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(54) **Stabilizált melanokortin ligandumok**

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(54) **STABILIZED MELANOCORTIN LIGANDS**

STABILISIERTE MELANOCORTIN-LIGANDEN

LIGANDS DE MÉLANOCORTINE STABILISÉS

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Description

FIELD OF THE INVENTION

[0001] The present disclosure relates to melanocortin ligands having a degradation-resistant C-terminal extension to minimize or abolish cardiovascular effects for use in the treatment of various pathological conditions.

BACKGROUND OF THE INVENTION

Description of Related Art

[0002] The following discussion refers to a number of publications by author(s) and year of publication. Discussion of such publications herein is given to present a more complete background and is not to be construed as an admission that such publications are "prior art".

[0003] Melanocortins are a group of small peptides that bind to a family of five known melanocortin receptors (MC1R through MC5R) (Cone, R.D., 2006, Endocr. Rev., 27(7):736-749). They are derived from a common precursor protein, pro-opiomelanocortin (POMC), which is expressed in the neurons of the central and peripheral nervous system, and in the pituitary gland (Voisey, J et al., 2003, Curr. Drug Targets, 4(7):586-597). The proteolytic cleavage of POMC results in α- β- and γ-melanocortin and adrenocorticohormone (ACTH), in addition to several other biologically important peptides.

[0004] Of the five known melanocortin receptors, MC3R and MC4R are thought to be expressed predominantly in the mammalian brain, with MC3R being most highly expressed in the arcuate nucleus of the hypothalamus, and MC4R being expressed in the thalamus, hypothalamus, and hippocampus. MC1R is expressed mainly in the periphery where it is found, for example, on melanoma cells and melanocytes and immune cells. In the neuronal system, MC1R is present only on neurons in the periaqueductal grey matter of the midbrain, where it is believed to have a role in controlling pain. MC2R is predominantly expressed in the adrenal cortex, where it controls steroidogenesis. MC5R is found predominantly in peripheral tissues such as the secretory epithelia of many exocrine glands, where it affects secretory and trophic controls.

[0005] Melanocortin peptides were initially thought to have a physiological function primarily directed to the control of skin pigmentation. However, in the last 25 years, many additional biological activities have been attributed to the melanocortins. Melanocortin peptides that are either agonists (activators) or antagonists (inhibitors) have been shown to control many physiological processes, including pigmentation, feeding, overall metabolic rate/energy homeostasis, endocrine and exocrine gland secretion, inflammation, sodium excretion by the kidney, pain sensation, addictive behavior, and sexual drive.

[0006] Therefore, melanocortin analogs have been synthesized for the potential regulation and treatment of many conditions, including weight regulation (e.g., obesity, anorexia, and cachexia), hormonal secretion, and hyposecretion of many exocrine glands (*e.g.*, Sjogren's Syndrome), immuno-relevant conditions, and sexual dysfunction (Cone, R.D., 2006, Endocr. Rev., 27(7):736-749; Cone, R.D., 2005, Nat. Neurosci, 8(5):571-578; Bazzani, C., et al., 2002, Resuscitation, 52(1):109-115; and Bertonlini, A., et al., 2009, Pharmacol. Res, 59(1):13-47). However, in regulating these physiological effects, melanocortin analogs have also been shown to cause hypertension (Gruber, et al., 1984, Hypertension, 6:468-474 and Klein, et al., 1985, Life Sci. 36:769-775). Experimental studies have shown that administration of melanocortin analogs (ligands) increases arterial pressure and heart rate, and can produce cardiac arrhythmias (Gruber and Callahan, 1989, Am. J. Physiol. 257:R681-R694; and unpublished data).

[0007] The physiological regulatory effects of a melanocortin peptide are achieved through the melanocortin pharmacophore: (His-Phe-Arg-Trp) (**SEQ ID NO: 1);** this pharmacophore being the minimum set of amino acids necessary for melanocortin-regulated activity (Holder, J.R. and C. Haskel-Luevano, 2004, Med. Res. Rev., 24(3):325-356). In general, all melanocortinpeptides share the same active core sequence: His-Phe-Arg-Trp (**SEQ ID NO: 1**), including melanotropin neuropeptides and adrenocorticotropin. The amino acids surrounding this core sequence in naturally occurring melanocortin peptides are believed to affect the relative affinity for a specific melanocortin receptor.

[0008] Various non-naturally occurring melanocortin analogs having enhanced affinity for melanocortin receptors have been synthesized. For example, Klemes et al. 1986, Biochem. Biophys. Res. Commun., 137(2):722-728 synthesized the melanocortin analogs (Ac-Nle-Asp-His-D-Phe-Arg-Trp) and (Ac-Nle-Asp-His-Phe-Arg Trp) (**SEQ ID NO: 2**). These modified analogs show increased potency for melanotropic activity. Several other melanocortin analogs have been identified. Further examples of melanocortin analogs that have been synthesized, having increased potency, include (Ac-Nle-cyclo-Asp-His-Phe-Arg-Trp-Lys) and (Ac-Nle-cyclo-Asp-His-D-Phe-Arg-Trp-Lys) (al-Obeidi et al., 1989, J. Med. Chem, 32(12):2555-2561); (Ac-Nle-cyclo-Asp-His-D-Nal 2'-Arg-Trp-Lys) and (Ac-cyclo-Cys-Glu-His-D-Nal 2'-Arg-Trp-Gly-Cys-Pro-Pro-Lys-Asp) (Balse-Srinivasan et al., 2003, J. Med. Chem., 46(17):3728-3733); (Ac-Nle-Glu-His-D-Phe-Arg-D-Trp-Gly) (al-Obeidi et al., 1989, Pept. Res., 2(1):140-146); and (His-Phe-Arg-Trp-Gly-Lys-Pro-Val) (**SEQ ID NO: 3**), (Masman et al., 2008, Bioorg. Med. Chem., 16(8):4347-58).

[0009] However, due to their potent cardiovascular side effects (Greenfield et al., 2009, N. Eng. J. Med. 360:44-52; Gupta, 2007, Reuters Aug. 30, 2007; Mishra, 2007, Reuters Sept. 10, 2007; Nordheim et al., 2006, Peptides 27:438-443), the melanocortin analogs synthesized to date have not yet resulted in a governmental regulatory agency approved therapeutic drug for treating any of the many melanocortin-related conditions. The clinically unacceptable cardiovascular effects of melanocortin analogs are mediated by a second pharmacophore (Arg-Trp) located within the first pharmacophore. (Klein et al., 1985, Life Sci., 36:769-775; Gruber and Callahan, 1989, Am. J. Physiol., 257:R681-694). This second pharmacophore is believed to interact with a subset of the RFamide receptor family, resulting in elevation of central sympathetic drive and initiation of cardiovascular effects. The generalized motif of an Arg-aromatic di-peptide sequence at or near the C-terminus of many synthetic melanocortin ligands is a more inclusive description of the pharmacophore of the RFamide class (Gruber and Callahan, Am. J. Physiol., 1989, 257:R681-694; Klein et al., 1985, Life Sci. 36:769-775; Clements et al., 2001, Biochem. Biophys. Res. Commun., 284:1189-1193).

[0010] Although it has long been believed that melanocortin cardiovascular effects cannot be separated from the non-hypertensive, and potentially therapeutic, physiological effects, Gruber and Callahan showed that this is incorrect. (Gruber and Callahan 1989, Am. J. Physiol., 257:R681-694). Peptide C-terminal extension of a melanocortin analog can minimize *acute* cardiovascular activity, while preserving melanocortin effects. Effectively, the additional C-terminal amino acids temporarily "hide" the cardiovascular/RFamide-like pharmacophore (Arg-Trp) by moving it deeper within the molecular structure of the peptide. This acutely suppresses the cardiovascular effects without affecting the melanocortin activity.

[0011] Nonetheless, many of the C-terminal extensions on melanocortin analogs that have shown minimized cardiovascular activity in *in vitro* assays have been shown to be degraded *in vivo.* Melanocortin analogs having C-terminal extensions may initially confer only the desired effects, but once degradation occurs, the (Arg-Trp) RFamide pharmacophore is unmasked, conferring the associated cardiovascular effects.

[0012] Bednarek et al. (2001), Journal of Medicinal Chemistry 44 (22): 3665-3672 relates to selective, high affinity peptide antagonists of α-melanotropin action at human melanocortin receptor 4 (synthesis and biological evaluation *in-vitro*).

[0013] Giuliani et al. (2007), British Journal of Pharmacology 150 (5): 595-603 reports that selective melanocortin MC_4 receptor agonists reverse haemorrhagic shocks and prevent multiple organ damage.

[0014] US 2005/038230 relates to linear and cyclic peptides which are specific to melanocortin receptors and exhibit agonist, antagonist, or mixed agonist-antagonist activity.

SUMMARY OF THE INVENTION

[0015] The present invention is defined in the claims. Accordingly, the invention provides a non-naturally occurring melanocortin ligand comprising a melanocortin analog coupled to a degradation-resistant C-terminal extension and an N-terminal extension, the non-naturally occurring melanocortin ligand comprising Formula I:

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \textbf{(Formula I)},$$

wherein the melanocortin analog comprises R^1 to R^7, wherein:

- R^1 is absent or is selected from the group consisting of cysteine, norleucine, acetylated norleucine, acetylated cysteine, D-phenylalanine, acetylated D-phenylalanine, succinic acid, o-phthalic acid, tyrosine, aspartic acid, glutaric acid, CO-cis-CH=CH-CO, an *n*-pentanoyl group, and an *n*-hexanoyl group;
- R^2 is absent or is selected from the group consisting of proline, aspartic acid, glutamic acid, glycine, cysteine, norleucine, arginine, succinic acid, glutaric acid, CO-cis-CH=CH-CO, an *n*-pentanoyl group, and an *n*-hexanoyl group;
- R^3 is selected from the group consisting of histidine, histidine methylated at positions 1 or 3, D-proline, L-proline, D-Nal(2'), L-Nal(2'), succinic acid, *t*ButGly, Hyp(Bzl), Mamb, Oic, norleucine, Aba, β-alanine, and Tic;
- R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2'), pCl-D-Phe, and (*o*-Phe)Phe;
- R^5 is selected from the group consisting of arginine, homoarginine, ornithine, alanine, proline, Pip, Nip, Tic, Phg, Sar, and Azt;
- R^6 is selected from D-tryptophan, L-tryptophan, D-Nal(2'), L-Nal(2'), Tic, and Bip;
- R^7 is selected from the group consisting of cysteine, lysine, and 2,3-diamino-propionic acid;

wherein if R^3 is Aba, then R^4 is selected from the group consisting of D-Phe, D-Nal(2'), and pCl-D-Phe; and
wherein if R^2 is an *n*-pentanoyl group or an *n*-hexanoyl group, then R^1, Y^1, Y^2, and Y^3 are absent;
wherein the N-terminal extension comprises Y^1 to Y^3:

- Y^1 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, and L-proline;

Y^2 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring;

Y^3 is absent or is selected from the group consisting of cysteine, D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring;

wherein the degradation-resistant C-terminal extension comprises X^1 to X^3 and

X^1 is D-threonine,;
X^2 is D-proline,;
X^3 is D-threonine

wherein the melanocortin ligand is cyclized, and

when R^2 is cysteine and R^7 is cysteine a disulfide bond is formed between R^2 and R^7;
when R^2 is glutamic acid or aspartic acid and R7 is lysine a side-chain lactam bridge is formed between R^2 and R^7; and
when R^2 or R^3 is succinic acid and R^7 is 2,3-diamino-propionic acid a lactam closure is formed between R^2 or R^3 and R^7.

[0016] Further aspects of the invention are defined in the claims.

[0017] Since melanocortin drugs would potentially be used to treat chronic conditions, they must not produce potentially dangerous side effects during prolonged administration. Thus, suppression of melanocortin ligand cardiovascular effects, during chronic administration, is important for a clinically safe melanocortin drug. This requires prolonged *in vivo* separation of the RFamide cardiovascular actions of the melanocortin pharmacophore from its therapeutic melanocortin effects. This would allow melanocortin analogs to be used as treatments for a variety of pathological conditions, with minimal risk of cardiovascular pathology.

[0018] Thus, a non-naturally occurring melanocortin ligand as defined in the claims comprises inter alia a melanocortin analog coupled to a degradation-resistant C-terminal extension, effectively producing chronic separation of melanocortin from RFamide cardiovascular activity.

DETAILED DESCRIPTION

[0019] A composition is described herein comprising a non-naturally occurring melanocortin ligand coupled to a degradation-resistant C-terminal extension to suppress exposure and effect of the RFamide/cardiovascular pharmacophore, and an N-terminal extension to prevent N-to-C-terminus (*i.e.*, left to right) enzymatic degradation of the melanocortin pharmacophore. A degradation-resistant C-terminal extension as described herein is at least one amino acid, at least one modified amino acid, a peptide mimetic (non-amino acid small molecule), or combinations thereof. A degradation-resistant C-terminal extension is one selected to resist degradation under physiological conditions, thereby allowing the melanocortin analog to maintain at least one melanocortin physiological regulatory effect while exhibiting minimized or abolished cardiovascular effects when acutely or chronically administered to a human or mammal.

Terminology

[0020] *Melanocortin analog* refers to at least a melanocortin pharmacophore. Melanocortin analogs are molecules that bind melanocortin receptors under physiological conditions. Melanocortin analogs include non-naturally occurring melanocortin polypeptides and truncated and/or modified versions of a melanocortin full-length protein or polypeptide. For example, the full-length POMC protein, prior to proteolytic cleavage of "sub-peptides," consists of 241 amino acids. Tissue-specific proteolytic cleavage of POMC yields peptides ranging in size from 13 amino acids to 76 amino acids (Bicknell and Lawry, 2000, Encyclopedia of Stress, vol. 3, 257-265, Academic Press). Synthesized, non-naturally occurring melanocortin analogs having increased melanocortin receptor activity as discussed herein are approximately 7-12 amino acids in size. Melanocortin analogs exhibit binding functionality with melanocortin receptors. The binding is either activating (agonist) or inhibitory (antagonist). In addition to peptides, the melanocortin analogs include small molecule analogs of melanocortin or a portion thereof comprised of organic or inorganic compounds or a combination of peptide and small molecule-*i.e.*, peptide mimetics.

[0021] The melanocortin analogs can be structurally similar and/or functionally similar to the melanocortin proteins in their ability to bind melanocortin receptors. Further, the melanocortin analogs generally contain the pharmacophore: His-Phe-Arg-Trp (**SEQ ID NO: 1**) or a modified version thereof, or a structural or functional peptide mimetic thereof.

[0022] *Peptide mimetic* is a non-amino acid molecule that mimics a peptide (a chain of amino acids) or one amino acid residue.

[0023] *Pharmacophore* is the minimum set of amino acid residues necessary to achieve a physiological effect; or a small molecule that is (with respect to a receptor) a structural mimic of the amino acid residues required for binding to and activation of a receptor. His-Phe-Arg-Trp (**SEQ ID NO: 1**) and their analogs are the pharmacophore of melanocortin for the regulated physiological effect. Therefore, non-naturally occurring melanocortin pharmacophore analogs can be small peptides or organic molecules designed to mimic the appearance or function (including activation or deactivation of receptor activity) of the melanocortin pharmacophore core sequence peptide.

[0024] *Cardiovascular effects* include the medical definition of hypertension, namely that of high blood pressure (at least above 120/80 mm Hg, and especially if above 140/90 mm Hg (systolic/diastolic), pathological effects on the vasculature, kidney and heart, and other associated effects. Conversely, hypotension is when the blood pressure drops below medically accepted norms. Cardiac arrhythmias imply an alteration in the normal symmetrical appearance of the pulsatile pressure wave of arterial pressure. This can be increased beats per minute (tachycardia) or decreased beats per minute (bradycardia). It also may imply an alteration in the normal wave pattern of the electrocardiogram.

[0025] *Substantial degradation* refers to the degradation of the C-terminal extension, the N-terminal extension, or other regions of the melanocortin analog of the melanocortin ligand of the present invention, by physiological enzymes and other factors, in such a manner or to a degree that the RFamide pharmacophore is again capable of initiating a cardiovascular effect through the RFamide receptor or other physiological systems, comparable to melanocortin ligands or melanocortin analogs without a C-terminal extension. According to a preferred aspect of the present disclosure, a melanocortin analog having a C-terminal extension that resists substantial degradation is one in which no more than 50% of the administered ligand can reestablish a cardiovascular effect, preferably no more than 25%, and more preferably less than 10%, as compared to a melanocortin analog that lacks a C-terminal extension.

[0026] *A pharmaceutical composition* includes a ligand of this disclosure, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The carrier may be a liquid formulation, for example, a buffered, isotonic, aqueous solution. Pharmaceutically acceptable carriers also can include excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like.

[0027] *A pharmaceutically acceptable salt* refers to a salt prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic and organic acids and bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc, and similar salts. Particularly preferred are ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable, organic, non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines, including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and similar basic ion exchange resins.

[0028] When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and similar acids. Particularly preferred are citric, fumaric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

[0029] It will be understood that, as used herein, references to the compounds of Formula I and Formula II are meant to also include the pharmaceutically acceptable salts of these compounds, such as hydrochloride salts, etc.

[0030] *Abbreviations* in the listing of compounds have their conventional meaning. Thus, "Nle" is norleucine; "Nal" is noralanine; "D-Nal" is D-noralanine; "Asp" is aspartic acid; "His" is histidine; "D-Phe" is D-phenylalanine; "Arg" is arginine; "Trp" is tryptophan; "Lys" is lysine; "Gly" is glycine; "Pro" is proline; "Tyr" is tyrosine; "Ser" is serine; "Cys" is cysteine; "Val" is valine; "D/L-Thr" is either D-threonine or L-threonine; "D/L-Pro" is either D-proline or L-proline. Additionally, "Ac" is N-acetyl and "cyclo" refers to a cyclic structure, which is also shown in the literature as "c" or referred to as a "lactam".

[0031] Additional abbreviations are defined as follows: Nal(2')=D-2'-naphthylalanine; tBu=tert-butyl; Hyp(Bzl)=benzyl-L-hydroxy-proline; Mamb=3-aminomethyl-benzoic acid; glutaric acid linker=CO-$(CH_2)_3$-CO; Pen=L-Penicillamine; Aib=2-Aminoisobutyric acid; Tic=1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid; Aba=4-amino-1,2.4,5-tetra-hydro-2-benzazepin-3-one; Pip=piperidine-2-carboxylic acid; Nip=piperidine-3-carboxylic acid; Tic=tetrahydroquinoline-3-carboxylic acid; Bip=biphenylalanine; Phg=α-Phenyl-glycine; Sar=Sarcosine; Azt=3'-azido-3'-deoxythymidine; Oic=Octohydroindole-2-carboxylic acid.

Melanocortin Analog

[0032] A non-naturally occurring melanocortin ligand may be represented by Formula I as shown, and comprises a

melanocortin analog coupled to a degradation-resistant C-terminal extension and an optional N-terminal extension:

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \text{(Formula I)}$$

wherein Y^1-Y^2-Y^3 represents optional stabilizing N-terminal residues or an amino acid residue mimetic; R^1 to R^7 represent residues of the melanocortin analog; and X^1-X^2-X^3 represent degradation-resistant C-terminal residues or an amino acid residue mimetic.

[0033] Collectively, R^1 to R^7 (R^1-R^2-R^3-R^4-R^5-R^6-R^7) can be one of many known melanocortin analogs, wherein each of the seven residues is independently an amino acid or peptide mimetic. Some melanocortin analogs have less than seven residues. R^1 to R^7, collectively, may represent alpha melanocortin analogs. R^1 to R^7, collectively, may also represent melanocortin analogs which bind to MC3-MC5 receptors as agonists or antagonists.

[0034] A melanocortin ligand may be represented by Formula I above, and residues R^1 to R^7, collectively, represent the melanocortin analog, wherein

R^1 is absent or is selected from the group consisting of cysteine, norleucine, acetylated norleucine, acetylated cysteine, D-phenylalanine, methylated D-phenylalanine, succinic acid, o-pthalic acid, tyrosine, aspartic acid, glutaric acid, CO-*cis*-CH=CH-CO, an n-pentanoyl group, and an n-hexanoyl group;

R^2 is absent or is selected from the group consisting of proline, aspartic acid, glutamic acid, glycine, cysteine, norleucine, arginine, succinic acid, glutaric acid, CO-cis-CH=CH-CO, an n-pentanoyl group, and an n-hexanoyl group;

R^3 is selected from the group consisting of histidine, histidine methylated at positions 1 or 3, D-proline, L-proline, D-Nal(2'), L-Nal(2'), succinic acid, tButGly, Hyp(Bzl), Mamb, Oic, norleucine, Aba, β-alanine, and Tic;

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2'), pCl-D-Phe, and (o-Phe)Phe;

R^5 is selected from the group consisting of arginine, homoarginine, ornithine, alanine, proline, Pip, Nip, Tic, Phg, Sar, and Azt;

R^6 is selected from D-tryptophan, L-tryptophan, D-Nal(2'), L-Nal(2'), Tic, and Bip;

R^7 is absent or is selected from the group consisting of glycine, glutamic acid, cysteine, lysine, and 2,3-diamino-propionic acid;

wherein if R^3 is Aba, then R^4 is selected from the group consisting of D-Phe, D-Nal(2'), and pCl-D-Phe; and

wherein if R^2 is an n-pentanoyl group or an n-hexanoyl group, then R^1, Y^1, Y^2, and Y^3 are absent.

[0035] A melanocortin ligand may also be represented by Formula II:

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}R^9\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \text{(Formula II).}$$

[0036] Collectively, R^1 to R^9 (R^1-R^2-R^3-R^4-R^5-R^6-R^7-R^8-R^9) can be one of many known melanocortin analogs, wherein each of the nine residues is an amino acid or peptide mimetic. Some melanocortin analogs have less than nine residues. R^1 to R^9, collectively, may represent gamma melanocortin analogs. R^1 to R^9, collectively, may also represent melanocortin analogs which bind to MC3 receptors as antagonists.

[0037] A melanocortin ligand may be represented by Formula II above, and residues R^1 to R^9, collectively, represent the melanocortin analog, wherein:

R^1 is tyrosine;
R^2 is valine;
R^3 is selected from the group consisting of methionine, norleucine, cysteine, and L-penicillamine;
R^4 is selected from the group consisting of glycine, D-cysteine, L-cysteine, aspartic acid, and norleucine;
R^5 is selected from the group consisting of histidine, norleucine, proline, and Aib;
R^6 is selected from the group consisting of phenylalanine, D-Nal(2'), and L-Nal(2');
R^7 is arginine;
R^8 is selected from the group consisting of tryptophan and D-Nal(2'); and
R^9 is absent or is selected from the group consisting of aspartic acid, cysteine, penicillamine, and lysine.

[0038] A melanocortin ligand may also be represented by Formula I or Formula II, wherein at least one D-phenylalanine residue, or all D-phenylalanine residues are halogenated (*e.g.*, fluorine or chlorine) to confer improved melanocortin protein-ligand interaction with its corresponding MC receptor(s) (Ippolito, J.A and D.W. Christianson, 1992, Int. J. Biol. Macromol, 14(4):193-197.)

C-terminal Extension

[0039] To the R^1 to R^7 melanocortin analog of Formula I, or to the R^1 to R^9 (R^1-R^2-R^3-R^4-R^5-R^6-R^7-R^8-R^9) melanocortin

analog of Formula II, a C-terminal extension is intended to confer degradation-resistance of the C-terminal extension to prevent exposure of the RFamide sequence.

[0040] A C-terminal extension may be represented by X^1-X^2-X^3 of Formula I, wherein

X^1 is selected from the group consisting of cysteine, D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring;

X^2 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring; and

X^3 is absent or is selected from the group consisting of D-threonine, L-threonine, and a piperazin-2-one ring.

[0041] A C-terminal extension may also be represented by X^1-X^2-X^3 of Formula II, wherein

X^1 is selected from the group consisting of cysteine, D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring;

X^2 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring; and

X^3 is absent or is selected from the group consisting of D-threonine, L-threonine, and a piperazin-2-one ring.

[0042] A C-terminal extension may have a conformation that chronically inhibits degradation from carboxy peptidases. Examples of a C-terminal extension that chronically inhibit degradation include the di-and tripeptides of D-Pro-D-Pro, D-Thr-D-Pro, D-Thr-D-Pro-D-Thr, as described in Tugyi et al., 2005, Proc. Nat. Acad. Sci. (USA), 102(2):413-418.

[0043] A proline mimetic (piperazin-2-one ring) may be substituted for D-Pro. In one approach, a proline mimetic is synthesized as described by Teixido, M., et al., 2007, Brain Res. Bull., 73(1-3):103-107. The piperazin-2-one ring is also discussed in Bhatt, U. and Just, G., 2000, Helvetica Chimica Acta, 83:722-727. For the replacement of proline with a piperazin-2-one ring, an ethylene bridge is incorporated between the nitrogen molecules of two adjacent α-amino groups. This produces a six-membered ring, containing two nitrogen and four carbon atoms, a structure that is similar to a proline ring (albeit six-membered) between the two adjacent amino acid residue functional groups.

[0044] In accordance with the teaching herein, the C-terminal extension of the melanocortin analog is resistant to substantial degradation prior to the ligand being cleared from the bloodstream in the human or animal body. A C-terminal extension may be of sufficient stability such that the melanocortin ligand does not cause cardiovascular effects, or has minimized cardiovascular effects when administered to a human or animal. As stability of peptides, amino acids, and small molecules varies widely, melanocortin ligands may have variable length C-terminal extensions in the extracellular physiological environment. The C-terminal extension is of sufficient stability (e.g., length, steric structure) such that any degradation in the body prior to its clearance from the bloodstream will not re-expose the cardiovascular pharmacophore to achieve its effect.

N-terminal Extension

[0045] An N-terminal extension may be coupled to the melanocortin analog. The N-terminal extension is represented as Y^1-Y^2-Y^3 in Formula I, wherein

Y^1 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, and L-proline;

Y^2 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring; and

Y^3 is absent or is selected from the group consisting of cysteine, D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring.

[0046] An N-terminal extension may also be represented as Y^1-Y^2-Y^3 in Formula II, wherein

Y^1 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, and L-proline;

Y^2 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring; and

Y^3 is absent or is one selected from the group consisting of cysteine, D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring.

Cyclization of the Melanocortin Ligand of Formula I

[0047] Cyclized melanocortin analogs have shown improved efficacy and stability (Balse-Srinivasan et al., 2003, J. Med. Chem., 46(17):3728-3733 and Bednarek et al., 2001, Biochem. Biophys. Res. Commun., 286(3):641-645; Kavarana, et al., 2002, J. Med. Chem., 45(12):2644-2650). A non-naturally occurring melanocortin ligand represented by Formula I may be cyclized. The following represents a non-limiting list of examples of how the melanocortin ligand represented by Formula I can be cyclized:

[0048] A disulfide bond between R^1 or R^2 and R^7 or X^1 when R^1 or R^2 is cysteine and R^7 or X^1 is cysteine, as described in Balse-Srinivasan et al., 2003, J. Med. Chem., 46(23):4965-4973. When X^1 is cysteine, X^2 is not absent, but is selected from the group consisting of D-threonine, L-threonine, D-proline, L-proline and a piperazin-2-one ring.

[0049] A lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid, as described in Mayorov et al., 2006, J. Med. Chem., 49:1946-1952, and Bednarek et al., 2001, Biochem Biophys. Res. Commun., 286(3):641-645.

[0050] A side-chain lactam bridge between R^2 and R^7 when R^2 is glutamic acid or aspartic acid and R^7 is lysine, as described in Bednarek et al., 2001 Biochem Biophys. Res. Commun., 286(3):641-645.

[0051] A lactam closure between R^1 and R^7 when R^1 is succinic acid or o-pthalic acid and R^7 is lysine, as described in Bednarek et al., 2001, Biochem Biophys. Res. Commun., 286(3):641-645 and Kavarana, et al., 2002, J. Med. Chem., 45(12):2644-2650.

[0052] A lactam closure between R^2 or R^3 and R^7 when R^2 or R^3 is succinic acid and R^7 is 2,3-diamino-propionic acid as described in Bednarek et al., 2001, Biochem Biophys. Res. Commun., 286(3):641-645.

[0053] A "backbone" cyclized peptide is formed by covalent bond formation between the N and/or C terminus of a linear peptide of interest. An example of this is described in the bonding of two amide nitrogens via a bridge consisting of alkyl groups and an amide, as described by Hess et al., 2007, J. Med. Chem., 50:6201-6211.

Amino Acids-isomers and non-standard amino acids

[0054] The amino acid residues, as disclosed herein for non-naturally occurring melanocortin ligands, can be either D- or L-amino acids or can be substituted with their non-standard, isomeric counterparts. For example, alpha amino acids can be substituted with beta amino acids, and L amino acids can be substituted with D amino acids. An amino acid disclosed herein that is not designated as a D- or L-isomer, can be either isomer. The invention, as mentioned, is defined in the claims.

Cyclization of the Melanocortin Ligand of Formula II

[0055] A non-naturally occurring melanocortin ligand represented by Formula II may be cyclized. The melanocortin analog represented by Formula II can be cyclized through a lactam side chain between R^4 and R^9 when R^4 is aspartic acid and R^9 is lysine, as described (Bednarek et al., 2001, Biochem Biophys. Res. Commun., 286(3):641-645 and Mayorov et al., 2006, J. Med. Chem., 49:1946-1952.

Melanocortin Ligands for MC Receptor Binding

[0056] A non-naturally occurring melanocortin ligand may be an MC4 receptor agonist, an MC4 receptor antagonist, an MC3 receptor agonist, an MC3 receptor antagonist, and/or an MC5 agonist, of the alpha melanocyte-stimulating hormone (MSH) group.

[0057] For example, a non-naturally occurring melanocortin ligand may be an MC3 antagonist of the gamma melanocyte-stimulating hormone group.

[0058] A non-naturally occurring melanocortin ligand may also be an MC3 agonist of the gamma melanocyte-stimulating hormone group.

Synthesis of Peptides and Extensions

[0059] In general, the melanocortin ligands disclosed are synthesized by solid-phase synthesis, for example, and purified according to methods known in the art. A number of well-known procedures utilizing a variety of resins and reagents are used to prepare the compounds of this invention. Organic molecules are similarly synthesized according to methods known in the art.

[0060] Ligands of this invention may be in the form of any pharmaceutically acceptable salt. Acid addition salts of the ligands of this invention are prepared in a suitable solvent from the molecule and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic, or methanesulfonic. Where the ligands include an acidic moiety, suitable pharmaceutically acceptable salts may include alkali metal salts, such as sodium or potassium salts, or alkaline earth metal salts, such as calcium or magnesium salts.

[0061] Peptides may be prepared by solid-phase methodology by using *p*-benzyloxy-benzylalcohol resin for free C-terminus peptides with manual synthesis. All amino acids are coupled as 9-fluroenylmethoxycarbonyl (Fmoc)-derivatives, as described by Fields et al., 1992, Synthetic Peptides: A User's Guide, W.H. Freeman and Company, New York, 77-183; and Fields and Noble, 1990, Int. J. Peptide Protein Res., 35:161-214; Fields et al., 1991, Peptide Res. 4:95-101. In brief, the tert-butyl group is applied as a protecting group for 1-hydroxybenzotriazole/N,N'diisopropylcarbodiimide in situ active ester methodology in N,N-dimethylforaminide (DMF). Fmoc groups are removed by 20% piperidine in DMF, or 2% piperidine and 2% diazabicyclo[5.4.0]undec-7-ene in DMF, respectively. The success of the coupling and deprotection is monitored by ninhydrin test and/or isatine assay. After the completion of the synthesis, the peptides are cleaved from the resin with trifluoroacetic acid containing 5% water. The crude products are purified by RP-HPLC on a Supelcosil

C18 column by using gradient elution with the following eluents: A, 0.1% trifluoroacetic acid in water; and B, 0.1% trifluoroacetic acid in acetonitrile/water (80:20, vol/vol). After an isocratic elution with over 5% eluent B for 5 min, a linear gradient from 0-25% B or 5-30% B is generated over 25 minutes at room temperature and with a flow rate of 4 mL/min. UV detection is performed at lambda = 214 nm. The purity of the peptides is investigated by analytical RP-HPLC on a Synergi (4.6 mm × 25 cm, MAX-RP 80 Angstrom, 4 μm) column.

[0062] The following references disclose methods for synthesizing the residues and linkages disclosed herein. For the piperizin-2-one ring-see Bhatt, U and Just, G, 2000, Helvetica Chimica Acta, 83:722-727; Mohamed, N., et al., 1998, Tetrahedron Lett., 39:8213-8216; Teixido, M., et al., 2007, Brain Res. Bull., 73(1-3):103-107. For Nal(2')-see Kavarana, MJ et al., 2000, J. Med. Chem., 45:2644-22650; and Holder, J.R., et al., 2002, J. Med Chem., 45:5736-5744. For the dipeptide mimetics of Aba-D-Phe, Aba-pCL-D-Phe, and Aba-D-Nal(2')-see Ballet, S., et al., Bioorganic & Med. Chem. Lett., 2007, 17:2492-2498. For OIC, BIP and PIP-see Bednarek, M.A., et al., 2007, J. Med Chem, 50:2520-2526. For glutaric acid linker-see Mayorov, A.V. et al., , 2008, J. Med. Chem. 51:187-195. For Hyp(Bzl), t-butylglycine, and MAMB-see Grieco, P., et al., 2007, Peptides 28:1191-1196. For Azt, Pip, Nip, Tic, Oic-see Bednarek, M.A., 2007, Chem. Biol. Drug Design, 69:350-355. For lactam cyclization-see Mayorov, A.V,. et al., 2006, J. Med. Chem. 49:1946-1952. For Pen and Aib-see Balse-Srinivasan. P., et al., 2003 J. Med. Chem, 46:4965-4973. For an n-pentanoyl group and n-hexanoyl group-see Cheung A.W.-H., et al., 2003, Bio-organic & Med. Chem. Lett., 13:1307-1311. ORN (ornithine) and homoArg-see Holder, J.R. et al., 2003, Peptides, 24:73-82. For Phg-see Holder, J. R. et al., 2002, J. Med. Chem., 45, 3073-3081. For 2,3 diaminopropionic acid-see 2004, Vig, B.S., et al., J. Med. Chem., 47(2):446-455.

Assaying Cardiovascular Effects Using Melanocortin Ligand of the Present Invention

[0063] There are many possible methods that would be known, obvious, or available to the skilled person for directly and indirectly assaying the degradation and cardiovascular effects of a melanocortin ligand of the present invention.

[0064] Both acute and chronic cardiovascular testing are assayed using the melanocortin ligands of the present invention in order to determine if the C-terminal extensions as described herein can protect the RF-pharmacophore from exposure. In this way, the C-terminal degradation resistance is measured indirectly, but in a therapeutically applicable manner. Furthermore, with both the acute and chronic cardiovascular measurements, the cardiovascular effects are then known upon introduction/administration of the melanocortin ligand into a human or mammal, and until the melanocortin ligand is cleared from the bloodstream of the human or mammal body. Acute cardiovascular recordings allow for a continuous analysis of the actions of these drugs over a period of hours, allowing for intensive observation of effects following ligand administration. The cardiovascular parameters for acute cardiovascular testing include: direct arterial pressure components (systolic, diastolic, mean arterial pressure, and heart rate) and the EKG. The arterial pressure components are measured via a Millar solid state pressure transducer in the femoral artery. This allows for a more precise evaluation of any arterial pressure/heart rate abnormalities. The signal from the Millar transducer is amplified in a Transonic arterial pressure module, and then sent to a computer running EMKA software (EMKA Technologies, Inc., Falls Church, VA). Arterial pressure component signals are typically measured on a second-to-second basis, although millisecond or beat-by-beat analysis is an alternative measurement. The latter analysis can be performed retrospectively, via an experiment play-back. Initially, arterial pressure components to be analyzed include peak MAP (mean arterial pressure) and HR (heart rate) responses, and the areas under each respective curve. Because melanocortin analogs having exposed RF pharmacophores produce prolonged and variable pressor and cardioaccelerator actions, the area under each curve (AUC) is calculated (see, for example, D'Angelo et al., 2005, Am. J. Physiol. Heart Circ. Physiol., 288(4):H1829-H1835), as are the first and second derivatives for the equations describing each cardiovascular parameter curve. For chronic cardiovascular testing, telemetry systems allow for the monitoring of multiple animals over long periods of time (days or weeks). Each animal is only recorded for a few seconds (*e.g.*, 5-10 sec) per minute to maximize battery life and allow multiple animals to be monitored. However, newer models now allow for wireless recharging of implanted transmitters. One telemetry model for chronic cardiovascular testing is described below.

[0065] A telemetry system can be used for simultaneous and continuous monitoring with direct input to a computer running EMKA ecgAuto-Cardio2+. In this approach a telemetry transmitter is surgically implanted, using aseptic procedures, into the abdominal cavity of a rat. During surgery, the catheter of the transmitter is inserted into the abdominal aorta and secured with tissue adhesive. Telemetry unit ECG electrodes are sutured subcutaneously onto the upper right chest muscle and upper left abdominal wall muscle. These units simultaneously provide ECG and arterial pressure signals. Animals are typically allowed 7-10 days of surgical recovery, using return of the circadian rhythmicity of arterial pressure and HR as an objective metric. For acute experiments, a femoral IV line is tunneled to the upper back, exteriorized, and stored within a steel button assembly, sutured to the animal's back. The transmitter will produce an arterial pressure signal (via a cannulated abdominal aorta) and an ECG signal using the lead II configuration. For this, leads are implanted under the musculature of the upper right quadrant of the chest, and within the musculature of the upper left abdominal region. These procedures are well described in the literature (Stieber et al., 2006, Mol. Pharmacol., 69(4): 1328-37), as well as the manufacturer's procedures.

[0066] For chronic administration of the melanocortin ligand into a rat model, both Alza minipumps for IV infusion and sustained release pellets are used (Strader, A.D., et al., 2007, J. Pharmacol. Exp. Ther., 322(3): 1153-1161; and Innovative Research of America, Sarasota, FL). The starting effective daily dose for a melanocortin ligand of the present invention is 1 mg/kg/day for 14 days, and is titrated up to 10 mg/kg per day. As a control for drug degradation in the minipumps, parallel incubated (37 °C) controls were run and assessed for any peptide breakdown by high performance liquid chromatography (HPLC).

[0067] Methods of administration include injection, oral, nasal, and mucosal administration. If the administration is by injection, the injection may be intravenous, subcutaneous, intramuscular, intraperitoneal, or other means known in the art. The melanocortin ligand of this invention may be formulated by any means known in the art, including but not limited to formulation as tablets, capsules, caplets, suspensions, powders, lyophilized preparations, suppositories, ocular drops, skin patches, oral soluble formulations, sprays, aerosols and the like, and may be mixed and formulated with buffers, binders, excipients, stabilizers, anti-oxidants, and other agents known in the art. Nasal administration includes any form of intranasal administration of a melanocortin ligand of this invention. A melanocortin ligand of this invention may be in an aqueous solution, such as a solution including saline, citrate, or other common excipients or preservatives. The melanocortin ligand may also be in a dry, powder or lyophilized formulation.

[0068] Reduced cardiovascular effects (blood pressure and arrhythmias) are relative in the human or animal when administered with different melanocortin ligands of the present invention. It is reduced relatively when compared between a melanocortin ligand having a C-terminal extension according to the present invention versus its counterpart without a C-terminal extension.

[0069] A pharmaceutical composition and/or a kit comprising the melanocortin ligand of the present invention is used to regulate and treat many conditions ranging from weight regulation (*e.g.*, obesity, anorexia, and cachexia), hormonal secretion, exocrine gland hypersecretion), immuno-relevant conditions, and sexual dysfunction.

Applications

[0070] Physiological regulatory effects of a melanocortin ligand of the present invention, ranging from hormonal, neuronal, enzymatic and other extracellular and intracellular mechanisms further affect bodily conditions such as weight regulation (e.g., obesity, anorexia, and cachexia), hormonal secretion (e.g., dry eye and/or dry mouth syndrome), as well as immuno-relevant conditions and sexual dysfunction. The dysfunction of many of these physiological mechanisms leads to disease. In the present application, physiological regulatory effects are distinguishable and apart from cardiovascular effects.

[0071] In one embodiment, physiological regulatory effects of a melanocortin ligand of the present invention are rendered using agonist melanocortin analogs (al-Obeidi et al., J. Med Chem, 1989, 32(12), 2555-2561). In another embodiment, physiological regulatory effects are rendered using antagonist melanocortin analogs (Hruby et al., 1995, J. Med. Chem., 38:3454-3461; Jayawickreme et al., 1994, J. Biol. Chem., 269:29846-29854).

[0072] In summary, a non-naturally occurring melanocortin ligand is provided, comprised of a melanocortin analog coupled to a degradation-resistant C-terminal extension and, optionally, an N-terminal extension, to produce a stable melanocortin ligand having diminished or abolished cardiovascular activity while retaining desired melanocortin regulatory activity.

SEQUENCE LISTING

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Claims

1. A non-naturally occurring melanocortin ligand comprising a melanocortin analog coupled to a degradation-resistant C-terminal extension and an N-terminal extension, the non-naturally occurring melanocortin ligand comprising Formula I:

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \textbf{(Formula I)},$$

wherein the melanocortin analog comprises R^1 to R^7, wherein:

R^1 is absent or is selected from the group consisting of cysteine, norleucine, acetylated norleucine, acetylated cysteine, D-phenylalanine, acetylated D-phenylalanine, succinic acid, o-phthalic acid, tyrosine, aspartic acid, glutaric acid, CO-cis-CH=CH-CO, an *n*-pentanoyl group, and an *n*-hexanoyl group;
R^2 is absent or is selected from the group consisting of proline, aspartic acid, glutamic acid, glycine, cysteine, norleucine, arginine, succinic acid, glutaric acid, CO-cis-CH=CH-CO, an *n*-pentanoyl group, and an *n*-hexanoyl-

group;
R^3 is selected from the group consisting of histidine, histidine methylated at positions 1 or 3, D-proline, L-proline, D-Nal(2'), L-Nal(2'), succinic acid, *t*ButGly, Hyp(Bzl), Mamb, Oic, norleucine, Aba, β-alanine, and Tic;
R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2'), pCl-D-Phe, and (o-Phe)Phe;
R^5 is selected from the group consisting of arginine, homoarginine, ornithine, alanine, proline, Pip, Nip, Tic, Phg, Sar, and Azt;
R^6 is selected from D-tryptophan, L-tryptophan, D-Nal(2'), L-Nal(2'), Tic, and Bip;
R^7 is selected from the group consisting of cysteine, lysine, and 2,3-diamino-propionic acid;

wherein if R^3 is Aba, then R^4 is selected from the group consisting of D-Phe, D-Nal(2'), and pCl-D-Phe; and
wherein if R^2 is an *n*-pentanoyl group or an *n*-hexanoyl group, then R^1, Y^1, Y^2, and Y^3 are absent;
wherein the N-terminal extension comprises Y^1 to Y^3:

Y^1 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, and L-proline;
Y^2 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring;
Y^3 is absent or is selected from the group consisting of cysteine, D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring;

wherein the degradation-resistant C-terminal extension comprises X^1 to X^3 and

X^1 is D-threonine,;
X^2 is D-proline,;
X^3 is D-threonine

wherein the melanocortin ligand is cyclized through a moiety selected from the group consisting of:

when R^2 is cysteine and R^7 is cysteine a disulfide bond is formed between R^2 and R^7;
when R^2 is glutamic acid or aspartic acid and R7 is lysine a side-chain lactam bridge is formed between R^2 and R^7; and
when R^2 or R^3 is succinic acid and R^7 is 2,3-diamino-propionic acid a lactam closure is formed between R^2 or R^3 and R^7.

2. The non-naturally occurring melanocortin ligand of claim 1, wherein D-phenylalanine is halogenated at the *para* position when R^4 is D-phenylalanine.

3. The non-naturally occurring melanocortin ligand of claim 1, wherein the melanocortin analog is an MC4 receptor agonist, an MC4 receptor antagonist, an MC3 receptor agonist, an MC3 receptor antagonist, and/or an MC5 agonist.

4. A pharmaceutical composition comprising the non-naturally occurring melanocortin ligand of claim 1 and a pharmaceutical salt.

5. The pharmaceutical composition of claim 4, wherein, when used in therapy, any cardiovascular effects are diminished.

6. A non-naturally occurring melanocortin ligand comprising a melanocortin analog coupled to a degradation-resistant C-terminal extension and an N-terminal extension, the non-naturally occurring melanocortin ligand comprising Formula II:

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}R^9\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \textbf{(Formula II)}$$

wherein the melanocortin analog comprises R^1 to R^9, wherein:

R^1 is tyrosine;
R^2 is valine;
R^3 is selected from the group consisting of methionine, norleucine, cysteine, and L-penicillamine;
R^4 is aspartic acid;

R^5 is selected from the group consisting of histidine, norleucine, proline, and Aib;
R^6 is selected from the group consisting of phenylalanine, D-Nal(2'), and L-Nal(2');
R^7 is arginine;
R^8 is selected from the group consisting of tryptophan and D-Nal(2'); and
R^9 is lysine;

wherein the N-terminal extension comprises Y^1 to Y^3:

Y^1 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, and L-proline;
Y^2 is absent or is selected from the group consisting of D-threonine, L-threonine, D-proline, L-proline, and a piperazin-2-one ring;
Y^3 is absent or is selected from the group consisting of cysteine, D-threonine, L-threonine, D-proline, L-proline and a piperazin-2-one ring;

wherein the degradation-resistant C-terminal extension comprises X^1 to X^3 and:

X^1 is D-threonine;
X^2 is D-proline; and
X^3 is D-threonine; and

wherein the melanocortin ligand is cyclized and a side chain lactam bridge is formed between R^4 and R^9.

7. The non-naturally occurring melanocortin ligand of claim 6, wherein the melanocortin analog is an MC3 antagonist.

8. A pharmaceutical composition comprising the non-naturally occurring melanocortin ligand of claim 6 and a pharmaceutical salt.

9. The pharmaceutical composition of claim 8, wherein, when used in therapy, any cardiovascular effects are diminished.

Patentansprüche

1. Nicht natürlich vorkommender Melanocortin-Ligand, welcher ein Melanocortin-Analog umfasst, das an eine abbaubeständige C-terminale Verlängerung und eine N-terminale Verlängerung gekoppelt ist, wobei der nicht natürlich vorkommende Melanocortin-Ligand Formel I umfasst:

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \text{(Formel I)},$$

wobei das Melanocortin-Analog R^1 bis R^7 umfasst, worin:

R^1 nicht vorliegt oder aus der Gruppe ausgewählt ist bestehend aus Cystein, Norleucin, acetyliertem Norleucin, acetyliertem Cystein, D-Phenylalanin, acetyliertem D-Phenylalanin, Bernsteinsäure, *o*-Phthalsäure, Tyrosin, Asparaginsäure, Glutarsäure, CO-cis-CH=CH-CO, einer *n*-Pentanoyl-Gruppe und einer *n*-Hexanoyl-Gruppe;
R^2 nicht vorliegt oder aus der Gruppe ausgewählt ist bestehend aus Prolin, Asparaginsäure, Glutaminsäure, Glycin, Cystein, Norleucin, Arginin, Bernsteinsäure, Glutarsäure, CO-cis-CH=CH-CO, einer *n*-Pentanoyl-Gruppe und einer *n*-Hexanoyl-Gruppe;
R^3 aus der Gruppe ausgewählt ist bestehend aus Histidin, Histidin, das an Positionen 1 oder 3 methyliert ist, D-Prolin, L-Prolin, D-Nal(2'), L-Nal(2'), Bernsteinsäure, *t*ButGly, Hyp(Bzl), Mamb, Oic, Norleucin, Aba, β-Alanin und Tic;
R^4 aus der Gruppe ausgewählt ist bestehend aus Histidin, D-Phenylalanin, L-Phenylalanin, D-Nal(2'), pCl-D-Phe und (o-Phe)Phe;
R^5 aus der Gruppe ausgewählt ist bestehend aus Arginin, Homoarginin, Ornithin, Alanin, Prolin, Pip, Nip, Tic, Phg, Sar und Azt;
R^6 ausgewählt ist aus D-Tryptophan, L-Tryptophan, D-Nal(2'), L-Nal(2'), Tic und Bip;
R^7 aus der Gruppe ausgewählt ist bestehend aus Cystein, Lysin und 2,3-Diamino-Propionsäure;

wobei, wenn R^3 Aba ist, dann R^4 aus der Gruppe ausgewählt ist bestehend aus D-Phe, D-Nal(2') und pCl-D-Phe; und

wobei, wenn R^2 eine n-Pentanoyl-Gruppe oder eine *n*-Hexanoyl-Gruppe ist, dann R^1, Y^1, Y^2 und Y^3 nicht vorliegen;
wobei die N-terminale Verlängerung Y^1 bis Y^3 umfasst:

Y^1 nicht vorliegt oder aus der Gruppe ausgewählt ist bestehend aus D-Threonin, L-Threonin, D-Prolin und L-Prolin;
Y^2 nicht vorliegt oder aus der Gruppe ausgewählt ist bestehend aus D-Threonin, L-Threonin, D-Prolin, L-Prolin und einem Piperazin-2-on-Ring;
Y^3 nicht vorliegt oder aus der Gruppe ausgewählt ist bestehend aus Cystein, D-Threonin, L-Threonin, D-Prolin, L-Prolin und einem Piperazin-2-on-Ring;

wobei die abbaubeständige C-terminale Verlängerung X^1 bis X^3 umfasst und

X^1 D-Threonin ist;
X^2 D-Prolin ist;
X^3 D-Threonin ist,

wobei der Melanocortin-Ligand durch einen Rest zyklisiert wird, der aus der Gruppe ausgewählt ist bestehend aus:

wenn R^2 Cystein ist und R^7 Cystein ist, wird eine Disulfidbindung zwischen R^2 und R^7 gebildet;
wenn R^2 Glutaminsäure oder Asparaginsäure ist und R^7 Lysin ist, wird eine Seitenketten-Lactam-Brücke zwischen R^2 und R^7 gebildet; und
wenn R^2 oder R^3 Bernsteinsäure ist und R^7 2,3-Diamino-Propionsäure ist, wird ein Lactam-Ringschluss zwischen R^2 oder R^3 und R^7 gebildet.

2. Nicht natürlich vorkommender Melanocortin-Ligand gemäß Anspruch 1, wobei D-Phenylalanin an der *para*-Position halogeniert ist, wenn R^4 D-Phenylalanin ist.

3. Nicht natürlich vorkommender Melanocortin-Ligand gemäß Anspruch 1, wobei das Melanocortin-Analog ein MC4-Rezeptor-Agonist, ein MC4-Rezeptor-Antagonist, ein MC3-Rezeptor-Agonist, ein MC3-Rezeptor-Antagonist und/oder ein MC5-Agonist ist.

4. Pharmazeutische Zusammensetzung, welche den nicht natürlich vorkommenden Melanocortin-Liganden gemäß Anspruch 1 und ein pharmazeutisches Salz umfasst.

5. Pharmazeutische Zusammensetzung gemäß Anspruch 4, wobei, wenn sie in der Therapie verwendet wird, jegliche kardiovaskulären Wirkungen vermindert werden.

6. Nicht natürlich vorkommender Melanocortin-Ligand, welcher ein Melanocortin-Analog umfasst, das an eine abbaubeständige C-terminale Verlängerung und eine N-terminale Verlängerung gekoppelt ist, wobei der nicht natürlich vorkommende Melanocortin-Ligand Formel II umfasst:

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}R^9\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \text{(Formel II)},$$

wobei das Melanocortin-Analog R^1 bis R^9 umfasst, worin:

R^1 Tyrosin ist;
R^2 Valin ist;
R^3 aus der Gruppe ausgewählt ist bestehend aus Methionin, Norleucin, Cystein und L-Penicillamin;
R^4 Asparaginsäure ist;
R^5 aus der Gruppe ausgewählt ist bestehend aus Histidin, Norleucin, Prolin und Aib;
R^6 aus der Gruppe ausgewählt ist bestehend aus Phenylalanin, D-Nal(2') und L-Nal(2');
R^7 Arginin ist;
R^8 aus der Gruppe ausgewählt ist bestehend aus Tryptophan und D-Nal(2');
R^9 Lysin ist;

wobei die N-terminale Verlängerung Y^1 bis Y^3 umfasst:

Y^1 nicht vorliegt oder aus der Gruppe ausgewählt ist bestehend aus D-Threonin, L-Threonin, D-Prolin und L-

Prolin;
Y^2 nicht vorliegt oder aus der Gruppe ausgewählt ist bestehend aus D-Threonin, L-Threonin, D-Prolin, L-Prolin und einem Piperazin-2-on-Ring;
Y^3 nicht vorliegt oder aus der Gruppe ausgewählt ist bestehend aus Cystein, D-Threonin, L-Threonin, D-Prolin, L-Prolin und einem Piperazin-2-on-Ring;

wobei die abbaubeständige C-terminale Verlängerung X^1 bis X^3 umfasst und

X^1 D-Threonin ist;
X^2 D-Prolin ist;
X^3 D-Threonin ist,

wobei der Melanocortin-Ligand zyklisiert wird und eine Seitenketten-Lactam-Brücke zwischen R^4 und R^9 gebildet wird.

7. Nicht natürlich vorkommender Melanocortin-Ligand gemäß Anspruch 6, wobei das Melanocortin-Analog ein MC3-Antagonist ist.

8. Pharmazeutische Zusammensetzung, welche den nicht natürlich vorkommenden Melanocortin-Liganden gemäß Anspruch 6 und ein pharmazeutisches Salz umfasst.

9. Pharmazeutische Zusammensetzung gemäß Anspruch 8, wobei, wenn sie in der Therapie verwendet wird, jegliche kardiovaskulären Wirkungen vermindert werden.

Revendications

1. Ligand d'origine non naturelle de la mélanocortine comprenant un analogue de la mélanocortine couplé à une extension C-terminale résistant à la dégradation et à une extension N-terminale, le ligand d'origine non naturelle de la mélanocortine, comprenant la Formule I :

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \textbf{(Formule I)}$$

dans lequel l'analogue de la mélanocortine comprend R^1 à R^7, dans lesquels :

R^1 est absent ou choisi dans le groupe constitué par la cystéine, la norleucine, la norleucine acétylée, la cystéine acétylée, la D-phénylalanine, la D-phénylalanine acétylée, l'acide succinique, l'acide *o*-phtalique, la tyrosine, l'acide aspartique, l'acide glutarique, CO-cis-CH=CH-CO, un groupe *n*-pentanoyle et un groupe *n*-hexanoyle ;
R^2 est absent ou choisi dans le groupe constitué par la proline, l'acide aspartique, l'acide glutamique, la glycine, la cystéine, la norleucine, l'arginine, l'acide succinique, l'acide glutarique, CO-cis-CH=CH-CO, un groupe *n*-pentanoyle et un groupe *n*-hexanoyle ;
R^3 est choisi dans le groupe constitué par l'histidine, l'histidine méthylée en position 1 ou 3, la D-proline, la L-proline, D-Nal(2'), L-Nal(2'), l'acide succinique, tButGly, Hyp(Bzl), Mamb, Oic, la norleucine, Aba, la β-alanine etTic;
R^4 est choisi dans le groupe constitué par l'histidine, la D-phénylalanine, la L-phénylalanine, D-Nal(2'), pCl-D-Phe et (*o*-Phe)Phe;
R^5 est choisi dans le groupe constitué par l'arginine, l'homoarginine, l'ornithine, l'alanine, la proline, Pip, Nip, Tic, Phg, Sar et Azt ;
R^6 est choisi parmi le D-tryptophane, le L-tryptophane, D-Nal(2'), L-Nal(2'), Tic et Bip;
R^7 est choisi dans le groupe constitué par la cystéine, la lysine et l'acide 2,3-diamino-propionique ;

dans lequel, si R^3 est Aba, R^4 est choisi dans le groupe constitué par D-Phe, D-Nal(2') et pCl-D-Phe; et
dans lequel, si R^2 est un groupe *n*-pentanoyle ou un groupe *n*-hexanoyle, R^1, Y^1, Y^2 et Y^3 sont absents ;
dans lequel l'extension N-terminale comprend Y^1 à Y^3 :

Y^1 est absent ou choisi dans le groupe constitué par la D-thréonine, la L-thréonine, la D-proline et la L-proline;
Y^2 est absent ou choisi dans le groupe constitué par la D-thréonine, la L-thréonine, la D-proline, la L-proline et un cycle de pipérazin-2-one;

Y^3 est absent ou choisi dans le groupe constitué par la cystéine, la D-thréonine, la L-thréonine, la D-proline, la L-proline, et un cycle de pipérazin-2-one;

dans lequel l'extension C-terminale résistant à la dégradation comprend X^1 à X^3 et

X^1 représente la D-thréonine ;
X^2 représente la D-proline;
X^3 représente la D-thréonine ;

dans lequel le ligand de la mélanocortine est cyclisé par l'intermédiaire d'un fragment choisi dans le groupe constitué comme suit :

lorsque R^2 représente la cystéine et que R^7 représente la cystéine, une liaison de disulfure est formée entre R^2 et R^7 ;
lorsque R^2 représente l'acide glutamique ou l'acide aspartique et que R^7 représente la lysine, un pont lactame de chaîne latérale est formé entre R^2 et R^7 ; et,
lorsque R^2 ou R^3 représente l'acide succinique et que R^7 représente l'acide 2,3-diamino-propionique, une fermeture de lactame est formée entre R^2 ou R^3 et R^7.

2. Ligand d'origine non naturelle de la mélanocortine selon la revendication 1, dans lequel la D-phénylalanine est halogénée en position *para* lorsque R^4 représente la D-phénylalanine.

3. Ligand d'origine non naturelle de la mélanocortine selon la revendication 1, dans lequel l'analogue de la mélanocortine est un agoniste du récepteur MC4, un antagoniste du récepteur MC4, un agoniste du récepteur MC3, un antagoniste du récepteur MC3 et/ou un agoniste du MC5.

4. Composition pharmaceutique comprenant le ligand d'origine non naturelle de la mélanocortine selon la revendication 1 et un sel pharmaceutique.

5. Composition pharmaceutique selon la revendication 4 dans laquelle, lorsqu'elle est utilisée en thérapie, tous les effets cardio-vasculaires sont diminués.

6. Ligand d'origine non naturelle de la mélanocortine comprenant un analogue de la mélanocortine couplé à une extension C-terminale résistant à la dégradation et à une extension N-terminale, le ligand d'origine non naturelle de la mélanocortine, comprenant la Formule II :

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}R^9\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \textbf{(Formule II)}$$

dans lequel l'analogue de la mélanocortine comprend R^1 à R^9, dans lesquels :

R^1 représente la tyrosine;
R^2 représente la valine ;
R^3 est choisi dans le groupe constitué par la méthionine, la norleucine, la cystéine et la L-pénicillamine;
R^4 représente l'acide aspartique ;
R^5 est choisi dans le groupe constitué par l'histidine, la norleucine, la proline et Aib;
R^6 est choisi dans le groupe constitué par la phénylalanine, D-Nal(2') et L-Nal(2') ;
R^7 représente l'arginine;
R^8 est choisi dans le groupe constitué par le tryptophane et D-Nal(2') ; et
R^9 représente la lysine;

dans lequel l'extension N-terminale comprend Y^1 à Y^3 :

Y^1 est absent ou choisi dans le groupe constitué par la D-thréonine, la L-thréonine, la D-proline et la L-proline ;
Y^2 est absent ou choisi dans le groupe constitué par la D-thréonine, la L-thréonine, la D-proline, la L-proline, et un cycle de pipérazin-2-one ;
Y^3 est absent ou choisi dans le groupe constitué par la cystéine, la D-thréonine, la L-thréonine, la D-proline, la L-proline et un cycle de pipérazin-2-one ;

dans lequel l'extension C-terminale résistant à la dégradation comprend X^1 à X^3 et

X^1 représente la D-thréonine ;
X^2 représente la D-proline ; et
X^3 représente la D-thréonine ; et

dans lequel le ligand de la mélanocortine est cyclisé et un pont de lactame de chaine latérale est formé entre R^4 et R^9.

7. Ligand d'origine non naturelle de la mélanocortine selon la revendication 6, dans lequel l'analogue de la mélanocortine est un antagoniste du MC3.

8. Composition pharmaceutique comprenant le ligand d'origine non naturelle de la mélanocortine selon la revendication 6 et un sel pharmaceutique.

9. Composition pharmaceutique selon la revendication 8, dans laquelle, lorsqu'elle est utilisée en thérapie, tous les effets cardio-vasculaires sont diminués.

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Szabadalmi igénypontok

1. Nem-természetes melanokortin ligandum, amely magában foglal egy degradáció rezisztens C-terminális hosszabbításhoz és egy N-terminális hosszabbításhoz kapcsolt melanokortin analógot, a nem-természetes melanokortin ligandum az I képletet foglalja magában:

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \textbf{(I képlet)},$$

ahol a melanokortin analóg az R^1 - R^7 csoportokat tartalmazza, ahol:

R^1 hiányzik vagy jelentését az alábbiakból álló csoportból választjuk: cisztein, norleucin, acetilezett norleucin, acetilezett cisztein, D-fenilalanin, acetilezett D-fenilalanin, borostyánkősav, o-ftálsav, tirozin, aszparaginsav, glutársav, CO-cisz-CH=CH-CO, *n*-pentanoil-csoport, és *n*-hexanoil-csoport;

R^2 hiányzik vagy jelentését az alábbiakból álló csoportból választjuk: prolin, aszparaginsav, glutaminsav, glicin, cisztein, norleucin, arginin, borostyánkősav, glutársav, CO-cisz-CH=CH-CO, *n*-pentanoil-csoport, és *n*-hexanoil-csoport;

R^3 jelentését az alábbiakból álló csoportból választjuk: hisztidin, 1-es vagy 3-as helyzetben metilált hisztidin, D-prolin, L-prolin, D-Nal(2'), L-Nal(2'), borostyánkősav, *t*ButGly, Hyp(Bzl), Mamb, Oic, norleucin, Aba, β-alanin, és Tic;

R^4 jelentését az alábbiakból álló csoportból választjuk: hisztidin, D-fenilalanin, L-fenilalanin, D-Nal(2'), pCl-D-Phe, és (o-Phe)Phe;

R^5 jelentését az alábbiakból álló csoportból választjuk: arginin, homoarginin, ornitin, alanin, prolin, Pip, Nip, Tic, Phg, Sar, és Azt;

R^6 jelentését az alábbiakból választjuk: D-triptofán, L-triptofán, D-Nal(2'), L-Nal(2'), Tic, és Bip;

R^7 jelentését az alábbiakból álló csoportból választjuk: cisztein, lizin, és 2,3-diamino-propionsav;

ahol amikor R^3 jelentése Aba, akkor R^4 jelentését az alábbiakból álló csoportból választjuk: D-Phe, D-Nal(2'), és pCl-D-Phe; és

ahol amikor R^2 jelentése *n*-pentanoilcsoport vagy *n*-hexanoilcsoport, akkor R^1, Y^1, Y^2, és Y^3 hiányzik;

ahol az N-terminális hosszabbítás az Y^1 - Y^3 csoportokat tartalmazza:

Y^1 hiányzik vagy jelentését az alábbiakból álló csoportból választjuk: D-treonin, L-treonin, D-prolin, és L-prolin;

Y^2 hiányzik vagy jelentését az alábbiakból álló csoportból választjuk: D-treonin, L-treonin, D-prolin, L-prolin, és piperazin-2-on gyűrű;

Y^3 hiányzik vagy jelentését az alábbiakból álló csoportból választjuk: cisztein, D-treonin, L-treonin, D-prolin, L-prolin, és piperazin-2-on gyűrű;

ahol a degradáció rezisztens C-terminális hosszabbítás az X^1 - X^3 csoportokat tartalmazza és

X^1 jelentése D-treonin,;

X^2 jelentése D-prolin,;

X^3 jelentése D-threonin

ahol a melanokortin ligandum az alábbiakból álló csoportból választott egységen keresztül ciklizált:

amikor R^2 jelentése cisztein és R^7 jelentése cisztein, akkor egy diszulfid híd képződik R^2 és R^7 között;

amikor R^2 jelentése glutaminsav vagy aszparaginsav és R^7 jelentése lizin, akkor egy oldallánc laktám híd képződik R^2 és R^7 között; és

amikor R^2 vagy R^3 jelentése borostyánkősav és R^7 jelentése 2,3-diamino-propionsav, akkor egy laktám záródik R^2 vagy R^3 és R^7 között.

2. Az 1. igénypont szerinti nem-természetes melanokortin ligandum, ahol a D--fenilalanin a *para*-helyzetben halogénezett, amikor R^4 jelentése D-fenilalanin.

3. Az 1. igénypont szerinti nem-természetes melanokortin ligandum, ahol a melanokortin analóg egy MC4 receptor agonista, egy MC4 receptor antagonista, egy MC3 receptor agonista, egy MC3 receptor antagonista, és/vagy egy MC5 agonista.

4. Gyógyszerkészítmény, amely az 1. igénypont szerinti nem-természetes melanokortin ligandumot és egy gyógyszerészeti sót tartalmaz.

5. A 4. igénypont szerinti gyógyszerkészítmény, ahol, amennyiben a terápiában alkalmazzák, a kardiovaszkuláris hatások csökkennek.

6. Nem-természetes melanokortin ligandum, amely magában foglal egy degradáció rezisztens C-terminális hosszabbításhoz és egy N-terminális hosszabbításhoz kapcsolt melanokortin analógot, a nem-természetes melanokortin ligandum a II képletet foglalja magában:

$$Y^1\text{-}Y^2\text{-}Y^3\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}R^9\text{-}X^1\text{-}X^2\text{-}X^3 \qquad \textbf{(II képlet)}$$

ahol a melanokortin analóg az R^1 – R^9 csoportokat tartalmazza, ahol:

R^1 jelentése tirozin;

R^2 jelentése valin;

R^3 jelentését az alábbiakból álló csoportból választjuk: metionin, norleucin, cisztein, és L--penicillamin;

R^4 jelentése aszparaginsav;

R^5 jelentését az alábbiakból álló csoportból választjuk: hisztidin, norleucin, prolin, és Aib;

R^6 jelentését az alábbiakból álló csoportból választjuk: fenilalanin, D-Nal(2'), és L-Nal(2');

R^7 jelentése arginin;

R^8 jelentését az alábbiakból álló csoportból választjuk: triptofán és D-Nal(2'); és

R^9 jelentése lizin;

ahol az N-terminális hosszabbítás az Y^1 - Y^3 csoportokat tartalmazza:

Y^1 hiányzik vagy jelentését az alábbiakból álló csoportból választjuk: D-treonin, L-treonin, D-prolin, és L-prolin;

Y^2 hiányzik vagy jelentését az alábbiakból álló csoportból választjuk: D-treonin, L-treonin, D-prolin, L-prolin, és piperazin-2-on gyűrű;

Y^3 hiányzik vagy jelentését az alábbiakból álló csoportból választjuk: cisztein, D-treonin, L--treonin, D-prolin, L-prolin, és piperazin-2-on gyűrű;

ahol a degradáció rezisztens C-terminális hosszabbítás az X^1 - X^3 csoportokat tartalmazza és:

X^1 jelentése D-treonin,;

X^2 jelentése D-prolin,;

X^3 jelentése D-threonin; és

ahol a melanokortin ligandum ciklizált és egy oldallánc laktámgyűrű képződött R^4 és R^9 között.

7. A 6. igénypont szerinti nem-természetes melanokortin ligandum, ahol a melanokortin analóg egy MC3 antagonista.

8. Gyógyszerkészítmény, amely a 6. igénypont szerinti nem-természetes melanokortin ligandumot és egy gyógyszerészeti sót tartalmaz.

9. A 8. igénypont szerinti gyógyszerkészítmény, ahol, amennyiben a terápiában alkalmazzák, a kardiovaszkuláris hatások csökkennek.

A meghatalmazott:

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