(54) **METHOD OF TREATING MELANOCORTIN-4 RECEPTOR-ASSOCIATED DISORDERS IN HETEROZYGOUS CARRIERS**

VERFAHREN ZUR BEHANDLUNG VON MELANOCORTIN-4-REZEPTORASSOZIIERTEN ERKRANKUNGEN BEI HETEROZYGOTEN TRÄGERN

PROCÉDÉ DE TRAITEMENT DE TROUBLES ASSOCIÉS AU RÉCEPTEUR DE LA MÉLANOCORTINE-4 DANS DES PORTEURS HÉTÉROZYGOTES

EP 3 539 551 B1

Description

RELATED APPLICATION

[0001]   This application claims the benefit of U.S. Provisional Application No. 61/581,391, filed on December 29, 2011.

INCORPORATION BY REFERENCE OF MATERIAL IN ASCII TEXT FILE

[0002]   This application incorporates by reference the Sequence Listing contained in the following ASCII text file being submitted concurrently herewith:

a) File name: 46051001.txt; created December 26, 2012, 314 KB in size.

BACKGROUND OF THE INVENTION

[0003]   Melanocortin 4 receptor (MC4R) mutations can result in genetically derived cause of human obesity or metabolic syndrome. MC4R receptor is a heterotrimeric G-protein-coupled receptor, which transduces signals by activating adenylate cyclase. Expressed in hypothalamic nuclei and other neuronal and non-neuronal tissues, controlling feeding behavior and enegy homeostasis, MC4R integrates an agonist (anorexigenic) signal provided by the α-melanocyte stimulating hormone (α-MSH), and an antagonist (orexigenic) signal provided by the agouti-related peptide (AGPR).

[0004]   As shown in FIG. 1, MC4R is a part of the leptin-melanocortin pathway. Leptin is released from adipose tissue and binds to leptin receptors (LEPR) on AGPR- and pro-opiomelanocortin (POMC)-releasing neurons in the arcuate nucleus (ARC) of the hypothalamus. Leptin binding inhibits AGPR release and stimulates the release of POMC, which undergoes post-translational modification by the prohormone convertase PC1/3 to generate a range of peptides, including α-MSH. AGPR binding to MC4R suppresses MC4R activity, while α-MSH binding stimulates the MC4R. Suppressed receptor activity generates orexigenic signal, whereas stimulated receptor activity generates anorexigenic signal. Signals from MC4R modulate feeding behavior through secondary effector neurons.

[0005]   Humans affected by a monogenic MC4R-caused disorders, *e.g.*, obesity, are mostly heterozygous carriers of mutant human MC4R (hMC4R) gene with an autosomal dominant inheritance and penetrance and expressivity that varies with age and generational influences. The functional consequences of hMC4R mutations can be schematically divided into the following categories: nonfunctional receptor (*e.g.* due to missense or frameshift mutations), intracellular retention of the expressed receptor, altered basal activity of the receptor, and altered α-MSH stimulation of the receptor.

SUMMARY OF THE INVENTION

[0006]   The need exists for a method of treating disorders associated with MC4R mutations. It has now been discovered that certain individuals that carry an MC4R mutations can respond to pharmacological agents that activate MC4R-mediated signaling pathway. These individuals are heterozygous carriers of an MC4R mutation. Based on this discovery, it is now possible to treat MC4R-mediated disorders in a class of patients that was previously considered unresponsive to MC4R agonists.

[0007]   Accordingly, an example embodiment of the present invention is a method of treating a disorder in a subject in need thereof. The method comprises administering to said subject an effective amount of an agonist of the melanocortin-4 receptor (MC4R). The subject is a heterozygous carrier of an MC4R mutation, and the disorder results from an attenuated response of MC4R to α-melanocortin stimulating hormone (a-MSH).

[0008]   In a particular embodiment, the disorder is obesity (for example, obesity caused by an MC4R mutation, such as loss of function) and the subject is heterozygous with respect to the MC4R gene. In this embodiment, treatment of such a subject with a pharmacological agent that activates MC4R-mediated signaling pathway, such as described herein, may confer a number of unexpected advantages and benefits. For instance, most subjects heterozygous for MC4R may respond to treatment with sustained weight loss. A proportion of subjects may have MC4R functionality restored to wild type levels, resulting in body weight and body composition normalization. Additional benefits may include overcoming hyperinsulinemia, and improving glucose control and hyperphagia. A further benefit may be that weight loss is sustained throughout the treatment period as well as for prolonged periods of time on treatment cessation.

[0009]   Additional unexpected benefits of treating an MC4R-mediated obesity in an MC4R-heterozygous subject by a a pharmacological agent that activates MC4R-mediated signaling pathway, when compared to an obese subject that is wild-type with respect to MC4R, may include one or more of: an unexpectedly long ability to sustain a drug holiday, without gaining weight; a more profound improvement in insulin and glucose management; a longer lasting and sustained reduction in meal size and food intake; a more profound effect on reducing sleep apnea and increasing quality of sleep; an unexpected and more profound improvement effect on parameters of male or female sexual dysfunction; a more

profound reduction in the incidence of obesity-associated cancers; a more profoundly reduced incidence in obesity-associated inflammatory disease including rheumatoid arthritis and endothelial and micro-vascular dysfunction; a more profoundly reduced incidence of heart attack and stroke; more profound improvements in cardiovascular parameters including heart rate and blood pressure.

[0010]   There are additional benefits to treatment of an MC4R-mediated obesity in an MC4R-heterozygous subject (MC4R +/-) by a pharmacological agent that activates MC4R-mediated signaling pathway, when compared to an obese subject that is wild-type with respect to MC4R. MC4R +/- obese individuals are more at risk than wild type obese individuals of the consequences of obesity because of the intractability of their obesity, and the duration of the MC4R-mediated obesity, that often has a high rate of childhood onset. For example, MC4+/- obese individuals are resistant to weight management by diet/exercise regimens. (Reinhhr et. al, "Lifestyle Intervention in Obese Children With Variations in the Melanocortin 4 Receptor Gene," Obesity Journal, Vol. 17 No. 2, 2009). It is well-established, however, that higher childhood body-mass index (BMI) values elevate the risk of having a Coronary Heart Disease event in adulthood. (Baker et al., "Childhood Body-Mass Index and the Risk of Coronary Heart Disease in Adulthood," N. Engl. J. Med 2007; 357:2329-2337 (2007).) Treatment of this higher risk patient group may provide a treatment option not previously available (e.g., a treatment that achieves long term weight management).

BRIEF DESCRIPTION OF THE DRAWINGS

[0011]   The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.
[0012]   The foregoing will be apparent from the following more particular description of example embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating embodiments of the present invention.

FIG. 1 is a schematic diagram of the leptin-melanocortin pathway.
FIGS. 2A and 2B show Tables 1 and 2 which list examples of the MC4R mutations that cause obesity in humans.
FIG. 3 is a bar plot showing the effect of administration of a compound of SEQ ID NO: 140 to mice as described in Example 1.

DETAILED DESCRIPTION OF THE INVENTION

[0013]   A description of example embodiments of the invention follows.
[0014]   The present invention relates to a method of treating a disorder in a subject suffering from an attenuated response of MC4R to α-melanocortin stimulating hormone (a-MSH). The method comprises administering an effective amount of an agonist of the melanocortin-4 receptor (MC4R). In an example embodiment, the subject is a heterozygous carrier of an MC4R mutation resulting in the attenuated response of MC4R to α-melanocortin stimulating hormone (a-MSH). Because heterozygous carriers retain an ability to respond to the natural ligand of MC4R, treating MC4R-associated disorders in heterozygous carriers by administration of an MC4R agonist does not rely on the knowledge of the type of the MC4R mutation.
[0015]   In one example embodiment, the disorder is obesity, for example, MC4R-associated obesity. In another example embodiment, the disorder is metabolic syndrome.
[0016]   As used herein, the term "obese" refers to a subject having a body mass index (BMI) within the ranges defined as "obese" by the Center for Desease Control. *See,* URL http://www.cdc.gov/obesity/defining.html, last accessed on October 28, 2011. For example, an adult who has a BMI of 30 or higher is considered obese,
[0017]   As used herein, the term "metabolic syndrome" refers to a group of symptoms that occur together and increase the risk for coronary artery disease, stroke, and type 2 diabetes. According to the American Heart Association and the National Heart, Lung, and Blood Institute, metabolic syndrome also referred to as Syndrom X) is present if a subject has three or more of the following signs:

1) Blood pressure equal to or higher than 130/85 mmHg;
2) Fasting blood sugar (glucose) equal to or higher than 100 mg/dL;
3) Large waist circumference (length around the waist):

- Men - 40 inches or more;
- Women - 35 inches or more;

4) Low HDL cholesterol:

- Men - under 40 mg/dL;
- Women - under 50 mg/dL;

5) Triglycerides equal to or higher than 150 mg/dL.

Metabolic syndrome can be diagnosed by testing subject's blood pressure, blood glucose level, HDL cholesterol level, LDL cholesterol level, total cholesterol level, and triglyceride level.

[0018] As used herein, the phrase "attenuated response" refers to reduction, but not complete abrogation, of a signaling activity of a receptor in response to its cognate naturally occurring or synthetic ligand.

[0019] As used herein, the term "agonist" refers to any chemical compound, either naturally occurring or synthetic, that, upon interacting with (*e.g.*, binding to) its target, here, MC4R, raises the signaling activity of MC4R above its basal level. An agonist can be a superagonist (*i.e.* a compound that is capable of producing a greater maximal response than the endogenous agonist for the target receptor, and thus has an efficacy of more than 100%), a full agonist (*i.e.* a compound that elicits a maximal response following receptor occupation and activation) or a partial agonist (*i.e.* a compounds that can activate receptors but are unable to elicit the maximal response of the receptor system).

[0020] Examples of naturally occurring MC4R agonists include α-MSH, β-MSH, γ-MSH and adenocorticitropic hormone (ACTH) or a functional fragment thereof. Examples of synthetic MC4R agonists will be described in detail below.

[0021] As used herein, an "effective amount" is a therapeutically or prophylactically sufficient amount of the MC4R agonist to treat the target disorder. Examples of effective amounts typically range from about from 0.005 mg/ kg of body weight to 500 mg/kg of body weight. In other examples, effective amounts range from about from 0.01 mg/ kg of body weight to 50 mg/kg of body weight, or from 0.01 mg/kg of body weight to 20 mg/kg of body weight.

[0022] As used herein "treating" includes achieving, partially or substantially, one or more of the following results: partially or totally reducing the body weight (as measured, for example, by a body mass index, BMI); ameliorating or improving a clinical symptom or indicators associated with obesity, such as type-II diabetes, pre-diabetic condition, blood level of haemoglobin A1C (HblAc) above 6%, hyperinsulimenia, hyperlipidemia, insulin insensitivity, glucose intolerance etc; delaying, inhibiting or preventing the progression of obesity and obesity related indication; or partially or totally delaying, inhibiting or preventing the onset or development of obesity or obesity related indication. Delaying, inhibiting or preventing the progression of the obesity includes for example, delaying, inhibiting or preventing the progression of a subject having normal weight to obesity.

[0023] The term "treating" further includes partially or totally reducing the risk for coronary artery disease, stroke, and type 2 diabetes associated with the metabolic syndrome as well as ameliorating or improving a clinical symptom or signs of metabolic syndrome associated with metabolic syndrome, such as any one or more of the five indicators listed above. For example, the term "treating" includes delaying, inhibiting or preventing the progression of parameters associated with the metabolic syndrome, including insulin resistance, glucose clearance and parameters of cardiovascular disease including heart rate and blood pressure.

[0024] "Prophylactic treatment" refers to treatment before onset of obesity to prevent, inhibit or reduce its occurrence.

[0025] As used herein, the term "subject" refers to a mammal, preferably a human, but can also mean an animal in need of veterinary treatment, 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).

[0026] hMC4R is a well-characterized protein encoded by a genomic sequence having GenBank accession number CH471077.

[0027] Mutations in the MC4R receptor are an associated cause of severe childhood obesity. The carrier prevalence for MC4R mutations in a juvenile-onset obese population has been noted to be around 2.5% with a highest prevalence of 6% among severe obese children. Humans with MC4R mutations show a more or less similar phenotype as has been described for mice with mutations in the MC4 receptor gene. Those people show clear hyperphagia, hyperinsulinaemia, increased fat mass, accompanied by lean body mass, bone mineral density and linear growth rate, with no changes in cortisol levels, gonadotropin, thyroid and sex steroid levels. In contrast to MC4 receptor deletion, hyperphagia and hyperinsulinaemia tends to subside with age in human subjects. Similar to the MC4R knockout mice, the phenotype in heterozygote carriers is intermediate in comparison to homozygote carriers. The exhibited hyperphagia observed upon a test meal is less severe than that observed in people with a leptin deficiency. The severity of MC4 receptor dysfunction seen in assays in vitro can predict the amount of food ingested at a test meal by the subject harboring that particular mutation and correlates with the onset and severity of the obese phenotype. At east 90 different MC4 receptor mutations have been associated with obesity and additional mutations in the MC4 receptor are likely to be discovered, leading to a similar obesity phenotype.

[0028] Examples of the MC4R mutations that cause obesity in humans are shown in FIGS. 2A and 2B as Table 1 and Table 2 (adopted from Farooqi et al., The Journal of Clinical Investigation, July 2000, vol. 106 (2), pp. 271-279 and Vaisse et al., The Journal of Clinical Investigation, July 2000, vol. 106(2), pp. 253-262).

[0029] Additional mutations that potentially casue obesity in humans include , R18H, R18L, S36Y, P48S, V50M, F51L,

E61K, I69T, D90N, S94R, G98R, I121T, A154D, Y157S, W174C, G181D, F202L, A219 V, I226T, G231S, G238D, N240S, C271R, S295P, P299L, E308K, I317V, L325F, and 750DelGA, as described in Xiang et al., "Pharmacological characterization of 30 human melanocortin-4 receptor polymorphisms with the endogenous proopiomelanocortin-derived agonists, synthetic agonists, and the endogenous agouti-related protein antagonist." Biochemistry, 2010 Jun 8; 49(22):4583-600.

[0030] Further examples of mutations that potentially cause obesity in humans are those listed in Online Mendelian Inheritance in Man (OMIM), a database of human genes and genetic disorders, under the accession number 155541 (MC4R) (more precisely, accession nos. 155541.0001-155541.0023) at the URL http://omim.org/entry/155541. Representative examples include 4-BP DEL, NT631; 4-BP INS, NT732; TYR35TER; ASP37VAL; SER58CYS; ILE102SER; ASN274SER; 1-BP INS, 112A; 4-BP DEL, 211CTCT; ILE125LYS; ALA175THR; ILE316SER; TYR287TER; ASN97ASP; 15-BP DEL (delta88-92 codons); and SER127LEU.
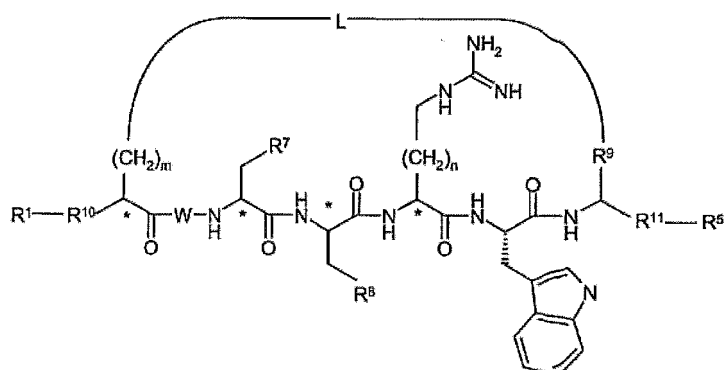
[0031] In example embodiments, the MC4R mutation results in retention of the MC4R signaling activity.

[0032] Mutations in the genomic sequence encoding MC4R can be detected by the methods that are well known to a person of ordinary skill in the art. For example, the genomic sequence can be cloned using nucleotide primers, such as *e.g.*, the primers described in Farooqi et al., The Journal of Clinical Investigation, July 2000, vol. 106 (2), pp. 271-279 and Vaisse et al., The Journal of Clinical Investigation, July 2000, vol. 106(2), pp. 253-262, and the cloned sequence analyzed using commercially available sequencers and software.

[0033] Activity of MC4R can be measured by the methods well known to a person of ordinary skill in the art. For example, cells can be transiently transfected with the cloned MC4R DNA, the transfected cells contacted by an agonist of MC4R (*e.g.* α-MSH), and the intracellular level of cAMP, the secondary messenger of MC4R, measured by an electrochemiluminescence assay described, *e.g.,* in Roubert et al., Journal of Endocrinology (2010) 207, pp. 177-183. A reduction in MC4R signaling can be ascertained by comparing the intracellular level of cAMP produced in response to a given agonist by a wild type MC4R to that produced by a mutant MC4R.

[0034] In an example embodiment, an agonist employed by the methods of the present invention can be any known agonist of MC4R. In some example embodiment, the MC4R agonist is not an adrenocorticotropic hormone (ACTH) or a fragment thereof.

[0035] In an example embodiment, an MC4R agonist is any of the peptides disclosed in International Application published as WO/2005/000339. Specifically, examples include peptides of the following structural formula:

,

wherein

W is Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, Phe, Lys, Leu, Cya, or is absent; R^1 is -H, -C(O)CH$_3$, -C(O)(CH$_2$)$_{1-4}$CH$_3$, -C(O)(CH$_2$)$_{1-4}$NHC(NH)NH$_2$, Tyr-βArg-, Ac-Tyr-β-hArg-, gluconoyl-Tyr-Arg-, Ac-diaminobutyryl-, Ac-diaminopropionyl-, N-propionyl-, N-butyryl-, N-valeryl-, N-methyl-Tyr-Arg-, N-glutaryl-Tyr-Arg-, N-succinyl-Tyr-Arg-, R^6-SO$_2$NHC(O)CH$_2$CH$_2$C(O)-, R^6-SO$_2$NHC(O)CH$_2$CH$_2$C(O)Arg-, R^6-SO$_2$NHCH$_2$CH$_2$CH$_2$C(O)-, C$_3$-C$_7$ cycloalkylcarbonyl, pheylsulfonyl, C$_8$-C$_{14}$ bicyclic arylsulfonyl, phenyl-(CH$_2$)$_q$C(O)-, C$_8$-C$_{14}$ bicyclic aryl-(CH$_2$)$_q$C(O)-,

or

wherein

R^2 is -H, -NH$_2$, -NHC(O)CH$_3$, -NHC(O)(CH$_2$)$_{1-4}$CH$_3$, -NH-TyrC(O)CH$_3$, R^6SO$_2$NH-, Ac-Cya-NH-, Tyr-NH-, HO-(C$_6$H$_5$)-CH$_2$CH$_2$C(O)NH-, or CH$_3$-(C$_6$H$_5$)-C(O)CH$_2$CH$_2$C(O)NH-;

R^3 is C$_1$-C$_4$ straight or branched alkyl, NH$_2$-CH$_2$-(CH$_2$)$_q$-, HO-CH$_2$-, (CH$_3$)$_2$CHNH(CH$_2$)$_4$-, R^6(CH$_2$)$_q$-, R^6SO$_2$NH-, Ser, Ile,

q is 0, 1, 2, or 3;

R^6 is a phenyl or C$_8$-C$_{14}$ bicyclic aryl;

m is 1 or 2;

n is 1, 2, 3, or 4;

R^9 is (CH$_2$)$_p$ or (CH$_3$)$_2$C-;

p is 1 or 2;

R_{10} is NH- or is absent;

R^7 is a 5- or 6-membered heteroaryl or a 5- or 6-membered heteroaryl ring optionally substituted with R^4;

R^4 is H, C$_1$-C$_4$ straight or branched alkyl, phenyl, benzyl, or (C$_6$H$_5$)-CH$_2$-O-CH$_2$-;

R^8 is phenyl, a phenyl ring optionally substituted with X, or cyclohexyl;

X is H, Cl, F, Br, methyl, or methoxy;

R^{11} is -C(O) or -CH$_2$;

R^5 is -NH$_2$, -OH, glycinol, NH$_2$-Pro-Ser-, NH$_2$-Pro-Lys-, HO-Ser-, HO-Pro-Ser-, HO-Lys-, Ser alcohol, -Ser-Pro alcohol, -Lys-Pro alcohol, HOCH$_2$CH$_2$-O-CH$_2$CH$_2$NH-, NH$_2$-Phe-Arg-, NH$_2$-Glu-, NH$_2$CH$_2$RCH$_2$NH-, RHN-, RO- where R is a C$_1$-C$_4$ straight or branched alkyl; and

L is -S-S- or -S-CH$_2$-S-.

[0036] Other examples of MC4R agonists include peptides of the following structural formula:

wherein:

W is a single bond, Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, or Phe;
R^1 is -H, -C(O)CH$_3$, -C(O)(CH$_2$)$_{1-4}$CH$_3$, -C(O)(CH$_2$)$_{1-4}$-NHC(NH)NH$_2$, Tyr-βArg, gluconoyl-Tyr-Arg, Ac-Dab, Ac-Dap, N-succinyl-Tyr-Arg, N-propionyl, N-valeryl, N-glutaryl-Tyr-Arg, N-butyryl,

or

wherein
R^2 is -H, -NH$_2$, -NHC(O)CH$_3$, -NHC(O)(CH$_2$)$_{1-4}$CH$_3$, or -NH-TyrC(O)CH$_3$;
R^3 is C$_1$-C$_4$ straight or branched alkyl, Ser, Ile,

q is 0, 1, 2, or 3;

m is 1 or 2;

p is 1 or 2;

R^4 is H or C_1-C_4 straight or branched alkyl;

X is H, Cl, F, Br, methyl, or methoxy; and

R^5 is -NH_2, -OH, glycinol, -Ser-Pro-NH2, -Lys-Pro-NH$_2$, -Ser-OH, -Ser-Pro-OH, -Lys-Pro-OH -Arg-Phe-NH$_2$, -Glu-NH$_2$, -NHR, or -OR, where R is a C_1-C_4 straight or branched alkyl.

[0037] In yet another example embodiment, the MC4R agonist can be represented by the following structural formula:
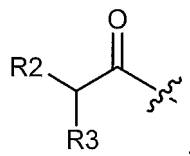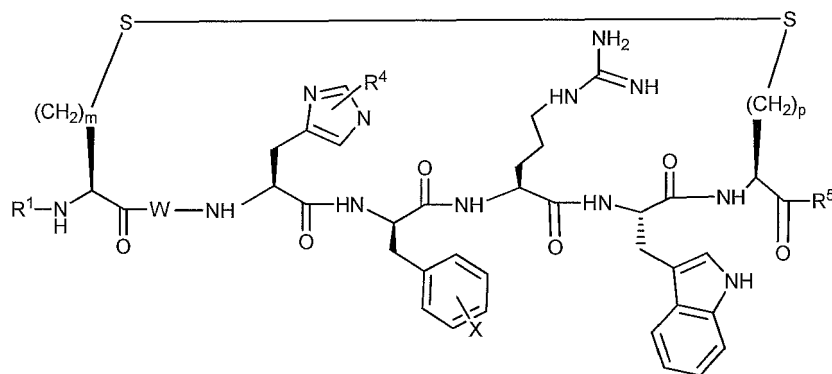

wherein

W is Glu, Gln, Asp, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, Phe, Lys, Leu, Cya, or is absent;

R^1 is -H, -C(O)CH$_3$, -C(O)(CH$_2$)$_{1-4}$CH$_3$, -C(O)(CH$_2$)$_{1-4}$NHC(NH)NH$_2$, Tyr-βArg-, Ac-Tyr-β-hArg-, gluconoyl-Tyr-Arg-, Ac-diaminobutyryl-, Ac-diaminopropionyl-, N-propionyl-, N-butyryl-, N-valeryl-, N-methyl-Tyr-Arg-, N-glutaryl-Tyr-Arg-, N-succinyl-Tyr-Arg-, R^6-SO$_2$NHC(O)CH$_2$CH$_2$C(O)-, R^6-SO$_2$NHC(O)CH$_2$CH$_2$C(O)Arg-, R^6-SO$_2$NHCH$_2$CH$_2$CH$_2$C(O)-, C_3-C_7 cycloalkylcarbonyl, phenylsulfonyl, C_8-C_{14} bicyclic arylsulfonyl, phenyl-(CH$_2$)$_q$C(O)-, C_8-C_{14} bicyclic aryl-(CH$_2$)$_q$C(O)-,

or

wherein

R^2 is -H, -NH$_2$, -NHC(O)CH$_3$, -NHC(O)(CH$_2$)$_{1-4}$CH$_3$, -NH-TyrC(O)CH$_3$, R^6SO$_2$NH-, Ac-Cya-NH-, Tyr-NH-, HO-(C$_6$H$_5$)-CH$_2$CH$_2$C(O)NH-, or CH$_3$-(C$_6$H$_5$)-C(O)CH$_2$CH$_2$C(O)NH-;

R^3 is C_1-C_4 straight or branched alkyl, NH_2-CH_2-$(CH_2)_q$-, HO-CH_2-, $(CH_3)_2CHNH(CH_2)_4$-, $R^6(CH_2)_q$-, R^6SO_2NH-, Ser, Ile,

q is 0, 1, 2, or 3;
R^6 is a phenyl or C_8-C_{14} bicyclic aryl;
m is 1 or 2;
p is 1 or 2;
R^4 is H, C_1-C_4 straight or branched alkyl, phenyl, benzyl, or (C_6H_5)-CH_2-O-CH_2-;
X is H, Cl, F, Br, methyl, or methoxy; and
R^5 is -NH_2, -OH, glycinol, NH_2-Pro-Ser-, NH_2-Pro-Lys-, HO-Ser-, HO-Pro-Ser-, HO-Lys-, -Ser alcohol, -Ser-Pro alcohol, -Lys-Pro alcohol, $HOCH_2CH_2$-O-CH_2CH_2NH-, NH_2-Phe-Arg-, NH_2-Glu-, $NH_2CH_2RCH_2NH$-, or RO- where R is a C_1-C_4 straight or branched alkyl.

[0038]   Additional examples of MC4R agonists useful to practice the present invention are found in WO2011104378; WO2011104379; WO201060901; WO200887189, WO200887188, WO200887187, WO200887186; US20110065652; WO2010144341; WO2010144344; WO201065799; WO201065800; WO201065801; WO201065802; WO201037081; WO2009152079;   WO2009151383;   US20100311648;   US20100280079;   WO201081666;   WO201034500; WO200910299; WO2008116665; WO201052256; WO201052255; WO201126015; US20100120783; WO201096854; US20100190793;

[0039]   WO201025142; and WO201015972. Further examples of MC4R agonists useful to practice the present invention are found in U.S. Pat. No. 8,263,608; U.S. Pat. No. 8,247,530; U.S. Pat. No. 8,114,844; and U.S. Pat. No. 7,968,548.

[0040]   In one example embodiment, the agonist of MC4R is a tripeptide D-Phe-Arg-Trp (SEQ ID NO: 560) or a pharmaceutical salt thereof. In another example, the agonist is any peptide that includes SEQ ID NO: 560 or a pharmaceutical salt thereof. In yet another example, the MC4R agonist is an acetylated tripeptide Ac-D-Phe-Arg-Trp-NH_2 (SEQ ID NO: 561) or a pharmaceutical salt thereof.

[0041]   In an example embodiment, the agonists of MC4R are those of Formula (I) or a pharmaceutically acceptable salt, hydrate, solvate or a prodrug thereof (see International Patent Application Publication Number WO 2007/008704):
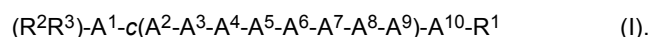
$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1 \qquad (I).$$

In Formula (I):

A^1 is Acc, HN-$(CH_2)_m$-C(O), L- or D-amino acid, or deleted;
A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;
A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;
A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or $(X^1, X^2, X^3, X^4, X^5)$Phe;
A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-$(X^1, X^2, X^3, X^4, X^5)$Phe, L-Phe or D-(Et)Tyr;
A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N($R^4 R^5$))-C(O);
A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;
A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;
A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;
A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;
R^1 is OH or NH_2;
each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, $(C_1$-$C_{30})$alkyl, $(C_1$-$C_{30})$heteroalkyl, $(C_1$-$C_{30})$acyl, $(C_2$-$C_{30})$alkenyl, $(C_2$-$C_{30})$alkynyl, aryl$(C_1$-$C_{30})$alkyl, aryl$(C_1$-$C_{30})$acyl, substituted $(C_1$-$C_{30})$alkyl, substituted $(C_1$-$C_{30})$heteroalkyl, substituted $(C_1$-$C_{30})$acyl, substituted $(C_2$-$C_{30})$alkenyl, substituted $(C_2$-$C_{30})$alkynyl, substituted aryl$(C_1$-$C_{30})$alkyl, and substituted aryl$(C_1$-$C_{30})$acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH$_2$;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X', X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH$_2$, NO$_2$, or CN.

[0042]   In exemplary embodiments of the agonists of Formula (I):

(I) when R^4 is (C_1-C_{40})acyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})acyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkyl-sulfonyl, or -C(NH)-NH$_2$, then R^5 is H or (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, or substituted aryl(C_1-C_{40})alkyl;

(II) when R^2 is (C_1-C_{30})acyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})acyl, or substituted aryl(C_1-C_{30})acyl, then R^3 is H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, or substituted aryl(C_1-C_{30})alkyl;

(III) either A^3 or A^8 or both must be present in said compound;

(IV) when A^2 is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen, then A^9 is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen;

(V) when A^2 is Asp or Glu, then A^9 is Dab, Dap, Orn, or Lys;

(VI) when A^8 is Ala or Gly, then A^1 is not Nle; and

(VII) when A^1 is deleted, then R^2 and R^3 cannot both be H.

[0043]   In an example embodiment, the agonists employed by the methods described herein are the compounds of Formula I, wherein:

A^1 is A6c, Arg, D-Arg, Cha, D-Cha, hCha, Chg, D-Chg, Gaba, Ile, Leu, hLeu, Met, β-hMet, 2-Nal, D-2-Nal, Nip, Nle, Oic, Phe, D-Phe, hPhe, hPro, Val, or deleted;

A^2 is Asp, Cys, D-Cys, hCys, D-hCys, Glu, Pen, or D-Pen;

A^3 is D-Abu, Aib, Ala, β-Ala, D-Ala, D-Cha, Gaba, D-Glu, Gly, D-Ile, D-Leu, D-Tle, D-Val, or deleted;

A^4 is H is or 3-Pal;

A^5 is D-Bal, D-1-Nal, D-2-Nal, D-Phe, D-Trp, or D-(Et)Tyr;

A^6 is Arg, or hArg;

A^7 is Bal, Bip, 1-Nal, 2-Nal, Trp, D-Trp;

A^8 is A6c, D-Ala, Aha, Ahx, Ala, β-Ala, Apn, Gaba, Gly or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Lys, Pen, or D-Pen;

A^{10} is Thr, or deleted,

wherein at least one of A^3 or A^8 is deleted, but not both, or pharmaceutically acceptable salts thereof.

[0044]   In an example embodiments, agonists of Formula (I) useful in practicing the invention described herein are compounds of the following formula or a pharmaceutically acceptable salt thereof:

SEQ ID NO: 1 Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH$_2$;

SEQ ID NO: 2 Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)- NH$_2$;

SEQ ID NO: 3 Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)- NH$_2$;

SEQ ID NO: 4 D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr- NH$_2$;

SEQ ID NO: 5 D-Phe-c(Cys-His-D-Phe-Arg- Trp-p-Ala-D-Cys)- Thr-NH$_2$;

SEQ ID NO: 6 D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH$_2$;

SEQ ID NO: 7 Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH$_2$;

SEQ ID NO: 8 Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH$_2$;

SEQ ID NO: 9 Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH$_2$;

SEQ ID NO: 10 Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH$_2$;

SEQ ID NO: 11 Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH$_2$;

SEQ ID NO: 12 Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH$_2$;
SEQ ID NO: 13 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 14 Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 15 Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 16 Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 17 Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 18 Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 19 Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 20 Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 21 Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 22 Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 23 Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 24 Ac-Nle-c(Cys-D-Ala- His-D-Phe-Arg-Trp- D-Cys)-NH$_2$;
SEQ ID NO: 25 Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH$_2$;
SEQ ID NO: 26 Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH$_2$;
SEQ ID NO: 27 Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH$_2$;
SEQ ID NO: 28 Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH$_2$;
SEQ ID NO: 29 Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH$_2$;
SEQ ID NO: 30 Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)- NH$_2$;
SEQ ID NO: 31 Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)- NH$_2$; SEQ ID NO: 32 Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH$_2$;
SEQ ID NO: 33 Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH$_2$;
SEQ ID NO: 34 Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH$_2$;
SEQ ID NO: 35 Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 36 Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 37 Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 38 Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 39 Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO:40 Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$; SEQ ID NO: 41 Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH$_2$;
SEQ ID NO: 42 Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 43 Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH$_2$;
SEQ ID NO: 44 Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH$_2$;
SEQ ID NO: 45 n-butanoyl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 46 n-butyryl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 47 Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 48 Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 49 Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 50 Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)- NH$_2$;
SEQ ID NO: 51 Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)- NH$_2$;
SEQ ID NO: 52 Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)- NH$_2$;
SEQ ID NO: 53 Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)- NH$_2$;
SEQ ID NO: 54 Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)- NH$_2$;
SEQ ID NO: 55 Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)- NH$_2$;
SEQ ID NO: 56 Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-p-Ala-Lys)- NH$_2$;
SEQ ID NO: 57 Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 58 Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)- NH$_2$;
SEQ ID NO: 59 Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)- NH$_2$;
SEQ ID NO: 60 Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)- NH$_2$;
SEQ ID NO: 61 Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 62 Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)- NH$_2$;
SEQ ID NO: 63 Ac-Nle-c(Cys-His-D-Phe-Arg-D-Tip-β-Ala-Cys)-NH$_2$;
SEQ ID NO: 64 Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH$_2$;
SEQ ID NO: 65 Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 66 Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)- NH$_2$;
SEQ ID NO: 67 Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH$_2$;
SEQ ID NO: 68 n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)- NH$_2$;
SEQ ID NO: 69 n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)- NH$_2$;

SEQ ID NO: 70 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)- NH$_2$;
SEQ ID NO: 71 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)- NH$_2$;
SEQ ID NO: 72 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH$_2$;
SEQ ID NO: 73 Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 74 Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)- NH$_2$;
SEQ ID NO: 75 Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)- NH$_2$;
SEQ ID NO: 76 Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 77 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)- NH$_2$;
SEQ ID NO: 78 Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)- NH$_2$;
SEQ ID NO: 79 D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr- NH$_2$;
SEQ ID NO: 80 D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH$_2$;
SEQ ID NO: 81 D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr- NH$_2$;
SEQ ID NO: 82 D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr- NH$_2$;
SEQ ID NO: 83 D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr- NH$_2$;
SEQ ID NO: 84 D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr- NH$_2$;
SEQ ID NO: 85 Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)- NH$_2$;
SEQ ID NO: 86 Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)- NH$_2$;
SEQ ID NO: 87 Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH$_2$;
SEQ ID NO: 88 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;
SEQ ID NO: 89 Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 90 Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 91 Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
SEQ ID NO: 92 Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 93 Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 94 Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 95 Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)- NH$_2$;
SEQ ID NO: 96 Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)- NH$_2$;
SEQ ID NO: 97 Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)- NH$_2$;
SEQ ID NO: 98 Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 99 Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 100 Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)- NH$_2$;
SEQ ID NO: 101 Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 102 Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 103 Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 104 Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 105 Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 106 Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 107 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;
SEQ ID NO: 108 Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH$_2$;
SEQ ID NO: 109 Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH$_2$;
SEQ ID NO: 110 Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-P-Ala-Lys)- NH$_2$;
SEQ ID NO: 111 Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)- NH$_2$;
SEQ ID NO: 112 Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)- NH$_2$;
SEQ ID NO: 113 Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 114 Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)- NH$_2$;
SEQ ID NO: 115 Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-OH;
SEQ ID NO: 116 Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-OH;
SEQ ID NO: 117 D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-OH;
SEQ ID NO: 118 D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-OH;
SEQ ID NO: 119 D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-OH;
SEQ ID NO: 120 Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-OH;
SEQ ID NO: 121 Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-OH;
SEQ ID NO: 122 Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
SEQ ID NO: 123 Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
SEQ ID NO: 124 Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
SEQ ID NO: 125 Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
SEQ ID NO: 126 Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
SEQ ID NO: 127 Ac-D-Chg-c(Asp-His-D-Phe-Arg-Tip-Gaba-Lys)-OH;

SEQ ID NO: 128 Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
SEQ ID NO: 129 Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-OH;
SEQ ID NO: 130 Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-OH;
SEQ ID NO: 131 Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-OH;
SEQ ID NO: 132 Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-OH;
SEQ ID NO: 133 Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-OH;
SEQ ID NO: 134 Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-OH;
SEQ ID NO: 135 Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-OH;
SEQ ID NO: 136 Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-OH;
SEQ ID NO: 137 Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;
SEQ ID NO: 138 Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH;
SEQ ID NO: 139 Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 140 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 141 Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)- NH$_2$;
SEQ ID NO: 142 Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)- NH$_2$;
SEQ ID NO: 143 Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH$_2$;
SEQ ID NO: 144 Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)- NH$_2$;
SEQ ID NO: 145 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)- NH$_2$;
SEQ ID NO: 146 Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)- NH$_2$;
or
SEQ ID NO: 147 Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)- NH$_2$;

or pharmaceutically acceptable salts thereof.

[0045] In an example embodiment, an agonist of MC4R receptor useful for practicing methods described herein is any of the compounds described by Formula (II) or a pharmaceutically acceptable salt, hydrate, solvate or a prodrug thereof (see International Patent Application Publication Number WO 2007/008704):

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}NH_2 \qquad (II)$$
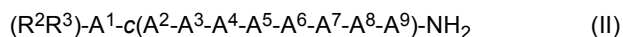
[0046] In formula (II):

A^1 is Nle or deleted;
A^2 is Cys or Asp;
A^3 is Glu or D-Ala;
A^4 is H is;
A^5 is D-Phe;
A^6 is Arg;
A^7 is Trp, 2-Nal or Bal;
A^8 is Gly, Ala, D-Ala, (3-Ala, Gaba or Apn;
A^9 is Cys or Lys;
each of R^2 and R^3 is independently selected from the group consisting of H or $(C_1\text{-}C_6)$acyl.

[0047] In exemplary embodiments of Formula (II):

(I) when R^2 is $(C_1\text{-}C_6)$acyl, then R^3 is H; and
(II) when A^2 is Cys, then A^9 is Cys.

[0048] In alternative example embodiments of the present invention, the compounds useful for practicing the methods disclosed herein are:

SEQ ID NO: 148 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)- NH$_2$;
SEQ ID NO: 149 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH$_2$;
SEQ ID NO: 150 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH$_2$;
SEQ ID NO: 151 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)- NH$_2$;
SEQ ID NO: 152 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)- NH$_2$;
SEQ ID NO: 153 Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)- NH$_2$;
SEQ ID NO: 154 Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH$_2$;
SEQ ID NO: 155 Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)- NH$_2$;

SEQ ID NO: 156 Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)- NH$_2$;
SEQ ID NO: 157 Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)- NH$_2$;
or
SEQ ID NO: 158 Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH$_2$;

or a pharmaceutically acceptable salt thereof.

[0049] In an exemplary embodiment, the agonists of MC4R useful for practicing the methods described herein is any of the compounds of Formula (III), or a pharmaceutically acceptable salt, hydrate, solvate or a prodrug thereof (see International Application Publication Number WO 2007/008684):

$$(R^2R^3)\text{-}B^1\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}A^{11}\text{-}A^{12}\text{-}A^{13}\text{-}A^{13}\text{-}B^2\text{-}B^3\text{-}R^1 \qquad (III).$$
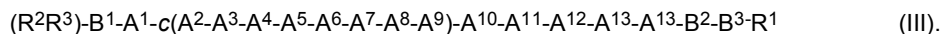
[0050] In Formula (III):

B^1 is a peptide moiety which contains 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids, wherein at least 5 amino acids are independently selected from the group consisting of L-Arg, D-Arg, L-hArg and D-hArg, or B^1 is optionally deleted;
A^1 is Acc, HN-(CH$_2$)$_m$-C(O), L- or D-amino acid or deleted;
A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp or Glu;
A^3 is Gly, Glu, Ala, β-Ala, Gaba, Aib, D-amino acid or deleted;
A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi or (X', X^2, X^3, X^4, X^5) Phe;
A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, D-(Et)Tyr, D-Dip, D-Bip or D-Bpa;
A^6 is Arg, hArg, Dab, Dap, Lys, Orn or HN-CH((CH$_2$)$_n$-N(R^{4}R^5))-C(O);
A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, Dip, Bpa, D-Trp, D-1-Nal, D-2-Nal, D-Bal, D-Bip, D-Dip or D-Bpa;
A^8 is Gly, D-Ala, Acc, Ala, β-Ala, Gaba, Apn, Ahx, Aha, HN-(CH$_2$)$_s$-C(O) or deleted;
A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn or Lys;
A^{10} is Acc, HN-(CH$_2$)$_t$-C(O), Pro, hPro, 3-Hyp, 4-Hyp, Thr, an L- or D-amino acid or deleted;
A^{11} is Pro, hPro, 3-Hyp, 4-Hyp or deleted;
A^{12} is Lys, Dab, Dap, Arg, hArg or deleted;
A^{13} is Asp, Glu or deleted;
B^2 is a peptide moiety containing 1, 2, 3, 4, or 5 amino acids or deleted,
B^3 is a peptide moiety which contains 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids wherein at least 5 amino acids are independently selected from the group consisting of L-Arg, D-Arg, L-hArg and D-hArg, or is deleted;
R^1 is OH or NH$_2$;
R^2 and R^3 each is, independently for each occurrence, selected from the group consisting of H, (C$_1$-C$_{30}$)alkyl, (C$_1$-C$_{30}$)heteroalkyl, (C$_1$-C$_{30}$)acyl, (C$_2$-C$_{30}$)alkenyl, (C$_2$-C$_{30}$)alkynyl, aryl(C$_1$-C$_{30}$)alkyl, aryl(C$_1$-C$_{30}$)acyl, substituted (C$_1$-C$_{30}$)alkyl, substituted (C$_1$-C$_{30}$)heteroalkyl, substituted (C$_1$-C$_{30}$)acyl, substituted (C$_2$-C$_{30}$)alkenyl, substituted (C$_2$-C$_{30}$)alkynyl, substituted aryl(C$_1$-C$_{30}$)alkyl and substituted aryl(C$_1$-C$_{30}$)acyl;
R^4 and R^5 each is, independently for each occurrence, H, (C$_1$-C$_{40}$)alkyl, (C$_1$-C$_{40}$)heteroalkyl, (C$_1$-C$_{40}$)acyl, (C$_2$-C$_{40}$)alkenyl, (C$_2$-C$_{40}$)alkynyl, aryl(C$_1$-C$_{40}$)alkyl, aryl(C$_1$-C$_{40}$)acyl, substituted (C$_1$-C$_{40}$)alkyl, substituted (C$_1$-C$_{40}$)heteroalkyl, substituted (C$_1$-C$_{40}$)acyl, substituted (C$_2$-C$_{40}$)alkenyl, substituted (C$_2$-C$_{40}$)alkynyl, substituted aryl(C$_1$-C$_{40}$)alkyl, substituted aryl(C$_1$-C$_{40}$)acyl, (C$_1$-C$_{40}$)alkylsulfonyl or C(NH)-NH$_2$;
n is, independently for each occurrence, 1, 2, 3, 4 or 5;
m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;
s is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;
t is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;
X^1, X^2, X^3, X^4 and X^5 each is, independently for each occurrence, H, F, Cl, Br, I, (C$_{1-10}$)alkyl, substituted (C$_{1-10}$)alkyl, (C$_{2-10}$)alkenyl, substituted (C$_{2-10}$)alkenyl, (C$_{2-10}$)alkynyl, substituted (C$_{2-10}$)alkynyl, aryl, substituted aryl, OH, NH$_2$, NO$_2$ or CN.

[0051] In an example embodiments of Formula (III):

(I) when R^4 is (C$_1$-C$_{40}$)acyl, aryl(C$_1$-C$_{40}$)acyl, substituted (C$_1$-C$_{40}$)acyl, substituted aryl(C$_1$-C$_{40}$)acyl, (C$_1$-C$_{40}$)alkyl-sulfonyl or C(NH)-NH$_2$, then R^5 is H, (C$_1$-C$_{40}$)alkyl, (C$_1$-C$_{40}$)heteroalkyl, (C$_2$-C$_{40}$)alkenyl, (C$_2$-C$_{40}$)alkynyl, aryl(C$_1$-C$_{40}$)alkyl, substituted (C$_1$-C$_{40}$)alkyl, substituted (C$_1$-C$_{40}$)heteroalkyl, substituted (C$_2$-C$_{40}$)alkenyl, substituted (C$_2$-C$_{40}$)alkynyl or substituted aryl(C$_1$-C$_{40}$)alkyl;
(II) when R^2 is (C$_1$-C$_{30}$)acyl, aryl(C$_1$-C$_{30}$)acyl, substituted (C$_1$-C$_{30}$)acyl or substituted aryl(C$_1$-C$_{30}$)acyl, then R^3 is H, (C$_1$-C$_{30}$)alkyl, (C$_1$-C$_{30}$)heteroalkyl, (C$_2$-C$_{30}$)alkenyl, (C$_2$-C$_{30}$)alkynyl, aryl(C$_1$-C$_{30}$)alkyl, substituted (C$_1$-C$_{30}$)alkyl,

substituted (C_1-C_{30})heteroalkyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl or substituted aryl(C_1-C_{30})alkyl;

(III) neither B^1 nor B^2 contains one or more of the following amino acid sequences: Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$, Tyr-Ala-Arg-Lys-Ala-(Arg)$_2$-Gln-Ala-(Arg)$_2$, Tyr-Ala-Arg-(Ala)$_2$-(Arg)$_2$-(Ala)$_2$-(Arg)$_2$, Tyr-Ala-(Arg)$_9$, Tyr-(Ala)$_3$-(Arg)$_7$, Tyr-Ala-Arg-Ala-Pro-(Arg)$_2$-Ala-(Arg)$_3$ or Tyr-Ala-Arg-Ala-Pro-(Arg)$_2$-Pro-(Arg)$_2$;

(IV) either B^1 or B^2 or both must be present in said compound;

(V) when A^2 is Cys, D-Cys, hCys, D-hCys, Pen or D-Pen, then A^9 is Cys, D-Cys, hCys, D-hCys, Pen or D-Pen; and

(VI) when A^2 is Asp or Glu, then A^9 is Dab, Dap, Orn or Lys.

[0052] In exemplary embodiments, in Formula (III);

B^1 is Arg-Lys-Gln-Lys-(Arg)$_5$, Arg-(Lys)$_2$-Arg-Gln-(Arg)$_4$, Arg-(Lys)$_2$-(Arg)$_3$-Gln-(Arg)$_2$, Arg-(Lys)$_2$-(Arg)$_4$-Gln-Arg, Arg-(Lys)$_2$-(Arg)$_5$-Gln, Arg-(Lys)$_2$-Gln-(Arg)$_5$, Arg-Gln-(Lys)$_2$-(Arg)$_5$, Arg-Gln-(Arg)$_7$, Arg-Gln-(Arg)$_8$, (Arg)$_2$-Gln-(Arg)$_6$, (Arg)$_2$-Gln-(Arg)$_7$, (Arg)$_3$-Gln-(Arg)$_5$, (Arg)$_3$-Gln-(Arg)$_6$, (Arg)$_4$-Gln-(Arg)$_4$, (Arg)$_4$-Gln-(Arg)$_5$, (Arg)$_5$, (Arg)$_5$-Gln-(Arg)$_3$, (Arg)$_5$-Gln-(Arg)$_4$, (Arg)$_6$, (Arg)$_6$-Gln-(Arg)$_3$, (Arg)$_7$, (Arg)$_7$-Gln-(Arg)$_2$, (Arg)$_8$, (Arg)$_s$-Gln-Arg, (Arg)$_9$, (Arg)$_9$-Gln, (D-Arg)$_5$, (D-Arg)$_6$, (D-Arg)$_7$, (D-Arg)$_8$, (D-Arg)$_9$, Gln-Arg-(Lys)$_2$-(Arg)$_5$, Gln-(Arg)$_8$, Gln-(Arg)$_9$, Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$, Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-Doc; or deleted;

B^2 is β-Ala, β-Ala-Gly, β-Ala-Tyr, β-Ala-Tyr-Gly, (β-Ala)$_2$, (β-Ala)$_2$-Gly, (β-Ala)$_2$-Tyr, (β-Ala)$_2$-Tyr-Gly, Doc, Doc-Gly, Doc-Tyr, Doc-Tyr-Gly, (Doc)$_2$, (Doc)$_2$-Gly, (Doc)$_2$-Tyr, Doc)$_2$-Tyr-Gly, or deleted;

B^3 is Arg-Lys-Gln-Lys-(Arg)$_5$, Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$, Arg-(Lys)$_2$-Arg-Gln-(Arg)$_4$, Arg-(Lys)$_2$-Gln-(Arg)$_5$, Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$, Arg-(Lys)$_2$-(Arg)$_3$-Gln-(Arg)$_2$, Arg-(Lys)$_2$-(Arg)$_4$-Gln-Arg, Arg-(Lys)$_2$-(Arg)$_5$-Gln, Arg-Gln-(Lys)$_2$-(Arg)$_5$, Arg-Gln-(Arg)$_7$, Arg-Gln-(Arg)$_s$, (Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$, (Arg)$_2$-Gln-(Arg)$_6$, (Arg)$_2$-Gln-(Arg)$_7$, (Arg)$_3$-Gln-(Arg)$_5$, (Arg)$_3$-Gln-(Arg)$_6$, (Arg)$_4$-Gln-(Arg)$_4$, (Arg)$_4$-Gln-(Arg)$_5$, (Arg)$_5$, (Arg)$_s$-Gln-(Arg)$_3$, (Arg)$_5$-Gln-(Arg)$_4$, (Arg)$_6$, (Arg)$_6$-Gln-(Arg)$_3$, (Arg)$_7$, (Arg)$_7$-Gln-(Arg)$_2$, (Arg)$_8$, (Arg)$_s$-Gln-Arg, (Arg)$_9$, (Arg)$_9$-Gln, (D-Arg)$_5$, (D-Arg)$_6$, (D-Arg)$_7$, (D-Arg)$_8$, (D-Arg)$_9$, Gln-Arg-(Lys)$_2$-(Arg)$_5$, Gln-(Arg)$_8$, Gln-(Arg)$_9$, or deleted;

A^1 is A6c, Cha, hCha, Chg, D-Chg, hChg, Gaba, hLeu, Met, β-hMet, D-2-Nal, Nip, Nle, Oic, Phe, D-Phe, hPhe, hPro, or deleted;

A^2 is Cys;

A^3 is D-Abu, Aib, Ala, β-Ala, D-Ala, D-Cha, Gaba, Glu, Gly, D-Ile, D-Leu, D-Met, D-Nle, D-Phe, D-Tle, D-Trp, D-Tyr, D-Val, or deleted;

A^4 is H;

A^5 is D-Bal, D-1-Nal, D-2-Nal, D-Phe, D-(X^1, X^2, X^3, X^4, X^5)Phe, D-Trp, or D-(Et)Tyr;

A^6 is Arg or hArg;

A^7 is Bal, Bip, 1-Nal, 2-Nal, Trp, or D-Trp;

A^8 is A5c, A6c, Aha, Ahx, Ala, β-Ala, Apn, Gaba, Gly, or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Lys, Pen, or D-Pen;

A^{10} is Pro, Thr or deleted;

A^{11} is Pro or deleted;

A^{12} is arg, Lys, or deleted;

A^{13} is Asp or deleted;

each of R^2 and R^3 is, independently, H or acyl;

or pharmaceutically acceptable salts thereof.

[0053] In exemplary embodiments, the MC4R agonists useful for practicing the methods of the present invention are at least one of the following compounds:

(SEQ ID NO: 159)

Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)- NH$_2$;

(SEQ ID NO: 160)

Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-Doc-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-NH$_2$;

(SEQ ID NO: 161)

Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 162)

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 163)

Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Doc)$_2$ -Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 164)

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Pro)$_2$-Lys-Asp-Tyr-Gly-Arg-(Lys)$_2$ -(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 165)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Gly-Cys)-(Pro)$_2$-Lys-Asp-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 166)

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(β-Ala)$_2$-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 167)

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Pro)$_2$-Lys-Asp-Doc-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 168)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Gly-Cys)-(Pro)$_2$-Lys-Asp-Doc-Tyr-Gly-Arg- (Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 169)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 170)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-Doc-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 171)

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Doc)$_2$-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 172)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 173)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 174)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 175)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 176)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-Arg-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 177)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-Gln-(Arg)$_5$-NH$_2$;

(SEQ ID NO: 178)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-Gln-Lys-(Arg)$_5$-NH$_2$;

(SEQ ID NO: 179)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_4$-Gln-Arg-NH$_2$;

(SEQ ID NO: 180)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Aib-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 181)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 182)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$ -Lys-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 183)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 184)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 185)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 186)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_6$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 187)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 188)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 189)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 190)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_3$-Gln-(Arg)$_2$-NH$_2$;

(SEQ ID NO: 191)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-Gln-(Lys)$_2$-(Arg)$_5$-NH$_2$;

(SEQ ID NO: 192)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_5$-Gln-NH$_2$;

(SEQ ID NO: 193)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 194)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 195)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_2$ -Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 196)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 197)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_2$ -Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 198)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 199)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Gly-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 200)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Gly-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 201)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 202)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 203)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Gly-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 204)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Gly-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 205)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 206)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 207)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 208)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 209)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 210)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 211)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 212)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Gly-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 213)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Gly-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 214)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 215)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 216)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 217)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 218)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 219)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 220)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 221)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 222)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 223)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 224)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 225)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 226)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 227)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 228)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 229)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 230)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 231)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 232)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 233)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 234)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 235)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 236)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 237)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 238)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 239)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 240)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 241)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 242)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 243)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 244)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 245)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-β-Ala-Tyr-Gly-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 246)

Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Arg-Asp-β-Ala-Tyr-Gly-(Arg)$_6$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 247)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$-Tyr-Gly-Arg-(Lys)$_2$-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 248)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-Arg-(Lys)$_2$-Arg-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 249)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-Arg-(Lys)$_2$ -(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 250)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 251)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 252)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 253)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 254)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 255)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 256)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 257)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-Arg-Lys-(Arg)$_3$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 258)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)$_2$-Lys-(Arg)$_2$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 259)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Arg-Lys-(Arg)$_3$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 260)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 261)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 262)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 263)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 264)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 265)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 266)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$ -(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 267)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$ -Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 268)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$ -Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 269)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 270)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$ -NH$_2$;

(SEQ ID NO: 271)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 272)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 273)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 274)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)$_5$ -Gln-(Arg)$_4$ -NH$_2$;

(SEQ ID NO: 275)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 276)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 277)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$ -(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 278)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$ -Gly-(Arg)$_5$-Gln-(Arg)$_4$ -NH$_2$;

(SEQ ID NO: 279)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$ -Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$ -NH$_2$;

(SEQ ID NO: 280)

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-Tyr-Gly- (Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 281)

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 282)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 283) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;
(SEQ ID NO: 284)

(SEQ ID NO: 284)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 285) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;
(SEQ ID NO: 286) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;
(SEQ ID NO: 287)

(SEQ ID NO: 287)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 288)

(SEQ ID NO: 288)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)$_2$ -Gly-(Arg)$_5$ -Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 289) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)$_2$-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 290)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 291) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Gly-(Arg)$_5$-Gln-(Arg)$_3$ -NH$_2$;
(SEQ ID NO: 292) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-(Arg)$_5$-Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 293)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 294)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)$_2$ -Gly-(Arg)$_5$-Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 295) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 296)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$ - NH$_2$;

(SEQ ID NO: 297) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;
(SEQ ID NO: 298) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 299)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)$_2$ -Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 300)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)$_2$ -Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 301) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 302)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$ - NH$_2$;

(SEQ ID NO: 303) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;
(SEQ ID NO: 304) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 305)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 306)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)$_2$ -Gly-(Arg)$_5$ -Gln-(Arg)$_4$ - NH$_2$;

(SEQ ID NO: 307) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 308)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 309)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 310)

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 311)

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 312)

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)$_5$ - Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 313)

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-β-Ala-(Arg)$_5$-Gln- (Arg)$_3$-NH$_2$;

(SEQ ID NO: 314)

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$-Gln- (Arg)$_3$ -NH$_2$;

(SEQ ID NO: 315)

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 316)

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly- (Arg)$_5$ -Gln- (Arg)$_3$ -NH$_2$;

(SEQ ID NO: 317)

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 318)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln- (Arg)$_3$ -NH$_2$;

(SEQ ID NO: 319)

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 320)

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 321)

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 322)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 323)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 324)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)$_2$ -Tyr-Gly-(Arg)$_5$ - Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 325)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 326)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 327)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-(Arg)$_5$-Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 328)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)$_2$ -Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 329)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)$_2$ -(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 330)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 331)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_4$ -NH$_2$;

(SEQ ID NO: 332)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)$_2$ -Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$ - NH$_2$;

(SEQ ID NO: 333)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 334)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$ -NH$_2$;

(SEQ ID NO: 335)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-(Arg)$_5$ -Gln-(Arg)$_4$ - NH$_2$;

(SEQ ID NO: 336)

(SEQ ID NO: 337)

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_4$- NH$_2$;

(SEQ ID NO: 338)

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$ - Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 339)

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 340)

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln- (Arg)$_3$-NH$_2$;

(SEQ ID NO: 341)

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 342)

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln- (Arg)$_3$-NH$_2$;

(SEQ ID NO: 343)

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 344)

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 345)

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 346)

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-β-Ala-Tyr- Gly-(Arg)$_5$ - Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 347)

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 348)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-β-Ala-Tyr-Gly -(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 349)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-β-Ala-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 350)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 351)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$- Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 352)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(β-Ala)$_2$ -Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 353)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 354)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 355)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-Doc-Gly-(Arg)$_5$-Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 356)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-Doc-(Arg)$_5$-Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 357)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(Doc)$_2$-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 358)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(Doc)$_2$-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 359)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 360)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$ - Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 361)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 362)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 363)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 364)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)$_2$ -Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 365)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)$_2$-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 366)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)$_2$ -Gly-(Arg)$_5$ - Gln-(Arg)$_3$ - NH$_2$;

(SEQ ID NO: 367)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)$_2$ -(Arg)$_5$ -Gln-(Arg)$_4$ -NH$_2$;

(SEQ ID NO: 368)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-Tyr- Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 369)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 370)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 371)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 372)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)$_2$-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 373)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)$_2$ -(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 374)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)$_2$-Gly-(Arg)$_5$ -Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 375)

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 376)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β- Ala-Tyr-Gly-(Arg)$_5$ -Gln- (Arg)$_3$ -NH$_2$;

(SEQ ID NO: 377)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β- Ala-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 378)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)$_2$ -Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 379)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)$_2$ -(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 380)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 381)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 382)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(Doc)$_2$-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 383)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β- Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$ -NH$_2$;

(SEQ ID NO: 384)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β-Ala-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 385)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)$_2$ -Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 386)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)$_2$ -(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 387)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 388)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 389)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(Doc)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 390)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(Doc)$_2$ -(Arg)$_5$-Gln-(Arg)$_4$ - NH$_2$;

(SEQ ID NO: 391)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-β- Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 392)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 393)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-β-Ala-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 394)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(β-Ala)$_2$ -Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 395)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(β-Ala)$_2$ -(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 396)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 397)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 398)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-Doc-(Arg)$_5$-Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 399)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(Doc)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 400)

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(Doc)$_2$ -(Arg)$_5$ - Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 401)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-β-Ala-Tyr -Gly-(Arg)$_5$- Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 402)

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-β-Ala-(Arg)$_5$-Gln- (Arg)$_3$-NH$_2$;

(SEQ ID NO: 403)

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$- NH$_2$;

(SEQ ID NO: 404) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 405)

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$-Gln- (Arg)$_3$ -NH$_2$;

(SEQ ID NO: 406) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)$_2$ -(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 407)

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$- NH$_2$;

(SEQ ID NO: 408) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$ -NH$_2$

(SEQ ID NO: 409)

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$-Gln- (Arg)$_4$ -NH$_2$;

(SEQ ID NO: 410) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 411)

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 412) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 413)

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)$_2$ -Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 414) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 415)

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 416) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 417)

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 418) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 419)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 420)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 421)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 422)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 423)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 424)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 425)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$ -Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 426)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 427)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 428)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 429)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$ -Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 430)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 431)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 432)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_4$ -NH$_2$;

(SEQ ID NO: 433)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$ -Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$- NH$_2$;

(SEQ ID NO: 434)

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 435)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 436)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$ -NH$_2$;

(SEQ ID NO: 437)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$ -Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 438)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 439)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 440)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 441)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$ -Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 442)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 443)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 444)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 445)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 446)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 447)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 448)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 449)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$-Tyr-Gly-(Arg)$_5$ -Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 450)

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 451)

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 452) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 453)

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 454) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 455)

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 456) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 457)

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 458) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 459)

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 460) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 461)

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 462) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_3$-NH$_2$;

(SEQ ID NO: 463)

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 464) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

(SEQ ID NO: 465)

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)$_2$-Tyr-Gly-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$;

or
(SEQ ID NO: 466) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)$_2$-(Arg)$_5$-Gln-(Arg)$_4$-NH$_2$, or pharmaceutically acceptable salts thereof.

[0054] In an example embodiment, the compounds useful for practicing the methods described herein are the compounds of Formula (IV):

Ac-c(Cys-Glu-His-A^1-Arg-A^2-A^3-Cys)-(Pro)$_2$-Lys-Asp-NH$_2$ (IV)
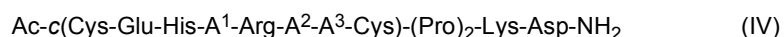
or pharmaceutically acceptable salts thereof. In Formula (IV):

A^1 is the D-isomer of X-Phe or 2-Nal where X is halogen;
A^2 is Bal, 1-Nal, 2-Nal, or Trp; and
A^3 is Aib, Ala, β-Ala or Gly,

[0055] In an example embodiments, the at least on eof the following compounds is used:

(SEQ ID NO: 467) Ac-c(Cys-Glu-His-D-4-Br-Phe-Arg-Trp-Gly-Cys)-(Pro)$_2$-Lys-Asp-NH$_2$;
(SEQ ID NO: 468) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)$_2$-Lys-Asp-NH$_2$;
(SEQ ID NO: 469) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-NH$_2$;
(SEQ ID NO: 470) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)$_2$-Lys-Asp-NH$_2$;
(SEQ ID NO: 471) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)$_2$-Lys-Asp-NH$_2$;
(SEQ ID NO: 472) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-β-Ala-Cys)-(Pro)$_2$-Lys-Asp-NH2;
or
(SEQ ID NO: 473) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Aib-Cys)-(Pro)$_2$-Lys-Asp-NH$_2$;

or pharmaceutically acceptable salts thereof.
[0056] In example embodiments, an MC4R agonist useful for practicing the methods described herein is at least one compound modified with a hydantoin moiety according to Formula (V), (VI) or (VII), or a pharmaceutically acceptable salt, hydrate, solvate or a prodrug thereof.
[0057] Formula (V) is described below: (see International Patent Application Number PCT/US08/06675).
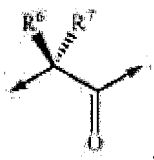

(V).
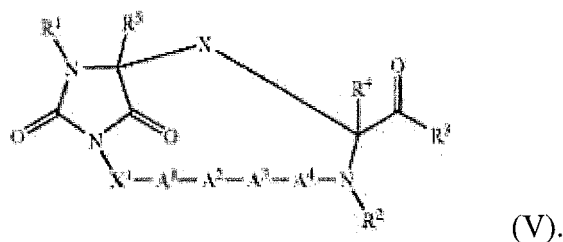
[0058] In Formula (V):

X is selected from the group consisting of -CH$_2$-S-S-CH$_2$-, -C(CH$_3$)$_2$-S-S-CH$_2$-, -CH$_2$-S-S-C(CH$_3$)$_2$-, -C(CH$_3$)$_2$-S-S-C(CH$_3$)$_2$-, -(CH$_2$)$_2$-S-S-CH$_2$-, -CH$_2$-S-S-(CH$_2$)$_2$-,-(CH$_2$)$_2$-S-S-(CH$_2$)$_2$-, -C(CH$_3$)$_2$-S-S-(CH$_2$)$_2$-, -(CH$_2$)$_2$-S-S-C(CH$_3$)$_2$-, -(CH$_2$)$_f$-C(O)-NR^8-(CH$_2$)$_f$- and -(CH$_2$)$_f$-NR^8-C(O)-(CH$_2$)$_f$-;
R^2 each is, independently, H, (C$_1$-C$_{10}$)alkyl or substituted (C$_1$-C$_{10}$)alkyl;
R^3 is -OH or -NH$_2$;
R^4 and R^5 each is, independently, H, (C$_1$-C$_{10}$)alkyl or substituted (C$_1$-C$_{10}$)alkyl;
X^1 is

,

A^1 is H is, 2-Pal, 3-Pal, 4-Pal, (X^1, X^2, X^3, X^4, X^5)Phe, Taz, 2-Thi, 3-Thi or is deleted;
A^2 is D-Bal, D-1-Nal, D-2-Nal, D-Phe or D-(X^1,X^2,X^3,X^4,X^5)Phe;
A^3 is Arg, hArg, Dab, Dap, Lys or Orn;
A^4 is Bal, 1-Nal, 2-Nal, (X^1, X^2, X^3, X^4, X^5)Phe or Trp;
R^6 and R^7 each is, independently for each occurrence thereof, H, (C$_1$-C$_{10}$)heteroalkyl, aryl(C$_1$-C$_5$)alkyl, substituted (C$_1$-C$_{10}$)alkyl, substituted (C$_1$-C$_{10}$)heteroalkyl or substituted aryl(C$_1$-C$_5$)alkyl provided that R^6 and R^7 may be joined together to form a ring;

R^8 is H, (C$_1$-C$_{10}$)alkyl or substituted (C$_1$-C$_{10}$)alkyl;

r is, independently for each occurrence thereof, 1, 2, 3, 4 or 5; and
t is, independently for each occurrence thereof, 1 or 2.

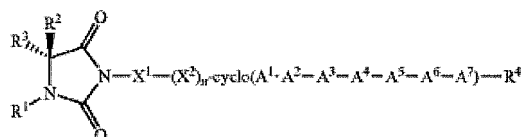**[0059]** Compounds according the foregoing formula can include compounds wherein X^1 is selected from the group consisting of:

, and

.
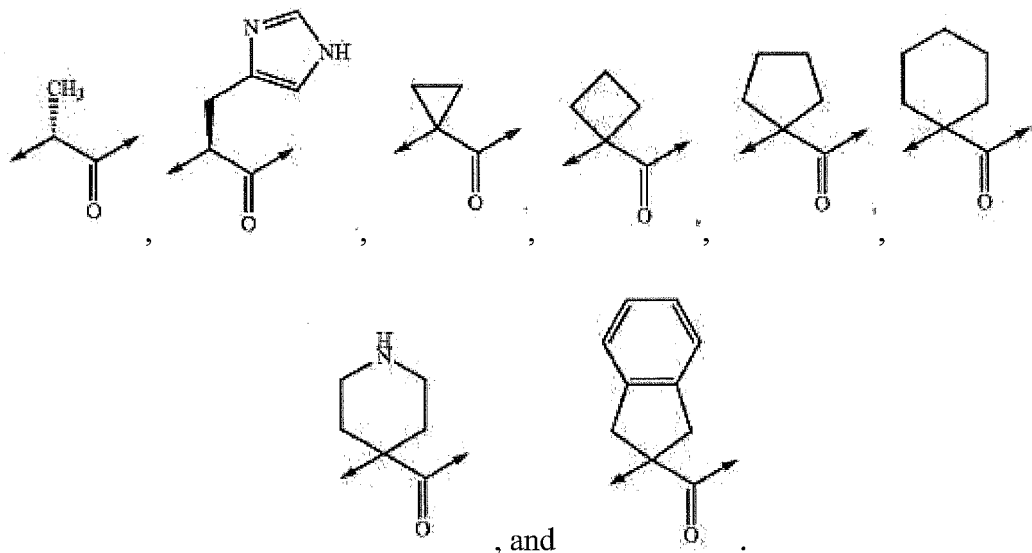
[0060] Representative embodiments of the foregoing class of compounds are as follows:
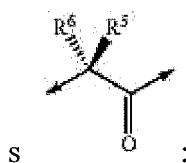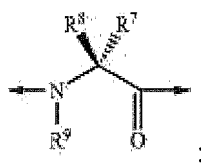
(SEQ ID NO: 474 c[Hydantoin(C(O)-(Cys-D-Ala))-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 475) c[Hydantoin(C(O)-(hCys-D-Ala))-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 476) c[Hydantoin(C(O)-(Cys-D-Ala))-His-D-2-Nal-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 477) c[Hydantom(C(O)-(hCys-D-Ala))-His-D-2-Nal-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 478) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 479) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Orn]-NH$_2$;
(SEQ ID NO: 480) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Dab]-NH$_2$;
(SEQ ID NO: 481) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Dap]-NH$_2$;
(SEQ ID NO: 482) c[Hydantoin(C(O)-(Asp-His))-D-2-Nal-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 483) c[Hydantoin(C(O)-(Asp-His))-D-Phe-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 484) c[Hydantoin(C(O)-(Asp-A3c))-D-Phe-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 485) c[Hydantoin(C(O)-(Asp-A5c))-D-Phe-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 486) c[Hydantoin(C(O)-(Asp-A6c))-D-Phe-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 487) c[Hydantoin(C(O)-(Asp-A3c))-D-2-Nal-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 488) c[Hydantoin(C(O)-(Asp-A5c))-D-2-Nal-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 489) c[Hydantoin(C(O)-(Asp-A6c))-D-2-Nal-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 490) c[Hydantoin(C(O)-(Asp-Aic))-D-Phe-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 491) c[Hydantoin(C(O)-(Asp-Apc))-D-Phe-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 492) c[Hydantoin(C(O)-(Asp-Aic))-D-2-Nal-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 493) c[Hydantoin(C(O)-(Asp-Apc))-D-2-Nal-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 494) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Orn]-NH$_2$;
(SEQ ID NO: 495) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Dab]-NH$_2$;
(SEQ ID NO: 496) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Dap]-NH$_2$;
(SEQ ID NO: 497) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Lys]-NH$_2$;
(SEQ ID NO: 498) c[Hydantoin(C(O)-(Glu-His))-D-Phe-Arg-Trp-Dap]-NH$_2$;
or
(SEQ ID NO: 499) c[Hydantoin(C(O)-(Glu-His))-D-Phe-Arg-Trp-Lys]-NH$_2$.

[0061] In an example embodiment, an MC4R agonist useful for practicing the methods described herein is at least one compound of Formula (VI), a pharmaceutically-acceptable salt, hydrate, solvate and/or prodrugs thereof (see International Patent Application Number PCT/US08/06675)

$$R^3 \underset{R^1}{\overset{R^2}{\underset{N}{\bigvee}}} \text{—} N \text{—} X^1 \text{—} (X^2)_n \text{—cyclo}(A^1\text{—}A^2\text{—}A^3\text{—}A^4\text{—}A^5\text{—}A^6\text{—}A^7) \text{—} R^4$$

(VI).

In Formula (VI):

X^1 is

$$\underset{S}{\overset{R^6 \quad R^5}{\bigvee}} \overset{O}{;}$$

X^2 is

$$\underset{R^9}{\overset{R^8 \quad R^7}{\underset{N}{\bigvee}}} \overset{O}{;}$$

A^1 is Asp, Cys, D-Cys, Dab, Dap, Glu, Lys, Orn, Pen or D-Pen;

A^2 is an L- or D-amino acid;

A^3 is H is, 2-Pal, 3-Pal, 4-Pal, $(X^1, X^2, X^3, X^4, X^5)$Phe, Taz, 2-Thi or 3-Thi;

A^4 is D-Bal, D-1-Nal, D-2-Nal, D-Phe or D-$(X^1, X^2, X^3, X^4, X^5)$Phe;

A^5 is Arg, hArg, Dab, Dap, Lys or Orn;

A^6 is Bal, 1-Nal, 2-Nal, $(X^1, X^2, X^3, X^4, X^5)$Phe or Trp;

A^7 is Asp, Cys, D-Cys, Dab, Dap, Glu, Lys, Orn, Pen or D-Pen;

R^1 is H, $(C_1\text{-}C_{10})$alkyl or substituted $(C_1\text{-}C_{10})$alkyl;

R^2 and R^3 each is, independently, H, $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_{10})$heteroalkyl, aryl$(C_1\text{-}C_5)$alkyl, substituted $(C_1\text{-}C_{10})$alkyl, substituted $(C_1\text{-}C_{10})$heteroalkyl or substituted aryl$(C_1\text{-}C_5)$alkyl or R^2 and R^3 may be fused together form a cyclic moiety;

R^4 is CO_2H or $C(O)NH_2$;

R^5 and R^6 each is, independently, H, $(C_1\text{-}00)$alkyl, $(C_1\text{-}C_{10})$heteroalkyl, aryl$(C_1\text{-}C_5)$alkyl, substituted $(C_1\text{-}C_{10})$alkyl, substituted $(C_1\text{-}C_{10})$heteroalkyl or substituted aryl$(C_1\text{-}C_5)$alkyl or R^5 and R^6 may be fused together form a cyclic moiety;

R^7 and R^8 each is, independently, H, $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_{10})$heteroalkyl, aryl$(C_1\text{-}C_5)$alkyl, substituted $(C_1\text{-}C_{10})$alkyl, substituted $(C_1\text{-}C_{10})$heteroalkyl or substituted aryl$(C_1\text{-}C_5)$alkyl; or R^7 and R^8 may be fused together form a cyclic moiety;

R^9 is H, $(C_1\text{-}C_{10})$alkyl or substituted $(C_1\text{-}C_{10})$alkyl; and

n is, independently for each occurrence thereof, 1, 2, 3, 4, 5, 6 or 7;

or a pharmaceutically acceptable salt thereof.

[0062]   Exemplary embodiments of the compounds of Formula (VI) are those compounds wherein:

A^1 is Cys;

A^2 is D-Ala, Asn, Asp, Gln, Glu or D-Phe;

A^3 is H is;

A^4 is D-2-Nal or D-Phe;

A^5 is Arg;

A^6 is Trp; and

A^7 is Cys or Pen;

each of R', R^2, R^3, and R^9 is, independently, H;

R^4 is $C(O)NH_2$;

each of R^5 and R^6 is, independently, H, (C_1-C_{10})heteroalkyl, substituted (C_1-C_{10})alkyl or substituted (C_1-C_{10})heteroalkyl or R^5 and R^6 may be fused together form a cyclic moiety; and each of R^7 and R^8 is, independently, H, (C_1-C_{10})alkyl, (C_1-C_{10})heteroalkyl, substituted (C_1-C_{10})alkyl or substituted (C_1-C_{10})heteroalkyl;

or pharmaceutically acceptable salts thereof.

[0063] Example compounds of the immediately foregoing Formula (VI) include:

(SEQ ID NO: 500) Hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 501) Hydantoin(C(O)-(Nle-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 502) Hydantoin(C(O)-(Gly-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 503) Hydantoin(C(O)-(Nle-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 504) Hydantoin(C(O)-(Gly-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 505) Hydantoin(C(O)-(Nle-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 506) Hydantoin(C(O)-(Gly-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 507) Hydantoin(C(O)-(Ala-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 508) Hydantoin(C(O)-(D-Ala-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 509) Hydantoin(C(O)-(Aib-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 510) Hydantoin(C(O)-(Val-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 511) Hydantoin(C(O)-(Ile-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 512) Hydantoin(C(O)-(Leu-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 513) Hydantoin(C(O)-(Gly-Gly))-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 514) Hydantoin(C(O)-(Nle-Gly))-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 515) Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 516) Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 517) Hydantoin(C(O)-(Arg-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 518) Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 519) Hydantoin(C(O)-(Arg-Gly))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 520) Hydantoin(C(O)-(Ala-Nle))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 521) Hydantoin(C(O)-(Val-Nle))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 522) Hydantoin(C(O)-(Gly-Nle))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 523) Hydantoin(C(O)-(A6c-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 524) Hydantoin(C(O)-(Gly-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 525) Hydantoin(C(O)-(Ala-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 526) Hydantoin(C(O)-(D-Ala-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 527) Hydantoin(C(O)-(Val-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 528) Hydantoin(C(O)-(Leu-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 529) Hydantoin(C(O)-(Cha-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 530) Hydantoin(C(O)-(Aib-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 531) Hydantoin(C(O)-(Gly-Arg))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 532) Hydantoin(C(O)-(Gly-Arg))-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 533) Hydantoin(C(O)-(Gly-Arg))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 534) Hydantoin(C(O)-(Gly-Arg))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 535) Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 536) Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
(SEQ ID NO: 537) Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;
or
(SEQ ID NO: 538) Hydantoin(C(O)-(Nle-Ala))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;

or a pharmaceutically acceptable salt thereof.

[0064] In an example embodiment, the MC4R agonists useful for practicing the methods described herein are compounds having a structure according to Formula (VII) as depicted below (see International Patent Application Number PCT/US08/06675):
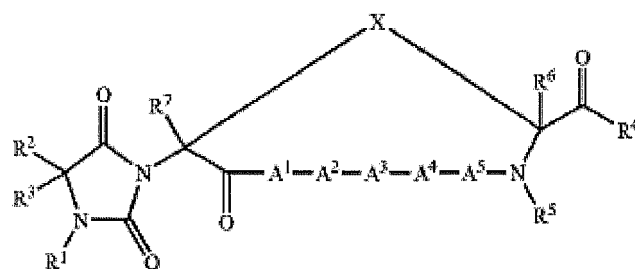
(VII).

wherein:

X is selected from the group consisting of -CH$_2$-S-S-CH$_2$-, -C(CH$_3$)$_2$SSCH$_2$-,-CH$_2$-S-S-C(CH$_3$)$_2$-, -C(CH$_3$)$_2$-S-S-C(CH$_3$)$_z$-,-(CH$_2$)$_2$-S-S-CH$_2$-, -CH$_2$-S-S-(CH$_2$)$_2$, (CH$_2$)$_2$-S-S-(CH$_2$)$_2$-,-C(CH$_3$)$_2$-S-S-(CH$_2$)$_2$-, -(CH$_2$)$_2$-S-S-C(CH$_3$)$_2$-, -(CH$_2$)$_t$-C(O)-NR^8-(CH$_2$)$_t$- and -(CH$_2$)-NR^8-C(O)-(CH$_2$)$_t$-;

each of R^1 and R^5 is, independently, H, (C$_1$-C$_{10}$)alkyl or substituted (C$_1$-C$_{10}$)alkyl;

each of R^2 and R^3 is, independently, H, (C$_1$-C$_{10}$)alkyl, (C$_1$-00)heteroalkyl, aryl(C$_1$-C$_5$)alkyl, substituted (C$_1$-C$_{10}$)alkyl, substituted (C$_1$-C$_{10}$)heteroalkyl or substituted aryl(C$_1$-C$_5$)alkyl or R^2 and R^3 may be fused together to form a ring;

R^4 is OH or NH$_2$;

each of R^6 and R^7 is, independently, H, (C$_1$-C$_{10}$)alkyl or substituted (C$_1$-C$_{10}$)alkyl;

A^1 is an L- or D-amino acid or deleted;

A^2 is H is, 2-Pal, 3-Pal, 4-Pal, (X^1, X^2, X^3, X^4, X^5)Phe, Taz, 2-Thi or 3-Thi;

A^3 is D-Bal, D-1-Nal, D-2-Nal, D-Phe or D-(X^1, X^2, X^3, X^4, X^5)Phe;

A^4 is Arg, hArg, Dab, Dap, Lys or Orn;

A^5 is Bal, 1-Nal, 2-Nal, (X^1, X^2, X^3, X^4, X^5)Phe or Trp;

r is, independently for each occurrence thereof, 1, 2, 3, 4 or 5; and

t is, independently for each occurrence thereof, 1 or 2;

or pharmaceutically acceptable salts thereof.

[0065] In an example embodiment of the compounds of Formula (VII), A^1 is Ala, D-Ala, Asn, Asp, Gln, Glu or Gly.

[0066] Example compounds according to Formula (VII) include the following compounds:

(SEQ ID NO: 539) c[Hydantoin(C(O)-(Nle-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 540) c[Hydantoin(C(O)-(Ala-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 541) c[Hydantoin(C(O)-(D-Ala-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 542) c[Hydantoin(C(O)-(Aib-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 543) c[Hydantoin(C(O)-(Val-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 544) c[Hydantoin(C(O)-(Abu-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 545) c[Hydantoin(C(O)-(Leu-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 546) c[Hydantoin(C(O)-(Ile-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 547) c[Hydantoin(C(O)-(Cha-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 548) c[Hydantoin(C(O)-(A6c-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 549) c[Hydantoin(C(O)-(Phe-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
(SEQ ID NO: 550) c[Hydantoin(C(O)-(Gly-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH$_2$;
or
(SEQ ID NO: 551) c[Hydantoin(C(O)-(Gly-Cys))-Glu-His-D-Phe-Arg-Trp-Cys]-NH$_2$;

or pharmaceutically acceptable salts thereof.

[0067] In an example embodiment, the MC4R agonist useful for practicing the methods described herein is at least one compound according to Formula (VIII) (see International Patent Application Number PCT/US08/07411):

(R^{2}R^3)-A^0-A^1-c(A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9)-A^{10}-R^1 (VIII)
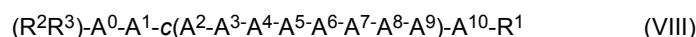
In Formual (VIII):

A^0 is an aromatic amino acid
A^1 is Acc, HN-(CH$_2$)$_{mf}$-C(O), an L- or D-amino acid;

A^2 is Asp, Cys, D-Cys, hCys, Glu, Pen, or D-Pen;

A^3 is Aib, Ala, β-Ala, Gaba, Gly or a D-amino acid;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, $(X^1, X^2, X^3, X^4, X^5)$Phe, Taz, 2-Thi, or 3-Thi;

A^5 is D-Bal, D-1-Nal, D-2-Nal, D-Phe, L-Phe, D-$(X^1, X^2, X^3, X^4, X^5)$Phe, L-Phe, D-Trp or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH$((CH_2)_n$-N$(R^4R^5))$-C(O);

A^7 is Bal, D-Bal, Bip, D-Bip, 1-Nal, D-1-Nal, 2-Nal, D-2-Nal, or D-Trp;

A^8 is Acc, Aha, Ahx, Ala, D-Ala, β-Ala, Apn, Gaba, Gly, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Dab, Dap, Lys, Orn, Pen, or D-Pen;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH, or NH_2;

each of R^2 and R^3 is, independently for each occurrence selected from the group consisting of H, $(C_1$-$C_{30})$alkyl, $(C_1$-$C_{30})$heteroalkyl, $(C_1$-$C_{30})$acyl, $(C_2$-$C_{30})$alkenyl, $(C_2$-$C_{30})$alkynyl, aryl$(C_1$-$C_{30})$alkyl, aryl$(C_1$-$C_{30})$acyl, substituted $(C_1$-$C_{30})$alkyl, substituted $(C_1$-$C_{30})$heteroalkyl, substituted $(C_1$-$C_{30})$acyl, substituted $(C_2$-$C_{30})$alkenyl, substituted $(C_2$-$C_{30})$alkynyl, substituted aryl$(C_1$-$C_{30})$alkyl, and substituted aryl$(C_1$-$C_{30})$acyl;

each of R^4 and R^5 is, independently for each occurrence, H, $(C_1$-$C_{40})$alkyl, $(C_1$-$C_{40})$heteroalkyl, $(C_1$-$C_{40})$acyl, $(C_2$-$C_{40})$alkenyl, $(C_2$-$C_{40})$alkynyl, aryl$(C_1$-$C_{40})$alkyl, aryl$(C_1$-$C_{40})$acyl, substituted $(C_1$-$C_{40})$alkyl, substituted $(C_1$-$C_{40})$heteroalkyl, substituted $(C_1$-$C_{40})$acyl, substituted $(C_2$-$C_{40})$alkenyl, substituted $(C_2$-$C_{40})$alkynyl, substituted aryl$(C_1$-$C_{40})$allyl, substituted aryl$(C_1$-$C_{40})$acyl, $(C_1$-$C_{40})$alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

$X^1, X^2, X^3, X^4,$ and X^5 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

[0068] In example embodiments of Formual (VIII),

(I) when R^4 is $(C_1$-$C_{40})$acyl, aryl$(C_1$-$C_{40})$acyl, substituted $(C_1$-$C_{40})$acyl, substituted aryl$(C_1$-$C_{40})$acyl, $(C_1$-$C_{40})$alkylsulfonyl, or -C(NH)-NH_2, then R^5 is H or $(C_1$-$C_{40})$alkyl, $(C_1$-$C_{40})$heteroalkyl, $(C_2$-$C_{40})$alkenyl, $(C_2$-$C_{40})$alkynyl, aryl$(C_1$-$C_{40})$alkyl, substituted $(C_1$-$C_{40})$alkyl, substituted $(C_1$-$C_{40})$heteroalkyl, substituted $(C_2$-$C_{40})$alkenyl, substituted $(C_2$-$C_{40})$alkynyl, or substituted aryl$(C_1$-$C_{40})$alkyl;

(II) when R^2 is $(C_1$-$C_{30})$acyl, aryl$(C_1$-$C_{30})$acyl, substituted $(C_1$-$C_{30})$acyl, or substituted aryl$(C_1$-$C_{30})$acyl, then R^3 is H, $(C_1$-$C_{30})$alkyl, $(C_1$-$C_{30})$heteroalkyl, $(C_2$-$C_{30})$alkenyl, $(C_2$-$C_{30})$alkynyl, aryl$(C_1$-$C_{30})$alkyl, substituted $(C_1$-$C_{30})$alkyl, substituted $(C_1$-$C_{30})$heteroalkyl, substituted $(C_2$-$C_{30})$alkenyl, substituted $(C_2$-$C_{30})$alkynyl, or substituted aryl$(C_1$-$C_{30})$alkyl;

(III) when A^2 is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen, then A^9 is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen;

(IV) when A^2 is Asp or Glu, then A^9 is Dab, Dap, Orn, or Lys;

(V) when A^8 is Ala or Gly, then A^1 is not Nle; or pharmaceutically acceptable salts thereof.

[0069] In example embodiments of compoudns of Formula (VIII):

A^0 is 1-Nal, 2-Nal, H is, Pff, Phe, Trp, or Tyr;

A^1 is Arg;

A^2 is Cys;

A^3 is D-Ala;

A^4 is H is;

A^5 is D-Phe

A^6 is Arg;

A^7 is Trp

A^8 is deleted;

A^9 is Cys; and

A^{10} is deleted;

or pharmaceutically acceptable salts thereof.

Particular compounds of the immediately foregoing group of compounds are of the formula:

(SEQ ID NO: 552) Ac-Tyr-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 553) Ac-2-Nal-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
(SEQ ID NO: 554) Ac-1-Nal-Arg-c(Cys-D-Ala-His-DPhe-Arg-Trp-Cys)-NH$_2$;
(SEQ ID NO: 555) Ac-Phe-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
(SEQ ID NO: 556) Ac-Trp-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
(SEQ ID NO: 557) Ac-Pff-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
(SEQ ID NO: 558) H-His-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;
or
(SEQ ID NO: 559) Ac-His-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$;

or a pharmaceutically acceptable salt thereof.

[0070] In one example embodiment, the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$ (SEQ ID NO: 140) or a pharmaceutically acceptable salt thereof. In another example embodiment, the MC4R agonist is Hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH$_2$ (SEQ ID NO: 500) or a pharmaceutically acceptable salt thereof.

[0071] Administration of a compound or pharmaceutically acceptable salt thereof or a composition comprising a compound or pharmaceutical salt of a compound of the invention useful to practice the methods described herein, can be continuous, hourly, four times daily, three time daily, twice daily, once daily, once every other day, twice weekly, once weekly, once every two weeks, once a month, or once every two months, or longer or some other intermittent dosing regimen.

[0072] Examples of administration of a compound or composition comprising a compound or pharmaceutical salt of a compound of the invention include peripheral administration. Examples of peripheral administration include oral, subcutaneous, intraperitoneal, intramuscular, intravenous, rectal, transdermal or intranasal forms of administration.

[0073] As used herein, peripherial administration includes all forms of administration of a compound or a composition comprising a compound of the instant invention which excludes intracranial administration. Examples of peripheral administration include, but are not limited to, oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, extended release, slow release implant, depot and the like), nasal, vaginal, rectal, sublingual or topical routes of administration, including transdermal patch applications and the like.

[0074] The nomenclature used to define the peptides is that typically used in the art wherein the amino group at the N-terminus appears to the left and the carboxyl group at the C-terminus appears to the right. Where the amino acid has D and L isomeric forms, it is the L form of the amino acid that is represented unless otherwise explicitly indicated.

[0075] The compounds of the invention useful for practicing the methods described herein may possess one or more chiral centers and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present invention. Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilizing methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of the invention.

[0076] The compounds described herein may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention. For example, a claim to 2-hydroxypyridinyl would also cover its tautomeric form, α-pyridonyl.

[0077] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

Symbol	Meaning
Abu	α-aminobutyric acid
Ac	acyl group
Acc	1-amino-1-cyclo(C$_3$-C$_9$)alkyl carboxylic acid
A3c	1-amino-1cyclopropanecarboxylic acid
A4c	1 -amino -1 -cyclobutanecarboxylic acid
A5c	1-amino-1-cyclopentanecarboxylic acid
A6c	1-amino-1-cyclohexanecarboxylic acid
Aha	7-aminoheptanoic acid
Ahx	6-aminohexanoic acid
Aib	α-aminoisobutyric acid
Aic	2-aminoindan-2-carboxylic acid
Ala or A	alanine
β-Ala	β-alanine
Apc	denotes the structure:

(continued)

Symbol	Meaning
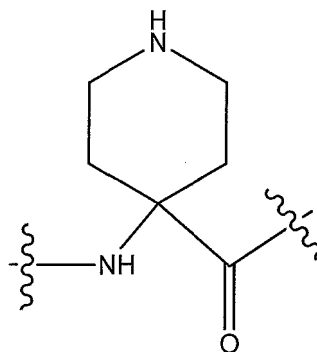
Apn	5-aminopentanoic acid (HN-(CH2)$_4$-C(O)
Arg or R	arginine
hArg	homoarginine
Asn or N	asparagine
Asp or D	aspartic acid
Bal	3-benzothienylalanine
Bip	4,4'-biphenylalanine, represented by the structure
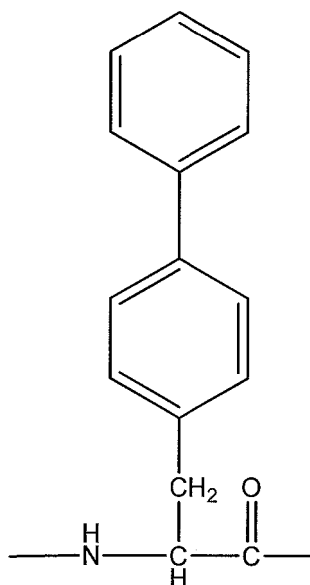
Bpa	4-benzoylphenylalanine
4-Br-Phe	4-bromo-phenylalanine
Cha	β-cyclohexylalanine
hCha	homo-cyclohexylalanine
Chg	cyclohexylglycine
Cys or C	cysteine
hCys	homocysteine
Dab	2,4-diaminobutyric acid
Dap	2,3-diaminopropionic acid
Dip	β,β-diphenylalanine
Doc	8-amino-3,6-dioxaoctanoic acid with the structure of:
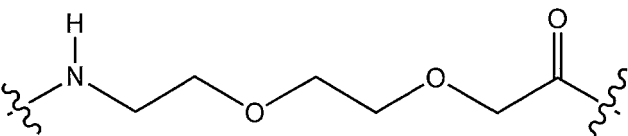
(continued)

Symbol	Meaning

Symbol	Meaning
2-Fua	β-(2-furyl)-alanine
Gaba	4-aminobutyric acid
Gln or Q	glutamine
Glu or E	glutamic acid
Gly or G	glycine
His or H	histidine
3-Hyp	trans-3-hydroxy-L-proline, i.e., (2S,3S)-3-hydroxy-pyrrolidine-2-carboxylic acid
4-Hyp	4-hydroxyproline, i.e., (2S,4R)-4-hydorxypyrrolidine-2-carboxylic acid
Ile or 1	isoleucine
Leu or L	leucine
hLeu	homoleucine
Lys or K	lysine
Met or M	methionine
β-hMet	β-homomethionine
1-Nal	β-(1-naphthyl)alanine
2-Nal	β-(2-naphthyl)alanine
Nip	nipecotic acid
Nle	norleucine
Ole	octahydroindole-2-carboxylic acid
Orn	ornithine
2-Pal	β-(2-pyridiyl)alanine
3-Pal	β-(3-pyridiyl)alanine
4-Pal	β-(4-pyridiyl)alanine
Pen	penicillamine
Pff	(S)-pentafluorophenylalanine
Phe or F	phenylalanine
hPhe	homophenylalanine
Pro or P	proline
hProP	homoproline
Ser or S	Serine
Tle	tert-Leucine
Taz	β-(4-thiazolyl)alanine
2-Thi	β-(2-thienyl)alanine
3-Thi	β-(3-thienyl)alanine
Thr or T	threonine
Trp or W	tryptopham
Tyr or Y	tyrosine
D-(Et) Tyr	has a structure of

(continued)

Symbol	Meaning
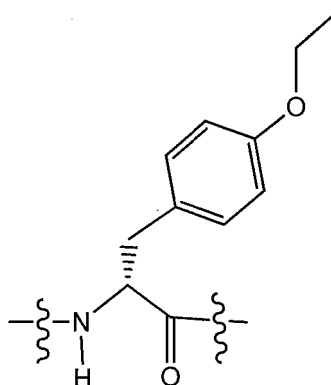
Val or V   Valine

[0078] Certain other abbreviations used herein are defined as follows:

Boc:	tert-butyloxycarbonyl
Bzl:	benzyl
DCM:	dichloromethane
DIC:	N,N-diisopropylcarbodiimide
DIEA:	diisopropylethyl amine
Dmab:	4-{N-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl)-amino}benzyl
DMAP:	4-(dimethylamino)pyridine
DMF:	dimethylformamide
DNP:	2,4-dinitrophenyl
Fm:	fluorenylmethyl
Fmoc:	fluorenylmethyloxycarbonyl
For:	formyl
HBTU:	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
cHex	cyclohexyl
HOAT:	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt:	1-hydroxy-benzotriazole
MBNA	4-methylbenzhydrylamine
Mmt:	4-methoxytrityl
NMP:	N-methylpyrrolidone
O-tBu	oxy-tert-butyl
Pbf:	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
tBu:	tert-butyl
TIS:	triisopropylsilane
TOS:	tosyl
Trt	trityl
TFA:	trifluoro acetic acide
TFFH:	tetramethylfluoroforamidiaium hexafluorophosphate
Z:	benzyloxycarbonyl

[0079] Unless otherwise indicated, with the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-C(R)(R')-CO-, wherein R and R' each is, independently, hydrogen or the side chain of an amino acid (e.g., R=CH$_3$ and R'=H for Ala), or R and R' may be joined to form a ring system.
[0080] For the N-terminal amino acid, the abbreviation stands for the structure of:
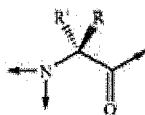
[0081] The designation "NH₂" in e.g., Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO:13), indicates that the C-terminus of the peptide is amidated. Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys) (SEQ ID NO:107), or alternatively Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH (SEQ ID NO: 107), indicates that the C-terminus is the free acid.

[0082] "-c(Cys-Cys)-" or "-cyclo(Cys-Cys)-" denotes the structure:
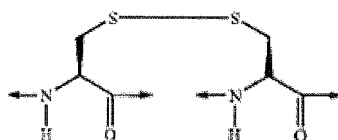
"-c(Cys-Pen)-" or "-cyclo(Cys-Pen)-" denotes the structure:
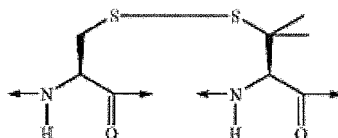
"-c(Asp-Lys)-" or "-cyclo(Asp-Lys)-" denotes the structure:
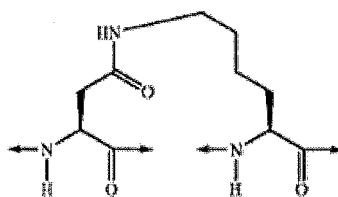
[0083] Applicants have devised the following shorthand used in naming the specific embodiments and/or species:
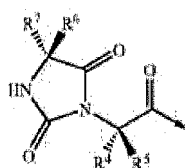
[0084] "HydantoinC(O)-(Aᵃ-Aᵇ)" denotes the structure:

wherein amino acid "Aᵃ" has the structure:
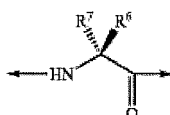
and amino acid "Aᵇ" the structure:
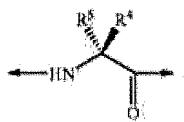
[0085] For example, a compound represented as "c[Hydantoin(C(O)-(Cys-A^b))-A^1-A^2-A^3-A^4-Cys]-" would have the following the structure:
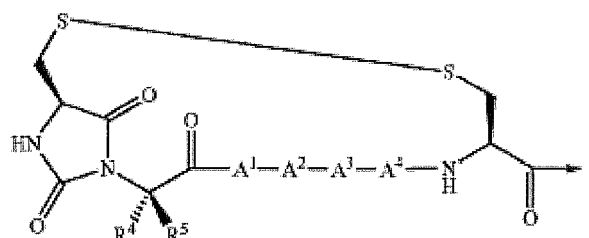
whereas a compound represented as "c[Hydantoin(C(O)-(A^b-Cys))-A^1-A^2-A^3-A^4-Cys]-" would have the structure:
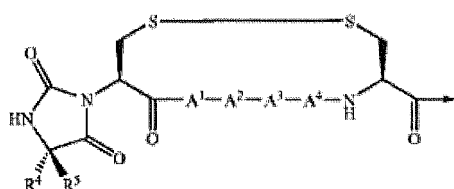
[0086] For further guidance, "c[Hydantoin(C(O)-(Asp-A^b))-A^1-A^2-A^3-A^4-Lys]-" represents the following compound:
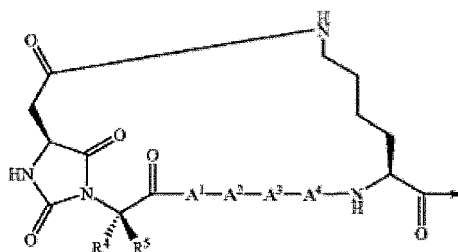
whereas "c[Hydantoin(C(O)-(Dap-A^b))-A^1-A^2-A^3-A^4-Asp]-" has the following formula:
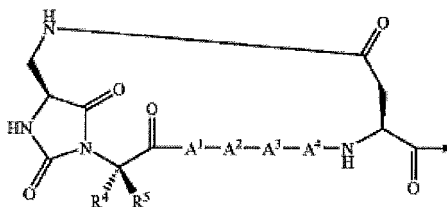
[0087] "Acyl" refers to R"-C(O)-, where R" is H, alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, alkenyl, substituted alkenyl, aryl, alkylaryl, or substituted alklyaryl, and is indicated in the general formula of a particular embodiment as "Ac".

[0088] "Alkyl" refers to a hydrocarbon group containing one or more carbon atoms, where multiple carbon atoms if present are joined by single bonds. The alkyl hydrocarbon group may be straight-chain or contain one or more branches or cyclic groups.

[0089] "Hydroxyalkyl" refers to an alkyl group wherein one or more hydrogen atoms of the hydrocarbon group are

substituted with one or more hydroxy radicals, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like.

[0090] "Substituted alkyl" refers to an alkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, -NH$_2$, -NHCH$_3$, -NO$_2$, and -C$_{1-20}$ alkyl, wherein said -C$_{1-20}$ alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens, -CF$_3$, -OCH$_3$,-OCF$_3$, and -(CH$_2$)$_{0-20}$-COOH. In different embodiments 1, 2, 3 or 4 substituents are present. The presence of -(CH$_2$)$_{0-20}$-COOH results in the production of an alkyl acid. Non-limiting examples of alkyl acids containing, or consisting of, -(CH$_2$)$_{0-20}$-COOH include 2-norbornane acetic acid, tert-butyric acid, 3-cyclopentyl propionic acid, and the like.

[0091] The term "halo" encompasses fluoro, chloro, bromo and iodo.

[0092] "Heteroalkyl" refers to an alkyl wherein one of more of the carbon atoms in the hydrocarbon group is replaced with one or more of the following groups: amino, amido, -O-, -S- or carbonyl. In different embodiments 1 or 2 heteroatoms are present.

[0093] "Substituted heteroalkyl" refers to a heteroalkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, -NH$_2$, -NHCH$_3$, -NO$_2$, and -C$_{1-20}$ alkyl, wherein said -C$_{1-20}$ alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens, -CF$_3$, -OCH$_3$, -OCF$_3$, and -(CH$_2$)$_{0-20}$-COOH. In different embodiments 1, 2, 3 or 4 substituents are present.

[0094] "Alkenyl" refers to a hydrocarbon group made up of two or more carbons where one or more carbon-carbon double bonds are present. The alkenyl hydrocarbon group may be straight-chain or contain one or more branches or cyclic groups.

[0095] "Substituted alkenyl" refers to an alkenyl wherein one or more hydrogens are replaced with one or more substituents selected from the group consisting of halogen (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, -NH$_2$,-NHCH$_3$, -NO$_2$, and -C$_{1-20}$ alkyl, wherein said -C$_{1-20}$ alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens, -CF$_3$, -OCH$_3$, -OCF$_3$, and -(CH$_2$)$_{0-20}$-COOH. In different embodiments 1, 2, 3 or 4 substituents are present. "Aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to three conjugated or fused ring systems. Aryl includes carbocyclic aryl, heterocyclic aryl and biaryl groups. Preferably, the aryl is a 5- or 6-membered ring. Preferred atoms for a heterocyclic aryl are one or more sulfur, oxygen, and/or nitrogen. Non-limiting examples of aryl include phenyl, 1-naphthyl, 2-naphthyl, indole, quinoline, 2-imidazole, 9-anthracene, and the like. Aryl substituents are selected from the group consisting of -C$_{1-20}$ alkyl, -C$_{1-20}$ alkoxy, halogen (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, -NH$_2$, -NO$_2$, -C$_{1-20}$ alkyl substituted with halogens, -CF$_3$, -OCF$_3$, and -(CH$_2$)$_{0-20}$-COOH. In different embodiments the aryl contains 0, 1, 2, 3, or 4 substituents.

[0096] "Alkylaryl" refers to an "alkyl" joined to an "aryl".

[0097] The term "(C$_{1-12}$)hydrocarbon moiety" encompasses alkyl, alkenyl and alkynyl and in the case of alkenyl and alkynyl there is C$_2$-C$_{12}$.

[0098] For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different. For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

[0099] The pharmaceutically acceptable salts of the compounds of the invention which contain a basic center are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, with carboxylic acids or with organo-sulfonic acids. Examples include the HCl, HBr, HI, sulfate or bisulfate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccharate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts. Compounds of the invention can also provide pharmaceutically acceptable metal salts, in particular non-toxic alkali and alkaline earth metal salts, with bases. Examples include the sodium, potassium, aluminum, calcium, magnesium, zinc and diethanolamine salts (Berge, S. M. et al., J. Pharm. Sci., 66:1-19 (1977); Gould, P. L., Int'l J. Pharmaceutics, 33:201-17 (1986); and Bighley, L. D. et al., Encyclo. Pharma. Tech ., Marcel Dekker Inc, New York, 13:453-97 (1996).

[0100] The pharmaceutically acceptable solvates of the compounds of the invention include the hydrates thereof. Also included within the scope of the invention and various salts of the invention are polymorphs thereof. Hereinafter, compounds their pharmaceutically acceptable salts, their solvates or polymorphs, defined in any aspect of the invention (except intermediate compounds in chemical processes) are referred to as "compounds of the invention".

[0101] Designation "(amino acid)$_n$" means that an amino acid is repeated n times. For example, designation "(Pro)$_2$" or "(Arg)$_3$" mean that proline or arginine residues are repeated, respectively, two or three times.

[0102] MC4R agonists and pharmaceutically acceptable salts thereof described herein can also be used to treat individuals, including human subjects sdefective melanocortin receptor signaling, due to mutations/defects upstream of

the MC4R. MC4R agonists and pharmaceutically acceptable salts thereof described herein can also be used to treat individuals, including human subjects that carry mutations in the genes coding for pro-opiomelanocortin (POMC) and leptin such that these mutations result in POMC haplo-insufficientcy or haplo-deficiency and/or leptin haplo-insufficiency or haplo-deficiency.

[0103]   In one example embodiment, an MC4R agonist is a compound represented by structural formula (X):

(X)
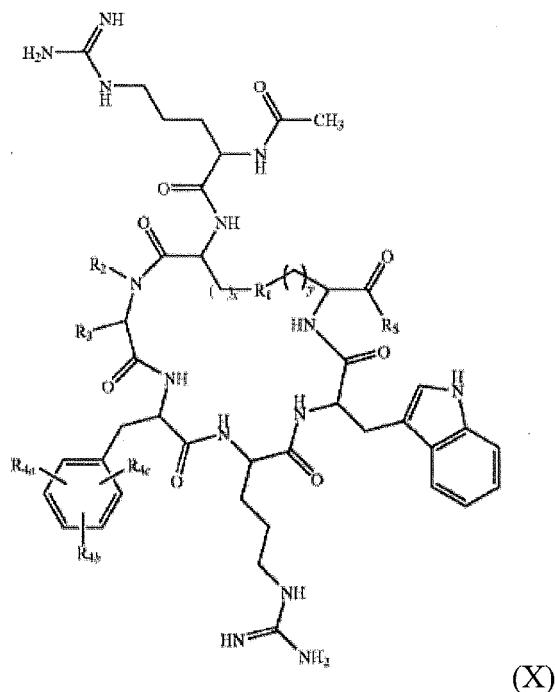
or a pharmaceutically acceptable salt thereof. In structural formula (X), the chemical substituents are defined as follows:

R_1 is -NH-C(O)- or -C(O)-NH-;
R_2 is -H, -CH_2-, or, R_2, together with R_3, forms a pyrrolidine ring optionally substituted with -OH;
R_3 is -$(CH_2)_2$- if R_2 is -CH_2-, and otherwise R_3 is selected from
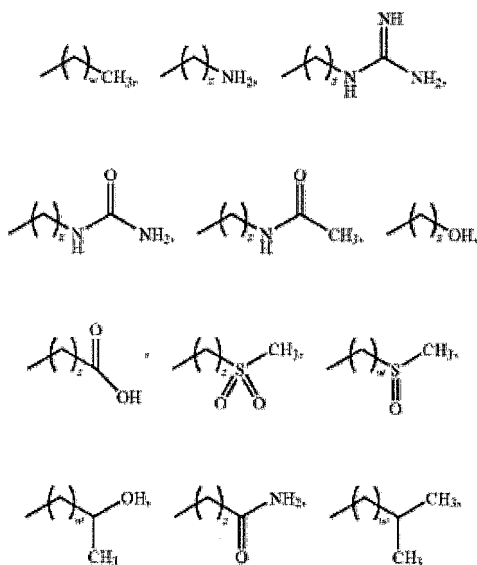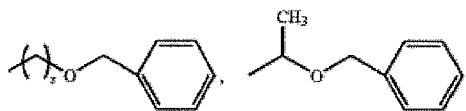
and

;
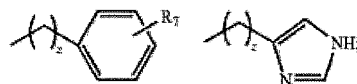
R_{4a}, R_{4b}, and R_{4c} are each independently selected from hydrogen, halo, (C_1-C_{10})alkyl-halo, (C_1-C_{10})alkyl-dihalo, (C_1-C_{10})alkyl-trihalo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, aryloxy, nitro, nitrile, sulfoniamide, amino, hydroxyl, carboxy, and akoxy-carbonyl. In one example embodiment, R_{4a}, R_{4b}, and R_{4c} is not hydrogen.

R_5 is -OH or -N(R_{6a})(R_{6b});

R_{6a} and R_{6b} are each independently H or C_1 to C_4 linear, branched or cyclic alkyl chain;

R_7 is -H or -C(O)-NH_2;

w is in each instance independently 0 to 5;

x is 1 to 5;

y is 1 to 5;

z is in each instance independently 1 to 5.

[0104] An example of a compound of structural formula (X) is a cyclic peptide defined by structural formula (XI):
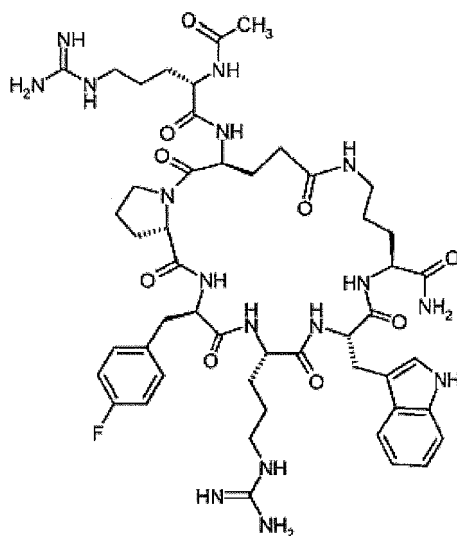
(XI),

or a pharmaceutically acceptable salt thereof.

EXEMPLIFICATION

Example 1: Model for Evaluating Whether Obese MC4R +/- Heterozygotic Mice Are Responsive to Treatment with Compound of SEQ ID NO: 140

[0105] The effect of MC4R agonist administration on a subject can be evaluated according to the following procedure.

[0106] The effects of a MC4 agonist in heterozygous MC4+/- mice and in weight-matched diet-induced-obesity (DIO) mice is evaluated. Heterozygous MC4+/- mice express a mild hyperphagic and obese phenotype when compared to the homozygous MC4-/- mice while retaining a putative response to MC4 stimulation. Weight-matched DIO mice are expressing the MC4 receptor (wild-type). In the course of the study, the effect of MC4 agonism on food intake and body weight in mice that are phenotypically obese but differ genetically in terms of the expression of the MC4 receptor is being

characterized.

[0107] Pre-Study activities: C57BL/6 mice (N = 50, males, 4 weeks of age) are pre-fed a high fat (HF) diet, commercially available from Research Diets Inc, New Brunswick, NJ, for10 weeks prior to enrollment onto study. The HF diet (D12492) is fed to the animals ad libitum.

[0108] Species (number, sex, age/weight): C57BL/6 mice (N = 40, males, 14 weeks of age at initiation of dose administration). Study criteria for animal enrollment based on body weight. B6-129/S-MC4+/- heterozygous mice (Jackson Labs or Taconic; N = 40, males, body weight matching the DIO mice, 12-14 weeks of age).

[0109] Formulations: all test materials are formulated once weekly.

[0110] Treatment: All animals are surgically implanted with a subcutaneous osmotic minipump (infusion duration of 14 days).

[0111] The design of this study is symmarized in Table A:

Table A

Study Design:						
Group No.	Mice	Animals per Group	Treatment	Dose Level and Volume	Treatment Regimen	Observation Period
1	MC4$^{+/-}$	10	Vehicle	0	Chronic Constant Infusion by Osmotic Minipump (Option 2)	14 days
2	DIO	10				
3	MC4$^{+/-}$	10	Peptide drug	Low		
4	DIO	10				
5	MC4$^{+/-}$	10		Mid		
6	DIO	10				
7	MC4$^{+/-}$	10		High		
8	DIO	10				

[0112] Cage side and clinical observations are performed daily, clinical observations are noted per exception. Food intake by mice is permitted daily. Body Weights: All animals have body weights measured once weekly during the pre-feed and twice weekly during administration, initiating prior to the initial dose administration. Doses are based on most recently collected body weight.

[0113] Fasting Whole Blood Glucose Levels and Plasma Sample Collection: Following an overnight fast, all animals have a fasting whole blood glucose level (via glucometer) and blood sample collected (~100 μL) on Days -1 and 14.

[0114] Euthanasia and Tissue Collection: All animals are scheduled for euthanasia on Day 15 in the AM. All animals have a maximum terminal blood collection made. Blood samples are processed for plasma for insulin measurement. All animals have the retroperitoneal adipose tissue and liver excised and weighed.

[0115] Insulin measurement: Insulin levels are determined in terminal plasma samples using a mouse insulin ELISA assay by the testing facility.

[0116] Reporting: Data submission including clinical observations, food intakes, body weights, insulin levels, fasting blood glucose and plasma collections, mortality record (if applicable), the study protocol and associated amendments, and all protocol deviations.

Example 2: Models for Clinical Evaluation of the Efficacy of Treatment of MC4R-Mediated Obesity Using Compounds Disclosed Herein

1. RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF COMPOUNDS OF THE PRESENT INVENTION ADMINISTERED TO HEALTHY OBESE NON-DIABETIC VOLUNTEERS

Objectives

Priamry:

[0117]

- Investigate the safety and tolerability of multiple dose levels of the compounds of the present invention when given by continuous subcutaneous (SC) infusion for 14 or 28 days.

Secondary:

[0118]

- Evaluate the pharmacokinetics (PK) of multiple dose levels of the compounds of the present invention when given by SC continuous infusion for 14 or 28 days.

Exploratory pharmacodynamic (PD) objectives of this study are to evaluate the effect of multiple dose levels of the compounds of the present invention when given by SC continuous infusion for 14 or 28 days on:

- Caloric intake, weight and waist circumference.
- Insulin sensitivity as measured by a Meal Tolerance Test (MTT).
- Hunger and satiety as measured by a Hunger/Satiety Questionnaire.
- Resting energy expenditure (REE) as measured by indirect calorimetry (to be performed at select centers with this capability).

Study Design

[0119] The study is designed to evaluate safety and tolerability of the compounds of the present invention administered up to 1 mg/kg/day for 14 or 28 days as a SC continuous infusion. The highest dose proposed to use in the study is no higher than 1 mg/kg. This is a randomized, double-blind, placebo-controlled, multiple ascending dose study during which 5 sequential cohorts of subjects will receive the compounds of the present invention or placebo by SC continuous infusion for 14 (Cohorts dosed for 14 days) or 28 days (Cohorts dosed for 28 days). Nine subjects will be enrolled in each cohort and subjects will be randomly allocated to receive the compounds of the present invention or placebo in a 6:3 ratio.
[0120] All subjects will remain confined to the Phase 1 clinical unit during treatment and under observation for at least 24 hours after the end of the study drug infusion.
[0121] A Clinical Safety Committee (CSC) will review blinded interim safety data from each dose level. Dose escalation will be recommended only if the previous dose level was deemed to be safe and well tolerated. Where appropriate, for safety reasons, additional interim dose levels (lower than the next scheduled dose) may be administered. Additionally, a sub-set of the general obese population may be enrolled. These subjects will meet all inclusion and exclusion criteria outlined in below, as well as one additional criterion: subjects must be heterozygous with a loss-of-function mutation in one of their two copies of the MC4 receptor gene. These subjects will have been pre-identified as having an MC4 receptor mutation. The rationale for this cohort is the lesser MC4 tone that is seen in heterozygous subjects, may give an altered sensitivity for these subjects to MC4 agonists such as the compounds of the present invention. If this cohort is enrolled, it is anticipated to be at a select site, nearer the end of the study.

Number of Subjects Planned

[0122] A sufficient number of healthy obese adult male and female subjects will be screened so that approximately 45 eligible subjects qualify for the study and are randomized. It is expected that approximately 45 subjects will be enrolled in approximately 5 dose groups to evaluate multiple days of dosing (14 or 28 days) of the compounds of the present invention administered by SC continuous infusion. Up to an additional 63 subjects may be enrolled to further characterize the compounds of the present invention with a maximum of approximately 108 subjects planned for treatment in the study. The additional subjects will be recruited in the event a subject needs to be replaced, a cohort is to be expanded or an intermediate dose is recommended by the CSC. It is intended that most cohorts will consist of 9 subjects (in a ratio of 2 active: 1 placebo). However some cohorts may be increased in order to enhance the sample size and further define any prior findings.

Diagnosis and Main Criteria for Inclusion

[0123] Subjects must meet all of the following inclusion criteria to be eligible for the study.

Inclusion criteria

[0124]

- Able to provide voluntary, written informed consent with comprehension of all aspects of the protocol, prior to any study procedures.
- Healthy obese male and female volunteers aged 18 to 55 years, inclusive.
- In good general health, without significant medical history, physical examination findings, or clinical laboratory abnormalities.
- Body Mass Index of 30-40 kg/m^2, inclusive.
- Stable body weight during the previous 6 months, based on Investigator judgment.
- Blood pressure <140/90 mmHg at Screening and D-1. Measurement may be repeated once within 24 hours, based on Investigator judgment.
- Females must not be pregnant and must have a negative serum pregnancy test result at the Screening Visit and Day -1.
- Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through the Final Study Visit: hormonal, condom with spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or IUD. Hormonal contraception must have started at least 3 months prior to screening. A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. Subjects must agree to practice the above birth control methods for 30 days from the final visit as a safety precaution.
- Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal range), do not require contraception during the study.
- Males with female partners of childbearing potential must agree to use two medically acceptable forms of contraception as described above, with one of the two forms being condom with spermicide, from the Screening Period through the Final Study Visit. Males with female partners of childbearing potential who themselves are surgically sterile (status post vasectomy) must agree to use condoms with spermicide over the same period of time. Male subjects must agree to practice the above birth control methods for 30 days from the final visit as a safety precaution.

Additional Inclusion Criteria for Heterozygous MC4 receptor mutation cohort:

[0125]

- Mutation of MC4R gene resulting in partial loss or complete loss of function of one of the MC4 receptor genes.

Exclusion criteria

[0126]

- Fasting blood glucose >126 mg/dL at screening.
- Resting heart rate <45 bpm or >90 bpm at screening.
- Abnormal thyroid stimulating hormone (TSH) or thyroxine (T$_4$) levels on screening.
- Elevated ALT or serum creatinine on screening or any clinically significant abnormalities on screening laboratory tests as determined by the Investigator.
- History of diabetes or of treated or medically diagnosed hypertension.
- Presence of a skin lesion suspicious for malignancy.
- History of malignancy except for treated cervical carcinoma in situ in the past 5 years.
- Active or history of any clinically significant medical condition including renal, hepatic, pulmonary, gastrointestinal, cardiovascular, genitourinary, endocrine, immunologic, metabolic, neurologic, psychiatric or hematological disease, based on Investigator judgment.
- Acute illness or history of illness, which in the opinion of the Investigator, could pose a threat or harm to the subject or obscure interpretation of laboratory test results or interpretation of study data.
- Positive hepatitis B surface antigen, positive hepatitis C antibody or positive HIV test at screening or a history of positive testing (e.g. liver biopsy, serology) suggesting acute or chronic hepatitis.
- Abnormal 12-lead electrocardiogram (ECG) at screening or pre-dose (Day -1 or Day 1), except minor deviations deemed to be of no clinical significance by the Investigator.
- Received any experimental drugs or devices within 30 days or 5 half lives, whichever is longer, prior to dosing.
- Ongoing participation in a prior clinical study at the time of screening.
- Blood donation within 60 days prior to screening or intent to donate within 60 days after Final Study Visit.
- Hospitalization for major surgery including but not limited to abdominal, thoracic, or cardiovascular surgery within the past 3 months prior to screening, or for a clinically significant non-surgical illness, based on Investigator judgment,

within the past 3 months.
- Planned elective surgery within 30 days of the Final Study Visit.
- Poor venous access or inability to tolerate venipuncture.
- History of drug hypersensitivity or anaphylaxis.
- History of hypersensitivity to proteins (e.g., allergy shots).
- Use of prescription medications on a regular basis. The last use of any prescription medication must have been greater than 5 half-lives for the specific medication or at least 14 days prior to admission (Day -1), whichever is longer. Hormonal contraception is allowed for female subjects.
- Use of a non-prescription drug and herbal substances during the study (through the Final Study Visit). The last dose of any non-prescription drug must have been taken greater than 5 half-lives for that drug before receiving study drug.
- Inability to attend all study visits or to comply with protocol requirements including fasting and restrictions on alcohol, caffeine, nicotine and concomitant medication intake.
- A significant history of drug/solvent abuse within 5 years of screening or a positive test for drugs of abuse test at screening or on Day -1.
- Positive alcohol (breath test) or nicotine screen at Screening Visit or Day -1.
- History of alcohol abuse (defined as average intake of three or more units of alcohol per day) within 5 years of the Screening Visit.
- History of tobacco or tobacco product use unless abstinent for at least one year prior to the Screening Visit.
- Previously randomized and dosed in this study.
- Any other reason, which in the opinion of the Investigator would confound proper evaluation of the study.

Test Products, Doses, and Mode of Administration

[0127] The compounds of the present invention and the placebo are formulated for administration by SC continuous infusion using an infusion pump.

[0128] The 5 dose levels planned, in ascending order, are:

- 0.01 mg/kg/24 hrs
- 0.1 mg/kg/24 hrs
- 0.25 mg/kg/24 hrs
- 0.5 mg/kg/24 hrs
- 1.0 mg/kg/24 hrs

[0129] The compounds of the present invention or placebo will be given by SC continuous infusion for 14 or 28 days. The dose levels evaluated may be modified based upon data from the single ascending dose study, or the prior MAD cohort.

Duration of Treatment

[0130] Overall study duration will be approximately 7 months. Individual subject participation in the study (screening, dosing, post-dosing assessments, follow-up) will be approximately 72 and 86 days for Cohorts dosed for 14 days and dosed for 28 days respectively.

[0131] The study will consist of a Screening Period, a Treatment Period and a Follow-up Period. The Screening Period will occur within 30 days prior to enrollment. The Treatment Period will consist of administration of a SC continuous infusion initiated on Day 1 and completed on Day 15 or Day 29 for Cohorts dosed for 14 days and Cohorts dosed for 28 days, respectively. Subjects will remain confined in the clinical research center (CRC) for approximately 24 hours following completion of the infusion and will be discharged from the CRC on Day 16 or 30 after all study procedures have been completed. Follow-up study visits are scheduled 1 and 4 weeks after the end of the study drug infusion.

Study Procedures

[0132] The procedures for each study period are briefly outlined below and are depicted in detail in the Schedule of Assessments (SOA).

Screening Period (Days -30 to -1)

[0133] After informed consent is obtained and eligibility assessed, screening assessments will be performed including: medical history; pregnancy test (all females); drug, nicotine and alcohol screen; safety laboratory tests (including clinical

chemistry, hematology and urinalysis), HbAlc and fructosamine, full physical examination (including weight, waist circumference and height), comprehensive skin examination performed by a Dermatologist, vital signs (including supine systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature); 12-lead electrocardiogram (ECG); HBsAg, HCV-Ab, HIV screening; samples of antibodies against the compounds of the present invention; Fitzpatrick scale; dietary recall review, indirect calorimetry (within 3 days of Day 1); previous and concomitant medication use.

Treatment Period

[0134]   Subjects will be admitted to the research unit on Day -1. After continued eligibility is confirmed, the following assessments will be performed: abbreviated physical exams including weight and waist circumference; vital signs; 12 lead ECG; safety laboratory tests (including clinical chemistry, hematology and urinalysis); lipid profile; level of antibodies against the compounds of the present invention; serum sample for storage; quantitative skin color measurement; photographic skin evaluation; Hunger/Satiety questionnaire; initiation of cardiac telemetry and ambulatory blood pressure (ABPM) monitoring; sample collection for 24 hour urine catecholamine and cortisol level determination; estimated caloric intake; Meal Tolerance Test (MTT), randomization; monitoring for AEs and concomitant medications.

[0135]   Upon initiation of study treatment on Day 1, the following assessments will be performed on Days 1-16 (Cohorts dosed for 14 days) or Days 1-29 (Cohorts dosed for 28 days) according to the SOA: abbreviated physical exam including weight and waist circumference; vital signs; cardiac telemetry, ABPM, 12-lead ECG, safety laboratory tests; lipid profile; sample collection for 24 hour urine catecholamine and cortisol level determination; sample collection for plasma free metanephrine levels, PK blood and urine sampling, melanocortin receptor genotyping; infusion site evaluation; quantitative skin color measurement; photographic skin evaluation; estimated caloric intake; MTT; HbAlc and fructosamine; Hunger/Satiety questionnaire; indirect calorimetry, monitoring for AEs and concomitant medications. Prior to discharge from the research unit, a serum pregnancy test will be performed on all females, and a comprehensive skin evaluation will be performed by a Dermatologist.

Follow-up Period

[0136]   One and 4 weeks after completion of the study treatment infusion, subjects will return to the research unit for the following assessments: complete physical exam including weight and waist circumference; comprehensive skin exam performed by a Dermatologist, quantitative skin color measurement; photographic skin evaluation; infusion site evaluation; vital signs; safety laboratory tests; lipid profile; HbAlc and fructosamine; levels of antibodies against the compounds of the present invention; Hunger/Satiety questionnaire, monitoring for AEs and concomitant medications.

Study Endpoints

Safety

[0137]   Safety will be evaluated by assessment of adverse events, ECGs, cardiac telemetry, ambulatory blood pressure monitoring, clinical laboratory evaluations (hematology, clinical chemistry including fasting blood glucose levels and urinalysis), lipid profile; levels of antibodies against the compounds of the present invention, urinary catecholamine levels, urinary free cortisol levels, plasma free metanephrine levels, vital signs (including blood pressure, respiratory rate, heart rate, and body temperature), physical examinations including infusion site evaluations and concomitant medication review.

Pharmacokinetic

[0138]   Serial blood sampling and urine collections for measurement of plasma and urinary levels of the compounds of the present invention will be conducted. All samples will be assayed for the compounds of the present invention from which the following PK parameters will be computed for each subject: $AUC_{0-\tau}$, C_{ave}, C_{max}, T_{max}, λz, $T_{1/2}$, CL/F, Vz/F, accumulation ratios, total urinary excretion and renal clearance.

Pharmacodynamic

[0139]   Caloric intake, weight and waist circumference, insulin sensitivity (as measured by MTT), hunger and satiety (using a Hunger/Satiety Questionnaire) and REE (using indirect calorimetry) will be assessed as exploratory PD endpoints. HbAc1 and fructosamine levels will also be assessed.

Sample Size Determination

[0140] The sample size for this Phase 1 first multiple-dose study in humans was not based on formal statistical determinations. The sample size for this study was chosen in consideration of limiting exposure to this new compound while providing information to evaluate the safety and effect of the compounds of the present invention in a Phase 1 first multiple-dose study.

Statistical Methods

[0141] Continuous variables will be summarized by dose (all placebo pooled) with descriptive statistics (number of observations, mean, SD, median, maximum, and minimum). Categorical variables will be tabulated by frequency of subjects by dose (all placebo pooled) and for the active treatment doses combined. The PD endpoints may be analyzed via analysis of variance if appropriate. All subject information and safety measurements will be based on the Safety Population.

CSC Data Review and Stopping Rules

[0142] The study design is such that successively higher doses will be administered to different groups of subjects after the safety and tolerability of the preceding dose has been established. Dose escalation recommendations are to be made by the CSC based upon a review of clinical safety data through Day 16 (Cohorts dosed for 14 days) or Day 30 (Cohorts dosed for 28 days).

Rules for Suspension of Dosing for a Subject:

[0143]

- An increase in SBP, sustained for a minimum of 30 minutes, either to >35 mmHg above mean baseline pre-dose SBP, or to >165 mmHg;
- An increase in DBP, sustained for a minimum of 30 minutes, either to >20 mmHg above mean baseline pre-dose DBP, or to >100 mmHg;
- Any increase in BP that is judged to be symptomatic, per the Investigator, regardless of duration;
- An increase in HR, sustained for a minimum of 30 minutes (or less in the judgment of the Investigator), to >35 bpm above mean baseline pre-dose HR;
- A prolonged spontaneous erection lasting more than 60 minutes, or a spontaneous painful erection of any duration based on Investigator judgment;
- Any other treatment-emergent AE that in the judgment of the Investigator poses a significant safety risk for that subject in the context of continued infusion of study drug.

Rules for Suspension or Termination of Dose Escalation:

[0144]

- An SAE that is deemed by the Investigator to be possibly or probably related to study drug occurs in any subject treated with the compounds of the present invention;
- A CTCAE Grade 3 (severe treatment emergent AE) or higher that is possibly or probably related occurs in a subject treated with the compounds of the present invention;
- A possibly or probably related treatment emergent AE not listed by the CTCAE occurs in a subject treated with the compounds of the present invention that is graded as severe or life threatening.

[0145] The CSC may also recommend suspension of the compounds of the present invention dose escalation based upon other conditions as deemed medically appropriate.

Rules for Suspension of Further Dosing:

[0146] The study may be immediately suspended and no additional doses administered if one or more subjects at any dose level develop any of the following adverse events deemed to be possibly or probably attributable to study drug:

- Anaphylaxis (i.e., angioedema, hypotension, bronchospasm, hypoxia or respiratory distress) in a subject treated

with the compounds of the present invention;

• Any clinically significant treatment-related AE that poses an undue risk to subjects in the opinion of the CSC.

2. RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF THE COMPOUND OF THE PRESENT INVENTION IN PATIENTS WITH OBESITY DUE TO AN MC4R MUTATION

Objectives

[0147]   The primary objective is to assess the effect of the compounds of the present invention vs. placebo on mean percent body weight loss when administered for 90 days by continuous SC infusion.
[0148]   Secondary objectives are to assess:

• The mean body weight (BW) loss in the active treatment group compared to the placebo group from baseline to Day 90.
• The proportion of patients who lose ≥5% of their baseline body weight in the active treatment group compared to the placebo group from baseline to Day 90.
• The pharmacokinetics (PK) of the compounds of the present invention when given by continuous SC infusion for 90 days.
• The safety and tolerability of the compounds of the present invention when given by continuous SC infusion for 90 days.
• The effect of the compounds of the present invention versus placebo on ambulatory blood pressure monitoring parameters (ABPM) when given by continuous SC infusion for 90 days (sub-study).
• The mean percent weight loss, mean weight loss, and proportion of patients who lose ≥ 5% of their baseline body weight in the active treatment group compared to the placebo group from baseline to Day 90 in patients who are severely obese (e.g., BMI ≥ 40 Kg/m^2; sub-study).

Exploratory pharmacodynamic objectives of this study are to evaluate the effect of the compounds of the present invention when given by SC continuous infusion for 90 days in all patients, and those in the severely obese sub-study, on:

• The proportion of patients who achieve a ≥ 10% decrease in body weight in the active treatment group compared to placebo from baseline to Day 90.
• The change in glucose and insulin during a Meal Tolerance Test (MTT) from Baseline to Day 90.
• Change in fasting glucose, insulin, insulin sensitivity, triglycerides, cholesterol, HDL, LDL, hs-CRP and HbAlc from Baseline to Day 90.
• Change in waist circumference from Baseline to Day 90.
• Change in body composition (assessed by Dual Energy X-Ray Absorptiometry (DXA)) from Baseline to Day 90 (sub-study).
• Change in hunger and satiety from Baseline to Day 90.
• Change in Impact of Weight on Quality of Life - Lite questionnaire (IWQOL-Lite) total score from Baseline to Day 90.
• Change in depression/suicidality score (assessed by PHQ-9 and C-SSRS) from Baseline to Day 90.
• Change in skin pigmentation (assessed by mexameter) from Baseline to Day 90.

Study Design

[0149]   This is a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of the compounds of the present invention when administered for 90 days to obese patients, inclusive of a sub-set of patients who are severely obese (BMI ≥ 40 Kg/m^2).
[0150]   Patients who are obese (BMI between 35-50 Kg/m^2), but otherwise healthy, will be enrolled. This study will be conducted on an outpatient basis. All patients will be required to self-administer study drug via an approved insulin infusion pump (OmniPod®) during the ~7 day placebo practice period. Patients with continued eligibility who have demonstrated the ability to successfully manage self-administration of placebo during the practice period will be randomized to the double blind 90 day Treatment Period.

Number of Patients Planned

[0151]   Approximately 70 patients will be enrolled into the study. There will be three sub-studies within the protocol. The first will include those patients who are severely obese (BMI ≥ 40 Kg/m^2, who will be stratified separately). Approximately 20 severely obese patients will be enrolled into this sub-study; these subjects will be recruited at all sites. The two remaining sub-studies will be enrolled at select sites. The first will be an ABPM sub-study where approximately 30

patients will be enrolled, and the final sub-study will include DXA scans on approximately 20 patients.

Diagnosis and Main Criteria for Inclusion

[0152] Patients must meet all of the following inclusion criteria to be eligible for the study:

1. MC4R heterozygous patients: mutation of MC4R gene.
2. Be between the age of 18 and 65.
3. Able to provide voluntary, written informed consent with comprehension of all aspects of the protocol, prior to any study procedures.
4. In good general health, without significant medical history, physical examination findings, or clinical laboratory abnormalities.
5. Body Mass Index: 35-50 Kg/m^2, inclusive. It is planned that approximately 20 of these patients will have a BMI $\geq$ 40 Kg/m^2.
6. Stable body weight (+/- 5 Kg) during previous 6 months.
7. Blood pressure (<140/90 mmHg); may include stable dose ($\geq$ 30 days of use) of up to two anti-hypertensive medications to achieve control that are intended to remain on a stable dose during the protocol.
8. Willingness and demonstrates ability to self administer study medication subcutaneously via a continuous infusion pump during the placebo practice period.
9. Willing to maintain a healthy diet and exercise regime throughout study as recommended by counseling at study start.
10. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through the completion of study treatment: hormonal, condom with spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or IUD. Hormonal contraception must have started at least 3 months prior to screening. A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. Patients must agree to practice the above birth control methods for 30 days after completion of study treatment as a safety precaution.
11. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal range), do not require contraception during the study.
12. Males with female partners of childbearing potential must agree to use two medically acceptable forms of contraception as described above, with one of the two forms being condom with spermicide, from the Screening Period through 90 days after completion of study treatment. Males with female partners of childbearing potential who themselves are surgically sterile (status post vasectomy) must agree to use condoms with spermicide over the same period of time.

If any of the following exclusion criteria are met, the patient is not eligible for the study:

1. Fasting blood glucose greater than 140 mg/dL.
2. HbAlc $\geq$6.5%.
3. TSH level outside the normal range.
4. Creatinine > 1.5 times the upper limit of normal.
5. Liver function tests > 2 times the upper limit of normal.
6. Active or history of any significant medical condition including renal, hepatic, pulmonary, gastrointestinal, cardiovascular, genitourinary, endocrine, immunologic, metabolic, neurologic or hematological disease.
7. Patients with a history of the following:

   a. Uncontrolled hypertension;
   b. Diabetes requiring medical treatment, presently or in the past;
   c. Major depressive disorder within the last 2 years;
   d. Any lifetime history of a suicide attempt;
   e. Any suicidal behavior in the last month;
   f. Other severe psychiatric disorders (e.g. schizophrenia, bipolar disorder, severe eating disorders including bulimia).

8. A PHQ-9 score of $\geq$15.
9. Any suicidal ideation of type 4 or 5 on the C-SSRS.
10. Prior bariatric surgery.

11. History or close family history (parents or siblings) of melanoma.

12. Significant dermatologic findings as part of the Screening comprehensive skin evaluation performed by the dermatologist. Any concerning lesions identified during the screening period will be biopsied and results known to be benign prior to randomization. If the pre-treatment biopsy results are of concern, the patient will be excluded from the study.

13. Treated with anorectic agents or drugs with anorexia as a frequent side event.

14. Taking 3 or more anti-hypertensive medications.

15. Acute illness or history of illness, which in the opinion of the Investigator, could pose a threat or harm to the patient or obscure interpretation of laboratory test results or interpretation of study data.

16. History of any malignancy, past or present, including skin cancer, multiple severely dysplastic nevi, or nevoid basal cell carcinoma.

17. History of HIV infection.

18. History of significant drug hypersensitivity or anaphylaxis.

19. History of hypersensitivity to proteins (e.g., allergy shots).

20. Any clinically significant abnormalities on screening laboratories as determined by the Investigator.

21. Abnormal 12-lead electrocardiogram (ECG) at screening or pre-dose (Day 1), except minor deviations deemed to be of no clinical significance by the Investigator. QTc must be < 450 ms.

22. Received any experimental drugs or devices or have participated in a clinical study within 30 days prior to dosing.

23. Blood donation within 60 days prior to screening or intent to donate up to 60 days after Final Study Visit.

24. Hospitalization for surgery within the 3 months prior to screening except for minor outpatient procedures, or any planned hospitalizations during the study period.

25. Poor venous access or inability to tolerate venipuncture.

26. Inability to attend all study visits or comply with protocol requirements including fasting and restrictions on concomitant medication intake.

27. Participation in weight loss programs during the study period, including nutritional supplements/ replacements other than as recommended by nutritional counseling provided at study start.

28. Use of prescription medications on a regular basis with the following exceptions:

  a. Contraceptives (must be on for ≥3 months);
  b. Hormone replacement therapy (must be on stable dose for ≥3 months);
  c. Antihypertensives (<3 medications on a stable dose for ≥ 30 days);
  d. Statins (dose must be ≤ half the maximum dose; must be on a stable dose ≥3 months);
  e. Fibrates (must be on stable dose for ≥3 months);
  f. Niacin (must be on stable dose for ≥3 months);
  g. Thyroxin (stable dose for ≥ 30 days);
  h. The last use of any other prescription medication must have been greater than 5 half-lives for the specific medication or at least 14 days prior to randomization, whichever is longer.

29. Women who are pregnant or are breast feeding.

30. Previously randomized and dosed in this study or previously exposed to the compounds of the present invention.

31. History of alcohol or drug abuse within 5 years of Screening Visit.

32. Any other reason, which in the opinion of the Investigator would confound proper evaluation of the study.

Test Products, Doses, and Mode of Administration

[0153]   The compounds of the present invention will be supplied as sterile solutions for infusion. The product will be manufactured at a concentration of 2.0 mg/mL at pH 5 with a fill volume of 11 mL/vial. Placebo will be vehicle. Drug products and placebo consist of sodium phosphate and citric acid, including 0.5% phenol as a preservative. Both the compounds of the present invention and placebo multiuse vials may be punctured multiple times under sterile conditions. The compounds of the present invention and placebo will be administered as a continuous subcutaneous infusion using the FDA approved insulin infusion pump, Insulet's OmniPod® (infusion pump which is wireless/tubeless and does not require a traditional infusion set, inclusive of an auto-injector whereby the patient never sees the needle or cannula). A total daily dose of 1 mg/24 hours of the compounds of the present invention, or equivalent volume of placebo, will be self-administered via continuous SC infusion during the treatment period.

Duration of Treatment

[0154]   The overall study duration will be approximately 9 months, as currently planned. Individual patient participation

in the study (Screening Period, Treatment Period and Follow-up Period) will be approximately 7 months.

Screening, inclusive of the placebo practice period, will occur within 30 days prior to randomization. Patients who successfully complete the open label placebo practice period will be randomized to double blind treatment for 90 days. The Final Visit will occur approximately 90 days after the last dose of study drug is administered (Day 180).

Study Procedures

[0155] The study will consist of a Screening Period inclusive of 2 visits. Patients who demonstrate compliance with the continuous infusion will be randomized to a double-blind treatment regimen (at Visit 3) and will begin 90 days of double-blind, self-administered SC continuous infusion, outpatient treatment. Additional clinic visits are scheduled on approximately Day 7 (Visit 4), Day 14 (Visit 5), Day 28 (Visit 6), Day 56 (Visit 7) and at the end of treatment (Day 90, Visit 8). Patients will also be contacted by telephone weekly during the first month of treatment, followed by bi-weekly contact during the remaining Treatment Period to encourage compliance and to assess adverse events. Follow up Visits will be scheduled monthly for 3 months after completion of the 90-day Treatment Period. The Final Visit will occur ~90 days after the last dose of study drug is administered (Day 180, Visit 11).

Screening Period (Days -30 to -1)

[0156] The Screening Period consists of 2 visits; the first where patients will be assessed for study qualification. Eligible patients will then proceed onto the second screening visit which will consist of an open label placebo practice period to ensure study patients can self-administer placebo drug via an FDA approved SC insulin infusion pump for approximately 1 week.

Visit 1

[0157] During Visit 1, following signed, written informed consent, confirmation of eligibility will be performed. Medical history, physical examination (including vital signs, height and weight and waist circumference measurements), a comprehensive skin exam will be conducted by the Dermatologist, quantitative skin measurement, Fitzpatrick scale and Edmond Obesity Staging System (EOSS) assessments, concomitant medication review, clinical laboratory tests including HbA1c, serum pregnancy test or follicle-stimulating hormone test, and a 12-lead ECG will be performed at this visit. The PHQ-9 and C-SSRS will be administered. Hunger and satiety questionnaire will also be administered.

Visit 2

[0158] During visit 2, patients confirmed to be eligible at Visit 1 and who continue to meet the inclusion and exclusion criteria upon review of medical history since the prior visit as well as AE and concomitant medication review, will have their weight and waist circumference measured and vital signs measured. Study staff will train patients and instruct them on proper technique of how to use the OmniPod® at this visit. Patients will be required to demonstrate understanding by successfully filling the OmniPod® with placebo, successfully placing the pod on an appropriate body area, and starting the infusion while at site. The study patients will change the OmniPod® approximately 2-3 times during the ~7 day period between Visits 2 and 3.

[0159] For those patients participating in the ABPM sub-study, an additional clinic visit will be necessary.

Treatment Period (Days 1-90)

[0160] Patients will return to the clinic approximately 7 days after starting the placebo practice period. Study patients who successfully complete the open label placebo practice period will return for Visit 3 (Day 1), and be randomized to 90 days of double-blind study treatment. Additional clinic visits are scheduled on approximately Day 7 (Visit 4), Day 14 (Visit 5), Day 28 (Visit 6), Day 56 (Visit 7) and at the end of treatment (Day 90, Visit 8). During these visits, a variety of efficacy, safety and exploratory assessments will be performed, according to the SOA.

[0161] Efficacy will be evaluated by measuring body weight. Safety will be evaluated by assessment of adverse events, vital signs (including blood pressure, respiratory rate, heart rate, and body temperature), ECGs, ABPM (sub-study), clinical laboratory evaluations (hematology, clinical chemistry including fasting blood glucose and insulin levels and urinalysis), lipid profile; levels of antibodies against the compounds of the present invention, quantitative skin assessments (mexameter) and photographic skin evaluation, protocol defined pigmented skin lesion biopsies, physical examinations including infusion site evaluations and concomitant medication review. Additionally, changes in depression/suicidality as assessed by the C-SSRS and PHQ-9 will be monitored. Plasma concentrations of the compounds of the present invention will be summarized and may be compared to PD parameters.

[0162] Exploratory measurements will be assessed by insulin sensitivity (as measured by MTT and HOMA-IR), effects on Hs-CRP and HbA1c, hunger and satiety (using a Hunger/Satiety Questionnaire), body composition (using DXA at select sites), changes in waist circumference, and changes in IWQOL-Lite, PHQ-9 and C-SSRS will be assessed as exploratory endpoints.

[0163] For patients who do not complete the full 90 day treatment period, attempts will be made to have the patient return for continued follow-up visits in order to monitor patient safety, as well as any effects on pharmacodynamic assessments.

Follow-up Period (Days 91-180)

[0164] Upon completion of the 90 day Treatment Period, Patients will enter a 90 day post-treatment Follow-up Period consisting of 3 monthly visits, where a variety of safety and efficacy assessments according to the SOA. The Final Study Visit will occur on approximately Day 180.

[0165] In the event an AE is ongoing at the time of the Final Visit, additional visits should be scheduled, at a frequency deemed appropriate by the Investigator, in order to follow the event to resolution. If a patient experiences a Serious Adverse Event for which follow-up laboratories and review are required, the Investigator will schedule additional post-treatment visits as necessary.

Study Endpoints

[0166] The primary endpoint will be evaluated by assessment of mean percent body weight loss. Secondary endpoints will be evaluated by assessments of weight, as well as safety and tolerability, including the ABPM sub-study. Plasma concentrations of the compounds of the present invention will be summarized and may be compared to various endpoints. In addition, weight loss parameters will be summarized in the severely obese patient sub-study.

Safety

[0167] Safety will be evaluated by assessment of adverse events, vital signs (including blood pressure, respiratory rate, heart rate, and body temperature), ECGs, clinical laboratory evaluations (hematology, clinical chemistry including fasting blood glucose and insulin levels and urinalysis), lipid profile; levels of antibodies against the compounds of the present invention, quantitative skin assessments (mexameter) and photographic skin evaluation, protocol defined pigmented skin lesion biopsies, physical examinations including infusion site evaluations and concomitant medication review. Additionally, changes in depression/suicidality as assessed by the C- SSRS and PHQ-9 will be monitored.

Pharmacokinetic

[0168] Plasma concentrations of the compounds of the present invention will summarized and may be compared to PD endpoints.

Exploratory

[0169] Exploratory measurements will be assessed by insulin sensitivity (as measured by MTT and HOMA-IR), effects on Hs-CRP and HbA1c, hunger and satiety (using a Hunger/Satiety Questionnaire), body composition (using DXA at select sites), changes in waist circumference, and changes in IWQOL-Lite and C-SSRS will be assessed as exploratory endpoints.

Sample Size Determination

[0170] Sample size per arm was calculated to target a 5 percentage point difference in mean weight change between a treatment arm and the placebo arm. From data reported by Gadde (2011), an SD of 5.7% was computed for weight change after 16 weeks of treatment. Assuming the SD in this study will be 5% to 6%, the sample size of N=30 completing subjects (accounting for 5 dropouts per dose group) has 97% power to yield a statistically significant (alpha=0.025, 1-sided) difference between an active dose group and placebo if the true underlying difference in means is 5 percentage points, and the SD is 5%. If the SD is 6%, there is 89% power.

Statistical Methods

[0171] Continuous variables will be summarized by dose group with descriptive statistics (e.g., number of observations,

mean, SD, median, maximum, and minimum). Categorical variables will be tabulated by frequency of patients per dose group. All patient information and safety measurements will be based on the Safety Population, which will include all patients who receive a dose of study drug and have a post baseline observation.

[0172] Analyses will be based on observed data only; no data will be imputed.

[0173] Continuous efficacy endpoints will be assessed via a longitudinal mixed analysis of variance model which will include fixed effects terms for treatment, timepoint, treatment-by-timepoint interaction, and baseline covariate, and random effect for subjects. The assumption of normality will be assessed via the Shapiro-Wilk statistic. If substantial departure from normality is observed, a transformation such as log (post/pre) or rank may be used to analyze the data.

[0174] The comparison of the compounds of the present invention with placebo will be carried out via 1-sided statistical test at alpha=0.025.

Guidelines for Additional Safety Monitoring and Suspension of Dosing of a Patient

[0175] Patients will be monitored carefully during the treatment period during on site clinic visits as well as periodic telephone calls made to the patients by the study staff. In the event a patient is withdrawn from treatment due to an AE, the patient should be encouraged to complete the remaining study visits in order to monitor the event to resolution and obtain additional protocol defined safety assessments. Additionally, guidance will be provided for any worsening of depression or suicidality during the study. At all times, this guidance is subject to the clinical judgment of the Investigator and study consultants (if applicable).

[0176] The Investigator shall notify the Medical Monitor in the event any study participant fulfills any of the criteria defined in the appendices noted above, or undergoes additional monitoring for any of the events defined herein.

Example 3: *Treatment of Obese MC4R +/- Heterozygotic Mice with Compound of SEQ ID NO: 140*

[0177] Diet induced obesity (DIO) littermate C57B1/6J mice that were either wild type with respect to MC4R gene (+/+), or heterozygous for the MC4R gene (+/-), or homozygous MC4R knockout mice that do not express the MC4R gene at all (-/-) were exposed to the compound of SEQ ID NO: 140: Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 by Alzet pump infusion of at a concentration of 1200 nmol/kg/day for 8 days. Body weight was measured.

[0178] The data is presented in FIG. 3. The data shows that mice that were heterozygous for the MC4R gene (+/-) lost significant body weight (about 1 gram) over the treatment period while rodents that did not express the MC4R gene, did not show significant weight loss over this time period.

[0179] The weight change due to the exposure to the compound of SEQ ID NO: 140 in mice that are either wild type for the MC4R gene, or express only a single MC4R allele, or mice without any MC4R protein expression were compared. The data suggests that human patients with one functional MC4R allele, where their obesity is caused by the loss of function of the MC4R allele, will respond to the SEQ ID NO: 140, resulting in weight loss.

SEQUENCE LISTING

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<400> 45

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Xaa Asp His Phe Arg Trp Xaa Lys
1               5
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<210> 46
<211> 8
<212> PRT
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<220>
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<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<223> C-term NH2

<400> 46

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                              1                   5
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<210> 47
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<212> PRT
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<220>
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<220>
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<220>
<221> MOD_RES
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<223> Gaba

<220>
<223> C-term NH2

<400> 47

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1   5

<210> 48
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<220>
<223> C-term NH2

<400> 48

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                      1                   5
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<223> D-Phe

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<221> MOD_RES
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<223> Gaba

<220>
<223> C-term NH2

<400> 49

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           1   5

<210> 50
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<223> D-Phe

<220>
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<223> D-Trp

<220>
<223> C-term NH2

<400> 50

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                    1               5
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<210> 51
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<223> Cyclic

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<223> D-Phe

<220>
<221> MOD_RES
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<223> D-Trp

<220>
<223> C-term NH2

<400> 51

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                    1               5
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<210> 52
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<223> D-Trp

<220>
<223> C-term NH2

<400> 52

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                              1                   5
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<210> 53
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<223> D-Phe

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<223> D-Trp

<220>
<223> C-term NH2

<400> 53

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                              1                   5
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<210> 54

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<220>
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<223> D-Trp

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<400> 54

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            1                   5
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<210> 55
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<223> D-Phe

<220>
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<223> D-Trp

<220>
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<223> D-Ala

<220>
<223> C-term NH2

<400> 55

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                              1                   5
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<210> 56
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<220>
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<222> (4)..(4)
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<220>
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<220>
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 56

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Xaa Asp His Phe Arg Trp Ala Lys
1                   5
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<210> 57
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<223> C-term NH2

<400> 57

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Xaa Asp His Phe Arg Trp Xaa Lys
1                   5
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<210> 58
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<220>
<223> C-term NH2

<400> 58

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<210> 59
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<220>
<223> C-term NH2

<400> 59

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                              1                   5
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<210> 60
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<220>
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<220>
<223> C-term NH2

<400> 60

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<220>
<223> C-term NH2

<400> 61

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                    1                   5
```

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<223> D-Trp

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<223> Ahx

<220>
<223> C-term NH2

<400> 62

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                              1                   5
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<210> 63
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<223> D-Trp

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<220>
<223> C-term NH2

<400> 63

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                              1                   5
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<210> 64
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<223> D-Ala

<220>
<223> C-term NH2

<400> 64

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            1               5
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<223> Cyclic

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<220>
<223> C-term NH2

<400> 65

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            1               5
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<210> 66
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<223> Cyclic

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<223> D-2-Nal

<220>
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<223> 2-Nal

<220>
<223> C-term NH2

<400> 66

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                              1                   5
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<210> 67
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<223> Cyclic

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<223> 1-Nal

<220>
<223> C-term NH2

<400> 67

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                              1                   5
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<210> 68
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<223> Cyclic

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<222> (3)..(3)
<223> D-Ala

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<221> MOD_RES
<222> (5)..(5)
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<220>
<221> MOD_RES
<222> (7)..(7)
<223> 2-Nal

<220>
<223> C-term NH2

<400> 68

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                              1                   5
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<210> 69

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<220>
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<223> Cyclic

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<222> (3)..(3)
<223> D-Ala

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<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<223> C-term NH2

<400> 69

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                        1                   5
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<210> 70
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<223> Nle

<220>
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<223> Cyclic

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<223> D-Ala

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<223> 2-Nal

<220>
<223> C-term NH2

<400> 70

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Xaa Cys Ala His Phe Arg Xaa Cys
1               5
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<210> 71
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<223> Nle

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<223> Cyclic

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<220>
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<223> D-Phe

<220>
<221> MOD_RES
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<223> 1-Nal

<220>
<223> C-term NH2

<400> 71

Xaa Cys Ala His Phe Arg Xaa Cys
1   5

<210> 72
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<220>
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<220>
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<223> D-Phe

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<220>
<223> C-term NH2

<400> 72

Xaa Cys Ala His Phe Arg Xaa Cys
1   5

<210> 73
<211> 8
<212> PRT
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<223> D-Glu

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<220>
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<400> 73

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                              1               5
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<210> 74
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<223> D-Phe

<220>
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<223> D-Ala

<220>
<223> C-term NH2

<400> 74

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                              1               5
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<210> 75
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<220>
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<223> D-2-Nal

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<223> Bal

<220>
<223> C-term NH2

<400> 75

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                              1               5
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<210> 76

<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

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<223> Pen

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<223> D-Ala

<220>
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<222> (5)..(5)
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<220>
<223> C-term NH2

<400> 76

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Xaa Xaa Ala His Phe Arg Trp Cys
1               5
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<210> 77
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<212> PRT
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<220>
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<223> Cyclic

<220>
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<220>
<223> C-term NH2

<400> 77

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Xaa Cys Ala His Phe Arg Trp Xaa
1                   5
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<210> 78
<211> 8
<212> PRT
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<220>
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<223> Nle

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1                   5
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<220>
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1               5
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<223> D-Phe

<220>
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<223> Pen

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<223> C-term NH2

<400> 145

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<223> Cyclic

<220>
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<223> D-Phe

<220>
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<400> 146

Arg Asp His Phe Arg Trp Ala Lys
1   5

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<220>
<223> C-term NH2

<400> 147

Arg Asp His Phe Arg Trp Ala Lys
1   5

<210> 148
<211> 9
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<220>
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<223> D-Ala

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<220>
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<400> 148

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1                   5
```

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Xaa Cys Ala His Phe Arg Trp Ala Cys
1                   5
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1                   5
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                              Xaa Cys Ala His Phe Arg Trp Xaa Cys
                              1   5

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<223> D-Phe

<220>
<223> C-term NH2

<400> 153

                              Cys Glu His Phe Arg Trp Ala Cys
                              1   5

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<223> Cyclic

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<223> D-Phe

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<222> (6)..(6)
<223> 2-Nal

15

<220>
<223> C-term NH2

<400> 154

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                              Cys Glu His Phe Arg Xaa Ala Cys
                              1               5
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30   <223> Description of Artificial Sequence: Synthetic peptide

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35   <220>
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45   <220>
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<223> D-Phe

50   <220>
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<400> 155

55
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                              Cys Ala His Phe Arg Trp Ala Cys
                              1               5
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<210> 156

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<400> 156

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                        Cys Ala His Phe Arg Xaa Ala Cys
                        1                   5
```

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<223> D-Ala

<220>
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<220>
<223> C-term NH2

<400> 157

Xaa Cys Ala His Phe Arg Trp Ala Cys
1   5

<210> 158
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<400> 158

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                                1              5


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         <223> Nle

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         <223> Cyclic

         <220>
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         <222> (15)..(15)
         <223> D-2-Nal

         <220>
         <223> C-term NH2

         <400> 159

         Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Xaa Asp His Xaa Arg
         1               5                   10                  15


         Trp Lys

         <210> 160
         <211> 19
         <212> PRT
         <213> Artificial Sequence

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         <223> Nle
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<220>
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<223> D-2-Nal

<220>
<223> C-term NH2

<400> 160

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        Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Xaa Xaa Asp His Xaa
        1               5                   10                  15


        Arg Trp Lys
```

<210> 161
<211> 19
<212> PRT
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-2-Nal

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 161

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Xaa Asp His Xaa Arg Trp Lys Ala Tyr Gly Arg Lys Lys Arg Arg Gln
1               5                   10                  15
```

```
Arg Arg Arg
```

<210> 162
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<223> Cyclic

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<223> D-2-Nal

<220>
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<222> (8)..(8)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 162

```
Xaa Asp His Xaa Arg Trp Lys Ala Tyr Gly Arg Lys Lys Arg Arg Gln
1               5                   10                  15
```

```
Arg Arg Arg
```

<210> 163
<211> 20
<212> PRT
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190

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<223> Doc

<220>
<223> C-term NH2

<400> 163

```
Xaa Asp His Xaa Arg Trp Lys Xaa Xaa Tyr Gly Arg Lys Lys Arg Arg
1               5               10              15
```

```
Gln Arg Arg Arg
            20
```

<210> 164
<211> 22
<212> PRT
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<223> Cyclic

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<221> MOD_RES
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<223> D-2-Nal

<220>
<223> C-term NH2

<400> 164

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        Xaa Asp His Xaa Arg Trp Lys Pro Pro Lys Asp Tyr Gly Arg Lys Lys
        1                5                   10                  15

        Arg Arg Gln Arg Arg Arg
                    20
```

<210> 165
<211> 23
<212> PRT
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<220>
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<220>
<221> MOD_RES
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<223> D-2-Nal

<220>
<223> C-term NH2

<400> 165

```
        Cys Glu His Xaa Arg Trp Gly Cys Pro Pro Lys Asp Tyr Gly Arg Lys
        1                5                   10                  15

        Lys Arg Arg Gln Arg Arg Arg
                    20
```

<210> 166
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 166

```
        Xaa Asp His Xaa Arg Trp Lys Ala Ala Tyr Gly Arg Lys Lys Arg Arg
        1               5                   10                  15

        Gln Arg Arg Arg
                    20
```

<210> 167
<211> 23
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<223> D-2-Nal

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<223> Doc

<220>
<223> C-term NH2

<400> 167

```
        Xaa Asp His Xaa Arg Trp Lys Pro Pro Lys Asp Xaa Tyr Gly Arg Lys
        1                   5                   10                  15


        Lys Arg Arg Gln Arg Arg Arg
                        20
```

<210> 168
<211> 24
<212> PRT
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<220>
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<220>
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<223> D-2-Nal

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<223> Doc

<220>
<223> C-term NH2

<400> 168

```
        Cys Glu His Xaa Arg Trp Gly Cys Pro Pro Lys Asp Xaa Tyr Gly Arg
        1                   5                   10                  15


        Lys Lys Arg Arg Gln Arg Arg Arg
                        20
```

<210> 169
<211> 24
<212> PRT
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<220>
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<223> D-2-Nal

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<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 169

```
Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
1               5                   10                  15

Lys Lys Arg Arg Gln Arg Arg Arg
            20
```

<210> 170
<211> 24
<212> PRT
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<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Doc

<220>
<223> C-term NH2

<400> 170

```
        Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Xaa Tyr Gly Arg
        1               5                   10                  15

        Lys Lys Arg Arg Gln Arg Arg Arg
                        20
```

<210> 171
<211> 20
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<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 171

```
        Xaa Asp His Xaa Arg Trp Lys Xaa Xaa Tyr Gly Arg Lys Lys Arg Arg
        1               5                   10                  15

        Gln Arg Arg Arg
                20
```

<210> 172
<211> 24
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

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<223> 2-Nal

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<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 172

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        1               5                   10                  15


        Lys Lys Arg Arg Gln Arg Arg Arg
                        20
```

<210> 173
<211> 22
<212> PRT
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<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<223> Cyclic

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<223> D-2-Nal

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<222> (6)..(6)
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<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 173

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Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Arg
1               5                   10                  15

Arg Arg Gln Arg Arg Arg
            20
```

<210> 174
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

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<223> D-2-Nal

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<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 174

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        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Gly Arg Arg
        1               5               10              15
```

```
        Arg Arg Arg Gln Arg Arg Arg
                        20
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<210> 175
<211> 24
<212> PRT
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<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 175

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        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5               10              15
```

```
        Arg Arg Arg Arg Gln Arg Arg Arg
                        20
```

<210> 176
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<223> Description of Artificial Sequence: Synthetic peptide

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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 176

```
Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
1               5                   10                  15
```

```
Lys Lys Arg Gln Arg Arg Arg Arg
            20
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<210> 177
<211> 24
<212> PRT
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<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 177

```
        Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15
```

```
        Lys Lys Gln Arg Arg Arg Arg Arg
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<210> 178
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<212> PRT
<213> Artificial Sequence

<220>
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<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 178

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        Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15
```

```
        Lys Gln Lys Arg Arg Arg Arg Arg
                    20
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<210> 179
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 179

```
    Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
    1               5                   10                  15

    Lys Lys Arg Arg Arg Arg Gln Arg
                20
```

<210> 180
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
<221> DOMAIN
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<223> Cyclic

<220>
<221> MOD_RES
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<221> MOD_RES
<222> (15)..(15)
<223> Aib

<220>
<223> C-term NH2

<400> 180

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Xaa Arg
        1               5               10              15

        Lys Lys Arg Arg Gln Arg Arg Arg
                    20
```

<210> 181
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 181

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Arg Arg Arg
        1               5               10              15

        Arg Arg Gln Arg Arg Arg
                    20
```

<210> 182
<211> 22
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 182

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Arg
        1               5                   10                  15
```

```
        Arg Arg Gln Arg Arg Arg
                    20
```

<210> 183
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<222> (1)..(8)
<223> Cyclic

<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 183

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Arg
1               5                   10                  15
```

```
Arg Arg Arg Gln Arg Arg Arg
            20
```

<210> 184
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Cyclic

<220>
<221> MOD_RES
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 184

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Arg Arg Arg
        1               5               10                  15
```

```
        Arg Arg Gln Arg Arg Arg
                    20
```

<210> 185
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<222> (1)..(8)
<223> Cyclic

<220>
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<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 185

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Arg
        1               5               10                  15
```

```
        Arg Arg Gln Arg Arg Arg
                    20
```

<210> 186
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
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<223> D-2-Nal

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<221> MOD_RES
<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 186

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Arg
1               5                   10                  15
```

```
Arg Arg Arg Gln Arg Arg Arg
            20
```

<210> 187
<211> 23
<212> PRT
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<223> Cyclic

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<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 187

```
    Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Arg Arg Arg
    1               5               10                  15

    Arg Arg Arg Gln Arg Arg Arg
                20
```

<210> 188
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Cyclic

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<223> D-2-Nal

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<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 188

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Arg Arg Arg
        1               5               10                  15
```

```
        Arg Arg Gln Arg Arg Arg
                    20
```

<210> 189
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Cyclic

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<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 189

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Arg
        1               5               10                  15
```

```
        Arg Arg Arg Gln Arg Arg Arg
                    20
```

<210> 190
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

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<223> N-term Ac

<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 190

```
        Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15


        Lys Lys Arg Arg Arg Gln Arg Arg
                        20
```

<210> 191
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<222> (1)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 191

```
        Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15

        Gln Lys Lys Arg Arg Arg Arg Arg
                    20
```

<210> 192
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 192

```
        Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15

        Lys Lys Arg Arg Arg Arg Arg Gln
                    20
```

<210> 193
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 193

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15


        Lys Lys Arg Arg Gln Arg Arg Arg
                    20
```

<210> 194
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Cyclic

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<223> D-2-Nal

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<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 194

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5               10              15

        Lys Lys Arg Arg Gln Arg Arg Arg
                    20
```

<210> 195
<211> 22
<212> PRT
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<220>
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<223> Cyclic

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<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 195

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Lys
        1               5               10              15

                        Arg Arg Gln Arg Arg Arg
                                20
```

<210> 196
<211> 22
<212> PRT
<213> Artificial Sequence

5

<220>
<223> Description of Artificial Sequence: Synthetic peptide

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10
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<220>
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15
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20
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<220>
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<222> (6)..(6)
25
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
30
<223> Beta-Ala

<220>
<223> C-term NH2

35
<400> 196

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Lys Arg
1               5               10                  15
```

40

```
Arg Arg Gln Arg Arg Arg
            20
```

<210> 197
45
<211> 22
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50
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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55
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<223> Cyclic

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<223> D-2-Nal

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<221> MOD_RES
<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 197

```
      Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Lys
      1               5               10              15
```

```
      Arg Arg Gln Arg Arg Arg
                  20
```

<210> 198
<211> 24
<212> PRT
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<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 198

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15


        Arg Lys Arg Arg Gln Arg Arg Arg
                    20
```

<210> 199
<211> 23
<212> PRT
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<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 199

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Gly Arg Arg
        1               5                   10                  15


        Lys Arg Arg Gln Arg Arg Arg
                    20
```

<210> 200
<211> 23
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 200

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Gly Arg Lys
1               5               10                  15


Arg Arg Arg Gln Arg Arg Arg
            20
```

<210> 201
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<212> PRT
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<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 201

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15


        Arg Lys Arg Arg Gln Arg Arg Arg
                        20
```

<210> 202
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<222> (1)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 202

```
          Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
          1               5                   10                  15

                          Lys Arg Arg Arg Gln Arg Arg Arg
                                      20
```

<210> 203
<211> 23
<212> PRT
<213> Artificial Sequence

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<220>
<223> N-term Ac

<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 203

```
          Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Gly Arg Arg
          1               5                   10                  15


          Lys Arg Arg Gln Arg Arg Arg
                      20
```

<210> 204
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<222> (1)..(8)
<223> Cyclic

<220>
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<223> D-2-Nal

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<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 204

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Gly Arg Lys
1               5               10              15
```

```
Arg Arg Arg Gln Arg Arg Arg
            20
```

<210> 205
<211> 22
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<220>
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<220>
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<223> Cyclic

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<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 205

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Lys
        1               5               10                  15

        Arg Arg Gln Arg Arg Arg
                        20
```

<210> 206
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<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 206

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Lys Arg
        1               5               10              15


        Arg Arg Gln Arg Arg Arg
                    20
```

<210> 207
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<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 207

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5               10              15


        Lys Arg Arg Arg Gln Arg Arg Arg
                    20
```

<210> 208
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> D-2-Nal

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<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 208

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Lys
1               5               10              15
```

```
Arg Arg Gln Arg Arg Arg
            20
```

<210> 209
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> D-2-Nal

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<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 209

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Lys Arg
        1               5               10                  15

                        Arg Arg Gln Arg Arg Arg
                                    20
```

<210> 210
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
<221> DOMAIN
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
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<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 210

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5               10                  15

        Arg Lys Arg Arg Gln Arg Arg Arg
                    20
```

<210> 211
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
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<223> Bal

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 211

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        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5               10                  15

        Lys Arg Arg Arg Gln Arg Arg Arg
                    20
```

<210> 212
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> D-2-Nal

<220>
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<223> Bal

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 212

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Gly Arg Arg
        1               5               10                  15


        Lys Arg Arg Gln Arg Arg Arg
                        20
```

<210> 213
<211> 23
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<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 213

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Gly Arg Lys
        1               5                   10                  15

        Arg Arg Arg Gln Arg Arg Arg
                        20
```

<210> 214
<211> 22
<212> PRT
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<220>
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<223> D-2-Nal

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<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 214

```
        Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Arg Arg Arg
        1               5                   10                  15

        Arg Arg Gln Arg Arg Arg
                        20
```

<210> 215
<211> 22
<212> PRT
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<220>
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<220>
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<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 215

```
Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Arg Asp Ala Arg Arg Arg
1               5                   10                  15


Arg Arg Gln Arg Arg Arg
            20
```

<210> 216
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<220>
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<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 216

```
Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
1               5               10              15
```

```
Arg Arg Arg Arg Gln Arg Arg Arg
            20
```

<210> 217
<211> 24
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<220>
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<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 217

```
Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
1               5               10              15
```

```
Arg Arg Arg Arg Gln Arg Arg Arg
            20
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<210> 218
<211> 23
<212> PRT

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<223> D-2-Nal

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 218

```
Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Arg Arg Arg
1               5                   10                  15

        Arg Arg Gln Arg Arg Arg Arg
                20
```

<210> 219
<211> 23
<212> PRT
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<223> Cyclic

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<223> D-2-Nal

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<221> MOD_RES
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<220>
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 219

```
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        1               5                   10                  15

        Arg Arg Gln Arg Arg Arg Arg
                    20
```

<210> 220
<211> 25
<212> PRT
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<220>
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<220>
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<223> Cyclic

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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 220

```
        Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15

        Arg Arg Arg Arg Gln Arg Arg Arg Arg
                    20                  25
```

<210> 221
<211> 25
<212> PRT
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<223> Description of Artificial Sequence: Synthetic peptide

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<223> D-2-Nal

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<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 221

```
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        1               5                   10                  15
```

```
        Arg Arg Arg Arg Gln Arg Arg Arg Arg
                    20                  25
```

<210> 222
<211> 23
<212> PRT
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<223> D-2-Nal

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<223> 1-Nal

<220>
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<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 222

```
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        1               5                   10                  15

        Arg Arg Gln Arg Arg Arg Arg
                    20
```

<210> 223
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<223> 1-Nal

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<220>
<223> C-term NH2

<400> 223

```
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        1               5                   10                  15


        Arg Arg Gln Arg Arg Arg Arg
                    20
```

<210> 224
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<223> D-2-Nal

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<223> 1-Nal

<220>
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<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 224

```
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        1               5                   10                  15


        Arg Arg Arg Gln Arg Arg Arg
                    20
```

<210> 225
<211> 24
<212> PRT
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<220>
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<223> D-2-Nal

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<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 225

```
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        1               5                   10                  15

        Arg Arg Arg Arg Gln Arg Arg Arg
                    20
```

<210> 226
<211> 24
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<223> D-2-Nal

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<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 226

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
        1               5               10                  15

        Arg Arg Arg Arg Gln Arg Arg Arg
                        20
```

<210> 227
<211> 25
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<220>
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<223> 1-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 227

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5               10              15

        Arg Arg Arg Arg Gln Arg Arg Arg Arg
                    20              25
```

<210> 228
<211> 25
<212> PRT
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<220>
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<220>
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<223> D-2-Nal

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<222> (6)..(6)
<223> 1-Nal

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 228

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
        1               5               10              15

        Arg Arg Arg Arg Gln Arg Arg Arg Arg
                    20              25
```

<210> 229
<211> 25
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<223> D-2-Nal

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<223> 1-Nal

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 229

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5               10                  15


        Arg Arg Arg Arg Arg Gln Arg Arg Arg
                20                  25
```

<210> 230
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<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> 1-Nal

<220>
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<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 230

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
        1               5               10                  15

        Arg Arg Arg Arg Arg Gln Arg Arg Arg
                    20                  25
```

<210> 231
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<212> PRT
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<220>
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<223> D-2-Nal

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<223> 2-Nal

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 231

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Arg Arg Arg
        1               5               10                  15

        Arg Arg Arg Gln Arg Arg Arg
                    20
```

<210> 232
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<223> D-2-Nal

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<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 232

```
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        1               5               10                  15

        Arg Arg Gln Arg Arg Arg Arg
                20
```

<210> 233
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<223> D-2-Nal

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<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 233

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Arg Arg Arg
        1               5                   10                  15


        Arg Arg Gln Arg Arg Arg Arg
                    20
```

<210> 234
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> D-2-Nal

<220>
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<222> (6)..(6)
<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 234

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5               10              15

        Arg Arg Arg Arg Gln Arg Arg Arg
                        20
```

<210> 235
<211> 24
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<220>
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<223> 2-Nal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 235

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
        1               5                   10                  15


        Arg Arg Arg Arg Gln Arg Arg Arg
                        20
```

<210> 236
<211> 25
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<220>
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<222> (6)..(6)
<223> 2-Nal

<220>
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<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 236

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5                   10                  15


        Arg Arg Arg Arg Arg Gln Arg Arg Arg
                        20                  25
```

<210> 237
<211> 25
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<220>
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<223> 2-Nal

<220>
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 237

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
        1               5               10                  15


        Arg Arg Arg Arg Arg Gln Arg Arg Arg
                    20                  25
```

<210> 238
<211> 25
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<220>
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<223> D-2-Nal

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<222> (6)..(6)
<223> 2-Nal

<220>
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 238

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
        1               5               10              15

        Arg Arg Arg Arg Gln Arg Arg Arg Arg
                        20              25
```

<210> 239
<211> 25
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<220>
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<220>
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<223> D-2-Nal

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<223> 2-Nal

<220>
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<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 239

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
        1                5                   10                  15

        Arg Arg Arg Arg Gln Arg Arg Arg Arg
                    20              25
```

<210> 240
<211> 23
<212> PRT
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<220>
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<223> D-2-Nal

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<223> Bal

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 240

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Arg Arg Arg
        1                5                   10                  15

        Arg Arg Gln Arg Arg Arg Arg
                    20
```

<210> 241
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<220>
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 241

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Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Arg Arg Arg
1               5               10              15


Arg Arg Gln Arg Arg Arg Arg
            20
```

<210> 242
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<220>
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<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 242

```
        Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
        1               5               10              15


        Arg Arg Arg Arg Gln Arg Arg Arg
                        20
```

<210> 243
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> DOMAIN
<222> (1)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 243

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
1               5               10              15

Arg Arg Arg Arg Gln Arg Arg Arg Arg
            20              25
```

<210> 244
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<222> (1)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 244

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
1               5               10              15

Arg Arg Arg Arg Gln Arg Arg Arg Arg
            20              25
```

<210> 245
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<223> D-2-Nal

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 245

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp Ala Tyr Gly Arg
1               5               10              15

Arg Arg Arg Arg Arg Gln Arg Arg Arg
          20              25
```

<210> 246
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<222> (1)..(8)
<223> Cyclic

<220>
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<223> D-2-Nal

<220>
<221> MOD_RES

<222> (6)..(6)
<223> Bal

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 246

```
Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Arg Asp Ala Tyr Gly Arg
1               5               10                      15

Arg Arg Arg Arg Arg Gln Arg Arg Arg
            20              25
```

<210> 247
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 247

```
        Xaa Cys Ala His Phe Arg Trp Cys Xaa Xaa Tyr Gly Arg Lys Lys Arg
        1               5                   10                  15

        Arg Gln Arg Arg Arg
                        20
```

<210> 248
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 248

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Tyr Gly Arg Lys Lys Arg Gln
        1               5                   10                  15

        Arg Arg Arg Arg
                    20
```

<210> 249

<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 249

```
        Xaa Cys Ala His Phe Arg Trp Cys Xaa Tyr Gly Arg Lys Lys Arg Arg
        1                   5                   10                  15


        Gln Arg Arg Arg
                    20
```

<210> 250
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

```
<220>
<221> MOD_RES
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 250
```

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Arg Arg Arg Arg Arg Gln Arg
        1               5               10                  15
```

```
        Arg Arg
```

```
<210> 251
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 251

```
    Xaa Cys Ala His Phe Arg Trp Cys Ala Gly Arg Arg Arg Arg Arg Gln
    1               5                   10                  15


    Arg Arg Arg
```

<210> 252
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
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<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 252

```
Xaa Cys Ala His Phe Arg Trp Cys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15

Gln Arg Arg Arg
            20
```

<210> 253
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<223> Nle

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<223> Cyclic

<220>
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<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 253

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Gly Arg Arg Arg Arg Gln
        1                   5                   10                  15
```

```
        Arg Arg Arg Arg
                    20
```

<210> 254
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 254

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Tyr Gly Arg Arg Lys Arg Arg
        1                   5                   10                  15
```

```
        Gln Arg Arg Arg
                    20
```

<210> 255
<211> 20
<212> PRT

<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 255

```
Xaa Cys Ala His Phe Arg Trp Cys Ala Tyr Gly Arg Lys Arg Arg Arg
1               5                   10                  15

Gln Arg Arg Arg
        20
```

<210> 256
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 256

```
Xaa Cys Ala His Phe Arg Trp Cys Ala Gly Arg Arg Lys Arg Arg Gln
1               5               10              15

Arg Arg Arg
```

<210> 257
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)

<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 257

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Gly Arg Lys Arg Arg Arg Gln
        1               5                   10                  15


        Arg Arg Arg
```

<210> 258
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 258

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Arg Arg Lys Arg Arg Gln Arg
        1                   5                   10                  15

        Arg Arg
```

<210> 259
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 259

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Arg Lys Arg Arg Arg Gln Arg
        1                   5                   10                  15

        Arg Arg
```

<210> 260
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Nle

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<223> Cyclic

<220>
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<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 260

```
Xaa Cys Ala His Phe Arg Trp Cys Ala Ala Arg Arg Arg Arg Arg Gln
1               5                   10                  15

Arg Arg Arg
```

<210> 261
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 261

```
Xaa Cys Ala His Phe Arg Trp Cys Ala Ala Gly Arg Arg Arg Arg Arg
1               5                   10                  15
```

```
Gln Arg Arg Arg
            20
```

<210> 262
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 262

```
Xaa Cys Ala His Phe Arg Trp Cys Ala Ala Tyr Gly Arg Arg Arg Arg
1               5                   10                  15
```

```
Arg Gln Arg Arg Arg
            20
```

<210> 263
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 263

```
Xaa Cys Ala His Phe Arg Trp Cys Xaa Arg Arg Arg Arg Arg Gln Arg
1               5               10                  15

Arg Arg
```

<210> 264
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 264

```
          Xaa Cys Ala His Phe Arg Trp Cys Xaa Gly Arg Arg Arg Arg Arg Gln
          1               5                   10                  15
```

```
          Arg Arg Arg
```

```
          <210> 265
          <211> 20
          <212> PRT
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```
          <213> Artificial Sequence

          <220>
          <223> Description of Artificial Sequence: Synthetic peptide
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```
          <220>
          <223> N-term Ac

          <220>
          <221> MOD_RES
```
```
          <222> (1)..(1)
          <223> Nle

          <220>
          <221> DOMAIN
```
```
          <222> (2)..(8)
          <223> Cyclic

          <220>
          <221> MOD_RES
```
```
          <222> (3)..(3)
          <223> D-Ala

          <220>
          <221> MOD_RES
```
```
          <222> (5)..(5)
          <223> D-Phe

          <220>
          <221> MOD_RES
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```
          <222> (9)..(9)
          <223> Doc

          <220>
          <223> C-term NH2
```
```
          <400> 265

          Xaa Cys Ala His Phe Arg Trp Cys Xaa Tyr Gly Arg Arg Arg Arg Arg
          1               5                   10                  15
```
```
          Gln Arg Arg Arg
                      20
```

```
          <210> 266
          <211> 19
          <212> PRT
          <213> Artificial Sequence
```

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 266

```
        Xaa Cys Ala His Phe Arg Trp Cys Xaa Xaa Arg Arg Arg Arg Arg Gln
        1               5                   10                  15

        Arg Arg Arg
```

<210> 267
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 267

```
Xaa Cys Ala His Phe Arg Trp Cys Xaa Xaa Gly Arg Arg Arg Arg Arg
1               5                   10                  15

Gln Arg Arg Arg
            20
```

<210> 268
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 268

```
        Xaa Cys Ala His Phe Arg Trp Cys Xaa Xaa Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15

        Arg Gln Arg Arg Arg
                        20
```

<210> 269
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 269

```
Xaa Cys Ala His Phe Arg Trp Cys Ala Arg Arg Arg Arg Arg Gln Arg

    1               5                   10                  15


    Arg Arg Arg
```

<210> 270
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<223> N-term Ac

<220>
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<223> Nle

<220>
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<223> Cyclic

<220>
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<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 270

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15
```

```
        Gln Arg Arg Arg Arg
                        20
```

<210> 271
<211> 20
<212> PRT
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<220>
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<220>
<223> N-term Ac

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 271

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Ala Arg Arg Arg Arg Arg Gln
        1               5                   10                  15
```

```
        Arg Arg Arg Arg
                        20
```

<210> 272
<211> 21
<212> PRT

<220>
<223> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 272

```
    Xaa Cys Ala His Phe Arg Trp Cys Ala Ala Gly Arg Arg Arg Arg Arg
    1               5                   10                  15


    Gln Arg Arg Arg Arg
                20
```

<210> 273
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 273

```
        Xaa Cys Ala His Phe Arg Trp Cys Ala Ala Tyr Gly Arg Arg Arg Arg
        1               5                   10              15
```

```
        Arg Gln Arg Arg Arg Arg
                    20
```

<210> 274
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<223> D-Ala

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 274

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Xaa Cys Ala His Phe Arg Trp Cys Xaa Arg Arg Arg Arg Arg Gln Arg
1               5                   10                  15
```

```
Arg Arg Arg
```

<210> 275
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

<220>
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<223> Cyclic

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<222> (3)..(3)
<223> D-Ala

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)

<223> Doc

<220>
<223> C-term NH2

<400> 275

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Xaa Cys Ala His Phe Arg Trp Cys Xaa Gly Arg Arg Arg Arg Arg Gln
1               5                   10                  15

Arg Arg Arg Arg
            20
```

<210> 276
<211> 21
<212> PRT
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 276

```
        Xaa Cys Ala His Phe Arg Trp Cys Xaa Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15


        Gln Arg Arg Arg Arg
                        20
```

<210> 277
<211> 20
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<220>
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 277

```
        Xaa Cys Ala His Phe Arg Trp Cys Xaa Xaa Arg Arg Arg Arg Arg Gln
        1               5                   10                  15


        Arg Arg Arg Arg
                        20
```

<210> 278
<211> 21
<212> PRT

<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 278

```
        Xaa Cys Ala His Phe Arg Trp Cys Xaa Xaa Gly Arg Arg Arg Arg Arg
        1               5                   10                  15

        Gln Arg Arg Arg Arg
                    20
```

<210> 279
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 279

```
Xaa Cys Ala His Phe Arg Trp Cys Xaa Xaa Tyr Gly Arg Arg Arg Arg
1               5                   10              15

Arg Gln Arg Arg Arg Arg

      20
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<210> 280
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 280

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Tyr Gly Arg Arg Arg Arg Arg
        1               5               10                  15
```

```
        Gln Arg Arg Arg
                    20
```

<210> 281
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

```
<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 281

        Xaa Cys His Phe Arg Trp Xaa Cys Ala Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15


        Arg Arg


<210> 282
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 282

        Xaa Asp His Phe Arg Trp Ala Lys Ala Tyr Gly Arg Arg Arg Arg Arg
        1               5                   10                  15


        Gln Arg Arg Arg
                    20
```

<210> 283
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 283

```
    Xaa Asp His Phe Arg Trp Ala Lys Ala Arg Arg Arg Arg Arg Gln Arg
    1               5                   10                  15

                            Arg Arg
```

<210> 284
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(7)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 284

```
Xaa Asp His Phe Arg Trp Lys Ala Tyr Gly Arg Arg Arg Arg Arg Gln
1               5                   10                  15
```

```
Arg Arg Arg
```

<210> 285
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Beta-Ala

<220>

<223> C-term NH2

<400> 285

```
        Xaa Asp His Phe Arg Trp Lys Ala Gly Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15

        Arg Arg
```

<210> 286
<211> 17
<212> PRT
<213> Artificial Sequence

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<223> Nle

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<223> Cyclic

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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 286

```
        Xaa Asp His Phe Arg Trp Lys Ala Arg Arg Arg Arg Arg Gln Arg Arg
        1               5                   10                  15

        Arg
```

<210> 287
<211> 20
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

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<223> N-term Ac

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<223> Nle

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<222> (2)..(7)
<223> Cyclic

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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 287

```
        Xaa Asp His Phe Arg Trp Lys Ala Ala Tyr Gly Arg Arg Arg Arg Arg
        1               5                   10                  15

        Gln Arg Arg Arg
                 20
```

<210> 288
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

<220>
<221> DOMAIN
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 288

```
        Xaa Asp His Phe Arg Trp Lys Ala Ala Gly Arg Arg Arg Arg Arg Gln
        1               5               10                  15


        Arg Arg Arg
```

<210> 289
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(7)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 289

```
Xaa Asp His Phe Arg Trp Lys Ala Ala Arg Arg Arg Arg Arg Gln Arg
1               5                   10                  15
```

Arg Arg

<210> 290
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(7)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Doc

<220>
<223> C-term NH2

<400> 290

```
Xaa Asp His Phe Arg Trp Lys Xaa Tyr Gly Arg Arg Arg Arg Arg Gln
1               5                   10                  15
```

Arg Arg Arg

<210> 291
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> Nle

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<222> (2)..(7)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Doc

<220>
<223> C-term NH2

<400> 291

```
Xaa Asp His Phe Arg Trp Lys Xaa Gly Arg Arg Arg Arg Arg Gln Arg
1               5                   10                  15
```

```
Arg Arg
```

<210> 292
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

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<222> (2)..(7)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>

<221> MOD_RES
<222> (8)..(8)
<223> Doc

<220>
<223> C-term NH2

<400> 292


```
        Xaa Asp His Phe Arg Trp Lys Xaa Arg Arg Arg Arg Arg Gln Arg Arg
        1               5                   10                  15


        Arg
```

<210> 293
<211> 20
<212> PRT
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<220>
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<220>
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<223> Nle

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<222> (2)..(7)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 293


```
        Xaa Asp His Phe Arg Trp Lys Xaa Xaa Tyr Gly Arg Arg Arg Arg Arg
        1               5                   10                  15


        Gln Arg Arg Arg
                    20
```

<210> 294
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

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<223> Nle

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<222> (2)..(7)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 294

```
Xaa Asp His Phe Arg Trp Lys Xaa Xaa Gly Arg Arg Arg Arg Arg Gln
1               5                   10                  15

Arg Arg Arg
```

<210> 295
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> Nle

<220>
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<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 295

```
        Xaa Asp His Phe Arg Trp Lys Xaa Xaa Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15
```

```
        Arg Arg
```

<210> 296
<211> 20
<212> PRT
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<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Beta-Ala

<220>

<223> C-term NH2

<400> 296

```
Xaa Asp His Phe Arg Trp Lys Ala Tyr Gly Arg Arg Arg Arg Arg Gln
1               5               10              15
```

```
Arg Arg Arg Arg
                20
```

<210> 297
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

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<223> Nle

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<222> (2)..(7)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 297

```
Xaa Asp His Phe Arg Trp Lys Ala Gly Arg Arg Arg Arg Arg Gln Arg
1               5               10              15
```

```
Arg Arg Arg
```

<210> 298
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> Nle

<220>
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<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 298

```
        Xaa Asp His Phe Arg Trp Lys Ala Arg Arg Arg Arg Arg Gln Arg Arg
        1               5               10                  15

        Arg Arg
```

<210> 299
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

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<221> DOMAIN
<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 299

```
        Xaa Asp His Phe Arg Trp Lys Ala Ala Tyr Gly Arg Arg Arg Arg Arg
        1                   5                   10                  15

        Gln Arg Arg Arg Arg
                    20
```

<210> 300
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

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<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 300

```
Xaa Asp His Phe Arg Trp Lys Ala Ala Gly Arg Arg Arg Arg Gln
1               5               10              15

Arg Arg Arg Arg
            20
```

<210> 301
<211> 19
<212> PRT
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<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(7)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 301

```
Xaa Asp His Phe Arg Trp Lys Ala Ala Arg Arg Arg Arg Arg Gln Arg
1               5               10              15

Arg Arg Arg
```

<210> 302
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>

<223> N-term Ac

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nle

<220>
<221> DOMAIN
<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Doc

<220>
<223> C-term NH2

<400> 302

```
Xaa Asp His Phe Arg Trp Lys Xaa Tyr Gly Arg Arg Arg Arg Arg Gln
1               5               10              15

Arg Arg Arg Arg
          20
```

<210> 303
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)

<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Doc

<220>
<223> C-term NH2

<400> 303

```
        Xaa Asp His Phe Arg Trp Lys Xaa Gly Arg Arg Arg Arg Arg Gln Arg
        1               5               10              15
```

```
        Arg Arg Arg
```

<210> 304
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nle

<220>
<221> DOMAIN
<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Doc

<220>
<223> C-term NH2

<400> 304

```
        Xaa Asp His Phe Arg Trp Lys Xaa Arg Arg Arg Arg Arg Gln Arg Arg
        1               5               10              15
```

```
                                       Arg Arg


         <210> 305
 5       <211> 21
         <212> PRT
         <213> Artificial Sequence


         <220>
10       <223> Description of Artificial Sequence: Synthetic peptide


         <220>
         <223> N-term Ac


15       <220>
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         <223> Nle


20       <220>
         <221> DOMAIN
         <222> (2)..(7)
         <223> Cyclic


25       <220>
         <221> MOD_RES
         <222> (4)..(4)
         <223> D-Phe


30       <220>
         <221> MOD_RES
         <222> (8)..(9)
         <223> Doc


35       <220>
         <223> C-term NH2


         <400> 305


40           Xaa Asp His Phe Arg Trp Lys Xaa Xaa Tyr Gly Arg Arg Arg Arg Arg
             1               5                   10                  15


             Gln Arg Arg Arg Arg
45                       20


         <210> 306
         <211> 20
         <212> PRT
50       <213> Artificial Sequence


         <220>
         <223> Description of Artificial Sequence: Synthetic peptide


55       <220>
         <223> N-term Ac


         <220>
```

<221> MOD_RES
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 306

```
Xaa Asp His Phe Arg Trp Lys Xaa Xaa Gly Arg Arg Arg Arg Arg Gln
1               5                   10                  15
```

```
Arg Arg Arg Arg
            20
```

<210> 307
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nle

<220>
<221> DOMAIN
<222> (2)..(7)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>

<221> MOD_RES
<222> (8)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 307

```
    Xaa Asp His Phe Arg Trp Lys Xaa Xaa Arg Arg Arg Arg Arg Gln Arg
    1               5                   10                  15


    Arg Arg Arg
```

<210> 308
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Beta-Ala

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 308

```
Xaa Asp His Phe Arg Trp Ala Lys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5               10              15

Gln Arg Arg Arg
            20
```

<210> 309
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Beta-Ala

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 309

```
Xaa Asp His Phe Arg Trp Ala Lys Ala Arg Arg Arg Arg Arg Gln Arg
1               5               10              15

Arg Arg
```

<210> 310
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Ahx

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 310

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Tyr Gly Arg Arg Arg Arg Arg
        1               5                   10                  15

        Gln Arg Arg Arg
                    20
```

<210> 311
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Ahx

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 311

```
Xaa Cys His Phe Arg Trp Xaa Cys Ala Arg Arg Arg Arg Arg Gln Arg
1               5               10                  15
```

```
Arg Arg
```

<210> 312
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<223> D-Phe

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Beta-Ala

<220>
<221> MOD_RES
<222> (8)..(8)
<223> D-Cys

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 312

```
        Phe Cys His Phe Arg Trp Ala Cys Thr Ala Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15

        Arg Gln Arg Arg Arg
                        20
```

<210> 313
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> D-Phe

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Beta-Ala

<220>
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<222> (8)..(8)
<223> D-Cys

<220>
<221> MOD_RES
<222> (10)..(10)

<223> Beta-Ala

<220>
<223> C-term NH2

<400> 313

```
Phe Cys His Phe Arg Trp Ala Cys Thr Ala Arg Arg Arg Arg Arg Gln
1               5               10                  15

Arg Arg Arg
```

<210> 314
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
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<223> Apn

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 314

```
Xaa Cys His Phe Arg Trp Xaa Cys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15
```

```
Gln Arg Arg Arg
            20
```

<210> 315
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Apn

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 315

```
Xaa Cys His Phe Arg Trp Xaa Cys Ala Arg Arg Arg Arg Arg Gln Arg
1               5                   10                  15
```

```
Arg Arg
```

<210> 316
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
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<223> Cha

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 316

```
Xaa Asp His Phe Arg Trp Xaa Lys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15

Gln Arg Arg Arg
        20
```

<210> 317
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Cha

```
<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 317
```

Xaa Asp His Phe Arg Trp Xaa Lys Ala Arg Arg Arg Arg Arg Gln Arg
1   5   10   15

Arg Arg

```
<210> 318
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<222> (1)..(1)
<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
```

<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 318

```
Xaa Asp His Phe Arg Trp Xaa Lys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15

Gln Arg Arg Arg
            20
```

<210> 319
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<222> (1)..(1)
<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>

<223> C-term NH2

<400> 319

```
        Xaa Asp His Phe Arg Trp Xaa Lys Ala Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15

        Arg Arg
```

<210> 320
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<222> (1)..(1)
<223> Chg

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 320

```
        Xaa Asp His Phe Arg Trp Xaa Lys Ala Tyr Gly Arg Arg Arg Arg Arg
        1               5                   10                  15

        Gln Arg Arg Arg
                    20
```

<210> 321
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Chg

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 321

```
Xaa Asp His Phe Arg Trp Xaa Lys Ala Arg Arg Arg Arg Arg Gln Arg
1               5                   10                  15

Arg Arg
```

<210> 322
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
<222> (1)..(1)
<223> hCha

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 322

```
        Xaa Asp His Phe Arg Trp Xaa Lys Ala Tyr Gly Arg Arg Arg Arg Arg
        1                   5                   10                  15


        Gln Arg Arg Arg
                    20
```

<210> 323
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> hCha

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 323

```
        Xaa Asp His Phe Arg Trp Xaa Lys Ala Arg Arg Arg Arg Arg Gln Arg
        1               5               10                  15
```

```
        Arg Arg
```

<210> 324
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> hCha

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>

<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 324

```
Xaa Asp His Phe Arg Trp Xaa Lys Ala Ala Tyr Gly Arg Arg Arg Arg
1               5                   10                  15

Arg Gln Arg Arg Arg
            20
```

<210> 325
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<222> (1)..(1)
<223> hCha

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 325

```
            Xaa Asp His Phe Arg Trp Xaa Lys Ala Ala Arg Arg Arg Arg Arg Gln
            1               5                   10                  15

            Arg Arg Arg
```

<210> 326
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
<222> (1)..(1)
<223> hCha

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Doc

<220>
<223> C-term NH2

<400> 326

```
            Xaa Asp His Phe Arg Trp Xaa Lys Xaa Tyr Gly Arg Arg Arg Arg Arg
            1               5                   10                  15

            Gln Arg Arg Arg
                        20
```

<210> 327
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> hCha

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Doc

<220>
<223> C-term NH2

<400> 327

```
        Xaa Asp His Phe Arg Trp Xaa Lys Xaa Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15

        Arg Arg
```

<210> 328
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> hCha

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 328

```
        Xaa Asp His Phe Arg Trp Xaa Lys Xaa Xaa Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15
```

```
        Arg Gln Arg Arg Arg
                    20
```

<210> 329
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> MOD_RES
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<223> hCha

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 329

```
        Xaa Asp His Phe Arg Trp Xaa Lys Xaa Xaa Arg Arg Arg Arg Arg Gln
        1                   5                   10                  15
```

```
        Arg Arg Arg
```

<210> 330
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> hCha

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>

<223> C-term NH2

<400> 330

Xaa Asp His Phe Arg Trp Xaa Lys Ala Tyr Gly Arg Arg Arg Arg Arg
1   5   10   15

Gln Arg Arg Arg Arg
                20

<210> 331
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<220>
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<223> Cyclic

<220>
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<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 331

Xaa Asp His Phe Arg Trp Xaa Lys Ala Arg Arg Arg Arg Arg Gln Arg
1   5   10   15

Arg Arg Arg

<210> 332
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> hCha

<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
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<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 332

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Xaa Asp His Phe Arg Trp Xaa Lys Ala Ala Tyr Gly Arg Arg Arg Arg
1               5                   10                  15

Arg Gln Arg Arg Arg Arg
            20
```

<210> 333
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<223> D-Phe

<220>
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<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 333

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Xaa Asp His Phe Arg Trp Xaa Lys Ala Ala Arg Arg Arg Arg Arg Gln
1               5                   10                  15
```

```
Arg Arg Arg Arg
             20
```

<210> 334
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> hCha

<220>
<221> DOMAIN

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
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<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Doc

<220>
<223> C-term NH2

<400> 334

```
Xaa Asp His Phe Arg Trp Xaa Lys Xaa Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15

Gln Arg Arg Arg Arg
            20
```

<210> 335
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<223> hCha

<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
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<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Doc

<220>
<223> C-term NH2

<400> 335

```
    Xaa Asp His Phe Arg Trp Xaa Lys Xaa Arg Arg Arg Arg Arg Gln Arg
    1               5               10                      15
```

```
    Arg Arg Arg
```

<210> 336
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<223> hCha

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<223> D-Phe

<220>
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<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 336

```
        Xaa Asp His Phe Arg Trp Xaa Lys Xaa Xaa Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15


        Arg Gln Arg Arg Arg Arg
                    20
```

<210> 337
<211> 20
<212> PRT
<213> Artificial Sequence

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<220>
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<223> hCha

<220>
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<222> (2)..(8)
<223> Cyclic

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<223> D-Phe

<220>
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<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 337

```
        Xaa Asp His Phe Arg Trp Xaa Lys Xaa Xaa Arg Arg Arg Arg Arg Gln
        1               5                   10                  15


                            Arg Arg Arg Arg
                                    20
```

<210> 338
<211> 20

<212> PRT
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<220>
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<223> D-Chg

<220>
<221> DOMAIN
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<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 338

```
Xaa Asp His Phe Arg Trp Xaa Lys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15


Gln Arg Arg Arg
            20
```

<210> 339
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>

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<223> D-Chg

<220>
<221> DOMAIN
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<223> Cyclic

<220>
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<223> D-Phe

<220>
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<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 339

```
Xaa Asp His Phe Arg Trp Xaa Lys Ala Arg Arg Arg Arg Arg Gln Arg
1               5                   10                  15
```

```
Arg Arg
```

<210> 340
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> hPhe

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
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<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 340

```
Phe Asp His Phe Arg Trp Xaa Lys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5               10              15

Gln Arg Arg Arg
        20
```

<210> 341
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> hPhe

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES

<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 341

```
        Phe Asp His Phe Arg Trp Xaa Lys Ala Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15


        Arg Arg
```

<210> 342
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
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<222> (6)..(6)
<223> D-Trp

<220>
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<222> (7)..(7)
<223> Apn

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 342

```
    Xaa Cys His Phe Arg Trp Xaa Cys Ala Tyr Gly Arg Arg Arg Arg Arg
    1               5                   10                  15

    Gln Arg Arg Arg
                20
```

<210> 343
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (6) .. (6)
<223> D-Trp

<220>
<221> MOD_RES
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<223> Apn

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 343

```
Xaa Cys His Phe Arg Trp Xaa Cys Ala Arg Arg Arg Arg Arg Gln Arg
1                   5                   10                  15
```

Arg Arg

<210> 344
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
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<222> (6) .. (6)
<223> D-Trp

<220>
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<222> (7)..(7)
<223> Ahx

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 344

```
Xaa Cys His Phe Arg Trp Xaa Cys Ala Tyr Gly Arg Arg Arg Arg Arg
1                   5                   10                  15
```

```
Gln Arg Arg Arg
            20
```

<210> 345
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (6) .. (6)
<223> D-Trp

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Ahx

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 345

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15

        Arg Arg
```

<210> 346
<211> 20
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

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<223> N-term Ac

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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<223> D-Phe

<220>
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<222> (6) .. (6)
<223> D-Trp

<220>
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<223> Beta-Ala

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 346

```
Xaa Cys His Phe Arg Trp Ala Cys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15

Gln Arg Arg Arg
        20
```

<210> 347
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> Nle

<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
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<222> (6) .. (6)
<223> D-Trp

<220>
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<223> Beta-Ala

<220>
<221> MOD_RES
<222> (9) .. (9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 347

```
Xaa Cys His Phe Arg Trp Ala Cys Ala Arg Arg Arg Arg Arg Gln Arg
1               5               10              15
```

```
Arg Arg
```

<210> 348
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
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<223> D-Phe

<220>
<221> MOD_RES
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<223> Pen

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 348

```
Xaa Cys Ala His Phe Arg Trp Xaa Ala Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15
```

```
Gln Arg Arg Arg
            20
```

<210> 349
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> Nle

<220>
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<222> (2)..(8)
<223> Cyclic

<220>

<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Pen

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 349

```
        Xaa Cys Ala His Phe Arg Trp Xaa Ala Gly Arg Arg Arg Arg Arg Gln
        1                   5                   10                  15


        Arg Arg Arg
```

<210> 350
<211> 18
<212> PRT
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<220>
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<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Pen

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 350

```
        Xaa Cys Ala His Phe Arg Trp Xaa Ala Arg Arg Arg Arg Arg Gln Arg

            1               5                   10                  15


            Arg Arg
```

<210> 351
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
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<222> (5)..(5)
<223> D-Phe

<220>

<221> MOD_RES
<222> (8)..(8)
<223> Pen

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 351

```
        Xaa Cys Ala His Phe Arg Trp Xaa Ala Ala Tyr Gly Arg Arg Arg Arg
        1               5               10              15

        Arg Gln Arg Arg Arg
                    20
```

<210> 352
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Cyclic

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<223> D-Ala

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<223> D-Phe

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<220>

<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 352

```
Xaa Cys Ala His Phe Arg Trp Xaa Ala Ala Gly Arg Arg Arg Arg Arg
1               5               10              15

Gln Arg Arg Arg
            20
```

<210> 353
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

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<223> Cyclic

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<223> D-Ala

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<223> Pen

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>

<223> C-term NH2

<400> 353

```
        Xaa Cys Ala His Phe Arg Trp Xaa Ala Ala Arg Arg Arg Arg Arg Gln
        1               5                   10                  15


        Arg Arg Arg
```

<210> 354
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Pen

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 354

```
Xaa Cys Ala His Phe Arg Trp Xaa Xaa Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15
```

```
Gln Arg Arg Arg
            20
```

<210> 355
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Ala

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Pen

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 355

```
Xaa Cys Ala His Phe Arg Trp Xaa Xaa Gly Arg Arg Arg Arg Arg Gln
1               5                   10                  15
```

```
Arg Arg Arg
```

<210> 356
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> D-Ala

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Pen

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 356

```
Xaa Cys Ala His Phe Arg Trp Xaa Xaa Arg Arg Arg Arg Arg Gln Arg
1               5                   10                  15

Arg Arg
```

<210> 357
<211> 21
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<223> Cyclic

<220>
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<223> D-Ala

<220>
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<220>
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<223> Pen

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 357

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Xaa Cys Ala His Phe Arg Trp Xaa Xaa Xaa Tyr Gly Arg Arg Arg Arg
1               5                   10                  15

Arg Gln Arg Arg Arg
            20
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<210> 358
<211> 20
<212> PRT
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<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<223> D-Ala

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<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 358

```
Xaa Cys Ala His Phe Arg Trp Xaa Xaa Xaa Gly Arg Arg Arg Arg Arg
1               5                   10                  15

                        Gln Arg Arg Arg
                                    20
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<210> 359
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<223> Cyclic

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<223> D-Ala

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15

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<223> Pen

20

<220>
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<223> Doc

25

<220>
<223> C-term NH2

<400> 359

30

```
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        1               5               10                      15
```

```
        Arg Arg Arg
```

35

<210> 360
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<220>
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<223> Cyclic

<220>
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<223> D-(Et)Tyr

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Beta-Ala

<220>
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<222> (8)..(8)
<223> D-Cys

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 360

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Phe Cys His Tyr Arg Trp Ala Cys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5               10                  15
```

```
Gln Arg Arg Arg
        20
```

<210> 361
<211> 18
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<223> Cyclic

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<223> D-(Et)Tyr

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<223> Beta-Ala

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<223> D-Cys

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 361

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        1               5                   10                  15


        Arg Arg
```

<210> 362
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<223> Cyclic

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<223> D-(Et)Tyr

<220>
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<223> Beta-Ala

<220>
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<222> (8)..(8)
<223> D-Cys

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 362

```
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        1                   5                   10                  15

        Arg Arg Arg
```

<210> 363
<211> 19
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<223> D-(Et)Tyr

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<223> Beta-Ala

<220>
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<223> D-Cys

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 363

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        1                   5                   10                  15

        Arg Arg Arg
```

<210> 364

<211> 21
<212> PRT
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<220>
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<223> Cyclic

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<223> D-(Et)Tyr

<220>
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<222> (7)..(7)
<223> Beta-Ala

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<223> D-Cys

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 364

```
Phe Cys His Tyr Arg Trp Ala Cys Ala Ala Tyr Gly Arg Arg Arg Arg
1               5                   10                  15

Arg Gln Arg Arg Arg
            20
```

<210> 365
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<212> PRT
<213> Artificial Sequence

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<223> Cyclic

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<223> D-(Et)Tyr

<220>
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<223> D-Cys

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 365

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Phe Cys His Tyr Arg Trp Ala Cys Ala Ala Arg Arg Arg Arg Arg Gln
1               5                   10                  15


Arg Arg Arg
```

<210> 366
<211> 20
<212> PRT
<213> Artificial Sequence

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15 <220>
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<223> C-term NH2

<400> 366

25
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     Phe Cys His Tyr Arg Trp Ala Cys Ala Ala Gly Arg Arg Arg Arg Arg
     1               5               10              15


     Gln Arg Arg Arg
                 20
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30

<210> 367
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35 <213> Artificial Sequence

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<223> D-Cys

<220>
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 367

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        Phe Cys His Tyr Arg Trp Ala Cys Ala Ala Arg Arg Arg Arg Arg Gln
        1               5                   10                  15


        Arg Arg Arg Arg
                    20
```

<210> 368
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<212> PRT
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<223> Cyclic

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<222> (4)..(4)
<223> D-(Et)Tyr

<220>
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<223> Beta-Ala

<220>
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<223> D-Cys

<220>
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<223> Doc

<220>
<223> C-term NH2

<400> 368

Phe Cys His Tyr Arg Trp Ala Cys Xaa Tyr Gly Arg Arg Arg Arg Arg
1   5   10   15

Gln Arg Arg Arg
        20

<210> 369
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

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<223> D-(Et)Tyr

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<223> D-Cys

<220>
<221> MOD_RES
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<223> Doc

<220>
<223> C-term NH2

<400> 369

```
        Phe Cys His Tyr Arg Trp Ala Cys Xaa Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15
```

5

```
        Arg Arg
```

<210> 370
<211> 19
<212> PRT
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<223> D-(Et)Tyr

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<223> D-Cys

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<223> Doc

<220>
<223> C-term NH2

<400> 370

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        Phe Cys His Tyr Arg Trp Ala Cys Xaa Gly Arg Arg Arg Arg Arg Gln
        1               5                   10                  15
```

```
        Arg Arg Arg
```

<210> 371
<211> 19
<212> PRT

<213> Artificial Sequence

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<223> D-(Et)Tyr

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<223> Doc

<220>
<223> C-term NH2

<400> 371

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Phe Cys His Tyr Arg Trp Ala Cys Xaa Arg Arg Arg Arg Arg Gln Arg
1               5                   10                  15
```

```
Arg Arg Arg
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<210> 372
<211> 21
<212> PRT
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<220>
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<223> Cyclic

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<223> D-(Et)Tyr

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<223> D-Cys

<220>
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<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 372

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        1               5                   10                  15


        Arg Gln Arg Arg Arg
                    20
```

<210> 373
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

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<223> D-(Et)Tyr

<220>
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<223> Beta-Ala

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<223> D-Cys

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 373

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        1               5                   10                  15

        Arg Arg Arg
```

<210> 374
<211> 20
<212> PRT
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<220>
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<223> Cyclic

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<223> D-(Et)Tyr

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<223> D-Cys

<220>
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<223> Doc

<220>
<223> C-term NH2

<400> 374


```
        Phe Cys His Tyr Arg Trp Ala Cys Xaa Xaa Gly Arg Arg Arg     Arg
        1               5                   10                  15
```


```
        Gln Arg Arg Arg
                    20
```


<210> 375
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<212> PRT
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<223> D-(Et)Tyr

<220>
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<223> Beta-Ala

<220>
<221> MOD_RES
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<223> D-Cys

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 375

```
Phe Cys His Tyr Arg Trp Ala Cys Xaa Xaa Arg Arg Arg Arg Arg Gln
1               5                   10                  15
```

```
Arg Arg Arg Arg
        20
```

<210> 376
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Cyclic

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<223> D-(Et)Tyr

<220>
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<222> (5)..(5)
<223> hArg

<220>
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<223> Beta-Ala

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<222> (8)..(8)
<223> D-Cys

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 376

```
Phe Cys His Tyr Arg Trp Ala Cys Thr Ala Tyr Gly Arg Arg Arg Arg
1               5                   10                  15

                    Arg Gln Arg Arg Arg
                            20
```

<210> 377
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<212> PRT
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<220>
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<223> Cyclic

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<223> D-(Et)Tyr

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<223> hArg

<220>
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<223> D-Cys

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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 377

```
Phe Cys His Tyr Arg Trp Ala Cys Thr Ala Arg Arg Arg Arg Arg Gln
1               5                   10                  15

    Arg Arg Arg
```

<210> 378
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

<220>
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<223> D-(Et)Tyr

<220>
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<222> (5)..(5)
<223> hArg

<220>
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<223> Beta-Ala

<220>
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<223> D-Cys

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 378

```
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        1               5                   10                  15
```

        Arg Arg Gln Arg Arg Arg
                    20

<210> 379
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Cyclic

<220>
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<223> D-(Et)Tyr

<220>
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<223> hArg

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<223> Beta-Ala

<220>
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<220>
<221> MOD_RES
<222> (10)..(11)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 379

```
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    1               5                   10                  15

    Gln Arg Arg Arg
                20
```

<210> 380
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

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<223> D-(Et)Tyr

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<222> (5)..(5)
<223> hArg

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<223> D-Cys

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<223> Doc

<220>
<223> C-term NH2

<400> 380

```
Phe Cys His Tyr Arg Trp Ala Cys Thr Xaa Tyr Gly Arg Arg Arg Arg
1               5                   10              15
```

```
Arg Gln Arg Arg Arg
            20
```

<210> 381
<211> 19
<212> PRT
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<223> D-(Et)Tyr

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<223> hArg

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<223> D-Cys

<220>
<221> MOD_RES
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<223> Doc

<220>
<223> C-term NH2

<400> 381

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        1               5                   10                  15
```

5   Arg Arg Arg

<210> 382
<211> 22
<212> PRT
10   <213> Artificial Sequence

<220>
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20   <220>
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<223> Cyclic

25   <220>
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<223> D-(Et)Tyr

30   <220>
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<223> hArg

35   <220>
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<223> Beta-Ala

40   <220>
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<223> D-Cys

45   <220>
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<223> Doc

50   <220>
<223> C-term NH2

<400> 382

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        Phe Cys His Tyr Arg Trp Ala Cys Thr Xaa Xaa Tyr Gly Arg Arg Arg
        1               5                   10                  15
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```
        Arg Arg Gln Arg Arg Arg
                    20
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<210> 383
<211> 22
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<220>
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<223> Cyclic

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<223> Beta-Ala

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<223> D-Cys

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 383

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Phe Cys His Tyr Arg Trp Ala Cys Thr Ala Tyr Gly Arg Arg Arg Arg
1               5                   10                  15

Arg Gln Arg Arg Arg Arg
            20
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<210> 384
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<220>
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<223> D-(Et)Tyr

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<223> D-Cys

<220>
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 384

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Phe Cys His Tyr Arg Trp Ala Cys Thr Ala Arg Arg Arg Arg Arg Gln
1               5                   10                  15

Arg Arg Arg Arg
          20
```

<210> 385
<211> 23
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<223> D-Cys

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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 385

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1               5                   10                  15

Arg Arg Gln Arg Arg Arg Arg
            20
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<210> 386
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<212> PRT
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<223> D-Cys

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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 386

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Phe Cys His Tyr Arg Trp Ala Cys Thr Ala Ala Arg Arg Arg Arg Arg
1               5                   10                  15
```

```
Gln Arg Arg Arg Arg
            20
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<210> 387
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<223> D-Cys

<220>
<221> MOD_RES
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<223> Doc

<220>
<223> C-term NH2

<400> 387

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1               5                   10              15

Arg Gln Arg Arg Arg Arg
            20
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<210> 388
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<212> PRT
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<223> Cyclic

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<223> hArg

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<223> D-Cys

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 388

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        1               5                   10                  15


        Arg Arg Arg Arg
                    20
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<210> 389
<211> 23
<212> PRT
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<223> hArg

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<223> D-Cys

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Doc

<220>
<223> C-term NH2

<400> 389

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1                   5                   10                  15

Arg Arg Gln Arg Arg Arg Arg
                20
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<210> 390
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<223> Cyclic

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<223> D-(Et)Tyr

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<223> D-Cys

<220>
<221> MOD_RES
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<223> Doc

<220>
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<400> 390

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         1               5                   10                  15
```

```
         Gln Arg Arg Arg Arg
                 20
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<210> 391
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<220>
<223> C-term NH2

<400> 391

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        1               5                   10                  15

        Arg Gln Arg Arg Arg
                    20
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<210> 392
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<223> Beta-Ala

<220>

<223> C-term NH2

<400> 392

Phe Cys His Tyr Arg Xaa Ala Cys Thr Ala Tyr Gly Arg Arg Arg Arg
1   5   10   15

Arg Gln Arg Arg Arg Arg
                20

<210> 393
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<223> D-Cys

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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 393

```
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1               5                   10                  15
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```
Arg Arg Arg
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<210> 394
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<223> Beta-Ala

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<400> 394

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        1               5               10              15
```

```
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                    20
```

<210> 395
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<223> Beta-Ala

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<400> 395

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1               5                   10                  15

Gln Arg Arg Arg
            20
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<210> 396
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<400> 396

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1                 5                   10                  15

Arg Gln Arg Arg Arg
              20
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    1               5               10              15

    Arg Gln Arg Arg Arg Arg
                20
```

<210> 398
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<212> PRT
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<223> Doc

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    1               5               10                  15

    Arg Arg Arg
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<210> 399
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1               5               10              15

Arg Arg Gln Arg Arg Arg
            20
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<210> 400
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<223> Doc

<220>
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1               5                   10              15
```

```
Gln Arg Arg Arg
            20
```

<210> 401
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<212> PRT
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<220>
<223> C-term NH2

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        1               5                   10                  15

        Arg Gln Arg Arg Arg
                        20
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<210> 402
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<223> D-Phe

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<223> Beta-Ala

<220>
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        1               5                   10                  15

        Arg Arg Arg
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<210> 403
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 403

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1               5               10              15

Gln Arg Arg Arg
        20
```

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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 404

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1               5               10                  15
```

```
Arg Arg
```

<210> 405
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<223> Beta-Ala

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        1                   5                   10                  15

        Arg Gln Arg Arg Arg
                    20
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<210> 406
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<223> Apn

<220>
<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 406

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        Xaa Cys His Phe Arg Trp Xaa Cys Ala Ala Arg Arg Arg Arg Arg Gln
        1                   5                   10                  15


        Arg Arg Arg
```

<210> 407
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<220>
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<223> D-Phe

<220>
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<223> Apn

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 407

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Tyr Gly Arg Arg Arg Arg Arg
        1                   5                   10                  15


        Gln Arg Arg Arg Arg
                        20
```

<210> 408
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Cyclic

<220>
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<223> D-Phe

<220>
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<223> Apn

<220>
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 408

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1               5                   10                  15
```

```
Arg Arg Arg
```

<210> 409
<211> 22
<212> PRT
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<220>
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<223> Cyclic

<220>
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<223> D-Phe

<220>
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<223> Apn

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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 409

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        1               5                   10                  15


        Arg Gln Arg Arg Arg Arg
                        20
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<223> Cyclic

<220>
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<223> D-Phe

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<223> Apn

<220>
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 410


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1               5               10                  15
```


```
Arg Arg Arg Arg
            20
```


<210> 411
<211> 20
<212> PRT
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<223> Apn

<220>
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<223> Doc

<220>
<223> C-term NH2

<400> 411


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Xaa Cys His Phe Arg Trp Xaa Cys Xaa Tyr Gly Arg Arg Arg Arg Arg
1               5               10                  15
```


```
Gln Arg Arg Arg
            20
```


<210> 412
<211> 18
<212> PRT
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<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
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<223> Apn

<220>
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<223> Doc

<220>
<223> C-term NH2

<400> 412

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Xaa Cys His Phe Arg Trp Xaa Cys Xaa Arg Arg Arg Arg Arg Gln Arg
1               5               10                  15

Arg Arg
```

<210> 413
<211> 21
<212> PRT
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<220>
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<222> (4)..(4)
<223> D-Phe

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<223> Apn

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<221> MOD_RES
<222> (9)..(10)
<223> Doc

15
<220>
<223> C-term NH2

<400> 413

20
```
Xaa Cys His Phe Arg Trp Xaa Cys Xaa Xaa Tyr Gly Arg Arg Arg Arg
1               5               10          15
```

```
Arg Gln Arg Arg Arg
            20
```

25

<210> 414
<211> 19
<212> PRT
30 <213> Artificial Sequence

<220>
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<223> Cyclic

45
<220>
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50
<220>
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<223> Apn

55
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<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 414

```
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        1               5               10              15
```

```
        Arg Arg Arg
```

<210> 415
<211> 21
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<223> Apn

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<223> Doc

<220>
<223> C-term NH2

<400> 415

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        1               5               10              15
```

```
        Gln Arg Arg Arg Arg
                        20
```

<210> 416
<211> 19

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<223> D-Phe

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<223> Apn

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<223> Doc

<220>
<223> C-term NH2

<400> 416

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        1                   5                   10                  15

        Arg Arg Arg
```

<210> 417
<211> 22
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<223> Doc

<220>
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<400> 417

```
Xaa Cys His Phe Arg Trp Xaa Cys Xaa Xaa Tyr Gly Arg Arg Arg Arg
1                   5                   10                  15

Arg Gln Arg Arg Arg Arg
                20
```

<210> 418
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<223> D-Phe

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<223> Apn

<220>

<221> MOD_RES
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<223> Doc

<220>
<223> C-term NH2

<400> 418

Xaa Cys His Phe Arg Trp Xaa Cys Xaa Xaa Arg Arg Arg Arg Arg Gln

1   5   10   15

Arg Arg Arg Arg
            20

<210> 419
<211> 20
<212> PRT
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<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<223> D-Leu

<220>
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<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 419

```
Xaa Cys Leu His Phe Arg Trp Cys Ala Tyr Gly Arg Arg Arg Arg
1               5               10              15
```

```
Gln Arg Arg Arg
         20
```

<210> 420
<211> 18
<212> PRT
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<220>
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<220>
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<220>
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<223> Cyclic

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<223> D-Leu

<220>
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<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 420

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Xaa Cys Leu His Phe Arg Trp Cys Ala Arg Arg Arg Arg Arg Gln Arg
1               5               10              15
```

```
Arg Arg
```

<210> 421
<211> 21
<212> PRT
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<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<223> D-Leu

<220>
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<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 421

```
        Xaa Cys Leu His Phe Arg Trp Cys Ala Ala Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15

        Arg Gln Arg Arg Arg
                    20
```

<210> 422
<211> 19
<212> PRT
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<220>
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<220>
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<220>
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<223> Nle

<220>
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Leu

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 422

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1               5                   10                  15


Arg Arg Arg
```

<210> 423
<211> 20
<212> PRT
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<223> Nle

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<223> Cyclic

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<220>

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<223> D-Phe

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<223> Doc

<220>
<223> C-term NH2

<400> 423

```
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    1               5               10                  15

                            Gln Arg Arg Arg
                                        20
```

<210> 424
<211> 18
<212> PRT
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<220>
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<220>
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<220>
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<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
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<400> 424

```
Xaa Cys Leu His Phe Arg Trp Cys Xaa Arg Arg Arg Arg Arg Gln Arg
1               5                   10                  15

Arg Arg
```

<210> 425
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<212> PRT
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<220>
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<223> Cyclic

<220>
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<223> D-Leu

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 425

```
Xaa Cys Leu His Phe Arg Trp Cys Xaa Xaa Tyr Gly Arg Arg Arg Arg
1               5                   10                  15

Arg Gln Arg Arg Arg
                20
```

<210> 426
<211> 19

<212> PRT
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<220>
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<220>
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<223> Cyclic

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<222> (3)..(3)
<223> D-Leu

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 426

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Xaa Cys Leu His Phe Arg Trp Cys Xaa Xaa Arg Arg Arg Arg Arg Gln
1               5                   10                  15


Arg Arg Arg
```

<210> 427
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Nle

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<223> Cyclic

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<222> (3)..(3)
<223> D-Leu

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 427

```
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        1                   5                   10                  15

        Gln Arg Arg Arg Arg
                        20
```

<210> 428
<211> 19
<212> PRT
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<220>
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<220>
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<223> Nle

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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Leu

<220>
<221> MOD_RES
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<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 428

Xaa Cys Leu His Phe Arg Trp Cys Ala Arg Arg Arg Arg Arg Gln Arg
1   5   10   15

Arg Arg Arg

<210> 429
<211> 22
<212> PRT
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<220>
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<223> D-Leu

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)

<223> Beta-Ala

<220>
<223> C-term NH2

<400> 429

```
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        1               5                   10                  15

        Arg Gln Arg Arg Arg Arg
                    20
```

<210> 430
<211> 20
<212> PRT
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<220>
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<220>
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Leu

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 430

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        Xaa Cys Leu His Phe Arg Trp Cys Ala Ala Arg Arg Arg Arg Gln
        1               5               10                  15


        Arg Arg Arg Arg
                    20
```

<210> 431
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Leu

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 431

```
        Xaa Cys Leu His Phe Arg Trp Cys Xaa Tyr Gly Arg Arg Arg Arg Arg
        1               5               10                  15


        Gln Arg Arg Arg Arg
                    20
```

<210> 432
<211> 19
<212> PRT

<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Nle

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<223> Cyclic

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<222> (3)..(3)
<223> D-Leu

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 432

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        Xaa Cys Leu His Phe Arg Trp Cys Xaa Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15


        Arg Arg Arg
```

<210> 433
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

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<223> D-Leu

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<223> D-Phe

<220>
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<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 433

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1               5                   10              15

Arg Gln Arg Arg Arg Arg
            20
```

<210> 434
<211> 20
<212> PRT
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<220>
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<223> D-Leu

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<220>
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<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 434

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Xaa Cys Leu His Phe Arg Trp Cys Xaa Xaa Arg Arg Arg Arg Arg Gln
1               5                   10                  15

Arg Arg Arg Arg
            20
```

<210> 435
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
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<223> Cyclic

<220>
<221> MOD_RES
<222> (3)..(3)
<223> D-Cha

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)

<223> Beta-Ala

<220>
<223> C-term NH2

<400> 435

```
    Xaa Cys Xaa His Phe Arg Trp Cys Ala Tyr Gly Arg Arg Arg Arg Arg
    1               5                   10                  15

    Gln Arg Arg Arg
                20
```

<210> 436
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
<221> DOMAIN
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Cha

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 436

```
        Xaa Cys Xaa His Phe Arg Trp Cys Ala Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15


        Arg Arg
```

```
<210> 437
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<220>
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Cha

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 437
```

```
        Xaa Cys Xaa His Phe Arg Trp Cys Ala Ala Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15


        Arg Gln Arg Arg Arg
                    20
```

```
<210> 438
<211> 19
<212> PRT
<213> Artificial Sequence
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<220>
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<220>
<223> N-term Ac

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<223> Nle

<220>
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Cha

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 438

```
Xaa Cys Xaa His Phe Arg Trp Cys Ala Ala Arg Arg Arg Arg Arg Gln
1               5                   10                  15

Arg Arg Arg
```

<210> 439
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Cha

<220>
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<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 439

```
Xaa Cys Xaa His Phe Arg Trp Cys Xaa Tyr Gly Arg Arg Arg Arg Arg
1                   5                   10                  15

Gln Arg Arg Arg
            20
```

<210> 440
<211> 18
<212> PRT
<213> Artificial Sequence

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<223> Cyclic

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<223> D-Cha

<220>
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<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 440

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        1                   5                   10                  15


        Arg Arg
```

<210> 441
<211> 21
<212> PRT
<213> Artificial Sequence

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<223> Cyclic

<220>
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<223> D-Cha

<220>
<221> MOD_RES
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<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>

<223> C-term NH2

<400> 441

Xaa Cys Xaa His Phe Arg Trp Cys Xaa Xaa Tyr Gly Arg Arg Arg Arg
1   5   10   15

Arg Gln Arg Arg Arg
            20

<210> 442
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Cha

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 442

Xaa Cys Xaa His Phe Arg Trp Cys Xaa Xaa Arg Arg Arg Arg Arg Gln
1   5   10   15

Arg Arg Arg

<210> 443
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
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<223> Nle

<220>
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<223> Cyclic

<220>
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<222> (3)..(3)
<223> D-Cha

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 443

```
Xaa Cys Xaa His Phe Arg Trp Cys Ala Tyr Gly Arg Arg Arg Arg Arg
1               5                   10                  15

Gln Arg Arg Arg Arg
            20
```

<210> 444
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

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<220>
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<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 444

```
      Xaa Cys Xaa His Phe Arg Trp Cys Ala Arg Arg Arg Arg Arg Gln Arg
      1               5               10                  15
```

```
      Arg Arg Arg
```

<210> 445
<211> 22
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<223> Cyclic

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<223> D-Phe

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<220>
<223> C-term NH2

<400> 445

```
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1                   5                   10                  15

Arg Gln Arg Arg Arg Arg
                20
```

<210> 446
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<223> D-Phe

<220>

<221> MOD_RES
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<223> Beta-Ala

<220>
<223> C-term NH2

<400> 446

```
        Xaa Cys Xaa His Phe Arg Trp Cys Ala Ala Arg Arg Arg Arg Arg Gln
        1               5                   10                  15
```

```
        Arg Arg Arg Arg
                    20
```

<210> 447
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<223> Cyclic

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<223> D-Phe

<220>
<221> MOD_RES
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<223> Doc

<220>
<223> C-term NH2

<400> 447

```
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        1               5               10                  15

        Gln Arg Arg Arg Arg
                    20
```

<210> 448
<211> 19
<212> PRT
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<220>
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<223> Cyclic

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<223> D-Cha

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<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 448

```
        Xaa Cys Xaa His Phe Arg Trp Cys Xaa Arg Arg Arg Arg Arg Gln Arg
        1               5               10                  15

        Arg Arg Arg
```

<210> 449
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Cyclic

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<223> D-Cha

<220>
<221> MOD_RES
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<223> D-Phe

<220>
<221> MOD_RES
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<223> Doc

<220>
<223> C-term NH2

<400> 449

```
        Xaa Cys Xaa His Phe Arg Trp Cys Xaa Xaa Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15

        Arg Gln Arg Arg Arg Arg
                    20
```

<210> 450
<211> 20
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<223> Nle

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<223> Cyclic

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<222> (3)..(3)
<223> D-Cha

<220>
<221> MOD_RES
<222> (5)..(5)
<223> D-Phe

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 450

```
Xaa Cys Xaa His Phe Arg Trp Cys Xaa Xaa Arg Arg Arg Arg Arg Gln
1               5                   10                  15
```

```
Arg Arg Arg Arg
                20
```

<210> 451
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

<220>
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<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)

<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 451

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Tyr Gly Arg Arg Arg Arg Arg
        1               5                   10                  15


        Gln Arg Arg Arg
                    20
```

<210> 452
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

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<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 452

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Arg Arg Arg Arg Arg Gln Arg
        1               5               10                  15
```

        Arg Arg

<210> 453
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 453

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Ala Tyr Gly Arg Arg Arg Arg
        1               5               10                  15


        Arg Gln Arg Arg Arg
                    20
```

<210> 454
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

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<223> Cyclic

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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 454

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Ala Arg Arg Arg Arg Arg Gln
        1               5                   10                  15


        Arg Arg Arg
```

<210> 455
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

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<223> D-Phe

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<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 455

Xaa Cys His Phe Arg Trp Xaa Cys Ala Tyr Gly Arg Arg Arg Arg Arg
1   5   10   15

Gln Arg Arg Arg Arg
                20

<210> 456
<211> 19
<212> PRT
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<220>
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<223> Cyclic

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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 456

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Arg Arg Arg Arg Arg Gln Arg
        1               5                   10                  15


        Arg Arg Arg
```

<210> 457
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 457

```
        Xaa Cys His Phe Arg Trp Xaa Cys Ala Ala Tyr Gly Arg Arg Arg Arg
        1               5                   10                  15


        Arg Gln Arg Arg Arg Arg
                    20
```

<210> 458
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

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<223> D-Phe

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<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Beta-Ala

<220>
<223> C-term NH2

<400> 458

```
Xaa Cys His Phe Arg Trp Xaa Cys Ala Ala Arg Arg Arg Arg Arg Gln
1                   5                   10                  15
```

```
Arg Arg Arg Arg
            20
```

<210> 459
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 459

```
        Xaa Cys His Phe Arg Trp Xaa Cys Xaa Tyr Gly Arg Arg Arg Arg Arg
        1               5               10                  15
```

```
        Gln Arg Arg Arg
                20
```

<210> 460
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)

<223> Doc

<220>
<223> C-term NH2

<400> 460

```
        Xaa Cys His Phe Arg Trp Xaa Cys Xaa Arg Arg Arg Arg Arg Gln Arg
        1               5               10              15

        Arg Arg
```

<210> 461
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 461

```
        Xaa Cys His Phe Arg Trp Xaa Cys Xaa Xaa Tyr Gly Arg Arg Arg Arg
        1               5               10              15

        Arg Gln Arg Arg Arg
                    20
```

<210> 462
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<223> Cyclic

<220>
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<223> D-Phe

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 462

```
        Xaa Cys His Phe Arg Trp Xaa Cys Xaa Xaa Arg Arg Arg Arg Arg Gln
        1               5                   10                  15


        Arg Arg Arg
```

<210> 463
<211> 21
<212> PRT
<213> Artificial Sequence

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<221> DOMAIN
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<223> Cyclic

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<223> D-Phe

<220>
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<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 463

```
    Xaa Cys His Phe Arg Trp Xaa Cys Xaa Tyr Gly Arg Arg Arg Arg Arg
    1               5               10              15

    Gln Arg Arg Arg Arg
                20
```

<210> 464
<211> 19
<212> PRT
<213> Artificial Sequence

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<223> Nle

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<223> Cyclic

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<223> D-Phe

<220>
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<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Doc

<220>
<223> C-term NH2

<400> 464

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        1               5               10              15
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```
        Arg Arg Arg
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<210> 465
<211> 22
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<220>
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<223> Nle

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<223> Cyclic

<220>
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<223> D-Phe

<220>
<221> MOD_RES
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<223> Gaba

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Doc

<220>
<223> C-term NH2

<400> 465

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        1               5                   10                  15


        Arg Gln Arg Arg Arg Arg
                    20
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<210> 466
<211> 20
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<220>
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<223> Gaba

<220>
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<223> Doc

<220>
<223> C-term NH2

<400> 466

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        1               5                   10                  15


        Arg Arg Arg Arg
                    20
```

<210> 467
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<212> PRT
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<220>

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<220>
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<223> D-4-Br-Phe

<220>
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<400> 467

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<210> 468
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<220>
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<223> D-2-Nal

<220>
<223> C-term NH2

<400> 468

```
            Cys Glu His Xaa Arg Trp Ala Cys Pro Pro Lys Asp
            1               5               10
```

<210> 469
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<220>
<223> C-term NH2

<400> 469

```
          Cys Glu His Xaa Arg Xaa Ala Cys Pro Pro Lys Asp
          1               5                   10
```

<210> 470
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<220>
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<220>
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<220>
<223> C-term NH2

<400> 470

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```

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<220>
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<400> 471

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```

<210> 472
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437

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                1                5                   10
```

<210> 473
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<220>
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<210> 474

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<223> D-Phe

<220>
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<400> 474

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His Phe Arg Trp Cys
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<220>
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<220>
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<220>
<223> C-term NH2

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<210> 477
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<220>

<223> C-term NH2

<400> 477

His Xaa Arg Trp Cys
1   5

<210> 478
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<400> 478

His Phe Arg Trp Lys
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<400> 479

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<220>
<223> C-term NH2

<400> 481

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<220>
<223> C-term NH2

<400> 482

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<210> 483
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<400> 483

Phe Arg Trp Lys
1

<210> 484
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<220>
<223> C-term NH2

<400> 484

Phe Arg Trp Lys
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Xaa Arg Trp Lys
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Xaa Arg Trp Lys
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                                    1

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<220>
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<223> C-term NH2

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His Phe Arg Trp Xaa
1   5

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<220>
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                              1               5
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<400> 496

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                              His Phe Arg Trp Xaa
                              1               5
```

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<220>
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<400> 497

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                              His Phe Arg Trp Lys
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<220>
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<400> 498

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                              1
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<220>
<223> C-term NH2

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Phe Arg Trp Lys
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<220>
<223> C-term NH2

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Cys Glu His Phe Arg Trp Cys
1   5

<210> 501
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<220>
<223> C-term NH2

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1   5

<210> 502
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Cys Glu His Phe Arg Trp Cys
1   5

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          1                   5
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<400> 504

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Cys Ala His Phe Arg Trp Cys
1               5
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<210> 505
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Claims

1. A composition for use in a method of treating obesity or a metabolic syndrome in a subject in need thereof, wherein the composition comprises Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$ (SEQ ID NO: 140) or a pharmaceutically acceptable salt thereof, and the subject has a gene mutation or a gene defect upstream of the melanocortin-4 receptor (MC4R).

2. The composition for use of claim 1, wherein the gene mutation or a gene defect occurs in the gene encoding for pro-opiomelanocortin (POMC).

3. The composition for use of claim 1, wherein the gene mutation or a gene defect occurs in the gene encoding for leptin or leptin receptor (LEPR).

4. The composition for use of any one of claims 1-3, wherein the obesity or metabolic syndrome results from an attenuated response of MC4R to α-melanocortin stimulating hormone (a-MSH).

5. The composition for use of any one of claims 1-4, wherein the composition is used in a method of treating obesity.

6. The composition for use of any one of claims 1-4, wherein the composition is used in a method of treating a metabolic syndrome.

7. The composition for use of any one of claims 1-6, wherein the Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$ (SEQ ID NO: 140) or a pharmaceutically acceptable salt thereof is an agonist of a melacortin-4 receptor (MC4R).

8. The composition for use of any one of claims 1-7, wherein the subject is a human.

Patentansprüche

1. Zusammensetzung für die Verwendung in einem Verfahren zum Behandeln von Fettleibigkeit oder eines metabolischen Syndroms in einem Subjekt, das dessen Bedarf, wobei die Zusammensetzung Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$ (SEQ ID NO: 140) oder ein pharmazeutisch unbedenkliches Salz davon umfasst, und das Subjekt eine Genmutation oder einen Gendefekt stromaufwärts des Melanocortin-4-Rezeptors (MC4R) aufweist.

2. Zusammensetzung für die Verwendung nach Anspruch 1, wobei die Genmutation oder ein Gendefekt in dem Gen auftritt, das für Pro-Opiomelanocortin (POMC) kodiert.

3. Zusammensetzung für die Verwendung nach Anspruch 1, wobei die Genmutation oder der Gendefekt in dem Gen auftritt, das für Leptin oder den Leptinrezeptor (LEPR) kodiert.

4. Zusammensetzung für die Verwendung nach einem der Ansprüche 1-3, wobei die Fettleibigkeit oder das metabolische Syndrom aus einer abgeschwächten Reaktion von MC4R auf α-Melanocortin-stimulierendes Hormon (a-MSH) resultiert.

5. Zusammensetzung für die Verwendung nach einem der Ansprüche 1-4, wobei die Zusammensetzung in einem Verfahren zum Behandeln von Fettleibigkeit verwendet wird.

6. Zusammensetzung für die Verwendung nach einem der Ansprüche 1-4, wobei die Zusammensetzung in einem Verfahren zum Behandeln eines metabolischen Syndroms verwendet wird.

7. Zusammensetzung für die Verwendung nach einem der Ansprüche 1-6, wobei das Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$ (SEQ ID NO: 140) oder ein pharmazeutisch unbedenkliches Salz davon ein Agonist eines Melacortin-4-Rezeptors (MC4R) ist.

8. Zusammensetzung für die Verwendung nach einem der Ansprüche 1-7, wobei das Subjekt ein Mensch ist.

Revendications

1. Composition destinée à être utilisée dans une méthode de traitement de l'obésité ou d'un syndrome métabolique chez un sujet qui en a besoin, la composition comprenant Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH$_2$ (SEQ ID NO : 140) ou un sel pharmaceutiquement acceptable de celui-ci, et le sujet présentant une mutation génétique ou un défaut génétique en amont du récepteur de la mélanocortine 4 (MC4R).

2. Composition destinée à être utilisée selon la revendication 1, dans laquelle la mutation génétique ou un défaut génétique se produit dans le gène codant pour la proopiomélanocortine (POMC).

3. Composition destinée à être utilisée selon la revendication 1, dans laquelle la mutation génétique ou un défaut génétique se produit dans le gène codant pour la leptine ou le récepteur de la leptine (LEPR).

4. Composition destinée à être utilisée selon l'une quelconque des revendications 1 à 3, dans laquelle l'obésité ou le syndrome métabolique résulte d'une réponse atténuée de MC4R à l'hormone stimulant la mélanocortine α (α-MSH).

5. Composition destinée à être utilisée selon l'une quelconque des revendications 1 à 4, la composition étant utilisée dans une méthode de traitement de l'obésité.

6. Composition destinée à être utilisée selon l'une quelconque des revendications 1 à 4, la composition étant utilisée dans une méthode de traitement d'un syndrome métabolique.

7. Composition destinée à être utilisée selon l'une quelconque des revendications 1 à 6, dans laquelle Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO : 140) ou un sel pharmaceutiquement acceptable de celui-ci est un agoniste d'un récepteur de la mélanocortine 4 (MC4R).

8. Composition destinée à être utilisée selon l'une quelconque des revendications 1 à 7, dans laquelle le sujet est un être humain.
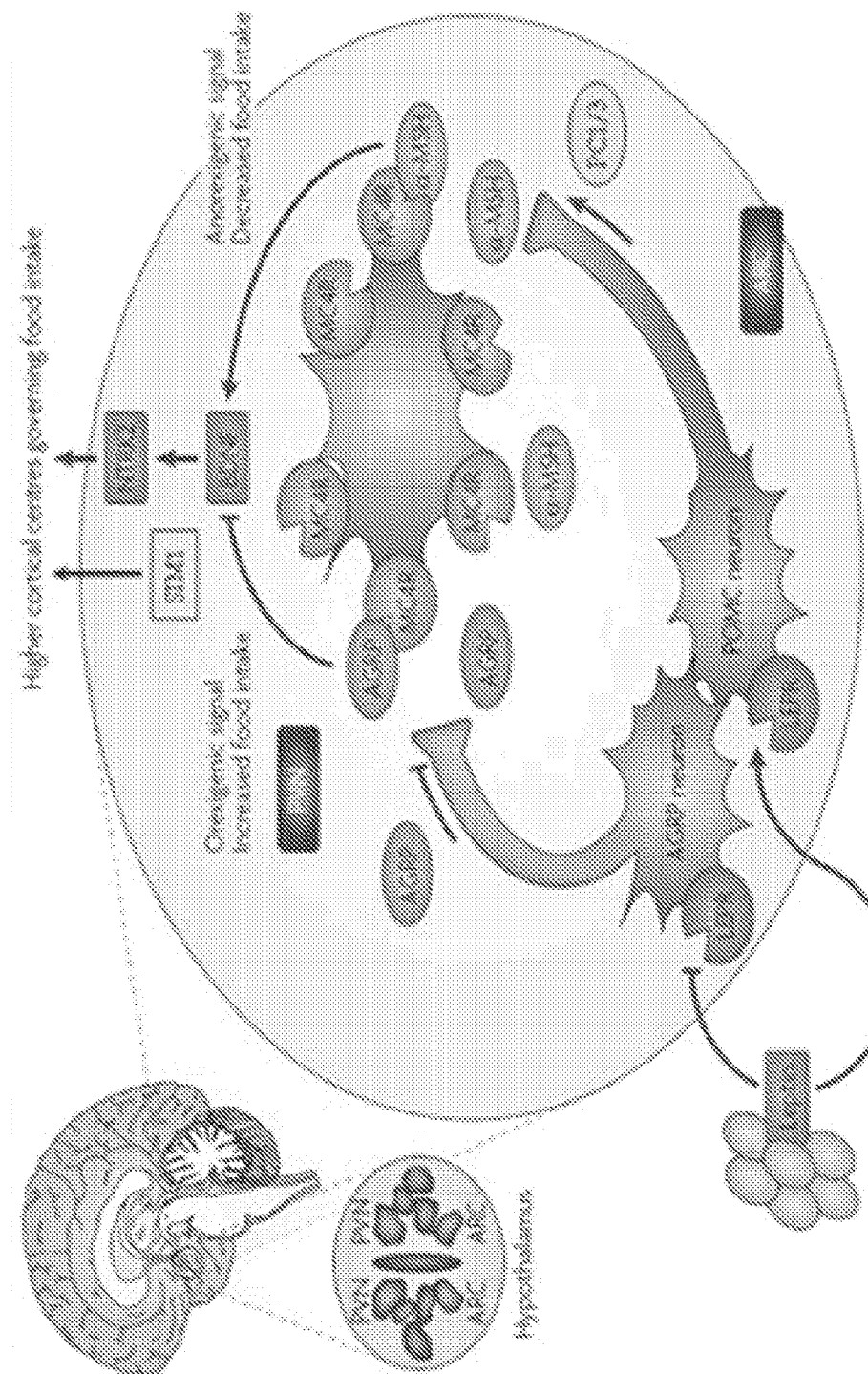
FIG. 1

Table 1

Sequence variants of *MC4R* detected in 243 subjects with severe early-onset obesity

Sequence Variant	Number of obese subjects with mutation[A]	Number of controls with mutation[B]	Number of subjects previously described
GT insertion at codon 279	2	0	None
C deletion 28-bp downstream of stop codon	1	0	None
N62S	1 (hom)	0	None
T112M	1	0	2 (11, 12)
R165Q	1	0	None
V253I	1	0	None
C271Y	1	0	None
I251L	7	3	1 (12)
V103I	3	1	2 (11, 12)

FIG. 2A

Table 2

MC4-R mutation screening in morbidly obese patients and nonobese controls

Base change	Effect on amino acid sequence	Morbidly obese (n − 209)	Control 1 (n − 254)	Control 2 (n − 112)
A-307-G	Val103 Ile	8	8	3
A-751-C	Ile251Leu	3	3	0
C-593-T	Silent	1	ND	1
47-48insG	16 + 12 amino-acids	1	0	0
A-31-G	Thr11Ser	1	0	0
C-52-T	Arg18Cys	1	0	0
C-449-T	Thr150Ile	1	0	0
A-508-G	Ile170Val	1	0	0
C-493-T	Arg165Trp	1	0	0
T-749-A	Leu250Gln	1	0	0
T-902-C	Ile301Thr	1	0	0

The morbidly obese and the control 2 populations were screened by PCR-SSCP. The control 1 population was screened by PCT-RFLP for every functionally relevant mutation detected in the morbidly obese population. ND, not determined.
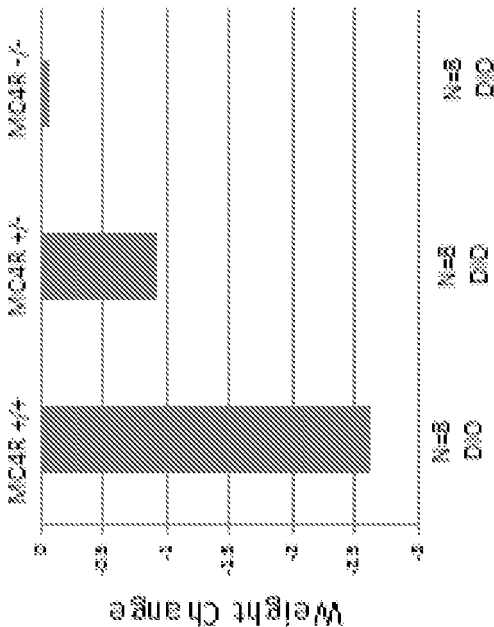
FIG. 2B

FIG. 3

REFERENCES CITED IN THE DESCRIPTION

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