least one of the Cys residues is covalently attached to a PEG molecule, or

30 at least one of the Lys residues is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid is covalently attached to a PEG molecule, or any combination thereof.

For example, if Xaa₂₉ of the peptide sequence is Gly and Xaa₃₀ is absent, the next amino acid bonded to Gly at position 29 is an amino acid listed for position 31 or, if position 31 is also absent, an amino acid listed for position 32 is bonded to Gly at position 29, and so forth. Additionally, for example, if Xaa₂₉ is Gly and Xaa₃₀ through Xaa₄₀ are absent, Gly may be the C-terminal amino acid and may be amidated.

Preferably, an alternative selective VPAC2 receptor peptide agonist of the present invention has the amino acid sequence of Formula 3 (SEQ ID NO: 6), modified so that from one, two, three, four, five, six, seven, eight, nine, or ten amino acids differ from the amino acid in the corresponding position of SEQ ID NO: 1.

Another alternative embodiment of the present invention is a PEGylated VPAC2 receptor peptide agonist comprising a sequence of the formula:

His-Xaa₂-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Xaa₁₂-Leu-Xaa₁₄-Xaa₁₅-
Xaa₁₆-Xaa₁₇-Ala-Xaa₁₉-Xaa₂₀-Xaa₂₁-Tyr-Leu-Xaa₂₄-Xaa₂₅-Xaa₂₆-Xaa₂₇-
Asn-Xaa₂₉-Xaa₃₀-Xaa₃₁

Formula 1 (SEQ ID NO: 4)

wherein:

Xaa₂ is: Ser, Val, dA, or dS;

Xaa₁₂ is: Arg, Lys, hR, Orn, or Lys (isopropyl);

Xaa₁₄ is: Arg, Leu, Lys, hR, Orn, or Lys (isopropyl);

Xaa₁₅ is: Lys, Ala, Arg, hR, Orn, or Lys (isopropyl);

Xaa₁₆ is: Gln, Lys, Ala, hR, Orn, or Lys (isopropyl);

Xaa₁₇ is: Met, Val, Ala, or Leu;

Xaa₁₉ is: Val, Ala or Leu;

Xaa₂₀ is: Lys, Gln, Arg, hR, Orn, or Lys (isopropyl);

Xaa₂₁ is: Lys or Arg;

Xaa₂₄ is: Asn or Gln;

Xaa₂₅ is: Ser, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, or Tyr;

Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, or Phe;

Xaa₂₇ is: Leu, hR, Arg, Lys, or Lys (isopropyl);

Xaa₂₉ is: Lys, Ser, Arg, hR, or absent;

Xaa₃₀ is: Arg, Lys, or absent; and

Xaa₃₁ is: Tyr, Phe, or absent,

provided that at least one Xaa selected from the group consisting of: Xaa₂, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₂₀, Xaa₂₅, Xaa₂₆, Xaa₂₇, and Xaa₃₁ is an amino acid that differs from the amino acid at the corresponding position in SEQ ID NO: 1,

provided that if Xaa₂₉ is absent then Xaa₃₀ and Xaa₃₁ are also absent, and if Xaa₃₀ is absent then Xaa₃₁ is also absent;

and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the sequence and wherein the C-terminal extension comprises an amino acid sequence selected from the group consisting of:

a) Formula 5 (SEQ ID NO: 8);

provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, or Xaa₁₃ of Formula 5 is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated; and

b) Formula 6 (SEQ ID NO: 9);

provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ of Formula 6 is absent, the next amino acid present downstream is the next amino acid in the sequence and wherein the C-terminal amino acid may be amidated,

and wherein:

at least one of the Cys residues is covalently attached to a PEG molecule, or

at least one of the Lys residues is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid is covalently attached to a PEG molecule, or any combination thereof.

Preferably, an alternative selective VPAC2 receptor peptide agonist of the present invention has the amino acid sequence of Formula 1 (SEQ ID NO: 4), modified so that from one, two, three, four, five, six, seven, eight, nine, or ten amino acids differ from the amino acid in the corresponding position of SEQ ID NO: 1.

A further alternative embodiment of the present invention is a VPAC2 receptor peptide agonist comprising a sequence of the Formula 1 (SEQ ID NO: 4), wherein the sequence has at least one amino acid substitution selected from the group consisting of:

Xaa₂ is: Val or dA;

Xaa₁₄ is: Leu;

Xaa₁₅ is: Ala;

Xaa₁₆ is: Lys;

Xaa₁₇ is: Ala;

Xaa₂₀ is: Gln;

Xaa₂₅ is: Phe, Ile, Leu, Val, Trp, or Tyr;

5 Xaa₂₆ is: Thr, Trp, or Tyr;

Xaa₂₇ is: hR; and

Xaa₃₁ is: Phe,

and provided that if Xaa₂₉ is absent then Xaa₃₀ and Xaa₃₁ are also absent and if Xaa₃₀ is absent then Xaa₃₁ is absent.

10 The peptide of Formula 1 (SEQ ID NO: 4) can further comprise a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the peptide of Formula 1 (SEQ ID NO: 4) and wherein the C-terminal extension comprises an amino acid sequence selected from the group consisting of:

a) Formula 5 (SEQ ID NO: 8);

15 provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, or Xaa₁₂ of Formula 5 is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated; and

b) Formula 6 (SEQ ID NO: 9);

20 provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ of Formula 6 is absent, the next amino acid present downstream is the next amino acid in the sequence and wherein the C-terminal amino acid may be amidated.

Additional alternative embodiments of the present invention include a VPAC2 receptor peptide agonist further comprising a N-terminal modification linked to the N-terminus of the peptide sequence wherein the N-terminal modification involves acylation, 25 alkylation, acetylation, a carbobenzoyl group, a succinimide group, a sulfonamide group, a carbamate group, or a urea group. N-terminal modification includes, but is not limited to eighteen carbons (C-18), ten carbons (C-10), and six carbons (C-6). N-terminal modification also includes HS(CH₂)₂CO.

30 Other alternative embodiments of the present invention include a VPAC2 receptor peptide agonist further comprising a N-terminal modification linked to the N-terminus of

the peptide sequence wherein the N-terminal modification is selected from the group consisting of D-histidine and isoleucine.

Alternative embodiments of the present invention also include a VPAC2 receptor peptide agonist further comprising a N-terminal modification linked to the N-terminus of the peptide sequence wherein the N-terminal modification is selected from the group consisting of acetyl, propionyl, butyryl, pentanoyl, hexanoyl, Met, 3-phenylpropionyl, phenylacetyl, benzoyl, and norleucine.

The VPAC2 receptor peptide agonists of the present invention, therefore, have the advantage that they have enhanced selectivity, potency and/or stability over known VPAC2 receptor peptide agonists. In particular, the addition of the extension sequence of exendin-4 as the c-capping sequence surprisingly increased the VPAC2 receptor selectivity as well as increasing proteolytic stability. The covalent attachment of one or more molecules of PEG to particular residues of a VPAC2 receptor peptide agonist results in a biologically active, PEGylated VPAC2 receptor peptide agonist with an extended half-life and reduced clearance when compared to that of non-PEGylated VPAC2 receptor peptide agonists.

A "selective VPAC2 receptor peptide agonist" of the present invention is a peptide that selectively activates the VPAC2 receptor to induce insulin secretion. Preferably, the sequence for a selective VPAC2 receptor peptide agonist of the present invention has from about twenty-eight to about thirty-five naturally occurring and/or non-naturally occurring amino acids and may or may not additionally comprise a C-terminal extension. More preferably, the selective VPAC2 receptor peptide agonist has from twenty-eight to thirty-one naturally occurring and/or non-naturally occurring amino acids and may or may not additionally comprise a C-terminal extension.

A "selective PEGylated VPAC2 receptor peptide agonist" is a selective VPAC2 receptor peptide agonist covalently attached to one or more molecules of polyethylene glycol (PEG), or a derivative thereof, wherein each PEG is attached to a cysteine or lysine amino acid, to a K(W) or K(CO(CH₂)₂SH), or to the carboxy terminus of a peptide.

Selective PEGylated VPAC2 receptor peptide agonists may have a C-terminal extension. The "C-terminal extension" of the present invention comprises a sequence having from one to thirteen naturally occurring or non-naturally occurring amino acids linked to the C-terminus of the sequence of Formula 10, 12, 13 or 16 at the N-terminus of

the C-terminal extension via a peptide bond. Any one of the Cys, Lys, K(W), or K(CO(CH₂)₂SH) residues in the C-terminal extension can be covalently attached to a PEG molecule, or the carboxy-terminal amino acid of the C-terminal extension can be covalently attached to a PEG molecule.

5 As used herein, the term "linked to" with reference to the term C-terminal extension, includes the addition or attachment of amino acids or chemical groups directly to the C-terminus of the peptide of the Formula 10, 12, 13, or 16.

Optionally, the selective PEGylated VPAC2 receptor peptide agonist may also have an N-terminus modification. The term "N-terminal modification" as used herein
10 includes the addition or attachment of amino acids or chemical groups directly to the N-terminal of a peptide and the formation of chemical groups, which incorporate the nitrogen at the N-terminus of a peptide.

The N-terminal modification may comprise the addition of one or more naturally occurring or non-naturally occurring amino acids to the VPAC2 receptor peptide agonist
15 sequence, preferably there are not more than ten amino acids, with one amino acid being more preferred. Naturally occurring amino acids which may be added to the N-terminus include methionine and isoleucine. A modified amino acid added to the N-terminus may be D-histidine. Alternatively, the following amino acids may be added to the N-terminus: (SEQ ID NO: 14) Ser-Trp-Cys-Glu-Pro-Gly-Trp-Cys-Arg, wherein the Arg is linked to
20 the N-terminus of the peptide agonist. Preferably, any amino acids added to the N-terminus are linked to the N-terminus by a peptide bond.

The term "linked to" as used herein, with reference to the term N-terminal modification, includes the addition or attachment of amino acids or chemical groups directly to the N-terminus of the PEGylated VPAC2 receptor agonist. The addition of the
25 above N-terminal modifications may be achieved under normal coupling conditions for peptide bond formation.

The N-terminus of the peptide agonist may also be modified by the addition of an alkyl group (R), preferably a C₁-C₁₆ alkyl group, to form (R)NH-.

Alternatively, the N-terminus of the peptide agonist may be modified by the
30 addition of a group of the formula -C(O)R¹ to form an amide of the formula R¹C(O)NH-. The addition of a group of the formula -C(O)R¹ may be achieved by reaction with an organic acid of the formula R¹COOH. Modification of the N-terminus of an amino acid

sequence using acylation is demonstrated in the art (e.g. Gozes *et al.*, *J. Pharmacol Exp Ther*, 273:161-167 (1995)). Addition of a group of the formula $-C(O)R^1$ may result in the formation of a urea group (see WO 01/23240, WO 2004/006839) or a carbamate group at the N-terminus. Also, the N-terminus may be modified by the addition of
 5 pyroglutamic acid or 6-aminohexanoic acid.

The N-terminus of the peptide agonist may be modified by the addition of a group of the formula $-SO_2R^5$, to form a sulfonamide group at the N-terminus.

The N-terminus of the peptide agonist may also be modified by reacting with succinic anhydride to form a succinimide group at the N-terminus. The succinimide
 10 group incorporates the nitrogen at the N-terminus of the peptide.

The N-terminus may alternatively be modified by the addition of methionine sulfoxide, biotinyl-6-aminohexanoic acid, or $-C(=NH)-NH_2$. The addition of $-C(=NH)-NH_2$ is a guanidation modification, where the terminal NH_2 of the N-terminal amino acid becomes $-NH-C(=NH)-NH_2$.

15 Most of the sequences of the present invention, including the N- terminal modifications and the C- terminal extensions contain the standard single letter or three letter codes for the twenty naturally occurring amino acids. The other codes used are defined as follows:

Ac = Acetyl

20 C₆ = hexanoyl

d = the D isoform (non-naturally occurring) of the respective amino acid,

e.g., dA = D-alanine, dS = D-serine, dK = D-lysine

hR = homoarginine

_ = position not occupied

25 Aib = amino isobutyric acid

CH₂ = methylene

Met(O) = methionine sulfoxide

OMe = methoxy

Nle = Nor-leucine

30 NMe = N-methyl attached to the alpha amino group of an amino acid,

e.g., NMeA = N-methyl alanine, NMeV = N-methyl valine

Orn = ornithine

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Cit = citrulline

K (Ac) = ϵ -acetyl lysine

M = methionine

I = isoleucine

5 PEG = polyethylene glycol

Biotin-Acp = Biotinyl-6-aminohexanoic acid (6-aminocaproic acid)

K(W) = ϵ -(L-tryptophyl)-lysineK(CO(CH₂)₂SH) = ϵ -(3'-mercaptopropionyl)-lysine
 = a lactam bridge

10 The term "VPAC2" is used to refer to and in conjunction with the particular receptor (Lutz, *et al.*, *FEBS Lett.*, 458: 197-203 (1999); Adamou, *et al.*, *Biochem. Biophys. Res. Commun.*, 209: 385-392 (1995)) that the agonists of the present invention activate. This term also is used to refer to and in conjunction with the agonists of the present invention.

15 VIP naturally occurs as a single sequence having 28 amino acids. However, PACAP exists as either a 38 amino acid peptide (PACAP-38) or as a 27 amino acid peptide (PACAP-27) with an amidated carboxyl (Miyata, *et al.*, *Biochem Biophys Res Commun.*, 170:643-648 (1990)). The sequences for VIP, PACAP-27, and PACAP-38 are as follows:

20

Peptide	Seq.ID #	Sequence
VIP	SEQ ID NO: 1	HSDAVFTDNYTRLRKQMAVKKYLNSILN
PACAP-27	SEQ ID NO: 2	HSDGIFTDSYSRYRKQMAVKKYLA AVL-NH ₂
PACAP-38	SEQ ID NO: 3	HSDGIFTDSYSRYRKQMAVKKYLA AVLGKRYQRVKNK-NH ₂

The term "naturally occurring amino acid" as used herein means the twenty amino acids coded for by the human genetic code (i.e. the twenty standard amino acids). These twenty amino acids are: Alanine, Arginine, Asparagine, Aspartic Acid, Cysteine,

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Glutamine, Glutamic Acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine and Valine.

Examples of “non-naturally occurring amino acids” include both synthetic amino acids and those modified by the body. These include D-amino acids, arginine-like amino acids (e.g., homoarginine), and other amino acids having an extra methylene in the side chain (“homo” amino acids), and modified amino acids (e.g. norleucine, lysine (isopropyl) – wherein the side chain amine of lysine is modified by an isopropyl group). Also included are amino acids such as ornithine and amino isobutyric acid.

“Selective” as used herein refers to a VPAC2 receptor peptide agonist with increased selectivity for the VPAC2 receptor compared to other known receptors. The degree of selectivity is determined by a ratio of VPAC2 receptor binding affinity to VPAC1 receptor binding affinity and by a ratio of VPAC2 receptor binding affinity to PAC1 receptor binding affinity. Preferably, the agonists of the present invention have a selectivity ratio where the affinity for the VPAC2 receptor is at least 50 times greater than for the VPAC1 and/or for PAC1 receptors. More preferably, the affinity is at least 100 times greater for VPAC2 than for VPAC1 and/or for PAC1. Even more preferably, the affinity is at least 200 times greater for VPAC2 than for VPAC1 and/or for PAC1. Still more preferably, the affinity is at least 500 times greater for VPAC2 than for VPAC1 and/or for PAC1. Yet more preferably, the affinity is at least 1000 times greater for VPAC2 than for VPAC1 and/or for PAC1. Binding affinity is determined as described below in Example 4.

“Percent (%) sequence identity” as used herein is used to denote sequences which when aligned have similar (identical or conservatively replaced) amino acids in like positions or regions, where identical or conservatively replaced amino acids are those which do not alter the activity or function of the protein as compared to the starting protein. For example, two amino acid sequences with at least 85% identity to each other have at least 85% similar (identical or conservatively replaced residues) in a like position when aligned optimally allowing for up to 3 gaps, with the proviso that in respect of the gaps a total of not more than 15 amino acid residues is affected. Percent sequence identity may be calculated by determining the number of residues that differ between a peptide encompassed by the present invention and a reference peptide such as P83 (SEQ ID NO: 83), taking that number and dividing it by the number of amino acids in the

reference peptide (e.g. 39 amino acids for P83), multiplying the result by 100, and subtracting that resulting number from 100. For example, a sequence having 39 amino acids with four amino acids that are different from P83 would have a percent (%) sequence identity of 90% (e.g. $100 - ((4 / 39) \times 100)$). For a sequence that is longer than 5 39 amino acids, the number of residues that differ from the P83 sequence will include the additional amino acids over 39 for purposes of the aforementioned calculation. For example, a sequence having 41 amino acids, with four amino acids different from the 39 amino acids in the P83 sequence and with two additional amino acids at the carboxy terminus which are not present in the P83 sequence, would have a total of six amino acids 10 that differ from P83. Thus, this sequence would have a percent (%) sequence identity of 84% (e.g. $100 - ((6 / 39) \times 100)$). The degree of sequence identity may be determined using methods well known in the art (see, for example, Wilbur, W.J. and Lipman, D.J., *Proc. Natl. Acad. Sci. USA* 80:726-730 (1983) and Myers E. and Miller W., *Comput. Appl. Biosci.* 4:11-17 (1988)). One program which may be used in determining the 15 degree of similarity is the MegAlign Lipman-Pearson one pair method (using default parameters) which can be obtained from DNASTAR Inc, 1128, Selfpark Street, Madison, Wisconsin, 53715, USA as part of the Lasergene system. Another program, which may be used, is Clustal W. This is a multiple sequence alignment package developed by Thompson *et al* (*Nucleic Acids Research*, 22(22):4673-4680(1994)) for DNA or protein 20 sequences. This tool is useful for performing cross-species comparisons of related sequences and viewing sequence conservation. Clustal W is a general purpose multiple sequence alignment program for DNA or proteins. It produces biologically meaningful multiple sequence alignments of divergent sequences. It calculates the best match for the selected sequences, and lines them up so that the identities, similarities and differences 25 can be seen. Evolutionary relationships can be seen via viewing Cladograms or Phylograms.

The sequence for a selective PEGylated VPAC2 receptor peptide agonist of the present invention is selective for the VPAC2 receptor and preferably has a sequence identity in the range of 60% to 70%, 60% to 65%, 65% to 70%, 70% to 80%, 70% to 30 75%, 75% to 80%, 80% to 90%, 80% to 85%, 85% to 90%, 90% to 97%, 90% to 95%, or 95% to 97%, with P83 (SEQ ID NO: 83). Preferably, the sequence has a sequence identity of greater than 71% with P83 (SEQ ID NO: 83). More preferably, the sequence

has greater than 74% sequence identity with P83 (SEQ ID NO: 83). Even more preferably, the sequence has greater than 76% sequence identity with P83 (SEQ ID NO: 83). Yet more preferably, the sequence has greater than 79% sequence identity or 84% sequence identity with P83 (SEQ ID NO: 83).

5 The term "C₁-C₁₆ alkyl" as used herein means a monovalent saturated straight, branched or cyclic chain hydrocarbon radical having from 1 to 16 carbon atoms. Thus the term "C₁-C₁₆ alkyl" includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-heptyl, n-octyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The C₁-C₁₆ alkyl group may be optionally substituted with one or more
10 substituents.

 The term "C₁-C₆ alkyl" as used herein means a monovalent saturated straight, branched or cyclic chain hydrocarbon radical having from 1 to 6 carbon atoms. Thus the term "C₁-C₆ alkyl" includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The
15 C₁-C₆ alkyl group may be optionally substituted with one or more substituents.

 The term "C₂-C₆ alkenyl" as used herein means a monovalent straight, branched or cyclic chain hydrocarbon radical having at least one double bond and having from 2 to 6 carbon atoms. Thus the term "C₂-C₆ alkenyl" includes vinyl, prop-2-enyl, but-3-enyl, pent-4-enyl and isopropenyl. The C₂-C₆ alkenyl group may be optionally substituted with
20 one or more substituents.

 The term "C₂-C₆ alkynyl" as used herein means a monovalent straight or branched chain hydrocarbon radical having at least one triple bond and having from 2 to 6 carbon atoms. Thus the term "C₂-C₆ alkynyl" includes prop-2-ynyl, but-3-ynyl and pent-4-ynyl. The C₂-C₆ alkynyl may be optionally substituted with one or more substituents.

25 The term "halo" or "halogen" means fluorine, chlorine, bromine or iodine.

 The term "aryl" when used alone or as part of a group is a 5 to 10 membered aromatic or heteroaromatic group including a phenyl group, a 5 or 6- membered monocyclic heteroaromatic group, each member of which may be optionally substituted with 1, 2, 3, 4 or 5 substituents (depending upon the number of available substitution
30 positions), a naphthyl group or an 8-, 9- or 10- membered bicyclic heteroaromatic group, each member of which may be optionally substituted with 1, 2, 3, 4, 5 or 6 substituents (depending on the number of available substitution positions). Within this definition of

aryl, suitable substitutions include C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, amino, hydroxy, halogen, -SH and CF₃.

The term "aryl C₁-C₄ alkyl" as used herein means a C₁-C₄ alkyl group substituted with an aryl. Thus the term "aryl C₁-C₄ alkyl" includes benzyl, 1-phenylethyl (α -methylbenzyl), 2-phenylethyl, 1-naphthalenemethyl or 2-naphthalenemethyl.

The term "naphthyl" includes 1-naphthyl, and 2-naphthyl. 1-naphthyl is preferred.

The term "benzyl" as used herein means a monovalent unsubstituted phenyl radical linked to the point of substitution by a -CH₂- group.

The term "5- or 6-membered monocyclic heteroaromatic group" as used herein means a monocyclic aromatic group with a total of 5 or 6 atoms in the ring wherein from 1 to 4 of those atoms are each independently selected from N, O and S. Preferred groups have 1 or 2 atoms in the ring which are each independently selected from N, O and S. Examples of 5-membered monocyclic heteroaromatic groups include pyrrolyl (also called azolyl), furanyl, thienyl, pyrazolyl (also called 1H-pyrazolyl and 1,2-diazolyl), imidazolyl, oxazolyl (also called 1,3-oxazolyl), isoxazolyl (also called 1,2-oxazolyl), thiazolyl (also called 1,3-thiazolyl), isothiazolyl (also called 1,2-thiazolyl), triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl and thiatriazolyl. Examples of 6-membered monocyclic heteroaromatic groups include pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl and triazinyl.

The term "8-, 9- or 10-membered bicyclic heteroaromatic group" as used herein means a fused bicyclic aromatic group with a total of 8, 9 or 10 atoms in the ring system wherein from 1 to 4 of those atoms are each independently selected from N, O and S. Preferred groups have from 1 to 3 atoms in the ring system which are each independently selected from N, O and S. Suitable 8-membered bicyclic heteroaromatic groups include imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]thienyl, thieno[2,3-d][1,3]thiazolyl and thieno[2,3-d]imidazolyl. Suitable 9-membered bicyclic heteroaromatic groups include indolyl, isoindolyl, benzofuranyl (also called benzo[b]furanyl), isobenzofuranyl (also called benzo[c]furanyl), benzothienyl (also called benzo[b]thienyl), isobenzothienyl (also called benzo[c]thienyl), indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl,

2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl and imidazo[1,2-a]pyridine. Suitable 10-membered bicyclic heteroaromatic groups include quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-naphthyridyl, 1,6-naphthyridyl, 1,7-naphthyridyl and 1,8-naphthyridyl.

5 The term "C₁-C₆ alkoxy" as used herein means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 6 carbon atoms linked to the point of substitution by a divalent O radical. Thus the term "C₁-C₆ alkoxy" includes, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy. The C₁-C₆ alkoxy group may be optionally
10 substituted with one or more substituents.

 The term "PEG" as used herein means a polyethylene glycol molecule. In its typical form, PEG is a linear polymer with terminal hydroxyl groups and has the formula HO-CH₂CH₂-(CH₂CH₂O)*n*-CH₂CH₂-OH, where *n* is from about 8 to about 4000. The terminal hydrogen may be substituted with a protective group such as an alkyl or alkanol
15 group. Preferably, PEG has at least one hydroxy group, more preferably it is a terminal hydroxy group. It is this hydroxy group which is preferably activated to react with the peptide. There are many forms of PEG useful for the present invention. Numerous derivatives of PEG exist in the art and are suitable for use in the invention. (See, e.g., U.S. Patent Nos: 5,445,090; 5,900,461; 5,932,462; 6,436,386; 6,448,369; 6,437,025;
20 6,448,369; 6,495,659; 6,515,100 and 6,514,491; and Zalipsky, S. *Bioconjugate Chem.* 6:150-165, 1995). The PEG molecule covalently attached to VPAC2 receptor peptide agonists in the present invention is not intended to be limited to a particular type. The molecular weight of the PEG molecule is preferably from 500-100,000 daltons and more preferably 10,000, 20,000, 30,000, 40,000, 50,000, or 60,000 daltons and most preferably
25 20,000 or 40,000 daltons. PEG may be linear or branched and PEGylated VPAC2 receptor peptide agonists of the invention may have one, two or three PEG molecules attached to the peptide. It is more preferable that there be one or two PEG molecules per PEGylated VPAC2 receptor peptide agonist, however, when there is more than one PEG molecule per peptide molecule, it is preferred that there be no more than three. It is
30 further contemplated that both ends of the PEG molecule may be homo- or hetero-functionalized for crosslinking two or more VPAC2 receptor peptide agonists together. Where there are two PEG molecules present, the PEG molecules will preferably be

20,000 dalton PEG molecules. However, PEG molecules having a different molecular weight may be used, for example, one 10,000 dalton PEG molecule and one 30,000 PEG molecule.

In the present invention, a PEG molecule may be covalently attached to a Cys or
5 Lys residue or to the C-terminal residue. The PEG molecule may also be covalently attached to a Trp residue which is coupled to the side chain of a Lys residue (K(W)). Alternatively, a K(CO(CH₂)₂SH) group may be PEGylated to form K(CO(CH₂)₂S-PEG). Any Lys residue in the peptide agonist may be substituted for a K(W) or K(CO(CH₂)₂SH), which may then be PEGylated. In addition, any Cys residue in the
10 peptide agonist may be substituted for a modified cysteine residue, for example, hC. The modified Cys residue may be covalently attached to a PEG molecule.

The term "PEGylation" as used herein means the covalent attachment of one or more PEG molecules as described above to the VPAC2 receptor peptide agonists of the present invention.

15 "Insulinotropic activity" refers to the ability to stimulate insulin secretion in response to elevated glucose levels, thereby causing glucose uptake by cells and decreased plasma glucose levels. Insulinotropic activity can be assessed by methods known in the art, including using experiments that measure VPAC2 receptor binding activity or receptor activation (e.g. insulin secretion by insulinoma cell lines or islets,
20 intravenous glucose tolerance test (IVGTT); intraperitoneal glucose tolerance test (IPGTT), and oral glucose tolerance test (OGTT)). Insulinotropic activity is routinely measured in humans by measuring insulin levels or C-peptide levels. Selective VPAC2 receptor peptide agonists of the present invention have insulinotropic activity.

"*In vitro* potency" as used herein is the measure of the ability of a peptide to
25 activate the VPAC2 receptor in a cell-based assay. *In vitro* potency is expressed as the "EC₅₀" which is the effective concentration of compound that results in a 50% of maximum increase in activity in a single dose-response experiment. For the purposes of the present invention, *in vitro* potency is determined using the Alpha Screen assay. See Example 3 for further details of this assay.

30 The term "plasma half-life" refers to the time in which half of the relevant molecules circulate in the plasma prior to being cleared. An alternatively used term is "elimination half-life." The term "extended" or "longer" used in the context of plasma

half-life or elimination half-life indicates there is a statistically significant increase in the half-life of a PEGylated VPAC2 receptor peptide agonist relative to that of the reference molecule (e.g., the non-PEGylated form of the peptide or the native peptide) as determined under comparable conditions. Preferably a PEGylated VPAC2 receptor peptide agonist of the present invention has an elimination half-life of at least one hour, more preferably at least 3, 5, 7, 10, 15, 20 or 24 hours and most preferably at least 48 hours. The half-life reported herein is the elimination half-life; it is that which corresponds to the terminal log-linear rate of elimination. The person skilled in the art appreciates that half-life is a derived parameter that changes as a function of both clearance and volume of distribution.

Clearance is the measure of the body's ability to eliminate a drug. As clearance decreases due, for example, to modifications to a drug, half-life would be expected to increase. However, this reciprocal relationship is exact only when there is no change in the volume of distribution. A useful approximate relationship between the terminal log-linear half-life ($t_{1/2}$), clearance (C), and volume of distribution (V) is given by the equation: $t_{1/2} \approx 0.693 (V/C)$. Clearance does not indicate how much drug is being removed but, rather, the volume of biological fluid such as blood or plasma that would have to be completely freed of drug to account for the elimination. Clearance is expressed as a volume per unit of time. The PEGylated VPAC2 receptor peptide agonists of the present invention preferably have a clearance value of 200 ml/h/kg or less, more preferably 180, 150, 120, 100, 80, 60 ml/h/kg or less and most preferably 50, 40 or 20 ml/h/kg or less.

According to a preferred embodiment of the present invention, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein Xaa₃ is Asp or Glu, Xaa₈ is Asp or Glu, Xaa₁₂ is Arg, hR, Lys, or Orn, Xaa₁₄ is Arg, Gln, Aib, hR, Orn, Cit, Lys, Ala, or Leu, Xaa₁₅ is Lys, Aib, Orn, or Arg, Xaa₁₆ is Gln or Lys, Xaa₁₇ is Val, Leu, Ala, Ile, Lys, or Nle, Xaa₂₀ is Lys, Val, Leu, Aib, Ala, Gln, or Arg, Xaa₂₁ is Lys, Aib, Orn, Ala, Gln, or Arg, Xaa₂₇ is Lys, Orn, hR, or Arg, Xaa₂₈ is Asn, Gln, Lys, hR, Aib, Pro, or Orn and Xaa₂₉ is Lys, Orn, hR, or absent, and a C-terminal extension comprising an amino acid sequence of Formula 7 (SEQ ID NO: 15).

It is more preferred that the C-terminal extension in this embodiment is selected from: GGPSSGAPPPS (SEQ ID NO: 10), GGPSSGAPPPS-NH₂ (SEQ ID NO: 11), GGPSSGAPPPC (SEQ ID NO: 22), GGPSSGAPPPC-NH₂ (SEQ ID NO: 23), GRPSSGAPPPS (SEQ ID NO: 16) and GRPSSGAPPPS-NH₂ (SEQ ID NO: 17).

5 According to another embodiment of the present invention, the PEGylated VPAC2 receptor peptide agonist comprises a sequence of the Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein Xaa₁₄ is Leu, Xaa₁₅ is Ala, Xaa₁₆ is Lys, Xaa₁₇ is Leu, and Xaa₂₀ is Gln.

10 According to another preferred embodiment of the present invention, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein Xaa₃₀ and Xaa₃₁ are absent, and a C-terminal extension comprising an amino acid sequence of Formula 7 (SEQ ID NO: 15).

15 Alternatively, in yet another preferred embodiment of the present invention, the PEGylated VPAC2 receptor peptide agonist comprises an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein Xaa₂₉, Xaa₃₀ and Xaa₃₁ are absent, and a C-terminal extension comprising an amino acid sequence of Formula 7 (SEQ ID NO: 15).

20 It is more preferred that the C-terminal extension in the above embodiments is selected from: GGPSSGAPPPS (SEQ ID NO: 10), GGPSSGAPPPS-NH₂ (SEQ ID NO: 11), GGPSSGAPPPC (SEQ ID NO: 22), GGPSSGAPPPC-NH₂ (SEQ ID NO: 23), GRPSSGAPPPS (SEQ ID NO: 16) and GRPSSGAPPPS-NH₂ (SEQ ID NO: 17).

25 According to another preferred embodiment of the present invention, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein either Xaa₁₄ or Xaa₁₅ is Aib and either Xaa₂₀ or Xaa₂₁ is Aib, more preferably Xaa₁₅ is Aib and Xaa₂₀ is Aib, and a C-terminal extension comprising an amino acid sequence of Formula 7 (SEQ ID NO: 15).

30 According to yet another preferred embodiment of the present invention, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein either Xaa₁₄ or Xaa₁₅ is Aib and either Xaa₂₀ or Xaa₂₁ is Aib

and Xaa₂₈ is Gln and Xaa₂₉ is Lys or absent, and a C-terminal extension comprising an amino acid sequence of Formula 7 (SEQ ID NO: 15).

In a further preferred embodiment of the present invention, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of
5 Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein either Xaa₁₄ or Xaa₁₅ is Aib and either Xaa₂₀ or Xaa₂₁ is Aib and Xaa₁₂ of the peptide sequence is hR or Orn, Xaa₂₇ is hR or Orn and Xaa₂₉ is hR or Orn and a C-terminal extension comprising an amino acid sequence of Formula 7 (SEQ ID NO: 15).

According to yet another preferred embodiment of the present invention, there is
10 provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein Xaa₁₅ is Aib, Xaa₂₀ is Aib, and Xaa₁₂, Xaa₂₁, Xaa₂₇, and Xaa₂₈ are all Orn, and a C-terminal extension comprising an amino acid sequence of Formula 7 (SEQ ID NO: 15). In this embodiment, it is especially preferred that Xaa₈ is Glu, Xaa₉ is
15 Gln, and Xaa₁₀ is Tyr(OMe).

In another preferred embodiment of the present invention, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 16 (SEQ ID NO: 28) and a C-terminal extension comprising an amino acid sequence of Formula 7 (SEQ ID NO: 15).

20 In the above preferred embodiments of the present invention, it is especially preferred that the VPAC2 receptor peptide agonist further comprises a N-terminal modification, wherein the N-terminal modification is the addition of a group selected from: acetyl, propionyl, butyryl, pentanoyl, hexanoyl, methionine, methionine sulfoxide, 3-phenylpropionyl, phenylacetyl, benzoyl, norleucine, D-histidine, isoleucine, 3-
25 mercaptopropionyl, biotinyl-6-aminohexanoic acid and -C(=NH)-NH₂, and more preferably is the addition of acetyl or hexanoyl.

In a preferred embodiment, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein either Xaa₁₄ or
30 Xaa₁₅ is Aib and either Xaa₂₀ or Xaa₂₁ is Aib, more preferably Xaa₁₅ is Aib and Xaa₂₀ is Aib, and a C-terminal extension selected from: GGPSSGAPPPS (SEQ ID NO: 10), GGPSSGAPPPS-NH₂ (SEQ ID NO: 11), GGPSSGAPPPC (SEQ ID NO: 22), and

GGPSSGAPPPC-NH₂ (SEQ ID NO: 23), GRPSSGAPPPS (SEQ ID NO: 16) and GRPSSGAPPPS-NH₂ (SEQ ID NO: 17) and wherein the PEGylated VPAC2 receptor peptide agonist further comprises a N-terminal modification which modification is the addition of hexanoyl or acetyl.

- 5 In another preferred embodiment, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein either Xaa₁₄ or Xaa₁₅ is Aib and either Xaa₂₀ or Xaa₂₁ is Aib, Xaa₂₈ is Gln and Xaa₂₉ is Lys or absent, and a C-terminal extension selected from: GGPSSGAPPPS (SEQ ID NO: 10),
- 10 GGPSSGAPPPS-NH₂ (SEQ ID NO: 11), GGPSSGAPPPC (SEQ ID NO: 22), and GGPSSGAPPPC-NH₂ (SEQ ID NO: 23), GRPSSGAPPPS (SEQ ID NO: 16) and GRPSSGAPPPS-NH₂ (SEQ ID NO: 17), and wherein the PEGylated VPAC2 receptor peptide agonist further comprises a N-terminal modification which modification is the addition of hexanoyl or acetyl.
- 15 In yet another preferred embodiment, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein either Xaa₁₄ or Xaa₁₅ is Aib and either Xaa₂₀ or Xaa₂₁ is Aib, Xaa₁₂ is hR or Orn, Xaa₂₇ is hR or Orn and Xaa₂₉ is hR or Orn, and a C-terminal extension selected from: GGPSSGAPPPS (SEQ ID NO: 10), GGPSSGAPPPS-NH₂ (SEQ ID NO: 11), GGPSSGAPPPC (SEQ ID NO: 22), and GGPSSGAPPPC-NH₂ (SEQ ID NO: 23), GRPSSGAPPPS (SEQ ID NO: 16) and GRPSSGAPPPS-NH₂ (SEQ ID NO: 17) and wherein the VPAC2 receptor peptide agonist further comprises a N-terminal modification which modification is the addition of hexanoyl or acetyl.
- 25 In yet further preferred embodiment, there is provided a PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence of Formula 10 (SEQ ID NO: 18), Formula 12 (SEQ ID NO: 20) or Formula 13 (SEQ ID NO: 21) wherein Xaa₁₅ is Aib, Xaa₂₀ is Aib, Xaa₁₂, Xaa₂₁, Xaa₂₇, and Xaa₂₈ are all Orn, Xaa₈ is Glu, Xaa₉ is Gln, and Xaa₁₀ is Tyr(OMe), and a C-terminal extension selected from: GGPSSGAPPPS (SEQ ID NO: 10), GGPSSGAPPPS-NH₂ (SEQ ID NO: 11), GGPSSGAPPPC (SEQ ID NO: 22), and GGPSSGAPPPC-NH₂ (SEQ ID NO: 23), GRPSSGAPPPS (SEQ ID NO: 16) and GRPSSGAPPPS-NH₂ (SEQ ID NO: 17) and wherein the VPAC2 receptor peptide agonist
- 30

further comprises a N-terminal modification which modification is the addition of hexanoyl or acetyl.

In combination with any one of the preferred embodiments described above, it is preferred that there is at least one PEG molecule covalently attached to Xaa₂₅ or any subsequent residue in Formula 10, 12, 13 or 16 and/or there is at least one PEG molecule covalently attached to a residue in the C-terminal extension of the peptide agonist. It is also preferred that one or two of the Cys residues in the peptide agonist are covalently attached to a PEG molecule, or one or two of the Lys residues in the peptide agonist are covalently attached to a PEG molecule.

A preferred alternative sequence for selective PEGylated VPAC2 receptor peptide agonists of the present invention comprises an amino acid sequence of the Formula 1 (SEQ ID NO: 4), provided that if Xaa₂₉ or Xaa₃₀ of Formula 1 is absent each amino acid downstream is absent and wherein the C-terminal amino acid may be amidated.

Throughout this specification, with respect to when an Xaa is absent, the next amino acid present downstream is the next amino acid in the sequence or is also absent. For example, if Xaa₂₉ is Lys and Xaa₃₀ is absent, the next amino acid bonded to Lys at position 29 is an amino acid listed for position 31 or absent, and so forth.

Another alternative preferred sequence for selective PEGylated VPAC2 receptor peptide agonists of the present invention comprises an amino acid sequence of the

Formula 1 (SEQ ID NO: 4), wherein: Xaa₂ is: Ser, Val, or dA; Xaa₁₂ is: Arg or Lys; Xaa₁₄ is: Arg, Leu, or Lys; Xaa₁₅ is: Lys, Ala, or Arg; Xaa₁₆ is: Gln, Lys, or Ala; Xaa₁₇ is: Met, Val, Ala, or Leu; Xaa₁₉ is: Val, Ala or Leu; Xaa₂₀ is: Lys, Gln, or Arg; Xaa₂₁ is: Lys or Arg; Xaa₂₄ is: Asn or Gln; Xaa₂₅ is: Ser, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, or Tyr; Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, or Tyr; Xaa₂₇ is: Leu, hR, Arg, or Lys; Xaa₂₉ is: Lys, Ser, Arg, or absent; Xaa₃₀ is: Arg, Lys, or absent; and Xaa₃₁ is: Tyr, Phe, or absent.

Another alternative preferred sequence for selective PEGylated VPAC2 receptor peptide agonists of the present invention comprises an amino acid sequence of the Formula 1 (SEQ ID NO: 4), wherein: Xaa₂ is: Val or dA; Xaa₁₄ is: Leu; Xaa₁₅ is: Ala; Xaa₁₆ is: Lys; Xaa₁₇ is: Ala; Xaa₂₀ is: Gln; Xaa₂₅ is: Phe, Ile, Leu, Val, Trp, or Tyr; Xaa₂₆ is: Thr, Trp, or Tyr; Xaa₂₇ is: hR; and Xaa₃₁ is: Phe.

Another alternative preferred sequence for selective PEGylated VPAC2 receptor peptide agonists of the present invention comprises an amino acid sequence of the

Formula 1 (SEQ ID NO: 4), wherein: Xaa₂ is: Ser, Val, or dA; Xaa₁₂ is: Arg, Lys, hR, Orn, or Lys (isopropyl); Xaa₁₄ is: Arg, Leu, or Lys; Xaa₁₅ is: Lys, Ala, or Arg; Xaa₁₆ is: Gln, Lys, or Ala; Xaa₁₇ is: Met, Val, Ala, or Leu; Xaa₁₉ is: Val, Ala, or Leu; Xaa₂₀ is: Lys, Gln, or Arg; Xaa₂₁ is: Lys or Arg; Xaa₂₄ is: Asn or Gln, Xaa₂₅ is: Ser, Phe, Ile, Leu, Val, Trp, Tyr, Thr, Gln, or Asn; Xaa₂₆ is: Ile, Thr, Trp, Tyr, Leu, or Val; Xaa₂₇ is: Leu, Lys, hR, or Arg; Xaa₂₉ is: Lys, Ser, Arg, hR, or absent; Xaa₃₀ is: Arg, Lys, or absent; and Xaa₃₁ is: Tyr, Phe, or absent.

Yet another alternative preferred sequence for selective PEGylated VPAC2 receptor peptide agonists of the present invention comprises an amino acid sequence of the Formula 1 (SEQ ID NO: 4), wherein: Xaa₁₄ is Leu when Xaa₁₅ is Ala and Xaa₁₆ is Lys. Even more preferably, Xaa₁₄ is Leu when Xaa₁₅ is Ala, Xaa₁₆ is Lys, Xaa₁₇ is Leu, and Xaa₂₀ is Gln.

Another alternative preferred peptide sequence for selective PEGylated VPAC2 receptor peptide agonists of the present invention comprises an amino acid sequence of the Formula 2 (SEQ ID NO: 5), provided that if Xaa₂₉ or Xaa₃₀ of Formula 2 is absent each amino acid downstream is absent and wherein the C-terminal amino acid may be amidated.

Another preferred alternative peptide sequence for selective PEGylated VPAC2 receptor peptide agonists of the present invention comprises an amino acid sequence of the Formula 3 (SEQ ID NO: 6), provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆, Xaa₃₇, Xaa₃₈, or Xaa₃₉ of Formula 3 is absent, the next amino acid present downstream is the next amino acid in the sequence and wherein the C-terminal amino acid may be amidated.

Preferred alternative peptide sequences for selective PEGylated VPAC2 receptor peptide agonists include:

SEQ ID NO	Sequence
381.	HSDAVFTDNYTRLRKQMAVKKYLNSIKK-NH ₂
382.	HSDAVFTDNYTRLRKQMAVKKYLNSIKKGGT
383.	HSDAVFTENYTKLRKQLAAKKYLNDLLNGGT
384.	HSDAVFTDNYTKLRKQLAAKKYLNDILNGGT
385.	HSDAVFTENYTKLRKQLAAKKYLNDLKKGGTSWCEPGWCR
386.	HSDAVFTDNYTRLRKQLAAKKYLNSIKKGGT
387.	HSDAVFTDNYTRLRKQLAAKKYLNDIKNGGT

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388. HSDAVFTDNYTRLRKQLAVKKYLNSIKKGGT
389. HSDAVFTDNYTRLRKQMAAKKYLNSIKKGGT
390. HSDAVFTDNYTRLRKQLAVKKYLNDIKNGGT
391. HSDAVFTDNYTRLRKQLAAKKYLNSIKNGGT
5 392. HSDAVFTDNYTRLRKQLAAKKYLNDIKKKRY
393. HSDAVFTDNYTRLRKQMAVKKYLNSIKK
394. HSDAVFTDNYTRLRKQMAVKKYLNSIKN
395. HSDAVFTDNYTRLRKQMAVKKYLNSILK
396. HSDAVFTDNYTELRKQMAVKKYLNSILN
10 397. HSDAVFTDNYTRLRKQMAVKKYLNDILN
398. HSDAVFTDNYTRLRKQMAAKKYLNSIKN
399. HSDAVFTDNYTRLRKQMAAKKYLNSILK
400. HSDAVFTDNYTRLRKQMAAKKYLNSIKK
401. HSDAVFTDNYTRLRKQMAAKKYLNSIKKKRY
15 402. HSDAVFTDNYTRLRKQMAAKKYLNSIKKKR
403. HSDAVFTDNYTRLRKQMAAKKYLNSIKKK
404. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKRY
405. HSDAVFTDNYTRLRKQMAVKKYLNSIKKKRY
406. HSDAVFTDNYTRLRKQMAVKKYLNSIKKKR
20 407. HSDAVFTDNYTRLRKQMAVKKYLNSIKKK
408. HSDAVFTDNYTRLRKQMAVKKYLNSIKNKRY
409. HSDAVFTDNYTRLRKQVAAKKYLQSIKK
410. HSDAVFTDNYTRLRKQIAAKKYLQTIKK
411. HSDAVFTENYTRLRKQMAVKKYLNSLKK-NH₂
25 412. HSDAVFTDNYTRLRKQLAAKKYLNDILKGGT
413. HSDAVFTDNYTRLRKQLAAKKYLNDILNGGT
414. HSDAVFTDNYTRLRKQLAVKKYLNDILKGGT
415. HSDAVFTDNYTRLRKQVAAKKYLNSIKK
416. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKR
30 417. HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRY
418. HSDAVFTDNYTRLRKQLAAKKYLNTIKNKRY
419. HSDAVFTDNYTRLRKQVAAKKYLNSIKNKRY
420. HSDAVFTDNYTRLRKQMAAKKYLQSIKNKRY
421. HSDAVFTDNYTRLRKQMAAKKYLNTIKNKRY
35 422. HSDAVFTDQYTRLRKQMAAKKYLNSIKNKRY
423. HSDAVFTDQYTRLRKQLAAKKYLNTIKNKRY
424. HSDAVFTDNYTRLRKQMAAHKYLNSIKNKRY
425. HSDAVFTDNYTRLRKQMAAKHYLNSIKNKRY
426. HSDAVFTDQYTRLRKQLAAHKYLNTIKNKRY
40 427. HSDAVFTDQYTRLRKQLAAKHYLNTIKNKRY
428. HSDAVFTDNYTRLRKQVAAKKYLQSIKKKR
429. HSDAVFTDNYTRLRKQVAAKKYLNSIKKKR
430. HSDAVFTDNYTRLRKQVAAKKYLNSIKNKRY
431. HSDAVFTDNYTRLRKQVAVKKYLQSIKKKR
45 432. HSDAVFTDNYTRLRKQVAVKKYLQSIKKK
433. HSDAVFTDNYTRLRKQVAVKKYLQSIKNKRY
434. HSDAVFTDNYTRLRKQVAAKKYLQSIKKRY

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435. HSDAVFTDNYTRLRKQVAAKKYLQSILKKR
436. HSDAVFTDNYTRLRKQVAAKKYLQSILKK
437. HSDAVFTDNYTRLRKQVAAKKYLQSIKNK
438. HSDAVFTDNYTRLRKQVAVKKYLQSILKKRY
5 439. HSDAVFTDNYTRLRKQVAVKKYLQSILKKR
440. HSDAVFTDNYTRLRKQVAVKKYLQSILKK
441. HSDAVFTDNYTRLRKQVAVKKYLQSIKNK
442. HSDAVFTDNYTRLRKQVAAKKYLQSILNKRY
443. HSDAVFTDNYTRLRKQVAAKKYLQSILNKR
10 444. HSDAVFTDNYTRLRKQVAAKKYLQSILNK
445. HSDAVFTDNYTRLRKQMAEKKYLNSIKNKR
446. HSDAVFTDNYTRLRKQMAFKKYLNSIKNKR
447. HSDAVFTDNYTRLRKQMAGKKYLNSIKNKR
448. HSDAVFTDNYTRLRKQMAHKKYLNSIKNKR
15 449. HSDAVFTDNYTRLRKQMAIKKYLNSIKNKR
450. HSDAVFTDNYTRLRKQMAKKKYLNSIKNKR
451. HSDAVFTDNYTRLRKQMALKKYLNSIKNKR
452. HSDAVFTDNYTRLRKQMAMKKYLNSIKNKR
453. HSDAVFTDNYTRLRKQMANKKYLNSIKNKR
20 454. HSDAVFTDNYTRLRKQMAPKKYLNSIKNKR
455. HSDAVFTDNYTRLRKQMAQKKYLNSIKNKR
456. HSDAVFTDNYTRLRKQMARKKYLNSIKNKR
457. HSDAVFTDNYTRLRKQMASKKYLNSIKNKR
458. HSDAVFTDNYTRLRKQMATKKYLNSIKNKR
25 459. HSDAVFTDNYTRLRKQMAVKKYLNSIKNKR
460. HSDAVFTDNYTRLRKQMAWKKYLNSIKNKR
461. HSDAVFTDNYTRLRKQMAYKKYLNSIKNKR
462. HSDAVFTDNYTRLRKQMAAKKYLNSIANKR
463. HSDAVFTDNYTRLRKQMAAKKYLNSIDNKR
30 464. HSDAVFTDNYTRLRKQMAAKKYLNSIENKR
465. HSDAVFTDNYTRLRKQMAAKKYLNSIFNKR
466. HSDAVFTDNYTRLRKQMAAKKYLNSIGNKR
467. HSDAVFTDNYTRLRKQMAAKKYLNSIHNKR
468. HSDAVFTDNYTRLRKQMAAKKYLNSIINKR
35 469. HSDAVFTDNYTRLRKQMAAKKYLNSIMNKR
470. HSDAVFTDNYTRLRKQMAAKKYLNSINNKR
471. HSDAVFTDNYTRLRKQMAAKKYLNSIPNKR
472. HSDAVFTDNYTRLRKQMAAKKYLNSIQNKR
473. HSDAVFTDNYTRLRKQMAAKKYLNSIRNKR
40 474. HSDAVFTDNYTRLRKQMAAKKYLNSISNKR
475. HSDAVFTDNYTRLRKQMAAKKYLNSITNKR
476. HSDAVFTDNYTRLRKQMAAKKYLNSIVNKR
477. HSDAVFTDNYTRLRKQMAAKKYLNSIWNKR
478. HSDAVFTDNYTRLRKQMAAKKYLNSIYNKR
45 479. HSDAVFTDNYTRLRKQMAAKKYLNSIKNAR
480. HSDAVFTDNYTRLRKQMAAKKYLNSIKNDR
481. HSDAVFTDNYTRLRKQMAAKKYLNSIKNER

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482. HSDAVFTDNYTRLRKQMAAKKYLNSIKNFR
483. HSDAVFTDNYTRLRKQMAAKKYLNSIKNGR
484. HSDAVFTDNYTRLRKQMAAKKYLNSIKNHR
485. HSDAVFTDNYTRLRKQMAAKKYLNSIKNIR
5 486. HSDAVFTDNYTRLRKQMAAKKYLNSIKNLR
487. HSDAVFTDNYTRLRKQMAAKKYLNSIKNMR
488. HSDAVFTDNYTRLRKQMAAKKYLNSIKNNR
489. HSDAVFTDNYTRLRKQMAAKKYLNSIKNPR
490. HSDAVFTDNYTRLRKQMAAKKYLNSIKNQR
10 491. HSDAVFTDNYTRLRKQMAAKKYLNSIKNRR
492. HSDAVFTDNYTRLRKQMAAKKYLNSIKNSR
493. HSDAVFTDNYTRLRKQMAAKKYLNSIKNTR
494. HSDAVFTDNYTRLRKQMAAKKYLNSIKNVR
495. HSDAVFTDNYTRLRKQMAAKKYLNSIKNWR
15 496. HSDAVFTDNYTRLRKQMAAKKYLNSIKNYR
497. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKA
498. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKD
499. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKE
500. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKF
20 501. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKG
502. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKH
503. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKI
504. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKK
505. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKL
25 506. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKM
507. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKN
508. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKP
509. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKQ
510. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKS
30 511. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKT
512. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKV
513. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKW
514. HSDAVFTDNYTRLRKQMAAKKYLNSIKNKY
515. HSDAVFTDNYTRLRKQVAACKKYLQSIKNKRYSWCEPGWCR
35 516. HSDAVFTDDYTRLRKEVAACKKYLESIKDKRY
517. HSDAVFTDNYTRLRKQMAAKKYLNSIKNRI
518. HSDAVFTDNYTRLRKQMAGKKYLNSIKNRI
519. HSDAVFTDNYTRLRKQMAKKKYLNSIKNRI
520. HSDAVFTDNYTRLRKQMARKKYLNSIKNRI
40 521. HSDAVFTDNYTRLRKQMASKKYLNSIKNRI
522. HSDAVFTDNYTRLRKQMAAKKYLNSIPNRI
523. HSDAVFTDNYTRLRKQMAGKKYLNSIPNRI
524. HSDAVFTDNYTRLRKQMAKKKYLNSIPNRI
525. HSDAVFTDNYTRLRKQMARKKYLNSIPNRI
45 526. HSDAVFTDNYTRLRKQMASKKYLNSIPNRI
527. HSDAVFTDNYTRLRKQMAAKKYLNSIQNRI
528. HSDAVFTDNYTRLRKQMAGKKYLNSIQNRI

529. HSDAVFTDNYTRLRKQMAKKKYLN SIQNRI
530. HSDAVFTDNYTRLRKQMARKKYLN SIQNRI
531. HSDAVFTDNYTRLRKQMASKKYLN SIQNRI
532. HSDAVFTDNYTRLRKQMAAKKYLN SIRQNRI
5 533. HSDAVFTDNYTRLRKQMAGKKYLN SIRQNRI
534. HSDAVFTDNYTRLRKQMAKKKYLN SIRQNRI
535. HSDAVFTDNYTRLRKQMARKKYLN SIRQNRI
536. HSDAVFTDNYTRLRKQMASKKYLN SIRQNRI
537. HSDAVFTENYTKLRKQLAAKKYLN DLKKGGT-NH2
10 538. HSDAVFTENYTKLRKQLAAKKYLN DLKKGGT
539. HSDAVFTENYTKLRKQLAAKKYLN DLKKGGT
540. HSDAVFTENYTKLRKQLAAKKYLN DLKK
541. HSDAVFTDNYTRLRKQLAAKKYLN DIKKGGT
542. HSDAVFTDNYTRLRKQLAAKKYLN DIKK-NH2
15 543. HSDAVFTDNYTRLRKQMAVKKYLN DLKKGGT
544. HSDAVFTDNYTRLRKQMAAKKYLN DIKKGGT
545. HSDAVFTDNYTRLRKQLAVKKYLN DIKKGGT
546. HSDAVFTDNYTRLRKQLAAKKYLN DIKKGG
547. HSDAVFTDNYTRLRKQLAAKKYLN DIKKGG
20 548. HSDAVFTDNYTRLRKQLAAKKYLN DIKK
549. HSDAVFTDNYTRLRKQLAAKKYLN DIKKQ
550. HSDAVFTDNYTRLRKQLAAKKYLN DIKKNQ
551. HSDAVFTDNYTRLREQMAVKKYLN SILN
552. HSDAVFTDNYTRLRKQLAVKKYLN SILN
25 553. HSDAVFTDNYTRLRKQMAAKKYLN SILN
554. HSDAVFTENYTKLRKQLAAKKYLN DLKKGGT
555. HSDAVFTDNYTRLRKQMACKKYLN SIKNKR
556. HSDAVFTDNYTRLRKQMADKKYLN SIKNKR
557. HSDAVFTDNYTRLRKQMAAKKYLN SICNKR
30 558. HSDAVFTDNYTRLRKQMAAKKYLN SIKNKR
559. HSDAVFTDQYTRLRKQVAAKKYLQSIKQKRY
560. HTDAVFTDQYTRLRKQVAAKKYLQSIKQKRY
561. HSDAVFTDQYTRLRKQMAAKKYLQSIKQKRY
562. HSDAVFTDQYTRLRKQVAAKKYLQSIKQK
35 563. HTEAVFTDQYTRLRKQVAAKKYLQSIKQKRY
564. HSDAVFTDQYTRLRKQLAVKKYLQDIKQGGT
565. HSDAVFTDQYTRLRKQMAAKKYLQSIKQKR
566. HSDAVFTDQYTRLRKQLAAKKYLQTIKQKRY
567. HSDAVFTDQYTRLRKQMAAKKYLQTIKQKRY
40 568. HSDAVFTDQYTRLRKQMAAHKYLQSIKQKRY
569. HSDAVFTDQYTRLRKQMAAKHYLQSIKQKRY
570. HSDAVFTDQYTRLRKQMAGKKYLQSIKQKR
571. HSDAVFTDQYTRLRKQMAKKKYLQSIKQKR
572. HSDAVFTDQYTRLRKQMARKKYLQSIKQKR
45 573. HSDAVFTDQYTRLRKQMASKKYLQSIKQKR
574. HSDAVFTDQYTRLRKQMAAKKYLQSIQKR
575. HSDAVFTDQYTRLRKQMAAKKYLQSIQQR

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	576.	HSDAVFTDQYTRLRKQMAAKKYLSIRQKR
	577.	HSDAVFTDQYTRLRKQMAAKKYLSIKQRR
	578.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKA
	579.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKF
5	580.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKH
	581.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKI
	582.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKK
	583.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKL
	584.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKM
10	585.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKP
	586.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKQ
	587.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKS
	588.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKT
	589.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKV
15	590.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKW
	591.	HSDAVFTDQYTRLRKQMAAKKYLSIKQKY
	592.	HSDAVFTDQYTRLRKQMAGKKYLSIKQRI
	593.	HSDAVFTDQYTRLRKQMAKKKYLSIKQRI
	594.	HSDAVFTDQYTRLRKQMASKKYLSIKQRI
20	595.	HSDAVFTDQYTRLRKQMAAKKYLSIPQRI
	596.	HSDAVFTDQYTRLRKQMASKKYLSIRQRI
	597.	HSDAVFTDNYTRLRKQVAAKKYLSIKQKRY
	598.	HTDAVFTDNYTRLRKQVAAKKYLSIKQKRY
	599.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKRY
25	600.	HSDAVFTDNYTRLRKQVAAKKYLSIKQK
	601.	HTEAVFTDNYTRLRKQVAAKKYLSIKQKRY
	602.	HSDAVFTDNYTRLRKQLAVKKYLQDIKGGT
	603.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKR
	604.	HSDAVFTDNYTRLRKQLAAKKYLOTIKQKRY
30	605.	HSDAVFTDNYTRLRKQMAAKKYLOTIKQKRY
	606.	HSDAVFTDNYTRLRKQMAAHKYLSIKQKRY
	607.	HSDAVFTDNYTRLRKQMAAKHYLSIKQKRY
	608.	HSDAVFTDNYTRLRKQMAGKKYLSIKQKR
	609.	HSDAVFTDNYTRLRKQMAKKKYLSIKQKR
35	610.	HSDAVFTDNYTRLRKQMARKKYLSIKQKR
	611.	HSDAVFTDNYTRLRKQMASKKYLSIKQKR
	612.	HSDAVFTDNYTRLRKQMAAKKYLSIPQKR
	613.	HSDAVFTDNYTRLRKQMAAKKYLSIQQKR
	614.	HSDAVFTDNYTRLRKQMAAKKYLSIRQKR
40	615.	HSDAVFTDNYTRLRKQMAAKKYLSIKQRR
	616.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKA
	617.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKF
	618.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKH
	619.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKI
45	620.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKK
	621.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKL
	622.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKM

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623.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKP
624.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKQ
625.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKS
626.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKT
5 627.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKV
628.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKW
629.	HSDAVFTDNYTRLRKQMAAKKYLSIKQKY
630.	HSDAVFTDNYTRLRKQMAGKKYLSIKQRI
631.	HSDAVFTDNYTRLRKQMAKKKYLSIKQRI
10 632.	HSDAVFTDNYTRLRKQMASKKYLSIKQRI
633.	HSDAVFTDNYTRLRKQMAAKKYLSIPQRI
634.	HSDAVFTDNYTRLRKQMASKKYLSIRQRI
635.	HSDAVFTDQYTRLRKQVAAKKYLSIKNKRY
636.	HTDAVFTDQYTRLRKQVAAKKYLSIKNKRY
15 637.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKRY
638.	HSDAVFTDQYTRLRKQVAAKKYLSIKNK
639.	HTEAVFTDQYTRLRKQVAAKKYLSIKNKRY
640.	HSDAVFTDQYTRLRKQLAVKKYLQDIKNGGT
641.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKR
20 642.	HSDAVFTDQYTRLRKQLAAKKYLQTIKNKRY
643.	HSDAVFTDQYTRLRKQMAAKKYLQTIKNKRY
644.	HSDAVFTDQYTRLRKQMAAHKYLSIKNKRY
645.	HSDAVFTDQYTRLRKQMAAKHYLSIKNKRY
646.	HSDAVFTDQYTRLRKQMAGKKYLSIKNKR
25 647.	HSDAVFTDQYTRLRKQMAKKKYLSIKNKR
648.	HSDAVFTDQYTRLRKQMARKKYLSIKNKR
649.	HSDAVFTDQYTRLRKQMASKKYLSIKNKR
650.	HSDAVFTDQYTRLRKQMAAKKYLSIPNKR
651.	HSDAVFTDQYTRLRKQMAAKKYLSIQNKR
30 652.	HSDAVFTDQYTRLRKQMAAKKYLSIRNKR
653.	HSDAVFTDQYTRLRKQMAAKKYLSIKNRR
654.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKA
655.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKF
656.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKH
35 657.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKI
658.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKK
659.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKL
660.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKM
661.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKP
40 662.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKQ
663.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKS
664.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKT
665.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKV
666.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKW
45 667.	HSDAVFTDQYTRLRKQMAAKKYLSIKNKY
668.	HSDAVFTDQYTRLRKQMAGKKYLSIKNRI
669.	HSDAVFTDQYTRLRKQMAKKKYLSIKNRI

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670.	HSDAVFTDQYTRLRKQMASKKYLQSIKNRI
671.	HSDAVFTDQYTRLRKQMAAKKYLQSIPNRI
672.	HSDAVFTDQYTRLRKQMASKKYLQSIRNRI
673.	HSDAVFTDQYTRLRKQVAAKKYLQSIQKRYC
5 674.	HTDAVFTDQYTRLRKQVAAKKYLQSIQKRYC
675.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKRYC
676.	HSDAVFTDQYTRLRKQVAAKKYLQSIQKRC
677.	HTEAVFTDQYTRLRKQVAAKKYLQSIQKRYC
678.	HSDAVFTDQYTRLRKQLAVKKYLQDIKQGGTC
10 679.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKRC
680.	HSDAVFTDQYTRLRKQLAAKKYLQTIKQKRYC
681.	HSDAVFTDQYTRLRKQMAAKKYLQTIKQKRYC
682.	HSDAVFTDQYTRLRKQMAAHKYLQSIQKRYC
683.	HSDAVFTDQYTRLRKQMAAKHYLQSIQKRYC
15 684.	HSDAVFTDQYTRLRKQMAGKKYLQSIQKRC
685.	HSDAVFTDQYTRLRKQMAKKKYLQSIQKRC
686.	HSDAVFTDQYTRLRKQMARKKYLQSIQKRC
687.	HSDAVFTDQYTRLRKQMASKKYLQSIQKRC
688.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKRC
20 689.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKRC
690.	HSDAVFTDQYTRLRKQMAAKKYLQSIRQKRC
691.	HSDAVFTDQYTRLRKQMAAKKYLQSIQRRRC
692.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKAC
693.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKFC
25 694.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKHC
695.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKIC
696.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKKC
697.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKLC
698.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKMC
30 699.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKPC
700.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKQC
701.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKSC
702.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKTC
703.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKVC
35 704.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKWC
705.	HSDAVFTDQYTRLRKQMAAKKYLQSIQKYC
706.	HSDAVFTDQYTRLRKQMAGKKYLQSIQRIC
707.	HSDAVFTDQYTRLRKQMAKKKYLQSIQRIC
708.	HSDAVFTDQYTRLRKQMASKKYLQSIQRIC
40 709.	HSDAVFTDQYTRLRKQMAAKKYLQSIQRIC
710.	HSDAVFTDQYTRLRKQMASKKYLQSIRQIC

Another preferred alternative sequence for selective VPAC2 receptor peptide agonists of the present invention comprises an amino acid sequence of the Formula 4

45 (SEQ ID NO: 7), provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆,

Xaa₃₇, Xaa₃₈, or Xaa₃₉ of Formula 4 is absent, the next amino acid present downstream is the next amino acid in the sequence and wherein the C-terminal amino acid may be amidated.

Preferably, the C-terminal extension for an alternative embodiment of the present invention comprises an amino acid sequence of the Formula 5 (SEQ ID NO: 8), provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, or Xaa₁₂ of Formula 5 is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated. For example, if Xaa₁ is Gly and Xaa₂ is absent, the next amino acid bonded to Gly at position 1 is an amino acid listed for position 3 or, if position 3 is also absent, an amino acid listed for position 4 is bonded to Gly at position 1, and so forth. Additionally, for example, if Xaa₁ is Gly and Xaa₂ through Xaa₁₃ are absent, Gly may be the C-terminal amino acid and may be amidated.

Also, the C-terminal extension for an alternative embodiment of the present invention preferably comprises an amino acid sequence of the Formula 6 (SEQ ID NO: 9), provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ of Formula 6 is absent, the next amino acid present downstream is the next amino acid in the sequence and wherein the C-terminal amino acid may be amidated. For example, if Xaa₁ is Gly and Xaa₂ is absent, the next amino acid bonded to Gly at position 1 is an amino acid listed for position 3 or, if position 3 is also absent, an amino acid listed for position 4 is bonded to Gly at position 1, and so forth. Additionally, for example, if Xaa₁ is Gly and Xaa₂ through Xaa₁₁ are absent, Gly may be the C-terminal amino acid and may be amidated.

More preferably, the C-terminal extension of an alternative embodiment of the present invention includes the following sequences:

SEQ ID #	Sequence
SEQ ID NO: 10	GGPSSGAPPPS
SEQ ID NO: 11	GGPSSGAPPPS-NH ₂

Preferably, the C-terminal extension differs from SEQ ID NO: 10 or SEQ ID NO: 11 by no more than eight amino acids, still preferably by no more than seven amino acids, yet still preferably by no more than six amino acids, more preferably by no more than five

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amino acids, even more preferably by no more than four amino acids, still more preferably by no more than three amino acids, yet more preferably by no more than two amino acids, and most preferably by no more than one amino acid.

Another alternative more preferable C-terminal extension of the present invention
5 can also include variants of these sequences, including:

SEQ ID #	Sequence
SEQ ID NO: 12	GGPSSGAPPS-NH ₂
SEQ ID NO: 13	GGPSSGAPPPS-OH

These sequences contain the standard single letter codes for the twenty naturally occurring amino acids. SEQ ID NO: 11 and SEQ ID NO: 12 contain sequences that are amidated at the C-terminus of the sequence.

10 Preferably, the C-terminal extension differs from SEQ ID NO: 12, or SEQ ID NO: 13 by no more than eight amino acids, still preferably by no more than seven amino acids, yet still preferably by no more than six amino acids, more preferably by no more than five amino acids, even more preferably by no more than four amino acids, still more preferably by no more than three amino acids, yet more preferably by no more than two
15 amino acids, and most preferably by no more than one amino acid.

Another alternative preferred C-terminal extension of the present invention comprises an amino acid sequence of the Formula 7 (SEQ ID NO: 15), provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ of Formula 7 is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension
20 and wherein the C-terminal amino acid may be amidated.

Another alternative preferred C-terminal extension of the present invention includes (Lys)_n or (Glu)_n wherein n is the number of lysine or glutamic acid residues added to the C-terminus and wherein n can be anywhere from one to eight residues.

The following alternative selective PEGylated VPAC2 receptor peptide
25 agonists are preferred:

Agonist #	SEQ ID NO:	Sequence

PEG-P164	711	C6-HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAPPPC (PEG)
PEG-P120	712	C6-HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPC (PEG)
PEG-P119a	713	C6-HSDAVFTDNYTRLLAK(PEG)LALQRYLQSIRNKRYGGPSSGAPPPS
PEG-P119b	714	C6-HSDAVFTDNYTRLLAKLALQK(PEG)YLQSIRNKRYGGPSSGAPPPS
PEG-P31a	715	C6-HSDAVFTDNYTRLRK(PEG)QVAAKKYLQSIKNKRYGGPSSGAPPPS
PEG-P31b	716	C6-HSDAVFTDNYTRLRRQVAAK(PEG)RYLQSIKNKRYGGPSSGAPPPS
PEG-P31c	717	C6-HSDAVFTDNYTRLRRQVAARK(PEG)YLQSIRNKRYGGPSSGAPPPS
PEG-P31d	718	C6-HSDAVFTDNYTRLRK(PEG)QVAAK(PEG)RYLQSIRNKRYGGPSSGAPPPS
PEG-P213	719	C6-HSDAVFTDNYTRLRK(PEG)QVAAK(PEG)RYLQSIRNGGPSSGAPPPS
PEG-P214	720	C6-HSDAVFTDNYTRLRK(PEG)QVAAARRYLQSIKNKRYGGPSSGAPPPS
PEG-P215	721	C6-HSDAVFTDNYTRLRRQVAAK(PEG)RYLQSIRNGGPSSGAPPPS
PEG-P216	24	C6-HSDAVFTDNYTRLRRQVAARK(PEG)YLQSIRNGGPSSGAPPPS
PEG-P201	25	C6-HSDAVFTENY(OMe)TKLRKQNleAAKKYLNDLKKGGPSSGAPPPC

PEGylation of proteins may overcome many of the pharmacological and toxicological/immunological problems associated with using peptides or proteins as therapeutics. However, for any individual peptide it is uncertain whether the PEGylated

form of the peptide will have significant loss in bioactivity as compared to the unPEGylated form of the peptide.

The bioactivity of PEGylated proteins can be affected by factors such as: i) the size of the PEG molecule; ii) the particular sites of attachment; iii) the degree of
5 modification; iv) adverse coupling conditions; v) whether a linker is used for attachment or whether the polymer is directly attached; vi) generation of harmful co-products; vii) damage inflicted by the activated polymer; or viii) retention of charge. Work performed on the PEGylation of cytokines, for example, shows the effect PEGylation may have. Depending on the coupling reaction used, polymer modification of cytokines has resulted
10 in dramatic reductions in bioactivity. [Francis, G.E., *et al.*, (1998) PEGylation of cytokines and other therapeutic proteins and peptides: the importance of biological optimization of coupling techniques, *Intl. J. Hem.* 68:1-18]. Maintaining the bioactivity of PEGylated peptides is even more problematic than for proteins. As peptides are smaller than proteins, modification by PEGylation may potentially have a greater effect on
15 bioactivity.

The VPAC2 receptor peptide agonists of the present invention are modified by the covalent attachment of one or more molecules of a polyethylene glycol (PEG) and generally have improved pharmacokinetic profiles due to slower proteolytic degradation and renal clearance. Attachment of PEG molecule(s) (PEGylation) will increase the
20 apparent size of the VPAC2 receptor peptide agonists, thus reducing renal filtration and altering biodistribution. PEGylation can shield antigenic epitopes of the VPAC2 receptor peptide agonists, thus reducing reticuloendothelial clearance and recognition by the immune system and also reducing degradation by proteolytic enzymes, such as DPP-IV.

Covalent attachment of one or more molecules of polyethylene glycol to a small,
25 biologically active VPAC2 receptor peptide agonist poses the risk of adversely affecting the agonist, for example, by destabilising the inherent secondary structure and bioactive conformation and reducing bioactivity, so as to make the agonist unsuitable for use as a therapeutic. The present invention, however, is based on the finding that covalent attachment of one or more molecules of PEG to particular residues of a VPAC2 receptor
30 peptide agonist surprisingly results in a biologically active, PEGylated VPAC2 receptor peptide agonist with an extended half-life and reduced clearance when compared to that

of non PEGylated VPAC2 receptor peptide agonists. The compounds of the present invention include selective PEGylated VPAC2 receptor peptide agonists.

In order to determine the potential PEGylation sites in a VPAC2 receptor peptide agonist, serine scanning may be conducted. A Ser residue is substituted at a particular position in the peptide and the Ser-modified peptide is tested for potency and selectivity. If the Ser substitution has minimal impact on potency and the Ser-modified peptide is selective for the VPAC2 receptor, the Ser residue is then substituted for a Cys or Lys residue, which serves as a direct or indirect PEGylation site. Indirect PEGylation of a residue is the PEGylation of a chemical group or residue which is bonded to the PEGylation site residue. Indirect PEGylation of Lys includes PEGylation of K(W) and K(CO(CH₂)₂SH).

The invention described herein provides VPAC2 receptor peptide agonists covalently attached to one or more molecules of polyethylene glycol (PEG), or a derivative thereof wherein each PEG is attached to a Cys or Lys amino acid, to a K(W) or a K(CO(CH₂)₂SH), or to the carboxy terminal amino acid of the peptide agonist. PEGylation can enhance the half-life of the selective VPAC2 receptor peptide agonists, resulting in PEGylated VPAC2 receptor peptide agonists with an elimination half-life of at least one hour, preferably at least 3, 5, 7, 10, 15, 20, or 24 hours and most preferably at least 48 hours. The PEGylated VPAC2 receptor peptide agonists of the present invention preferably have a clearance value of 200 ml/h/kg or less, more preferably 180, 150, 140, 100, 80, 60 ml/h/kg or less and most preferably less than 50, 40 or 20 ml/h/kg.

The present invention encompasses the discovery that specific amino acids added to the C-terminus of a peptide sequence for a PEGylated VPAC2 receptor peptide agonist provide features that may protect the peptide as well as may enhance activity, selectivity, and/or potency. For example, these C-terminal extensions may stabilize the helical structure of the peptide and sites within the peptide prone to enzymatic cleavage that are located near the C-terminus. Furthermore, many of the C-terminally extended peptides disclosed herein may be more selective for the VPAC2 receptor and can be more potent than VIP, PACAP, and other known VPAC2 receptor peptide agonists. An example of a preferred C-terminal extension is the extension peptide of exendin-4 as the C-capping sequence. Exendin-4 is found in the salivary excretions from the Gila Monster, *Heloderma Suspectum*, (Eng et al., *J.Biol.Chem.*, 267(11):7402-7405 (1992)).

It has furthermore been discovered that modification of the N-terminus of the VPAC2 receptor peptide agonist may enhance potency and/or provide stability against DPP-IV cleavage.

VIP and some known VPAC2 receptor peptide agonists are susceptible to
5 cleavage by various enzymes and, thus, have a short *in vivo* half-life. Various enzymatic cleavage sites in the VPAC2 receptor peptide agonists are discussed below. The cleavage sites are discussed relative to the amino acid positions in VIP (SEQ ID NO: 1), and are applicable to the sequences noted herein.

Cleavage of the peptide agonist by the enzyme dipeptidyl-peptidase-IV (DPP-IV)
10 occurs between position 2 (serine in VIP) and position 3 (aspartic acid in VIP). The addition of a N-terminal modification and/or various substitutions at position 2 may improve stability against DPP-IV cleavage. Examples of amino acids at position 2 that may improve stability against DPP-IV inactivation preferably include valine, D-alanine, or D-serine. More preferably, position 2 is valine or D-alanine. Examples of N-terminal
15 modifications that may improve stability against DPP-IV inactivation include the addition of acetyl, propionyl, butyryl, pentanoyl, hexanoyl, methionine, methionine sulfoxide, 3-phenylpropionyl, phenylacetyl, benzoyl, norleucine, D-histidine, isoleucine, 3-mercaptopropionyl, biotinyl-6-aminohexanoic acid and $-C(=NH)-NH_2$. Preferably, the N-terminal modification is the addition of acetyl or hexanoyl.

20 There are chymotrypsin cleavage sites in wild-type VIP between the amino acids 10 and 11 (tyrosine and threonine) and those at 22 and 23 (tyrosine and leucine). Making substitutions at position 10 and/or 11 and position 22 and/or 23 may increase the stability of the peptide at these sites.

There is also a trypsin cleavage site between arginine at position 12 and leucine at
25 position 13 of wild-type VIP. Examples of substitutions which render the peptide resistant to cleavage by trypsin at this site include substitution of the arginine at position 12 with ornithine and substitution of leucine at position 13 with amino isobutyric acid.

In wild-type VIP, and in numerous VPAC2 receptor peptide agonists known in the art, there are cleavage sites between the basic amino acids at positions 14 and 15 and
30 between those at positions 20 and 21. The selective VPAC2 receptor agonists of the present invention generally have improved proteolytic stability *in vivo* due to substitutions in these sites. These substitutions can render the peptide resistant to

cleavage by trypsin-like enzymes, including trypsin. Examples of amino acids at position 14 that confer some resistance to cleavage by trypsin-like enzymes alone or in combination with the amino acids specified for position 15 below include glutamine, amino isobutyric acid, homoarginine, ornithine, citrulline, lysine, alanine and leucine.

- 5 Also, position 14 may be arginine when position 15 is an amino acid other than lysine. Also, position 14 can be arginine when position 15 is lysine, but this specific combination does not address enzymatic cleavage. Examples of amino acids at position 15 that confer some resistance to cleavage by trypsin-like enzymes alone or in combination with amino acids specified above for position 14 include amino isobutyric acid, ornithine and
- 10 arginine. Also, position 15 may be lysine when position 14 is an amino acid other than arginine. Also, position 15 can be lysine when position 14 is arginine, but this specific combination does not address enzymatic cleavage. Examples of amino acids at position 20 that confer some resistance to cleavage by trypsin-like enzymes alone or in combination with amino acids specified for position 21 include valine, leucine, amino
- 15 isobutyric acid, alanine, glutamine, and arginine. Also, position 20 may be lysine when position 21 is an amino acid other than lysine. Also, position 20 can be lysine when position 21 is lysine, but this specific combination does not address enzymatic cleavage. An example of an amino acid at position 21 that confers some resistance to cleavage by trypsin-like peptides alone or in combination with amino acids specified for position 20
- 20 include amino isobutyric acid, ornithine, alanine, glutamine, or arginine. Also, position 21 may be lysine when position 20 is an amino acid other than lysine. Also, position 21 can be lysine when position 20 is lysine, but this specific combination does not address enzymatic cleavage. The improved stability of a representative number of selective PEGylated VPAC2 receptor peptide agonists with resistance to peptidase cleavage and
- 25 encompassed by the present invention is demonstrated in Example 6.

- The bond between the amino acids at positions 25 and 26 of wild-type VIP is susceptible to enzymatic cleavage. This cleavage site can be completely or partially eliminated through substitution of the amino acid at position 25 and/or the amino acid at position 26. Examples of amino acids at position 25 that confer at least some resistance
- 30 to enzymatic cleavage include phenylalanine, isoleucine, leucine, threonine, valine, tryptophan, glutamine, asparagine, tyrosine, or amino isobutyric acid. Also, position 25 may be serine when position 26 is an amino acid other than isoleucine. Also, position 25

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can be serine when position 26 is isoleucine, but this specific combination does not address enzymatic cleavage. Examples of amino acids at position 26 that confer at least some resistance to enzymatic cleavage alone or in combination with the amino acids specified above for position 25 include leucine, threonine, valine, tryptophan, tyrosine, 5 phenylalanine, or amino isobutyric acid. Also, position 26 may be isoleucine when position 25 is an amino acid other than serine. Also, position 26 can be isoleucine when position 25 is serine, but this specific combination does not address enzymatic cleavage.

The region of the VPAC2 receptor peptide agonist encompassing the amino acids at positions 27, 28, 29, 30 and 31 is also susceptible to enzyme cleavage. The addition of 10 a C-terminal extension peptide may render the peptide agonist more stable against neutroendopeptidase (NEP). The addition of the extension peptide may also increase selectivity for the VPAC2 receptor. Trypsin-like enzymes may also attack these positions. If that occurs, the peptide agonist may lose its C-terminal extension with the additional carboxypeptidase activity leading to an inactive form of the peptide.

15 In addition to selective VPAC2 receptor peptide agonists with resistance to cleavage by various peptidases, the selective PEGylated VPAC2 peptide receptor agonists of the present invention may also encompass peptides with enhanced selectivity for the VPAC2 receptor, increased potency, and/or increased stability compared with some peptides known in the art. Examples of amino acid positions that may affect such 20 properties include positions: 3, 8, 12, 14, 15, 16, 17, 20, 21, 27, 28, and 29 of Formula 10, 12, or 13. For example, the amino acid at position 3 is preferably aspartic acid or glutamic acid; the amino acid at position 8 is preferably aspartic acid or glutamic acid; the amino acid at position 12 is preferably arginine, homoarginine, ornithine, or lysine; the amino acid at position 14 is preferably arginine, glutamine, amino isobutyric acid, 25 homoarginine, ornithine, citrulline, lysine, alanine, or leucine; the amino acid at position 15 is preferably lysine, amino isobutyric acid, ornithine, or arginine; the amino acid at position 16 is preferably glutamine or lysine; the amino acid at position 17 is preferably valine, alanine, leucine, isoleucine, lysine, or norleucine; the amino acid at position 20 is preferably lysine, valine, leucine, amino isobutyric acid, alanine, glutamine, or arginine; 30 the amino acid at position 21 is preferably lysine, amino isobutyric acid, ornithine, alanine, glutamine, or arginine; the amino acid at position 27 is preferably lysine, ornithine, homoarginine, or arginine; the amino acid at position 28 is preferably

asparagine, glutamine, lysine, homoarginine, amino isobutyric acid, proline, or ornithine; and, if present, the amino acid at position 29 is preferably lysine, ornithine, or homoarginine. Preferably, these amino acid substitutions may be combined with substitutions at positions that affect the five aforementioned regions susceptible to cleavage by various enzymes.

The increased potency and selectivity for various VPAC2 receptor peptide agonists of the present invention is demonstrated in Examples 3 and 4. For example, Table 1 in Example 3 provides a list of selective PEGylated VPAC2 receptor peptide agonists and their corresponding *in vitro* potency results. Preferably, the selective PEGylated VPAC2 receptor peptide agonists of the present invention have an EC₅₀ value less than 200 nM. More preferably, the EC₅₀ value is less than 50 nM. Even more preferably, the EC₅₀ value is less than 30 nM. Still more preferably, the EC₅₀ value is less than 10 nM.

Table 2 in Example 4 provides a list of VPAC2 receptor peptide agonists and their corresponding selectivity results for human VPAC2, VPAC1, and PAC1. See Example 4 for further details of these assays. These results are provided as a ratio of VPAC2 binding affinity to VPAC1 binding affinity and as a ratio of VPAC2 binding affinity to PAC1 binding affinity. Preferably, the agonists of the present invention have a selectivity ratio where the affinity for VPAC2 is at least 50 times greater than for VPAC1 and/or for PAC1. More preferably, the affinity is at least 100 times greater than for VPAC1 and/or for PAC1. Even more preferably, the affinity is at least 200 times greater than for VPAC1 and/or for PAC1. Still more preferably, the affinity is at least 500 times greater than for VPAC1 and/or for PAC1. Yet more preferably, the affinity is at least 1000 times greater than for VPAC1 and/or for PAC1.

As used herein, "selective VPAC2 receptor peptide agonists" also include pharmaceutically acceptable salts of the compounds described herein. A selective VPAC2 receptor peptide agonist of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic bases, and inorganic and organic acids, to form a salt. Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-

bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, trifluoroacetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, 5 propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, 10 gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium 15 hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, and the like.

The selective PEGylated VPAC2 receptor peptide agonists of the present invention can be administered parenterally. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, 20 subcutaneous, intradermal, or intraperitoneal injection. These agonists can be administered to the subject in conjunction with an acceptable pharmaceutical carrier, diluent, or excipient as part of a pharmaceutical composition for treating NIDDM, or the disorders discussed below. The pharmaceutical composition can be a solution or, if administered parenterally, a suspension of the VPAC2 receptor peptide agonist or a 25 suspension of the VPAC2 receptor peptide agonist complexed with a divalent metal cation such as zinc. Suitable pharmaceutical carriers may contain inert ingredients which do not interact with the peptide or peptide derivative. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), 30 phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Some examples of suitable excipients include lactose, dextrose, sucrose, trehalose, sorbitol, and mannitol.

Standard pharmaceutical formulation techniques may be employed such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. The selective PEGylated VPAC2 receptor peptide agonists of the present invention may be formulated for administration through the buccal, topical, oral,
5 transdermal, nasal, or pulmonary route.

The PEGylated VPAC2 receptor peptide agonists of the invention may be formulated for administration such that blood plasma levels are maintained in the efficacious range for extended time periods. The main barrier to effective oral peptide drug delivery is poor bioavailability due to degradation of peptides by acids and
10 enzymes, poor absorption through epithelial membranes, and transition of peptides to an insoluble form after exposure to the acidic pH environment in the digestive tract. Oral delivery systems for peptides such as those encompassed by the present invention are known in the art. For example, PEGylated VPAC2 receptor peptide agonists can be encapsulated using microspheres and then delivered orally. For
15 example, PEGylated VPAC2 receptor peptide agonists can be encapsulated into microspheres composed of a commercially available, biocompatible, biodegradable polymer, poly(lactide-co-glycolide)-COOH and olive oil as a filler (see Joseph, et al. *Diabetologia* 43:1319-1328 (2000)). Other types of microsphere technology is also available commercially such as Medisorb® and Prolease® biodegradable polymers
20 from Alkermes. Medisorb® polymers can be produced with any of the lactide isomers. Lactide:glycolide ratios can be varied between 0:100 and 100:0 allowing for a broad range of polymer properties. This allows for the design of delivery systems and implantable devices with resorption times ranging from weeks to months. Emisphere has also published numerous articles discussing oral delivery technology
25 for peptides and proteins. For example, see WO 95/28838 by Leone-bay et al. which discloses specific carriers comprised of modified amino acids to facilitate absorption.

The selective PEGylated VPAC2 receptor peptide agonists described herein can be used to treat subjects with a wide variety of diseases and conditions. Agonists encompassed by the present invention exert their biological effects by acting at a receptor
30 referred to as the VPAC2 receptor. Subjects with diseases and/or conditions that respond favourably to VPAC2 receptor stimulation or to the administration of VPAC2 receptor peptide agonists can therefore be treated with the VPAC2 agonists of the present

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invention. These subjects are said to “be in need of treatment with VPAC2 agonists” or “in need of VPAC2 receptor stimulation”.

The selective PEGylated VPAC2 receptor peptide agonists of the present invention may be employed to treat diabetes, including both type 1 and type 2 diabetes (non-insulin dependent diabetes mellitus or NIDDM). Also included are subjects requiring prophylactic treatment with a VPAC2 receptor agonist, e.g., subjects at risk for developing NIDDM. Such treatment may also delay the onset of diabetes and diabetic complications. Additional subjects include those with impaired glucose tolerance or impaired fasting glucose, subjects whose body weight is about 25% above normal body weight for the subject's height and body build, subjects having one or more parents with NIDDM, subjects who have had gestational diabetes, and subjects with metabolic disorders such as those resulting from decreased endogenous insulin secretion. The selective VPAC2 receptor peptide agonists may be used to prevent subjects with impaired glucose tolerance from proceeding to develop type 2 diabetes, prevent pancreatic β -cell deterioration, induce β -cell proliferation, improve β -cell function, activate dormant β -cells, differentiate cells into β -cells, stimulate β -cell replication, and inhibit β -cell apoptosis. Other diseases and conditions that may be treated or prevented using compounds of the invention in methods of the invention include: Maturity-Onset Diabetes of the Young (MODY) (Herman, et al., *Diabetes* 43:40, 1994); Latent Autoimmune Diabetes Adult (LADA) (Zinmet, et al., *Diabetes Med.* 11:299, 1994); impaired glucose tolerance (IGT) (Expert Committee on Classification of Diabetes Mellitus, *Diabetes Care* 22 (Supp. 1):S5, 1999); impaired fasting glucose (IFG) (Charles, et al., *Diabetes* 40:796, 1991); gestational diabetes (Metzger, *Diabetes*, 40:197, 1991); metabolic syndrome X, dyslipidemia, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and insulin resistance.

The selective PEGylated VPAC2 receptor peptide agonists of the invention may also be used in methods of the invention to treat secondary causes of diabetes (Expert Committee on Classification of Diabetes Mellitus, *Diabetes Care* 22 (Supp. 1):S5, 1999). Such secondary causes include glucocorticoid excess, growth hormone excess, pheochromocytoma, and drug-induced diabetes. Drugs that may induce diabetes include, but are not limited to, pyriminil, nicotinic acid, glucocorticoids, phenytoin, thyroid hormone, β -adrenergic agents, α -interferon and drugs used to treat HIV infection.

The selective PEGylated VPAC2 receptor peptide agonists of the present invention may be effective in the suppression of food intake and the treatment of obesity.

The selective PEGylated VPAC2 receptor peptide agonists of the present invention may also be effective in the prevention or treatment of such disorders as

5 atherosclerotic disease, hyperlipidemia, hypercholesteremia, low HDL levels, hypertension, primary pulmonary hypertension, cardiovascular disease (including atherosclerosis, coronary heart disease, coronary artery disease, and hypertension), cerebrovascular disease and peripheral vessel disease; and for the treatment of lupus, polycystic ovary syndrome, carcinogenesis, and hyperplasia, asthma, male and female

10 reproduction problems, sexual disorders, ulcers, sleep disorders, disorders of lipid and carbohydrate metabolism, circadian dysfunction, growth disorders, disorders of energy homeostasis, immune diseases including autoimmune diseases (e.g., systemic lupus erythematosus), as well as acute and chronic inflammatory diseases, rheumatoid arthritis, and septic shock.

15 The selective PEGylated VPAC2 receptor peptide agonists of the present invention may also be useful for treating physiological disorders related to, for example, cell differentiation to produce lipid accumulating cells, regulation of insulin sensitivity and blood glucose levels, which are involved in, for example, abnormal pancreatic β -cell function, insulin secreting tumors and/or autoimmune hypoglycemia due to

20 autoantibodies to insulin, autoantibodies to the insulin receptor, or autoantibodies that are stimulatory to pancreatic β -cells, macrophage differentiation which leads to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, adipocyte gene expression, adipocyte differentiation, reduction in the pancreatic β -cell mass, insulin secretion, tissue sensitivity to insulin, liposarcoma cell growth, polycystic

25 ovarian disease, chronic anovulation, hyperandrogenism, progesterone production, steroidogenesis, redox potential and oxidative stress in cells, nitric oxide synthase (NOS) production, increased gamma glutamyl transpeptidase, catalase, plasma triglycerides, HDL, and LDL cholesterol levels, and the like.

In addition, the selective VPAC2 receptor peptide agonists of the invention may

30 be used for treatment of asthma (Bolin, et al., *Biopolymer* 37:57-66 (1995); U.S. Patent No. 5,677,419; showing that polypeptide R3PO is active in relaxing guinea pig tracheal smooth muscle); hypotension induction (VIP induces hypotension, tachycardia, and facial

flushing in asthmatic patients (Morice, et al., *Peptides* 7:279-280 (1986); Morice, et al., *Lancet* 2:1225-1227 (1983)); male reproduction problems (Siow, et al., *Arch. Androl.* 43(1):67-71 (1999)); as an anti-apoptosis/neuroprotective agent (Brenneman, et al., *Ann. N. Y. Acad. Sci.* 865:207-12 (1998)); cardioprotection during ischemic events (Kalfin, et al., *J. Pharmacol. Exp. Ther.* 1268(2):952-8 (1994); Das, et al., *Ann. N. Y. Acad. Sci.* 865:297-308 (1998)), manipulation of the circadian clock and its associated disorders (Hamar, et al., *Cell* 109:497-508 (2002); Shen, et al., *Proc. Natl. Acad. Sci.* 97:11575-80, (2000)), and as an anti-ulcer agent (Tuncel, et al., *Ann. N. Y. Acad. Sci.* 865:309-22, (1998)).

10 An "effective amount" of a selective PEGylated VPAC2 receptor peptide agonist is the quantity that results in a desired therapeutic and/or prophylactic effect without causing unacceptable side effects when administered to a subject in need of VPAC2 receptor stimulation. A "desired therapeutic effect" includes one or more of the following: 1) an amelioration of the symptom(s) associated with the disease or condition; 15 2) a delay in the onset of symptoms associated with the disease or condition; 3) increased longevity compared with the absence of the treatment; and 4) greater quality of life compared with the absence of the treatment. For example, an "effective amount" of a VPAC2 agonist for the treatment of NIDDM is the quantity that would result in greater control of blood glucose concentration than in the absence of treatment, thereby resulting 20 in a delay in the onset of diabetic complications such as retinopathy, neuropathy, or kidney disease. An "effective amount" of a selective VPAC2 receptor peptide agonist for the prevention of NIDDM is the quantity that would delay, compared with the absence of treatment, the onset of elevated blood glucose levels that require treatment with anti-hypoglycemic drugs such as sulfonylureas, thiazolidinediones, insulin, and/or 25 bisguanidines.

 An "effective amount" of the selective PEGylated VPAC2 receptor peptide agonist administered to a subject will also depend on the type and severity of the disease and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. The dose of selective VPAC2 peptide receptor agonist effective to 30 normalize a patient's blood glucose will depend on a number of factors, among which are included, without limitation, the subject's sex, weight and age, the severity of inability to

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regulate blood glucose, the route of administration and bioavailability, the pharmacokinetic profile of the peptide, the potency, and the formulation.

A typical dose range for the selective PEGylated VPAC2 receptor peptide agonists of the present invention will range from about 1 μg per day to about 5000 μg per day. Preferably, the dose ranges from about 1 μg per day to about 2500 μg per day, more preferably from about 1 μg per day to about 1000 μg per day. Even more preferably, the dose ranges from about 5 μg per day to about 100 μg per day. A further preferred dose range is from about 10 μg per day to about 50 μg per day. Most preferably, the dose is about 20 μg per day.

10 A "subject" is a mammal, preferably a human, but can also be an animal, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

The selective VPAC2 receptor peptide agonists of the present invention can be prepared by using standard methods of solid-phase peptide synthesis techniques. Peptide synthesizers are commercially available from, for example, Rainin-PTI Symphony Peptide Synthesizer (Tucson, AZ). Reagents for solid phase synthesis are commercially available, for example, from Glycopep (Chicago, IL). Solid phase peptide synthesizers can be used according to manufacturers instructions for blocking interfering groups, protecting the amino acid to be reacted, coupling, decoupling, and capping of unreacted amino acids.

Typically, an α -N-protected amino acid and the N-terminal amino acid on the growing peptide chain on a resin is coupled at room temperature in an inert solvent such as dimethylformamide, N-methylpyrrolidone or methylene chloride in the presence of coupling agents such as dicyclohexylcarbodiimide and 1-hydroxybenzotriazole and a base such as diisopropylethylamine. The α -N-protecting group is removed from the resulting peptide resin using a reagent such as trifluoroacetic acid or piperidine, and the coupling reaction repeated with the next desired N-protected amino acid to be added to the peptide chain. Suitable amine protecting groups are well known in the art and are described, for example, in Green and Wuts, *"Protecting Groups in Organic Synthesis"*, John Wiley and Sons, 1991. Examples include t-butyloxycarbonyl (tBoc) and fluorenylmethoxycarbonyl (Fmoc).

The selective VPAC2 receptor peptide agonists are also synthesized using standard automated solid-phase synthesis protocols using t-butoxycarbonyl- or fluorenylmethoxycarbonyl-alpha-amino acids with appropriate side-chain protection. After completion of synthesis, peptides are cleaved from the solid-phase support with simultaneous side-chain deprotection using standard hydrogen fluoride methods or trifluoroacetic acid (TFA). Crude peptides are then further purified using Reversed-Phase Chromatography on Vydac C18 columns using acetonitrile gradients in 0.1% trifluoroacetic acid (TFA). To remove acetonitrile, peptides are lyophilized from a solution containing 0.1 % TFA, acetonitrile and water. Purity can be verified by analytical reversed phase chromatography. Identity of peptides can be verified by mass spectrometry. Peptides can be solubilized in aqueous buffers at neutral pH.

The peptide agonists of the present invention may also be made by recombinant methods known in the art using both eukaryotic and prokaryotic cellular hosts.

Once a peptide for use in the present invention is prepared and purified, it is modified by covalently linking at least one PEG molecule to Cys or Lys residues, to K(W) or K(CO(CH₂)₂SH), or to the carboxy-terminal amino acid. A wide variety of methods have been described in the art to produce peptides covalently conjugated to PEG and the specific method used for the present invention is not intended to be limiting (for review article see, Roberts, M. et al. *Advanced Drug Delivery Reviews*, 54:459-476, 2002).

An example of a PEG molecule which may be used is methoxy-PEG2-MAL-40K, a bifurcated PEG maleimide (Nektar, Huntsville, Alabama). Other examples include, but are not limited to bulk mPEG-SBA-20K (Nektar) and mPEG2-ALD-40K (Nektar).

Carboxy-terminal attachment of PEG may be attached via enzymatic coupling using recombinant VPAC2 receptor peptide agonist as a precursor or alternative methods known in the art and described, for example, in U.S. Patent 4,343,898 or *Intl. J. Pept. & Prot. Res.* 43:127-38 (1994).

One method for preparing the PEGylated VPAC2 receptor peptide agonists of the present invention involves the use of PEG-maleimide to directly attach PEG to a thiol group of the peptide. The introduction of a thiol functionality can be achieved by adding or inserting a Cys or hC residue onto or into the peptide at positions described above. A thiol functionality can also be introduced onto the side-chain of the peptide (e.g. acylation

of lysine ϵ -amino group by a thiol-containing acid, such as mercaptopropionic acid). A PEGylation process of the present invention utilizes Michael addition to form a stable thioether linker. The reaction is highly specific and takes place under mild conditions in the presence of other functional groups. PEG maleimide has been used as a reactive polymer for preparing well-defined, bioactive PEG-protein conjugates. It is preferable that the procedure uses a molar excess, preferably from 1 to 10 molar excess, of a thiol-containing VPAC2 receptor peptide agonist relative to PEG maleimide to drive the reaction to completion. The reactions are preferably performed between pH 4.0 and 9.0 at room temperature for 10 minutes to 40 hours. The excess of unPEGylated thiol-containing peptide is readily separated from the PEGylated product by conventional separation methods. The PEGylated VPAC2 receptor peptide agonist is preferably isolated using reverse-phase HPLC or size exclusion chromatography. Specific conditions required for PEGylation of VPAC2 receptor peptide agonists are set forth in Example 7. Cysteine PEGylation may be performed using PEG maleimide or bifurcated PEG maleimide.

An alternative method for preparing the PEGylated VPAC2 receptor peptide agonists of the invention, involves PEGylating a lysine residue using a PEG-succinimidyl derivative. In order to achieve site specific PEGylation, the Lys residues which are not used for PEGylation are substituted for Arg residues.

Another approach for PEGylation is via Pictet-Spengler reaction. A Trp residue with its free amine is needed to incorporate the PEG molecule onto a VPAC2 receptor selective peptide. One approach to achieve this is to site specifically introduce a Trp residue onto the amine of a Lys sidechain via an amide bond during the solid phase synthesis (see Example 9).

Various preferred features and embodiments of the present invention will now be described with reference to the following non-limiting examples.

Example 1

Preparation of the Selective VPAC2 Receptor Peptide Agonists by Solid Phase t-Boc

Chemistry:

Selective VPAC2 receptor peptide agonists may be prepared using the following method and then PEGylating using one of the methods described in Examples 7, 8 and 9.

Approximately 0.5-0.6 grams (0.38-0.45 mmole) Boc Ser(Bzl)-PAM resin is placed in a standard 60 mL reaction vessel. Double couplings are run on an Applied Biosystems ABI430A peptide synthesizer. The following side-chain protected amino acids (2 mmole cartridges of Boc amino acids) are obtained from Midwest Biotech (Fishers, IN) and are used in the synthesis:

Arg-Tosyl (TOS), Asp- δ -cyclohexyl ester (OcHx), Glu- δ -cyclohexyl ester (OcHx), His-benzyloxymethyl(BOM), Lys-2-chlorobenzyloxycarbonyl (2Cl-Z), Ser-O-benzyl ether (OBzl), Thr-O-benzyl ether (OBzl), Trp-formyl (CHO) and Tyr-2-bromobenzyloxycarbonyl (2Br-Z) and Boc Gly PAM resin. Trifluoroacetic acid (TFA), di-isopropylethylamine (DIEA), 0.5 M hydroxybenzotriazole (HOBt) in DMF and 0.5 M dicyclohexylcarbodiimide (DCC) in dichloromethane are purchased from PE-Applied Biosystems (Foster City, CA). Dimethylformamide (DMF-Burdick and Jackson) and dichloromethane (DCM-Mallinkrodt) is purchased from Mays Chemical Co. (Indianapolis, IN).

Standard double couplings are run using either symmetric anhydride or HOBt esters, both formed using DCC. At the completion of the syntheses, the N-terminal Boc group is removed and the peptidyl resins are treated with 20% piperidine in DMF to deformylate the Trp side chain if Trp is present in the sequence. For the N-terminal acylation, four-fold excess of symmetric anhydride of the corresponding acid is added onto the peptide resin. The symmetric anhydride is prepared by diisopropylcarbodiimide (DIC) activation in DCM. The reaction is allowed to proceed for 4 hours and monitored by ninhydrin test. After washing with DCM, the resins are transferred to a TEFLON reaction vessel and are dried *in vacuo*.

Cleavages are done by attaching the reaction vessels to a HF (hydrofluoric acid) apparatus (Penninsula Laboratories). 1 mL m-cresol per gram/resin is added and 10 mL HF (purchased from AGA, Indianapolis, IN) is condensed into the pre-cooled vessel. 1 mL DMS per gram resin is added when methionine is present. The reactions are stirred one hour in an ice bath. The HF is removed *in vacuo*. The residues are suspended in ethyl ether. The solids are filtered and are washed with ether. Each peptide is extracted into aqueous acetic acid and either is freeze dried or is loaded directly onto a reverse-phase column.

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Purifications are run on a 2.2 x 25cm VYDAC C18 column in buffer A (0.1% Trifluoroacetic acid in water, B: 0.1% TFA in acetonitrile). A gradient of 20% to 90% B is run on an HPLC (Waters) over 120 minutes at 10 mL/minute while monitoring the UV at 280 nm (4.0 A) and collecting one minute fractions. Appropriate fractions are
 5 combined, frozen and lyophilized. Dried products are analyzed by HPLC (0.46 x 15 cm METASIL AQ C18) and MALDI mass spectrometry.

Example 2

Preparation of the Selective VPAC2 Receptor Peptide Agonists by Solid Phase FMoc

10 *Chemistry:*

Selective VPAC2 receptor peptide agonists may be prepared using the following method and then PEGylating using one of the methods described in Examples 7, 8 and 9.

Approximately 114 mg (50 mMole) FMOC Ser(tBu) WANG resin (purchased from GlycoPep, Chicago, IL) is placed in each reaction vessel. The synthesis is
 15 conducted on a Rainin Symphony Peptide Synthesizer. Analogs with a C-terminal amide are prepared using 75 mg (50 μ mole) Rink Amide AM resin (Rapp Polymere, Tuebingen, Germany).

The following FMOC amino acids are purchased from GlycoPep (Chicago, IL), and NovaBiochem (La Jolla, CA): Arg-2,2,4,6,7-pentamethyldihydrobenzofuran-5-
 20 sulfonyl (Pbf), Asn-trityl (Trt), Asp- β -t-Butyl ester (tBu), Glu- δ -t-butyl ester (tBu), Gln-t-butyl (Pbf), Asn-trityl (Trt), His-trityl (Trt), Lys-t-butyloxycarbonyl (Boc), Ser-t-butyl ether (OtBu), Thr-t-butyl ether (OtBu), Trp-t-butyloxycarbonyl (Boc), Tyr-t-butyl ether (OtBu).

Solvents dimethylformamide (DMF-Burdick and Jackson), N-methyl pyrrolidone (NMP-Burdick and Jackson), dichloromethane (DCM-Mallinkrodt) are purchased from
 25 Mays Chemical Co. (Indianapolis, IN).

Hydroxybenzotriazole (HOBt), di-isopropylcarbodiimide (DIC), di-isopropylethylamine (DIEA), and piperidine (Pip) are purchased from Aldrich Chemical Co (Milwaukee, WI).

All amino acids are dissolved in 0.3 M in DMF. Three hour DIC/HOBt activated
 30 couplings are run after 20 minutes deprotection using 20% Piperidine/DMF. Each resin is washed with DMF after deprotections and couplings. After the last coupling and

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deprotection, the peptidyl resins are washed with DCM and are dried *in vacuo* in the reaction vessel. For the N-terminal acylation, four-fold excess of symmetric anhydride of the corresponding acid is added onto the peptide resin. The symmetric anhydride is prepared by diisopropylcarbodiimide (DIC) activation in DCM. The reaction is allowed to proceed for 4 hours and monitored by ninhydrin test. The peptide resin is then washed with DCM and dried *in vacuo*.

The cleavage reaction is mixed for 2 hours with a cleavage cocktail consisting of 0.2 mL thioanisole, 0.2 mL methanol, 0.4 mL triisopropylsilane, per 10 mL trifluoroacetic acid (TFA), all purchased from Aldrich Chemical Co., Milwaukee, WI. If Cys is present in the sequence, 2% of ethanedithiol is added. The TFA filtrates are added to 40 mL ethyl ether. The precipitants are centrifuged 2 minutes at 2000 rpm. The supernatants are decanted. The pellets are resuspended in 40 mL ether, re-centrifuged, re-decanted, dried under nitrogen and then *in vacuo*.

0.3-0.6 mg of each product is dissolved in 1 mL 0.1% TFA/acetonitrile (ACN), with 20 μ L being analyzed on HPLC [0.46 x 15cm METASIL AQ C18, 1mL/min, 45C°, 214 nM (0.2A), A=0.1%TFA, B=0.1%TFA/50%ACN. Gradient = 50% B to 90% B over 30 minutes].

Purifications are run on a 2.2 x 25 cm VYDAC C18 column in buffer A (0.1% trifluoroacetic acid in water, B: 0.1% TFA in acetonitrile). A gradient of 20% to 90% B is run on an HPLC (Waters) over 120 minutes at 10 mL/minute while monitoring the UV at 280 nm (4.0A) and collecting 1 minute fractions. Appropriate fractions are combined, frozen and lyophilized. Dried products are analyzed by HPLC (0.46 x 15 cm METASIL AQ C18) and MALDI mass spectrometry.

25 Example 3 *In vitro* potency:

Alpha screen: Cells are washed in the culture flask once with PBS. The cells are then rinsed with enzyme free dissociation buffer. The dissociated cells are removed. The cells are then spun down and washed in stimulation buffer. For each data point, 50,000 cells suspended in stimulation buffer are used. To this buffer, Alpha screen acceptor beads are added along with the stimuli. This mixture is incubated for 60 minutes. Lysis buffer and Alpha screen donor beads are added and are incubated for 60 to 120 minutes. The Alpha screen signal (indicative of intracellular cAMP levels) is read in a suitable

instrument (e.g. AlphaQuest from Perkin-Elmer). Steps including Alpha screen donor and acceptor beads are performed in reduced light. The EC_{50} for cAMP generation is calculated from the raw signal or is based on absolute cAMP levels as determined by a standard curve performed on each plate.

- 5 Results for each agonist are, at minimum, from two analyses performed in a single run. For some agonists, the results are the mean of more than one run. The tested peptide concentrations are: 10000, 1000, 100, 10, 3, 1, 0.1, 0.01, 0.003, 0.001, 0.0001 and 0.00001 nM.

The activity (EC_{50} (nM)) for the human VPAC2 receptor is reported in Table 1.

10 Table 1

Human VPAC2-R mediated cAMP generation (EC_{50} ; nM)	
VIP	1.00
PACAP-27	2.33
P137	8.31
P190	2.14
P217	>3000
P219	25.46
P245	450.14
P246	398.31
P247	132.87
P283	31.71
P286	6.65
P300	6.62
P328	6.61
P331	9.74
P337	7.57
P340	7.74
P373	33.86
P378	37.35
P380	12.07
P399	9.76
P404	17.01
P411	25.23
P413	28.37
P415	13.38
P420	19.21
P426	47.66
P428	61.06
P430	50.50

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P432	20.10
P434	29.04
P436	>10000
P438	37.54
P443	26.08
P447	84.14
P449	94.12
P452	24.51
P456	25.22
P461	6.73
P462	94.31
P466	>10000

EC₅₀ values given are single results or the mean of two or more independent runs.

Example 4 Selectivity:

- Binding assays:* Membrane prepared from a stable VPAC2 cell line (see Example 3) or from cells transiently transfected with human VPAC1 or PAC1 are used. A filter binding assay is performed using 125I-labeled VIP for VPAC1 and VPAC2 and 125I-labeled PACAP-27 for PAC1 as the tracers.

For this assay, the solutions and equipment include:

- 10 Presoak solution: 0.5 % Polyethyleneamine in Aqua dest.
 Buffer for flushing filter plates: 25 mM HEPES pH 7.4
 Blocking buffer: 25 mM HEPES pH 7.4; 0.2 % protease free BSA
 Assay buffer: 25 mM HEPES pH 7.4; 0.5 % protease free BSA
 Dilution and assay plate: PS-Microplate, U form
 15 Filtration Plate: Multiscreen FB Opaque Plate; 1.0 μ M Type B Glasfiber filter

- In order to prepare the filter plates, the presoak solution is aspirated by vacuum filtration. The plates are flushed twice with 200 μ L flush buffer. 200 μ L blocking buffer is added to the filter plate. The filter plate is then incubated with 200 μ L presoak solution
 20 for 1 hour at room temperature.

 The assay plate is filled with 25 μ L assay buffer, 25 μ L membranes (2.5 μ g) suspended in assay buffer, 25 μ L compound (agonist) in assay buffer, and 25 μ L tracer (about 40000 cpm) in assay buffer. The filled plate is incubated for 1 hour with shaking.

The transfer from assay plate to filter plate is conducted. The blocking buffer is aspirated by vacuum filtration and washed two times with flush buffer. 90 μ L is transferred from the assay plate to the filter plate. The 90 μ L transferred from assay plate is aspirated and washed three times with 200 μ L flush buffer. The plastic support is removed. It is dried for 1 hour at 60 °C. 30 μ L Microscint is added. The count is performed.

The selectivity (IC₅₀) for human VPAC2, VPAC1, and PAC1 is reported in Table 2. Values reported are single results or the mean of two or more independent runs.

Table 2

Human receptor binding (IC ₅₀ ; nM)			
Agonist #	VPAC2	VPAC1	PAC1
PACAP-27	2.52	4.0	9.5
VIP	5.06	3.3	>1000
P137	0.64	852.7	>25000
P190	4.44	>3000	>25000
P219	67.92	>25000	n.d.
P245	920.53	>25000	n.d.
P246	>1000	>25000	n.d.
P247	352.78	>25000	n.d.
P283	17.69	>3000	>25000
P286	0.46	>3000	>25000
P300	1.76	>3000	>25000
P328	4.54	>3000	>25000
P331	15.09	>3000	>25000
P337	5.07	>3000	>25000
P340	4.76	>3000	>25000
P373	111.29	>25000	>25000
P378	95.59	n.d.	>25000
P380	15.86	>3000	>25000
P399	10.06	>3000	>25000
P404	13.1	>3000	>25000
P411	49.1	n.d.	>25000
P413	31.22	>3000	>25000
P415	14.28	>3000	>25000
P420	48.26	>3000	>25000
P426	38.07	>3000	>25000
P428	76.53	>3000	>25000
P430	49.70	>3000	>25000
P432	130.00	>3000	>25000
P434	14.24	>3000	>25000

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P436	>100	>3000	>25000
P438	56.78	>3000	>25000
P443	13.93	>3000	>25000
P447	13.95	>3000	>25000
P449	>100	>3000	>25000
P452	93.87	>3000	>25000
P456	217.34	>3000	>25000
P461	7.42	>3000	>25000
P462	42.33	>3000	>25000
P466	>100	>3000	>25000

n.d. = Not determined

Rat receptor selectivity is estimated by comparing functional potency (cAMP generation) in CHO-PO cells transiently expressing rat VPAC1 or rat VPAC2 receptors.

- 5 CHO-PO cells transiently expressing rat VPAC1 or VPAC2, are seeded with 10,000 cells/well three days before the assay. The cells are kept in 200 μ L culture medium. On the day of the experiment, the medium is removed and the cells are washed twice. The cells are incubated in assay buffer plus IBMX for 15 minutes at room temperature. Afterwards, the stimuli are added and are dissolved in assay buffer. The stimuli are
- 10 present for 30 minutes. The assay buffer is then gently removed. The cell lysis reagent of the DiscoverX cAMP kit is added. Thereafter, the standard protocol for developing the cAMP signal as described by the manufacturer is used (DiscoverX Inc., USA). EC_{50} values for cAMP generation are calculated from the raw signal or are based on absolute cAMP levels as determined by a standard curve performed on each plate.

- 15 Results for each agonist are the mean of two independent runs. The typically tested concentrations of peptide are: 1000, 300, 100, 10, 1, 0.3, 0.1, 0.01, 0.001, 0.0001 and 0 nM.

- 20 Table 3: Rat VPAC1 and VPAC2 *In vitro* potency (cAMP generation). CHO-PO cells are transiently transfected with rat VPAC1 or VPAC2 receptor DNA. The activity (EC_{50} in nM) for these receptors is reported in the table below.

Agonist #	rVPAC1	rVPAC2
VIP	0.015	0.67
PACAP-27	0.07	n.d.
P137	29.7	8.0
P300	n.d.	5.8

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P328	212.5	7.5
P337	114.2	5.6
P340	116.5	4.0
P373	349.6	72.2
P378	529.8	119.4
P380	>1000	66.4
P399	170.6	18.4
P404	23.4	24.4
P411	266.4	55.3
P413	219.5	71.1
P415	47.6	9.8
P420	>1000	35.6
P426	>200	56.8
P428	>1000	77.2
P430	315.0	49.9
P432	>100	16.7
P434	>500	39.8
P436	>1000	>1000
P438	>200	50.8
P443	304.9	28.4
P447	>1000	144.7
P449	421.4	123.7
P452	189.2	38.6
P456	>1000	80.2
P461	90.4	5.6
P462	>1000	119.5
P465	>1000	12.4

EC₅₀ values given are from one single determination or the mean of two or more independent EC₅₀ determinations.

Example 5 In vivo assays:

- 5 *Intravenous glucose tolerance test (IVGTT):* Normal Wistar rats are fasted overnight and are anesthetized prior to the experiment. A blood sampling catheter is inserted into the rats. The compound is given in the jugular vein. Blood samples are taken from the carotid artery. A blood sample is drawn immediately prior to the injection of glucose along with the compound. After the initial blood sample, glucose mixed with
- 10 compound is injected intravenously (i.v.). Compound may also be injected intravenously or subcutaneously prior to the glucose challenge. A glucose challenge of 0.5 g/kg body weight is given, injecting a total of 1.5 mL vehicle with glucose and agonist per kg body weight. The peptide concentrations are varied to produce the desired dose in $\mu\text{g/kg}$.

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Blood samples are drawn at 2, 4, 6 and 10 minutes after giving glucose. The control group of animals receives the same vehicle along with glucose, but with no compound added. In some instances, a 30 minute post-glucose blood sample is drawn. Aprotinin is added to the blood sample (250-500 kIU/ml blood). The serum is then analyzed for glucose and insulin using standard methodologies.

The assay uses a formulated and calibrated peptide stock in PBS. Normally, this stock is a prediluted 100 μ M stock. However, a more concentrated stock with approximately 1 mg agonist per mL is used. The specific concentration is always known. Variability in the maximal response is mostly due to variability in the vehicle dose.

Protocol details are as follows:

SPECIES/STRAIN/WEIGHT	Rat/Wistar Unilever/approximately 275 - 300 g
TREATMENT DURATION	Single dose
DOSE VOLUME/ROUTE	1.5 mL/kg/iv
VEHICLE	8% PEG300, 0.1% BSA in water
FOOD/WATER REGIMEN	Rats are fasted overnight prior to surgery.
LIVE-PHASE PARAMETERS	Animals are sacrificed at the end of the test.
IVGTT: Performed on rats (with two catheters, jugular vein and carotid artery) of each group, under pentobarbital anesthesia.	Glucose IV bolus: 500 mg/kg as 10% solution (5 mL/kg) at time = 0. Compound iv: 0 – 240 min prior to glucose Blood samplings (300 μ L from carotid artery; EDTA as anticoagulant; aprotinin and PMSF as antiproteolytics; kept on ice): 0, 2, 4, 6, and 10 minutes. Parameter determined: Insulin.
TOXICOKINETICS	Plasma samples remaining after insulin measurements are kept at -20°C and compound levels are determined.

Table 4a

Peptide	Time between glucose & compound	% increase AUC: Dose = 10 μ g/kg	% increase AUC: Dose = 30 μ g/kg	% increase AUC: Dose = 100 μ g/kg	IVGTT (ED ₅₀ ; μ g/kg)
P137	0h	+366	n.d.	n.d.	n.d.
P137	4h	+193	+321	+487	n.d.
P190	0h	+73	n.d.	n.d.	n.d.
P461	24h*	n.d.	n.d.	+71	n.d.

*Compound given subcutaneously

AUC = Area under curve (insulin, 0 - 10 min after glucose)

Glucose lowering in diabetic ZDF rats. ZDF rats, 8-9 weeks old with fed glucose levels of approximately 300 mg/dl are used for this experiment. The animals are randomised into control (vehicle) and treatment group(s) on the day of the experiment and are conscious throughout the experiment. The compound is injected intravenously at the start of the experiment and blood samples are drawn from the tail vein immediately prior to compound injection and then 0.5, 1, 2, 3, 4 and 24h after compound injection. The animals are deprived of food during the first 2 or 4h of the experiment. The blood samples are collected in EDTA tubes, aprotinin added and immediately put on ice pending insulin and glucose analysis using standard methods.

Table 4b Glucose lowering in conscious food-deprived ZDF rats

P137 (μ g/kg)	Analyte	Time after injection						
		0h	0.5 h	1h	2h	3h	4h	24h
vehicle	glucose (mg/dl)	343	284	289	305	n.d.	317	339
vehicle	insulin (ng/ml)	12.6	12.8	13.5	13.4	n.d.	17.9	15.3
10	glucose (mg/dl)	344	277	244	199	n.d.	361	336
10	insulin (ng/ml)	12.5	21.2	18.5	20.0	n.d.	18.5	15.0
30	glucose (mg/dl)	329	254	218	156	n.d.	347	347
30	insulin (ng/ml)	10.9	27.0	23.7	23.1	n.d.	20.8	16.0
Vehicle	glucose (mg/dl)	298	n.d.	332	253	219	215	366
Vehicle	insulin (ng/ml)	17.1	n.d.	13.0	10.5	9.3	10.6	10.3
100	glucose (mg/dl)	307	n.d.	362	360	323	304	400
100	insulin (ng/ml)	17.8	n.d.	19.9	15.9	15.4	15.1	11.1

Animals are given access to food after the 2h timepoint (10 & 30 μ g/kg) or after the 4h time point (100 μ g/kg).

15

Pharmacokinetic profiles of PEGylated peptides. Healthy Fisher 344 rats (3 animals per group) are injected with 100 μ g compound/kg (compound amount based on peptide content and dissolved in PBS buffer). Blood samples are drawn 3, 12, 24, 48, 72, 96 and 168 hour post dosing and the peptide content in plasma is analysed by a radio-immunoassay (RIA) directed against the N-terminus of the peptide. PK parameters are then calculated using a model-independent method (WinNonlin Pro, Pharsight Corp., Mountain View, CA, USA).

20

Table 4c. PK parameters of PEGylated compounds. Mean and (SD) values for N=3.

Compound	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-last} (ng*h/mL)	T _{1/2} (h)	Cl/F (mL/h/kg)	Vd/F (mL/kg)
P217	247 (140)	20 (7)	13086 (6079)	49 (17)	7 (5)	421 (110)
P300	46 (16)	10 (3)	1343 (245)	15 (2)	72 (12)	1557 (359)
P328	94 (21)	12 (0)	3244 (500)	19 (2)	31 (5)	803 (32)
P337	122 (52)	13 (11)	3531 (1385)	13 (1)	31 (12)	574 (270)
P340	44 (27)	6 (5)	515 (189)	NC* NC	NC NC	NC NC
P373	240 (159)	13 (11)	10803 (2919)	31 (2)	10 (2)	424 (99)
P399	200 (45)	16 (7)	7066 (1136)	15 (2)	14 (2)	308 (53)
P404	133 (68)	20 (7)	6070 (2814)	23 (4)	17 (6)	556 (207)
P430	159 (31)	20 (7)	10122 (1848)	35 (6)	10 (2)	500 (166)
P432	392 (160)	16 (7)	21471 (5061)	35 (9)	5 (1)	229 (23)
P447	239 (71)	16 (7)	11727 (2293)	28 (3)	8 (1)	328 (27)

*NC = not calculated due to insufficient data

Example 6 Rat Serum Stability Studies:

5 In order to determine the stability of VPAC2 receptor peptide agonists in rat serum, obtain CHO-VPAC2 cells clone #6 (96 well plates/50,000 cells/well and 1 day culture), PBS 1X (Gibco), the peptides for the analysis in a 100 μ M stock solution, rat serum from a sacrificed normal Wistar rat, aprotinin, and a DiscoverX assay kit. The rat serum is stored at 4°C until use and is used within two weeks.

10 On Day 0, two 100 μ L aliquots of 10 μ M peptide in rat serum are prepared by adding 10 μ L peptide stock to 90 μ L rat serum for each aliquot. 250 kIU aprotinin / mL is added to one of these aliquots. The aliquot is stored with aprotinin at 4°C. The aliquot is stored without aprotinin at 37°C. The aliquots are incubated for 18 hours.

15 On Day 1, after incubation of the aliquots prepared on day 0 for 24 hours, an incubation buffer containing PBS + 1.3 mM CaCl₂, 1.2 mM MgCl₂, 2 mM glucose, and

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- 0.25 mM IBMX is prepared. A plate with 11 serial 5X dilutions of peptide for the 4°C and 37°C aliquot is prepared for each peptide studied. 2000 nM is used as the maximal concentration if the peptide has an EC₅₀ above 1 nM and 1000 nM as maximal concentration if the peptide has an EC₅₀ below 1 nM from the primary screen (see
- 5 Example 3). The plate(s) are washed with cells twice in incubation buffer. The plates are allowed to hold 50 µL incubation media per well for 15 minutes. 50 µL solution per well is transferred to the cells from the plate prepared with 11 serial 5X dilutions of peptide for the 4°C and 37°C aliquot for each peptide studied, using the maximal concentrations that are indicated by the primary screen, in duplicate. This step dilutes the peptide
- 10 concentration by a factor of two. The cells are incubated at room temperature for 30 minutes. The supernatant is removed. 40 µL/well of the DiscoverX antibody/extraction buffer is added. The cells are incubated on the shaker (300 rpm) for 1 hour. Normal procedure with the DiscoverX kit is followed. cAMP standards are included in column 12. EC₅₀ values are determined from the cAMP assay data. The remaining amount of
- 15 active peptide is estimated by the formula $EC_{50, 4C}/EC_{50, 37C}$ for each condition.

Table 5 Estimated peptide stability after 24h in rat serum at 37C

Agonist #	Estimated serum stability (%) ¹
P137	114.8
P219	56.5
P300	161.9
P306	142.4
P328	374.2
P373	73.6
P380	299.7
P399	204.1
P404	320.7
P415	220.9
P420	104.6
P426	46.9
P428	68.3
P430	54.9
P432	102.1
P434	61.9
P436	71.6
P438	31.2
P443	74.9

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P449	59.7
P452	62.8
P456	55.5
P461	67.3
P466	777.0

¹Values >100% may represent release of intact peptide from the PEG conjugate

Table 6 Estimated peptide stability after 72h in rat serum at 37C

Compound #	Estimated 72h stability (%) ¹
P137	52.8
P219	45.6
P247	16.7
P286	60.5
P328	348.0
P337	158.1
P373	47.1

¹Values >100% may represent release of intact peptide from the PEG conjugate

5

Example 7

PEGylation of selective VPAC2 receptor peptide agonists using thiol-based chemistry:

PEGylation reactions are run under conditions that permit the formation of a thioether bond. Specifically, the pH of the solution ranges from about 4 to 9 and the thiol-containing peptide concentrations range from 1 to 10 molar excess of methoxy-PEG2-MAL concentration. The PEGylation reactions are normally run at room temperature. The PEGylated VPAC2 receptor peptide agonist is then isolated using reverse-phase HPLC or size exclusion chromatography (SEC). PEGylated peptide analogues are characterized using analytical RP-HPLC, HPLC-SEC, SDS-PAGE, and/or MALDI Mass Spectrometry.

Usually a thiol function is introduced into or onto a selective VPAC2 receptor peptide agonist by adding a cysteine or a homocysteine or a thiol-containing moiety at either or both termini or by inserting a cysteine or a homocysteine or a thiol-containing moiety into the sequence. Thiol-containing VPAC2 receptor peptide agonists are reacted with 40 kDa polyethylene glycol-maleimide (PEG-maleimide) to produce derivatives with PEG covalently attached via a thioether bond. For example, P164, [CH₃-(CH₂)₄-CO-HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAPPPC, 42 AA, 23 mg,

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4.8 μmol], is dissolved in 4 mL of 200 mM phosphate buffer containing 20 mM EDTA, pH 7.5. The solution is then purged with argon. To this solution is added 230 mg of methoxy-PEG2-MAL-40K, a bifurcated PEG maleimide (Lot# PT-06D-01, Nektar, Huntsville, Alabama) (1:1 ratio of PEG to peptide). The reaction is performed for 2 hours.

- 5 Then 86 mg of the PEGylated peptide (P190) is obtained after preparative RP-HPLC. The peptide conjugate is characterized by size-exclusion HPLC, and tested for *in vitro* activity.

Starting from P120, $[\text{CH}_3-(\text{CH}_2)_4\text{-CO-HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPC}]$, 42 AA, 22 mg, 4.6 μmol] and 200 mg of methoxy-PEG2-MAL-40K, 131.4 mg of PEGylated material (P137) is obtained according to the procedure described above.

Using the same method, 65 mg of PEGylated conjugate (P201) is obtained by reacting 11.3 mg of P200, $[\text{CH}_3-(\text{CH}_2)_4\text{-CO-HSDAVFTENY(OMe)TKLRKQNleAAKKYLNDLKKGGPSSGAPPPC}]$, 2.6 μmol] with 98 mg of methoxy-PEG2-MAL-40K).

20mg of P327, $[\text{CH}_3-(\text{CH}_2)_4\text{-CO-HSDAVFTDNYTOmLRAibQVAAAibKYLQSIOrnNOmGGPSSGAPPPC-NH}_2]$ is dissolved in 3ml of 100mM NH_4Ac buffer containing 10mM EDTA, pH 6.8. The solution is purged with argon. 175mg of methoxy-PEG2-MAL-40K is added to the solution. The reaction is performed for 1 hour. 106mg of the PEGylated peptide (P128) is isolated by preparative RP-HPLC, characterised by SE-HPLC, and tested for *in-vitro* activity.

Example 8

25 *PEGylation via acylation on the sidechain of lysine*

In order to achieve site-specific PEGylation of selective VPAC2 receptor peptide agonists, all the Lys residues are changed into Arg residues except for these Lys residues where PEGylation is intended. For example, the following peptides are used for single or dual site PEGylation:

- 30 $\text{CH}_3-(\text{CH}_2)_4\text{-CO-HSDAVFTDNYTRLRKQVAAKRYLQSIrNGGPSSGAPPPS}$ (P213),
 $\text{CH}_3-(\text{CH}_2)_4\text{-CO-HSDAVFTDNYTRLRKQVAARRYLQSIrNGGPSSGAPPPS}$ (P214),

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CH₃-(CH₂)₄-CO-HSDAVFTDNYTRLRRQVAAKRYLQSIRNGGPSSGAPPPS (P215),
CH₃-(CH₂)₄-CO-HSDAVFTDNYTRLRRQVAARKYLQSIRNGGPSSGAPPPS (P216).

For the PEGylation of P213, the peptide is dissolved in 200 mM sodium borate buffer at pH 8.5 and a 1.5-fold molar excess of bulk mPEG-SBA-20K (Nektar, Lot#: PT-04E-11) is added (see scheme below). The reaction is allowed to stir at room temperature for 2-3 hours and then purified by preparative HPLC.

Example 9

PEGylation via Pictet-Spengler reaction

For PEGylation via Pictet-Spengler reaction to occur, a Trp residue with its free amine is needed to incorporate the PEG molecule onto the selective VPAC2 receptor peptide agonist. One approach to achieve this is to add a Lys residue onto the C-terminus of the peptide and then to couple a Trp residue onto the sidechain of Lys. The extensive SAR indicates that this modification does not change the properties of the parent peptide in terms of its *in vitro* potency and selectivity.

PEG with a functional aldehyde, for example mPEG2-ALD-40K (Nektar, Lot #: PT-6C-05), is used for the reaction. The site specific PEGylation involves the formation a tetracarboline ring between PEG and the peptide. PEGylation is conducted in glacial acetic acid at room temperature for 1 to 48 hours. A 1 to 10 molar excess of the PEG aldehyde is used in the reaction. After the removal of acetic acid, the PEGylated VPAC2 receptor peptide agonist is isolated by preparative RP-HPLC.

Other modifications of the present invention will be apparent to those skilled in the art without departing from the scope of the invention.

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CLAIMS

1. A PEGylated VPAC2 receptor peptide agonist comprising a sequence of the formula:

5 Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Thr-Xaa₈-Xaa₉-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃-
Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Xaa₂₃-Xaa₂₄-
Xaa₂₅-Xaa₂₆-Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁-Xaa₃₂-Xaa₃₃-Xaa₃₄-Xaa₃₅-
Xaa₃₆-Xaa₃₇-Xaa₃₈-Xaa₃₉-Xaa₄₀

Formula 10 (SEQ ID NO:18)

10 wherein:

Xaa₁ is: His, dH, or is absent;

Xaa₂ is: dA, Ser, Val, Gly, Thr, Leu, dS, Pro, or Aib;

Xaa₃ is: Asp or Glu;

Xaa₄ is: Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, Gly, dA, Aib, or NMeA;

15 Xaa₅ is: Val, Leu, Phe, Ile, Thr, Trp, Tyr, dV, Aib, or NMeV;

Xaa₆ is: Phe, Ile, Leu, Thr, Val, Trp, or Tyr;

Xaa₈ is: Asp, Glu, Ala, Lys, Leu, Arg, or Tyr;

Xaa₉ is: Asn, Gln, Asp, Glu, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₁₀ is: Tyr, Trp, Tyr(OMe), Ser, Cys, or Lys;

20 Xaa₁₂ is: Arg, Lys, Gln, hR, Orn, Lys (isopropyl), Aib, Cit, Ala, Leu, Gln, Phe, Ser, or Cys;

Xaa₁₃ is: Leu, Phe, Glu, Ala, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₁₄ is: Arg, Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, Cit, Ser, or Cys;

Xaa₁₅ is: Lys, Ala, Arg, Glu, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit,

25 Ser, Cys, K(W), or K(CO(CH₂)₂SH);

Xaa₁₆ is: Gln, Lys, Glu, Ala, hR, Orn, Lys (isopropyl), Cit, Ser, Cys, K(CO(CH₂)₂SH), or K(W);

Xaa₁₇ is: Val, Ala, Leu, Ile, Met, Nle, Lys, Aib, Ser, Cys, K(CO(CH₂)₂SH), or K(W);

Xaa₁₈ is: Ala, Ser, Cys, Lys, K(CO(CH₂)₂SH), or K(W);

30 Xaa₁₉ is: Val, Ala, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Trp, Tyr, Cys, Asp, K(CO(CH₂)₂SH), or K(W);

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Xaa₂₀ is: Lys, Gln, hR, Arg, Ser, His, Orn, Lys (isopropyl), Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, Cys, K(CO(CH₂)₂SH), or K(W);

Xaa₂₁ is: Lys, His, Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, Cys, Val, Tyr, Ile, Thr, Trp, K(W), or K(CO(CH₂)₂SH);

5 Xaa₂₂ is: Tyr, Trp, Phe, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, Cys, Lys, K(W), or K(CO(CH₂)₂SH);

Xaa₂₃ is: Leu, Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, Cys, Lys, K(W), or K(CO(CH₂)₂SH);

Xaa₂₄ is: Gln, Glu, Asn, Ser, Cys, Lys, K(CO(CH₂)₂SH), or K(W);

10 Xaa₂₅ is: Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, Lys, K(CO(CH₂)₂SH), or K(W);

Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, Phe, Aib, Ser, Cys, Lys, K(CO(CH₂)₂SH), or K(W);

Xaa₂₇ is: Lys, hR, Arg, Gln, Ala, Asp, Glu, Phe, Gly, His, Ile, Met, Asn, Pro, Ser, Thr, Val, Trp, Tyr, Lys (isopropyl), Cys, Leu, Orn, dK, K(W), or K(CO(CH₂)₂SH);

15 Xaa₂₈ is: Asn, Asp, Gln, Lys, Arg, Aib, Orn, hR, Cit, Pro, dK, Ser, Cys, K(CO(CH₂)₂SH), or K(W);

Xaa₂₉ is: Lys, Ser, Arg, Asn, hR, Ala, Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Gln, Thr, Val, Trp, Tyr, Cys, Orn, Cit, Aib, K(W), K(CO(CH₂)₂SH), or is absent;

Xaa₃₀ is: Arg, Lys, Ile, Ala, Asp, Glu, Phe, Gly, His, Leu, Met, Asn, Pro, Gln, Ser, Thr, Val, Trp, Tyr, Cys, hR, Cit, Aib, Orn, K(W), K(CO(CH₂)₂SH), or is absent;

20 Xaa₃₁ is: Tyr, His, Phe, Thr, Cys, Ser, Lys, Gln, K(W), K(CO(CH₂)₂SH), or is absent;

Xaa₃₂ is: Ser, Cys, Lys, or is absent;

Xaa₃₃ is: Trp or is absent;

Xaa₃₄ is: Cys or is absent;

Xaa₃₅ is: Glu or is absent;

25 Xaa₃₆ is: Pro or is absent;

Xaa₃₇ is: Gly or is absent;

Xaa₃₈ is: Trp or is absent;

Xaa₃₉ is: Cys or is absent; and

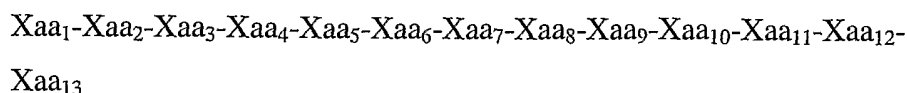
Xaa₄₀ is: Arg or is absent

30 provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆, Xaa₃₇,

Xaa₃₈, or Xaa₃₉ is absent, the next amino acid present downstream is the next amino acid in the peptide agonist sequence,

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and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the peptide of Formula 10 and wherein the C-terminal extension comprises an amino acid sequence of the formula:



5

Formula 17 (SEQ ID NO: 29)

wherein:

Xaa₁ is: Gly, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₂ is: Gly, Arg, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

10 Xaa₃ is: Pro, Thr, Ser, Ala, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₄ is: Ser, Pro, His, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₅ is: Ser, Arg, Thr, Trp, Lys, Cys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₆ is: Gly, Ser, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₇ is: Ala, Asp, Arg, Glu, Lys, Gly, Cys, K(W), K(CO(CH₂)₂SH), or absent;

15 Xaa₈ is: Pro, Ser, Ala, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₉ is: Pro, Ser, Ala, Cys, Lys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₁₀ is: Pro, Ser, Ala, Arg, Lys, His, Cys, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₁₁ is: Ser, Cys, His, Pro, Lys, Arg, K(W), K(CO(CH₂)₂SH), or absent;

Xaa₁₂ is: His, Ser, Arg, Lys, Cys, K(W), K(CO(CH₂)₂SH), or absent; and

~~20~~ Xaa₁₃ is: His, Ser, Arg, Lys, Cys, K(W), K(CO(CH₂)₂SH), or absent;

provided that at least five of Xaa₁ to Xaa₁₃ of the C-terminal extension are present and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, or Xaa₁₂ is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated,

25

and wherein;

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

30

at least one of the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

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at least one of the $K(CO(CH_2)_2SH)$ in the peptide agonist is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid of the peptide agonist is covalently attached to a PEG molecule, or a combination thereof.

5

2. A PEGylated VPAC2 receptor peptide agonist according to claim 1 comprising a sequence of the formula:

Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Thr-Xaa₈-Xaa₉-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃-
Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Xaa₂₃-Xaa₂₄-
Xaa₂₅-Xaa₂₆-Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁-Xaa₃₂

10

Formula 12 (SEQ ID NO: 20)

wherein:

Xaa₁ is: His, dH, or is absent;

Xaa₂ is: dA, Ser, Val, Gly, Thr, Leu, dS, Pro, or Aib;

15 Xaa₃ is: Asp or Glu;

Xaa₄ is: Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, Gly, dA, Aib, or NMeA;

Xaa₅ is: Val, Leu, Phe, Ile, Thr, Trp, Tyr, dV, Aib, or NMeV;

Xaa₆ is: Phe, Ile, Leu, Thr, Val, Trp, or Tyr;

Xaa₈ is: Asp, Glu, Ala, Lys, Leu, Arg, or Tyr;

20 Xaa₉ is: Asn, Glu, Glu, Ser, Cys, or Lys;

Xaa₁₀ is: Tyr, Trp, Tyr(OMe), Ser, Cys, or Lys;

Xaa₁₂ is: Arg, Lys, hR, Orn, Aib, Cit, Ala, Leu, Gln, Phe, Ser, or Cys;

Xaa₁₃ is: Leu, Phe, Glu, Ala, Aib, Ser, Cys, Lys, or $K(CO(CH_2)_2SH)$;

Xaa₁₄ is: Arg, Leu, Lys, Ala, hR, Orn, Phe, Gln, Aib, Cit, Ser, or Cys;

25 Xaa₁₅ is: Lys, Ala, Arg, Glu, Leu, hR, Orn, Phe, Gln, Aib, K(Ac), Cit, Ser, Cys, or K(W);

Xaa₁₆ is: Gln, Lys, Ala, hR, Orn, Cit, Ser, Cys, or $K(CO(CH_2)_2SH)$;

Xaa₁₇ is: Val, Ala, Leu, Ile, Met, Nle, Lys, Aib, Ser, Cys, or $K(CO(CH_2)_2SH)$;

Xaa₁₈ is: Ala, Ser, Cys, or Lys;

Xaa₁₉ is: Ala, Gly, Leu, Ser, Cys, Lys, or $K(CO(CH_2)_2SH)$;

30 Xaa₂₀ is: Lys, Gln, hR, Arg, Ser, Orn, Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac),
Cit, or Cys;

Xaa₂₁ is: Lys, Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, or Cys;

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Xaa₂₂ is: Tyr, Trp, Phe, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, Cys, or Lys;

Xaa₂₃ is: Leu, Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, Cys, or Lys;

Xaa₂₄ is: Gln, Asn, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₂₅ is: Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, Lys, or
 5 K(CO(CH₂)₂SH);

Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, Phe, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₂₇ is: Lys, hR, Arg, Gln, Orn, dK, Ser, or Cys;

Xaa₂₈ is: Asn, Gln, Lys, Arg, Aib, Orn, hR, Cit, Pro, dK, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₉ is: Lys, Ser, Arg, Asn, hR, Orn, Cit, Aib, Cys, or is absent;

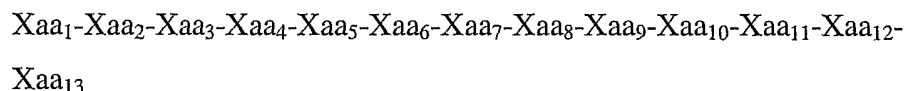
10 Xaa₃₀ is: Arg, Lys, Ile, hR, Cit, Aib, Orn, Ser, Cys, or is absent;

Xaa₃₁ is: Tyr, His, Phe, Lys, Ser, Cys, Gln, or is absent; and

Xaa₃₂ is: Cys, Ser, Lys, or is absent;

provided that if Xaa₂₉, Xaa₃₀, or Xaa₃₁ is absent, the next amino acid present
 downstream is the next amino acid in the peptide agonist sequence,

15 and a C-terminal extension wherein the N-terminus of the C-terminal extension is
 linked to the C-terminus of the peptide of Formula 12 and wherein the C-terminal
 extension comprises an amino acid sequence of the formula:



20 Formula 11 (SEQ ID NO: 19)

wherein:

Xaa₁ is: Gly, Cys, Lys, or absent;

Xaa₂ is: Gly, Arg, Cys, Lys, or absent;

Xaa₃ is: Pro, Thr, Ser, Ala, Cys, Lys, or absent;

25 Xaa₄ is: Ser, Pro, His, Cys, Lys, or absent;

Xaa₅ is: Ser, Arg, Thr, Trp, Lys, Cys, or absent;

Xaa₆ is: Gly, Ser, Cys, Lys, or absent;

Xaa₇ is: Ala, Asp, Arg, Glu, Lys, Gly, Cys, or absent;

Xaa₈ is: Pro, Ser, Ala, Cys, Lys, or absent;

30 Xaa₉ is: Pro, Ser, Ala, Cys, Lys, or absent;

Xaa₁₀ is: Pro, Ser, Ala, Arg, Lys, His, Cys, or absent;

Xaa₁₁ is: Ser, Cys, His, Pro, Lys, Arg, or absent;

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Xaa₁₂ is: His, Ser, Arg, Lys, Cys, or absent; and

Xaa₁₃ is: His, Ser, Arg, Lys, Cys, or absent;

provided that at least five of Xaa₁ to Xaa₁₃ of the C-terminal extension are present and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁,

5 or Xaa₁₂ is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated,

and wherein;

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

10 at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to a PEG molecule, or

the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

15 the carboxy-terminal amino acid of the peptide agonist is covalently attached to a PEG molecule, or a combination thereof.

3. A PEGylated VPAC2 receptor peptide agonist according to claim 1 or claim 2 comprising a sequence of the formula:

20 His-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Phe-Thr-Xaa₈-Xaa₉-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃-
Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Xaa₂₃-Xaa₂₄-
Xaa₂₅-Xaa₂₆-Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁

Formula 13 (SEQ ID NO: 21)

wherein:

25 Xaa₂ is: dA, Ser, Val, dS, or Aib;

Xaa₃ is: Asp or Glu;

Xaa₄ is: Ala, dA, or Aib;

Xaa₅ is: Val, Leu, dV, or Aib;

Xaa₈ is: Asp, Glu, or Ala;

30 Xaa₉ is: Asn, Gln, Glu, Ser, Cys, or Lys;

Xaa₁₀ is: Tyr, or Tyr(OMe);

Xaa₁₂ is: Ala, Arg, Lys, hR, Orn, Ser, or Cys;

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Xaa₁₃ is: Leu, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₁₄ is: Arg, Leu, Lys, Ala, hR, Orn, Phe, Gln, Aib, Cit, Ser, or Cys;

Xaa₁₅ is: Lys, Ala, Arg, Leu, Orn, Phe, Gln, Aib, K(Ac), Ser, Cys, or K(W);

Xaa₁₆ is: Gln, Lys, Ser, Cys, or K(CO(CH₂)₂SH);

5 Xaa₁₇ is: Val, Ala, Leu, Ile, Met, Nle, Lys, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₈ is: Ala, Ser, Cys, or Lys;

Xaa₁₉ is: Ala, Leu, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₂₀ is: Lys, Gln, hR, Arg, Ser, Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), or Cys;

10 Xaa₂₁ is: Lys, Arg, Ala, Phe, Aib, Leu, Gln, K(Ac), Orn, Ser, or Cys;

Xaa₂₂ is: Tyr, Trp, Phe, Leu, Ile, Val, Ser, Cys, Lys, or Tyr(OMe);

Xaa₂₃ is: Leu, Ser, Cys, or Lys;

Xaa₂₄ is: Gln, Asn, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₂₅ is: Ser, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Cys, Lys, or

15 K(CO(CH₂)₂SH);

Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, Phe, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH);

Xaa₂₇ is: Lys, hR, Arg, dK, Orn, Ser, or Cys;

Xaa₂₈ is: Asn, Gln, Lys, hR, Aib, Orn, dK, Pro, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₉ is: Lys, Ser, Arg, hR, Orn, Cys, or is absent;

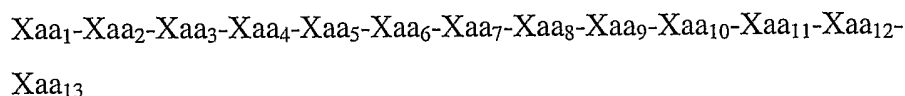
20 Xaa₃₀ is: Arg, Lys, hR, Ser, Cys, or is absent;

Xaa₃₁ is: Tyr, Phe, Lys, Ser, Cys, or is absent; and

Xaa₃₂ is: Cys, Ser, Lys, or absent;

provided that if Xaa₂₉, Xaa₃₀, or Xaa₃₁ is absent, the next amino acid present downstream is the next amino acid in the peptide agonist sequence,

25 and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the peptide of Formula 13 and wherein the C-terminal extension comprises an amino acid sequence of the formula:



30 Formula 11 (SEQ ID NO: 19)

wherein:

Xaa₁ is: Gly, Cys, Lys, or absent;

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Xaa₂ is: Gly, Arg, Cys, Lys, or absent;

Xaa₃ is: Pro, Thr, Ser, Ala, Cys, Lys, or absent;

Xaa₄ is: Ser, Pro, His, Cys, Lys, or absent;

Xaa₅ is: Ser, Arg, Thr, Trp, Lys, Cys, or absent;

5 Xaa₆ is: Gly, Ser, Cys, Lys, or absent;

Xaa₇ is: Ala, Asp, Arg, Glu, Lys, Gly, Cys, or absent;

Xaa₈ is: Pro, Ser, Ala, Cys, Lys, or absent;

Xaa₉ is: Pro, Ser, Ala, Cys, Lys, or absent;

Xaa₁₀ is: Pro, Ser, Ala, Arg, Lys, His, Cys, or absent;

10 Xaa₁₁ is: Ser, Cys, His, Pro, Lys, Arg, or absent;

Xaa₁₂ is: His, Ser, Arg, Lys, Cys, or absent; and

Xaa₁₃ is: His, Ser, Arg, Lys, Cys, or absent;

provided that at least five of Xaa₁ to Xaa₁₃ of the C-terminal extension are present and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁,

15 or Xaa₁₂ is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated,

and wherein;

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

20 at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to a PEG molecule, or

the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

25 the carboxy-terminal amino acid of the peptide agonist is covalently attached to a PEG molecule, or a combination thereof.

4. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₃ of Formula 10, 12 or 13 is Asp or Glu.

30

5. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₈ of Formula 10, 12 or 13 is Asp or Glu.

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6. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₁₂ of Formula 10, 12 or 13 is Arg, hR, Lys, or Orn.

5 7. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₁₄ of Formula 10, 12 or 13 is Arg, Gln, Aib, hR, Orn, Cit, Lys, Ala, or Leu.

10 8. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₁₅ of Formula 10, 12 or 13 is Lys, Aib, Orn, or Arg.

9. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₁₆ of Formula 10, 12 or 13 is Gln or Lys.

15 10. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₁₇ of Formula 10, 12 or 13 is Val, Leu, Ala, Ile, Lys or Nle.

11. A PEGylated VPAC2 receptor peptide agonist according to claim 10 wherein Xaa₁₇ of Formula 10, 12 or 13 is Val or Leu.

20

12. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₂₀ of Formula 10, 12 or 13 is Lys, Val, Leu, Aib, Ala, Gln, or Arg.

25 13. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₂₁ of Formula 10, 12 or 13 is Lys, Aib, Orn, Ala, Gln, or Arg.

30 14. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₂₇ of Formula 10, 12 or 13 is Lys, Orn, hR, or Arg.

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15. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₂₈ of Formula 10, 12 or 13 is Asn, Gln, Lys, hR, Aib, Pro or Orn.

5 16. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₂₉ of Formula 10, 12 or 13 is Lys, Orn, hR, or is absent.

17. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein Xaa₃₀ and/or Xaa₃₁ of Formula 10, 12 or 13 are absent.

10

18. A PEGylated VPAC2 receptor peptide agonist according to any one of claims 1 to 16 wherein Xaa₂₉, Xaa₃₀ and Xaa₃₁ of Formula 10, 12 or 13 are absent.

15 19. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein either Xaa₁₄ or Xaa₁₅ of Formula 10, 12 or 13 is Aib.

20. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein either Xaa₂₀ or Xaa₂₁ of Formula 10, 12 or 13 is Aib.

20 21. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein either Xaa₁₄ or Xaa₁₅ and either Xaa₂₀ or Xaa₂₁ of Formula 10, 12 or 13 is Aib.

25 22. A PEGylated VPAC2 receptor peptide agonist according to claim 21 wherein Xaa₁₅ is Aib and Xaa₂₀ is Aib.

23. A PEGylated VPAC2 receptor peptide agonist according to claim 21 or 22 further comprising Gln at position Xaa₂₈ and Lys at position Xaa₂₉, wherein Xaa₂₉ may be absent.

30

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24. A PEGylated VPAC2 receptor peptide agonist according to claim 21 or 22 further comprising hR or Orn at position Xaa₁₂, hR or Orn at position Xaa₂₇, and hR or Orn at position Xaa₂₉.

5 25. A PEGylated VPAC2 receptor peptide agonist according to claim 22 further comprising Orn at positions Xaa₁₂, Xaa₂₁, Xaa₂₇ and Xaa₂₈.

26. A PEGylated VPAC2 receptor peptide agonist according to claim 25 further comprising Glu at position Xaa₈, Gln at position Xaa₉, and Tyr(OMe) at position
10 Xaa₁₀.

27. A PEGylated VPAC2 receptor peptide agonist according to any one of claims 1 to 3 comprising the formula:

His-Ser-Xaa₃-Ala-Val-Phe-Thr-Xaa₈-Xaa₉-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃- Xaa₁₄-
15 Xaa₁₅-Xaa₁₆-Xaa₁₇-Ala-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂- Leu-Xaa₂₄-Xaa₂₅-Xaa₂₆-
Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁-Xaa₃₂

Formula 16 (SEQ ID NO: 28)

Xaa₃ is: Asp, or Glu;

20 Xaa₈ is: Asp, or Glu;

Xaa₉ is: Asn, Gln, or Cys;

Xaa₁₀ is: Tyr, or Tyr(OMe);

Xaa₁₂ is: Arg, Orn, or hR;

Xaa₁₃ is: Leu, Cys, or K(CO(CH₂)₂SH);

25 Xaa₁₄ is: Arg, Leu, or Aib;

Xaa₁₅ is: Lys, Ala, Arg, Aib, or K(W);

Xaa₁₆ is: Gln, Lys, or K(CO(CH₂)₂SH);

Xaa₁₇ is: Val, Leu, Cys, or K(CO(CH₂)₂SH);

Xaa₁₉ is: Ala, Leu, Cys, or K(CO(CH₂)₂SH);

30 Xaa₂₀ is: Lys, Gln, Arg, Aib, or Cys;

Xaa₂₁ is: Lys, Arg, Aib, or Orn;

Xaa₂₂ is: Tyr, or Tyr(OMe);

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Xaa₂₄ is: Gln, Cys, or K(CO(CH₂)₂SH);

Xaa₂₅ is: Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₆ is: Ile, Cys, or K(CO(CH₂)₂SH);

Xaa₂₇ is: Lys, Arg, Orn, or hR;

5 Xaa₂₈ is: Asn, hR, Orn, Cys, or K(CO(CH₂)₂SH);

Xaa₂₉ is: Orn, Lys, hR, or is absent;

Xaa₃₀ is: Arg, hR, or is absent;

Xaa₃₁ is: Tyr, or is absent; and

Xaa₃₂ is: Cys, or is absent

10 provided that if Xaa₂₉, Xaa₃₀ or Xaa₃₁ is absent, the next amino acid present downstream is the next amino acid in the peptide agonist sequence,

and a C-terminal extension wherein the N-terminus of the C-terminal extension is linked to the C-terminus of the peptide of Formula 16 and wherein the C-terminal extension comprises an amino acid sequence of the formula:

15 Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Xaa₇-Xaa₈-Xaa₉-Xaa₁₀-Xaa₁₁-Xaa₁₂-
Xaa₁₃

Formula 11 (SEQ ID NO: 19)

wherein:

Xaa₁ is: Gly, Cys, Lys, or absent;

20 Xaa₂ is: Gly, Arg, Cys, Lys, or absent;

Xaa₃ is: Pro, Thr, Ser, Ala, Cys, Lys, or absent;

Xaa₄ is: Ser, Pro, His, Cys, Lys, or absent;

Xaa₅ is: Ser, Arg, Thr, Trp, Lys, Cys, or absent;

Xaa₆ is: Gly, Ser, Cys, Lys, or absent;

25 Xaa₇ is: Ala, Asp, Arg, Glu, Lys, Gly, Cys, or absent;

Xaa₈ is: Pro, Ser, Ala, Cys, Lys, or absent;

Xaa₉ is: Pro, Ser, Ala, Cys, Lys, or absent;

Xaa₁₀ is: Pro, Ser, Ala, Arg, Lys, His, Cys, or absent;

Xaa₁₁ is: Ser, Cys, His, Pro, Lys, Arg, or absent;

30 Xaa₁₂ is: His, Ser, Arg, Lys, Cys, or absent; and

Xaa₁₃ is: His, Ser, Arg, Lys, Cys, or absent;

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provided that at least five of Xaa₁ to Xaa₁₃ of the C-terminal extension are present and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, or Xaa₁₂ is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated, and

5 wherein:

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

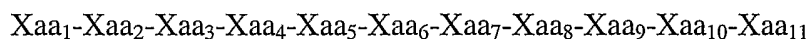
10 at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to a PEG molecule, or

the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid of the peptide agonist is covalently attached to a PEG molecule, or a combination thereof.

15

28. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein the C-terminal extension comprises an amino acid sequence of the formula:



20 Formula 7 (SEQ ID NO:15)

wherein:

Xaa₁ is: Gly, Cys, or absent;

Xaa₂ is: Gly, Arg, or absent;

Xaa₃ is: Pro, Thr, or absent;

25 Xaa₄ is: Ser, or absent;

Xaa₅ is: Ser, or absent;

Xaa₆ is: Gly, or absent;

Xaa₇ is: Ala, or absent;

Xaa₈ is: Pro, or absent;

30 Xaa₉ is: Pro, or absent;

Xaa₁₀ is: Pro, or absent; and

Xaa₁₁ is: Ser, Cys, or absent;

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provided that at least five of Xaa₁ to Xaa₁₁ of the C-terminal extension are present and provided that if Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, or Xaa₁₀ is absent, the next amino acid present downstream is the next amino acid in the C-terminal extension and wherein the C-terminal amino acid may be amidated.

5

29. A VPAC2 receptor peptide agonist according to any one of the preceding claims wherein the C-terminal extension is selected from:

SEQ ID NO: 10	GGPSSGAPPPS
SEQ ID NO: 11	GGPSSGAPPPS-NH ₂
SEQ ID NO: 22	GGPSSGAPPPC
SEQ ID NO: 23	GGPSSGAPPPC-NH ₂
SEQ ID NO: 16	GRPSSGAPPPS
SEQ ID NO: 17	GRPSSGAPPPS-NH ₂

10 30. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein there is at least one PEG molecule covalently attached to Xaa₂₅ or any subsequent residue in Formula 10, 12, 13, or 16.

15 31. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein there is at least one PEG molecule covalently attached to a residue in the C-terminal extension of the peptide agonist.

32. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein:

20 two of the Cys residues in the peptide agonist are each covalently attached to a PEG molecule, or

two of the Lys residues in the peptide agonist are each covalently attached to a PEG molecule.

25 33. A PEGylated VPAC2 receptor peptide agonist according to any one of claims 1 to 31 wherein:

one of the Cys residues in the peptide agonist is covalently attached to a PEG molecule, or

one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule.

5

34. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein the PEG molecule is branched.

10

35. A PEGylated VPAC2 receptor peptide agonist according to any one of claims 1 to 33 wherein the PEG molecule is linear.

36. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims wherein each PEG molecule is 20,000, 40,000 or 60,000 daltons in molecular weight.

15

37. A PEGylated VPAC2 receptor peptide agonist according to any one of claims 1 to 32 and 34 to 36 wherein there are two PEG molecules and each is 20,000 daltons in molecular weight.

20

38. A PEGylated VPAC2 receptor peptide agonist according to any one of the preceding claims further comprising a N-terminal modification at the N-terminus of the peptide agonist wherein the N-terminal modification is selected from:

(a) addition of D-histidine, isoleucine, methionine, or norleucine;

(b) addition of a peptide comprising the sequence Ser-Trp-Cys-Glu-Pro-Gly-Trp-Cys-Arg wherein the Arg is linked to the N-terminus of the peptide agonist;

25

(c) addition of C₁-C₁₆ alkyl optionally substituted with one or more substituents independently selected from aryl, C₁-C₆ alkoxy, -NH₂, -OH, halogen and -CF₃;

(d) addition of -C(O)R¹ wherein R¹ is a C₁-C₁₆ alkyl optionally substituted with one or more substituents independently selected from aryl, C₁-C₆ alkoxy, -NH₂, -OH,

30

halogen, -SH and -CF₃; a aryl or aryl C₁-C₄ alkyl optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, -NH₂, -OH, halogen and -CF₃; -NR²R³ wherein R² and R³

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- are independently hydrogen, C₁-C₆ alkyl, aryl or aryl C₁-C₄ alkyl; -OR⁴ wherein R⁴ is C₁-C₁₆ alkyl optionally substituted with one or more substituents independently selected from aryl, C₁-C₆ alkoxy, -NH₂, -OH, halogen and -CF₃, aryl or aryl C₁-C₄ alkyl optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, -NH₂, -OH, halogen and -CF₃; or 5-pyrrolidin-2-one;
- 5 (e) addition of -SO₂R⁵ wherein R⁵ is aryl, aryl C₁-C₄ alkyl or C₁-C₁₆ alkyl;
- (f) formation of a succinimide group optionally substituted with C₁-C₆ alkyl or -SR⁶, wherein R⁶ is hydrogen or C₁-C₆ alkyl;
- 10 (g) addition of methionine sulfoxide;
- (h) addition of biotinyl-6-aminohexanoic acid (6-aminocaproic acid); and
- (i) addition of -C(=NH)-NH₂.

39. A PEGylated VPAC2 receptor peptide agonist according to claim 38
- 15 wherein the N-terminal modification is the addition of a group selected from: acetyl, propionyl, butyryl, pentanoyl, hexanoyl, methionine, methionine sulfoxide, 3-phenylpropionyl, phenylacetyl, benzoyl, norleucine, D-histidine, isoleucine, 3-mercaptopropionyl, biotinyl-6-aminohexanoic acid, and -C(=NH)-NH₂.

- 20 40. A PEGylated VPAC2 receptor peptide agonist according to claim 38 or 39 wherein the N-terminal modification is the addition of acetyl or hexanoyl.

41. A PEGylated VPAC2 receptor peptide agonist comprising an amino acid sequence selected from:

Agonist #	Sequence
P41	HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYC(PEG40K)
P137	C6-HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPC(PEG40K)
P190	C6-HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAPPPC(PEG40K)
P202	C6-HSDAVFTDNYTRLLAKLALQKYLQSIKNKGGPSSGAPPPC(PEG40K)

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P217	C6-HSDAVFTDNYTRLRK(PEG20K)QVAAK(PEG20K)RYLQSIRNGGPSSGAPPPS
P219	C6-HSDAVFTDNYTRLRRQVAAK(PEG20K)RYLQSIRNGGPSSGAPPPS
P245	C6-HSDAVFTDNYTRLRK(PEG40K)QVAARRYLQSIRNGGPSSGAPPPS
P246	C6-HSDAVFTDNYTRLRRQVAAK(PEG40K)RYLQSIRNGGPSSGAPPPS
P247	C6-HSDAVFTDNYTRLRRQVAARK(PEG40K)YLQSIRNGGPSSGAPPPS
P283	C6-HSDAVFTDNYTRLAibKQVAAAibKYLQSIKNKRYGGPSSGAPPPC(PEG40K)-NH ₂
P286	C6-HSDAVFTDNYTRLRAibQVAAKAibYLQSIKNKRYGGPSSGAPPPC(PEG40K)-NH ₂
P300	C6-HSDAVFTDNYTRLRAibQVAAAibKYLQSIKNKRYGGPSSGAPPPC(PEG40K)-NH ₂
P328	C6-HSDAVFTDNYTOmLRAibQVAAAibKYLQSIOMNOmGGPSSGAPPPC(PEG40K)-NH ₂
P331	C6-HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRGGPSSGAPPPC(PEG40K)-NH ₂
P337	C6-HSDAVFTDNYTOmLRAibQVAAAibKYLQSIhRhRGGPSSGAPPPC(PEG40K)-NH ₂
P340	C6-HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRhRYGGPSSGAPPPC(PEG40K)-NH ₂
P373	C6-HSDAVFTDNYTOmLRAibQVAAAibKYLQC(PEG40K)IOMTOmGGPSSGAPPPS
P380	C6-HSEAVFTEQYTOmLRAibQVAAAibOmYLQSIOMOmGGPSSGAPPPC(PEG40K)-NH ₂
P378	C6-HSDAVFTDNYTOmLRAibQVAAC(PEG40K)OmYLQSIOMNOmGGPSSGAPPPS-NH ₂
P272	Biotin-Acp-HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPC(PEG40K)
P399	C6-HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSIOMOmGGPSSGAPPPC(PEG40K)-NH ₂
P404	C6-HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSIOMOmGGPSSGAPPPC(PEG60K)-NH ₂

P411	C6- HSDAVFTDNYTOmLRAibQVAAC(PEG20K)OmYLQSIOrnNOmGGPSS GAPPPS-NH ₂
P413	C6- HSDAVFTDNYTOmLRK(WPEG40K)QVAAAibKYLQSIOrnNOmGGPSS GAPPPS
P415	C6- HSDAVFTEQY(OMe)TOmLRAibQLAAAibOmY(OMe)LQSIOrnOmGGP SSGAPPPC(PEG40K)-NH ₂
P420	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSC(PEG40K)OmOm GGPSSGAPPPS-NH ₂
P426	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLC(PEG40K)SIOrnOmG GPSSGAPPPS-NH ₂
P428	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLK(CO(CH ₂) ₂ SPEG40K) SIOrnOmGGPSSGAPPPS-NH ₂
P430	C6- HSDAVFTEQY(OMe)TOmLRAibQVAC(PEG40K)AibOmYLQSIOrnOmG GPSSGAPPPS-NH ₂
P432	C6- HSDAVFTEQY(OMe)TOmLRAibQVAK(CO(CH ₂) ₂ SPEG40K)AibOmYLQ SIOrnOmGGPSSGAPPPS-NH ₂
P434	C6- HSDAVFTEQY(OMe)TOmLRAibQC(PEG40K)AAAibOmYLQSIOrnOmG GPSSGAPPPS-NH ₂
P438	C6- HSDAVFTEQY(OMe)TOmLRAibC(PEG40K)VAAAibOmYLQSIOrnOmG GPSSGAPPPS-NH ₂
P443	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSIOrnC(PEG40K)Om GGPSSGAPPPS-NH ₂
P447	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQC(PEG20K)IOmOm GGPSSGAPPPC(PEG20K)-NH ₂
P449	C6- HSDAVFTEC(PEG40K)Y(OMe)TOmLRAibQVAAAibOmYLQSIOrnOmG GPSSGAPPPS-NH ₂
P452	C6- HSDAVFTEQY(OMe)TOmLRAibC(PEG20K)VAAAibOmYLQSIOrnOmG GPSSGAPPPS-NH ₂
P456	C6- HSDAVFTEQY(OMe)TOmC(PEG40K)RAibQVAAAibOmYLQSIOrnOm GGPSSGAPPPS-NH ₂

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P461	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYlK(CO(CH ₂) ₂ SPEG20K) SIOrnOrnGGPSSGAPPPS-NH ₂
P462	C6- HSDAVFTEQY(OMe)TOmLRAibQVAK(CO(CH ₂) ₂ SPEG20K)AibOmYlQ SIOrnOrnGGPSSGAPPPS-NH ₂
P422	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYlQSK(CO(CH ₂) ₂ SPEG4 0K)OrnOrnGGPSSGAPPPS-NH ₂
P424	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYlQK(CO(CH ₂) ₂ SPEG40 K)IOmOrnGGPSSGAPPPS-NH ₂
P436	C6- HSDAVFTEQY(OMe)TOmLRAibQK(CO(CH ₂) ₂ SPEG40K)AAAibOmYlQ SIOrnOrnGGPSSGAPPPS-NH ₂
P440	C6- HSDAVFTEQY(OMe)TOmLRAibK(CO(CH ₂) ₂ SPEG40K)VAAAibOmYlQ SIOrnOrnGGPSSGAPPPS-NH ₂
P445	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYlQSIOrnK(CO(CH ₂) ₂ SP EG40K)OrnGGPSSGAPPPS-NH ₂
P458	C6- HSDAVFTEQY(OMe)TOmK(CO(CH ₂) ₂ SPEG40K)RAibQVAAAibOmYl QSIOrnOrnGGPSSGAPPPS-NH ₂
P464	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYlQSK(CO(CH ₂) ₂ SPEG2 0K)OrnOrnGGPSSGAPPPS-NH ₂
P465	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYlQK(CO(CH ₂) ₂ SPEG20 K)IOmOrnGGPSSGAPPPS-NH ₂
P466	C6- HSDAVFTEQY(OMe)TOmLRAibQK(CO(CH ₂) ₂ SPEG20K)AAAibOmYlQ SIOrnOrnGGPSSGAPPPS-NH ₂
P467	C6- HSDAVFTEQY(OMe)TOmLRAibK(CO(CH ₂) ₂ SPEG20K)VAAAibOmYlQ SIOrnOrnGGPSSGAPPPS-NH ₂
P468	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYlQSIOrnK(CO(CH ₂) ₂ SP EG20K)OrnGGPSSGAPPPS-NH ₂

42. A PEGylated VPAC2 receptor peptide agonist according to claim 41 comprising an amino acid sequence selected from:

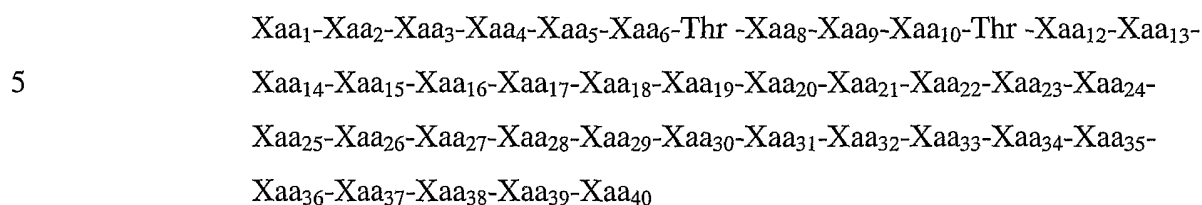
Agonist #	Sequence

P137	C6-HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPC(PEG40K)
P190	C6-HSDAVFTDNYTRLLAKLALQKYLQSIKNKRYGGPSSGAPPPC(PEG40K)
P217	C6-HSDAVFTDNYTRLRK(PEG20K)QVAAK(PEG20K)RYLQSIRNGGPSSGAPPPS
P219	C6-HSDAVFTDNYTRLRRQVAAK(PEG20K)RYLQSIRNGGPSSGAPPPS
P245	C6-HSDAVFTDNYTRLRK(PEG40K)QVAARRYLQSIRNGGPSSGAPPPS
P246	C6-HSDAVFTDNYTRLRRQVAAK(PEG40K)RYLQSIRNGGPSSGAPPPS
P247	C6-HSDAVFTDNYTRLRRQVAARK(PEG40K)YLQSIRNGGPSSGAPPPS
P283	C6-HSDAVFTDNYTRLAibKQVAAAibKYLQSIKNKRYGGPSSGAPPPC(PEG40K)-NH ₂
P286	C6-HSDAVFTDNYTRLRAibQVAAKAibYLQSIKNKRYGGPSSGAPPPC(PEG40K)-NH ₂
P300	C6-HSDAVFTDNYTRLRAibQVAAAibKYLQSIKNKRYGGPSSGAPPPC(PEG40K)-NH ₂
P328	C6-HSDAVFTDNYTOmLRAibQVAAAibKYLQSIOrnNOmGGPSSGAPPPC(PEG40K)-NH ₂
P331	C6-HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRGGPSSGAPPPC(PEG40K)-NH ₂
P337	C6-HSDAVFTDNYTOmLRAibQVAAAibKYLQSIhRhRGGPSSGAPPPC(PEG40K)-NH ₂
P340	C6-HSDAVFTDNYThRLRAibQVAAAibKYLQSIhRNhRhRYGGPSSGAPPPC(PEG40K)-NH ₂
P373	C6-HSDAVFTDNYTOmLRAibQVAAAibKYLQC(PEG40K)IOmNOmGGPSSGAPPPS
P380	C6-HSEAVFTEQYTOmLRAibQVAAAibOrnYLQSIOrnOrnGGPSSGAPPPC(PEG40K)-NH ₂
P378	C6-HSDAVFTDNYTOmLRAibQVAAC(PEG40K)OrnYLQSIOrnNOmGGPSSGAPPPS-NH ₂
P272	Biotin-Acp-HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRYGGPSSGAPPPC(PEG40K)

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P399	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSIOrnOmGGPSSGA PPPC(PEG40K)-NH ₂
P404	C6- HSDAVFTEQY(OMe)TOmLRAibQVAAAibOmYLQSIOrnOmGGPSSGA PPPC(PEG60K)-NH ₂
P432	C6- HSDAVFTEQY(OMe)TOmLRAibQVAK(CO(CH ₂) ₂ SPEG40K)AibOmYLQ SIOrnOmGGPSSGAPPPS-NH ₂

43. A PEGylated VPAC2 receptor peptide agonist comprising a sequence of the formula:



Formula 14 (SEQ ID NO: 26)

wherein:

- 10 Xaa₁ is: any naturally occurring amino acid, dH, or is absent;
Xaa₂ is: any naturally occurring amino acid, dA, dS, or Aib;
Xaa₃ is: Asp or Glu;
Xaa₄ is: any naturally occurring amino acid, dA, Aib, or NMeA;
Xaa₅ is: any naturally occurring amino acid, dV, or Aib;
15 Xaa₆ is: any naturally occurring amino acid;
Xaa₈ is: Asp, Glu, Ala, Lys, Leu, Arg, or Tyr;
Xaa₉ is: Asn, Gln, Asp, Glu, Ser, or Cys;
Xaa₁₀ is: any naturally occurring aromatic amino acid, or Tyr (OMe);
Xaa₁₂ is: hR, Orn, Lys (isopropyl), Aib, Cit, or any naturally occurring amino acid except
20 Pro;
Xaa₁₃ is: Aib, K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;
Xaa₁₄ is: hR, Orn, Lys (isopropyl), Aib, Cit, or any naturally occurring amino acid except
Pro;
Xaa₁₅ is: hR, Orn, Lys (isopropyl), Aib, K (Ac), Cit, K(W), or any naturally occurring
25 amino acid except Pro;

Xaa₁₆ is: hR, Orn, Lys (isopropyl), Cit, K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;

Xaa₁₇ is: Nle, Aib, K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;

Xaa₁₈ is: any naturally occurring amino acid;

5 Xaa₁₉ is: K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;

Xaa₂₀ is: hR, Orn, Lys (isopropyl), Aib, K(Ac), Cit, or any naturally occurring amino acid except Pro;

Xaa₂₁ is: hR, Orn, Aib, K(Ac), Cit, or any naturally occurring amino acid except Pro;

Xaa₂₂ is: Aib, Tyr (OMe), or any naturally occurring amino acid except Pro;

10 Xaa₂₃ is: Aib or any naturally occurring amino acid except Pro;

Xaa₂₄ is: K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;

Xaa₂₅ is: Aib, K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;

Xaa₂₆ is: K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;

Xaa₂₇ is: hR, Lys (isopropyl), Orn, dK, or any naturally occurring amino acid except Pro;

15 Xaa₂₈ is: any naturally occurring amino acid, Aib, hR, Cit, Orn, dK, or K(CO(CH₂)₂SH);

Xaa₂₉ is: any naturally occurring amino acid, hR, Orn, Cit, Aib, or is absent;

Xaa₃₀ is: any naturally occurring amino acid, hR, Orn, Cit, Aib, or is absent; and

Xaa₃₁ to Xaa₄₀ are any naturally occurring amino acid or are absent;

provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆, Xaa₃₇,

20 Xaa₃₈ or Xaa₃₉ is absent, the next amino acid present downstream is the next amino acid in the peptide agonist sequence and that the peptide agonist comprises at least one amino acid substitution selected from:

Xaa₂ is: dA, Val, Gly, Leu, dS, or Aib;

Xaa₄ is: Ile, Tyr, Phe, Val, Thr, Leu, Trp, dA, Aib, or NMeA;

25 Xaa₅ is: Leu, Phe, Thr, Trp, Tyr, dV, or Aib;

Xaa₈ is: Leu, Arg, or Tyr;

Xaa₉ is: Glu, Ser, or Cys;

Xaa₁₀ is: Trp;

Xaa₁₂ is: Ala, hR, Aib, Lys (isopropyl), Cit, Gln, or Phe;

30 Xaa₁₃ is: Phe, Glu, Ala, Aib, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₄ is: Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, or Cit;

Xaa₁₅ is: Ala, Arg, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit, or K(W);

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Xaa₁₆ is: Lys, Lys (isopropyl), hR, Orn, Cit, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₇ is: Lys, Aib, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₈ is: Ser, or Cys;

Xaa₁₉ is: K(CO(CH₂)₂SH);

- 5 Xaa₂₀ is: Gln, hR, Arg, Ser, Orn, Lys(isopropyl), Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, or Cys;

Xaa₂₁ is: Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, or Cys;

Xaa₂₂ is: Trp, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, or Cys;

Xaa₂₃ is: Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, or Cys;

- 10 Xaa₂₄ is: Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₅ is: Phe, Ile, Leu, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, or K(CO(CH₂)₂SH);

Xaa₂₆ is: Thr, Trp, Tyr, Phe, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₇ is: hR, Orn, or dK;

Xaa₂₈ is: Pro, Arg, Aib, Orn, hR, Cit, dK, Cys, or K(CO(CH₂)₂SH);

- 15 Xaa₂₉ is: hR, Cys, Orn, Cit, or Aib;

Xaa₃₀ is: hR, Cit, Aib, or Orn; and

Xaa₃₁ is: His, or Phe,

and wherein:

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG

20 molecule, or

at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to a PEG molecule, or

- 25 the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid of the peptide agonist is covalently attached to a PEG molecule, or

any combination thereof.

- 30 44. A PEGylated VPAC2 receptor peptide agonist according to claim 43 comprising a sequence of the formula:

His-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Phe-Thr-Xaa₈-Xaa₉-Xaa₁₀-Thr-Xaa₁₂-Xaa₁₃-
 Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Xaa₂₃-Xaa₂₄-
 Xaa₂₅-Xaa₂₆-Xaa₂₇-Xaa₂₈-Xaa₂₉-Xaa₃₀-Xaa₃₁-Xaa₃₂-Xaa₃₃-Xaa₃₄-Xaa₃₅-
 Xaa₃₆-Xaa₃₇-Xaa₃₈-Xaa₃₉-Xaa₄₀

5 Formula 15 (SEQ ID NO: 27)

wherein:

Xaa₂ is: dA, Ser, Val, Gly, Thr, Leu, dS, Pro, or Aib;

Xaa₃ is: Asp or Glu;

Xaa₄ is: Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, Gly, dA, Aib, or NMeA;

10 Xaa₅ is: Val, Leu, Phe, Ile, Thr, Trp, Tyr, dV, or Aib;

Xaa₈ is: Asp, Glu, Ala, Lys, Leu, Arg, or Tyr;

Xaa₉ is: Asn, Gln, Asp, Glu, Ser, or Cys;

Xaa₁₀ is: Tyr, Trp, or Tyr(OMe);

Xaa₁₂ is: Arg, Lys, Glu, hR, Orn, Lys (isopropyl), Aib, Cit, Ala, Leu, Gln, or Phe;

15 Xaa₁₃ is: Leu, Phe, Glu, Ala, Aib, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₄ is: Arg, Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, or Cit;

Xaa₁₅ is: Lys, Ala, Arg, Glu, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit, or
 K(W);

Xaa₁₆ is: Gln, Lys, Glu, Ala, hR, Orn, Lys (isopropyl), Cit, Ser, Cys, or K(CO(CH₂)₂SH);

20 Xaa₁₇ is: Val, Ala, Leu, Ile, Met, Nie, Lys, Aib, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₈ is: Ala, Ser, or Cys;

Xaa₁₉ is: Val, Ala, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Trp,
 Tyr, Cys, Asp, or K(CO(CH₂)₂SH);

Xaa₂₀ is: Lys, Gln, hR, Arg, Ser, His, Orn, Lys (isopropyl), Ala, Aib, Trp, Thr, Leu, Ile,

25 Phe, Tyr, Val, K(Ac), Cit, or Cys;

Xaa₂₁ is: Lys, His, Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, or Cys;

Xaa₂₂ is: Tyr, Trp, Phe, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, or Cys;

Xaa₂₃ is: Leu, Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, or Cys;

Xaa₂₄ is: Gln, Glu, Asn, Ser, Cys, or K(CO(CH₂)₂SH);

30 Xaa₂₅ is: Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, or
 K(CO(CH₂)₂SH);

Xaa₂₆ is: Ile, Leu, Thr, Val, Trp, Tyr, Phe, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₇ is: Lys, hR, Arg, Gln, Ala, Asp, Glu, Phe, Gly, His, Ile, Met, Asn, Ser, Thr, Val,

Trp, Tyr, Lys (isopropyl), Cys, Leu, Orn, or dK;

Xaa₂₈ is: Asn, Asp, Gln, Lys, Arg, Aib, Orn, hR, Cit, Pro, dK, Cys, or K(CO(CH₂)₂SH);

Xaa₂₉ is: Lys, Ser, Arg, Asn, hR, Ala, Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Gln,

5 Thr, Val, Trp, Tyr, Cys, Orn, Cit, Aib or is absent;

Xaa₃₀ is: Arg, Lys, Ile, Ala, Asp, Glu, Phe, Gly, His, Leu, Met, Asn, Pro, Gln, Ser, Thr,

Val, Trp, Tyr, Cys, hR, Cit, Aib, Orn, or is absent;

Xaa₃₁ is: Tyr, His, Phe, Thr, Cys, or is absent;

Xaa₃₂ is: Ser, Cys, or is absent;

10 Xaa₃₃ is: Trp or is absent;

Xaa₃₄ is: Cys or is absent;

Xaa₃₅ is: Glu or is absent;

Xaa₃₆ is: Pro or is absent;

Xaa₃₇ is: Gly or is absent;

15 Xaa₃₈ is: Trp or is absent;

Xaa₃₉ is: Cys or is absent; and

Xaa₄₀ is: Arg or is absent

provided that if Xaa₂₉, Xaa₃₀, Xaa₃₁, Xaa₃₂, Xaa₃₃, Xaa₃₄, Xaa₃₅, Xaa₃₆, Xaa₃₇,

Xaa₃₈, or Xaa₃₉ is absent, the next amino acid present downstream is the next amino acid

20 in the peptide agonist sequence,

and that the peptide agonist comprises at least one amino acid substitution selected from:

Xaa₂ is: dA, Val, Gly, Leu, dS, or Aib;

Xaa₄ is: Ile, Tyr, Phe, Val, Thr, Leu, Trp, dA, Aib, or NMeA;

25 Xaa₅ is: Leu, Phe, Thr, Trp, Tyr, dV, or Aib;

Xaa₈ is: Leu, Arg, or Tyr;

Xaa₉ is: Glu, Ser, or Cys;

Xaa₁₀ is: Trp;

Xaa₁₂ is: Ala, hR, Aib, Lys (isopropyl), Cit, Gln, or Phe;

30 Xaa₁₃ is: Phe, Glu, Ala, Aib, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₄ is: Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, or Cit;

Xaa₁₅ is: Ala, Arg, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit, or K(W);

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Xaa₁₆ is: Lys, Lys (isopropyl), hR, Orn, Cit, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₇ is: Lys, Aib, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₁₈ is: Ser, or Cys;

Xaa₁₉ is: K(CO(CH₂)₂SH);

- 5 Xaa₂₀ is: Gln, hR, Arg, Ser, Orn, Lys(isopropyl), Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, or Cys;

Xaa₂₁ is: Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K (Ac), Cit, Ser, or Cys;

Xaa₂₂ is: Trp, Thr, Leu, Ile, Val, Tyr (OMe), Ala, Aib, Ser, or Cys;

Xaa₂₃ is: Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, or Cys;

- 10 Xaa₂₄ is: Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₅ is: Phe, Ile, Leu, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, or K(CO(CH₂)₂SH);

Xaa₂₆ is: Thr, Trp, Tyr, Phe, Ser, Cys, or K(CO(CH₂)₂SH);

Xaa₂₇ is: hR, Orn, or dK;

Xaa₂₈ is: Pro, Arg, Aib, Orn, hR, Cit, dK, Cys, or K(CO(CH₂)₂SH);

- 15 Xaa₂₉ is: hR, Cys, Orn, Cit, or Aib;

Xaa₃₀ is: hR, Cit, Aib, or Orn; and

Xaa₃₁ is: His, or Phe,

and wherein:

at least one of the Cys residues in the peptide agonist is covalently attached to a PEG

- 20 molecule, or

at least one of the Lys residues in the peptide agonist is covalently attached to a PEG molecule, or

at least one of the K(CO(CH₂)₂SH) in the peptide agonist is covalently attached to a PEG molecule, or

- 25 the K(W) in the peptide agonist is covalently attached to a PEG molecule, or

the carboxy-terminal amino acid of the peptide agonist is covalently attached to the PEG molecule, or

any combination thereof.

- 30 45. A PEGylated VPAC2 receptor peptide agonist according to any one of claims 1 to 44 for use as a medicament.

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46. The use of a PEGylated VPAC2 receptor peptide agonist according to any one of claims 1 to 44 for the manufacture of a medicament for the treatment non-insulin-dependent diabetes.

5 47. The use of a PEGylated VPAC2 receptor peptide agonist according to any one of claims 1 to 44 for the manufacture of a medicament for the treatment of insulin-dependent diabetes.

10 48. A VPAC2 receptor peptide agonist substantially as hereinbefore described with reference to the examples.

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<220>

<223> Synthetic Construct

<400> 10

Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	Pro	Pro	Ser
1				5						10

<210> 11

<211> 11

<212> PRT

<213> Artificial

<220>

<223> Synthetic Construct

<220>

<221> MOD_RES

<222> (11)..(11)

<223> Amidation

<400> 11

Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	Pro	Pro	Ser
1				5						10

<210> 12

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<211> 10
<212> PRT
<213> Artificial

<220>
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<220>
<221> MOD_RES
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<223> Amidation

<400> 12

Gly Gly Pro Ser Ser Gly Ala Pro Pro Ser
1 5 10

<210> 13
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 13

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
1 5 10

<210> 14
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 14

Ser Trp Cys Glu Pro Gly Trp Cys Arg
1 5

<210> 15
<211> 11
<212> PRT
<213> Artificial

<220>
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<220>
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<222> (1)..(1)
<223> Xaa at position 1 is Gly, Cys, or absent

<220>
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<222> (2)..(2)
<223> Xaa at position 2 is Gly, Arg, or absent

<220>
<221> MISC_FEATURE

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<222> (3)..(3)
 <223> Xaa at position 3 is Pro, Thr, or absent

 <220>
 <221> MISC_FEATURE
 <222> (4)..(4)
 <223> Xaa at position 4 is Ser, or absent

 <220>
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 <222> (5)..(5)
 <223> Xaa at position 5 is Ser, or absent

 <220>
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 <222> (6)..(6)
 <223> Xaa at position 6 is Gly, or absent

 <220>
 <221> MISC_FEATURE
 <222> (7)..(7)
 <223> Xaa at position 7 is Ala, or absent

 <220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> Xaa at position 8 is Pro, or absent

 <220>
 <221> MISC_FEATURE
 <222> (9)..(9)
 <223> Xaa at position 9 is Pro, or absent

 <220>
 <221> MISC_FEATURE
 <222> (10)..(10)
 <223> Xaa at position 10 is Pro, or absent

 <220>
 <221> MISC_FEATURE
 <222> (11)..(11)
 <223> Xaa at position 11 is Ser, Cys, or absent

 <400> 15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1 5 10

<210> 16
 <211> 11
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 16

Gly Arg Pro Ser Ser Gly Ala Pro Pro Pro Ser
 1 5 10

<210> 17
 <211> 11
 <212> PRT
 <213> Artificial

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<220>
<223> Synthetic Construct

<220>
<221> MOD_RES
<222> (11)..(11)
<223> AMIDATION

<400> 17

Gly Arg Pro Ser Ser Gly Ala Pro Pro Pro Ser
1 5 10

<210> 18
<211> 40
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<220>
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<222> (1)..(1)
<223> Xaa at position 1 is His, dH, or is absent

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa at position 2 is dA, Ser, Val, Gly, Thr, Leu, dS, Pro, or Aib

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa at position 3 is Asp or Glu

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa at position 4 is Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, Gly, dA, Aib, or NMeA

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is Val, Leu, Phe, Ile, Thr, Trp, Tyr, dV, Aib, or NMeV

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa at position 6 is Phe, Ile, Leu, Thr, Val, Trp, or Tyr

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is Asp, Glu, Ala, Lys, Leu, Arg, or Tyr

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa at position 9 is Asn, Gln, Asp, Glu, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

<220>

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<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa at position 10 is Tyr, Trp, Tyr(OMe), Ser, Cys, or Lys

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa at position 12 is Arg, Lys, Glu, hR, Orn, Lys (isopropyl), Aib, Cit, Ala, Leu, Gln, Phe, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa at position 13 is Leu, Phe, Glu, Ala, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa at position 14 is Arg, Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, Cit, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa at position 15 is Lys, Ala, Arg, Glu, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit, Ser, Cys, K(W), or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> Xaa at position 16 is Gln, Lys, Glu, Ala, hR, Orn, Lys (isopropyl), Cit, Ser, Cys, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (17)..(17)
<223> Xaa at position 17 is Val, Ala, Leu, Ile, Met, Nle, Lys, Aib, Ser, Cys, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (18)..(18)
<223> Xaa at position 18 is Ala, Ser, Cys, Lys, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (19)..(19)
<223> Xaa at position 19 is Val, Ala, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Trp, Tyr, Cys, Asp, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (20)..(20)
<223> Xaa at position 20 is Lys, Gln, hR, Arg, Ser, His, Orn, Lys (isopropyl), Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, Cys, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> Xaa at position 21 is Lys, His, Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, Cys, Val, Tyr, Ile, Thr, Trp, K(W), or K(CO(CH₂)₂SH)

<220>

~4559933.txt

<221> MISC_FEATURE
<222> (22)..(22)
<223> Xaa at position 22 Tyr, Trp, Phe, Thr, Leu, Ile, Val, Tyr, (OMe), Ala, Aib, Ser, Cys, Lys, K(W), or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (23)..(23)
<223> Xaa at position 23 is Leu, Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, Cys, Lys, K(W), or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (24)..(24)
<223> Xaa at position 24 is Gln, Glu, Asn, Ser, Cys, Lys, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (25)..(25)
<223> Xaa at position 25 is Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, Lys, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (26)..(26)
<223> Xaa at position 26 is Ile, Leu, Thr, Val, Trp, Tyr, Phe, Aib, Ser, Cys, Lys, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (27)..(27)
<223> Xaa at position 27 is Lys, hR, Arg, Gln, Ala, Asp, Glu, Phe, Gly, His, Ile, Met, Asn, Pro, Ser, Thr, Val, Trp, Tyr, Lys (isopropyl), Cys, Leu, Orn, dK, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (28)..(28)
<223> Xaa at position 28 Asn, Asp, Gln, Lys, Arg, Aib, Orn, hR, Cit, Pro, dK, Ser, Cys, K(CO(CH₂)₂SH), or K(W)

<220>
<221> MISC_FEATURE
<222> (29)..(29)
<223> Xaa at position 29 is Lys, Ser, Arg, Asn, hR, Ala, Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Gln, Thr, Val, Trp, Tyr, Cys, Orn, Cit, Aib, K(W), K(CO(CH₂)₂SH), or is absent

<220>
<221> MISC_FEATURE
<222> (30)..(30)
<223> Xaa at position 30 is Arg, Lys, Ile, Ala, Asp, Glu, Phe, Gly, His, Leu, Met, Asn, Pro, Gln, Ser, Thr, Val, Trp, Tyr, Cys, hR, Cit, Aib, Orn, K(W), K(CO(CH₂)₂SH), or is absent

<220>
<221> MISC_FEATURE
<222> (31)..(31)
<223> Xaa at position 31 is Tyr, His, Phe, Thr, Cys, Ser, Lys, Gln, K(W), K(CO(CH₂)₂SH), or is absent

<220>
<221> MISC_FEATURE
<222> (32)..(32)
<223> Xaa at position 32 is Ser, Cys, Lys, or is absent

<220>

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<221> MISC_FEATURE
 <222> (33)..(33)
 <223> Xaa at position 33 is Trp or is absent

<220>
 <221> MISC_FEATURE
 <222> (34)..(34)
 <223> Xaa at position 34 is Cys or is absent

<220>
 <221> MISC_FEATURE
 <222> (35)..(35)
 <223> Xaa at position 35 is Glu or is absent

<220>
 <221> MISC_FEATURE
 <222> (36)..(36)
 <223> Xaa at position 36 is Pro or is absent

<220>
 <221> MISC_FEATURE
 <222> (37)..(37)
 <223> Xaa at position 37 is Gly or is absent

<220>
 <221> MISC_FEATURE
 <222> (38)..(38)
 <223> Xaa at position 38 is Trp or is absent

<220>
 <221> MISC_FEATURE
 <222> (39)..(39)
 <223> Xaa at position 39 is Cys or is absent

<220>
 <221> MISC_FEATURE
 <222> (40)..(40)
 <223> Xaa at position 40 is Arg or is absent

<400> 18

Xaa Xaa Xaa Xaa Xaa Xaa Thr Xaa Xaa Xaa Thr Xaa Xaa Xaa Xaa Xaa
 1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 20 25 30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 35 40

<210> 19
 <211> 13
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<220>
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 <222> (1)..(1)
 <223> Xaa at position 1 is Gly, Cys, Lys, or absent;

<220>

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<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa at position 2 is Gly, Arg, Cys, Lys, or absent

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa at position 3 is Pro, Thr, Ser, Ala, Cys, Lys, or absent

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa at position 4 is Ser, Pro, His, Cys, Lys, or absent

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is Ser, Arg, Thr, Trp, Lys, Cys, or absent

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa at position 6 is Gly, Ser, Cys, Lys, or absent

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa at position 7 is Ala, Asp, Arg, Glu, Lys, Gly, Cys, or absent

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is Pro, Ser, Ala, Cys, Lys, or absent

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa at position 9 is Pro, Ser, Ala, Cys, Lys, or absent

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa at position 10 is Pro, Ser, Ala, Arg, Lys, His, Cys, or absent

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> Xaa at position 11 is Ser, Cys, His, Pro, Lys, Arg, or absent

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa at position 12 is His, Ser, Arg, Lys, Cys, or absent

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa at position 13 is His, Ser, Arg, Lys, Cys, or absent

<400> 19

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 20
<211> 32

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<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<220>
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<222> (1)..(1)
<223> Xaa at position 1 is His, dH, or is absent

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa at position 2 is dA, Ser, Val, Gly, Thr, Leu, dS, Pro, or Aib

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa at position 3 Asp or Glu

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa at position 4 is Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, Gly, dA, Aib, or NMeA

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is Val, Leu, Phe, Ile, Thr, Trp, Tyr, dV, Aib, or NMeV

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa at position 6 is Phe, Ile, Leu, Thr, Val, Trp, or Tyr

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is Asp, Glu, Ala, Lys, Leu, Arg, or Tyr

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa at position 9 is Asn, Gln, Glu, Ser, Cys, or Lys

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa at position 10 is Tyr, Trp, Tyr (OMe), Ser, Cys, or Lys

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa at position 12 is Arg, Lys, hR, Orn, Aib, Cit, Ala, Leu, Gln, Phe, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa at position 13 is Leu, Phe, Glu, Ala, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE

~4559933.txt

<222> (14)..(14)
<223> Xaa at position 14 is Arg, Leu, Lys, Ala, hR, Orn, Phe, Gln, Aib, Cit, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa at position 15 is Lys, Ala, Arg, Glu, Leu, hR, Orn, Phe, Gln, Aib, K(Ac), Cit, Ser, Cys, or K(W)

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> Xaa at position 16 is Gln, Lys, Ala, hR, Orn, Cit, Ser, Cys or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (17)..(17)
<223> Xaa at position 17 is Val, Ala, Leu, Ile, Met, Nle, Lys, Aib, Ser, Cys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (18)..(18)
<223> Xaa at position 18 is Ala, Ser, Cys, or Lys

<220>
<221> MISC_FEATURE
<222> (19)..(19)
<223> Xaa at position 19 is Ala, Gly, Leu, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (20)..(20)
<223> Xaa at position 20 is Lys, Gln, hR, Arg, Ser, Orn, Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, or Cys

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> Xaa at position 21 is Lys, Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac), Cit, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> Xaa at position 22 is Tyr, Trp, Phe, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, Cys, or Lys

<220>
<221> MISC_FEATURE
<222> (23)..(23)
<223> Xaa at position 23 is Leu, Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, Cys, or Lys

<220>
<221> MISC_FEATURE
<222> (24)..(24)
<223> Xaa at position 24 is Gln, Asn, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (25)..(25)
<223> Xaa at position 25 is Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, Lys or K(CO(CH₂)₂SH)

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<220>
 <221> MISC_FEATURE
 <222> (26)..(26)
 <223> Xaa at position 26 is Ile, Leu, Thr, Val, Trp, Tyr, Phe, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

<220>
 <221> MISC_FEATURE
 <222> (27)..(27)
 <223> Xaa at position 27 is Lys, hR, Arg, Gln, Orn, dK, Ser, or Cys

<220>
 <221> MISC_FEATURE
 <222> (28)..(28)
 <223> Xaa at position 28 is Asn, Gln, Lys, Arg, Aib, Orn, hR, Cit, Pro, dK, Ser, Cys, or K(CO(CH₂)₂SH)

<220>
 <221> MISC_FEATURE
 <222> (29)..(29)
 <223> Xaa at position 29 is Lys, Ser, Arg, Asn, hR, Orn, Cit, Aib, Cys, or is absent;

<220>
 <221> MISC_FEATURE
 <222> (30)..(30)
 <223> Xaa at position 30 is Arg, Lys, Ile, hR, Cit, Aib, Orn, Ser, Cys, or is absent

<220>
 <221> MISC_FEATURE
 <222> (31)..(31)
 <223> Xaa at position 31 is Tyr, His, Phe, Lys, Ser, Cys, Gln, or is absent

<220>
 <221> MISC_FEATURE
 <222> (32)..(32)
 <223> Xaa at position 32 is Cys, Ser, Lys, or is absent

<400> 20
 Xaa Xaa Xaa Xaa Xaa Xaa Thr Xaa Xaa Xaa Thr Xaa Xaa Xaa Xaa Xaa
 1 5 10 15
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 20 25 30

<210> 21
 <211> 31
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<220>
 <221> MISC_FEATURE
 <222> (2)..(2)
 <223> Xaa at position 2 is dA, Ser, Val, dS, or Aib

<220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> Xaa at position 3 is Asp or Glu

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<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa at position 4 is Ala, dA, or Aib;

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is Val, Leu, dV, or Aib

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is Asp, Glu, or Ala

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa at position 9 is Asn, Gln, Glu, Ser, Cys, or Lys

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa at position 10 is Tyr, or Tyr(OMe)

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa at position 12 is Ala, Arg, Lys, hR, Orn, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa at position 13 is Leu, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa at position 14 is Arg, Leu, Lys, Ala, hR, Orn, Phe, Gln, Aib, Cit, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa at position 15 is Lys, Ala, Arg, Leu, Orn, Phe, Gln, Aib, K(Ac), Ser, Cys, or K(W)

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> Xaa at position 16 is Gln, Lys, Ser, Cys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (17)..(17)
<223> Xaa at position 17 is Val, Ala, Leu, Ile, Met, Nle, Lys, Ser, Cys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (18)..(18)
<223> Xaa at position 18 is Ala, Ser, Cys, or Lys

<220>
<221> MISC_FEATURE
<222> (19)..(19)
<223> Xaa at position 19 is Ala, Leu, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

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<220>
<221> MISC_FEATURE
<222> (20)..(20)
<223> Xaa at position 20 is Lys, Gln, hR, Arg, Ser, Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), or Cys

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> Xaa at position 21 is Lys, Arg, Ala, Phe, Aib, Leu, Gln, K(Ac), Orn, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> Xaa at position 22 is Tyr, Trp, Phe, Leu, Ile, Val, Ser, Cys, Lys, or Tyr(OMe)

<220>
<221> MISC_FEATURE
<222> (23)..(23)
<223> Xaa at position 23 is Leu, Ser, Cys, or Lys

<220>
<221> MISC_FEATURE
<222> (24)..(24)
<223> Xaa at position 24 is Gln, Asn, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (25)..(25)
<223> Xaa at position 25 is Ser, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Cys, Lys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (26)..(26)
<223> Xaa at position 26 is Ile, Leu, Thr, Val, Trp, Tyr, Phe, Aib, Ser, Cys, Lys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (27)..(27)
<223> Xaa at position 27 is Lys, hR, Arg, dK, Orn, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (28)..(28)
<223> Xaa at position 28 is Asn, Gln, Lys, hR, Aib, Orn, dK, Pro, Ser, Cys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (29)..(29)
<223> Xaa at position 29 is Lys, Ser, Arg, hR, Orn, Cys, or is absent

<220>
<221> MISC_FEATURE
<222> (30)..(30)
<223> Xaa at position 30 is Arg, Lys, hR, Ser, Cys, or is absent

<220>
<221> MISC_FEATURE
<222> (31)..(31)
<223> Xaa at position 31 is Tyr, Phe, Lys, Ser, Cys, or is absent

<220>

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<221> MISC_FEATURE
 <222> (32)..(32)
 <223> Xaa at position 32 is Cys, Ser, Lys, or absent

<400> 21

His Xaa Xaa Xaa Xaa Phe Thr Xaa Xaa Xaa Thr Xaa Xaa Xaa Xaa Xaa
 1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 20 25 30

<210> 22
 <211> 11
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 22

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
 1 5 10

<210> 23
 <211> 11
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<220>
 <221> MOD_RES
 <222> (11)..(11)
 <223> AMIDATION

<400> 23

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
 1 5 10

<210> 24
 <211> 39
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<220>
 <221> MOD_RES
 <222> (1)..(1)
 <223> C6 Acylation

<220>
 <221> MOD_RES
 <222> (21)..(21)
 <223> Peg

<400> 24

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Arg Gln
 1 5 10 15

Val Ala Ala Arg Lys Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
 35

<210> 25
 <211> 39
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<220>
 <221> MOD_RES
 <222> (1)..(1)
 <223> C6 Acylation

<220>
 <221> MISC_FEATURE
 <222> (10)..(10)
 <223> Tyr is methoxylated

<220>
 <221> MISC_FEATURE
 <222> (17)..(17)
 <223> X= Nle=Nor-leucine

<220>
 <221> MOD_RES
 <222> (21)..(25)
 <223> lactam bridge

<220>
 <221> MOD_RES
 <222> (39)..(39)
 <223> PEG

<400> 25

His Ser Asp Ala Val Phe Thr Glu Asn Tyr Thr Lys Leu Arg Lys Gln
 1 5 10 15

Xaa Ala Ala Lys Lys Tyr Leu Asn Asp Leu Lys Lys Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Cys
 35

<210> 26
 <211> 40
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

~4559933.txt

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa at position 1 is any naturally occurring amino acid, dH, or is absent

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa at position 2 is any naturally occurring amino acid; dA, ds, or Aib

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa at position 3 is Asp or Glu

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa at position 4 is any naturally occurring amino acid, dA, Aib, or NMeA

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is any naturally occurring amino acid, dV, or Aib

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa at position 6 is any naturally occurring amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is Asp, Glu, Ala, Lys, Leu, Arg, or Tyr

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa at position 9 is Asn, Gln, Asp, Glu, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa at position 10 is any naturally occurring aromatic amino acid, or Tyr (OMe)

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa at position 12 is hR, Orn, Lys (isopropyl), Aib, Cit, or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa at position 13 is Aib or K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa at position 14 is hR, Orn, Lys (isopropyl), Aib, Cit, or any

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naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa at position 15 is hR, Orn, Lys (isopropyl), Aib, K (Ac), Cit, K(W), or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> Xaa at position 16 is hR, Orn, Lys (isopropyl), Cit, K(CO(CH₂)₂SH) or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (17)..(17)
<223> Xaa at position 17 is Nle, Aib, K(CO(CH₂)₂SH) or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (18)..(18)
<223> Xaa at position 18 is any naturally occurring amino acid

<220>
<221> MISC_FEATURE
<222> (19)..(19)
<223> Xaa at position 19 is K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (20)..(20)
<223> Xaa at position 20 is : hR, Orn, Lys (isopropyl), Aib, K(Ac), Cit, or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> Xaa at position 21 is hR, Orn, Aib, K(Ac), Cit, or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> Xaa at position 22 is Aib, Tyr (OMe), or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (23)..(23)
<223> Xaa at position 23 is Aib or any naturally occurring amino acid except Pro

<220>
<221> MISC_FEATURE
<222> (24)..(24)
<223> Xaa at position 24 is K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro;

<220>
<221> MISC_FEATURE
<222> (25)..(25)
<223> Xaa at position 25 is Aib, K(CO(CH₂)₂SH), or any naturally occurring amino acid except Pro

<220>

~4559933.txt

<221> MISC_FEATURE
 <222> (26)..(26)
 <223> Xaa at position 26 is K(CO(CH₂)₂SH) or any naturally occurring amino acid except Pro;

 <220>
 <221> MISC_FEATURE
 <222> (27)..(27)
 <223> Xaa at position 27 is hR, Lys (isopropyl), Orn, dk, or any naturally occurring amino acid except Pro

 <220>
 <221> MISC_FEATURE
 <222> (28)..(28)
 <223> Xaa at position 28 is K(CO(CH₂)₂SH) or any naturally occurring amino acid, Aib, hR, Cit, Orn, or dk

 <220>
 <221> MISC_FEATURE
 <222> (29)..(29)
 <223> Xaa at position 29 is any naturally occurring amino acid, hR, Orn, Cit, Aib, or is absent

 <220>
 <221> MISC_FEATURE
 <222> (30)..(30)
 <223> Xaa at position 30 is any naturally occurring amino acid, hR, Orn, Cit, Aib, or is absent

 <220>
 <221> MISC_FEATURE
 <222> (31)..(40)
 <223> Xaa at position 31 to 40 are any naturally occurring amino acid or are absent

<400> 26

Xaa Xaa Xaa Xaa Xaa Xaa Thr Xaa Xaa Xaa Thr Xaa Xaa Xaa Xaa Xaa
 1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 20 25 30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 35 40

<210> 27
 <211> 40
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<220>
 <221> MISC_FEATURE
 <222> (2)..(2)
 <223> Xaa at position 2 is dA, Ser, Val, Gly, Thr, Leu, dS, Pro, or Aib

<220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> Xaa at position 3 is Asp or Glu

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<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa at position 4 is Ala, Ile, Tyr, Phe, Val, Thr, Leu, Trp, Gly, dA, Aib, or NMeA

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is Val, Leu, Phe, Ile, Thr, Trp, Tyr, dv, or Aib

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is Asp, Glu, Ala, Lys, Leu, Arg, or Tyr

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa at position 9 is Asn, Gln, Asp, Glu, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa at position 10 is Tyr, Trp, or Tyr(OMe)

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa at position 12 is Arg, Lys, Glu, hR, Orn, Lys (isopropyl), Aib, Cit, Ala, Leu, Gln, or Phe

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa at position 13 is Leu, Phe, Glu, Ala, Aib, Ser, Cys, or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa at position 14 is Arg, Leu, Lys, Ala, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, or Cit

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa at position 15 is Lys, Ala, Arg, Glu, Leu, hR, Orn, Lys (isopropyl), Phe, Gln, Aib, K(Ac), Cit, or K(W)

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> Xaa at position 16 is Gln, Lys, Glu, Ala, hR, Orn, Lys (isopropyl), Cit, Ser, Cys or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (17)..(17)
<223> Xaa at position 17 is Val, Ala, Leu, Ile, Met, Nle, Lys, Aib, Ser, Cys or K(CO(CH₂)₂SH)

<220>
<221> MISC_FEATURE
<222> (18)..(18)
<223> Xaa at position 18 is Ala, Ser, or Cys

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<220>
<221> MISC_FEATURE
<222> (19)..(19)
<223> Xaa at position 19 is Val, Ala, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Trp, Tyr, Cys, Asp, or K(CO(CH2)2SH)

<220>
<221> MISC_FEATURE
<222> (20)..(20)
<223> Xaa at position 20 is Lys, Gln, hR, Arg, Ser, His, Orn, Lys (isopropyl), Ala, Aib, Trp, Thr, Leu, Ile, Phe, Tyr, Val, K(Ac), Cit, or Cys

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> Xaa at position 21 is Lys, His, Arg, Ala, Phe, Aib, Leu, Gln, Orn, hR, K(Ac) Cit, Ser, or Cys;

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> Xaa at position 22 is Tyr, Trp, Phe, Thr, Leu, Ile, Val, Tyr(OMe), Ala, Aib, Ser, or Cys

<220>
<221> MISC_FEATURE
<222> (23)..(23)
<223> Xaa at position 23 is Leu, Phe, Ile, Ala, Trp, Thr, Val, Aib, Ser, or Cys;

<220>
<221> MISC_FEATURE
<222> (24)..(24)
<223> Xaa at position 24 is Gln, Glu, Asn, Ser, Cys, or K(CO(CH2)2SH)

<220>
<221> MISC_FEATURE
<222> (25)..(25)
<223> Xaa at position 25 is Ser, Asp, Phe, Ile, Leu, Thr, Val, Trp, Gln, Asn, Tyr, Aib, Glu, Cys, or K(CO(CH2)2SH)

<220>
<221> MISC_FEATURE
<222> (26)..(26)
<223> Xaa at position 26 is Ile, Leu, Thr, Val, Trp, Tyr, Phe, Ser, Cys, or K(CO(CH2)2SH)

<220>
<221> MISC_FEATURE
<222> (27)..(27)
<223> Xaa at position 27 is Lys, hR, Arg, Gln, Ala, Asp, Glu, Phe, Gly, His, Ile, Met, Asn, Ser, Thr, Val, Trp, Tyr, Lys (isopropyl), Cys, Leu, Orn, or dk

<220>
<221> MISC_FEATURE
<222> (28)..(28)
<223> Xaa at position 28 is Asn, Asp, Gln, Lys, Arg, Aib, Orn, hR, Cit, Pro, dk, Cys, or K(CO(CH2)2SH)

<220>
<221> MISC_FEATURE
<222> (29)..(29)
<223> Xaa at position 29 is Lys, Ser, Arg, Asn, hR, Ala, Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Gln, Thr, Val, Trp, Tyr, Cys, Orn,

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Cit, Aib or is absent

<220>
 <221> MISC_FEATURE
 <222> (30)..(30)
 <223> Xaa at position 30 is Arg, Lys, Ile, Ala, Asp, Glu, Phe, Gly, His, Leu, Met, Asn, Pro, Gln, Ser, Thr, Val, Trp, Tyr, Cys, hR, Cit, Aib, Orn, or is absent

<220>
 <221> MISC_FEATURE
 <222> (31)..(31)
 <223> Xaa at position 31 is Tyr, His, Phe, Thr, Cys, or is absent

<220>
 <221> MISC_FEATURE
 <222> (32)..(32)
 <223> Xaa at position 32 is Ser, Cys, or is absent;

<220>
 <221> MISC_FEATURE
 <222> (33)..(33)
 <223> Xaa at position 33 is Trp or is absent

<220>
 <221> MISC_FEATURE
 <222> (34)..(34)
 <223> Xaa at position 34 is Cys or is absent;

<220>
 <221> MISC_FEATURE
 <222> (35)..(35)
 <223> Xaa at position 35 is Glu or is absent;

<220>
 <221> MISC_FEATURE
 <222> (36)..(36)
 <223> Xaa at position 36 is Pro or is absent

<220>
 <221> MISC_FEATURE
 <222> (37)..(37)
 <223> Xaa at position 37 is Gly or is absent

<220>
 <221> MISC_FEATURE
 <222> (38)..(38)
 <223> Xaa at position 38 is Trp or is absent

<220>
 <221> MISC_FEATURE
 <222> (39)..(39)
 <223> Xaa at position 39 is Cys or is absent

<220>
 <221> MISC_FEATURE
 <222> (40)..(40)
 <223> Xaa at position 40 is Arg or is absent

<400> 27

His Xaa Xaa Xaa Xaa Phe Thr Xaa Xaa Xaa Thr Xaa Xaa Xaa Xaa Xaa
 1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 20 25 30

~4559933.txt

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 35 40

<210> 28
 <211> 32
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> Xaa at position 3 is Asp, or Glu

<220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> Xaa at position 8 is Asp, or Glu

<220>
 <221> MISC_FEATURE
 <222> (9)..(9)
 <223> Xaa at position 9 is Asn, Gln, or Cys

<220>
 <221> MISC_FEATURE
 <222> (10)..(10)
 <223> Xaa at position 10 is Tyr, or Tyr(OMe)

<220>
 <221> MISC_FEATURE
 <222> (12)..(12)
 <223> Xaa at position 12 is Arg, Orn, or hR

<220>
 <221> MISC_FEATURE
 <222> (13)..(13)
 <223> Xaa at position 13 is Leu, Cys, or K(CO(CH₂)₂SH)

<220>
 <221> MISC_FEATURE
 <222> (14)..(14)
 <223> Xaa at position 14 is Arg, Leu, or Aib

<220>
 <221> MISC_FEATURE
 <222> (15)..(15)
 <223> Xaa at position 15 is Lys, Ala, Arg, Aib, or K(W)

<220>
 <221> MISC_FEATURE
 <222> (16)..(16)
 <223> Xaa at position 16 is Gln, Lys, or K(CO(CH₂)₂SH)

<220>
 <221> MISC_FEATURE
 <222> (17)..(17)
 <223> Xaa at position 17 is Val, Leu, Cys, or K(CO(CH₂)₂SH)

<220>
 <221> MISC_FEATURE
 <222> (19)..(19)
 <223> Xaa at position 19 is Ala, Leu, Cys, or K(CO(CH₂)₂SH)

~4559933.txt

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<220>
<221> MISC_FEATURE
<222> (20)..(20)
<223> Xaa at position 20 is Lys, Gln, Arg, Aib, or Cys

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> Xaa at position 21 is Lys, Arg, Aib, or Orn

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> Xaa at position 22 is Tyr or Tyr(OMe)

<220>
<221> MISC_FEATURE
<222> (24)..(24)
<223> Xaa at position 24 is Gln, Cys, or K(CO(CH2)2SH)

<220>
<221> MISC_FEATURE
<222> (25)..(25)
<223> Xaa at position 25 is Ser, Cys, or K(CO(CH2)2SH)

<220>
<221> MISC_FEATURE
<222> (26)..(26)
<223> Xaa at position 26 is Ile, Cys, or K(CO(CH2)2SH)

<220>
<221> MISC_FEATURE
<222> (27)..(27)
<223> Xaa at position 27 is Lys, Arg, Orn, or hR

<220>
<221> MISC_FEATURE
<222> (28)..(28)
<223> Xaa at position 28 is Asn, hR, Orn, Cys, or K(CO(CH2)2SH)

<220>
<221> MISC_FEATURE
<222> (29)..(29)
<223> Xaa at position 29 is Orn, Lys, hR, or is absent

<220>
<221> MISC_FEATURE
<222> (30)..(30)
<223> Xaa at position 30 is Arg, hR, or is absent

<220>
<221> MISC_FEATURE
<222> (31)..(31)
<223> Xaa at position 31 is Tyr, or is absent

<220>
<221> MISC_FEATURE
<222> (32)..(32)
<223> Xaa at position 32 is Cys, or is absent

<400> 28

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His Ser Xaa Ala Val Phe Thr Xaa Xaa Xaa Thr Xaa Xaa Xaa Xaa Xaa
1      5      10      15

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Xaa Ala Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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20

25 ~4559933.txt

30

<210> 29
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa at position 1 is Gly, Cys, Lys, K(W), K(CO(CH2)2SH), or is absent

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa at position 2 is Gly, Arg, Cys, Lys, K(W), K(CO(CH2)2SH), or is absent

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa at position 3 is Pro, Thr, Ser, Ala, Cys, Lys, K(W), K(CO(CH2)2SH), or absent

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa at position 4 is Ser, Pro, His, Cys, Lys, K(W), K(CO(CH2)2SH), or absent

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is Ser, Arg, Thr, Trp, Lys, Cys, K(W), K(CO(CH2)2SH), or absent

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa at position 6 is Gly, Ser, Cys, Lys, K(W), K(CO(CH2)2SH), or absent

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa at position 7 is Ala, Asp, Arg, Glu, Lys, Gly, Cys, K(W), K(CO(CH2)2SH), or absent

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is Pro, Ser, Ala, Cys, Lys, K(W), K(CO(CH2)2SH), or absent

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa at position 9 is Pro, Ser, Ala, Cys, Lys, K(W), K(CO(CH2)2SH), or absent

<220>
<221> MISC_FEATURE

~4559933.txt

<222> (10)..(10)
 <223> Xaa at position 10 is Pro, Ser, Ala, Arg, Lys, His, Cys, K(W),
 K(CO(CH₂)₂SH), or absent

<220>
 <221> MISC_FEATURE
 <222> (11)..(11)
 <223> Xaa at position 11 is Ser, Cys, His, Pro, Lys, Arg, K(W),
 K(CO(CH₂)₂SH), or absent

<220>
 <221> MISC_FEATURE
 <222> (12)..(12)
 <223> Xaa at position 12 is His, Ser, Arg, Lys, Cys, K(W),
 K(CO(CH₂)₂SH), or absent

<220>
 <221> MISC_FEATURE
 <222> (13)..(13)
 <223> Xaa at position 13 is His, Ser, Arg, Lys, Cys, K(W),
 K(CO(CH₂)₂SH), or absent

<400> 29

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1 5 10

<210> 30
 <211> 42
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 30

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 31
 <211> 33
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 31

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Gly Gly
 20 25 30

~4559933.txt

Thr

<210> 32
<211> 33
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 32

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Lys Gly Gly
20 25 30

Thr

<210> 33
<211> 41
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 33

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Lys Gly Gly
20 25 30

Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 34
<211> 42
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<220>
<221> MISC_FEATURE
<222> (20)..(20)
<223> X=homoarginine

<400> 34

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

~4559933.txt

Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 35
 <211> 42
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 35

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Ile Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 36
 <211> 42
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 36

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Arg Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 37
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Val Ala Ala Ser Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Arg Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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His Ser Asp Ala Val Phe Thr Asp Asn Trp Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg His Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Gln Gly
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Cys
20 25 30

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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Val Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Thr Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Leu Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 56

His Pro Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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<400> 57

His Ser Asp Ile Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Leu Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 63

His Ser Asp Trp Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Phe Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Ile Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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<400> 66

His Ser Asp Ala Leu Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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<400> 67

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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Ile Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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<400> 69

His Ser Asp Ala Val Leu Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Thr Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 71

His Ser Asp Ala Val Val Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Trp Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Tyr Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Trp Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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<400> 75

His Ser Asp Ala Tyr Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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<400> 76

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Arg Gln
 1 5 10 15

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Val Ala Ala Arg Arg Tyr Leu Gln Ser Ile Arg Asn Arg Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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<400> 77

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Arg Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Arg Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Gln Asn Lys Arg Tyr Gly
 20 25 30

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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Asn Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Ile Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Arg Gly Gly Pro Ser
 20 25 30

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Ser Gly Ala Pro Pro Pro Ser
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<400> 83

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

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 Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Lys Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Glu Lys Glu Lys
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Ala Ala Ala Lys
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 88

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Lys
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 89

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Gly Arg Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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<400> 90

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Leu Lys
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 91

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Ala Lys Ala Lys
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Arg Gln
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Val Ala Ala Arg Arg Tyr Leu Gln Ser Ile Arg Asn Arg Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Val Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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Gln Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
20 25 30

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 96

His Ser Asp Gly Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Lys Leu Lys Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Lys Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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Met His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys
1 5 10 15

Gln Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
20 25 30

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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Gln Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
20 25 30

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Phe Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 101

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln

~4559933.txt

1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Leu Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 102
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<400> 102

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Thr Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 103
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<400> 103

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Val Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 104

~4559933.txt

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<400> 104

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Trp Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 105
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<400> 105

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Tyr Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 106
<211> 42
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<223> C6 Acylation

~4559933.txt

<400> 106

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Phe Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 107

<211> 42

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<222> (1)..(1)

<223> C6 Acylation

<400> 107

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ile Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 108

<211> 42

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<222> (1)..(1)

<223> C6 Acylation

<400> 108

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Leu Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser

~4559933.txt

35

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<400> 109

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Thr Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 110

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Val Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 111
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~4559933.txt

<220>
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 <223> C6 Acylation

<400> 111

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Trp Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 112
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<400> 112

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Lys
 1 5 10 15

Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 113
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<220>
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<400> 113

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

~4559933.txt

20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
 35 40

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<220>
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 <223> C6 Acylation

<400> 114

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Lys Gly Gly
 20 25 30

Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 115
 <211> 41
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 <223> C6 Acylation

<400> 115

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Ser Arg Gly Gly
 20 25 30

Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 116
 <211> 41
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<220>
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 <223> C6 Acylation

<400> 116

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Gly Gly
 20 25 30

Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 117
 <211> 42
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 <223> C6 Acylation

<400> 117

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Gln Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 118
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<220>
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 <223> C6 Acylation

<400> 118

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln

~4559933.txt

1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Asn Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 119
 <211> 39
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 119

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Arg Gly Arg Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
 35

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 <223> C6 Acylation

<400> 120

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Tyr Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 121
 <211> 42
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<400> 121

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Trp Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 122
<211> 42
<212> PRT
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<223> C6 Acylation

<400> 122

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Phe Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 123
<211> 42
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<400> 123

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

~4559933.txt

Val Ala Ala Lys Lys Thr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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 <223> C6 Acylation

<400> 124

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Leu Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 125
 <211> 42
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<400> 125

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Ile Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 126
 <211> 42
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<400> 126

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Val Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 127

<211> 42

<212> PRT

<213> Artificial

<220>

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<220>

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<222> (1)..(1)

<223> C6 Acylation

<400> 127

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Lys
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 128

<211> 42

<212> PRT

<213> Artificial

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<223> C6 Acylation

<400> 128

~4559933.txt

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Ala Gln
 1 5 10 15

Val Ala Ala Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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 <211> 42
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<400> 129

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Ala Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 130

Met His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala
 1 5 10 15

Lys Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
 20 25 30

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

~4559933.txt

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<400> 131

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Lys Ala Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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 <223> C6 Acylation

<400> 132

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Ala Gln
 1 5 10 15

Leu Ala Ala Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 133
 <211> 39
 <212> PRT
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<222> (1)..(1)
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<400> 133

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ala Gln Lys Tyr Leu Asn Gln Leu Lys Lys Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

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<400> 134

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Gln Lys Tyr Leu Asn Gln Leu Lys Lys Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

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<400> 135

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Val Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

~4559933.txt

Gly Pro Ser Ser Gly Ala Pro Pro Ser
 35 40

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<400> 136

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Tyr Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 137
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<400> 137

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Phe Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 138
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<400> 138

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Ile Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 139

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 140

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

~4559933.txt

Val Ala Ala Leu Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 141

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Thr Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 142
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<400> 142

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Trp Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 143
 <211> 39
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<222> (1)..(1)

<223> C6 Acylation

<400> 143

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
 35

<210> 144

<211> 42

<212> PRT

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<220>

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<222> (1)..(1)

<223> C6 Acylation

<400> 144

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Leu Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 145

<211> 42

<212> PRT

<213> Artificial

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<220>

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<222> (1)..(1)

<223> C6 Acylation

<400> 145

~4559933.txt

His Ser Asp Ala Val Phe Thr Ala Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 146
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 <222> (1)..(1)
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<400> 146

His Ser Asp Ala Val Phe Thr Glu Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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 <222> (1)..(1)
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<400> 147

His Ser Asp Ala Val Phe Thr Lys Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

~4559933.txt

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<222> (1)..(1)
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<400> 148

His Ser Asp Ala Val Phe Thr Leu Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 149
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<222> (1)..(1)
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<400> 149

His Ser Asp Ala Val Phe Thr Arg Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<220>
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~4559933.txt

<222> (1)..(1)
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<400> 150

His Ser Asp Ala Val Phe Thr Tyr Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 151
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<220>
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 <222> (1)..(1)
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<400> 151

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Lys
 1 5 10 15

Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
 35 40

<210> 152
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<220>
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<220>
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 <222> (1)..(1)
 <223> C6 Acylation

<400> 152

His Ser Asp Ala Val Phe Thr Glu Glu Tyr Thr Arg Leu Gln Lys Gln
 1 5 10 15

Val Ala Ala Lys Gln Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

~4559933.txt

Gly Pro Ser Ser Gly Ala Pro Pro Ser
 35 40

<210> 153
 <211> 42
 <212> PRT
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<400> 153

His Xaa Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 154
 <211> 42
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 <223> Xaa at position 14 is Aib

<400> 154

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser

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<400> 155

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<223> Xaa at position 20 is Aib

<400> 156

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<223> Xaa at position 21 is Aib

<400> 157

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Xaa Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 158

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Lys Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Gln Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Ala Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Lys Gln
 1 5 10 15

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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 162

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Phe Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 163

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Arg Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Gln Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Leu Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 166

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Phe Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 167

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Ala Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Arg Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Gln Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Ala Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Leu Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 172

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Phe Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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 <223> Xaa at position 25 is Aib

<400> 173

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln

1 5 ~4559933.txt 15
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Val Ala Ala Lys Lys Tyr Leu Gln Xaa Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<223> Xaa at position 26 is Aib

<400> 174

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Xaa Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 175

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Xaa Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala
 1 5 10 15

Lys Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
 20 25 30

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 177

His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Leu Ala Lys
 1 5 10 15

Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<223> ACETYLATION

<400> 178

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<223> ACETYLATION

<400> 179

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Gln
 1 5 10 15

Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 181

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Lys
 1 5 10 15

Val Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 182

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Lys
 1 5 10 15

Leu Ala Ala Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 183

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Lys
 1 5 10 15

Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Gly Gly Pro
 20 25 30

Ser Ser Gly Ala Pro Pro Pro Cys
 35 40

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<400> 184

Xaa His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys
 1 5 10 15

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Gln Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
 20 25 30

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 185

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Phe Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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 <223> HS(CH₂)₂CO Substituent

<400> 186

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Lys
 1 5 10 15

Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 187
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<400> 187

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<223> Ala is D-isomer

<400> 188

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 190

His Ser Asp Xaa Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<223> Val is D-isomer

<400> 191

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<222> (5)..(5)

<223> N-methyl valine

<400> 192

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 193

His Ser Asp Ala Xaa Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 194

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Arg Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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<400> 195

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Arg Arg Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
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25

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Ser Gly Ala Pro Pro Pro Ser
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<400> 196

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Arg Gln
1 5 10 15

Val Ala Ala Lys Arg Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

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<223> C6 Acylation

<400> 197

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Arg Gln
1 5 10 15

Val Ala Ala Arg Lys Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Arg Gln
 1 5 10 15

Val Ala Ala Arg Lys Tyr Leu Gln Ser Ile Arg Gln Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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<400> 199

His Ser Asp Ile Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 200

His Gly Glu Gly Thr Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln

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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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<223> C6_Acylation
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<400> 201

His Ser Asp Leu Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 202

His Ser Glu Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 203

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Xaa Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Ala Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Ala Lys Lys Tyr Trp Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Phe Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Thr Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Ile Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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<400> 211

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Val Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Ala Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Xaa Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 214

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
1 5 10 15

Leu Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
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Leu Ala Ala Lys Xaa Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<223> X=Aib

<400> 216

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
1 5 10 15

Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 217

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<223> X=Aib

<400> 217

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
1 5 10 15

Val Ala Ala Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
1 5 10 15

Val Ala Ala Lys Xaa Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
1 5 10 15

Val Ala Ala Lys Gln Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 220

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Gln Lys Gln
 1 5 10 15

Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 221

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Gln Lys Gln
 1 5 10 15

Val Ala Ala Lys Xaa Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 222

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Gln Lys Gln
 1 5 10 15

Val Ala Ala Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 223

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Gln Lys Gln
 1 5 10 15

Val Ala Ala Lys Gln Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 224

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Gln Xaa Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
1 5 10 15

Val Ala Ala Leu Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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<400> 226

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
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Val Ala Ala Ala Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 227

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
 1 5 10 15

Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 228
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<400> 228

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
1 5 10 15

Val Ala Ala Val Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 229
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<400> 229

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
1 5 10 15

Val Ala Ala Ala Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 230
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<400> 230

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
 1 5 10 15

Val Ala Ala Lys Xaa Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 231

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
 1 5 10 15

Val Ala Ala Leu Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 232
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<223> X=Aib

<400> 232

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
1 5 10 15

Val Ala Ala Val Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 233

<211> 40

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<222> (1)..(1)

<223> C6 Acylation

<400> 233

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Gly Gly Pro
20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 234

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<223> C6 Acylation

<400> 234

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

~4559933.txt

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Gly Arg Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
 35

<210> 235
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<400> 235

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Val Ala Gly Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 236
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<400> 236

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
 1 5 10 15

Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
 35 40

<210> 237
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<400> 237

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
 1 5 10 15

Leu Ala Ala Lys Xaa Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 238
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<400> 238

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
 1 5 10 15

Val Ala Ala Lys Xaa Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
 35 40

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<400> 239

His Ser Asp Ala Leu Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 240
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<400> 240

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 241
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 <222> (20)..(20)
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<400> 241

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
 1 5 10 15

Leu Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

<210> 242
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<223> X=Aib

<400> 242

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
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Leu Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Gly Gly Pro
20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 243

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<222> (20)..(20)

<223> X=Aib

<400> 243

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Xaa Lys Gln
1 5 10 15

Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Gln Lys Gly Gly Pro
20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 244

<211> 40

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<400> 244

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
1 5 10 15

Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Gln Lys Gly Gly Pro
20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
35 40

<210> 245
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<400> 245

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
1 5 10 15

Val Ala Ala Lys Xaa Tyr Leu Gln Ser Ile Lys Gln Lys Gly Gly Pro
20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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Ser Gly Ala Pro Pro Pro Ser
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Ser Ser Gly Ala Pro Pro Pro Cys
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Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Cys
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Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Cys
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Asn Xaa Xaa Tyr Gly
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Xaa Leu Arg Xaa Gln
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Asn Xaa Xaa Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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Val	Ala	Ala	Xaa	Lys	Tyr	Leu	Gln	Ser	Ile	Lys	Xaa	Lys	Gly	Gly	Pro
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Ser	Ser	Gly	Ala	Pro	Pro	Pro	Ser
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1				5					10					15	

Val	Ala	Ala	Xaa	Lys	Tyr	Leu	Gln	Ser	Ile	Lys	Pro	Lys	Gly	Gly	Pro
			20					25					30		

Ser	Ser	Gly	Ala	Pro	Pro	Pro	Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
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Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Gln Xaa Gly Gly Pro
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Leu Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Asn Xaa Gly Gly Pro
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Asn Xaa Gly Gly Pro
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Asn Xaa Gly Gly Pro
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Leu Ala Lys
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Ser Ser Gly Ala Pro Pro Pro Ser
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Ser Ser Gly Ala Pro Pro Pro Ser
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Ser Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Cys
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Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Cys
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Ser Ser Gly Ala Pro Pro Pro Ser
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Leu Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Xaa Lys Gly Gly Pro
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Ser Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Asn Xaa Gly Gly Pro
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Ser Ser Gly Ala Pro Pro Pro Ser
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Leu Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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20 25 30

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His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
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Val Ala Ala Xaa Xaa Tyr Leu Cys Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Xaa Tyr Leu Xaa Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
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Val Ala Cys Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Val Ala Xaa Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Cys Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Cys
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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Cys Xaa Gly Gly Pro
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Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
1 5 10 15

Val Ala Ala Xaa Xaa Tyr Leu Gln Cys Ile Xaa Xaa Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Cys
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 1 5 10 15

Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Cys Arg Xaa Gln
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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Cys
 20 25 30

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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
35 40

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Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
35 40

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Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Lys Asn Lys Gly Gly Pro
20 25 30

Ser Ser Gly Ala Pro Pro Pro Cys
35 40

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Val Ala Ala Lys Arg Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Lys Arg Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Lys Arg Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Arg Lys Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Xaa Gln
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Val Ala Ala Lys Xaa Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
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Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
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Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Asn Xaa Gly Gly Pro
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Ser Gly Ala Pro Pro Pro Cys
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 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Xaa Leu Arg Xaa Gln
 1 5 10 15

Val Ala Ala Xaa Lys Tyr Leu Gln Cys Ile Xaa Asn Xaa Gly Gly Pro
 20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Xaa Leu Arg Xaa Gln
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Val Ala Ala Cys Xaa Tyr Leu Gln Ser Ile Xaa Asn Xaa Gly Gly Pro
 20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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Xaa His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys
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Gln Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
 20 25 30

Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
 Page 210

35

40

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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Cys
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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Cys
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Xaa Leu Arg Xaa Gln
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 Val Ala Ala Cys Xaa Tyr Leu Gln Ser Ile Xaa Asn Xaa Gly Gly Pro
 20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Xaa Leu Arg Xaa Gln
 1 5 10 15

Val Ala Ala Xaa Lys Tyr Leu Gln Ser Ile Xaa Asn Xaa Gly Gly Pro
 20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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Leu Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Cys
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Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Xaa Tyr Leu Xaa Ser Ile Xaa Xaa Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Val Ala Cys Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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<400> 371

His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
 1 5 10 15

Val Ala Xaa Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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<400> 372

His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
1 5 10 15

Cys Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

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His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Cys
1 5 10 15

Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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<400> 374

His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Cys Xaa Gly Gly Pro
 20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
 35 40

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<400> 375

His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
 1 5 10 15

Val Ala Ala Xaa Xaa Tyr Leu Gln Cys Ile Xaa Xaa Gly Gly Pro Ser
 20 25 30

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Ser Gly Ala Pro Pro Pro Cys
35

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<400> 376

His Ser Asp Ala Val Phe Thr Glu Cys Tyr Thr Xaa Leu Arg Xaa Gln
1 5 10 15

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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

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His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Cys
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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Cys Arg Xaa Gln
1 5 10 15

Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
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Val Ala Ala Xaa Xaa Tyr Leu Xaa Ser Ile Xaa Xaa Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
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<400> 380

His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
1 5 10 15

Val Ala Xaa Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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<400> 381

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Lys Lys
20 25

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<220>

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<400> 382

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Lys Lys Gly Gly Thr
20 25 30

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<400> 383

His Ser Asp Ala Val Phe Thr Glu Asn Tyr Thr Lys Leu Arg Lys Gln
1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Asn Asp Leu Leu Asn Gly Gly Thr
20 25 30

<210> 384

<211> 31

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<400> 384

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Lys Leu Arg Lys Gln
1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Leu Asn Gly Gly Thr
20 25 30

<210> 385

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<212> PRT

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<400> 385

His Ser Asp Ala Val Phe Thr Glu Asn Tyr Thr Lys Leu Arg Lys Gln
1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Asn Asp Leu Lys Lys Gly Gly Thr Ser
20 25 30

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Trp Cys Glu Pro Gly Trp Cys Arg
35 40

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<400> 386

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Lys Gly Gly Thr
20 25 30

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<400> 387

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Lys Asn Gly Gly Thr
20 25 30

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<400> 388

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Leu Ala Val Lys Lys Tyr Leu Asn Ser Ile Lys Lys Gly Gly Thr
20 25 30

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<400> 389

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Lys Gly Gly Thr
 20 25 30

<210> 390
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<400> 390

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Leu Ala Val Lys Lys Tyr Leu Asn Asp Ile Lys Asn Gly Gly Thr
 20 25 30

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 <212> PRT
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<400> 391

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Gly Gly Thr
 20 25 30

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 <212> PRT
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<220>
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<400> 392

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Lys Lys Lys Arg Tyr
 20 25 30

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<223> Synthetic Construct

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Lys Lys
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<400> 394

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Lys Asn
20 25

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Lys
20 25

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<400> 396

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Glu Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Asn
20 25

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Asp Ile Leu Asn
20 25

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn
20 25

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Leu Lys
20 25

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<400> 400

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Lys
20 25

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<212> PRT
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<400> 401

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Lys Lys Arg Tyr
20 25 30

<210> 402
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<400> 402

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Lys Lys Arg
20 25 30

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<212> PRT
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<220>
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<400> 403

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Lys Lys
20 25

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<400> 404

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

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Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Arg Tyr
20 25 30

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<212> PRT
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<220>
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<400> 405

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Lys Lys Lys Arg Tyr
20 25 30

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<400> 406

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Lys Lys Lys Arg
20 25 30

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<400> 407

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Lys Lys Lys
20 25

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Arg Tyr
20 25 30

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<400> 409

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Lys
20 25

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Ile Ala Ala Lys Lys Tyr Leu Gln Thr Ile Lys Lys
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His Ser Asp Ala Val Phe Thr Glu Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Leu Lys Lys
20 25

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<400> 412

His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Leu Lys Gly Gly Thr
 20 25 30

<210> 413
 <211> 31
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Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Val Arg
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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Trp Arg
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1 5 10 15

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Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Asp
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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Glu
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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Phe
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys His
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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Ile
20 25 30

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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Lys
20 25 30

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Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Asn
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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Pro
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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Gln
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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Ser
20 25 30

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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Thr
20 25 30

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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Val
20 25 30

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Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Trp
20 25 30

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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Tyr
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Ser
20 25 30

Trp Cys Glu Pro Gly Trp Cys Arg
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His Ser Asp Ala Val Phe Thr Asp Asp Tyr Thr Arg Leu Arg Lys Glu
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Glu Ser Ile Lys Asp Lys Arg Tyr
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Arg Ile
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Gly Lys Lys Tyr Leu Asn Ser Ile Lys Asn Arg Ile
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Lys Lys Lys Tyr Leu Asn Ser Ile Lys Asn Arg Ile
20 25 30

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Met Ala Arg Lys Lys Tyr Leu Asn Ser Ile Lys Asn Arg Ile
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Met Ala Ser Lys Lys Tyr Leu Asn Ser Ile Lys Asn Arg Ile
20 25 30

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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Pro Asn Arg Ile
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Gly Lys Lys Tyr Leu Asn Ser Ile Pro Asn Arg Ile
20 25 30

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1 5 10 15

Met Ala Lys Lys Lys Tyr Leu Asn Ser Ile Pro Asn Arg Ile
20 25 30

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1 5 10 15

Met Ala Arg Lys Lys Tyr Leu Asn Ser Ile Pro Asn Arg Ile
20 25 30

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1 5 10 15

Met Ala Ser Lys Lys Tyr Leu Asn Ser Ile Pro Asn Arg Ile
20 25 30

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Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Gln Asn Arg Ile
20 25 30

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Met Ala Gly Lys Lys Tyr Leu Asn Ser Ile Gln Asn Arg Ile
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1 5 10 15

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Met Ala Ser Lys Lys Tyr Leu Asn Ser Ile Gln Asn Arg Ile
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Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Arg Asn Arg Ile
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Met Ala Gly Lys Lys Tyr Leu Asn Ser Ile Arg Asn Arg Ile
 20 25 30

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Met Ala Lys Lys Lys Tyr Leu Asn Ser Ile Arg Asn Arg Ile
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Met Ala Arg Lys Lys Tyr Leu Asn Ser Ile Arg Asn Arg Ile
 20 25 30

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Met Ala Ser Lys Lys Tyr Leu Asn Ser Ile Arg Asn Arg Ile
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Leu Ala Ala Lys Lys Tyr Leu Asn Asp Leu Lys Lys Gly Gly Thr
20 25 30

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Leu Ala Ala Lys Lys Tyr Leu Asn Asp Leu Lys Lys Gly Gly Thr
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Leu Ala Ala Lys Lys Tyr Leu Asn Asp Leu Lys Lys Gly Gly Thr
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Leu Ala Ala Lys Lys Tyr Leu Asn Asp Leu Lys Lys
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Lys Lys Gly Gly Thr
 20 25 30

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Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Lys Lys
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Met Ala Val Lys Lys Tyr Leu Asn Asp Leu Lys Lys Gly Gly Thr
20 25 30

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Met Ala Ala Lys Lys Tyr Leu Asn Asp Ile Lys Lys Gly Gly Thr
20 25 30

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Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Lys Lys Gly Gly
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Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Lys Lys Gly
20 25

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Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Lys Lys Gln
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1 5 10 15

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Leu Ala Ala Lys Lys Tyr Leu Asn Asp Ile Lys Lys Asn Gln
20 25 30

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Leu Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Asn
20 25

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Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Leu Asn
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Met Ala Cys Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Arg
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 1 5 10 15

Met Ala Asp Lys Lys Tyr Leu Asn Ser Ile Lys Asn Lys Arg
 20 25 30

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Cys Asn Lys Arg
 20 25 30

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Asn Ser Ile Lys Asn Cys Arg
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
20 25 30

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His Thr Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys
20 25

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1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
20 25 30

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1 5 10 15

Leu Ala Val Lys Lys Tyr Leu Gln Asp Ile Lys Gln Gly Gly Thr
20 25 30

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1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg
20 25 30

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Leu Ala Ala Lys Lys Tyr Leu Gln Thr Ile Lys Gln Lys Arg Tyr
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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Met Ala Ala Lys Lys Tyr Leu Gln Thr Ile Lys Gln Lys Arg Tyr
20 25 30

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1 5 10 15

Met Ala Ala His Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
20 25 30

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Met Ala Ala Lys His Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Gly Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Lys Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Arg Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ser Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg
20 25 30

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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Pro Gln Lys Arg
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Pro Gln Arg Ile
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
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His Thr Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
20 25 30

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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg
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Leu Ala Ala Lys Lys Tyr Leu Gln Thr Ile Lys Gln Lys Arg Tyr
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Met Ala Ala Lys Lys Tyr Leu Gln Thr Ile Lys Gln Lys Arg Tyr
20 25 30

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Met Ala Ala His Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
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Met Ala Ala Lys His Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr
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Met Ala Lys Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg
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Met Ala Arg Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg
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 1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Ile
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
 1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Lys
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Leu
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Met
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Pro
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Ser
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Met Ala Gly Lys Lys Tyr Leu Gln Ser Ile Lys Gln Arg Ile
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1 5 10 15

Met Ala Lys Lys Lys Tyr Leu Gln Ser Ile Lys Gln Arg Ile
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Ser Lys Lys Tyr Leu Gln Ser Ile Lys Gln Arg Ile
20 25 30

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1 5 10 15

Met Ala Ser Lys Lys Tyr Leu Gln Ser Ile Arg Gln Arg Ile
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1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
20 25 30

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His Thr Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys
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His Thr Glu Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
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Leu Ala Val Lys Lys Tyr Leu Gln Asp Ile Lys Asn Gly Gly Thr
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg
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Leu Ala Ala Lys Lys Tyr Leu Gln Thr Ile Lys Asn Lys Arg Tyr
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Met Ala Ala Lys Lys Tyr Leu Gln Thr Ile Lys Asn Lys Arg Tyr
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Met Ala Ala His Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr
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Met Ala Gly Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg
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Met Ala Lys Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg
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Met Ala Arg Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg
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Met Ala Ser Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg
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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Pro Asn Lys Arg
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Gln Asn Lys Arg
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Arg Arg
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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys His
 20 25 30

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 20 25 30

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20 25 30

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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Tyr
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Pro Asn Arg Ile
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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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20 25 30

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20 25 30

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1 5 10 15

Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr Cys
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr Cys
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr Cys
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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Cys
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20 25 30

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1 5 10 15

Met Ala Ala Lys His Tyr Leu Gln Ser Ile Lys Gln Lys Arg Tyr Cys
20 25 30

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Met Ala Gly Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Cys
20 25 30

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Met Ala Lys Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Cys
20 25 30

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Met Ala Arg Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Cys
 20 25 30

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 1 5 10 15

Met Ala Ser Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Arg Cys
 20 25 30

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 1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Pro Gln Lys Arg Cys
 20 25 30

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 1 5 10 15

Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Gln Gln Lys Arg Cys
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Arg Gln Lys Arg Cys
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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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 20 25 30

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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys His Cys
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Ile Cys
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Met Cys
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Pro Cys
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Gln Cys
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Thr Cys
20 25 30

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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Val Cys
20 25 30

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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Gln Lys Tyr Cys
20 25 30

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Met Ala Gly Lys Lys Tyr Leu Gln Ser Ile Lys Gln Arg Ile Cys
20 25 30

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20 25 30

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Met Ala Ser Lys Lys Tyr Leu Gln Ser Ile Lys Gln Arg Ile Cys
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Met Ala Ala Lys Lys Tyr Leu Gln Ser Ile Pro Gln Arg Ile Cys
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His Ser Asp Ala Val Phe Thr Asp Gln Tyr Thr Arg Leu Arg Lys Gln
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Val Ala Ala Lys Lys Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Cys
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35 40

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Leu Ala Leu Gln Lys Tyr Leu Gln Ser Ile Arg Asn Lys Arg Tyr Gly
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 20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Arg Gln
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Val Ala Ala Lys Arg Tyr Leu Gln Ser Ile Lys Asn Lys Arg Tyr Gly
20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
35 40

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Arg Gln
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20 25 30

Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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 20 25 30

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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 20 25 30

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His Ser Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
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20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Lys Arg Tyr Leu Gln Ser Ile Arg Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Ser

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Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Xaa Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
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Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Gly Gly Pro Ser
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Ser Gly Ala Pro Pro Pro Ser
35

<210> 738
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<212> PRT
<213> Artificial

<220>
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<223> C6 Acylation

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 <223> Tyr is methoxylated

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 <222> (12)..(12)
 <223> X= Ornithine

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 <223> X= Aib

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 <223> X= Ornithine

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 <223> X= K(CO(CH₂)₂SH) = epsilon-(3' - mercaptopropionyl)-lysine

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 <222> (29)..(29)
 <223> X= Ornithine

<220>
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 <222> (40)..(40)
 <223> Amidation

<400> 738

His Ser Asp Ala Val Phe Thr Glu Gln Tyr Thr Xaa Leu Arg Xaa Gln
 1 5 10 15

Val Ala Ala Xaa Xaa Tyr Leu Gln Ser Ile Xaa Xaa Xaa Gly Gly Pro
 20 25 30

Ser Ser Gly Ala Pro Pro Pro Ser
 35 40