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(54) Title: CRF1 RECEPTOR COMPOUNDS

(57) Abstract: The invention relates generally to compounds which are allosteric modulators (e.g., negative and positive allosteric modulators, allosteric agonists, and ago-allosteric modulators) of the G protein coupled receptor for corticotrophin releasing hormone (or factor) receptor 1, also known as the CRF1, CRHR1, CRFR1, CRHR, CRF-R. The CRF1 receptor compounds are derived from the intracellular loops and domains of CRF1 receptor. The invention also relates to the use of these CRF1 receptor compounds and pharmaceutical compositions comprising the CRF1 receptor compounds in the treatment of diseases and conditions associated with CRF1 receptor modulation, such as inflammatory bowel disease (peripherally acting), irritable bowel syndrome (IBS), stress response (colonic motor activity), anxiety, sleep disorder, addictive behavior, acute and chronic neurodegeneration, preterm labor and pain.



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CRF1 RECEPTOR COMPOUNDS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/198,194, filed on November 4, 2008. The entire teachings of the above application is incorporated
5 herein by reference.

BACKGROUND OF THE INVENTION

G protein coupled receptors (GPCRs) constitute one of the largest families of genes in the human genome. GPCRs are integral membrane signaling proteins. Hydrophobicity mapping of the amino acid sequences of G-protein coupled receptors has led to a model of
10 the typical G-protein-coupled receptor as containing seven hydrophobic membrane-spanning regions with the amino terminal on the extracellular side of the membrane and the carboxyl terminal on the intracellular side of the membrane.

GPCRs mediate the transmission of intracellular signals ("signal transduction") by activating guanine nucleotide-binding proteins (G proteins) to which the receptor is coupled.
15 GPCRs are activated by a wide range of endogenous stimuli, including peptides, amino acids, hormones, light, and metal ions. The following reviews are incorporated by reference: Hill, British J. Pharm 147: s27 (2006); Palczeski, Ann Rev Biochemistry 75: 743-767 (2006); Dorsham & Gutkind, Nature Reviews 7: 79-94 (2007); Kobilka & Schertler, Trends Pharmacol Sci. 2: 79-83 (2008).

20 GPCRs are important targets for drug discovery as they are involved in a wide range of cellular signaling pathways and are implicated in many pathological conditions (e.g., cardiovascular and mental disorders, cancer, AIDS). In fact, GPCRs are targeted by 40-50% of approved drugs, illustrating the critical importance of this class of pharmaceutical targets. Interestingly, this number represents only about 30 GPCRs, a small fraction of the total
25 number of GPCRs thought to be relevant to human disease. Over 1000 GPCRs are known in the human genome, and GPCRs remain challenging targets from a research and development perspective in part because these amembrane bound receptors with complex pharmacology.

There remains a need for the development of new pharmaceuticals that are GPCR modulators (e.g., agonists, partial agonists, inverse agonists and antagonists) and especially those that are allosteric modulators of GPCRs (e.g., negative and positive allosteric modulators, allosteric agonists, and ago-allosteric modulators).

5

SUMMARY OF THE INVENTION

The invention relates generally to compounds which are allosteric modulators (e.g., negative and positive allosteric modulators, allosteric agonists, and ago-allosteric modulators) of the G protein coupled receptor for corticotrophin releasing hormone (or factor) receptor 1, also known as the CRF1, CRHR1, CRFR1, CRHR, CRF-R. The CRF1 receptor compounds are derived from the intracellular loops and domains of CRF1 receptor. The invention also relates to the use of these CRF1 receptor compounds and pharmaceutical compositions comprising the CRF1 receptor compounds in the treatment of diseases and conditions associated with CRF1 receptor modulation, such as inflammatory bowel disease (peripherally acting), irritable bowel syndrome (IBS), stress response (colonic motor activity), anxiety, sleep disorder, addictive behavior, acute and chronic neurodegeneration, preterm labor and pain.

15

More specifically, the invention relates to a compound represented by Formula I:

T-L-P,

20

or pharmaceutically acceptable salts thereof, wherein:

P is a peptide comprising at least three contiguous amino-acid residues of an intracellular i1, i2, i3 loop or an intracellular i4 domain of the CRF1 receptor;

L is a linking moiety represented by C(O) and bonded to P at an N terminal nitrogen of an N-terminal amino-acid residue;

25

and T is a lipophilic tether moiety bonded to L, wherein the C-terminal amino acid residue of P is optionally functionalized.

30

The invention also relates to pharmaceutical compositions comprising one or more compounds of the invention and a carrier, and the use of the disclosed compounds and compositions in methods of treating diseases and conditions responsive to modulation of the CRF1 receptor.

DETAILED DESCRIPTION OF THE INVENTION

A description of example embodiments of the invention follows.

G PROTEIN COUPLED RECEPTORS (GPCRs)

5 G protein coupled receptors (GPCRs) constitute one of the largest superfamilies of genes in the human genome; these transmembrane proteins enable the cell to respond to its environment by sensing extracellular stimuli and initiating intracellular signal transduction cascades. GPCRs mediate signal transduction through the binding and activation of guanine nucleotide-binding proteins (G proteins) to which the receptor is coupled. Wide arrays of
10 ligands bind to these receptors, which in turn orchestrate signaling networks integral to many cellular functions. Diverse GPCR ligands include small proteins, peptides, amino acids, biogenic amines, lipids, ions, odorants and even photons of light. The following reviews are incorporated by reference: Hill, British J. Pharm 147: s27 (2006); Dorsam & Gutkind, Nature Reviews 7: 79-94 (2007).

15 In addition to modulating a diverse array of homeostatic processes, GPCR signaling pathways are integral components of many pathological conditions (e.g., cardiovascular and mental disorders, cancer, AIDS). In fact, GPCRs are targeted by 40-50% of approved drugs illustrating the critical importance of this class of pharmaceutical targets. Interestingly, this number represents only about 30 GPCRs, a small fraction of the total number of GPCRs
20 thought to be relevant to human disease. GPCRs are membrane bound receptors that exhibit complex pharmacological properties and remain challenging targets from a research and development perspective. Given their importance in human health combined with their prevalence (over 1000 known GPCRs in the human genome) GPCRs represent an important target receptor class for drug discovery and design.

25 GPCRs are integral membrane proteins that mediate diverse signaling cascades through an evolutionarily conserved structural motif. All GPCRs are thought to consist of seven hydrophobic transmembrane spanning α -helices with the amino terminus on the extracellular side of the membrane and the carboxyl terminus on the intracellular side of the membrane. The transmembrane helices are linked together sequentially by extracellular (e1,
30 e2, e3) and intracellular (cytoplasmic) loops (i1, i2, i3). The intracellular loops or domains are intimately involved in the coupling and turnover of G proteins and include: i1, which connects

TM1-TM2; i2, connecting TM3-TM4; i3, connecting TM5-TM6; and a portion of the C-terminal cytoplasmic tail (domain 4). Due in part to the topological homology of the 7TM domains and the recent high resolution crystal structures of several GPCRs (Palczewski et al., *Science* 289, 739-45 (2000), Rasmussen, S.G. et al., *Nature* 450, 383-7 (2007)) skilled modelers are now able to predict the general boundaries of GPCR loop domains through the alignment of several related receptors. These predictions are aided in part by a number of programs used by computational biologists, including EMBOSS, ClustalW2, Kalign, and MAFFT (Multiple Alignment using Fast Fourier Transform). Importantly, many of these programs are publically available (see, for example, The European Bioinformatics Institute (EMBL-EBI) web site <http://www.ebi.ac.uk/Tools/>) and most have web-based interfaces.

GPCR mediated signal transduction is initiated by the binding of a ligand to its cognate receptor. In many instances GPCR ligand binding is believed to take place in a hydrophilic pocket generated by a cluster of helices near the extracellular domain. However, other ligands, such as large peptides, are thought to bind to the extracellular region of protein and hydrophobic ligands are postulated to intercalate into a receptor binding pocket through the membrane between gaps in the helices. The process of ligand binding induces conformational changes within the receptor. These changes involve the outward movement of helix 6, which in turn alters the conformations of the intracellular loops and ultimately results in a receptor form that is able to bind and activate a heterotrimeric G protein (Farrens, D., et al. *Science* 274, 768-770 (1996), Gether, U. and Kobilka, B., *J. Biol. Chem.* 273, 17979-17982 (1998)). Upon binding the receptor catalyzes the exchange of GTP for GDP in the alpha subunit of the heterotrimeric G protein, which results in a separation of the G protein from the receptor as well a dissociation of the alpha and beta/gamma subunits of the G protein itself. Notably, this process is catalytic and results in signal amplification in that activation of one receptor may elicit the activation and turnover of numerous G proteins, which in turn may regulate multiple second messenger systems. Signaling diversity is further achieved through the existence of numerous G protein types as well as differing isoforms of alpha, beta and gamma subunits. Typically, GPCRs interact with G proteins to regulate the synthesis or inhibition of intracellular second messengers such as cyclic AMP, inositol phosphates, diacylglycerol and calcium ions, thereby triggering a cascade of intracellular events that eventually leads to a biological response.

GPCR signaling may be modulated and attenuated through cellular machinery as well as pharmacological intervention. Signal transduction may be 'switched off' with relatively fast kinetics (seconds to minutes) by a process called rapid desensitization. For GPCRs, this is caused by a functional uncoupling of receptors from heterotrimeric G proteins, without a detectable change in the total number of receptors present in cells or tissues. This process involves the phosphorylation of the receptor C terminus, which enables the protein arrestin to bind to the receptor and occlude further G protein coupling. Once bound by arrestin the receptor may be internalized into the cell and either recycled back to the cell surface or degraded. The alpha subunit of the G protein possesses intrinsic GTPase activity, which attenuates signaling and promotes re-association with the beta/gamma subunits and a return to the basal state. GPCR signaling may also be modulated pharmacologically. Agonist drugs act directly to activate the receptors, whereas antagonist drugs act indirectly to block receptor signaling by preventing agonist activity through their associating with the receptor. GPCR binding and signaling can also be modified through allosteric modulation, that is by ligands that bind not at the orthosteric binding site but through binding at an allosteric site elsewhere in the receptors. Allosteric modulators can include both positive and negative modulators of orthosteric ligand mediated activity, allosteric agonists (that act in the absence of the orthosteric ligand), and ago-allosteric modulators (ligands that have agonist activity on their own but that can also modulate the activity of the orthosteric ligand).

The large superfamily of GPCRs may be divided into subclasses based on structural and functional similarities. GPCR families include Class A Rhodopsin like, Class B Secretin like, Class C Metabotropic glutamate / pheromone, Class D Fungal pheromone, Class E cAMP receptors (Dictyostelium), the Frizzled/Smoothed family, and various orphan GPCRs. In addition, putative families include Ocular albinism proteins, Insect odorant receptors, Plant Mlo receptors, Nematode chemoreceptors, Vomeronasal receptors (VIR & V3R) and taste receptors.

CRF1 is a class B GPCR, also called family B or secretin-like. In general, class B receptors are activated by peptide ligands typically 30 to 40 amino acids in length. Activation of these receptors results in activation of adenylyl cyclase and signal transduction through increase in cAMP as a primary signaling pathway. Class B receptors have a large N-terminal extracellular domain with 4 very highly conserved cysteine residues. This domain is important for the binding of endogenous peptide ligands and resulting receptor activation.

While these receptors signal primarily through Gs activation of adenylyl cyclase, they also couple to Gq, resulting in calcium release and may also couple to Gi/G0, which modulate adenylyl cyclase activity.

Expression of CRF1 is widespread in the CNS and found at lower levels in peripheral
5 tissues including skin, ovary, testis and adrenal gland. CRF1 plays a pivotal role in the hypothalamic-pituitary-adrenal axis response to stress. Of the CRF family of peptides, which includes corticotrophin releasing hormone (CRF), urocortin I, II, and III, CRF1 is activated only by CRF and urocortin I. In the gastrointestinal (GI) tract, CRF1 activation mediates colonic motility, while activation of the related receptor CRF2 delays gastric
10 emptying. At least 8 isoforms of CRF1 have been identified, but not all isoforms appear to be functional. CRF1-deficient mice possess an impaired stress response and reduced anxiety.

PEPTIDES

As defined herein, P is a peptide comprising at least three contiguous amino-acid
15 residues (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19) of an intracellular i1, i2 or i3 loop or intracellular i4 domain of the CRF1 receptor. It is understood that, the N-terminal nitrogen of the N-terminal amino acid residue of P to which the linking moiety C(O) is bonded can be one of the at least three contiguous amino acid residues or it can be an amino acid residue distinct from the at least three contiguous amino acid residues.

20 Intracellular i1 loop as used herein refers to the loop which connects TM1 to TM2 and the corresponding transmembrane junctional residues.

Intracellular i2 loop as used herein refers to the loop which connects TM3 to TM4 and the corresponding transmembrane junctional residues.

25 Intracellular i3 loop as used herein refers to the loop which connects TM5 to TM6 and the corresponding transmembrane junctional residues.

Intracellular i4 domain as used herein refers to the C-terminal cytoplasmic tail and the transmembrane junctional residue.

In a specific embodiment, P comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at
30 least thirteen, at least fourteen, at least fifteen, at least sixteen, at least seventeen, at least eighteen or at least nineteen contiguous amino acid residues of the intracellular i1, i2 or i3 loop or intracellular i4 domain of the CRF1 receptor

In a more specific embodiment, the at least three contiguous amino acids of P (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19) are derived from the intracellular i1, i2 or i3 loop or intracellular i4 domain of the CRF1 receptor, wherein the amino acid sequence of each loop and the i4 domain is as described in Table 1.

5

Table 1:

Intracellular Loop or Domain	CRF1 Receptor
i1	VLFLRLRSIRCLRNIHWN (SEQ ID NO:1)
i2	HTAIVLTYSTDLRKWMFI (SEQ ID NO:24)
i3	FNIVRILMTKLRASTTSETIQYRKAVKA (SEQ ID NO: 71)
i4	EVRSAIRKRWHRWQDKHSIRARVARAMSIPTSPTRVSFHSIKQSTAV (SEQ ID NO: 99)

It is understood that in addition to the amino acids in the sequences in Table 1, the intracellular loop for the i1 loop, i2 loop, i3 loop and i4 domain can also include amino acids from transmembrane junctional residues. For example, the i1 loop can include SEQ ID NO: 1 where one or more residues from the transmembrane junctional residues are included on either the C-terminus, the N-terminus or both. For example, SEQ ID NO: 1 can include either an Threonine residue, Leucine residue or both at the C-terminus.

In another embodiment, P comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, at least fifteen, at least sixteen, at least seventeen, at least eighteen or at least nineteen contiguous amino acid residues of the i1 intracellular loop of the CRF1 receptor.

It is understood that for the embodiments presented herein, that when the amino acid residues of P are represented by X, M, Y or Z that the C-terminal amino acid residue does not include the -OH of the amino acid and that the end group R₁ that is bonded to the C-terminal residue includes -OH.

In one embodiment, P is derived from the i1 loop and is represented by the following structural formula or pharmaceutically acceptable salts thereof

$X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}-X_{19}-R_1$

wherein:

X_1 is absent or a valine residue;

X_2 is absent or a leucine or glycine residue;

5 X_3 is absent or a phenylalanine or serine residue;

X_4 is absent or a leucine or glycine residue;

X_5 is absent or an arginine residue;

X_6 is absent or a leucine or isoleucine residue;

X_7 is absent or an arginine residue;

10 X_8 is absent or a serine residue;

X_9 is absent or an isoleucine residue;

X_{10} is absent or an arginine residue;

X_{11} is absent or a cysteine or serine residue;

X_{12} is absent or a leucine residue;

15 X_{13} is absent or an arginine residue;

X_{14} is absent or an asparagine residue;

X_{15} is absent or an isoleucine residue;

X_{16} is absent or an isoleucine residue;

X_{17} is absent or a histidine residue;

20 X_{18} is absent or tryptophan residue;

X_{19} is absent or an asparagine residue; provided that at least five of X_1-X_{19} are present;

R_1 is OR_2 or $N(R_2)_2$;

each R_2 is independently hydrogen or (C_1-C_{10}) alkyl; and

25 from 0 to 5 amino acid residues are present in the D configuration.

It is understood that when P is described as X_1-X_{19} it is bonded to L as written. For example, X_1 is bonded to L. If X_1 is absent, then X_2 is bonded to L.

30 In a specific embodiment, at least four of X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} and X_{14} are present.

In a further specific embodiment,

X₇ is an arginine residue;
 X₈ is a serine residue;
 X₉ is an isoleucine residue; and
 X₁₀ is an arginine residue.

5

In another further specific embodiment,

X₁₁ is a cysteine or serine residue;
 X₁₂ is a leucine residue;
 X₁₃ is an arginine residue; and
 X₁₄ is an asparagine residue.

10

In another further specific embodiment, X₁₁ is a cysteine residue. Alternatively,
 wherein X₁₁ is a serine residue.

In another specific embodiment,

X₁₄ is an asparagine residue;
 X₁₅ is an isoleucine residue;
 X₁₆ is an isoleucine residue; and
 X₁₇ is a histidine residue.

15

In an even more specific embodiment, P is selected from the group consisting of SEQ

20 ID NOS: 1-23 as listed in Table 2 below:

Table 2:

i loop	CRF1 Sequence	SEQ ID NO:
i1	VLFLRLRSIRCLRNIHWN	1
i1	VLFLRLRSIRCLRNIHW	2
i1	GSGRLRSIRSLRNIIHWN	3
i1	VLFLRLRSIRCLRNIH	4
i1	FLRLRSIRCLRNIHWN	5
i1	GSGRLRSIRSLRNIIH	6
i1	LFIRIRSIRSLRNIIH	7
i1	VLFLRLRSIRCLRNI	8
i1	RLRSIRCLRNIHWN	9
i1	RLRSIRSLRNIIHWN	10

i1	VLFLRLRSIRCLRNI	11
i1	VLFLRLRSIRCLRNI	12
i1	RLRSIRSLRNIIH	13
i1	RSIRSLRNIIHWN	14
i1	VLFLRLRSIRCLR	15
i1	RSIRCLRNIHWN	16
i1	RSIRSLRNIIH	17
i1	RSIRCLRNIH	18
i1	RLRSIRSLRN	19
i1	RSLRNIIHWN	20
i1	RLRSIRSLR	21
i1	RSLRNIIH	22
i1	RSIRSLRN	23

In another specific embodiment, the at least three contiguous amino acids of P (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19) are derived from the i2 intracellular loop of the CRF1 receptor.

5 In one embodiment, P derived from the i2 loop and is represented by the following structural formula or a pharmaceutically acceptable salt thereof

$Y_1-Y_2-Y_3-Y_4-Y_5-Y_6-Y_7-Y_8-Y_9-Y_{10}-Y_{11}-Y_{12}-Y_{13}-Y_{14}-Y_{15}-Y_{16}-Y_{17}-Y_{18}-Y_{19}-R_1$,

wherein:

Y_1 is absent or a histidine residue;

10 Y_2 is absent or a threonine residue;

Y_3 is absent or an alanine residue;

Y_4 is absent or an isoleucine or a glycine residue;

Y_5 is absent or a valine or serine residue;

Y_6 is absent or a leucine or glycine residue;

15 Y_7 is absent or a threonine or serine residue;

Y_8 is absent or a tyrosine or glycine residue;

Y_9 is absent or serine, threonine or glycine residue;

Y_{10} is absent or a threonine, serine, tyrosine, glycine or alanine residue;

Y_{11} is absent or an aspartic acid, alanine, serine or glycine residue;

20 Y_{12} is absent or an arginine or alanine residue;

Y_{13} is absent or a leucine or an alanine residue;

Y₁₄ is absent or an arginine or alanine residue;

Y₁₅ is absent or a lysine or an alanine residue;

Y₁₆ is absent or a tryptophan, methionine or an alanine residue;

Y₁₇ is absent or a methionine, norleucine, phenylalanine or an alanine residue;

5 Y₁₈ is absent or a phenylalanine, isoleucine or an alanine residue;

Y₁₉ is absent or an isoleucine or alanine residue, provided that at least five of Y₁-Y₁₉,
are present; and

R₁ is OR₂ or N(R₂)₂;

each R₂ is independently hydrogen or (C₁-C₁₀)alkyl; and

10 from 0 to 5 amino acid residues are present in the D configuration.

It is understood that when P is described as Y₁- Y₁₉ it is bonded to L as written. For
example, Y₁ is bonded to L. If Y₁ is absent, then Y₂ is bonded to L.

In a specific embodiment, at least three of Y₇, Y₈, Y₉, Y₁₀, Y₁₁, Y₁₂, Y₁₃, Y₁₄, Y₁₅, Y₁₆,

15 Y₁₇, Y₁₈ and Y₁₉ are present.

In a further specific embodiment,

Y₉ is serine, threonine or glycine residue;

Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue; and

20 Y₁₁ is an aspartic acid, alanine, serine or glycine residue.

In another further specific embodiment,

Y₁₂ is an arginine or alanine residue;

Y₁₃ is a leucine or an alanine residue; and

25 Y₁₄ is an arginine or alanine residue.

In a further specific embodiment,

Y₉ is serine, threonine or glycine residue;

Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;

30 Y₁₁ is an aspartic acid, alanine, serine or glycine residue; and

Y₁₂ is an arginine or alanine residue.

In a further specific embodiment,

Y₁₁ is an aspartic acid, alanine, serine or glycine residue;

Y₁₂ is an arginine or alanine residue;

Y₁₃ is a leucine or an alanine residue; and

5 Y₁₄ is an arginine or alanine residue.

In a further specific embodiment,

Y₉ is serine, threonine or glycine residue;

Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;

10 Y₁₁ is an aspartic acid, alanine, serine or glycine residue;

Y₁₂ is an arginine or alanine residue; and

Y₁₃ is a leucine or an alanine residue.

In a further specific embodiment,

15 Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;

Y₁₁ is an aspartic acid, alanine, serine or glycine residue;

Y₁₂ is an arginine or alanine residue;

Y₁₃ is a leucine or an alanine residue; and

Y₁₄ is an arginine or alanine residue.

20

In yet another further specific embodiment,

Y₉ is serine, threonine or glycine residue;

Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;

Y₁₁ is an aspartic acid, alanine, serine or glycine residue;

25 Y₁₂ is an arginine or alanine residue;

Y₁₃ is a leucine or an alanine residue; and

Y₁₄ is an arginine or alanine residue.

In yet another further specific embodiment,

30 Y₉ is serine residue;

Y₁₀ is a threonine residue;

Y₁₁ is an aspartic acid residue;

Y₁₂ is an arginine residue;
Y₁₃ is a leucine residue; and
Y₁₄ is an arginine residue.

5 In a specific embodiment,
Y₇ is a threonine or serine residue;
Y₈ is a tyrosine or glycine residue;
Y₉ is a serine, threonine or glycine residue; and
Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue.

10 In another specific embodiment,
Y₇ is a threonine residue;
Y₈ is a tyrosine residue;
Y₉ is a serine residue; and
15 Y₁₀ is a threonine residue.

In a further specific embodiment, Y₁₁ is an aspartic acid, alanine, serine or glycine residue. Specifically, Y₁₁ is an aspartic acid residue.

20 In another specific embodiment,
Y₁₂ is an arginine or alanine residue;
Y₁₃ is or a leucine or an alanine residue;
Y₁₄ is an arginine or alanine residue; and
Y₁₅ is a lysine or an alanine residue.

25 In another specific embodiment, one of Y₁₂, Y₁₃, Y₁₄, and Y₁₅ is an alanine residue, provided that the other three of Y₁₂, Y₁₃, Y₁₄, and Y₁₅ are not an alanine residue.

In another specific embodiment,
30 Y₁₂ is an arginine residue;
Y₁₃ is a leucine residue;
Y₁₄ is an arginine residue; and

Y₁₅ is a lysine residue.

In a further specific embodiment, Y₁₆ is a tryptophan, methionine or an alanine residue. Specifically, Y₁₆ is a tryptophan residue. Alternatively, Y₁₆ is a methionine residue.

5 In another specific embodiment,
Y₁₅ is a lysine or an alanine residue;
Y₁₆ is a tryptophan, methionine or an alanine residue;
Y₁₇ is a methionine, norleucine, phenylalanine or an alanine residue; and
Y₁₈ is a phenylalanine, isoleucine or an alanine residue.

10 In another specific embodiment, one of Y₁₅, Y₁₆, Y₁₇, and Y₁₈ is an alanine residue, provided that the other three of Y₁₅, Y₁₆, Y₁₇, and Y₁₈ are not an alanine residue.

In another specific embodiment,
Y₁₅ is a lysine residue;
15 Y₁₆ is a tryptophan or methionine residue;
Y₁₇ is a methionine, norleucine, or phenylalanine residue; and
Y₁₈ is a phenylalanine or isoleucine residue.

In another specific embodiment,
Y₁₅ is a lysine residue;
20 Y₁₆ is a tryptophan residue;
Y₁₇ is a methionine residue; and
Y₁₈ is a phenylalanine residue.

In another specific embodiment, Y₁₉ is an isoleucine or alanine residue. Specifically, Y₁₉ is an isoleucine residue.

25 In a more specific embodiment, P is selected from the group consisting of SEQ ID NOS: 24-70 as listed in Table 3 below:

Table 3:

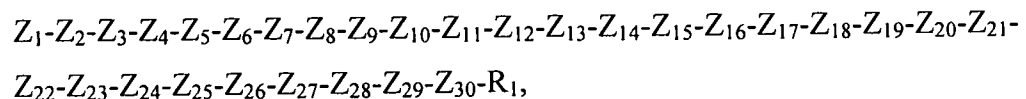
i loop	CRF1 Sequence	SEQ ID NO:
i2	HTAIVLTYSTDRLRKWMFI	24
i2	HTAIVLTYSTDRLRKWM	25

i2	AIVLTYSTDRLRKWMFI	26
i2	GSGTYSTDRLRKWMFI	27
i2	HTAIVLTYSTDRLRK	28
i2	GSGTYSTDRLRKWMF	29
i2	VLTYSTDRLRKWMFI	30
i2	HTAIVLTYSTDRLR	31
i2	LTYSTDRLRKWMFI	32
i2	TYSTDRLRKWMFI	33
i2	HTAIVLTYSTDRLR	34
i2	GSGTYDRLRKWM	35
i2	GSGTYSTDRLRK	36
i2	GSTDRLRKWMFI	37
i2	GSTDRLRKWMFA	38
i2	GSTDRLRKWMAI	39
i2	GSTDRLRKWAFI	40
i2	GSTDRLRKAMFI	41
i2	GSTDRLRKAXFI	42
i2	YSTDRLRKWMFI	43
i2	GSTDRLRKMF	44
i2	GSGRLRKWMFI	45
i2	STDRLRKWMFI	46
i2	YSTDRLRKWMF	47
i2	STDRLRKWMF	48
i2	ADRLRKWMFI	49
i2	GSRLRKWMFI	50
i2	TDRLRKWMFI	51
i2	TDRLRKWXFI	52
i2	TARLRKWMFI	53
i2	TDALRKWMFI	54
i2	TDRARKWMFI	55
i2	TDRLAKWMFI	56
i2	TDRLRAWMFI	57
i2	TDRLRKAMFI	58
i2	TDRLRKWAFI	59
i2	TDRLRKWMAI	60
i2	TDRLRKWMFA	61
i2	TYSTDRLRK	62
i2	STDRLRKMF	63

i2	GSGRLRKWM	64
i2	GRLRKWMFI	65
i2	DRLRKWMFI	66
i2	DRLRKWMAI	67
i2	GSTDRLRK	68
i2	RLRKWMFI	69
i2	RLRKWMAI	70

In yet another specific embodiment, P comprises at least three contiguous amino (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19) of the i3 intracellular loop of the CRF1 receptor.

5 In one embodiment, P is derived from the i3 loop and is represented by the following structural formula or a pharmaceutically acceptable salt thereof:



wherein :

- 10 Z_1 is absent or a phenylalanine residue;
 Z_2 is absent or an asparagine residue;
 Z_3 is absent or an isoleucine residue;
 Z_4 is absent or a valine residue;
 Z_5 is absent or an arginine residue;
15 Z_6 is absent or an isoleucine residue;
 Z_7 is absent or a leucine residue;
 Z_8 is absent or a methionine residue;
 Z_9 is absent or a threonine residue;
 Z_{10} is absent or a lysine residue;
20 Z_{11} is absent or a leucine residue;
 Z_{12} is absent or an arginine residue;
 Z_{13} is absent or an alanine residue;
 Z_{14} is absent or a serine residue;
 Z_{15} is absent or a threonine residue;
25 Z_{16} is absent or a threonine residue;
 Z_{17} is absent or a serine residue;

Z_{18} is absent or a glutamic acid residue;

Z_{19} is absent or a threonine residue;

Z_{20} is absent or an isoleucine residue;

Z_{21} is absent or a glutamine residue;

5 Z_{22} is absent or a tyrosine residue;

Z_{23} is absent or an arginine residue;

Z_{24} is absent or a lysine residue;

Z_{25} is absent or an alanine residue;

Z_{26} is absent or a valine residue;

10 Z_{27} is absent or a lysine residue;

Z_{28} is absent or an alanine or serine residue;

Z_{29} is absent or a threonine residue; and

Z_{30} is absent or a leucine residue;

provided that at least five of Z_1 - Z_{30} are present;

15 R_1 is OR_2 or $N(R_2)_2$;

each R_2 is independently hydrogen or (C_1-C_{10}) alkyl; and

from 0 to 5 amino acid residues are present in the D configuration.

It is understood that when P is described as Z_1 - Z_{30} it is bonded to L as written. For example, Z_1 is bonded to L. If Z_1 is absent, then Z_2 is bonded to L.

20

In a specific embodiment, at least three of Z_5 , Z_6 , Z_7 , Z_8 , and Z_9 are present.

In a further specific embodiment,

Z_5 is an arginine residue;

Z_6 is an isoleucine residue; and

25 Z_7 is a leucine residue.

In another further specific embodiment,

Z_7 is a leucine residue;

Z_8 is a methionine residue; and

30 Z_9 is a threonine residue.

In a another specific embodiment,

Z₅ is an arginine residue;
Z₆ is an isoleucine residue;
Z₇ is a leucine residue; and
Z₈ is a methionine residue.

5

In a another specific embodiment,
Z₆ is an isoleucine residue;
Z₇ is a leucine residue;
Z₈ is absent or a methionine residue; and
Z₉ is a threonine residue.

10

In a another specific embodiment,
Z₅ is an arginine residue;
Z₆ is an isoleucine residue;
Z₇ is a leucine residue;
Z₈ is a methionine residue; and
Z₉ is a threonine residue.

15

In yet another specific embodiment, at least three of Z₁₀, Z₁₁, Z₁₂, and Z₁₃ are present.

20

In a another specific embodiment,
Z₁₀ is a lysine residue;
Z₁₁ is a leucine residue; and
Z₁₂ is an arginine residue.

25

In a another specific embodiment,
Z₁₁ is a leucine residue;
Z₁₂ is an arginine residue; and
Z₁₃ is an alanine residue.

30

In yet another specific embodiment,
Z₁₀ is a lysine residue;
Z₁₁ is a leucine residue;
Z₁₂ is an arginine residue; and

Z₁₃ is an alanine residue.

In another specific embodiment, at least three of Z₁₄, Z₁₅, Z₁₆, and Z₁₇ are present.

5 In another specific embodiment,
 Z₁₄ is a serine residue;
 Z₁₅ is a threonine residue; and
 Z₁₆ is a threonine residue.

10 In another specific embodiment,
 Z₁₅ is a threonine residue;
 Z₁₆ is a threonine residue; and
 Z₁₇ is a serine residue;

15 In another specific embodiment,
 Z₁₄ is a serine residue;
 Z₁₅ is a threonine residue;
 Z₁₆ is a threonine residue; and
 Z₁₇ is a serine residue;

20 In another specific embodiment, at least three of Z₁₉, Z₂₀, Z₂₁, Z₂₂, and Z₂₃ are present.

 In another specific embodiment,
 Z₁₉ is a threonine residue;
25 Z₂₀ is an isoleucine residue; and
 Z₂₁ is a glutamine residue.

 In another specific embodiment,
 Z₂₁ is a glutamine residue;
30 Z₂₂ is a tyrosine residue; and
 Z₂₃ is an arginine residue.

In another specific embodiment,

Z₁₉ is a threonine residue;

Z₂₀ is an isoleucine residue;

Z₂₁ is a glutamine residue; and

5 Z₂₂ is a tyrosine residue.

In another specific embodiment,

Z₂₀ is an isoleucine residue;

Z₂₁ is a glutamine residue;

10 Z₂₂ is a tyrosine residue; and

Z₂₃ is an arginine residue.

In another specific embodiment,

Z₁₉ is a threonine residue;

15 Z₂₀ is an isoleucine residue;

Z₂₁ is a glutamine residue;

Z₂₂ is a tyrosine residue; and

Z₂₃ is an arginine residue.

20 In another specific embodiment, at least three of Z₂₄, Z₂₅, Z₂₆, Z₂₇, and Z₂₈ are present.

In another specific embodiment,

Z₂₄ is a lysine residue;

Z₂₅ is an alanine residue; and

Z₂₆ is a valine residue.

25 In another specific embodiment,

Z₂₆ is a valine residue;

Z₂₇ is a lysine residue; and

Z₂₈ is an alanine or serine residue.

30 In another specific embodiment,

Z₂₄ is a lysine residue;

Z₂₅ is an alanine residue;

Z_{26} is a valine residue; and

Z_{27} is a lysine residue.

In another specific embodiment,

5 Z_{25} is an alanine residue;

Z_{26} is a valine residue;

Z_{27} is a lysine residue; and

Z_{28} is an alanine or serine residue.

10 In another specific embodiment,

Z_{24} is a lysine residue;

Z_{25} is an alanine residue;

Z_{26} is a valine residue;

Z_{27} is a lysine residue; and

15 Z_{28} is an alanine or serine residue. Specifically, Z_{28} is an alanine residue.

In a more specific embodiment, P is selected from the group consisting of SEQ ID NOS: 71-98 as listed in Table 4 below:

Table 4:

i loop	Sequence	SEQ ID NO:
i3	FNIVRILMTKLRASTTSETIQYRKAVKA	71
i3	IVRILMTKLRASTTSETIQYRKAVKA	72
i3	FNIVRILMTKLRASTTSETIQYRKAV	73
i3	RILMTKLRASTTSETIQYRKAVKA	74
i3	FNIVRILMTKLRASTTSETIQYRK	75
i3	FNIVRILMTKLRASTTSETIQYR	76
i3	LMTKLRASTTSETIQYRKAVKA	77
i3	FNIVRILMTKLRASTTSETIQY	78
i3	TKLRASTTSETIQYRKAVKA	79
i3	LMTKLRASTTSETIQYRKAV	80
i3	LRASTTSETIQYRKAVKA	81
i3	LMTKLRASTTSETIQYRK	82
i3	LMTKLRASTTSETIQYR	83
i3	ASTTSETIQYRKAVKA	84

i3	ASTTSETIQYRKAVKS	85
i3	LMTKLRASTTSETIQ	86
i3	SETIQYRKAVKATL	87
i3	LMTKLRASTTSETI	88
i3	RILMTKLRASTTS	89
i3	SETIQYRKAVKA	90
i3	TKLRASTTSETI	91
i3	ASTTSETIQYR	92
i3	TKLRASTTSET	93
i3	KLRASTTSETI	94
i3	TIQYRKAVKA	95
i3	KLRASTTSET	96
i3	RILMTKLRA	97
i3	KLRASTTSE	98

In further specific embodiment, P comprises at least three contiguous amino (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19) of the i4 intracellular domain of the CRF1 receptor.

5 In one embodiment, P derived from the i4 domain and is represented by the following structural formula or a pharmaceutically acceptable salt thereof

M₁-M₂-M₃-M₄-M₅-M₆-M₇-M₈-M₉-M₁₀-M₁₁-M₁₂-M₁₃-M₁₄-M₁₅-M₁₆-M₁₇-M₁₈-M₁₉-
M₂₀-M₂₁-M₂₂-M₂₃-M₂₄-M₂₅-M₂₆-M₂₇-M₂₈-M₂₉-M₃₀-M₃₁-M₃₂-M₃₃-M₃₄-M₃₅-M₃₆-M₃₇-
M₃₈-M₃₉-M₄₀-M₄₁-M₄₂-M₄₃-M₄₄-M₄₅-M₄₆-M₄₇-R₁,

10 wherein:

M₁ is absent or a glutamic acid residue;

M₂ is absent or a valine residue;

M₃ is absent or an arginine residue;

M₄ is absent or a serine residue;

15 M₅ is absent or an alanine residue;

M₆ is absent or an isoleucine residue;

M₇ is absent or an arginine residue;

M₈ is absent or a lysine residue;

M₉ is absent or an arginine residue;

20 M₁₀ is absent or a tryptophan residue;

- M₁₁ is absent or a histidine residue;
M₁₂ is absent or an arginine residue;
M₁₃ is absent or a tryptophan residue;
M₁₄ is absent or a glutamine residue;
5 M₁₅ is absent or an aspartic acid residue;
M₁₆ is absent or a lysine residue;
M₁₇ is absent or a histidine or glycine residue;
M₁₈ is absent or a serine residue;
M₁₉ is absent or an isoleucine residue;
10 M₂₀ is absent or an arginine residue;
M₂₁ is absent or an alanine residue;
M₂₂ is absent or an arginine residue;
M₂₃ is absent or a valine residue;
M₂₄ is absent or an alanine residue;
15 M₂₅ is absent or an arginine residue;
M₂₆ is absent or an alanine residue;
M₂₇ is absent or a methionine residue;
M₂₈ is absent or a serine residue;
M₂₉ is absent or an isoleucine residue;
20 M₃₀ is absent or a proline residue;
M₃₁ is absent or a threonine residue;
M₃₂ is absent or a serine residue;
M₃₃ is absent or a proline residue;
M₃₄ is absent or a threonine residue;
25 M₃₅ is absent or an arginine residue;
M₃₆ is absent or a valine residue;
M₃₇ is absent or a serine residue;
M₃₈ is absent or a phenylalanine residue;
M₃₉ is absent or a histidine residue;
30 M₄₀ is absent or a serine residue;
M₄₁ is absent or an isoleucine residue;
M₄₂ is absent or a lysine residue;

M₄₃ is absent or a glutamine residue;

M₄₄ is absent or a serine residue;

M₄₅ is absent or a threonine residue;

M₄₆ is absent or an alanine residue; and

5 M₄₇ is absent or a valine residue; provided that at least five of M₁-M₄₇ are present;

R₁ is OR₂ or N(R₂)₂;

each R₂ is independently hydrogen or (C₁-C₁₀)alkyl; and

from 0 to 5 amino acid residues are present in the D configuration.

It is understood that when P is described as M₁- M₄₇ it is bonded to L as written. For

10 example, M₁ is bonded to L. If M₁ is absent, then M₂ is bonded to L.

In a specific embodiment, at least three of M₂-M₇ are present.

In another specific embodiment,

15 M₂ is a valine residue;

M₃ is an arginine residue; and

M₄ is a serine residue.

In another specific embodiment,

20 M₅ is an alanine residue;

M₆ is an isoleucine residue; and

M₇ is an arginine residue.

In another specific embodiment,

25 M₂ is a valine residue;

M₃ is an arginine residue;

M₄ is a serine residue; and

M₅ is an alanine residue.

30 In another specific embodiment,

M₄ is a serine residue;

M₅ is an alanine residue;

M₆ is an isoleucine residue; and
M₇ is an arginine residue.

In another specific embodiment,

5 M₂ is a valine residue;
M₃ is an arginine residue;
M₄ is a serine residue;
M₅ is an alanine residue;
M₆ is an isoleucine residue.

10

In another specific embodiment,

M₃ is an arginine residue;
M₄ is a serine residue;
M₅ is an alanine residue;
15 M₆ is an isoleucine residue; and
M₇ is an arginine residue.

In another specific embodiment,

M₂ is a valine residue;
20 M₃ is an arginine residue;
M₄ is a serine residue;
M₅ is an alanine residue;
M₆ is an isoleucine residue; and
M₇ is an arginine residue.

25

In another specific embodiment, at least three of M₉-M₁₃ are present.

In another specific embodiment,

M₉ is an arginine residue;
30 M₁₀ is a tryptophan residue;
M₁₁ is a histidine residue;
M₁₂ is an arginine residue.

In another specific embodiment,

M₁₀ is a tryptophan residue;

M₁₁ is a histidine residue;

5 M₁₂ is an arginine residue; and

M₁₃ is a tryptophan residue.

In another specific embodiment,

M₉ is an arginine residue;

M₁₀ is a tryptophan residue;

10 M₁₁ is a histidine residue;

M₁₂ is an arginine residue; and

M₁₃ is a tryptophan residue.

In another specific embodiment, at least three of M₁₈-M₂₂ are present.

15

In another specific embodiment,

M₁₈ is a serine residue;

M₁₉ is an isoleucine residue;

M₂₀ is an arginine residue; and

20 M₂₁ is an alanine residue.

In another specific embodiment,

M₁₉ is an isoleucine residue;

M₂₀ is an arginine residue;

25 M₂₁ is an alanine residue; and

M₂₂ is an arginine residue.

In another specific embodiment,

M₁₈ is a serine residue;

30 M₁₉ is an isoleucine residue;

M₂₀ is an arginine residue;

M₂₁ is an alanine residue; and

M₂₂ is an arginine residue.

In another specific embodiment, at least three of M₂₃-M₂₇ are present.

5 In another specific embodiment,
 M₂₃ is a valine residue;
 M₂₄ is an alanine residue;
 M₂₅ is an arginine residue; and
 M₂₆ is an alanine residue.

10 In another specific embodiment,
 M₂₄ is an alanine residue;
 M₂₅ is an arginine residue;
 M₂₆ is an alanine residue;
15 M₂₇ is a methionine residue.

 In another specific embodiment,
 M₂₃ is a valine residue;
 M₂₄ is an alanine residue;
20 M₂₅ is an arginine residue;
 M₂₆ is an alanine residue;
 M₂₇ is a methionine residue.

 In another specific embodiment, at least three of M₂₅-M₂₉ are present.

25 In another specific embodiment,
 M₂₅ is an arginine residue;
 M₂₆ is an alanine residue;
 M₂₇ is a methionine residue; and
30 M₂₈ is a serine residue.

In another specific embodiment,

M₂₆ is an alanine residue;

M₂₇ is a methionine residue;

M₂₈ is a serine residue; and

5 M₂₉ is an isoleucine residue.

In another specific embodiment,

M₂₅ is an arginine residue;

M₂₆ is an alanine residue;

10 M₂₇ is a methionine residue;

M₂₈ is a serine residue; and

M₂₉ is an isoleucine residue.

In another specific embodiment, at least three of M₃₂-M₃₆ are present.

15

In another specific embodiment,

M₃₂ is a serine residue;

M₃₃ is a proline residue;

M₃₄ is a threonine residue; and

20 M₃₅ is an arginine residue.

In another specific embodiment,

M₃₃ is a proline residue;

M₃₄ is a threonine residue;

25 M₃₅ is an arginine residue; and

M₃₆ is a valine residue.

In another specific embodiment,

M₃₂ is a serine residue;

M₃₃ is a proline residue;

30 M₃₄ is a threonine residue;

M₃₅ is an arginine residue; and

M₃₆ is a valine residue.

In a more specific embodiment, P is selected from the group consisting of SEQ ID NOS: 99-106 as listed in Table 5 below:

Table 5:

i loop	CRF1 Sequence	SEQ ID:
i4	EVRSAIRKRWHRWQDKHSIRARVARAMSIPTSPTRVSFHSIKQSTAV	99
i4	RAMSIPTSPTRVSFHSIKQSTAV	100
i4	HSIRARVARAMSIPTSPTRV	101
i4	RWQDKHSIRARVARAMSI	102
i4	EVRSAIRKRWHRWQD	103
i4	RWHRWQDKHSIRAR	104
i4	VRSAIRKRWHRW	105
i4	GSIRARVARAM	106

5

It is understood that the sequences presented in Tables 2-5 can be optionally functionalized at the C-terminus. Functionalized at the C-terminus means that the acid moiety present at the C-terminus is replaced by some other functional group. Suitable functional groups include $-C(O)N(R_2)_2$, $-C(O)OR_3$, or $C(O)NHC(O)OR_2$, where R_2 is hydrogen or a (C_1-C_{10}) alkyl group and R_3 is a (C_1-C_{10}) alkyl group.

10

It is understood that as long as P comprises the indicated number of contiguous amino acids residues from the CRF1 intracellular loop (i1, i2 or i3) or domain (i4) from which it is derived, the remainder of the peptide, if present, can be selected from:

(a) any natural amino acid residue, unnatural amino acid residue or a combination thereof;

15

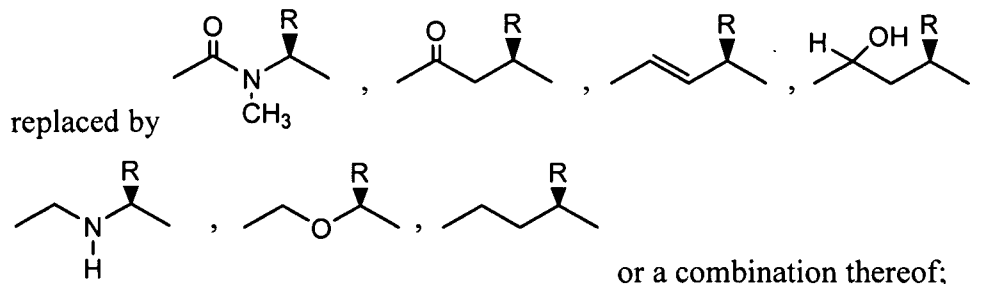
(b) a peptide sequence comprising natural amino acid residues, non-natural amino acid residues and combinations thereof;

(c) a peptide sequence according to (b) comprising one or more peptide backbone modifications;

(d) a peptide sequence according to (c) comprising one or more retro-inverso peptide linkages;

20

(e) a peptide sequence according to (c) wherein one or more peptide bonds are



(f) a peptide sequence according to (c) comprising one or more desipeptide

5 linkages, wherein the amide linkage is replaced with an ester linkage; and

(g) a peptide sequence according to (c) comprising one or more conformational restrictions; and

(h) a peptide sequence according to (c) comprising one or more of (d)-(g).

Furthermore, it is understood that even within the indicated number of contiguous
 10 amino acid residues derived from the GPCR intracellular loop (i1, i2 or i3) or domain (i4), there can be: peptide backbone modifications such as, but not limited to, those described in (e) above; retro-inverso peptide linkages; desipeptide linkages; conformational restrictions; or a combination thereof.

It is noted that P of Formula I can be optionally functionalized at the C-terminus.

15 Functionalized at the C-terminus means that the acid moiety present at the C-terminus is replaced by some other functional group. Suitable functional groups include $-C(O)N(R_2)_2$, $-C(O)OR_3$, or $C(O)NHC(O)OR_2$, where R_2 is hydrogen or a (C_1-C_{10}) alkyl group and R_3 is a (C_1-C_{10}) alkyl group. Functionalization of the C-terminus can result from the methods used to prepare.

20 Peptidomimetic as used herein refers to a compound comprising non-peptidic structural elements in place of a peptide sequence.

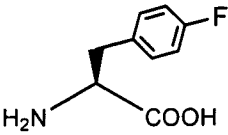
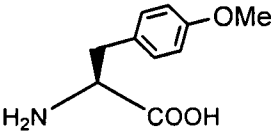
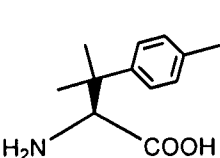
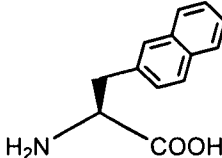
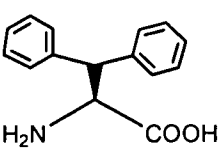
As used herein, the term "amino acid" includes both a naturally occurring amino acid and a non-natural amino acid.

As used herein, the term "naturally occurring amino acid" means a compound
 25 represented by the formula $NH_2-CHR-COOH$, wherein R is the side chain of a naturally occurring amino acids such as lysine, arginine, serine, tyrosine etc. as shown in the Table below.

Table of Common Naturally Occurring Amino Acids

	Amino acid	Three letter code	One letter code
Non-polar; neutral at pH 7.4	alanine	Ala	A
	isoleucine	Ile	I
	leucine	Leu	L
	methionine	Met	M
	phenylalanine	Phe	F
	proline	Pro	P
	tryptophan	Trp	W
	valine	Val	V
Polar, uncharged at pH 7.0	asparagine	Asn	N
	cysteine	Cys	C
	glycine	Gly	G
	glutamine	Gln	Q
	serine	Ser	S
	threonine	Thr	T
	tyrosine	Tyr	Y
Polar; charged at pH 7	glutamic acid	Glu	E
	arginine	Arg	R
	aspartic acid	Asp	D
	histidine	His	H
	lysine	Lys	K

"Non-natural amino acid" means an amino acid for which there is no nucleic acid codon. Examples of non-natural amino acids include, for example, the D-isomers of the natural α -amino acids such as D-proline (D-P, D-Pro) as indicated above; natural α -amino

acids with non-natural side chains (e.g., , , , , and  related to phenylalanine); Aib (aminobutyric acid), bAib (3-aminoisobutyric acid), Nva (norvaline), β -Ala, Aad (2-aminoadipic acid), bAad (3-aminoadipic acid), Abu (2-aminobutyric acid), Gaba (γ -

aminobutyric acid), Acp (6-aminocaproic acid), Dbu (2,4-diaminobutyric acid), α -aminopimelic acid, TMSA (trimethylsilyl-Ala), alle (allo-isoleucine), Nle (norleucine), tert-Leu, Cit (citrulline), Orn (ornithine, O), Dpm (2,2'-diaminopimelic acid), Dpr (2,3-diaminopropionic acid), α or β -Nal, Cha (cyclohexyl-Ala), hydroxyproline, Sar (sarcosine), and the like.

Unnatural amino acids also include cyclic amino acids; and amino acid analogs, for example, N $^{\alpha}$ -alkylated amino acids such as MeGly (N $^{\alpha}$ -methylglycine), EtGly (N $^{\alpha}$ -ethylglycine) and EtAsn (N $^{\alpha}$ -ethylasparagine); and amino acids in which the α -carbon bears two side-chain substituents. As with the natural amino acids, the residues of the unnatural amino acids are what are left behind when the unnatural amino acid becomes part of a peptide sequence as described herein.

Amino acid residues are amino acid structures as described above that lack a hydrogen atom of the amino group or the hydroxyl moiety of the carboxyl group or both resulting in the units of a peptide chain being amino-acid residues.

The D-isomers of the natural amino acids are designated herein with a lower case letter of the corresponding naturally occurring amino acid. For example, d-proline is designated "p" rather than "P" as is used for naturally occurring proline.

TETHERS (T)

T of Formula I is a lipophilic tether moiety which imparts lipophilicity to the CRF1 receptor compounds of the invention. The lipophilicity which T imparts, can promote penetration of the CRF1 receptor compounds into the cell membrane and tethering of the CRF1 receptor compounds to the cell membrane. As such, the lipophilicity imparted by T can facilitate interaction between the CRF1 receptor compounds of the invention and the cognate receptor.

The relative lipophilicity of compounds suitable for use as the lipophilic tether moiety of Formula I can be quantified by measuring the amount of the compound that partitions into an organic solvent layer (membrane-like) vs. an aqueous solvent layer (analogous to the extracellular or cytoplasmic environment). The partition coefficient in a mixed solvent composition, such as octanol/water or octanol/PBS, is the ratio of compound found at equilibrium in the octanol vs. the aqueous solvent (Partition coeff $P = \frac{[\text{compound}]_{\text{octanol}}}{[\text{compound}]_{\text{aqueous}}}$). Frequently, the partition coefficient is expressed in

logarithmic form, as the log P. Compounds with greater lipophilicity have a more positive log P than more hydrophilic compounds and tend to interact more strongly with membrane bilayers.

Computational programs are also available for calculating the partition coefficient for compounds suitable for use as the lipophilic tether moiety (T). In situations where the chemical structure is being varied in a systematic manner, for example by adding additional methylene units (-CH₂-) onto to an existing alkyl group, the trend in log P can be calculated using, for example, ChemDraw (CambridgeSoft, Inc).

In one embodiment, T is an optionally substituted (C₆-C₃₀)alkyl, (C₆-C₃₀)alkenyl, (C₆-C₃₀)alkynyl wherein 0-3 carbon atoms are replaced with oxygen, sulfur, nitrogen or a combination thereof.

In a specific embodiment, the (C₆-C₃₀)alkyl, (C₆-C₃₀)alkenyl, (C₆-C₃₀)alkynyl are substituted at one or more substitutable carbon atoms with halogen, -CN, -OH, -NH₂, NO₂, -NH(C₁-C₆)alkyl, -N((C₁-C₆)alkyl)₂, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, aryloxy, (C₁-C₆)alkoxycarbonyl, -CONH₂, -OCONH₂, -NHCONH₂, -N(C₁-C₆)alkylCONH₂, -N(C₁-C₆)alkylCONH(C₁-C₆)alkyl, -NHCONH(C₁-C₆)alkyl, -NHCON((C₁-C₆)alkyl)₂, -N(C₁-C₆)alkylCON((C₁-C₆)alkyl)₂, -NHC(S)NH₂, -N(C₁-C₆)alkylC(S)NH₂, -N(C₁-C₆)alkylC(S)NH(C₁-C₆)alkyl, -NHC(S)NH(C₁-C₆)alkyl, -NHC(S)N((C₁-C₆)alkyl)₂, -N(C₁-C₆)alkylC(S)N((C₁-C₆)alkyl)₂, -CONH(C₁-C₆)alkyl, -OCONH(C₁-C₆)alkyl, -CON((C₁-C₆)alkyl)₂, -C(S)(C₁-C₆)alkyl, -S(O)_p(C₁-C₆)alkyl, -S(O)_pNH₂, -S(O)_pNH(C₁-C₆)alkyl, -S(O)_pN((C₁-C₆)alkyl)₂, -CO(C₁-C₆)alkyl, -OCO(C₁-C₆)alkyl, -C(O)O(C₁-C₆)alkyl, -OC(O)O(C₁-C₆)alkyl, -C(O)H or -CO₂H; and p is 1 or 2.

In a specific embodiment, T is selected from the group consisting of:

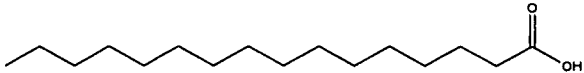
CH₃(CH₂)₉OPh-, CH₃(CH₂)₆C=C(CH₂)₆, CH₃(CH₂)₁₁O(CH₂)₃, CH₃(CH₂)₉O(CH₂)₂ and CH₃(CH₂)₁₃.

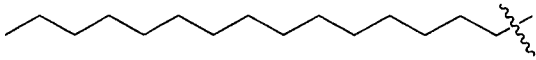
In a specific embodiment, T is selected from the group consisting of: CH₃(CH₂)₁₆, CH₃(CH₂)₁₅, CH₃(CH₂)₁₄, CH₃(CH₂)₁₃, CH₃(CH₂)₁₂, CH₃(CH₂)₁₁, CH₃(CH₂)₁₀, CH₃(CH₂)₉, CH₃(CH₂)₈, CH₃(CH₂)₉OPh-, CH₃(CH₂)₆C=C(CH₂)₆, CH₃(CH₂)₁₁O(CH₂)₃, and CH₃(CH₂)₉O(CH₂)₂ and CH₃(CH₂)₁₃.

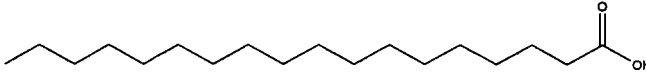
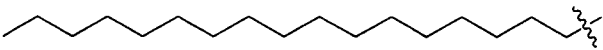
It is understood that the lipophilic moiety (T) of Formula I can be derived from precursor lipophilic compounds (e.g., fatty acids and bile acids). As used herein, "derived from" with regard to T, means that T is derived from a precursor lipophilic compound and

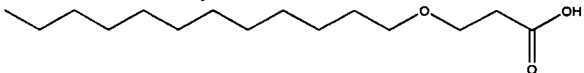
that reaction of the precursor lipophilic compound in preparing the CRF1 receptor compounds of Formula I, results in a lipophilic tether moiety represented by T in Formula I that is structurally modified in comparison to the precursor lipophilic compound.

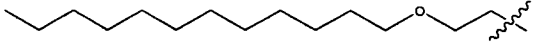
For example, the lipophilic tether moiety, T of Formula I, can be derived from a fatty acid or a bile acid. It is understood that in accordance with Formula I, when T is derived from a fatty acid (i.e., a fatty acid derivative) it is attached to L-P at the carbon atom alpha to the carbonyl carbon of the acid functional group in the fatty acid from which it is derived. For example, when T is derived from palmitic acid,

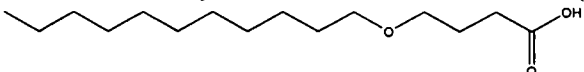
 , T of Formula I has the following structure:

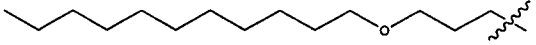
 . Similarly, when T is derived from stearic acid,

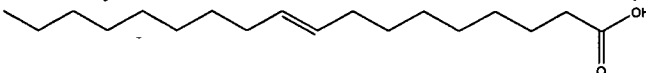
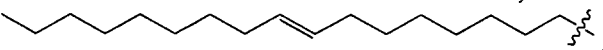
 , T of Formula I has the following structure:  .

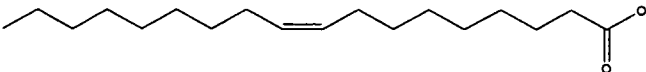
Similarly, when T is derived from 3-(dodecyloxy)propanoic acid,  , T of Formula I has the following structure:

 .

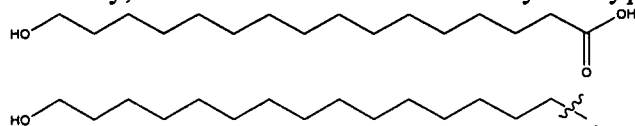
Similarly, when T is derived from 4-(undecyloxy)butanoic acid,  , T of Formula I has the following structure:

 .

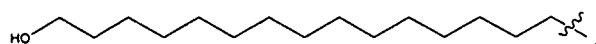
Similarly, when T is derived from elaidic acid,  , T of Formula I has the following structure:  .

Similarly, when T is derived from oleic acid,  , T of Formula I has the following structure:  .

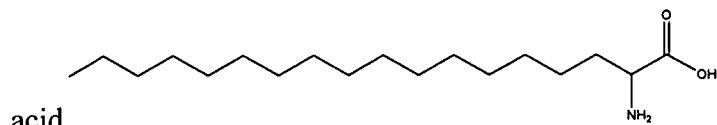
Similarly, when T is derived from 16-hydroxypalmitic acid,



, T of Formula I has the following structure:



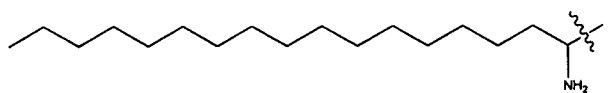
5 Similarly, when T is derived from 2-aminooctadecanoic acid



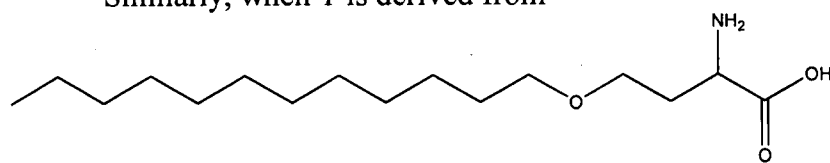
acid

, T of Formula I has the following

structure:

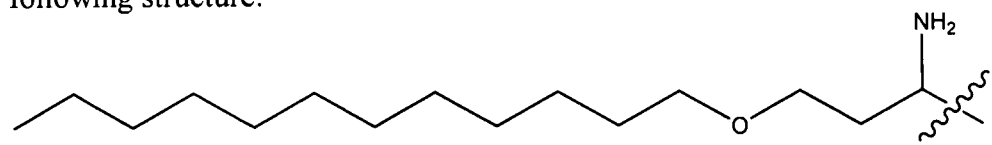


Similarly, when T is derived from 2-amino-4-(dodecyloxy)butanoic acid ,



, T of Formula I has the

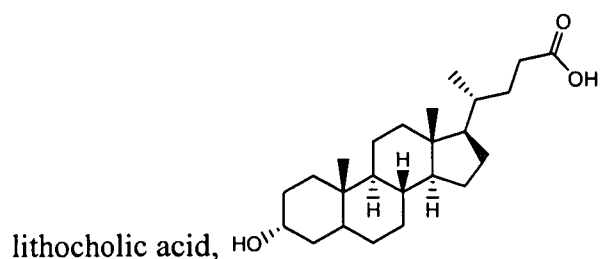
10 following structure:



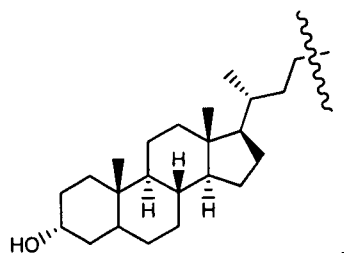
15 In a further embodiment, T is derived from a fatty acid. In a specific embodiment, T is derived from a fatty acid selected from the group consisting of: butyric acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, and lignoceric acid.

20 In another specific embodiment, T is derived from a fatty acid selected from the group consisting of: myristoleic acid, palmitoleic acid, oleic acid, linoleic acid, α -linolenic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, docosahexaenoic acid

25 In another embodiment, T of Formula I can be derived from a bile acid. Similar to the embodiment where T is a fatty acid derivative, it is understood that in accordance with Formula I, when T is derived from a bile acid (i.e., a bile acid derivative) it is attached to L-P at the carbon atom alpha to the carbonyl carbon of the acid functional group in the bile acid from which it is derived. For example, when T is derived from

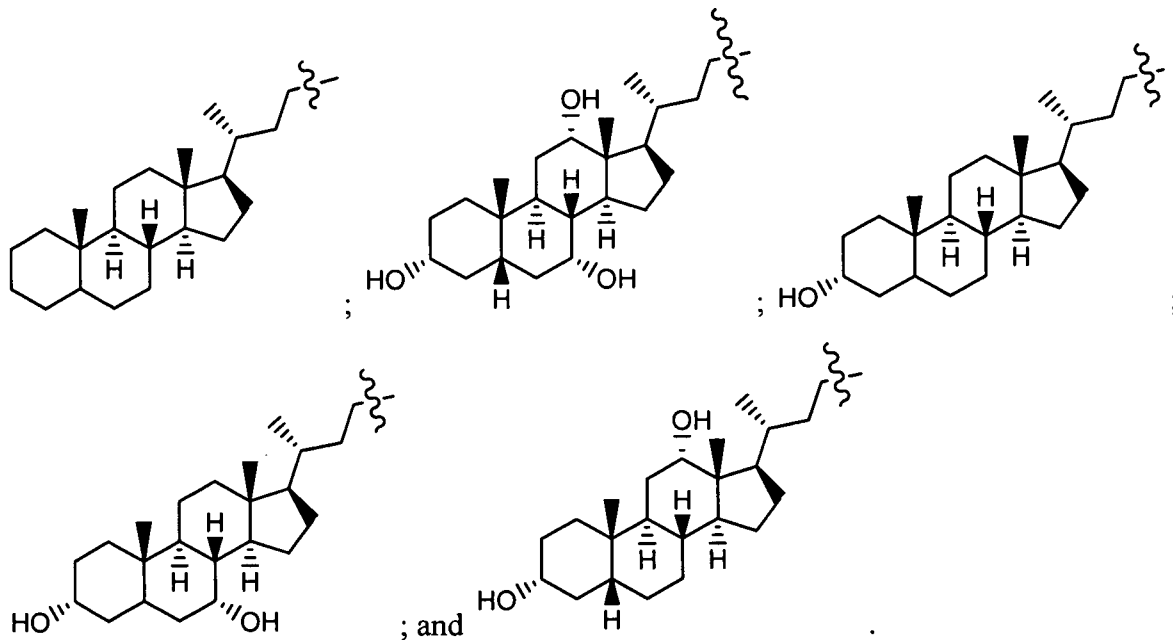


, T of Formula I has the following structure:

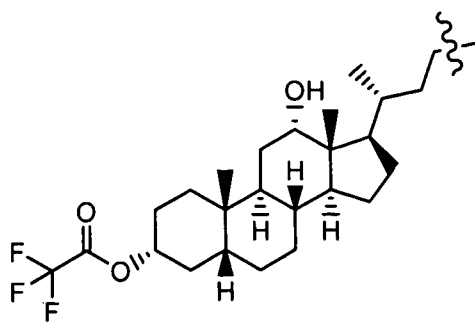


In a further embodiment, T is derived from a bile acid. In a specific embodiment, T is derived from a bile acid selected from the group consisting of: lithocholic acid, chenodeoxycholic acid, deoxycholic acid, cholanic acid, cholic acid, ursocholic acid, ursodeoxycholic acid, isoursodeoxycholic acid, lagodeoxycholic acid, dehydrocholic acid, hyocholic acid, hyodeoxycholic acid and the like.

For example, T is selected from:



In another further embodiment, T is derived from a bile acid described above that has been modified at other than the acid functional group. For example, T can be derived from any of the bile acids described above, where the hydroxy position has been modified to form an ester or a halo ester. For example, T can be:



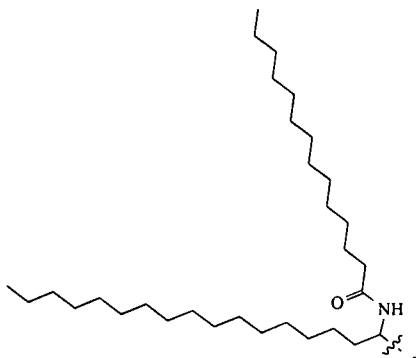
Other lipophilic moieties suitable for use as the lipophilic membrane tether, T, of Formula I, include but are not limited to steroids. Suitable steroids include, but are not limited to, sterols; progestagens; glucocorticoids; mineralcorticoids; androgens; and estrogens. Generally any steroid capable of attachment or which can be modified for incorporation into Formula I can be used. It is understood that the lipophilic membrane tether, T, may be slightly modified from the precursor lipophilic compound as a result of incorporation into Formula I.

Suitable sterols for use in the invention at T, include but are not limited to: cholestanol, coprostanol, cholesterol, epicholesterol, ergosterol, ergocalciferol, and the like. Preferred sterols are those that provide a balance of lipophilicity with water solubility.

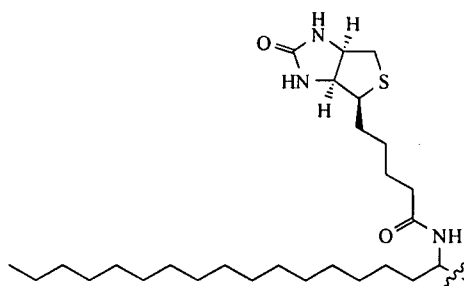
Suitable progestagens include, but are not limited to progesterone. Suitable glucocorticoids include, but are not limited to cortisol. Suitable mineralcorticoids include, but are not limited to aldosterone. Suitable androgens include, but are not limited to testosterone and androstenedione. Suitable estrogens include, but are not limited to estrone and estradiol.

In another specific embodiment, T can be derived from 2-tetradecanamideoctadecanoid acid. Similar to the embodiment where T is a fatty acid derivative, it is understood that in accordance with Formula I, when T is derived from 2-tetradecanamideoctadecanoid acid it is attached to L-P at the carbon atom alpha to the carbonyl carbon of the acid functional group in the bile acid from which it is derived. For

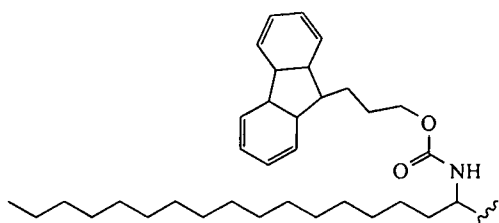
example, when T is derived from 2-tetradecanamideoctadecanoic acid, the tether is:



In another embodiment, T of Formula I can be derived from 2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)octadecanoic acid. For example, when T is derived from 2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)octadecanoic acid, the tether is:



In yet another embodiment, T of Formula I can be:



It is understood, that the compounds can contain one or more tether moieties.

In certain aspects, the tether moieties are the same. In other embodiments, the tether moieties are different.

COMPOUNDS (T-L-P)

In a first aspect, the GPCR Compound of the invention is represented by Formula I:

T-L-P,

or pharmaceutically acceptable salts thereof, wherein:

P is a peptide comprising at least three contiguous amino-acid residues of an intracellular i1, i2, i3 loop or an intracellular i4 domain of the CRF1 receptor;

L is a linking moiety represented by C(O) and bonded to P at an N terminal nitrogen of an N-terminal amino-acid residue;

and T is a lipophilic tether moiety bonded to L, wherein the C-terminal amino acid residue of P is optionally functionalized.

In a second aspect, P comprises at least six contiguous amino acid residues.

In a third aspect, P comprises at least 3 contiguous amino acids of the i1 loop.

In a specific embodiment of the third aspect, P is derived from the i1 loop and is

represented by the following structural formula or pharmaceutically acceptable salts thereof

$X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}-X_{19}-R_1$

wherein:

X_1 is absent or a valine residue;

X_2 is absent or a leucine or glycine residue;

X_3 is absent or a phenylalanine or serine residue;

X_4 is absent or a leucine or glycine residue;

X_5 is absent or an arginine residue;

X_6 is absent or a leucine or isoleucine residue;

X_7 is absent or an arginine residue;

X_8 is absent or a serine residue;

X_9 is absent or an isoleucine residue;

X_{10} is absent or an arginine residue;

X_{11} is absent or a cysteine or serine residue;

X_{12} is absent or a leucine residue;

X_{13} is absent or an arginine residue;

X_{14} is absent or an asparagine residue;

X_{15} is absent or an isoleucine residue;

X₁₆ is absent or an isoleucine residue;

X₁₇ is absent or a histidine residue;

X₁₈ is absent or tryptophan residue;

X₁₉ is absent or an asparagine residue; provided that at least five of X₁-X₁₉ are present;

R₁ is OR₂ or N(R₂)₂;

each R₂ is independently hydrogen or (C₁-C₁₀)alkyl; and

from 0 to 5 amino acid residues are present in the D configuration.

10 In a specific embodiment, at least four of X₇, X₈, X₉, X₁₀, X₁₁, X₁₂, X₁₃ and X₁₄ are present.

In a further specific embodiment,

X₇ is an arginine residue;

X₈ is a serine residue;

15 X₉ is an isoleucine residue; and

X₁₀ is an arginine residue.

In another further specific embodiment,

X₁₁ is a cysteine or serine residue;

X₁₂ is a leucine residue;

20 X₁₃ is an arginine residue; and

X₁₄ is an asparagine residue.

In another further specific embodiment, X₁₁ is a cysteine residue. Alternatively, wherein X₁₁ is a serine residue.

In another specific embodiment,

25 X₁₄ is an asparagine residue;

X₁₅ is an isoleucine residue;

X₁₆ is an isoleucine residue; and

X₁₇ is a histidine residue.

30 In a specific embodiment of the third aspect, the i1 loop of the CRF1 receptor from which P is derived has the following sequence: VLFLRLRSIRCLRNIHWN (SEQ ID NO: 1).

In another embodiment of the third aspect, P is a sequence selected from:

	VLFLRLRSIRCLRNIHWN	(SEQ ID NO: 1);
	VLFLRLRSIRCLRNIHW	(SEQ ID NO: 2);
	GSGRLRSIRSLRNIIHWN	(SEQ ID NO: 3);
5	VLFLRLRSIRCLRNIH	(SEQ ID NO: 4);
	FLRLRSIRCLRNIHWN	(SEQ ID NO: 5);
	GSGRLRSIRSLRNIIH	(SEQ ID NO: 6);
	LFIRIRSIRSLRNIIH	(SEQ ID NO: 7);
	VLFLRLRSIRCLRNIH	(SEQ ID NO: 8);
10	RLRSIRCLRNIHWN	(SEQ ID NO: 9);
	RLRSIRSLRNIIHWN	(SEQ ID NO: 10);
	VLFLRLRSIRCLRNI	(SEQ ID NO: 11);
	VLFLRLRSIRCLRNI	(SEQ ID NO: 12);
	RLRSIRSLRNIIH	(SEQ ID NO: 13);
15	RSIRSLRNIIHWN	(SEQ ID NO: 14);
	VLFLRLRSIRCLR	(SEQ ID NO: 15);
	RSIRCLRNIHW	(SEQ ID NO: 16);
	RSIRSLRNIIH	(SEQ ID NO: 17);
	RSIRCLRNIH	(SEQ ID NO: 18);
20	RLRSIRSLRN	(SEQ ID NO: 19);
	RSLRNIIHWN	(SEQ ID NO: 20);
	RLRSIRSLR	(SEQ ID NO: 21);
	RSLRNIIH	(SEQ ID NO: 22); and
	RSIRSLRN	(SEQ ID NO: 23).

25

In a fourth aspect, P comprises at least 3 contiguous amino acids of the i2 loop.

In a specific embodiment of the fourth aspect, P derived from the i2 loop and is represented by the following structural formula or a pharmaceutically acceptable salt thereof

$Y_1-Y_2-Y_3-Y_4-Y_5-Y_6-Y_7-Y_8-Y_9-Y_{10}-Y_{11}-Y_{12}-Y_{13}-Y_{14}-Y_{15}-Y_{16}-Y_{17}-Y_{18}-Y_{19}-R_1$,

30

wherein:

Y_1 is absent or a histidine residue;

Y_2 is absent or a threonine residue;

Y_3 is absent or an alanine residue;

Y_4 is absent or an isoleucine or a glycine residue;

Y_5 is absent or a valine or serine residue;

Y_6 is absent or a leucine or glycine residue;

5 Y_7 is absent or a threonine or serine residue;

Y_8 is absent or a tyrosine or glycine residue;

Y_9 is absent or serine, threonine or glycine residue;

Y_{10} is absent or a threonine, serine, tyrosine, glycine or alanine residue;

Y_{11} is absent or an aspartic acid, alanine, serine or glycine residue;

10 Y_{12} is absent or an arginine or alanine residue;

Y_{13} is absent or a leucine or an alanine residue;

Y_{14} is absent or an arginine or alanine residue;

Y_{15} is absent or a lysine or an alanine residue;

Y_{16} is absent or a tryptophan, methionine or an alanine residue;

15 Y_{17} is absent or a methionine, norleucine, phenylalanine or an alanine residue;

Y_{18} is absent or a phenylalanine, isoleucine or an alanine residue;

Y_{19} is absent or an isoleucine or alanine residue, provided that at least five of Y_1 - Y_{19} , are present; and

R_1 is OR_2 or $N(R_2)_2$;

20 each R_2 is independently hydrogen or (C_1-C_{10}) alkyl; and

from 0 to 5 amino acid residues are present in the D configuration.

It is understood that when P is described as Y_1 - Y_{19} it is bonded to L as written. For example, Y_1 is bonded to L. If Y_1 is absent, then Y_2 is bonded to L.

25 In a specific embodiment, at least three of Y_7 , Y_8 , Y_9 , Y_{10} , Y_{11} , Y_{12} , Y_{13} , Y_{14} , Y_{15} , Y_{16} , Y_{17} , Y_{18} and Y_{19} are present.

In a further specific embodiment,

Y_9 is serine, threonine or glycine residue;

30 Y_{10} is a threonine, serine, tyrosine, glycine or alanine residue; and

Y_{11} is an aspartic acid, alanine, serine or glycine residue.

In another further specific embodiment,

Y₁₂ is an arginine or alanine residue;

Y₁₃ is a leucine or an alanine residue; and

Y₁₄ is an arginine or alanine residue.

5

In a further specific embodiment,

Y₉ is serine, threonine or glycine residue;

Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;

Y₁₁ is an aspartic acid, alanine, serine or glycine residue; and

10 Y₁₂ is an arginine or alanine residue.

In a further specific embodiment,

Y₁₁ is an aspartic acid, alanine, serine or glycine residue;

Y₁₂ is an arginine or alanine residue;

15 Y₁₃ is a leucine or an alanine residue; and

Y₁₄ is an arginine or alanine residue.

In a further specific embodiment,

Y₉ is serine, threonine or glycine residue;

20 Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;

Y₁₁ is an aspartic acid, alanine, serine or glycine residue;

Y₁₂ is an arginine or alanine residue; and

Y₁₃ is a leucine or an alanine residue.

25 In a further specific embodiment,

Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;

Y₁₁ is an aspartic acid, alanine, serine or glycine residue;

Y₁₂ is an arginine or alanine residue;

Y₁₃ is a leucine or an alanine residue; and

30 Y₁₄ is an arginine or alanine residue.

In yet another further specific embodiment,

Y₉ is serine, threonine or glycine residue;

Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;

Y₁₁ is an aspartic acid, alanine, serine or glycine residue;

5 Y₁₂ is an arginine or alanine residue;

Y₁₃ is a leucine or an alanine residue; and

Y₁₄ is an arginine or alanine residue.

In yet another further specific embodiment,

10 Y₉ is serine residue;

Y₁₀ is a threonine residue;

Y₁₁ is an aspartic acid residue;

Y₁₂ is an arginine residue;

Y₁₃ is a leucine residue; and

15 Y₁₄ is an arginine residue.

In a specific embodiment,

Y₇ is a threonine or serine residue;

Y₈ is a tyrosine or glycine residue;

20 Y₉ is a serine, threonine or glycine residue; and

Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue.

In another specific embodiment,

Y₇ is a threonine residue;

25 Y₈ is a tyrosine residue;

Y₉ is a serine residue; and

Y₁₀ is a threonine residue.

In a further specific embodiment, Y₁₁ is an aspartic acid, alanine, serine or glycine
30 residue. Specifically, Y₁₁ is an aspartic acid residue.

In another specific embodiment,

Y₁₂ is an arginine or alanine residue;

Y₁₃ is or a leucine or an alanine residue;

Y₁₄ is an arginine or alanine residue; and

5 Y₁₅ is a lysine or an alanine residue.

In another specific embodiment, one of Y₁₂, Y₁₃, Y₁₄, and Y₁₅ is an alanine residue, provided that the other three of Y₁₂, Y₁₃, Y₁₄, and Y₁₅ are not an alanine residue.

10 In another specific embodiment,

Y₁₂ is an arginine residue;

Y₁₃ is a leucine residue;

Y₁₄ is an arginine residue; and

Y₁₅ is a lysine residue.

15 In a further specific embodiment, Y₁₆ is a tryptophan, methionine or an alanine residue. Specifically, Y₁₆ is a tryptophan residue. Alternatively, Y₁₆ is a methionine residue.

In another specific embodiment,

Y₁₅ is a lysine or an alanine residue;

20 Y₁₆ is a tryptophan, methionine or an alanine residue;

Y₁₇ is a methionine, norleucine, phenylalanine or an alanine residue; and

Y₁₈ is a phenylalanine, isoleucine or an alanine residue.

25 In another specific embodiment, one of Y₁₅, Y₁₆, Y₁₇, and Y₁₈ is an alanine residue, provided that the other three of Y₁₅, Y₁₆, Y₁₇, and Y₁₈ are not an alanine residue.

In another specific embodiment,

Y₁₅ is a lysine residue;

Y₁₆ is a tryptophan or methionine residue;

30 Y₁₇ is a methionine, norleucine, or phenylalanine residue; and

Y₁₈ is a phenylalanine or isoleucine residue.

In another specific embodiment,

Y₁₅ is a lysine residue;

Y₁₆ is a tryptophan residue;

Y₁₇ is a methionine residue; and

5 Y₁₈ is a phenylalanine residue.

In another specific embodiment, Y₁₉ is an isoleucine or alanine residue. Specifically, Y₁₉ is an isoleucine residue.

10 In a specific embodiment of the fourth aspect, the i2 loop of the CRF1 receptor from which P is derived has the following sequence: HTAIVLTYSTDRLRKWMFI (SEQ ID NO: 24).

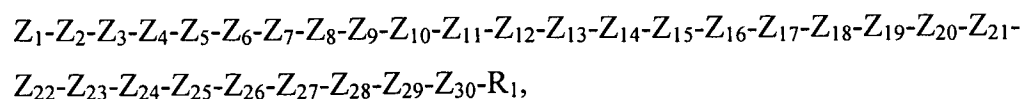
In another embodiment of the fourth aspect, P is a sequence selected from:

	HTAIVLTYSTDRLRKWMFI	(SEQ ID NO: 24);
	HTAIVLTYSTDRLRKWM	(SEQ ID NO: 25);
15	AIVLTYSTDRLRKWMFI	(SEQ ID NO: 26);
	GSGTYSTDRLRKWMFI	(SEQ ID NO: 27);
	HTAIVLTYSTDRLRK	(SEQ ID NO: 28);
	GSGTYSTDRLRKWMF	(SEQ ID NO: 29);
	VLTYSTDRLRKWMFI	(SEQ ID NO: 30);
20	HTAIVLTYSTDRLR	(SEQ ID NO: 31);
	LTYSTDLRKWMFI	(SEQ ID NO: 32);
	TYSTDRLRKWMFI	(SEQ ID NO: 33);
	HTAIVLTYSDR	(SEQ ID NO: 34);
	GSGTYDRLRKWM	(SEQ ID NO: 35);
25	GSGTYSTDRLRK	(SEQ ID NO: 36);
	GSTDRLRKWMFI	(SEQ ID NO: 37);
	GSTDRLRKWMFA	(SEQ ID NO: 38);
	GSTDRLRKWMAI	(SEQ ID NO: 39);
	GSTDRLRKWAFI	(SEQ ID NO: 40);
30	GSTDRLRKAMFI	(SEQ ID NO: 41);
	GSTDRLRKAXFI	(SEQ ID NO: 42);
	YSTDRLRKWMFI	(SEQ ID NO: 43);

	GSTDRLRKMF	(SEQ ID NO: 44);
	GSGRLRKWMFI	(SEQ ID NO: 45);
	STDRLRKWMFI	(SEQ ID NO: 46);
	YSTDRLRKWMF	(SEQ ID NO: 47);
5	STDRLRKWMF	(SEQ ID NO: 48);
	ADRLRKWMFI	(SEQ ID NO: 49);
	GSRLRKWMFI	(SEQ ID NO: 50);
	TDRLRKWMFI	(SEQ ID NO: 51);
	TDRLRKWXFI	(SEQ ID NO: 52);
10	TARLRKWMFI	(SEQ ID NO: 53);
	TDALRKWMFI	(SEQ ID NO: 54);
	TDRARKWMFI	(SEQ ID NO: 55);
	TDRLAKWMFI	(SEQ ID NO: 56);
	TDRLRAWMFI	(SEQ ID NO: 57);
15	TDRLRKAMFI	(SEQ ID NO: 58);
	TDRLRKWAFI	(SEQ ID NO: 59);
	TDRLRKWMAI	(SEQ ID NO: 60);
	TDRLRKWMFA	(SEQ ID NO: 61);
	TYSTDRLRK	(SEQ ID NO: 62);
20	STDRLRKMF	(SEQ ID NO: 63);
	GSGRLRKWM	(SEQ ID NO: 64);
	GRLRKWMFI	(SEQ ID NO: 65);
	DRLRKWMFI	(SEQ ID NO: 66);
	DRLRKWMAI	(SEQ ID NO: 67);
25	GSTDRLRK	(SEQ ID NO: 68);
	RLRKWMFI	(SEQ ID NO: 69); and
	RLRKWMAI	(SEQ ID NO: 70).

In a fifth aspect, P comprises at least 3 contiguous amino acids of the i3 loop.

In a specific embodiment of the fifth aspect, P is derived from the i3 loop and is
 30 represented by the following structural formula or a pharmaceutically acceptable salt thereof:



wherein :

Z₁ is absent or a phenylalanine residue;

Z₂ is absent or an asparagine residue;

Z₃ is absent or an isoleucine residue;

5 Z₄ is absent or a valine residue;

Z₅ is absent or an arginine residue;

Z₆ is absent or an isoleucine residue;

Z₇ is absent or a leucine residue;

Z₈ is absent or a methionine residue;

10 Z₉ is absent or a threonine residue;

Z₁₀ is absent or a lysine residue;

Z₁₁ is absent or a leucine residue;

Z₁₂ is absent or an arginine residue;

Z₁₃ is absent or an alanine residue;

15 Z₁₄ is absent or a serine residue;

Z₁₅ is absent or a threonine residue;

Z₁₆ is absent or a threonine residue;

Z₁₇ is absent or a serine residue;

Z₁₈ is absent or a glutamic acid residue;

20 Z₁₉ is absent or a threonine residue;

Z₂₀ is absent or an isoleucine residue;

Z₂₁ is absent or a glutamine residue;

Z₂₂ is absent or a tyrosine residue;

Z₂₃ is absent or an arginine residue;

25 Z₂₄ is absent or a lysine residue;

Z₂₅ is absent or an alanine residue;

Z₂₆ is absent or a valine residue;

Z₂₇ is absent or a lysine residue;

Z₂₈ is absent or an alanine or serine residue;

30 Z₂₉ is absent or a threonine residue; and

Z₃₀ is absent or a leucine residue;

provided that at least five of Z₁-Z₃₀ are present;

R_1 is OR_2 or $N(R_2)_2$;

each R_2 is independently hydrogen or (C_1-C_{10}) alkyl; and

from 0 to 5 amino acid residues are present in the D configuration.

In a specific embodiment, at least three of Z_5 , Z_6 , Z_7 , Z_8 , and Z_9 are present.

5 In a further specific embodiment,

Z_5 is an arginine residue;

Z_6 is an isoleucine residue; and

Z_7 is a leucine residue.

10 In another further specific embodiment,

Z_7 is a leucine residue;

Z_8 is a methionine residue; and

Z_9 is a threonine residue.

15 In a another specific embodiment,

Z_5 is an arginine residue;

Z_6 is an isoleucine residue;

Z_7 is a leucine residue; and

Z_8 is a methionine residue.

20

In a another specific embodiment,

Z_6 is an isoleucine residue;

Z_7 is a leucine residue;

Z_8 is absent or a methionine residue; and

25

Z_9 is a threonine residue.

In a another specific embodiment,

Z_5 is an arginine residue;

Z_6 is an isoleucine residue;

30

Z_7 is a leucine residue;

Z_8 is a methionine residue; and

Z_9 is a threonine residue.

In yet another specific embodiment, at least three of Z_{10} , Z_{11} , Z_{12} , and Z_{13} are present.

In a another specific embodiment,

Z_{10} is a lysine residue;

5 Z_{11} is a leucine residue; and

Z_{12} is an arginine residue.

In a another specific embodiment,

Z_{11} is a leucine residue;

Z_{12} is an arginine residue; and

10 Z_{13} is an alanine residue.

In yet another specific embodiment,

Z_{10} is a lysine residue;

Z_{11} is a leucine residue;

15 Z_{12} is an arginine residue; and

Z_{13} is an alanine residue.

In another specific embodiment, at least three of Z_{14} , Z_{15} , Z_{16} , and Z_{17} are present.

20 In another specific embodiment,

Z_{14} is a serine residue;

Z_{15} is a threonine residue; and

Z_{16} is a threonine residue.

25 In another specific embodiment,

Z_{15} is a threonine residue;

Z_{16} is a threonine residue; and

Z_{17} is a serine residue;

30 In another specific embodiment,

Z_{14} is a serine residue;

Z_{15} is a threonine residue;

Z₁₆ is a threonine residue; and
Z₁₇ is a serine residue;

In another specific embodiment, at least three of Z₁₉, Z₂₀, Z₂₁, Z₂₂, and Z₂₃ are present.

5

In another specific embodiment,
Z₁₉ is a threonine residue;
Z₂₀ is an isoleucine residue; and
Z₂₁ is a glutamine residue.

10

In another specific embodiment,
Z₂₁ is a glutamine residue;
Z₂₂ is a tyrosine residue; and
Z₂₃ is an arginine residue.

15

In another specific embodiment,
Z₁₉ is a threonine residue;
Z₂₀ is an isoleucine residue;
Z₂₁ is a glutamine residue; and
Z₂₂ is a tyrosine residue.

20

In another specific embodiment,
Z₂₀ is an isoleucine residue;
Z₂₁ is a glutamine residue;
Z₂₂ is a tyrosine residue; and
Z₂₃ is an arginine residue.

25

In another specific embodiment,
Z₁₉ is a threonine residue;
Z₂₀ is an isoleucine residue;
Z₂₁ is a glutamine residue;
Z₂₂ is a tyrosine residue; and

30

Z₂₃ is an arginine residue.

In another specific embodiment, at least three of Z₂₄, Z₂₅, Z₂₆, Z₂₇, and Z₂₈ are present.

In another specific embodiment,

5

Z₂₄ is a lysine residue;

Z₂₅ is an alanine residue; and

Z₂₆ is a valine residue.

In another specific embodiment,

Z₂₆ is a valine residue;

10

Z₂₇ is a lysine residue; and

Z₂₈ is an alanine or serine residue.

In another specific embodiment,

Z₂₄ is a lysine residue;

15

Z₂₅ is an alanine residue;

Z₂₆ is a valine residue; and

Z₂₇ is a lysine residue.

In another specific embodiment,

20

Z₂₅ is an alanine residue;

Z₂₆ is a valine residue;

Z₂₇ is a lysine residue; and

Z₂₈ is an alanine or serine residue.

25

In another specific embodiment,

Z₂₄ is a lysine residue;

Z₂₅ is an alanine residue;

Z₂₆ is a valine residue;

Z₂₇ is a lysine residue; and

30

Z₂₈ is an alanine or serine residue. Specifically, Z₂₈ is an alanine residue.

In a specific embodiment of the fifth aspect, the i3 loop of the CRF1 receptor from which P is derived has the following sequence: FNIVRILMTKLRAS TTSETIQYRKAVKA (SEQ ID NO: 71).

In another embodiment of the fifth aspect, P is a sequence selected from:

5	FNIVRILMTKLRAS TTSETIQYRKAVKA	(SEQ ID NO: 71);
	IVRILMTKLRAS TTSETIQYRKAVKA	(SEQ ID NO: 72);
	FNIVRILMTKLRAS TTSETIQYRKAV	(SEQ ID NO: 73);
	RILMTKLRAS TTSETIQYRKAVKA	(SEQ ID NO: 74);
	FNIVRILMTKLRAS TTSETIQYRK	(SEQ ID NO: 75);
10	FNIVRILMTKLRAS TTSETIQYR	(SEQ ID NO: 76);
	LMTKLRAS TTSETIQYRKAVKA	(SEQ ID NO: 77);
	FNIVRILMTKLRAS TTSETIQY	(SEQ ID NO: 78);
	TKLRAS TTSETIQYRKAVKA	(SEQ ID NO: 79);
	LMTKLRAS TTSETIQYRKAV	(SEQ ID NO: 80);
15	LRAS TTSETIQYRKAVKA	(SEQ ID NO: 81);
	LMTKLRAS TTSETIQYRK	(SEQ ID NO: 82);
	LMTKLRAS TTSETIQYR	(SEQ ID NO: 83);
	ASTTSETIQYRKAVKA	(SEQ ID NO: 84);
	ASTTSETIQYRKAVKS	(SEQ ID NO: 85);
20	LMTKLRAS TTSETIQ	(SEQ ID NO: 86);
	SETIQYRKAVKATL	(SEQ ID NO: 87);
	LMTKLRAS TTSETI	(SEQ ID NO: 88);
	RILMTKLRAS TTS	(SEQ ID NO: 89);
	SETIQYRKAVKA	(SEQ ID NO: 90);
25	TKLRAS TTSETI	(SEQ ID NO: 91);
	ASTTSETIQYR	(SEQ ID NO: 92);
	TKLRAS TTSET	(SEQ ID NO: 93);
	KLRAS TTSETI	(SEQ ID NO: 94);
	TIQYRKAVKA	(SEQ ID NO: 95);
30	KLRAS TTSET	(SEQ ID NO: 96);
	RILMTKLRA	(SEQ ID NO: 97); and
	KLRAS TTSE	(SEQ ID NO: 98).

In a sixth aspect, P comprises at least 3 contiguous amino acids of the i4 domain.

In a specific embodiment of the sixth aspect, P derived from the i4 domain and is represented by the following structural formula or a pharmaceutically acceptable salt thereof,

5 M₁-M₂-M₃-M₄-M₅-M₆-M₇-M₈-M₉-M₁₀-M₁₁-M₁₂-M₁₃-M₁₄- M₁₅-M₁₆-M₁₇-M₁₈-M₁₉-
M₂₀-M₂₁-M₂₂-M₂₃-M₂₄-M₂₅-M₂₆-M₂₇-M₂₈- M₂₉-M₃₀-M₃₁-M₃₂-M₃₃-M₃₄- M₃₅-M₃₆-M₃₇-
M₃₈-M₃₉-M₄₀-M₄₁-M₄₂-M₄₃-M₄₄-M₄₅-M₄₆-M₄₇-R₁,

wherein:

M₁ is absent or a glutamic acid residue;

10 M₂ is absent or a valine residue;

M₃ is absent or an arginine residue;

M₄ is absent or a serine residue;

M₅ is absent or an alanine residue;

M₆ is absent or an isoleucine residue;

15 M₇ is absent or an arginine residue;

M₈ is absent or a lysine residue;

M₉ is absent or an arginine residue;

M₁₀ is absent or a tryptophan residue;

M₁₁ is absent or a histidine residue;

20 M₁₂ is absent or an arginine residue;

M₁₃ is absent or a tryptophan residue;

M₁₄ is absent or a glutamine residue;

M₁₅ is absent or an aspartic acid residue;

M₁₆ is absent or a lysine residue;

25 M₁₇ is absent or a histidine or glycine residue;

M₁₈ is absent or a serine residue;

M₁₉ is absent or an isoleucine residue;

M₂₀ is absent or an arginine residue;

M₂₁ is absent or an alanine residue;

30 M₂₂ is absent or an arginine residue;

M₂₃ is absent or a valine residue;

M₂₄ is absent or an alanine residue;

M₂₅ is absent or an arginine residue;

M₂₆ is absent or an alanine residue;

M₂₇ is absent or a methionine residue;

M₂₈ is absent or a serine residue;

5 M₂₉ is absent or an isoleucine residue;

M₃₀ is absent or a proline residue;

M₃₁ is absent or a threonine residue;

M₃₂ is absent or a serine residue;

M₃₃ is absent or a proline residue;

10 M₃₄ is absent or a threonine residue;

M₃₅ is absent or an arginine residue;

M₃₆ is absent or a valine residue;

M₃₇ is absent or a serine residue;

M₃₈ is absent or a phenylalanine residue;

15 M₃₉ is absent or a histidine residue;

M₄₀ is absent or a serine residue;

M₄₁ is absent or an isoleucine residue;

M₄₂ is absent or a lysine residue;

M₄₃ is absent or a glutamine residue;

20 M₄₄ is absent or a serine residue;

M₄₅ is absent or a threonine residue;

M₄₆ is absent or an alanine residue; and

M₄₇ is absent or a valine residue; provided that at least five of M₁-M₄₇ are present;

R₁ is OR₂ or N(R₂)₂;

25 each R₂ is independently hydrogen or (C₁-C₁₀)alkyl; and

from 0 to 5 amino acid residues are present in the D configuration.

It is understood that when P is described as M₁-M₄₇ it is bonded to L as written. For example, M₁ is bonded to L. If M₁ is absent, then M₂ is bonded to L.

30 In a specific embodiment, at least three of M₂-M₇ are present.

In another specific embodiment,

M₂ is a valine residue;
M₃ is an arginine residue; and
M₄ is a serine residue.

5 In another specific embodiment,
M₅ is an alanine residue;
M₆ is an isoleucine residue; and
M₇ is an arginine residue.

10 In another specific embodiment,
M₂ is a valine residue;
M₃ is an arginine residue;
M₄ is a serine residue; and
M₅ is an alanine residue.

15 In another specific embodiment,
M₄ is a serine residue;
M₅ is an alanine residue;
M₆ is an isoleucine residue; and
20 M₇ is an arginine residue.

In another specific embodiment,
M₂ is a valine residue;
M₃ is an arginine residue;
25 M₄ is a serine residue;
M₅ is an alanine residue;
M₆ is an isoleucine residue.

30 In another specific embodiment,
M₃ is an arginine residue;
M₄ is a serine residue;
M₅ is an alanine residue;

M₆ is an isoleucine residue; and
M₇ is an arginine residue.

In another specific embodiment,

5

M₂ is a valine residue;

M₃ is an arginine residue;

M₄ is a serine residue;

M₅ is an alanine residue;

M₆ is an isoleucine residue; and

10

M₇ is an arginine residue.

In another specific embodiment, at least three of M₉-M₁₃ are present.

In another specific embodiment,

M₉ is an arginine residue;

M₁₀ is a tryptophan residue;

15

M₁₁ is a histidine residue;

M₁₂ is an arginine residue.

In another specific embodiment,

M₁₀ is a tryptophan residue;

20

M₁₁ is a histidine residue;

M₁₂ is an arginine residue; and

M₁₃ is a tryptophan residue.

In another specific embodiment,

M₉ is an arginine residue;

25

M₁₀ is a tryptophan residue;

M₁₁ is a histidine residue;

M₁₂ is an arginine residue; and

M₁₃ is a tryptophan residue.

30

In another specific embodiment, at least three of M₁₈-M₂₂ are present.

In another specific embodiment,

M₁₈ is a serine residue;
M₁₉ is an isoleucine residue;
M₂₀ is an arginine residue; and
M₂₁ is an alanine residue.

5

In another specific embodiment,
M₁₉ is an isoleucine residue;
M₂₀ is an arginine residue;
M₂₁ is an alanine residue; and
M₂₂ is an arginine residue.

10

In another specific embodiment,
M₁₈ is a serine residue;
M₁₉ is an isoleucine residue;
M₂₀ is an arginine residue;
M₂₁ is an alanine residue; and
M₂₂ is an arginine residue.

15

In another specific embodiment, at least three of M₂₃-M₂₇ are present.

20

In another specific embodiment,
M₂₃ is a valine residue;
M₂₄ is an alanine residue;
M₂₅ is an arginine residue; and
M₂₆ is an alanine residue.

25

In another specific embodiment,
M₂₄ is an alanine residue;
M₂₅ is an arginine residue;
M₂₆ is an alanine residue;
M₂₇ is a methionine residue.

30

In another specific embodiment,

M₂₃ is a valine residue;

M₂₄ is an alanine residue;

M₂₅ is an arginine residue;

5 M₂₆ is an alanine residue;

M₂₇ is a methionine residue.

In another specific embodiment, at least three of M₂₅-M₂₉ are present.

10 In another specific embodiment,

M₂₅ is an arginine residue;

M₂₆ is an alanine residue;

M₂₇ is a methionine residue; and

M₂₈ is a serine residue.

15

In another specific embodiment,

M₂₆ is an alanine residue;

M₂₇ is a methionine residue;

M₂₈ is a serine residue; and

20 M₂₉ is an isoleucine residue.

In another specific embodiment,

M₂₅ is an arginine residue;

M₂₆ is an alanine residue;

25 M₂₇ is a methionine residue;

M₂₈ is a serine residue; and

M₂₉ is an isoleucine residue.

In another specific embodiment, at least three of M₃₂-M₃₆ are present.

In another specific embodiment,

30 M₃₂ is a serine residue;

M₃₃ is a proline residue;

M₃₄ is a threonine residue; and

M₃₅ is an arginine residue.

In another specific embodiment,

M₃₃ is a proline residue;

M₃₄ is a threonine residue;

5 M₃₅ is an arginine residue; and

M₃₆ is a valine residue.

In another specific embodiment,

M₃₂ is a serine residue;

M₃₃ is a proline residue;

10 M₃₄ is a threonine residue;

M₃₅ is an arginine residue; and

M₃₆ is a valine residue.

In a specific embodiment of the sixth aspect, the i4 domain of the CRF1 receptor from which P is derived has the following sequence:

15 EVRSAIRKRWHRWQDKHSIRARVARAMSIPTSPTRVSFHSIKQSTAV (SEQ ID NO: 99).

In another embodiment of the sixth aspect, P is a sequence selected from:

	RAMSIPTSPTRVSFHSIKQSTAV	(SEQ ID NO: 100);
	HSIRARVARAMSIPTSPTRV	(SEQ ID NO: 101);
20	RWQDKHSIRARVARAMSI	(SEQ ID NO: 102);
	EVRSAIRKRWHRWQD	(SEQ ID NO: 103);
	RWHRWQDKHSIRAR	(SEQ ID NO: 104);
	VRSAIRKRWHRW	(SEQ ID NO: 105); and
	GSIRARVARAM	(SEQ ID NO: 106).

25 In a seventh aspect, T is an optionally substituted (C₆-C₃₀)alkyl, (C₆-C₃₀)alkenyl, (C₆-C₃₀)alkynyl, wherein 0-3 carbon atoms are replaced with oxygen, sulfur, nitrogen or a combination thereof. This value of T is applicable to the first, second, third, fourth, fifth and sixth aspects and the specific (i.e., specific, more specific and most specific) embodiments of

30 same.

In a specific embodiment of the seventh aspect, T is selected from: $\text{CH}_3(\text{CH}_2)_{16}$, $\text{CH}_3(\text{CH}_2)_{15}$, $\text{CH}_3(\text{CH}_2)_{14}$, $\text{CH}_3(\text{CH}_2)_{13}$, $\text{CH}_3(\text{CH}_2)_{12}$, $\text{CH}_3(\text{CH}_2)_{11}$, $\text{CH}_3(\text{CH}_2)_{10}$, $\text{CH}_3(\text{CH}_2)_9$, $\text{CH}_3(\text{CH}_2)_8$, $\text{CH}_3(\text{CH}_2)_9\text{OPh-}$, $\text{CH}_3(\text{CH}_2)_6\text{C}=\text{C}(\text{CH}_2)_6$, $\text{CH}_3(\text{CH}_2)_{11}\text{O}(\text{CH}_2)_3$, and $\text{CH}_3(\text{CH}_2)_9\text{O}(\text{CH}_2)_2$.

5 In another specific embodiment of the seventh aspect, T is a fatty acid derivative.

In a more specific embodiment of the seventh aspect, the fatty acid is selected from the group consisting of: butyric acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, myristoleic acid, palmitoleic acid, oleic acid, linoleic acid, α -linolenic acid, arachidonic acid,
 10 eicosapentaenoic acid, erucic acid, docosahexaenoic acid.

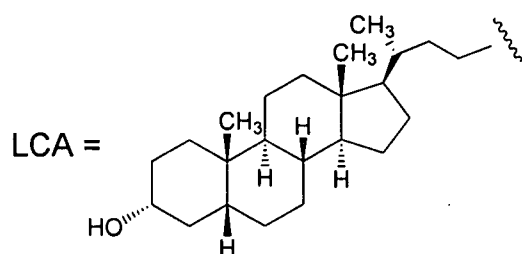
In an eighth aspect, T is a bile acid derivative. This value of T is applicable to the first, second, third, fourth, fifth and sixth aspects and the specific (i.e., specific, more specific and most specific) embodiments of same.

In a specific embodiment of the eighth aspect, the bile acid is selected from the group
 15 consisting of: lithocholic acid, chenodeoxycholic acid, deoxycholic acid, cholanolic acid, cholic acid, ursodeoxycholic acid, ursodeoxycholic acid, isoursodeoxycholic acid, lagodeoxycholic acid, dehydrocholic acid, hyocholic acid, and hyodeoxycholic acid.

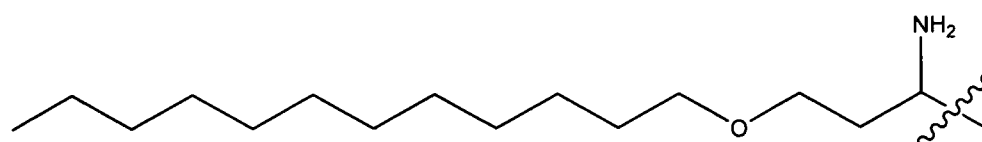
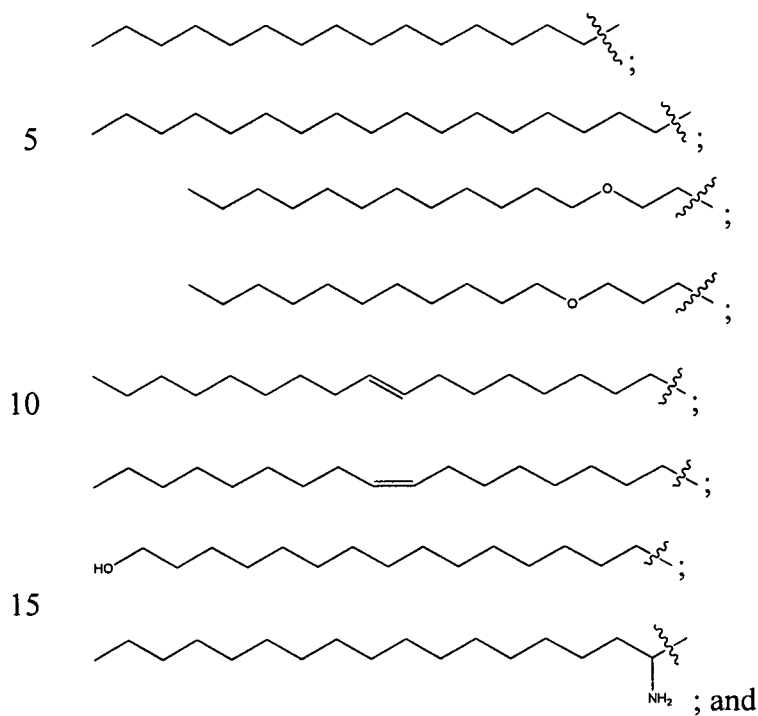
In a ninth aspect, T is selected from sterols; progestagens; glucocorticoids; mineralcorticoids; androgens; and estrogens. This value of T is applicable to the first,
 20 second, third, fourth, fifth and sixth aspects and the specific (i.e., specific, more specific and most specific) embodiments of same.

In a tenth aspect, T-L of Formula I is represented by a moiety selected from the group consisting of:

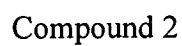
$\text{CH}_3(\text{CH}_2)_{15}-\text{C}(\text{O});$
 25 $\text{CH}_3(\text{CH}_2)_{13}-\text{C}(\text{O});$
 $\text{CH}_3(\text{CH}_2)_9\text{O}(\text{CH}_2)_2\text{C}(\text{O});$
 $\text{CH}_3(\text{CH}_2)_{10}\text{O}(\text{CH}_2)_2\text{C}(\text{O});$
 $\text{CH}_3(\text{CH}_2)_6\text{C}=\text{C}(\text{CH}_2)_6-\text{C}(\text{O});$
 LCA-C(O); and
 30 $\text{CH}_3(\text{CH}_2)_9\text{OPh}-\text{C}(\text{O})$ wherein



In an eleventh aspect, T of Formula I is represented by a moiety selected from the group consisting of:



20 In yet another embodiment, a GPCR compound of the invention is selected from one of the following compounds or a pharmaceutically acceptable salt thereof:

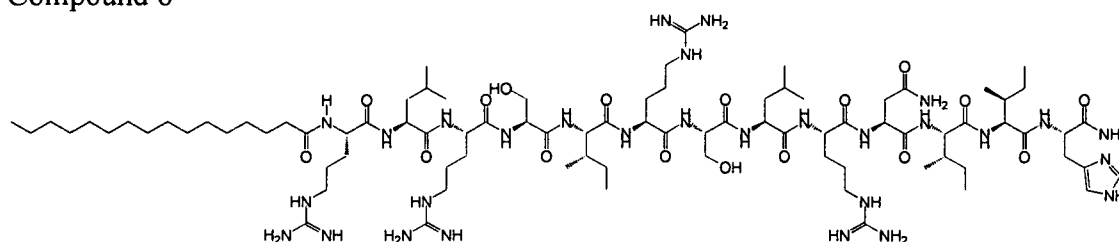
[illegible]

Compound 7

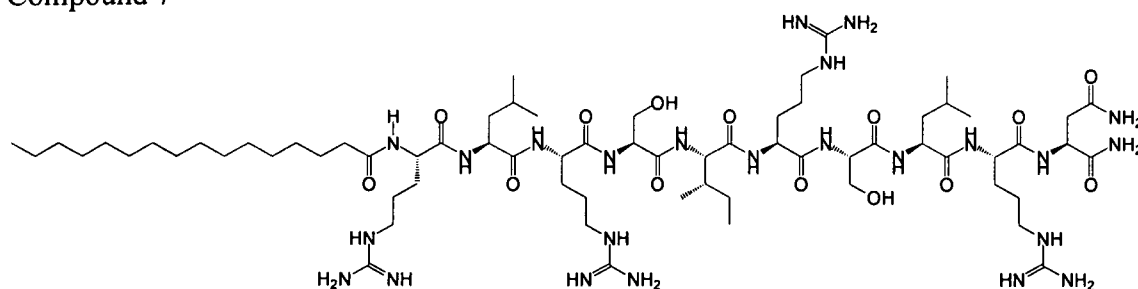
The chemical structure of Compound 7 is a long-chain macrocyclic peptide. It features a backbone of repeating amide bonds. The side chains include a long alkyl chain (C₁₅H₃₁), a benzyl group (C₆H₅CH₂), a hydroxymethyl group (CH₂OH), a guanidino group (CH₂NH-C(=NH)-NH₂), and a triazole ring (1,2,3-triazole). The structure is highly complex and symmetrical, with multiple amide bonds and side chains.

[illegible]

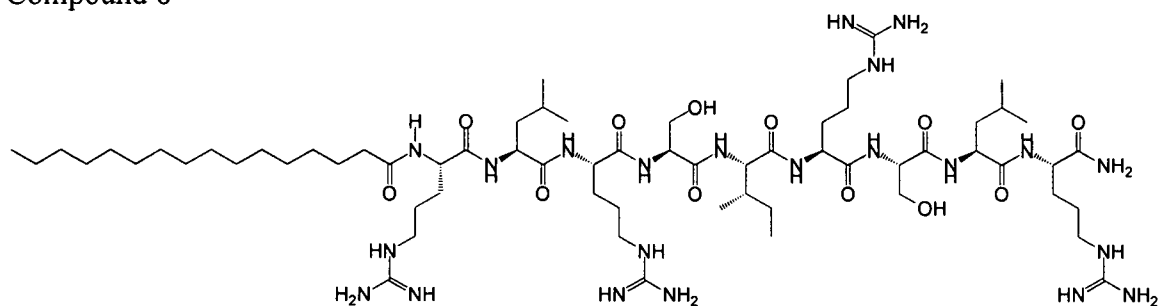
Compound 6



5 Compound 7

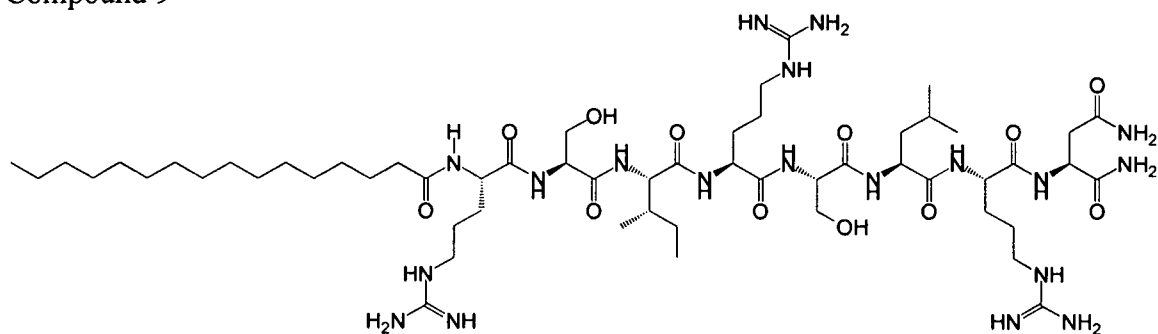


Compound 8

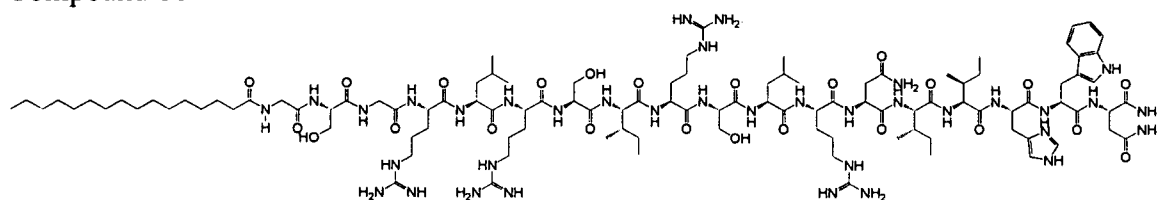


10

Compound 9

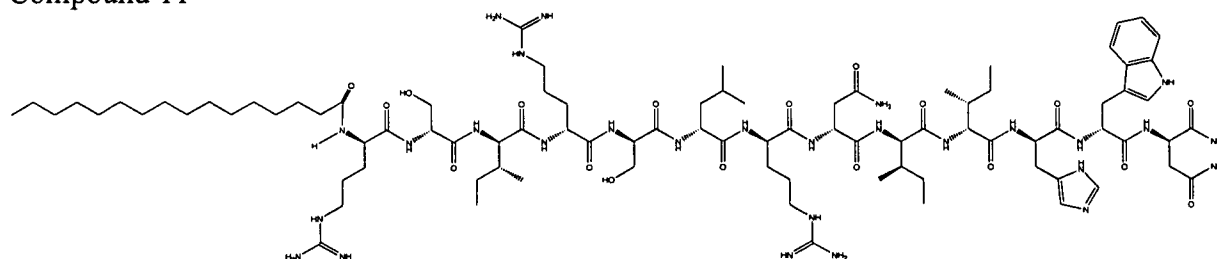
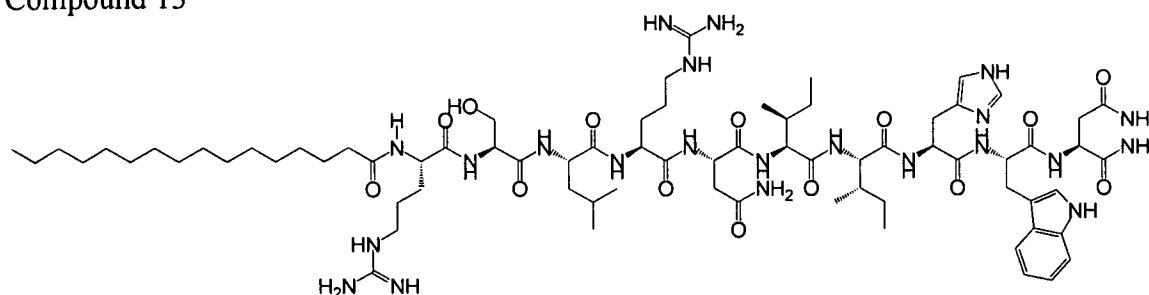


Compound 10



15

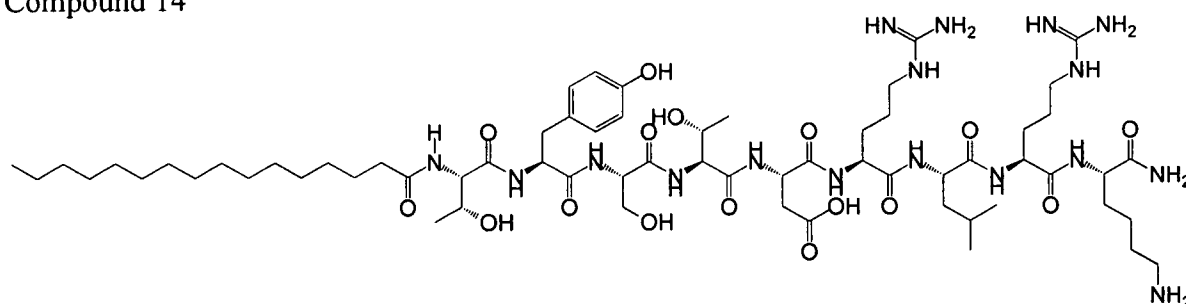
Compound 11

5 and
Compound 13

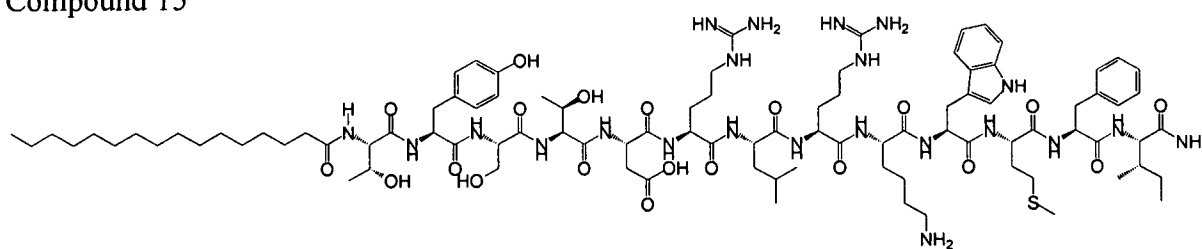
In the above listing of compounds, the structure follows the number identifier.

In yet another embodiment, a GPCR compound of the invention is selected from one
10 of the following compounds or a pharmaceutically acceptable salt thereof:

Compound 14



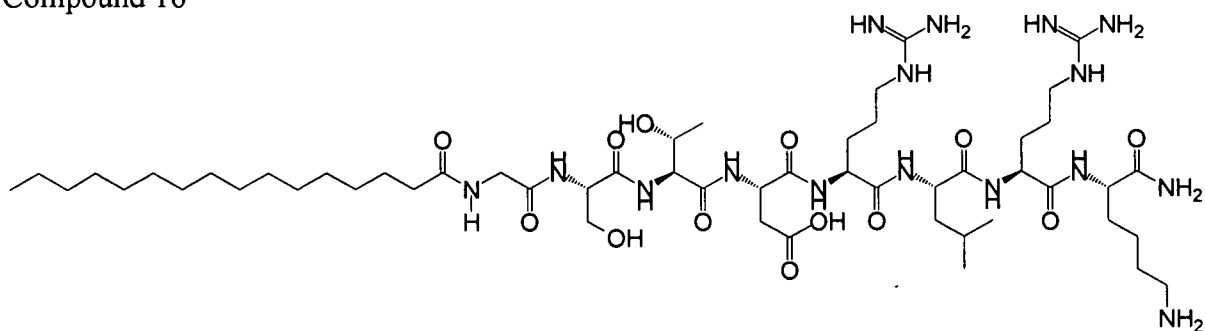
Compound 15



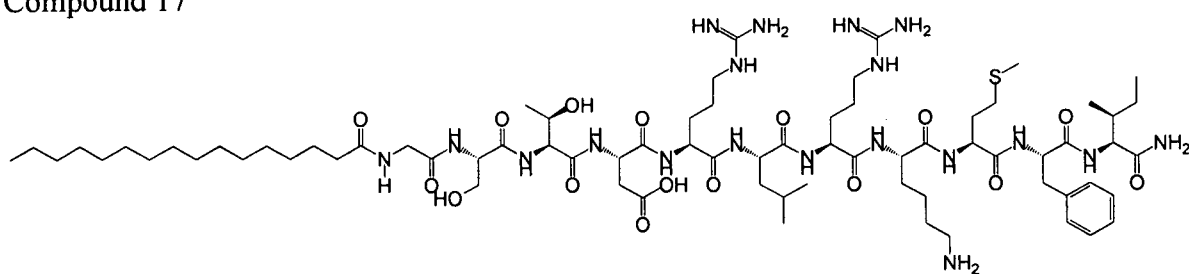
15

20

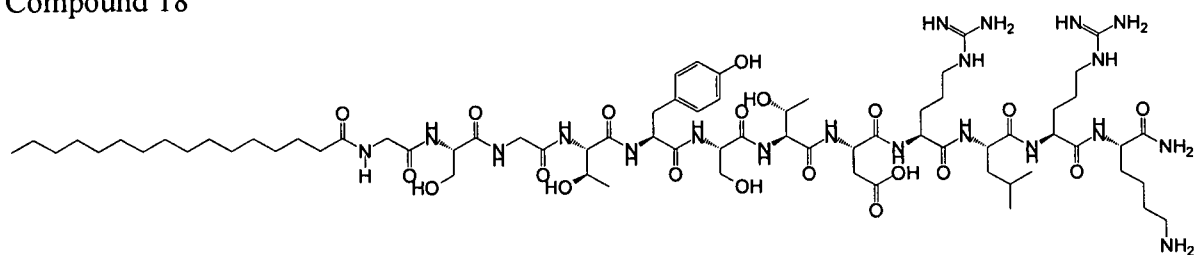
Compound 16



5 Compound 17

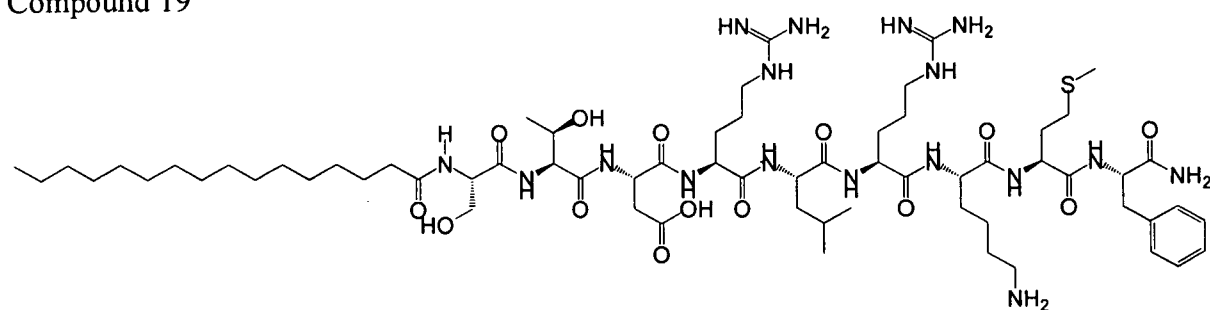


Compound 18



10

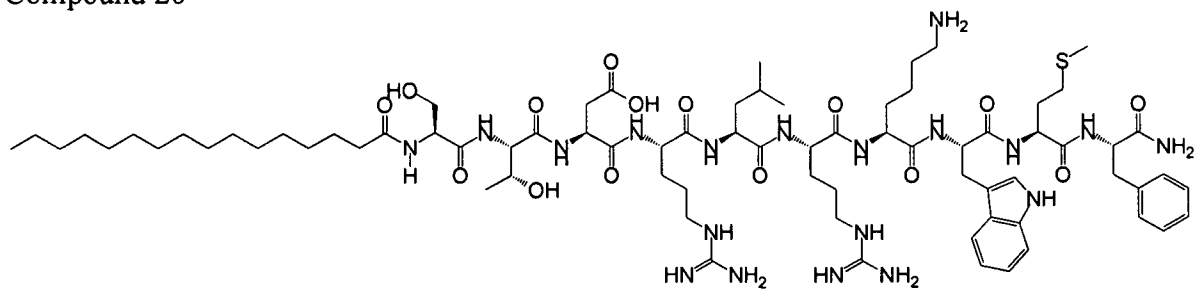
Compound 19



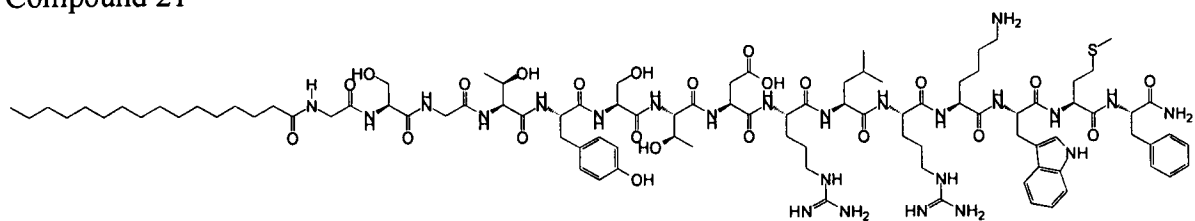
15

20

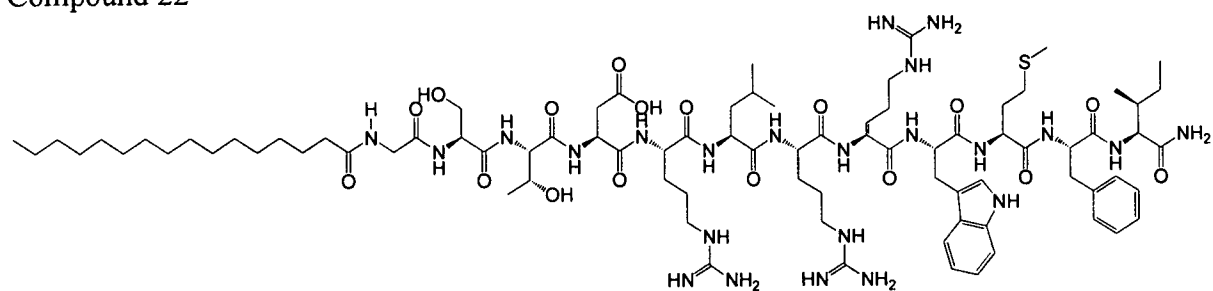
Compound 20



5 Compound 21

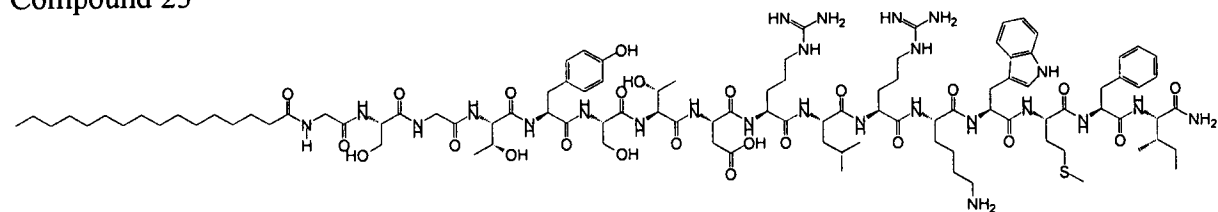


Compound 22



10

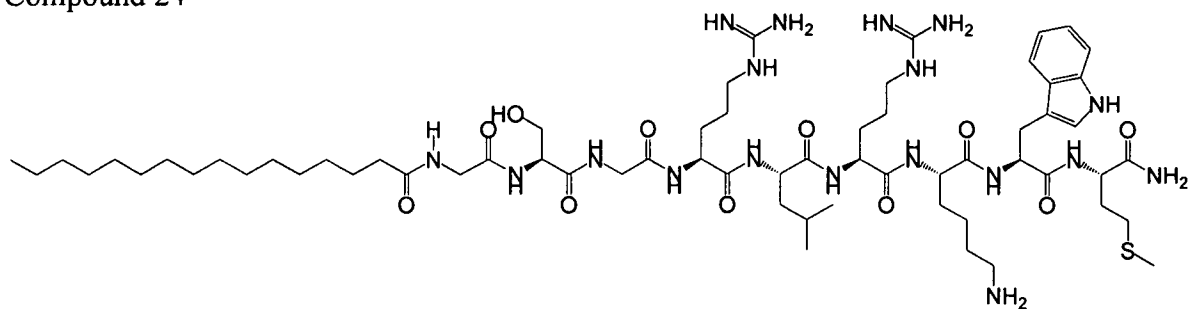
Compound 23



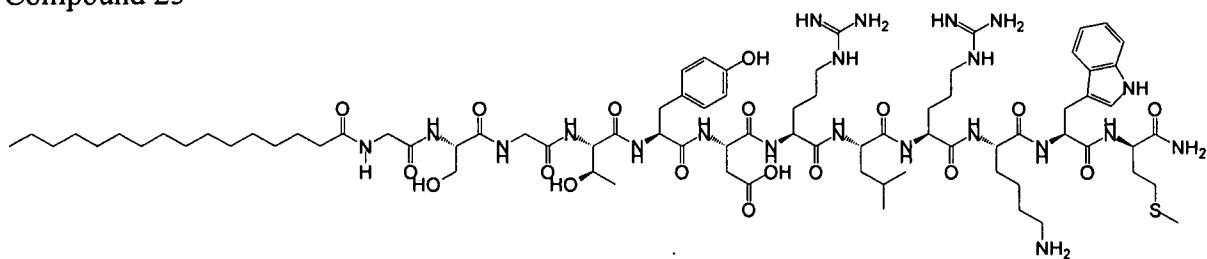
15

20

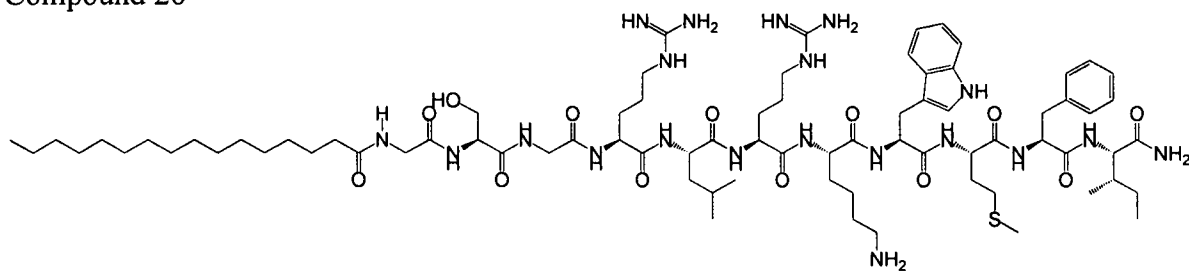
Compound 24



5 Compound 25

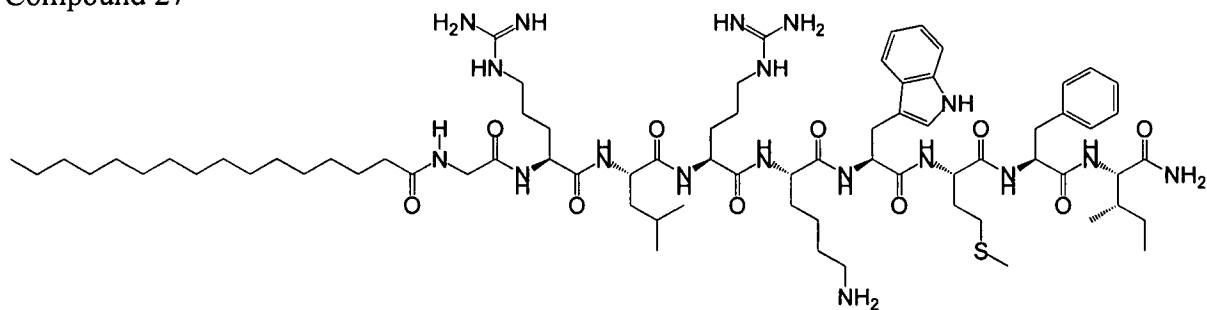


Compound 26



10

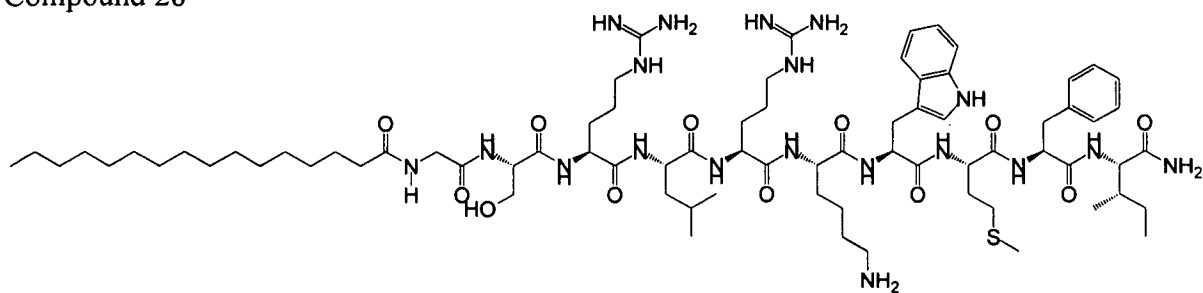
Compound 27



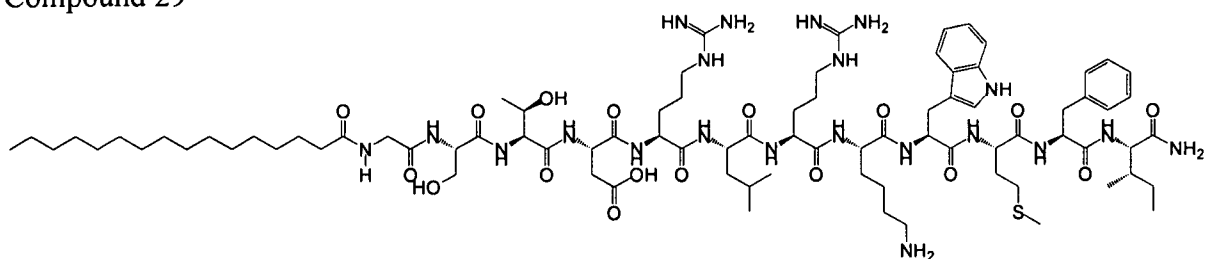
15

20

Compound 28

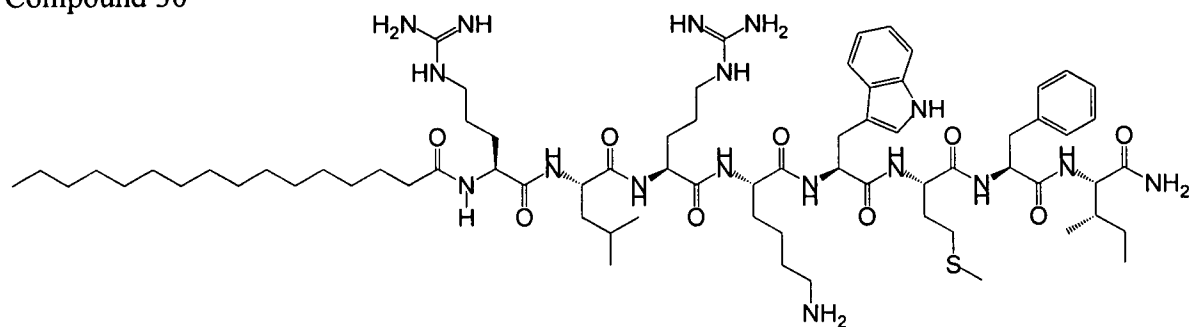


Compound 29

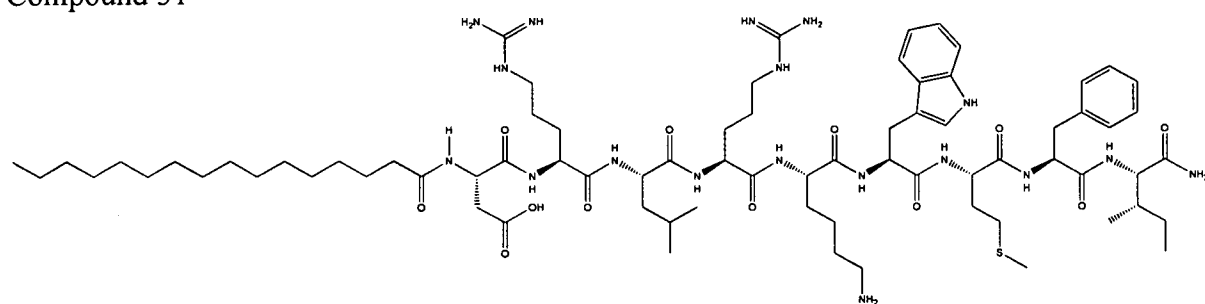


5

Compound 30

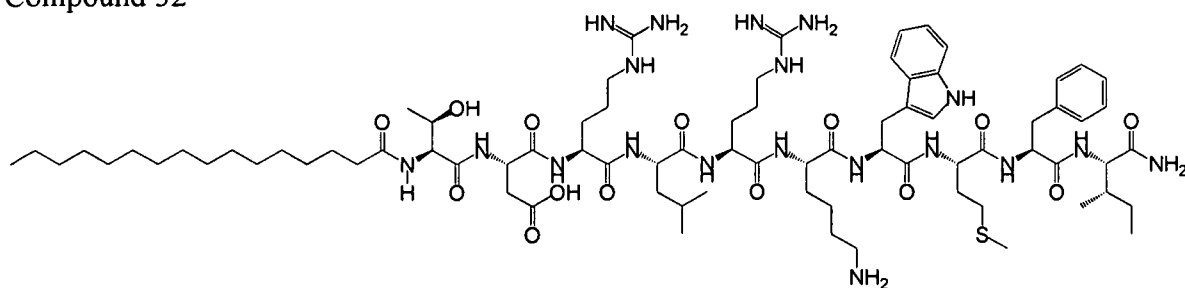


10 Compound 31

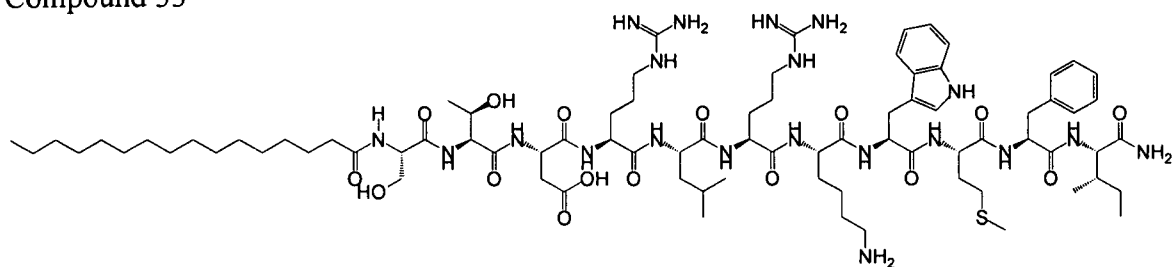


15

Compound 32

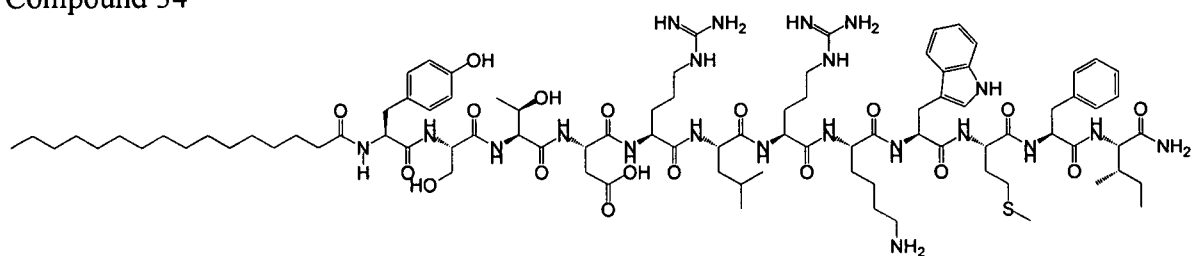


Compound 33

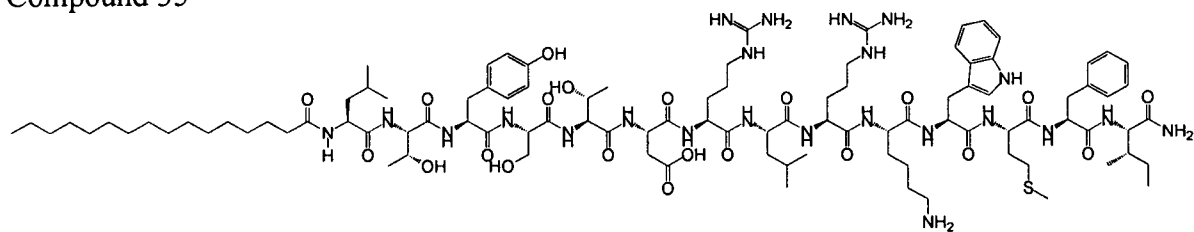


5

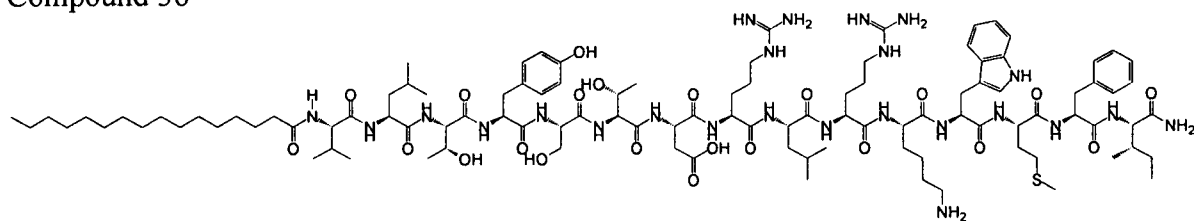
Compound 34



10 Compound 35

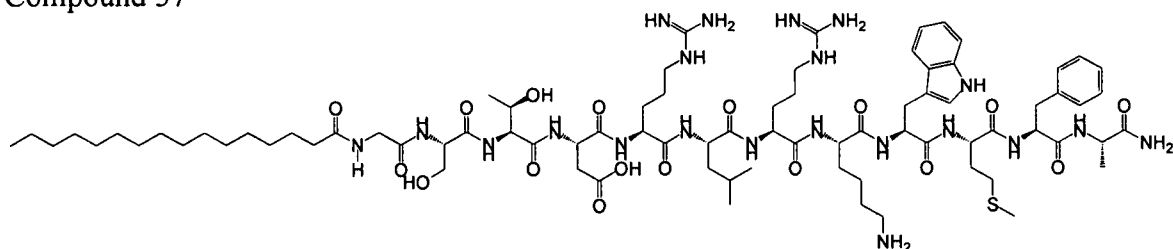


Compound 36

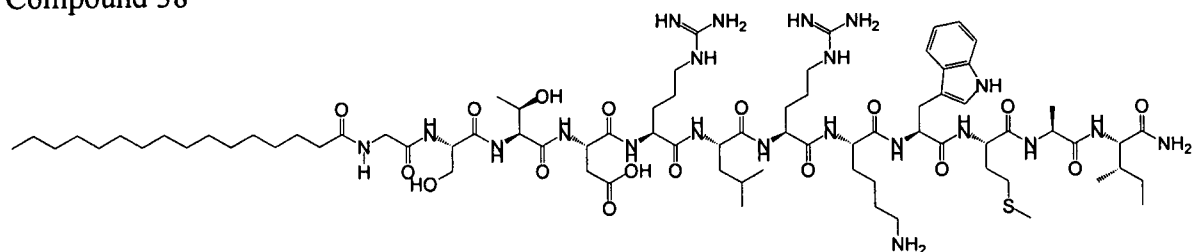


15

Compound 37

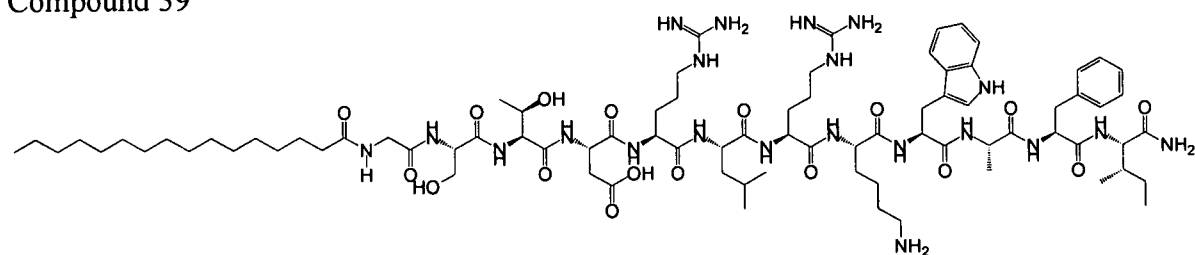


Compound 38

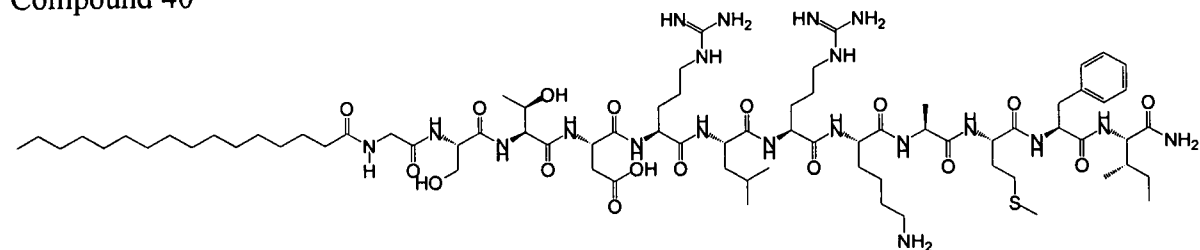


5

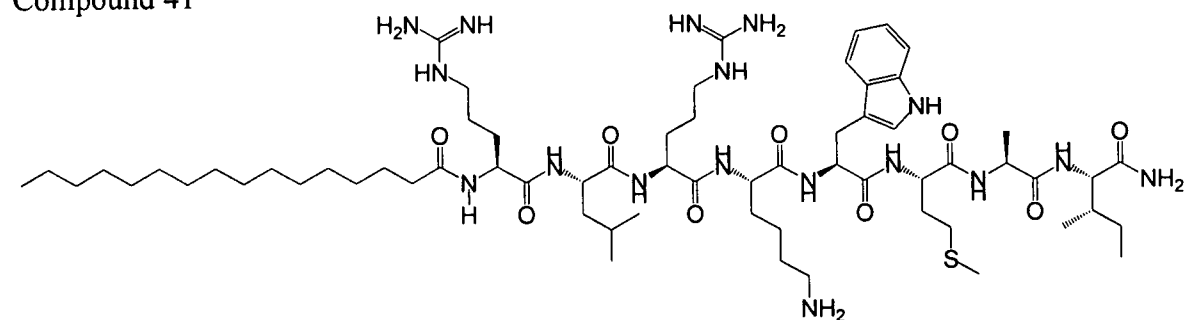
Compound 39



10 Compound 40

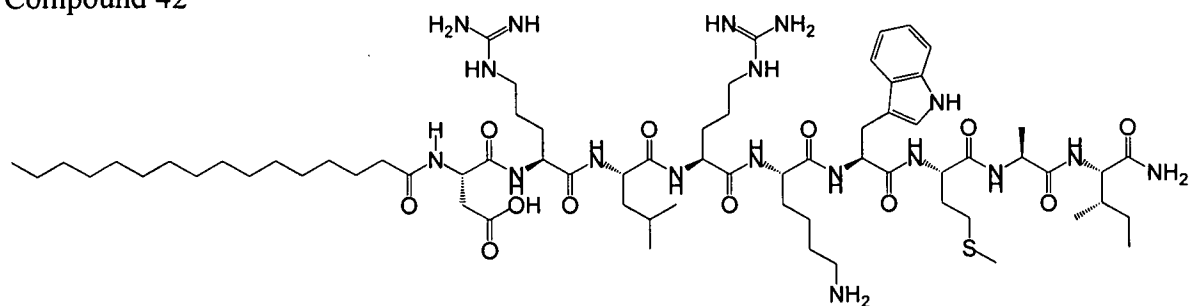


Compound 41

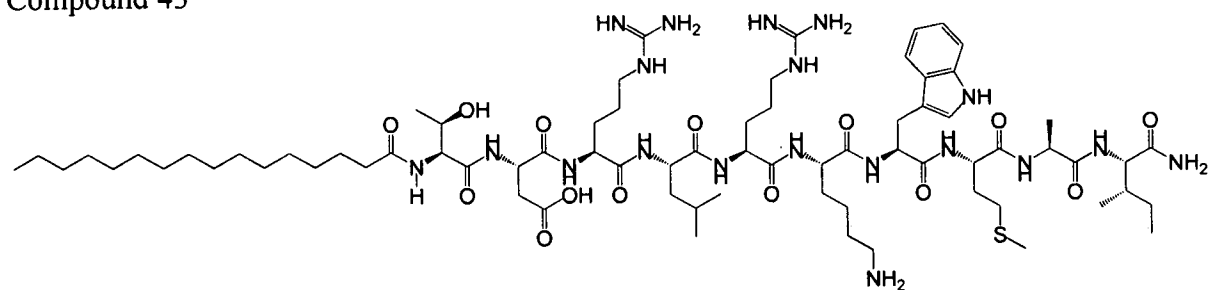


15

Compound 42

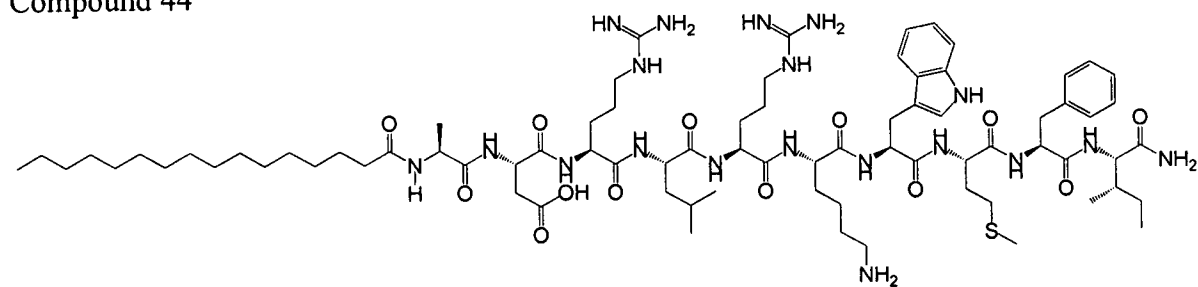


Compound 43

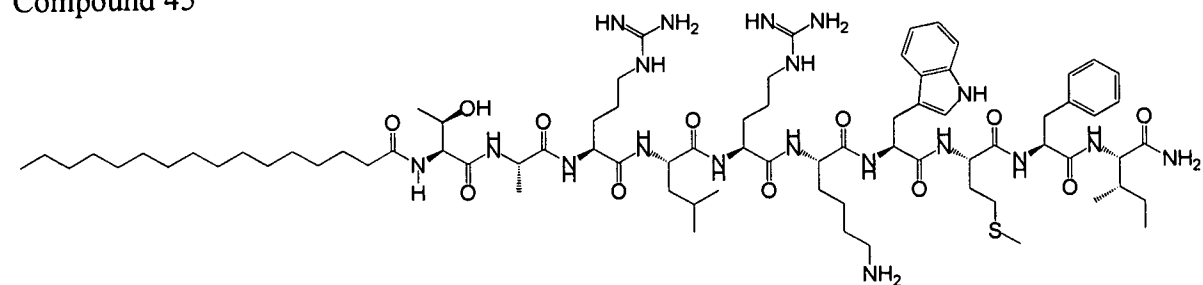


5

Compound 44



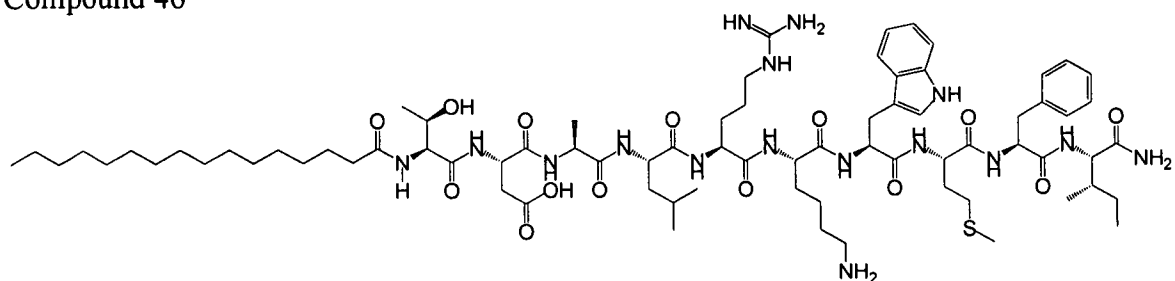
10 Compound 45



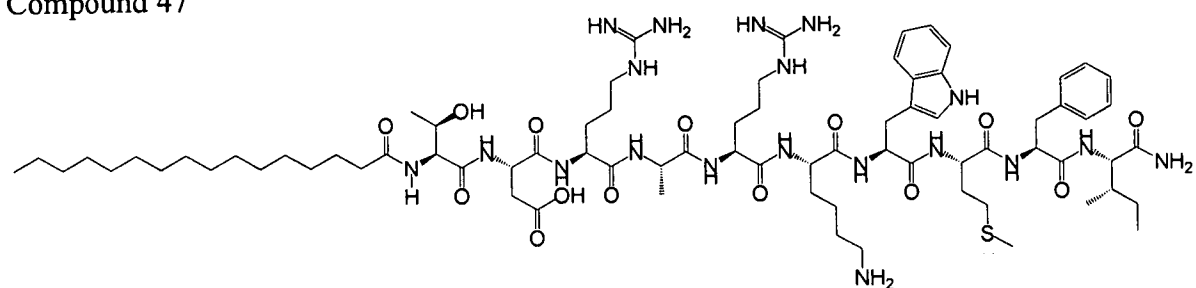
15

20

Compound 46

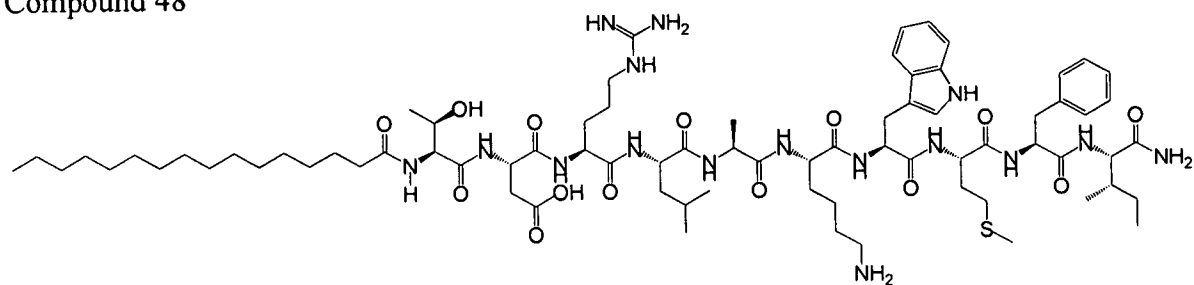


Compound 47

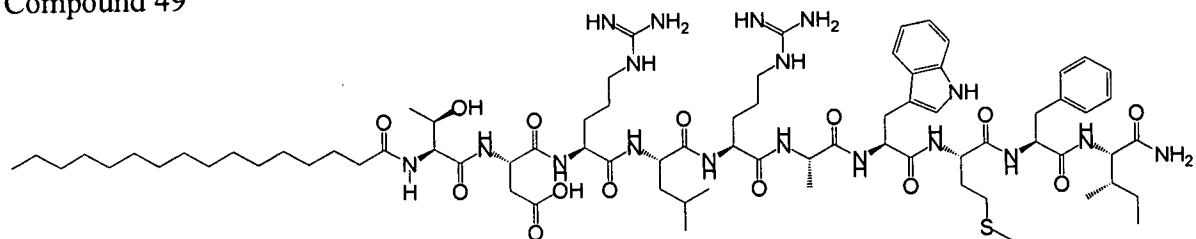


5

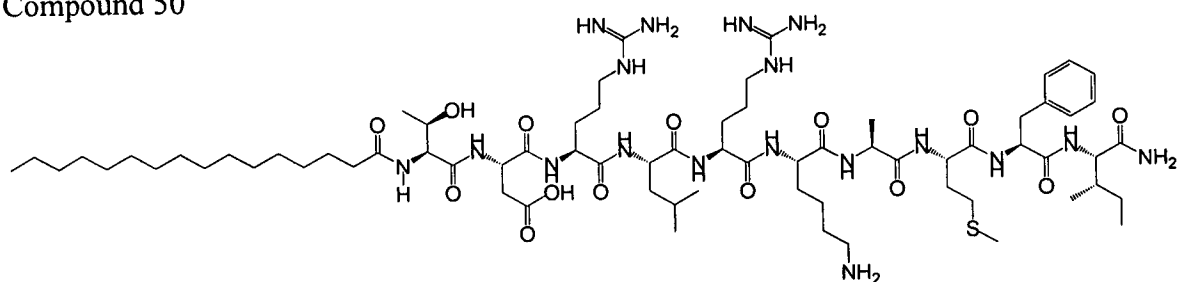
Compound 48



10 Compound 49

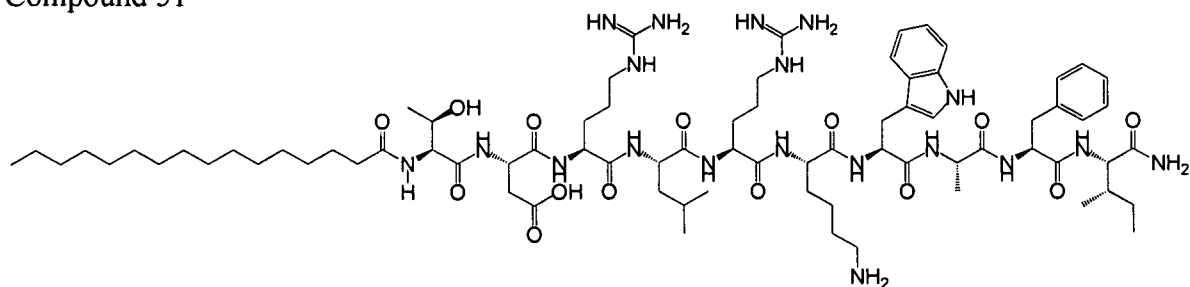


Compound 50

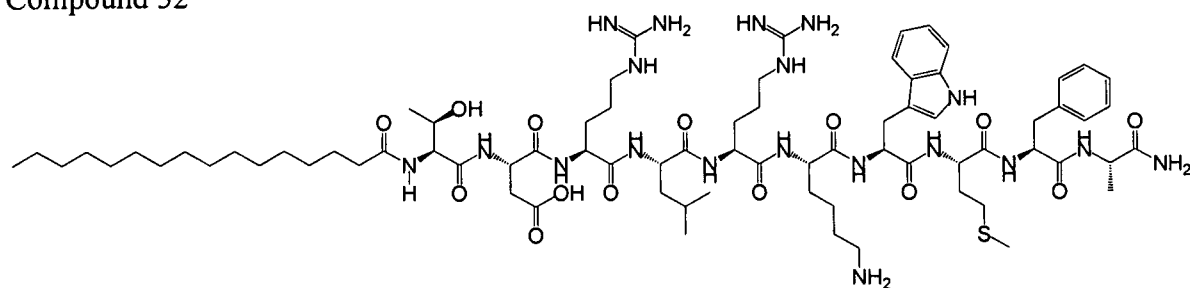


15

Compound 51

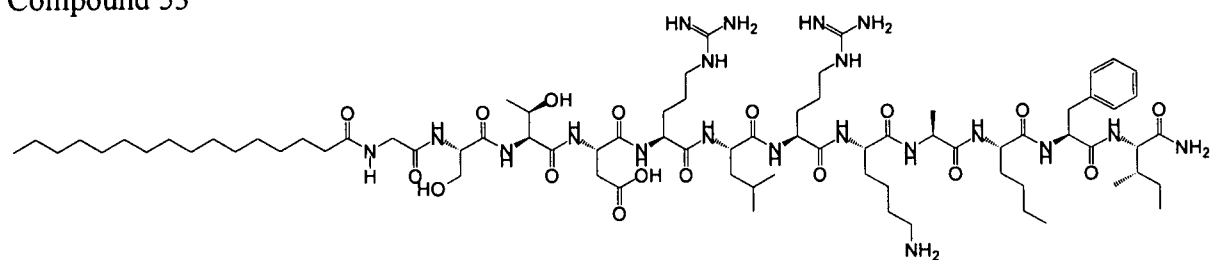


Compound 52



5

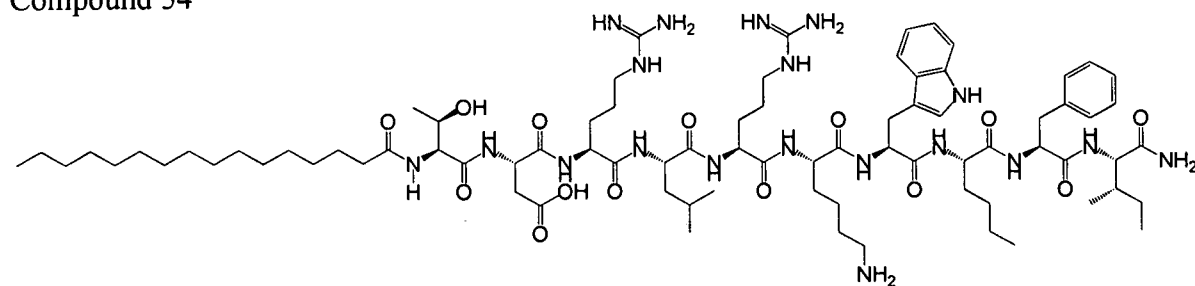
Compound 53



and

10

Compound 54

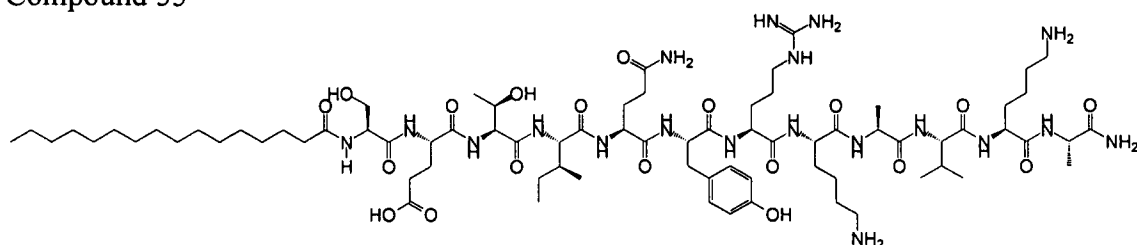


In the above listing of compounds, structures follow the compound number identifier.

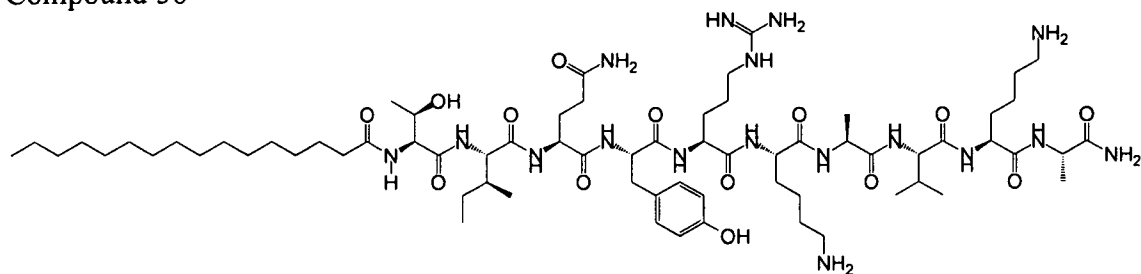
15

In yet another embodiment, a GPCR compound of the invention is selected from one of the following compounds or a pharmaceutically acceptable salt thereof:

Compound 55

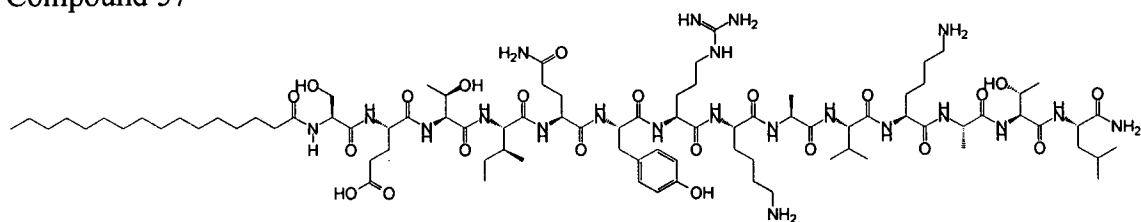


Compound 56

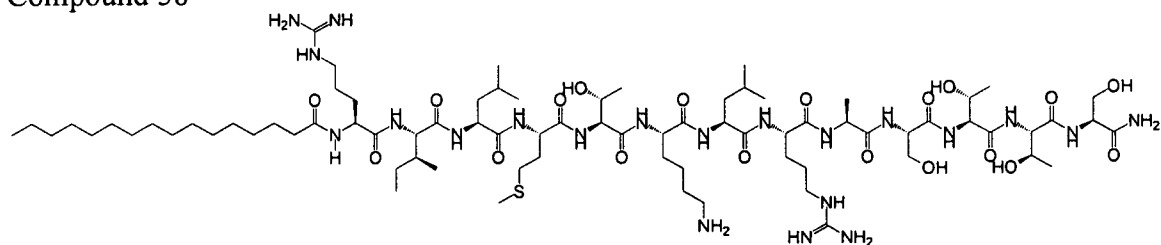


5

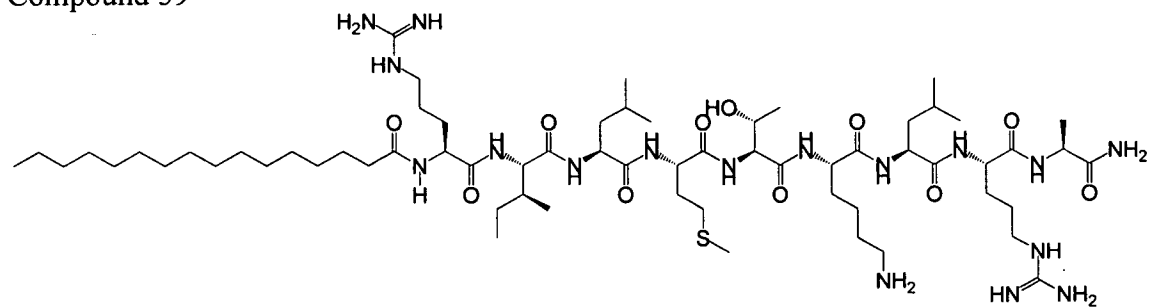
Compound 57



10 Compound 58

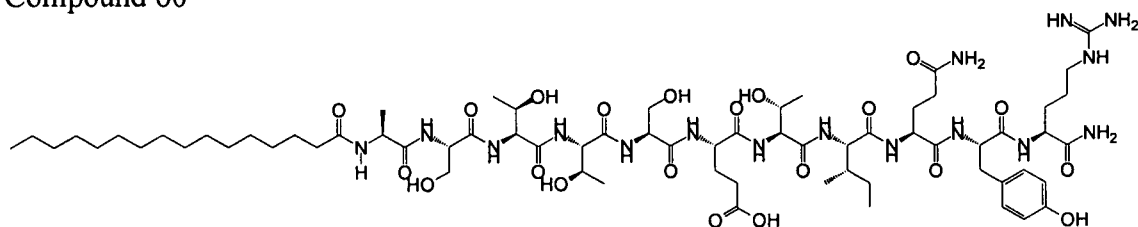


Compound 59

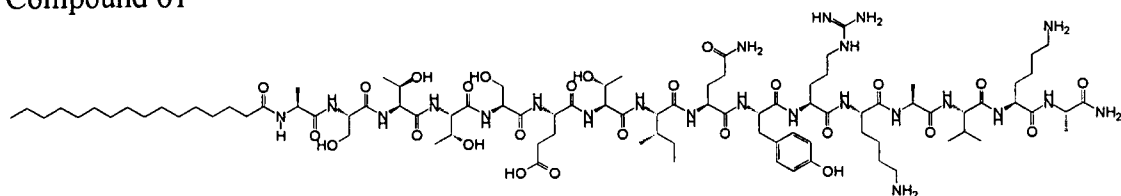


15

Compound 60

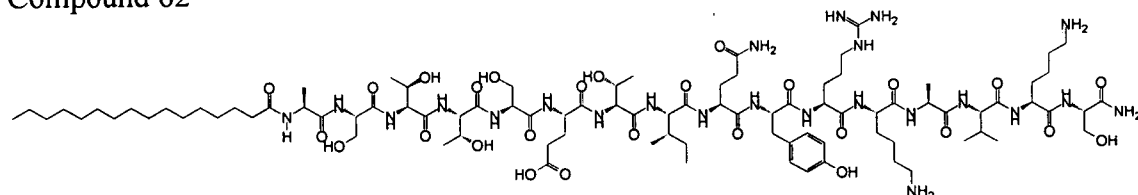


Compound 61



5 and

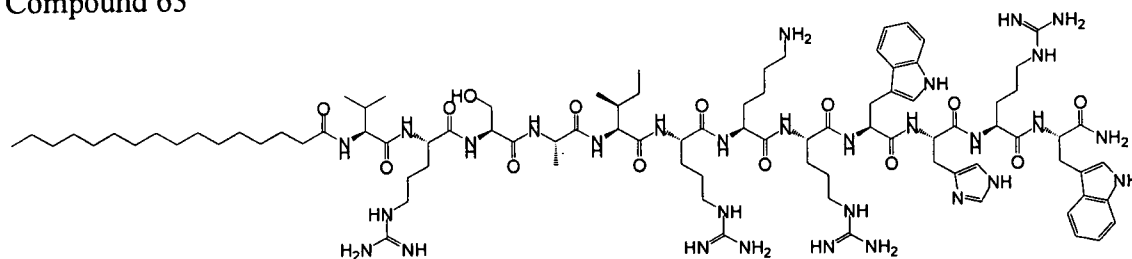
Compound 62



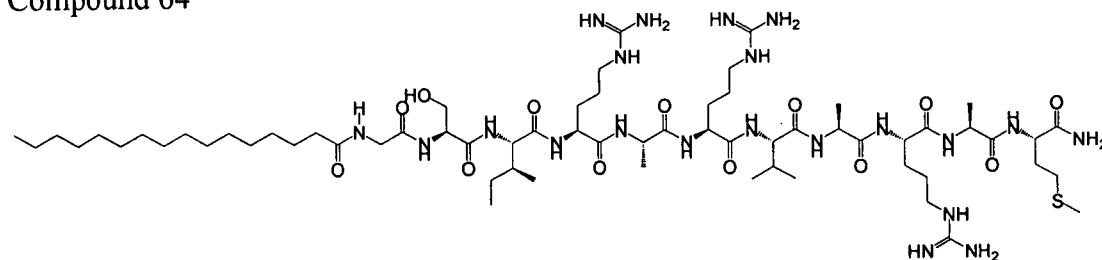
10 In the above listing of compounds the structure follows the compound number identifier.

In yet another embodiment, a GPCR compound of the invention is selected from one of the following compounds or a pharmaceutically acceptable salt thereof:

Compound 63



15 Compound 64



In the above listing of compounds, the structure follows the number identifier.

“Cycloalkyl” used alone or as part of a larger moiety such as “cycloalkylalkyl” refers to a monocyclic or polycyclic, non-aromatic ring system of 3 to 20 carbon atoms, 3 to 12 carbon atoms, or 3 to 9 carbon atoms, which may be saturated or unsaturated. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohexa-1,3-dienyl, cyclooctyl, cycloheptanyl, norbornyl, adamantyl, and the like.

“Heterocycloalkyl” refers to a saturated or unsaturated, non-aromatic, monocyclic or polycyclic ring system of 3 to 20 atoms, 3 to 12 atoms, or 3 to 8 atoms, containing one to four ring heteroatoms chosen from O, N and S. Examples of heterocyclyl groups include pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, tetrahydrothiophene, tetrahydrothiopyran, isoxazolidine, 1,3-dioxolane, 1,3-dithiolane, 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, morpholine, thiomorpholine, thiomorpholine-1,1-dioxide, tetrahydro-2H-1,2-thiazine-1,1-dioxide, isothiazolidine-1,1-dioxide, pyrrolidin-2-one, piperidin-2-one, piperazin-2-one, and morpholin-2-one, and the like.

“Halogen” and “halo” refer to fluoro, chloro, bromo or iodo.

“Haloalkyl” refers to an alkyl group substituted with one or more halogen atoms. By analogy, “haloalkenyl”, “haloalkynyl”, etc., refers to the group (for example alkenyl or alkynyl) substituted by one or more halogen atoms.

“Cyano” refers to the group –CN.

“Oxo” refers to a divalent =O group.

“Thioxo” refers to a divalent =S group.

“Ph” refers to a phenyl group.

“Carbonyl” refers to a divalent –C(O)- group.

“Alkyl” used alone or as part of a larger moiety such as “hydroxyalkyl”, “alkoxyalkyl”, “alkylamine” refers to a straight or branched, saturated aliphatic group having the specified number of carbons, typically having 1 to 12 carbon atoms. More particularly, the aliphatic group may have 1 to 10, 1 to 8, 1 to 6, or 1 to 4 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-hexyl, and the like.

“Alkenyl” refers to a straight or branched aliphatic group with at least one double bond. Typically, alkenyl groups have from 2 to 12 carbon atoms, from 2 to 8, from 2 to 6, or from 2 to 4 carbon atoms. Examples of alkenyl groups include ethenyl (–CH=CH₂), n-2-propenyl (allyl, –CH₂CH=CH₂), pentenyl, hexenyl, and the like.

“Alkynyl” refers to a straight or branched aliphatic group having at least 1 site of alkynyl unsaturation. Typically, alkynyl groups contain 2 to 12, 2 to 8, 2 to 6 or 2 to 4 carbon atoms. Examples of alkynyl groups include ethynyl ($-\text{C}\equiv\text{CH}$), propargyl ($-\text{CH}_2\text{C}\equiv\text{CH}$), pentynyl, hexynyl, and the like.

5 “Alkylene” refers to a bivalent saturated straight-chained hydrocarbon, e.g., $\text{C}_1\text{-C}_6$ alkylene includes $-(\text{CH}_2)_6-$, $-\text{CH}_2\text{-CH}(\text{CH}_2)_3\text{CH}_3$, and the like. “Bivalent means that the alkylene group is attached to the remainder of the molecule through two different carbon atoms.

10 “Alkenylene” refers to an alkylene group with in which one carbon-carbon single bond is replaced with a double bond.

“Alkynylene” refers to an alkylene group with in which one carbon-carbon single bond is replaced with a triple bond.

15 “Aryl” used alone or as part of a larger moiety as in “aralkyl” refers to an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring or multiple condensed rings. The term “aryl” also includes aromatic carbocycle(s) fused to cycloalkyl or heterocycloalkyl groups. Examples of aryl groups include phenyl, benzo[d][1,3]dioxole, naphthyl, phenantrenyl, and the like.

“Aryloxy” refers to an $-\text{OAr}$ group, wherein O is an oxygen atom and Ar is an aryl group as defined above.

20 “Aralkyl” refers to an alkyl having at least one alkyl hydrogen atom replaced with an aryl moiety, such as benzyl, $-(\text{CH}_2)_2\text{phenyl}$, $-(\text{CH}_2)_3\text{phenyl}$, $-\text{CH}(\text{phenyl})_2$, and the like.

“Alkyl cycloalkyl” refers to an alkyl having at least one alkyl hydrogen atom replaced with a cycloalkyl moiety, such as $-\text{CH}_2\text{-cyclohexyl}$, $-\text{CH}_2\text{-cyclohexenyl}$, and the like.

25 “Heteroaryl” used alone or a part of a larger moiety as in “heteroaralkyl” refers to a 5 to 14 membered monocyclic, bicyclic or tricyclic heteroaromatic ring system, containing one to four ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term “heteroaryl” also includes heteroaromatic ring(s) fused to cycloalkyl or heterocycloalkyl groups. Particular examples of heteroaryl groups include optionally substituted pyridyl, pyrrolyl, pyrimidinyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 30 pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-

dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinoliziny, quinazoliny, phthalaziny, quinoxaliny, cinnoliny, naphthyridiny, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, 5 tetrazolyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl, benzoquinolyl, and the like.

“Heteroaryloxy” refers to an –OHet group, wherein O is an oxygen atom and Het is a heteroaryl group as defined above.

10 “Heteroaralkyl” refers to an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl moiety, such as –CH₂-pyridinyl, –CH₂-pyrimidinyl, and the like.

“Alkoxy” refers to the group –O-R where R is “alkyl”, “cycloalkyl”, “alkenyl”, or “alkynyl”. Examples of alkoxy groups include for example, methoxy, ethoxy, ethenoxy, and the like.

15 “Alkyl heterocycloalkyl” refers to an alkyl having at least one alkyl hydrogen atom replaced with a heterocycloalkyl moiety, such as –CH₂-morpholino, –CH₂-piperidyl and the like.

“Alkoxycarbonyl” refers to the group –C(O)OR where R is “alkyl”, “alkenyl”, “alkynyl”, “cycloalkyl”, “heterocycloalkyl”, “aryl”, or “heteroaryl”.

20 “Hydroxyalkyl” and “alkoxyalkyl” are alkyl groups substituted with hydroxyl and alkoxy, respectively.

“Amino” means –NH₂; “alkylamine” and “dialkylamine” mean –NHR and –NR₂, respectively, wherein R is an alkyl group. “Cycloalkylamine” and “dicycloalkylamine” mean –NHR and –NR₂, respectively, wherein R is a cycloalkyl group. “Cycloalkylalkylamine” means –NHR wherein R is a cycloalkylalkyl group. “[Cycloalkylalkyl][alkyl]amine” means – 25 N(R)₂ wherein one R is cycloalkylalkyl and the other R is alkyl.

Haloalkyl and halocycloalkyl include mono, poly, and perhaloalkyl groups where the halogens are independently selected from fluorine, chlorine, bromine and iodine.

Suitable substituents for “alkyl”, “alkenyl”, “alkynyl”, “cycloalkyl”, “heterocycloalkyl”, “aryl”, or “heteroaryl”, etc., are those which will form a stable compound 30 of the invention. Examples of suitable substituents are those selected from the group

consisting of halogen, -CN, -OH, -NH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, aryl, heteroaryl, (C₃-C₇)cycloalkyl, (5-7 membered) heterocycloalkyl, -NH(C₁-C₆)alkyl, -N((C₁-C₆)alkyl)₂, (C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, -CONH₂, -OCONH₂, -NHCONH₂, -N(C₁-C₆)alkylCONH₂, -N(C₁-C₆)alkylCONH(C₁-C₆)alkyl, -NHCONH(C₁-C₆)alkyl, -NHCON((C₁-C₆)alkyl)₂, -N(C₁-C₆)alkylCON((C₁-C₆)alkyl)₂, -NHC(S)NH₂, -N(C₁-C₆)alkylC(S)NH₂, -N(C₁-C₆)alkylC(S)NH(C₁-C₆)alkyl, -NHC(S)NH(C₁-C₆)alkyl, -NHC(S)N((C₁-C₆)alkyl)₂, -N(C₁-C₆)alkylC(S)N((C₁-C₆)alkyl)₂, -CONH(C₁-C₆)alkyl, -OCONH(C₁-C₆)alkyl, -CON((C₁-C₆)alkyl)₂, -C(S)(C₁-C₆)alkyl, -S(O)_p(C₁-C₆)alkyl, -S(O)_pNH₂, -S(O)_pNH(C₁-C₆)alkyl, -S(O)_pN((C₁-C₆)alkyl)₂, -CO(C₁-C₆)alkyl, -OCO(C₁-C₆)alkyl, -C(O)O(C₁-C₆)alkyl, -OC(O)O(C₁-C₆)alkyl, -C(O)H or -CO₂H. More particularly, the substituents are selected from halogen, -CN, -OH, -NH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, phenyl, and (C₃-C₇)cycloalkyl. Within the framework of this invention, said "substitution" is also meant to encompass situations where a hydrogen atom is replaced with a deuterium atom. p is an integer with a value of 1 or 2.

Pharmaceutically acceptable salts of the compounds disclosed herein are included in the present invention. For example, an acid salt of a compound containing an amine or other basic group can be obtained by reacting the compound with a suitable organic or inorganic acid, resulting in pharmaceutically acceptable anionic salt forms. Examples of anionic salts include the acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, and triethiodide salts.

Salts of the compounds containing an acidic functional group can be prepared by reacting with a suitable base. Such a pharmaceutically acceptable salt can be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from physiologically acceptable organic bases such as trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-

hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine, collidine, quinine, quinoline, and basic amino acids such as lysine and arginine.

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PHARMACEUTICAL COMPOSITIONS

The invention also provides pharmaceutical compositions comprising an effective amount of a compound Formula I (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and a pharmaceutically acceptable carrier. The carrier(s) are "pharmaceutically acceptable" in that they are not deleterious to the recipient thereof in an amount used in the medicament.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this invention optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See United States patent 7,014,866; and United States patent publications 20060094744 and 20060079502.

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The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), pulmonary, vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA (17th ed. 1985).

Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance

bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz JD and Zaffaroni AC, US Patent 6,803,031, assigned to Alexza Molecular Delivery Corporation.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

Application of the patient therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the patient compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be

included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

Where an organ or tissue is accessible because of removal from the patient, such organ or tissue may be bathed in a medium containing a composition of this invention, a composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

In another embodiment, a composition of this invention further comprises a second therapeutic agent. In one embodiment, the second therapeutic agent is one or more additional compounds of the invention.

In another embodiment, the second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as the CRF1 receptor compound of Formula I.

In a particular embodiment, the second therapeutic is an agent useful in the treatment or prevention of a disease or condition selected from inflammatory bowel disease (peripherally acting), irritable bowel syndrome (IBS), stress response (colonic motor

activity), anxiety, sleep disorder, addictive behavior, acute and chronic neurodegeneration, preterm labor and pain.

In another embodiment, the second therapeutic is an agent useful in the treatment or prevention of IBS.

5 In one embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the
10 separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to
15 treat (therapeutically or prophylactically) the target disorder. For example, an effective amount is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy. Preferably, the compound is present in the
20 composition in an amount of from 0.1 to 50wt.%, more preferably from 1 to 30 wt.%, most preferably from 5 to 20wt.%.

The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., (1966) Cancer Chemother. Rep 50: 219. Body surface area may be approximately determined from height and weight of
25 the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The
30 normal monotherapeutic dosages of these second therapeutic agents are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000,

Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

The compounds for use in the method of the invention can be formulated in unit dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosage for subjects undergoing treatment, with each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form can be for a single daily treatment dose or one of multiple daily treatment doses (e.g., about 1 to 4 or more times per day). When multiple daily treatment doses are used, the unit dosage form can be the same or different for each dose.

METHODS OF TREATMENT

As used herein the term "subject" and "patient" typically means a human, but can also be an animal in need of treatment, e.g., companion animals (dogs, cats, and the like), farm animals (cows, pigs, horses, sheep, goats, and the like) and laboratory animals (rats, mice, guinea pigs, and the like).

The terms "treat" and "treating" are used interchangeably and include both therapeutic treatment and prophylactic treatment (reducing the likelihood of development). Both terms mean decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

"Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat (therapeutically or prophylactically) the target disorder. For example, an effective amount is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

The invention also includes methods of treating diseases, disorders or pathological conditions which benefit from modulation of the CRF1 receptor comprising administering an

effective amount of an CRF1 receptor compound of the invention to a subject in need thereof. Diseases and conditions which can benefit from modulation (inhibition or activation) of the CRF1 receptor include, but are not limited to, inflammatory bowel disease (peripherally acting), irritable bowel syndrome (IBS), stress response (colonic motor activity), anxiety, sleep disorder, addictive behavior, acute and chronic neurodegeneration, preterm labor and pain.

In one embodiment, an effective amount of a compound of this invention can range from about .005 mg to about 5000 mg per treatment. In more specific embodiments, the range is from about .05 mg to about 1000 mg, or from about 0.5 mg to about 500 mg, or from about 5 mg to about 50 mg. Treatment can be administered one or more times per day (for example, once per day, twice per day, three times per day, four times per day, five times per day, etc.). When multiple treatments are used, the amount can be the same or different. It is understood that a treatment can be administered every day, every other day, every 2 days, every 3 days, every 4 days, every 5 days, etc. For example, with every other day administration, a treatment dose can be initiated on Monday with a first subsequent treatment administered on Wednesday, a second subsequent treatment administered on Friday, etc. Treatment is typically administered from one to two times daily. Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician.

Alternatively, the effective amount of a compound of the invention is from about 0.01 mg/kg/day to about 1000 mg/kg/day, from about 0.1 mg/kg/day to about 100 mg/kg/day, from about 0.5 mg/kg/day to about 50 mg/kg/day, or from about 1 mg/kg/day to 10 mg/kg/day.

In another embodiment, any of the above methods of treatment comprises the further step of co-administering to said patient one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for co-administration with a compound that modulates the CRF1 receptor. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated.

The term "co-administered" as used herein means that a second therapeutic agent

may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

In one embodiment of the invention, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

KITS

The present invention also provides kits for use to treat the target disease, disorder or condition. These kits comprise (a) a pharmaceutical composition comprising a compound of Formula I, or a salt thereof, wherein said pharmaceutical composition is in a container; and (b) instructions describing a method of using the pharmaceutical composition to treat the target disease, disorder or condition.

The container may be any vessel or other sealed or sealable apparatus that can hold said pharmaceutical composition. Examples include bottles, ampules, divided or multi-chambered holders bottles, wherein each division or chamber comprises a single dose of said composition, a divided foil packet wherein each division comprises a single dose of said composition, or a dispenser that dispenses single doses of said composition. The container can be in any conventional shape or form as known in the art which is made of a

pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box. In one embodiment, the container is a blister pack.

The kits of this invention may also comprise a device to administer or to measure out a unit dose of the pharmaceutical composition. Such device may include an inhaler if said composition is an inhalable composition; a syringe and needle if said composition is an injectable composition; a syringe, spoon, pump, or a vessel with or without volume markings if said composition is an oral liquid composition; or any other measuring or delivery device appropriate to the dosage formulation of the composition present in the kit.

In certain embodiment, the kits of this invention may comprise in a separate vessel of container a pharmaceutical composition comprising a second therapeutic agent, such as one of those listed above for use for co-administration with a compound of this invention.

GENERAL METHODS FOR PREPARING CRF1 RECEPTOR COMPOUNDS

Synthesis of Peptides

The peptide component (P) of the compounds of the invention can be synthesized by incorporating orthogonally protected amino acids in a step-wise fashion. Any suitable synthetic methods can be used. Traditional Fmoc or Boc chemistry can be easily adapted to provide the desired peptide component (P) of the compounds of the invention. Fmoc is generally preferred, because the cleavage of the Fmoc protecting group is milder than the acid deprotection required for Boc cleavage, which requires repetitive acidic deprotections that lead to alteration of sensitive residues, and increase acid catalyzed side reactions. (G. B. FIELDS et al. in *Int. J. Pept. Protein*, 1990, 35, 161).

The peptides can be assembled linearly via Solid Phase Peptide Synthesis (SPPS), can be assembled in solution using modular condensations of protected or unprotected peptide components or a combination of both.

Solid Phase Peptide Synthesis

For SPPS, an appropriate resin is chosen that will afford the desired moiety on the C-terminus upon cleavage. For example upon cleavage of the linear peptide, a Rink amide resin will provide a primary amide on the C-terminus, whereas a Rink acid resin will provide an acid. Rink acid resins are more labile than Rink amide resins and the protected peptide could also be cleaved and subsequently the free acid activated to react with amines or other nucleophiles. Alternatively, other resins could provide attachment of other moieties prior to acylation, leading to cleavage of an alkylated secondary amide, ester or other desired C-terminal modification. A review of commonly used resins and the functional moiety that results after cleavage can be found in manufacturer literature such as NovaBiochem or Advanced Chemtech catalogues.

Typically a resin is chosen such that after cleavage the C-terminus is an amide bond. Rink amide resin is a resin that results in a C-terminal amide during cleavage. The orthogonally protected Fmoc amino acids are added stepwise using methods well known in literature (Bodansky M. Principles of Peptide synthesis (1993) 318p; Peptide Chemistry, a Practical Textbook (1993); Springer-Verlag). These procedures could be done manually or by using automated peptide synthesizers.

The process involves activating the acid moiety of a protected amino acid, using activating agents such as HBTU, HATU, PyBop or simple carbodiimides. Often an additive is used to decrease racemization during coupling such as HOBt or HOAt (M. SCHNÖLZER et al., *Int. J. Pept. Protein Res.*, 1992, 40, 180). Manually, the coupling efficiency can be determined photometrically using a ninhydrin assay. If the coupling efficiency is below 98%, a second coupling may be desired. After the second coupling a capping step may be employed to prevent long deletion sequences to form, simplifying the purification of the desired final compound. With automation, second couplings are not commonly required, unless a residue is known to be problematic such as Arginine.

Deprotection of the Fmoc is most commonly accomplished using piperidine (20%) in dimethylformamide (DMF). Alternatively other secondary amines may also be used such as morpholine, diethylamine or piperazine. This reaction is facile and normally is accomplished within 20 minutes using piperidine. After deprotection the resin is washed several times with DMF and DCM prior to coupling with the next residue. This process is repeated, assembling

the peptide linearly until the sequence is complete. The final Fmoc is removed, which allows for coupling with the tether moiety.

In a preferred synthesis, the peptide is formed by SPPS accomplished manually or in an automated fashion using a commercially available synthesizer such as the CEM

5 Microwave peptide synthesizer, Rainin Symphony synthesizer, or ABI 433 flow-through synthesizer. Commercially available Rink Amide resin is used for synthesizing the C-terminal amide peptides (*Rink, H. Tetrahedron Lett, 28, 4645, 1967*). Peptide synthesis reagents (coupling, deprotection agents) are commercially available and include HOBt, HBTU (Novabiochem) as well as DMF, DCM, Piperidine, NMP, and DIEA (Sigma-
10 Aldrich). Suitably protected amino acids for use in solid phase peptide synthesis are commercially available from many sources, including Sigma-Aldrich and CEM Corporation.

For example, a convenient preparation of peptides on a 0.1mmol or 0.25 mmol scale uses Rink amide solid-phase resin with a substitution of about 0.6mmol/g. Linear attachment of the amino acids is accomplished on a ABI continuous flow automated synthesizer using 5
15 eq of orthogonally protected amino acid (AA), and using HBTU/HOBt coupling protocol, (5 eq. of each reagent). In another preferred synthesis, peptides can be synthesized using a microwave instrument using 10 eq of reagents. Deprotection of Fmoc can be accomplished with 20% piperidine in DMF followed by washing with DMF and DCM.

In both cases (i.e., Rink acid and Rink amide resins), final Fmoc deprotection of the
20 N-terminus would leave a free amine after cleavage from the resin unless it is modified prior to cleavage. In the compounds of the invention, tether moieties are attached through amide bonds.

Solution Phase Synthesis of Peptides

For solution phase synthesis the desired peptide is generally broken down into peptide
25 fragments in units of 2-4 amino acids. The selected unit is dependent on the sequence, the stability of the fragment to racemization, and the ease of assembly. As each amino acid is added, only 1-1.5eq of the residue is required, versus the 5-10 equivalents of reagent required for SPPS. Preactivated amino acids such as OSu active ester and acid fluorides also can be used, requiring only a base for completion of the reaction.

30 Coupling times require 1.5-2 hours for each step. Two fragments are condensed in solution, giving a larger fragment that then can be further condensed with additional

fragments until the desired sequence is complete. The solution phase protocol uses only 1eq of each fragment and will use coupling reagents such as carbodiimides (DIC). For racemized prone fragments, PyBop or HBTU/HOBt can be used. Amino acids with Bsmoc/tBu or Fmoc/tBu and Boc/Benzyl protection are equally suitable for use.

- 5 When Fmoc is used, the use of 4-(aminomethyl) piperidine or tris(2-aminoethyl)amine as the deblocking agent can avoid undesired side reactions. The resulting Fmoc adduct can be extracted with a phosphate aqueous buffer of pH 5.5 (Organic Process Research & Development 2003, 7, 2837). If Bsmoc is used, no buffer is required, only aqueous extractions are needed. Deprotections using these reagents occur in 30-60 minutes.
- 10 Deblocking of the Fmoc group on the N-terminal residue provides a free terminal amine that is used for attachment of the tether moiety. In the compounds of the invention, tether moieties are attached through amide bonds to the N-terminal amine.

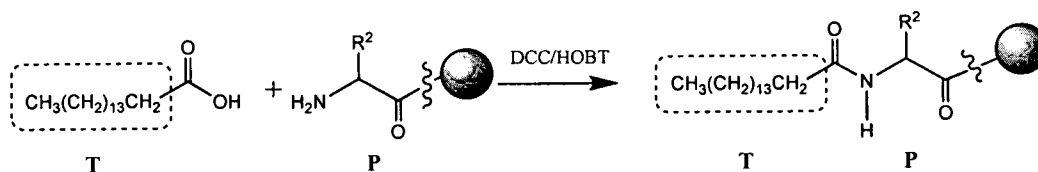
One advantage of solution phase synthesis is the ability to monitor the compound after every coupling step by mass spectrometry to see that the product is forming. In addition, a simple TLC system could be used to determine completion of reaction.

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Attachment of Tethers

Tethers are attached to the terminal nitrogen of the N-terminal amino acid of the peptide chain using amide bond coupling:

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The tether can be attached using solid phase procedures or in solution using an amide bond coupling. After the N-terminus is suitably coupled, the final compound is cleaved from the resin using an acidic cocktail (Peptide Synthesis and Applications, John Howl, Humana Press, 262p, 2005). Typically these cocktails use concentrated trifluoroacetic acid (80-95%) and various scavengers to trap carbocations and prevent side chain reactions. Typical scavengers include isopropylsilanes, thiols, phenols and water. The cocktail mixture is determined by the residues of the peptide. Special care needs to be taken with sensitive residues, such as methionine, aspartic acid, and cysteine. Typical deprotection occurs over 2-5 hours in the cocktail. A preferred deprotection cocktail

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include the use of triisopropylsilane (TIS), Phenol, thioanisole, dodecanethiol (DDT) and water. Methane sulfonic acid (MSA) may also be used in the cocktail (4.8%). A more preferred cocktail consists of (TFA:MSA:TIS:DDT:Water 82: 4.5:4.5:4.5:4.5; 10 mL/0.1 mmol resin).

After deprotection, the resin is removed via filtration, and the final compound is isolated via precipitation from an organic solvent such as diethyl ether, *m-tert*-butyl ether, or ethyl acetate and the resulting solid collected via filtration or lyophilized to a powder. Purification of the peptide using reverse phase HPLC may be required to achieve sufficient purity. Generally, a gradient of aqueous solvent with an organic solvent will provide sufficient separation from impurities and deletion sequences. Typically 0.1%TFA is used as the aqueous and organic modifier, however, other modifiers such as ammonium acetate can also be used. After purification, the compound is collected, analyzed and fractions of sufficient purity are combined and lyophilized, providing the compound as a solid.

Amino acid reagents

The following commercially available orthogonally protected amino acids used can be used in the synthesis of compounds of the invention: Fmoc-Tyr(tBu)-OH, Fmoc-Ala-OH*H₂O, Fmoc-Arg(Pbf)-OH, Fmoc, Asn(Trt)-OH, Fmoc-Asp(tBu), Fmoc-Cys(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glx(Pbf)-OH, Fmoc-Gly-OH, Fmoc-His(Trt)-OH, Fmoc-Leu-OH, Fmoc-Ile-OH, Fmoc, Lys(tBu)-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Typ-OH, and Fmoc-Val-OH. Additional amino acids suitable for incorporation into the compounds of the invention (e.g., D amino acids, substituted amino acids and other protecting group variations) are also commercially available or synthesized by methods known in the art.

Analytical Methods

The compounds of the invention are analyzed for purity by HPLC using the methods listed below. Purification is achieved by preparative HPLC.

Fast LC/MS Method

Column:	Phenomenex Luna C-5 20x 30mm
Flow:	1.0 ml/min
Solvent A:	0.1 % TFA in Type I water
Solvent B:	0.1% TFA in Acetonitrile
UV	220 nm
Injection:	20 ul

Gradient 5-95%B (7 minutes); 95-5%B (1 minute); 5% B (4 minutes)

Analytical Purity Method

5 Column: Phenomenex Luna C-5 20x 30mm
 Flow: 1.0 ml/min
 Solvent A: 0.1 % TFA in Type I water
 Solvent B: 0.1% TFA in Acetonitrile
 UV: 220 nm
 10 Injection: 20 ul
 Gradient: 2-95%B (10 minutes); 95-2%B (2 minutes); 2% B (2 minutes)

Preparative LC/MS Method

15 Column: Phenomenex Luna C-5 250x 150mm
 Flow: 5.0 ml/min
 Solvent A: 0.1 % TFA in Type I water
 Solvent B: 0.1% TFA in Acetonitrile
 UV: 220 nm
 20 Injection: 900 ul
 Gradient: 35%B (5 minutes); 35-85%B (13 minutes); 85-35% B (0.5 minutes); 35%B (1.5 minutes)

25

SYNTHESIS OF SELECTED COMPOUNDS

Compound 58 Pal- RILMTKLRASTTS-amide

Compound 58 was synthesized as described above on Rink amide resin at 0.1 mmol
 30 scale. Amino acids were coupled sequentially as described above. Following deprotection of the Fmoc group on the N-terminal residue serine, the N-terminal amine was capped with palmitic acid (10 eq.), HBTU (10 eq.) and DIEA (10 eq.) as described above. The pepducin was cleaved from the resin by TFA containing MS, TIS, DDT, and water (82: 4.5:4.5:4.5:4.5; 10 mL), filtered through a Medium frit Buchner funnel, triturated with ether and the resulting
 35 precipitate collected by centrifugation. Crude peptide was taken up in minimum amount of DMSO and purified by RP-HPLC as described previously. Fractions with correct MW were pooled and lyophilized and analyzed for purity using Method A. The yield of representative lots is illustrated in the following table.

40

Lot #	Yield (mg)
1	3.3
2	5

Compound 32 Pal- TDRLRKWMFI-amide

- 5 Compound 32 was synthesized as described for Compound 58. The yield of representative lots is illustrated in the following table.

Lot #	Yield (mg)
1	6

10 Compound 29 Pal- GSTDRLRKWMFI-amide

Compound 29 was synthesized as described for Compound 58. The yield of representative lots is illustrated in the following table.

15

Lot #	Yield (mg)
1	4
2	2.1
3	2.6
4	12.3

The compounds listed in Tables 6-9 were prepared according to the methods described herein.

20 **Table 6A. CRF1 i1 loop pepducins**

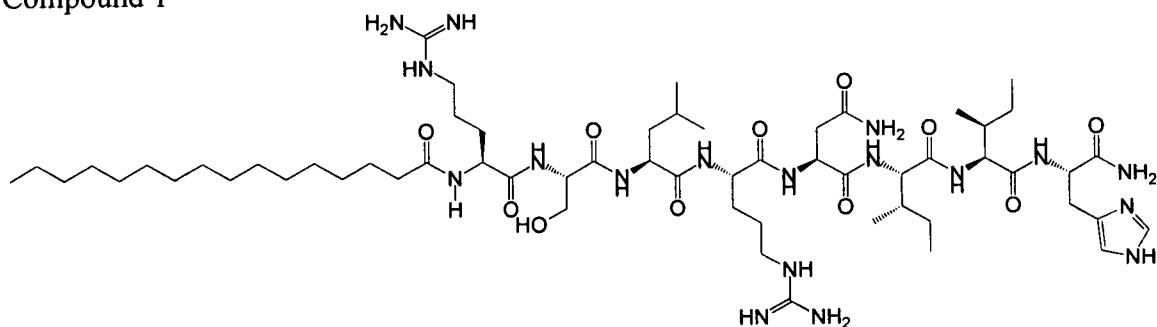
Compound	Sequence	N terminus	C terminus	MS Theoretical	MS Observed
Compound 1	RSLRNIIH	C ₁₅ H ₃₁ C(O)-	Amide	623.8015	623.6
Compound 2	RSIRSLRNIIH	C ₁₅ H ₃₁ C(O)-	Amide	802.0115	801.6
Compound 3	GSGRLRSIRSLRNIIH	C ₁₅ H ₃₁ C(O)-	Amide	691.849	692
Compound 4	LFIRIRSIRSLRNIIH	C ₁₅ H ₃₁ C(O)-	Amide	1123.428	1122.9
Compound 5	RLRSIRSLRNIIHWN	C ₁₅ H ₃₁ C(O)-	Amide	724.893	725

Compound 6	RLRSIRSLRNIIH	C ₁₅ H ₃₁ C(O)-	Amide	624.789	624.85
Compound 7	RLRSIRSLRN	C ₁₅ H ₃₁ C(O)-	Amide	754.956	755
Compound 8	RLRSIRSLR	C ₁₅ H ₃₁ C(O)-	Amide	697.905	697.7
Compound 9	RSIRSLRN	C ₁₅ H ₃₁ C(O)-	Amide	620.2845	620
Compound 10	GSGRLRSIRSLRNIIHWN	C ₁₅ H ₃₁ C(O)-	Amide	1187.4295	1187.4
Compound 11	RSIRSLRNIIHWN	C ₁₅ H ₃₁ C(O)-	Amide	952.168	951.8
Compound 13	RSLRNIIHWN	C ₁₅ H ₃₁ C(O)-	Amide	773.9575	

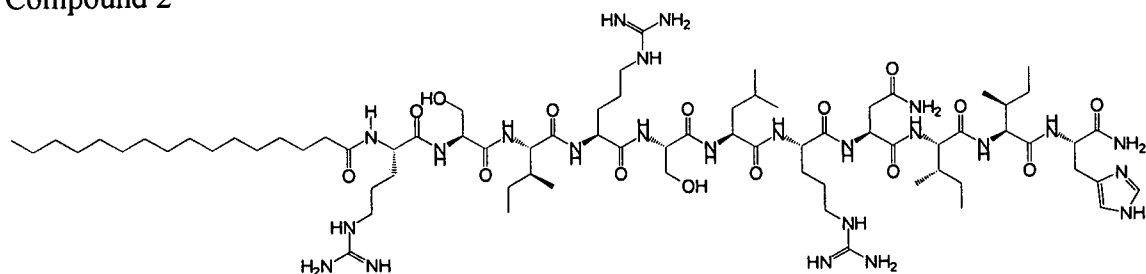
Table 6B. CRF1 i1 loop pepducin structures

Compound Number and Structure

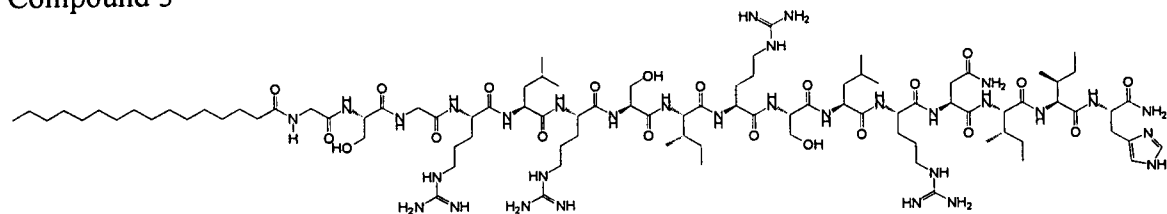
Compound 1



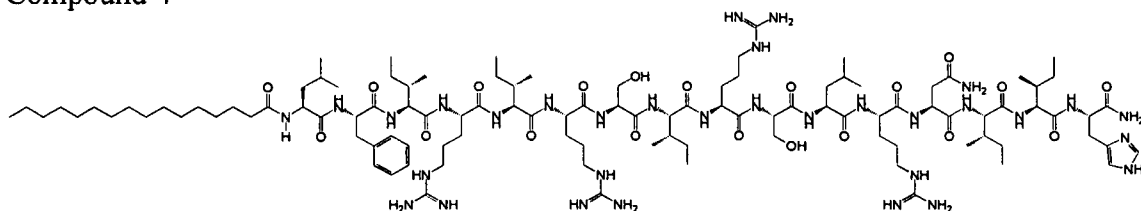
Compound 2



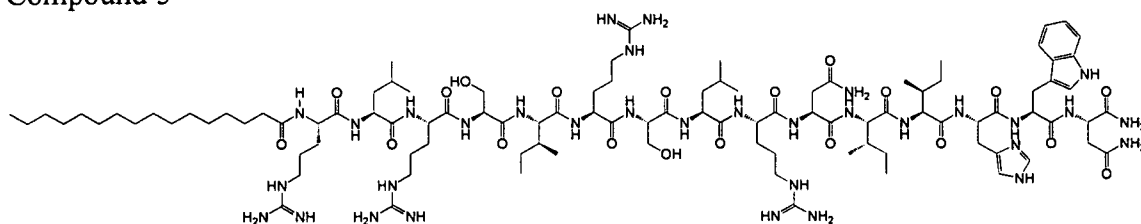
Compound 3



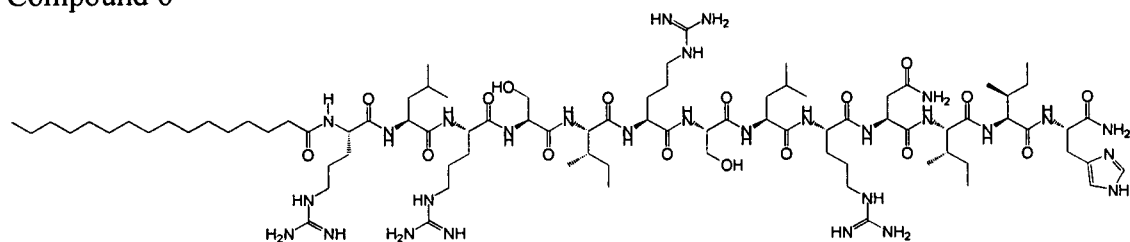
Compound 4



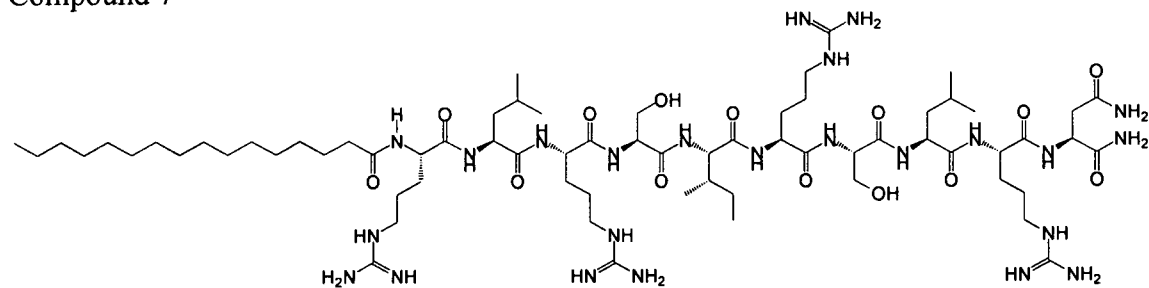
Compound 5



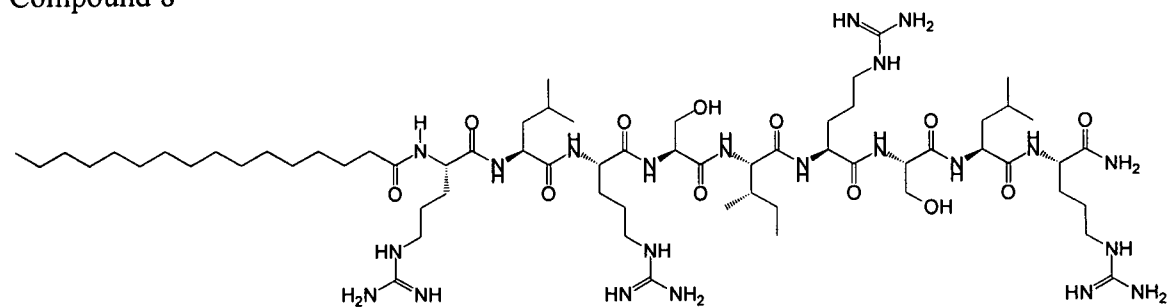
Compound 6



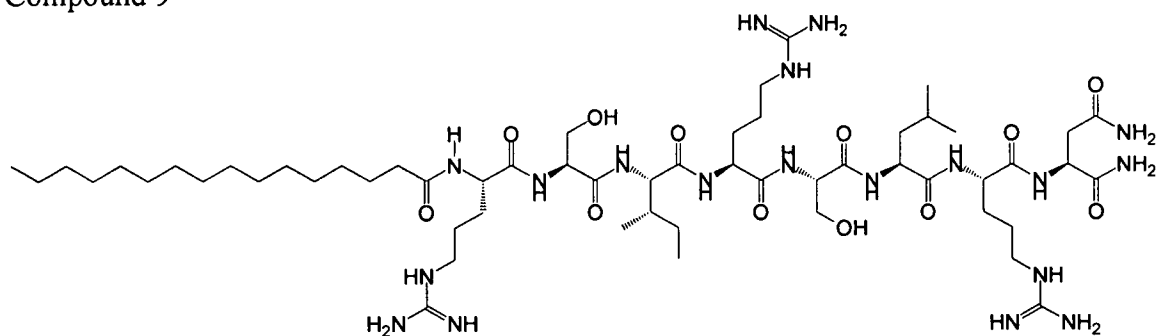
Compound 7



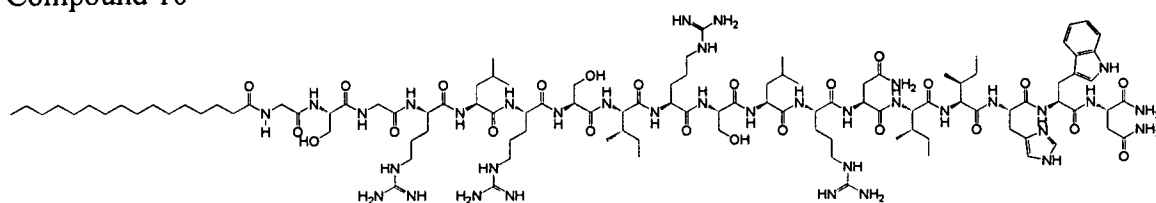
Compound 8



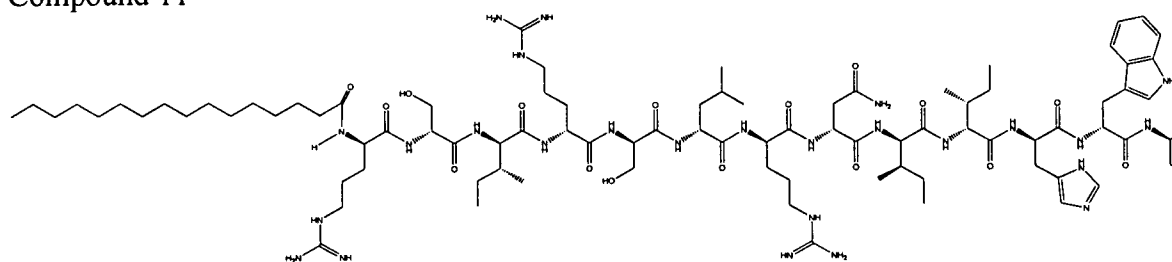
Compound 9



Compound 10



Compound 11



Compound 13

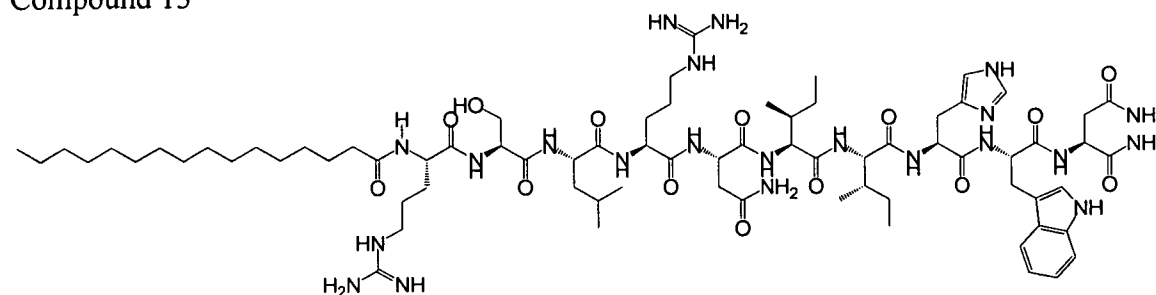
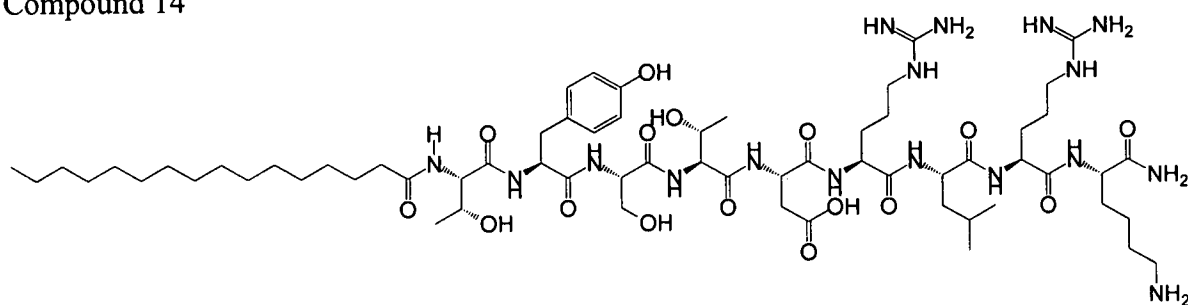
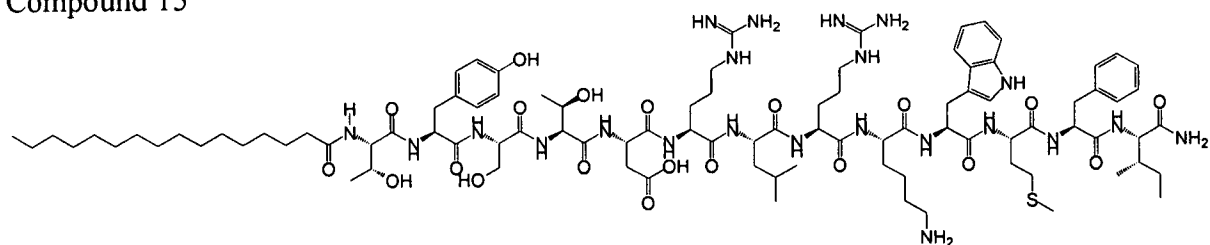


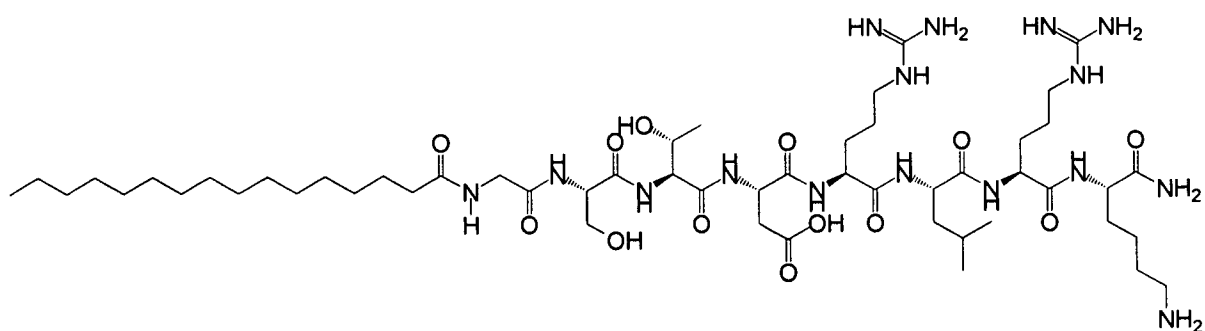
Table 7A. CRF1 i2 loop pepducins

Compd #	Sequence	N terminus	C terminus	MS Theoretical	MS Observed
Compound 14	TYSTDRLRK	C ₁₅ H ₃₁ C(O)-	Amide	689.343	689.45
Compound 15	TYSTDRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	978.212	977.95
Compound 16	GSTDRLRK	C ₁₅ H ₃₁ C(O)-	Amide	585.73	585.8

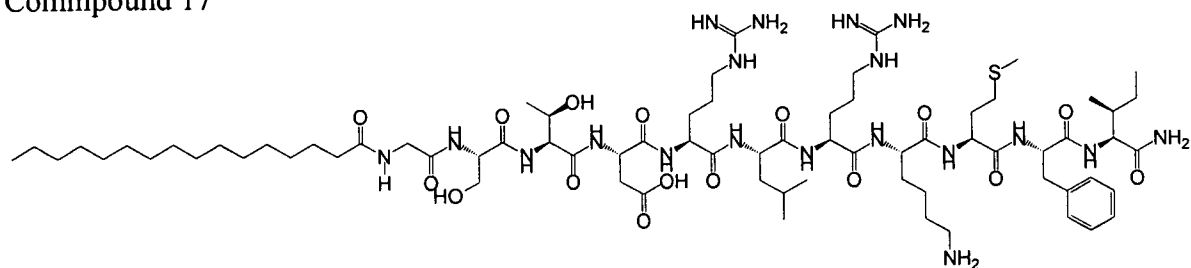
Compound 17	GSTDRLRKMF	C ₁₅ H ₃₁ C(O)-	Amide	781.494	781
Compound 18	GSGTYSTDRLRK	C ₁₅ H ₃₁ C(O)-	Amide	789.933	789.5
Compound 19	STDRLRKMF	C ₁₅ H ₃₁ C(O)-	Amide	696.3895	696
Compound 20	STDRLRKWMF	C ₁₅ H ₃₁ C(O)-	Amide	789.4945	789
Compound 21	GSGTYSTDRLRKWMF	C ₁₅ H ₃₁ C(O)-	Amide	1022.223	1021.5
Compound 22	GSTDRLRRWMFI	C ₁₅ H ₃₁ C(O)-	Amide	888.6055	888.1
Compound 23	GSGTYSTDRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	1078.71	1078.4
Compound 24	GSGRLRKWM	C ₁₅ H ₃₁ C(O)-	Amide	664.8635	664.5
Compound 25	GSGTYDRLRKWM	C ₁₅ H ₃₁ C(O)-	Amide	853.985	854
Compound 26	GSGRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	795.029	794.6
Compound 27	GRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	722.9645	722.7
Compound 28	GSRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	766.5035	766.2
Compound 29	GSTDRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	874.599	875
Compound 30	RLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	694.439	694.2
Compound 31	DRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	751.9825	751.7
Compound 32	TDRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	802.5345	802.2
Compound 33	STDRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	846.0735	846.1
Compound 34	YSTDRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	927.66	927.3
Compound 35	LYSTDRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	690.1936667	690.7
Compound 36	VLTYSTDRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	1084.356	1083.7
Compound 37	GSTDRLRKWMFA	C ₁₅ H ₃₁ C(O)-	Amide	853.559	853.2
Compound 38	GSTDRLRKWMAI	C ₁₅ H ₃₁ C(O)-	Amide	836.551	836
Compound 39	GSTDRLRKWAFI	C ₁₅ H ₃₁ C(O)-	Amide	844.54	844.5
Compound 40	GSTDRLRKAMFI	C ₁₅ H ₃₁ C(O)-	Amide	817.033	816.6
Compound 41	RLRKWMAI	C ₁₅ H ₃₁ C(O)-	Amide	656.391	656
Compound 42	DRLRKWMAI	C ₁₅ H ₃₁ C(O)-	Amide	713.935	713.5
Compound 43	TDRLRKWMAI	C ₁₅ H ₃₁ C(O)-	Amide	764.4865	764.2
Compound 44	ADRLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	787.5215	786.8
Compound 45	TARLRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	780.53	780.2
Compound 46	TDALRKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	759.981	759.2

Compound 47	TDRARKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	781.495	780.7
Compound 48	TDRLAKWMFI	C ₁₅ H ₃₁ C(O)-	Amide	759.981	759.1
Compound 49	TDRLRAWMFI	C ₁₅ H ₃₁ C(O)-	Amide	773.9875	773.2
Compound 50	TDRLRKAMFI	C ₁₅ H ₃₁ C(O)-	Amide	744.9685	744.3
Compound 51	TDRLRKWAFI	C ₁₅ H ₃₁ C(O)-	Amide	772.4755	771.8
Compound 52	TDRLRKWMFA	C ₁₅ H ₃₁ C(O)-	Amide	781.495	780.8
Compound 53	GSTDRLRKAXFI	C ₁₅ H ₃₁ C(O)-	Amide	808.0135	807.3
Compound 54	TDRLRKWXFI	C ₁₅ H ₃₁ C(O)-	Amide	793.5155	792.8

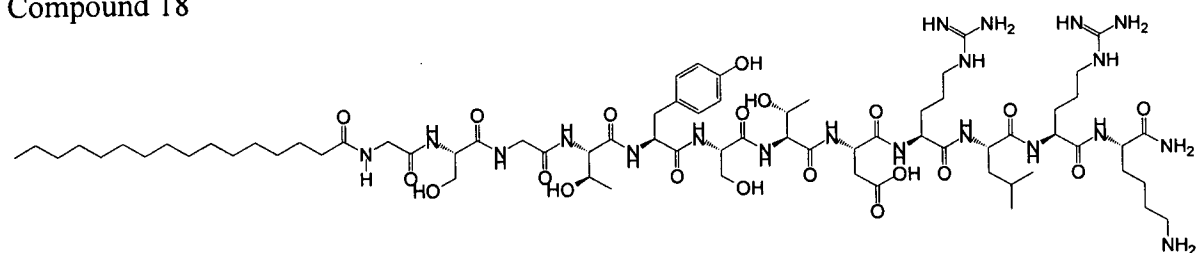
Table 7B. CRF1 i2 loop pepducin structures**Compound Number and Structure****Compound 14****Compound 15****Compound 16**



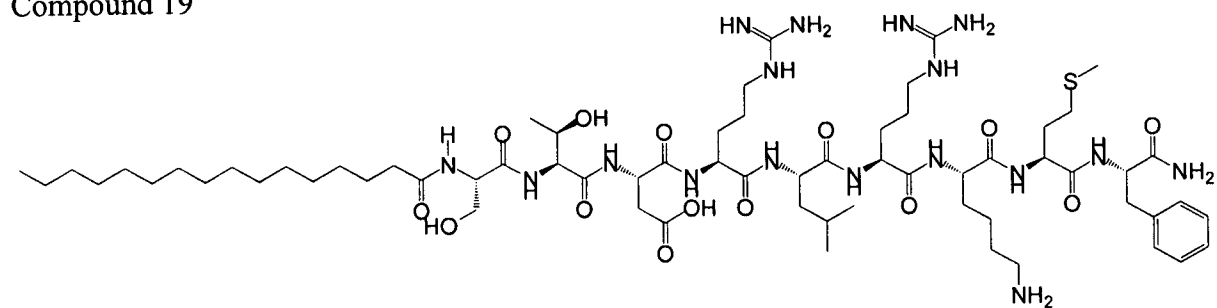
Compound 17



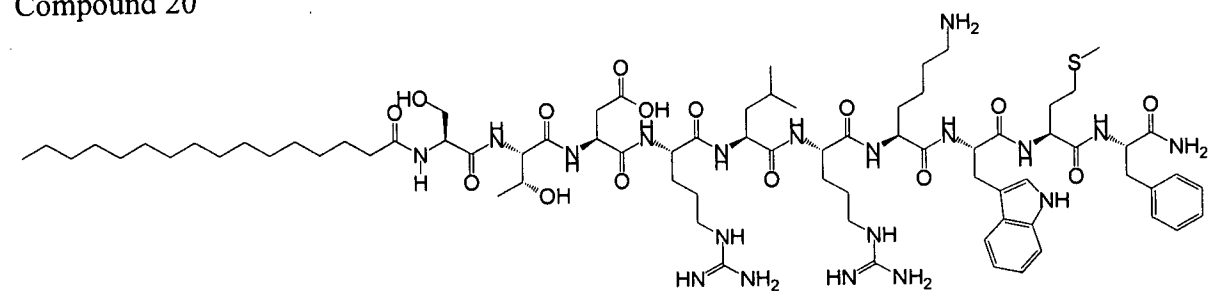
Compound 18



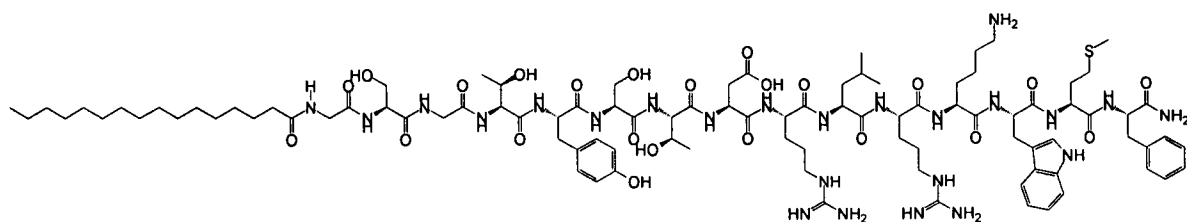
Compound 19



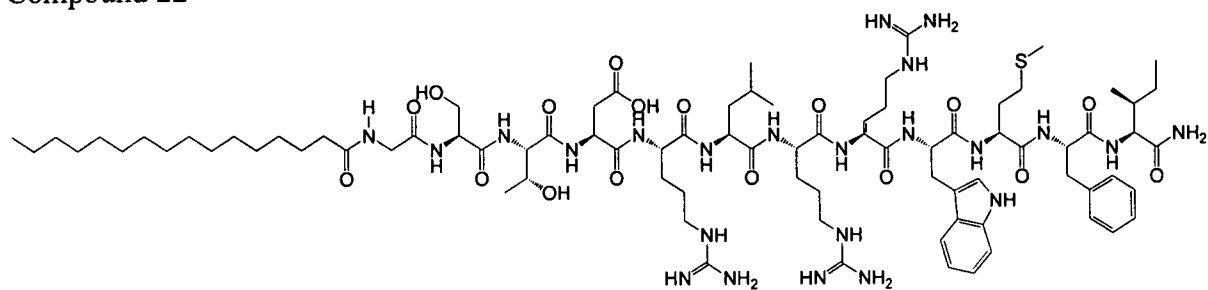
Compound 20



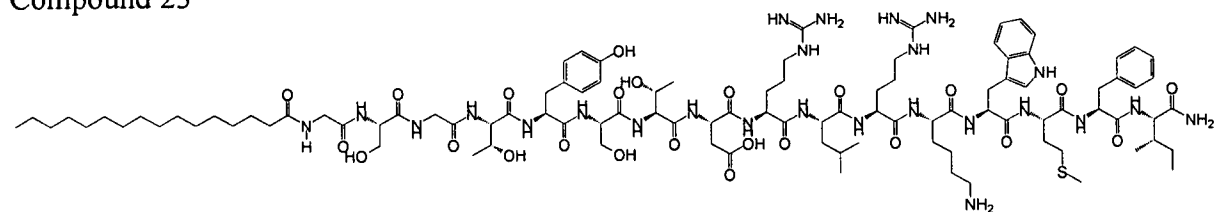
Compound 21



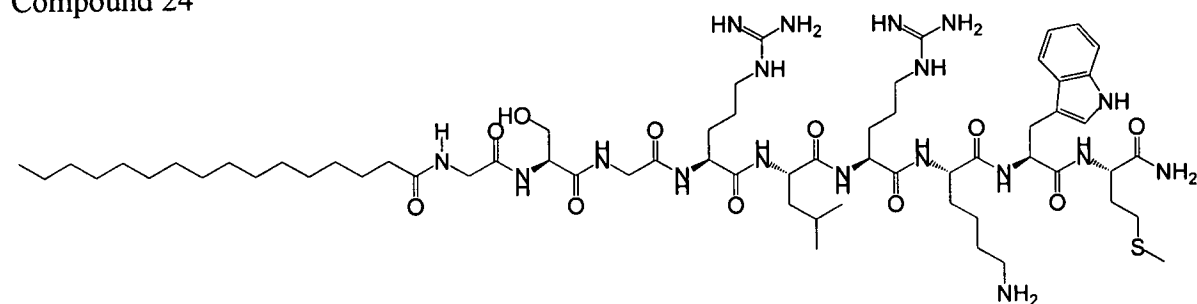
Compound 22



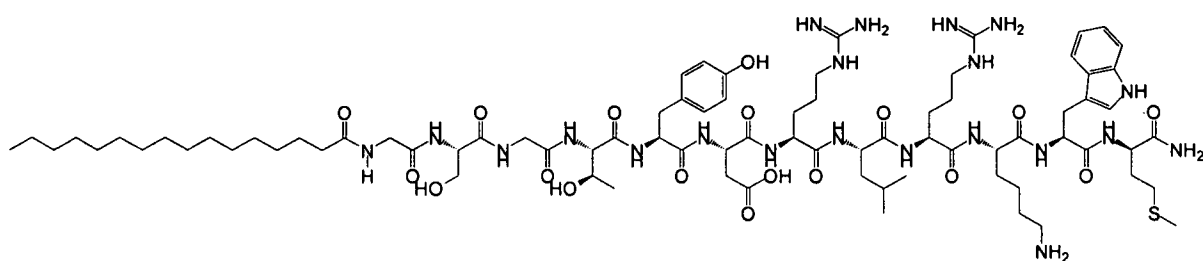
Compound 23



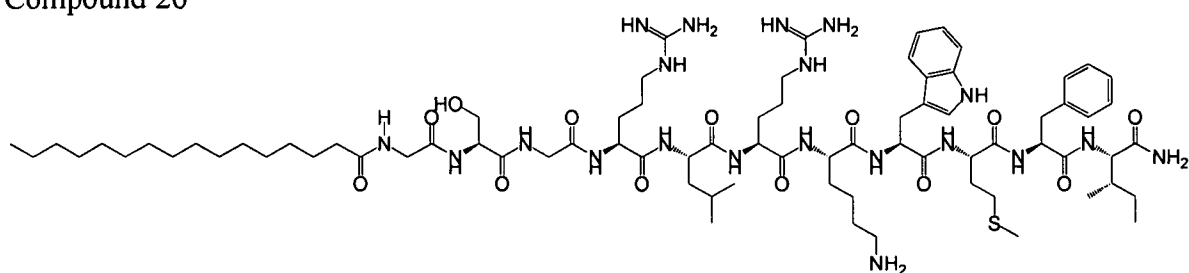
Compound 24



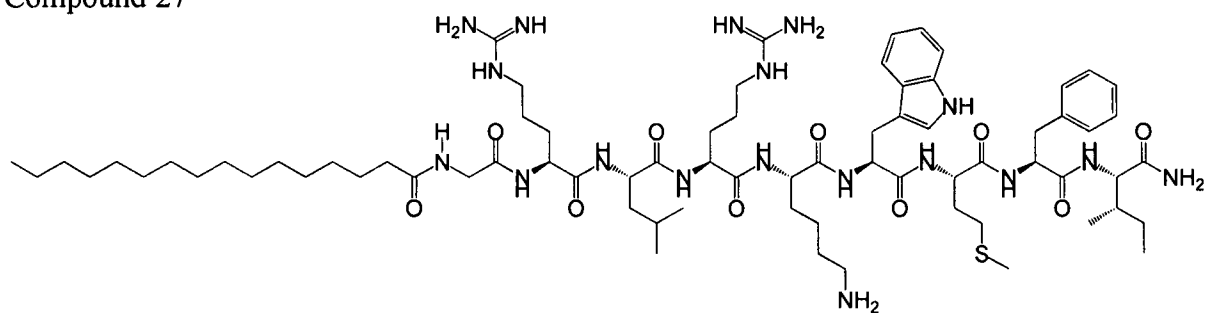
Compound 25



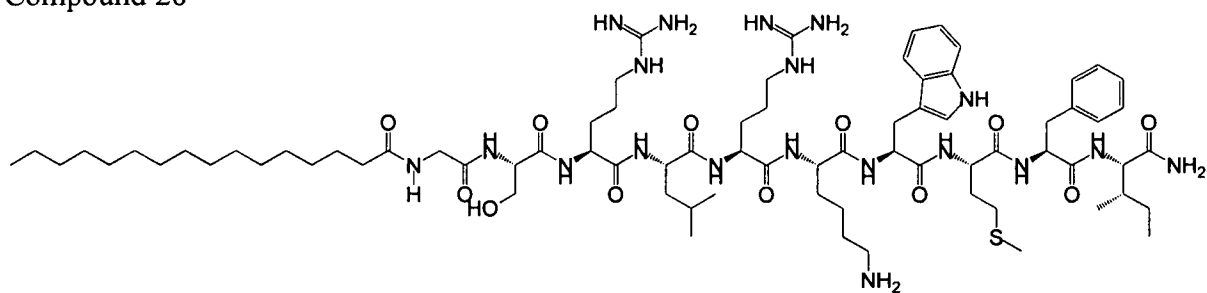
Compound 26



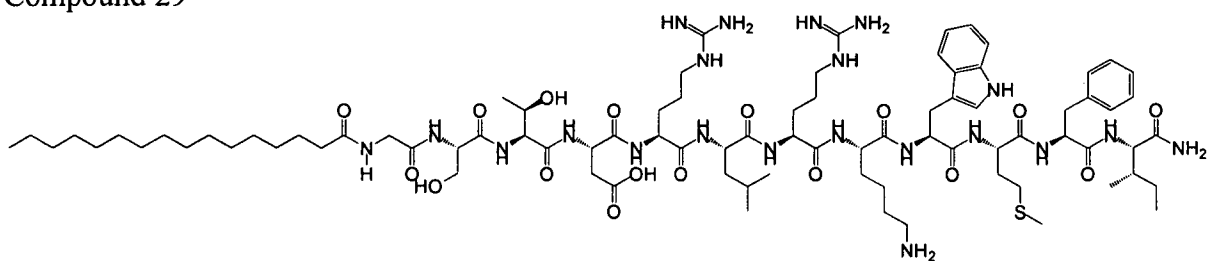
Compound 27



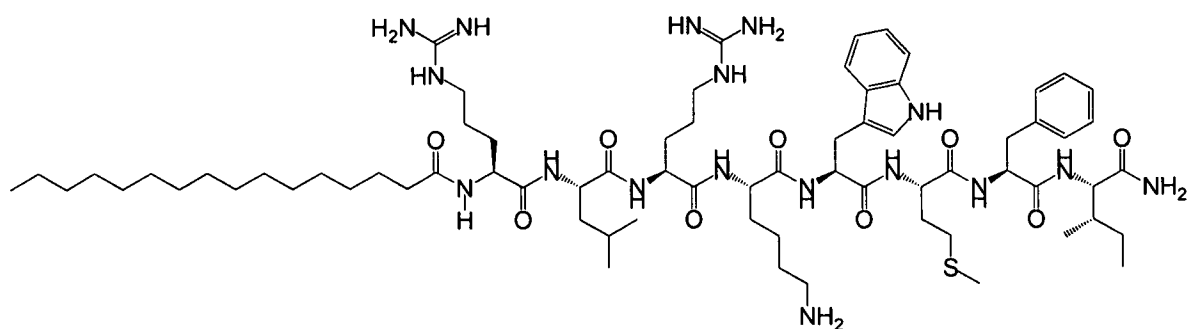
Compound 28



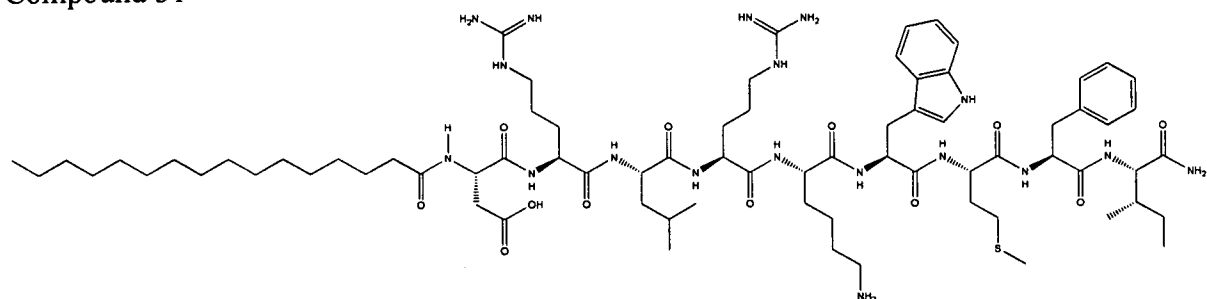
Compound 29



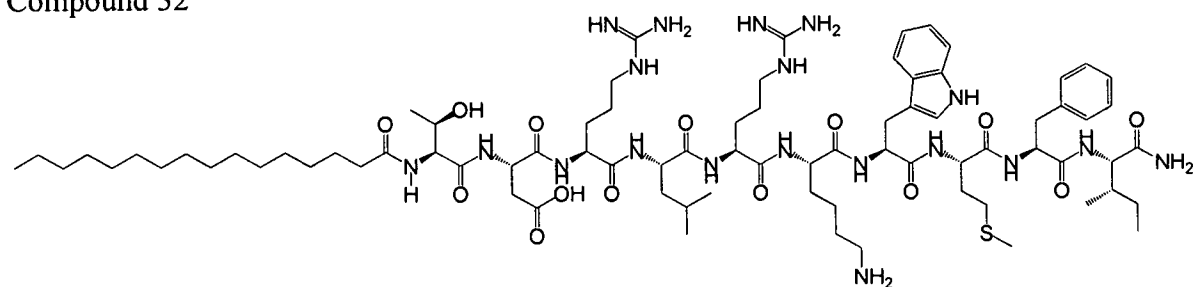
Compound 30



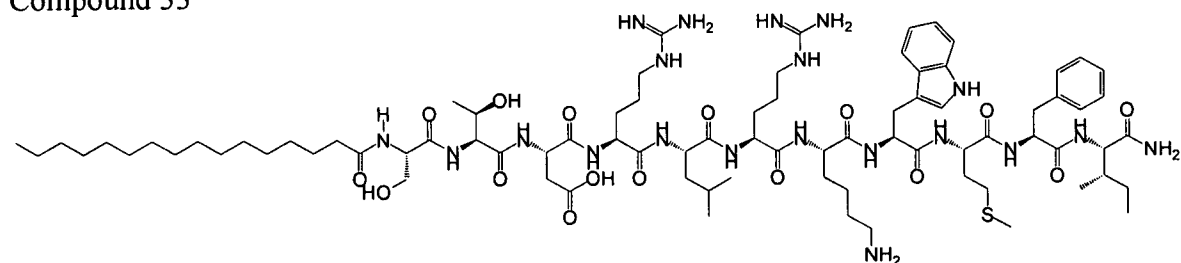
Compound 31



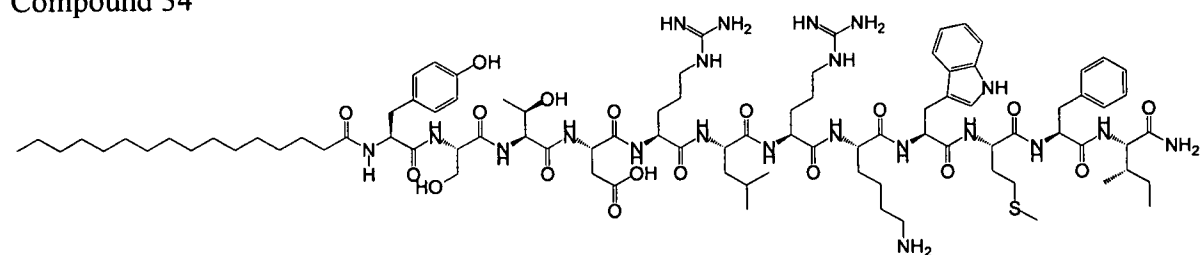
Compound 32



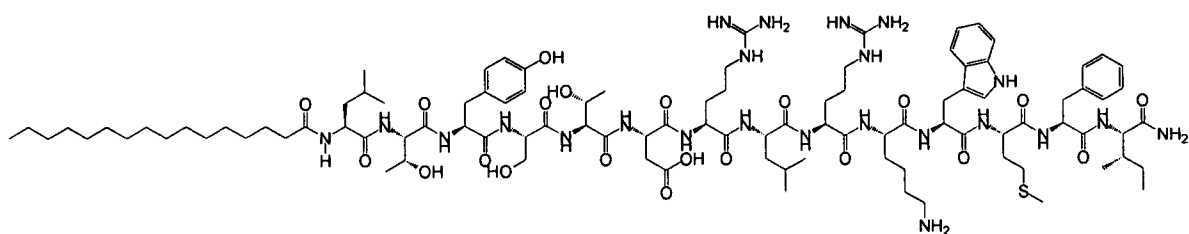
Compound 33



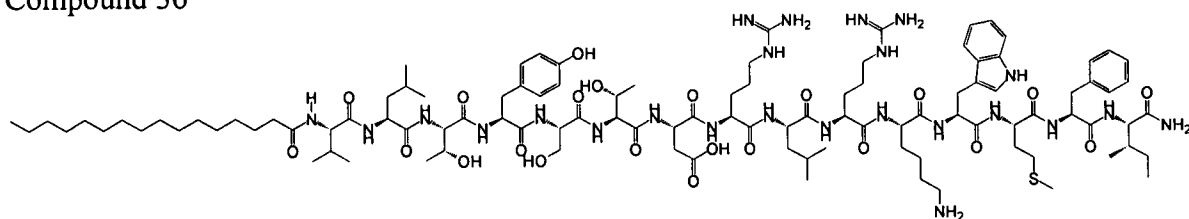
Compound 34



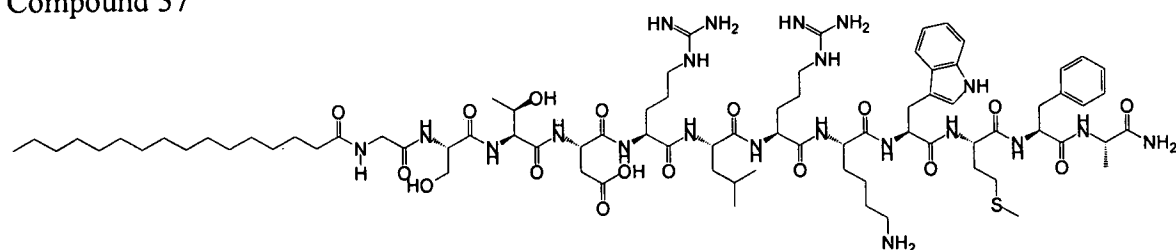
Compound 35



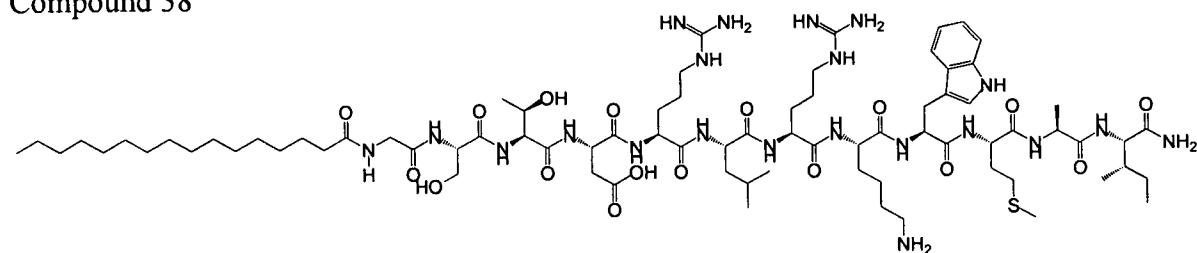
Compound 36



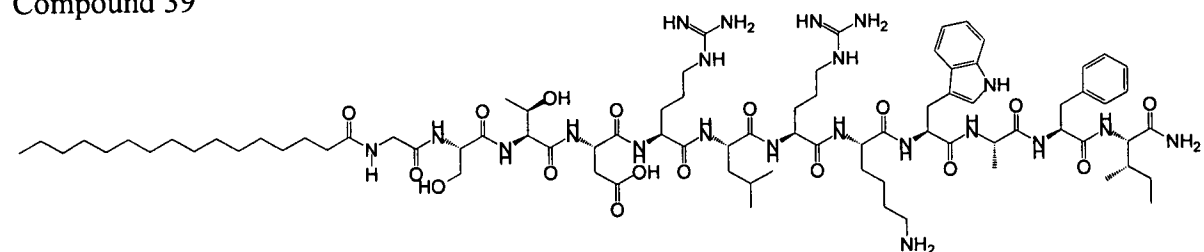
Compound 37



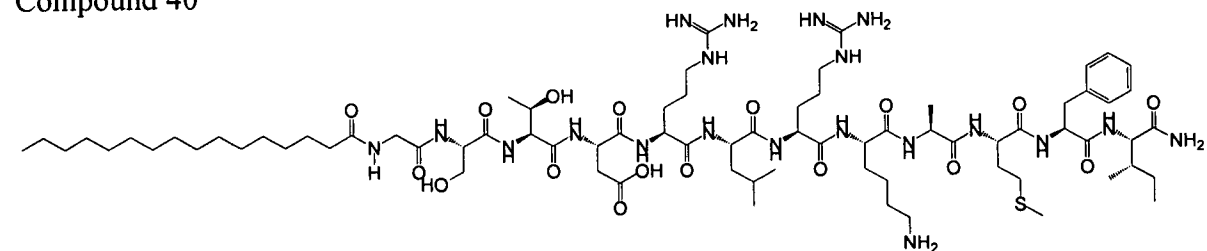
Compound 38



Compound 39



Compound 40



Compound 41

[illegible]

Compound 45

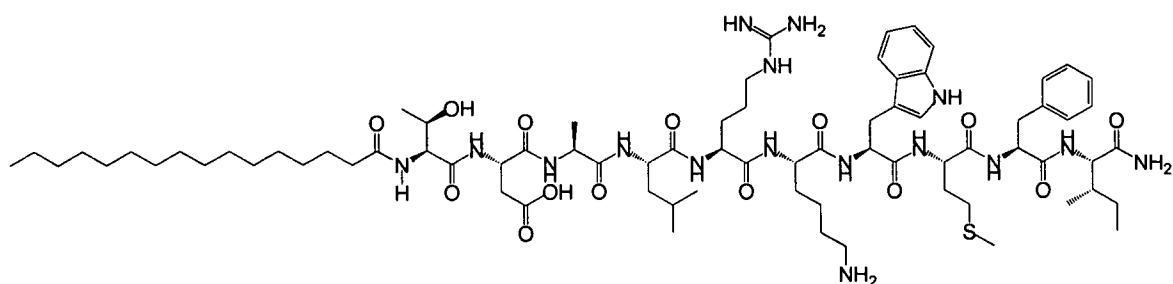
The chemical structure of Compound 45 is a complex polypeptide derivative. It features a long dodecanoate chain at the N-terminus, followed by a sequence of amino acids including threonine, glutamic acid, lysine, proline, arginine, lysine, tryptophan, methionine, alanine, and valine. The C-terminus is a primary amide. Stereochemistry is indicated with wedges and dashes at several chiral centers.

Compound 44

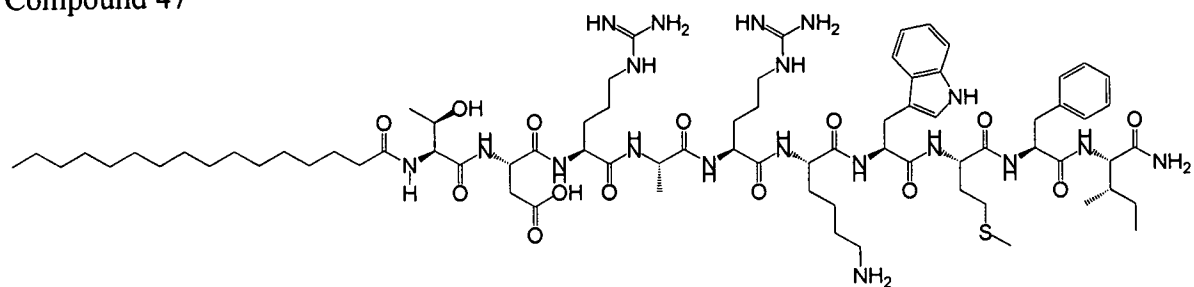
Chemical structure of Compound 44, a complex peptide derivative. The structure shows a long dodecanoate chain at the N-terminus, followed by a series of amino acid residues including a hydroxyproline, two arginines (one with a guanidino group), a tryptophan, and a phenylalanine. The C-terminus is a primary amide. Stereochemistry is indicated with wedges and dashes at several chiral centers.

[illegible]

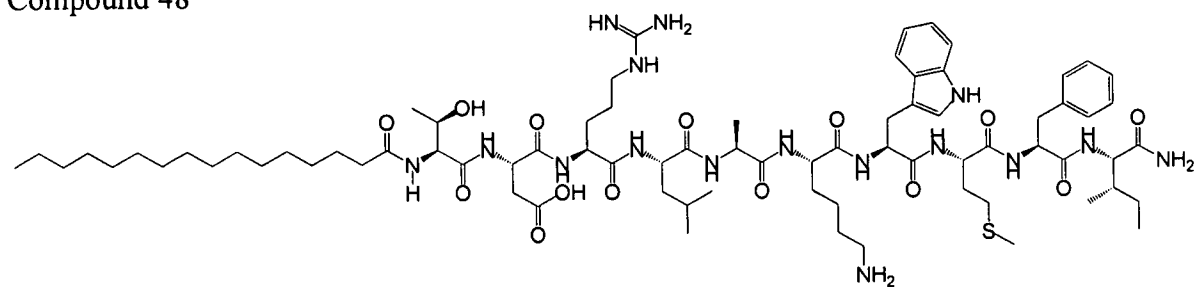
Compound 46



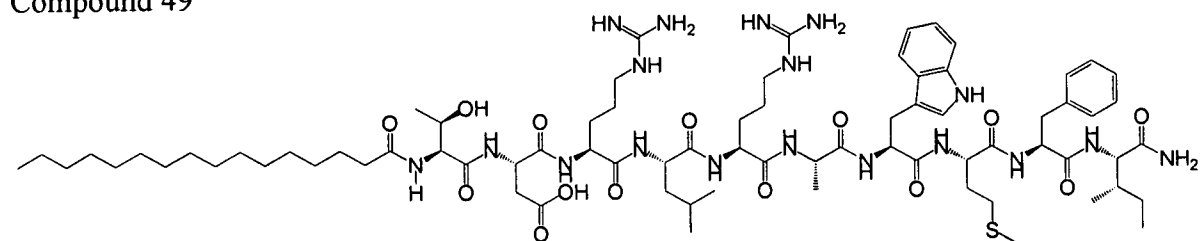
Compound 47



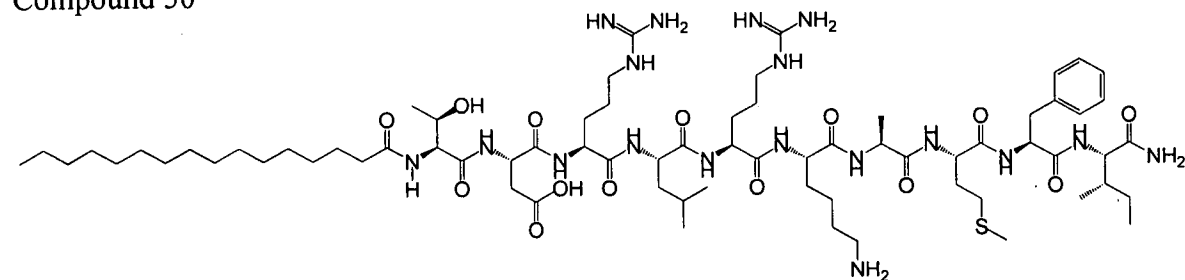
Compound 48



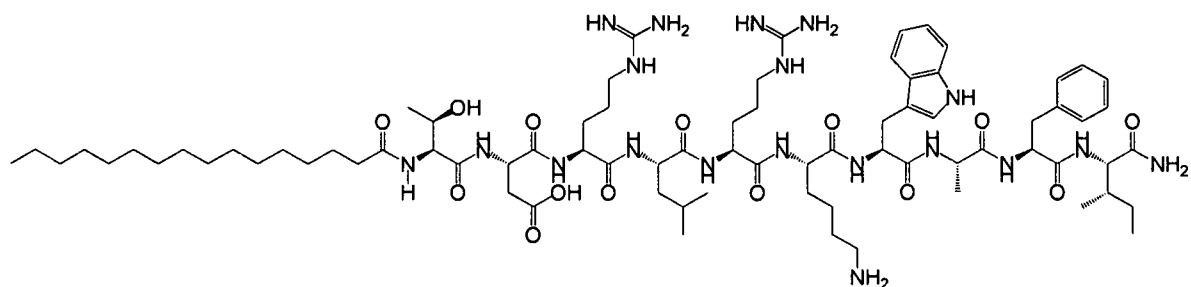
Compound 49



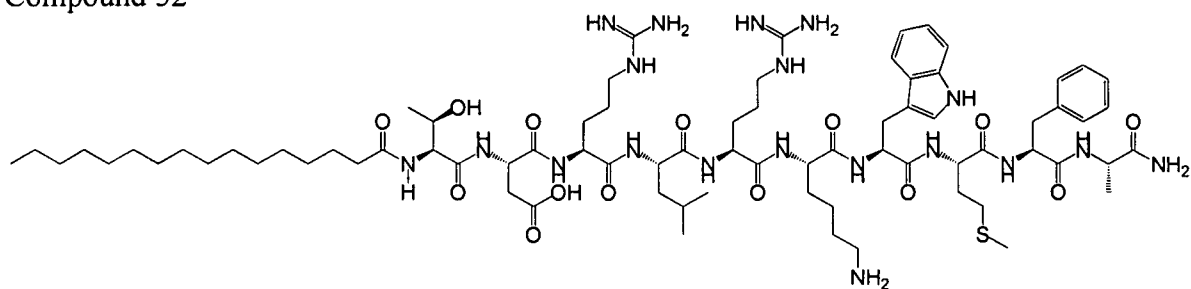
Compound 50



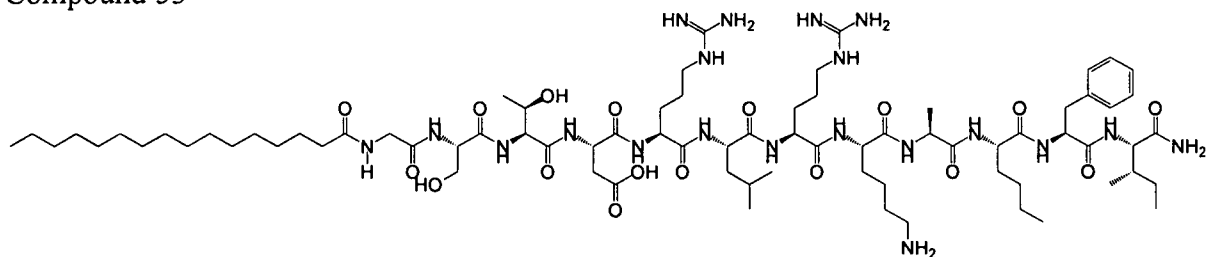
Compound 51



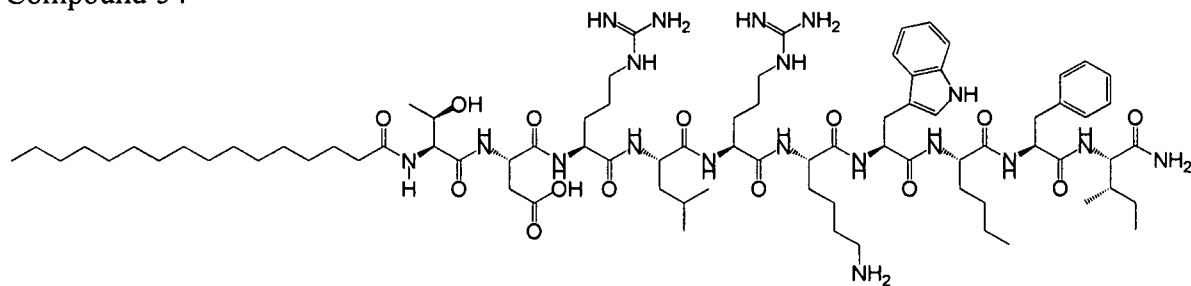
Compound 52



Compound 53



Compound 54

**Table 8A. CRF1 i3 loop pepducins**

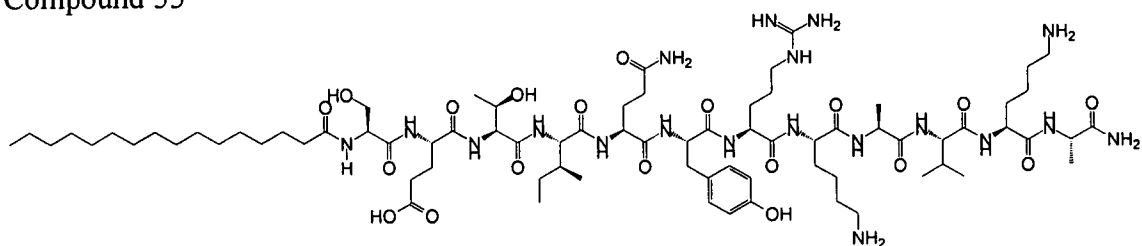
Compound	Sequence	N terminus	C terminus	MS Theoretical	MS Observed
Compound 55	SETIQYRKAVKA	C ₁₅ H ₃₁ C(O)-	Amide	816.506	816.1
Compound 56	TIQYRKAVKA	C ₁₅ H ₃₁ C(O)-	Amide	708.41	708.2
Compound 57	SETIQYRKAVKATL	C ₁₅ H ₃₁ C(O)-	Amide	923.6365	923.7
Compound 58	RILMTKLRASTTS	C ₁₅ H ₃₁ C(O)-	Amide	858.598	858

Compound 59	RILMTKLRA	C ₁₅ H ₃₁ C(O)-	Amide	670.417	670
Compound 60	ASTTSETIQYR	C ₁₅ H ₃₁ C(O)-	Amide	747.8715	747.4
Compound 61	ASTTSETIQYRKAVKA	C ₁₅ H ₃₁ C(O)-	Amide	664.7916667	664.85
Compound 62	ASTTSETIQYRKAVKS	C ₁₅ H ₃₁ C(O)-	Amide	670.1246667	670.2

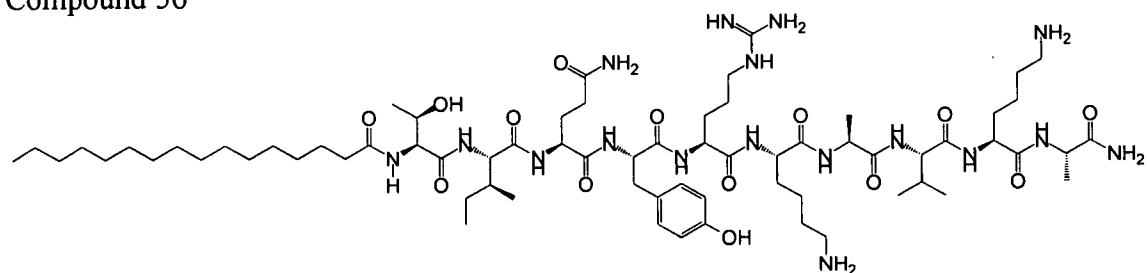
Table 8B. CRF1 i3 loop pepducin structures

Compound Number and Structure

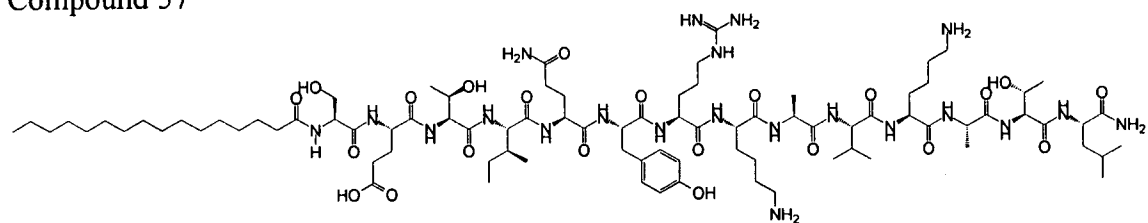
Compound 55



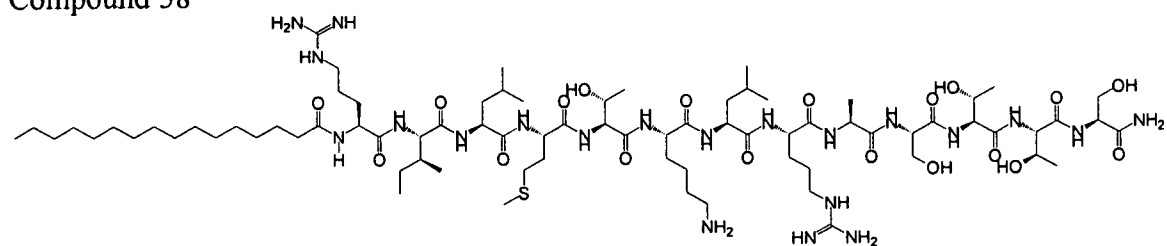
Compound 56



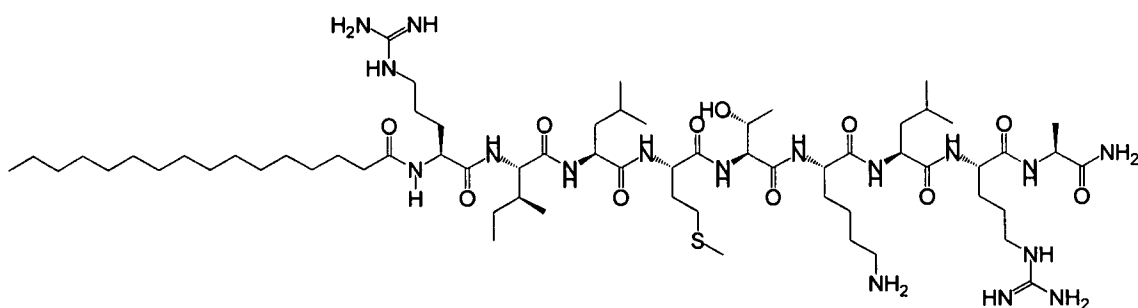
Compound 57



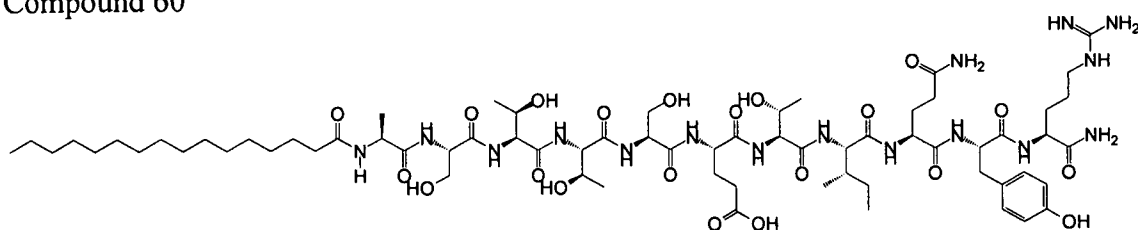
Compound 58



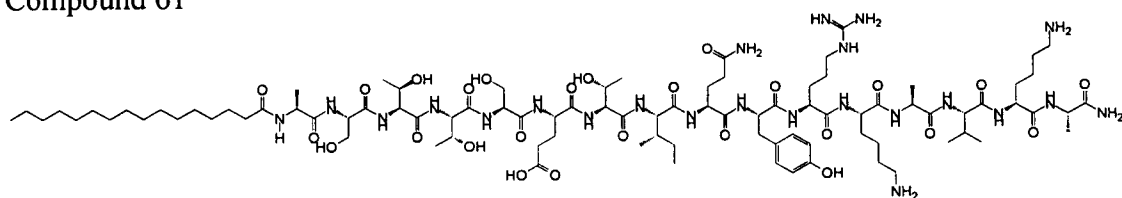
Compound 59



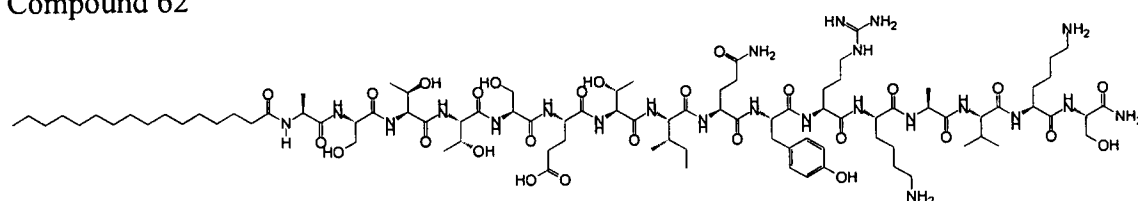
Compound 60



Compound 61



Compound 62



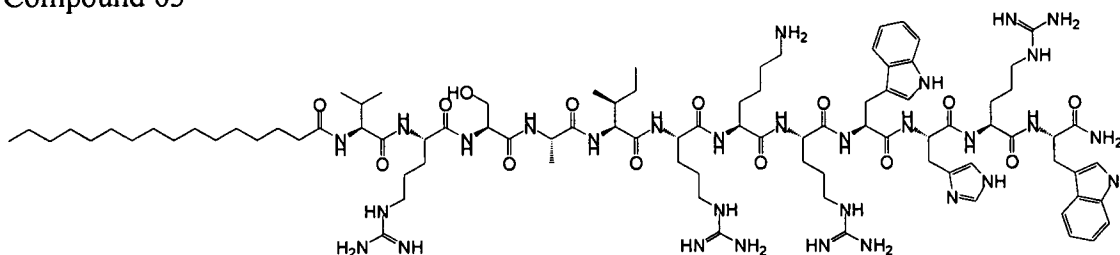
5 Table 9A. CRF1 i4 loop pepducins

Compound	Sequence	N terminus	C terminus	MS Theoretical	MS Observed
Compound 63	VRSAIRKRWHRW	C ₁₅ H ₃₁ C(O)-	Amide	945.1785	945.1
Compound 64	GSIRARVARAM	C ₁₅ H ₃₁ C(O)-	Amide		

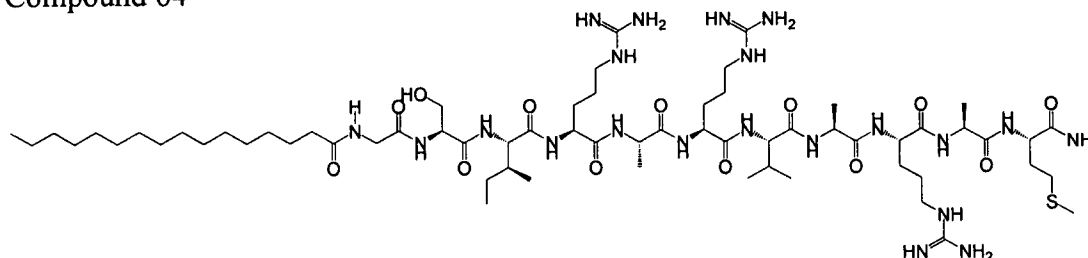
Table 9B. CRF1 i4 loop pepducin structures

Compound Number and Structure

Compound 63



Compound 64



METHODS OF SCREENING

5 FUNCTIONAL ASSAYS

Functional assays suitable for use in detecting and characterizing GPCR signaling include Gene Reporter Assays and Calcium Flux assays, cAMP and kinase activation assays. Several suitable assays are described in detail below.

Gene Reporter Assays

- 10 Cells expressing the CRF1 receptor can be transiently or stably transfected with a reporter gene plasmid construct containing an enhancer element which responds to activation of a second messenger signaling pathway or pathways, thereby controlling transcription of a cDNA encoding a detectable reporter protein. CRF1 expression can be the result of endogenous expression on a cell line or cell type or the result of stable or transient
- 15 transfection of DNA encoding the receptor of interest into a cell line by means commonly used in the art. Immortalized cell lines or primary cell cultures can be used. For example, HEK293 cells can be co-transfected with expression plasmids encoding the GPCR CRFR1 and a reporter plasmid containing firefly luciferase cDNA whose transcription is regulated by tandem repeats of a cAMP response element (CRE-luc).

To test for agonist or inverse agonist activity, cells containing the GPCR and the reporter gene construct can be challenged by the test compound for a predetermined period of time (e.g., 2-12 hours, typically 4 hours). Cells can then be assessed for levels of reporter gene product. If the activated pathway is stimulatory (e.g., Gs or Gq), agonist activity results in activation of transcription factors, in turn causing an increase in reporter gene transcription, detectable by an increase in reporter activity. Inverse agonists will suppress levels of reporter to below basal levels in a dose dependent manner. For example, cells transfected with CRF1 and CRE-luc are challenged by test compounds. Agonist response through Gs activation will cause an increase in cAMP levels in the cells containing both components of the system. Increased cAMP levels result in an increased rate of transcription of the CRE-regulated luciferase cDNA. This increased transcription results in an increased level of active luciferase enzyme, detectable as an increase in luminescence relative to unstimulated cells.

To test for antagonist or inhibitory activity through a stimulatory pathway, cells containing both the GPCR and the reporter gene construct can be activated by a receptor agonist to increase gene reporter product levels. Treatment with antagonists will counter the effect of agonist stimulation in a dose- and receptor-dependent manner. To test for agonist activity on receptor signaling through an inhibitory pathway (eg, Gi), cells can be treated with a systematic activator (e.g., forskolin) to increase levels of reporter gene product. Activation of Gi by treatment with receptor agonist will inhibit this expression by inhibiting adenylyl cyclase.

To screen for antagonist activity, test compounds can be assessed for the ability to counter agonist inhibition of adenylyl cyclase, resulting in increase reporter transcription.

Alternatively, a plasmid construct expressing the promiscuous G-protein Ga16 can be used to obtain a positive signal from a GPCR which normally couples to an inhibitory G-protein. Co-expression of the chimeric G-protein Gaq/Gai5 (Coward et al. Analytical Biochemistry 270, 242-248 (1999)) allows coupling to Gi-coupled receptors and conversion of second messenger signaling from the inhibitory Gi pathway to the stimulatory Gq pathway. Agonist and antagonist assessment in these systems is the same as the stimulatory pathways. Well-to-well variation caused by such factors as transfection efficiency, unequal plating of cells, and cell survival rates can be normalized in transient transfection assays by

co-transfecting a constitutively expressing reporter gene with a non-interfering signal independent of the regulated reporter.

Gene reporter assay for the CRF1

5 CRF1 signals predominantly through Gs. HEK293 cells stably expressing CRF1 can be seeded in a white opaque 96-well tissue culture plate (CulturePlate, Perkin Elmer) and can be transiently transfected with CRE (cAMP Response Element)-luciferase (Stratagene PathDetect) (1 ug/ml) using LipofectAMINE (Invitrogen) according to manufacturer's protocol in serum-free DMEM. 16-24 hours post-transfection, media can be replaced with
10 DMEM supplemented with 0.1-0.2% BSA with or without ligand and test compound for 4 hours. The media can be removed and cells can be lysed with 50 ul SteadyLite HTS (Perkin Elmer) reconstituted in Substrate Buffer and diluted 1:2 in PBS. After 10 minutes, luminescence can be measured using a TopCount NXT microplate reader.

When screening for antagonists, optimal agonist (CRF or urocortin I) concentrations
15 can be determined by experimentally derived calculations of EC₅₀ values. Activity linked to Gq signaling can be assessed using the above procedure substituting SRE-luciferase or NFAT-luciferase as the reporter gene.

Calcium Flux Assay

20 Calcium Flux Assay is one of the most widely used cell-based GPCR functional assays. It most often uses calcium sensing fluorescent dyes such as fura2 AM, fluo-4 and Calcium-4 to measure changes in intracellular calcium concentration. It is used mainly to detect GPCR signaling via Gαq subunit, but can be used to measure signaling through any pathway which leads to a detectable increase in intracellular calcium. Activation of these
25 Gq-coupled GPCRs leads to activation of phospholipase C, which subsequently leads to increase in inositol phosphate production. IP3 receptors on endoplasmic reticulum sense the change then release calcium into cytoplasm. Intracellular calcium binding to the fluorescent dyes can be detected by instruments that quantify fluorescent intensities, such as FLIPR Tetra, Flexstation (MDS) and FDSS (Hamamatsu). In addition to assess Gq-couple
30 receptor signaling, calcium flux assay can also be used to study Gs and Gi couple receptors by co-expressing CNG (cyclic nucleotide gated calcium channel) or chimeric G-proteins

(Gqi5, Gsi5 for example). Activation of some Gi-coupled receptors can also be detected by calcium flux assay via Gβγ mediated phospholipase C activation.

CRF1 assessment of calcium flux

5 An example of the use of the calcium flux assay can be assessing a-CRF1 activation of CRF1 in Y-79, a human retinoblastoma cell line which endogenously expresses functional CRF1. Y-79 cells can be seeded into 96-well black plates with clear bottom at 200K/well in Hank's balanced salt solution with 20mM HEPES, 0.1% BSA. After dye loaded by incubating in Calcium-4 dye at room temperature for 1 hour, cell plates can be placed in
10 Flexstation 3. The addition of test compound or reference antagonists can be done either by manual pipetting or by liquid handling on Flexstation. The latter allows the assesement of agonist activity of the test compound. After incubation of 15 minutes at 37°C, CRF can be added on Flexstation and receptor activation can be assessed by measuring changes in fluorescent intensity.

HTRF cAMP Assay and IP-One Assay (Cisbio)

 HTRF (homogeneous time resolved fluorescence) is a technology developed by Cisbio Bioassays based on TR-FRET (time-resolved fluorescence resonance energy transfer).
20 Cisbio Bioassays has developed a wide selection of HTRF-based assays compatible with whole cells, thereby enabling functional assays run under more physiological conditions. cAMP kits are based on a competitive immunoassay using cryptate-labeled anti-cAMP antibody and d2-labeled cAMP. This assay allows the measurement of increase in intracellular cAMP upon Gs-coupled receptor activation as well as decrease in forskolin
25 stimulated increase in cAMP upon Gi-coupled receptor activation. Cells expressing CRF1 endogenously or via transfection can be used to assess compound pharmacology using cAMP assays as a means to measure the activity of adenylyl cyclase resulting from CRF1 activation or inhibition.

 The IP-One assays are competitive immunoassays that use cryptate-labeled anti-IP1
30 monoclonal antibody and d2-labeled IP1. IP1 is a relatively stable downstream metabolite of IP3, and accumulates in cells following Gq receptor activation.

CRF1 assessment of cAMP

An example of the use of the cAMP assay can be assessing CRF activation of CRF1 in Y-79, a human retinoblastoma cell line which endogenously expresses functional CRF1. Y-79 cells were seeded into 96-well half area black plates at 30K/well in Hank's balanced salt solution with 50mM HEPES, 0.1% BSA, 200 uM IBMX. Compounds to be tested for agonist activity were added to cells, incubated for 30 minutes at 37 degrees C and assayed for cAMP concentration. To test for antagonist activity, compounds to be tested were added to cells, followed by the addition of agonist at an experimentally determined optimal concentration, generally the EC80. Plates were incubated for 30 minutes at 37 degrees C and assayed for cAMP. To determine concentration of cAMP in each well, d2-labeled cAMP in Conjugate/Lysis buffer was added to wells. This addition lysed the cells and input a known concentration of labeled cAMP. This was followed by the addition of anti-cAMP antibody conjugated to cryptate. FRET occurs when cryptate-labeled antibody binds to d2-labeled cAMP. Therefore, the specific signal is inversely proportional to the concentration of cAMP in the sample. Conversion of signal to concentration of cAMP in the well was accomplished by comparing the FRET signal of sample to a standard curve generated using known concentrations of cAMP.

Testing of compounds was conducted in this way and the results are set forth in Table 10. For the data in Table 5 IC50 values from: 1nM to 500nM are designated as *****; 501nM to 1000nM are designated as ****; 1001nM to 5000nM are designated as ***; 5001nM to 10,000nM are designated as **; and greater than 10,000nM are designated *.

Table 10. CRF1 cAMP screening data (Y79 cells, 300 nM pepducin against agonist dose response)

Sample Lot	Loop	Sequence	N terminus	C terminus	IC50	% Inhibition (± SD)
Compound 58	i3	RILMTKLRASTTS	Lipid	Amide	****	35
Compound 62	i3	ASTTSETIQYRKAVKS	Lipid	Amide	***	50
Compound 5	i1	RLRSIRSLRNIIHWN	Lipid	Amide	***	54 ± 13
Compound 22	i2	GSTDRLRRWMFI	Lipid	Amide	***	50 ± 15
Compound 26	i2	GSGRLRKWMFI	Lipid	Amide	***	63
Compound 64	i1	RSIRSLRNIIHWN	Lipid	Amide	***	55 ± 13
Compound 28	i2	GSRLRKWMFI	Lipid	Amide	***	52 ± 5

Compound 29	i2	GSTDRLRKWMFI	Lipid	Amide	****	53 ± 14
Compound 30	i2	RLRKWMFI	Lipid	Amide	***	39 ± 7
Compound 31	i2	DRLRKWMFI	Lipid	Amide	***	30 ± 17
Compound 32	i2	TDRLRKWMFI	Lipid	Amide	****	53 ± 9
Compound 33	i2	STDRLRKWMFI	Lipid	Amide	***	36 ± 9
Compound 34	i2	YSTDLRKWMFI	Lipid	Amide	****	21 ± 5
Compound 35	i2	LTYSTDLRKWMFI	Lipid	Amide	***	26 ± 15
Compound 36	i2	VLTYSTDRLRKWMFI	Lipid	Amide	*	19 ± 10
Compound 37	i2	GSTDRLRKWMFA	Lipid	Amide	***	45 ± 19
Compound 38	i2	GSTDRLRKWMAI	Lipid	Amide	***	60 ± 8
Compound 40	i2	GSTDRLRKAMFI	Lipid	Amide	****	61 ± 20
Compound 41	i2	RLRKWMAI	Lipid	Amide	****	40
Compound 42	i2	DRLRKWMAI	Lipid	Amide	**	65
Compound 43	i2	TDRLRKWMAI	Lipid	Amide	*	48
Compound 44	i2	ADRLRKWMFI	Lipid	Amide	*	42
Compound 45	i2	TARLRKWMFI	Lipid	Amide	*	70
Compound 46	i2	TDALRKWMFI	Lipid	Amide	*	58
Compound 47	i2	TDRARKWMFI	Lipid	Amide	***	62
Compound 48	i2	TDRLAKWMFI	Lipid	Amide	*	30
Compound 49	i2	TDRLRAWMFI	Lipid	Amide	*	42
Compound 50	i2	TDRLRKAMFI	Lipid	Amide	*	58
Compound 51	i2	TDRLRKWAFI	Lipid	Amide	****	47 ± 7
Compound 52	i2	TDRLRKWMFA	Lipid	Amide	*	70
Compound 53	i2	GSTDRLRKAXFI	Lipid	Amide	****	50 ± 14
Compound 54	i2	TDRLRKWXFI	Lipid	Amide	***	55 ± 7

Receptor Binding assays

- 5 Peptide ligands can be radio-labeled with I-125. Test compounds can be assessed by adding increasing amounts of unlabeled test against known tracer amounts of labeled ligand.

The test compounds can be assessed for the ability to compete for receptor binding sites (competitive) or to affect the affinity of ligands indirectly (non-competitive). In addition, the affinity of a compound for the receptor can be assessed by the ability of unlabeled compound to displace trace amounts of labeled test compound. Radio-labeled ligands can also be used to assess receptor numbers on cells or membranes.

IN VIVO ASSAYS

CRF1 activation leads to an increase in colonic motility. Peripheral administration of CRF or urocortin I intravenously or intraperitoneally induces propulsive colonic motor events, reduction of colonic transit time, and diarrhea in rodents.

Colonic function

Distal colonic function can be measured by assessing the time required to expel a plastic bead inserted into the distal colon of a rat. Efficacy of CRF1 compounds of this invention in this model would be assessed by the ability to reduce colonic motility, thereby lengthening the time to expulsion of the bead.

Visceral pain associated with colonic distension.

Colorectal distention results in contractions of the muscles of the abdomen and hind limbs. This response has been used as a quantitative indicator of visceral pain. Visceromotor response can be quantified using the abdominal withdrawal reflex (al-Chaer et al. *Gastroenterology* 119: 1276-1285 (2000)). Distension is achieved by the insertion into the descending colon and inflation of a latex balloon. A five-part scoring scale relates reflexive actions to intensity of nociception. A pain threshold can be determined by relating pressure in the distension balloon to the onset of a defined pain reflex. Effects of CRFR1 activation on visceral pain due to colonic distension can be assessed by administration of CRF or CRF1-specific agonists. CRF1 receptor compounds of the invention which inhibit CRF1 activation would be expected to increase the pain threshold.

The teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various

changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound represented by Formula I:

5

T-L-P,

or pharmaceutically acceptable salts thereof, wherein:

P is a peptide comprising at least three contiguous amino-acid residues of an intracellular i1, i2, i3 loop or an intracellular i4 domain of the CRF1 receptor;

10

L is a linking moiety represented by C(O) and bonded to P at an N terminal nitrogen of an N-terminal amino-acid residue;

and T is a lipophilic tether moiety bonded to L, wherein the C-terminal amino acid residue of P is optionally functionalized.

15

2. The compound of Claim 1, wherein P comprises at least six contiguous amino acid residues.

3. The compound of Claim 1, wherein P is derived from the i1 loop and is represented by the following structural formula or pharmaceutically acceptable salts thereof

20

X₁-X₂-X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇-X₁₈-X₁₉-R₁

wherein:

X₁ is absent or a valine residue;

X₂ is absent or a leucine or glycine residue;

X₃ is absent or a phenylalanine or serine residue;

25

X₄ is absent or a leucine or glycine residue;

X₅ is absent or an arginine residue;

X₆ is absent or a leucine or isoleucine residue;

X₇ is absent or an arginine residue;

X₈ is absent or a serine residue;

30

X₉ is absent or an isoleucine residue;

X₁₀ is absent or an arginine residue;

X₁₁ is absent or a cysteine or serine residue;

X₁₂ is absent or a leucine residue;

X₁₃ is absent or an arginine residue;

5 X₁₄ is absent or an asparagine residue;

X₁₅ is absent or an isoleucine residue;

X₁₆ is absent or an isoleucine residue;

X₁₇ is absent or a histidine residue;

X₁₈ is absent or tryptophan residue;

10 X₁₉ is absent or an asparagine residue; provided that at least five of X₁-X₁₉ are present;

R₁ is OR₂ or N(R₂)₂;

each R₂ is independently hydrogen or (C₁-C₁₀)alkyl; and

from 0 to 5 amino acid residues are present in the D configuration.

15

4. The compound of Claim 3, wherein at least four of X₇, X₈, X₉, X₁₀, X₁₁, X₁₂, X₁₃ and X₁₄ are present.

5. The compound of Claim 4, wherein

20 X₇ is an arginine residue;

X₈ is a serine residue;

X₉ is an isoleucine residue; and

X₁₀ is an arginine residue.

25 6. The compound of Claim 4, wherein

X₁₁ is a cysteine or serine residue;

X₁₂ is a leucine residue;

X₁₃ is an arginine residue; and

X₁₄ is an asparagine residue.

30

7. The compound of Claim 6, wherein X₁₁ is a cysteine residue.

8. The compound of Claim 6, wherein X_{11} is a serine residue.

9. The compound of Claim 3, wherein

X_{14} is an asparagine residue;

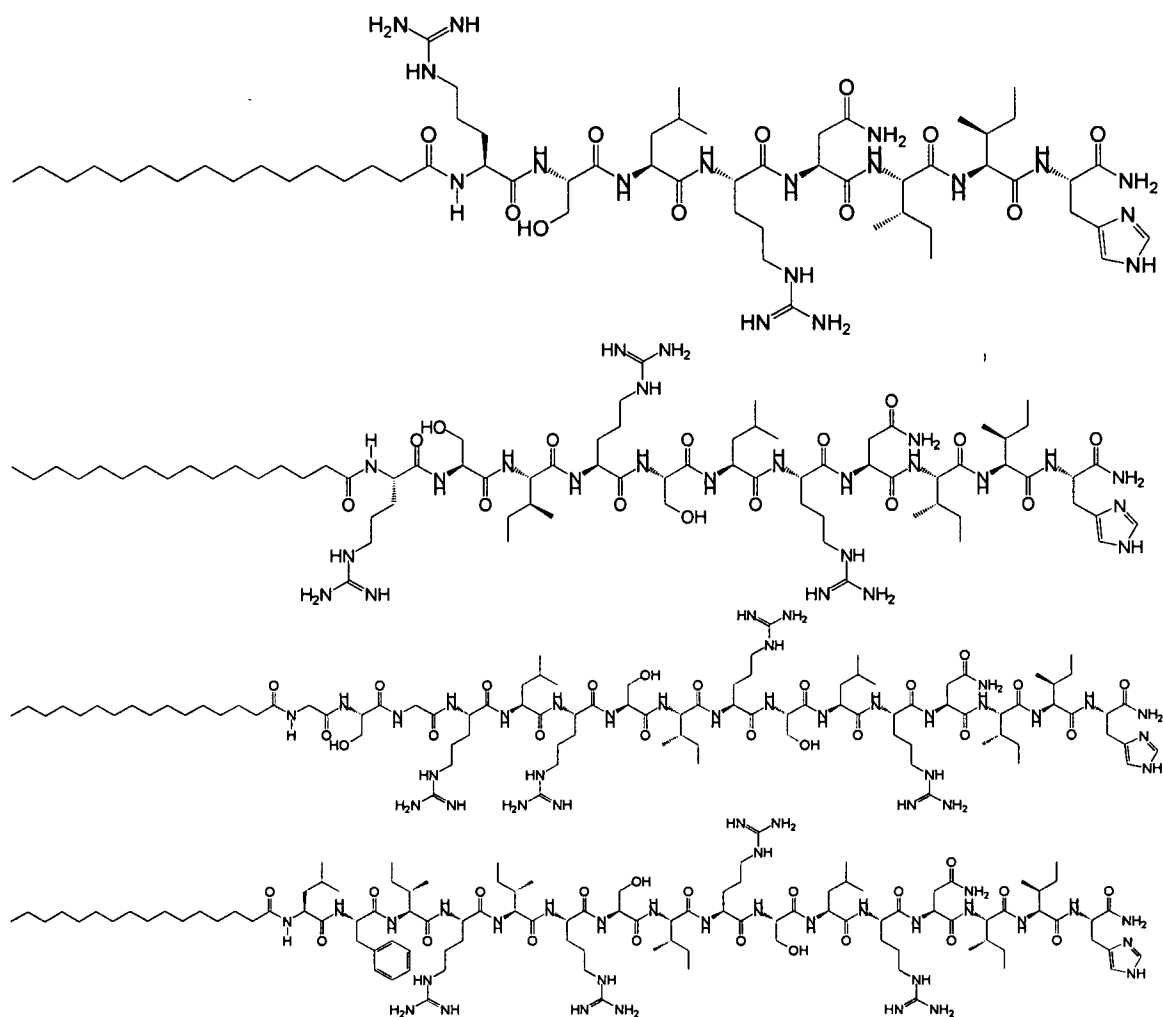
5 X_{15} is an isoleucine residue;

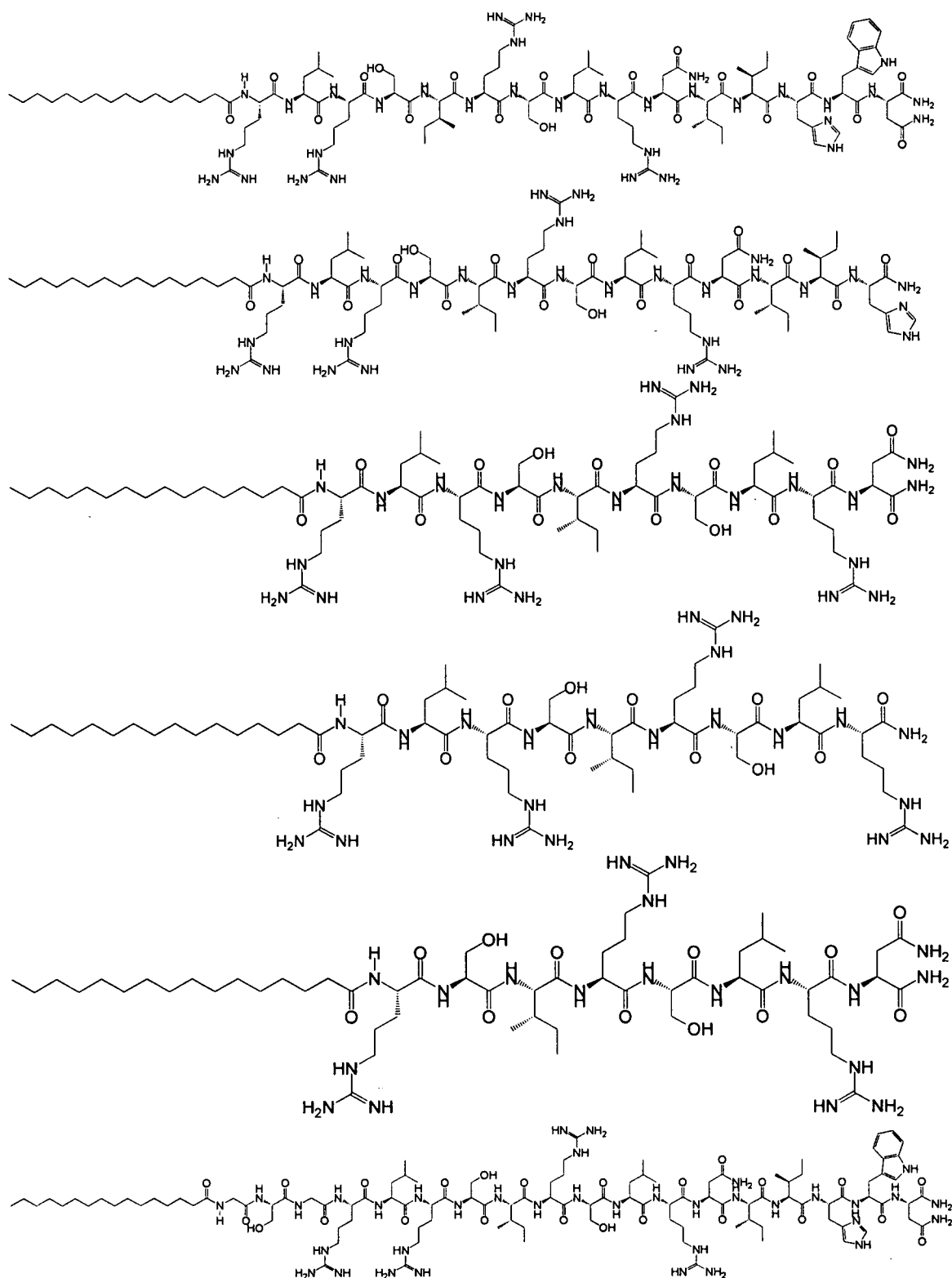
X_{16} is an isoleucine residue; and

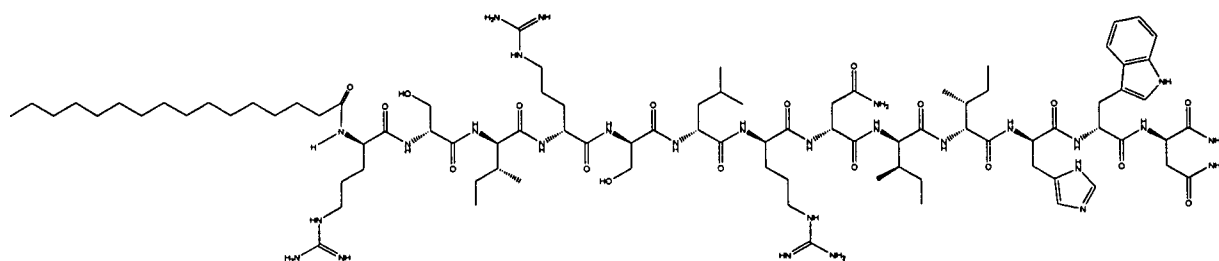
X_{17} is a histidine residue.

10. The compound of Claim 3, selected from:

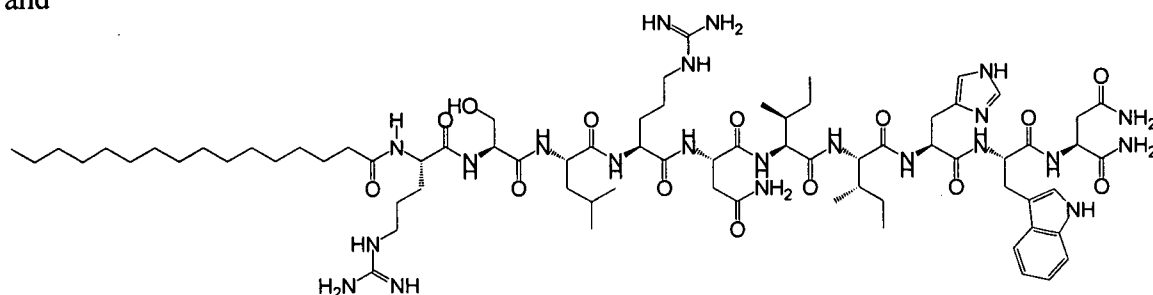
10







and



or a pharmaceutically acceptable salt of any of the foregoing.

- 5
11. The compound of Claim 1, wherein P comprises at least three contiguous amino acid residues of the i1 loop.
12. The compound of Claim 11, wherein P is derived from the following sequence:
- 10 VLFLRLRSIRCLRNIHWN (SEQ ID NO: 1).
13. The compound of Claim 12, wherein P is a sequence selected from:
- | | |
|-----------------------|------------------|
| VLFLRLRSIRCLRNIHWN | (SEQ ID NO: 1); |
| VLFLRLRSIRCLRNIHW | (SEQ ID NO: 2); |
| 15 GSGRLRSIRSLRNIIHWN | (SEQ ID NO: 3); |
| VLFLRLRSIRCLRNIH | (SEQ ID NO: 4); |
| FLRLRSIRCLRNIHWN | (SEQ ID NO: 5); |
| GSGRLRSIRSLRNIIH | (SEQ ID NO: 6); |
| LFIRIRSIRSLRNIIH | (SEQ ID NO: 7); |
| 20 VLFLRLRSIRCLRNI | (SEQ ID NO: 8); |
| RLRSIRCLRNIHWN | (SEQ ID NO: 9); |
| RLRSIRSLRNIIHWN | (SEQ ID NO: 10); |
| VLFLRLRSIRCLRNI | (SEQ ID NO: 11); |
| VLFLRLRSIRCLRNI | (SEQ ID NO: 12); |

	RLRSIRSLRNIIH	(SEQ ID NO: 13);
	RSIRSLRNIIHWN	(SEQ ID NO: 14);
	VLFLRLRSIRCLR	(SEQ ID NO: 15);
	RSIRCLRNIHWN	(SEQ ID NO: 16);
5	RSIRSLRNIIH	(SEQ ID NO: 17);
	RSIRCLRNIH	(SEQ ID NO: 18);
	RLRSIRSLRN	(SEQ ID NO: 19);
	RSLRNIIHWN	(SEQ ID NO: 20);
	RLRSIRSLR	(SEQ ID NO: 21);
10	RSLRNIIH	(SEQ ID NO: 22); and
	RSIRSLRN	(SEQ ID NO: 23).

14. The compound of Claim 1, wherein is P derived from the i2 loop and is represented by the following structural formula or a pharmaceutically acceptable salt thereof
- 15 $Y_1-Y_2-Y_3-Y_4-Y_5-Y_6-Y_7-Y_8-Y_9-Y_{10}-Y_{11}-Y_{12}-Y_{13}-Y_{14}-Y_{15}-Y_{16}-Y_{17}-Y_{18}-Y_{19}-R_1$,
wherein:
- Y_1 is absent or a histidine residue;
- Y_2 is absent or a threonine residue;
- Y_3 is absent or an alanine residue;
- 20 Y_4 is absent or an isoleucine or a glycine residue;
- Y_5 is absent or a valine or serine residue;
- Y_6 is absent or a leucine or glycine residue;
- Y_7 is absent or a threonine or serine residue;
- Y_8 is absent or a tyrosine or glycine residue;
- 25 Y_9 is absent or serine, threonine or glycine residue;
- Y_{10} is absent or a threonine, serine, tyrosine, glycine or alanine residue;
- Y_{11} is absent or an aspartic acid, alanine, serine or glycine residue;
- Y_{12} is absent or an arginine or alanine residue;
- Y_{13} is absent or a leucine or an alanine residue;
- 30 Y_{14} is absent or an arginine or alanine residue;
- Y_{15} is absent or a lysine or an alanine residue;
- Y_{16} is absent or a tryptophan, methionine or an alanine residue;

Y_{17} is absent or a methionine, norleucine, phenylalanine or an alanine residue;

Y_{18} is absent or a phenylalanine, isoleucine or an alanine residue;

Y_{19} is absent or an isoleucine or alanine residue, provided that at least five of Y_1 - Y_{19} , are present; and

R_1 is OR_2 or $N(R_2)_2$;

each R_2 is independently hydrogen or (C_1-C_{10}) alkyl; and

from 0 to 5 amino acid residues are present in the D configuration.

15. The compound of Claim 14, wherein at least three of Y_7 , Y_8 , Y_9 , Y_{10} , Y_{11} , Y_{12} , Y_{13} , Y_{14} , Y_{15} , Y_{16} , Y_{17} , Y_{18} and Y_{19} are present.

16. The compound of Claim 15, wherein

Y_9 is serine, threonine or glycine residue;

Y_{10} is a threonine, serine, tyrosine, glycine or alanine residue; and

Y_{11} is an aspartic acid, alanine, serine or glycine residue.

17. The compound of Claim 15, wherein

Y_{12} is an arginine or alanine residue;

Y_{13} is a leucine or an alanine residue; and

Y_{14} is an arginine or alanine residue.

18. The compound of Claim 16, wherein

Y_9 is serine, threonine or glycine residue;

Y_{10} is a threonine, serine, tyrosine, glycine or alanine residue;

Y_{11} is an aspartic acid, alanine, serine or glycine residue; and

Y_{12} is an arginine or alanine residue.

19. The compound of Claim 17, wherein

Y_{11} is an aspartic acid, alanine, serine or glycine residue;

Y_{12} is an arginine or alanine residue;

Y_{13} is a leucine or an alanine residue; and

Y_{14} is an arginine or alanine residue.

20. The compound of Claim 18, wherein
Y₉ is serine, threonine or glycine residue;
Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;
5 Y₁₁ is an aspartic acid, alanine, serine or glycine residue;
Y₁₂ is an arginine or alanine residue; and
Y₁₃ is a leucine or an alanine residue.
21. The compound of Claim 19, wherein
10 Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;
Y₁₁ is an aspartic acid, alanine, serine or glycine residue;
Y₁₂ is an arginine or alanine residue;
Y₁₃ is a leucine or an alanine residue; and
Y₁₄ is an arginine or alanine residue.
- 15 22. The compound of Claim 20 or 21, wherein
Y₉ is serine, threonine or glycine residue;
Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue;
Y₁₁ is an aspartic acid, alanine, serine or glycine residue;
20 Y₁₂ is an arginine or alanine residue;
Y₁₃ is a leucine or an alanine residue; and
Y₁₄ is an arginine or alanine residue.
23. The compound of Claim 21 or 22, wherein
25 Y₉ is serine residue;
Y₁₀ is a threonine residue;
Y₁₁ is an aspartic acid residue;
Y₁₂ is an arginine residue;
Y₁₃ is a leucine residue; and
30 Y₁₄ is an arginine residue.
24. The compound of Claim 15, wherein

Y₇ is a threonine or serine residue;
Y₈ is a tyrosine or glycine residue;
Y₉ is a serine, threonine or glycine residue; and
Y₁₀ is a threonine, serine, tyrosine, glycine or alanine residue.

5

25. The compound of Claim 24, wherein

Y₇ is a threonine residue;
Y₈ is a tyrosine residue;
Y₉ is a serine residue; and
Y₁₀ is a threonine residue.

10

26. The compound of Claim 25, wherein Y₁₁ is an aspartic acid, alanine, serine or glycine residue.

27. The compound of Claim 26, wherein Y₁₁ is an aspartic acid residue.

15

28. The compound of Claim 15, wherein

Y₁₂ is an arginine or alanine residue;
Y₁₃ is or a leucine or an alanine residue;
Y₁₄ is an arginine or alanine residue; and
Y₁₅ is a lysine or an alanine residue.

20

29. The compound of Claim 28, wherein one of Y₁₂, Y₁₃, Y₁₄, and Y₁₅ is an alanine residue, provided that the other three of Y₁₂, Y₁₃, Y₁₄, and Y₁₅ are not an alanine residue.

25

30. The compound of Claim 28, wherein

Y₁₂ is an arginine residue;
Y₁₃ is a leucine residue;
Y₁₄ is an arginine residue; and
Y₁₅ is a lysine residue.

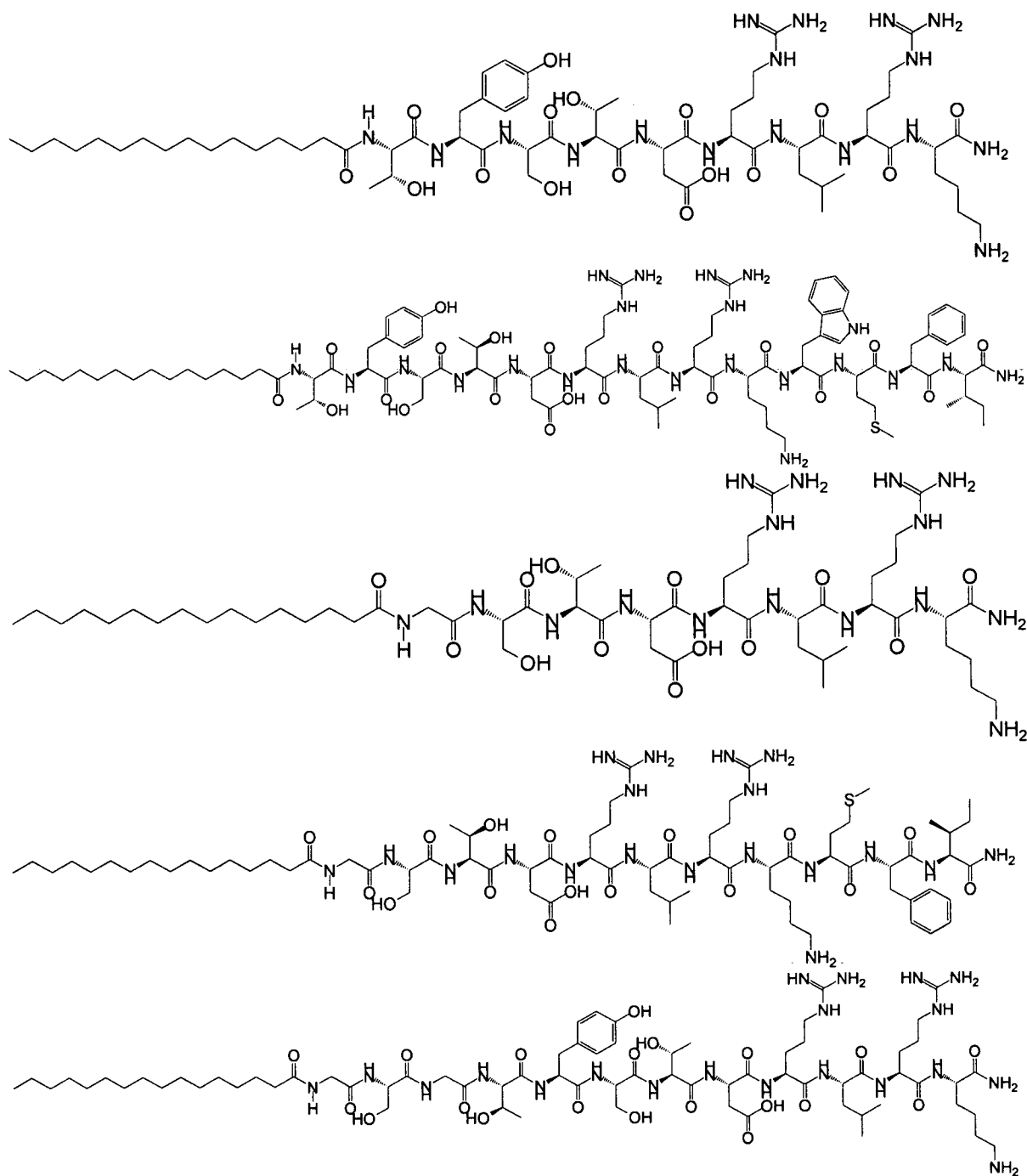
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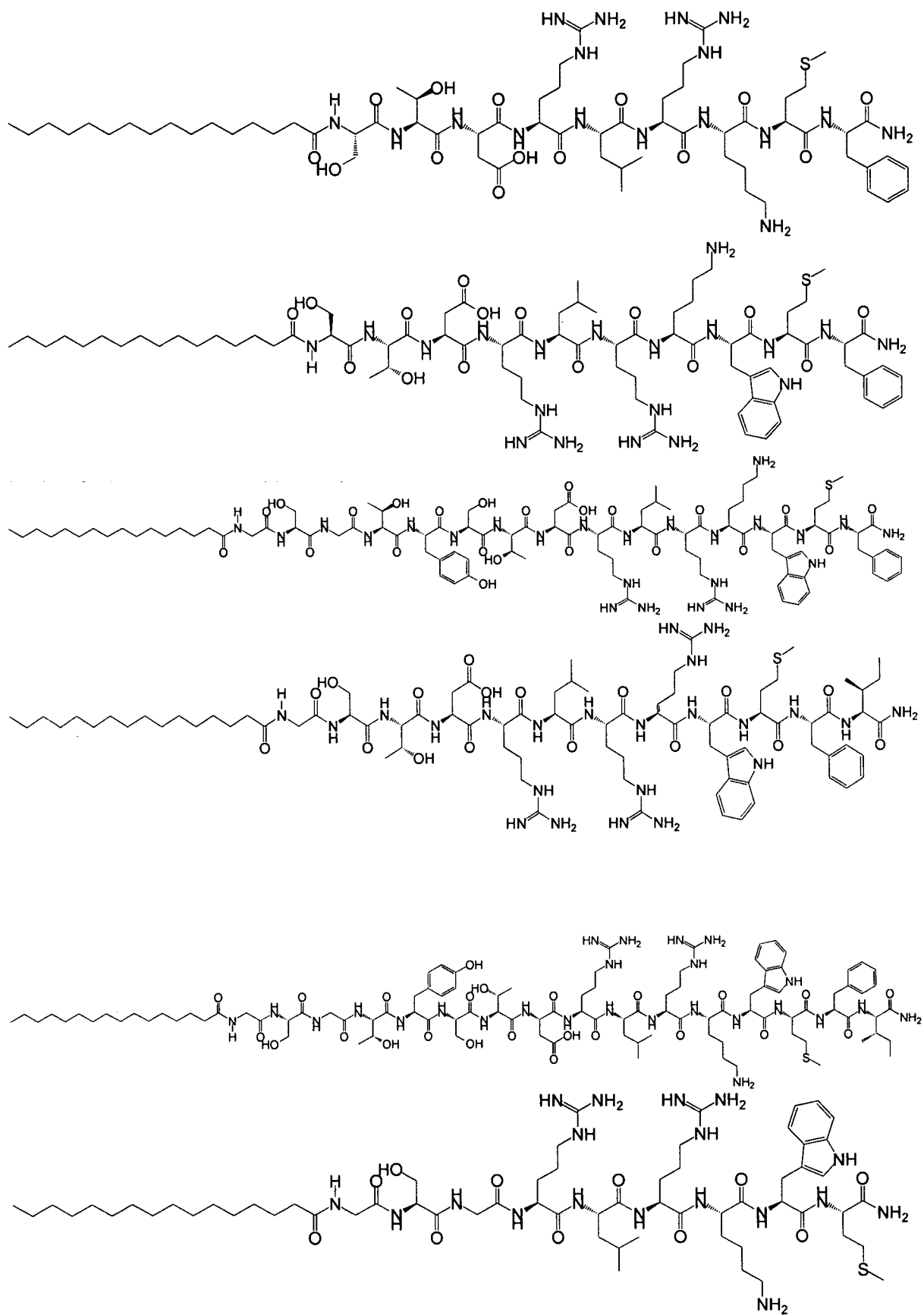
31. The compound of Claim 28 or 30, wherein Y₁₆ is a tryptophan, methionine or an alanine residue.
32. The compound of Claim 31, wherein Y₁₆ is a tryptophan residue.
- 5 33. The compound of Claim 31, wherein Y₁₆ is a methionine residue.
34. The compound of Claim 15, wherein
Y₁₅ is a lysine or an alanine residue;
10 Y₁₆ is a tryptophan, methionine or an alanine residue;
Y₁₇ is a methionine, norleucine, phenylalanine or an alanine residue; and
Y₁₈ is a phenylalanine, isoleucine or an alanine residue.
35. The compound of Claim 34, wherein one of Y₁₅, Y₁₆, Y₁₇, and Y₁₈ is an alanine
15 residue, provided that the other three of Y₁₅, Y₁₆, Y₁₇, and Y₁₈ are not an alanine residue.
36. The compound of Claim 34, wherein
Y₁₅ is a lysine residue;
20 Y₁₆ is a tryptophan or methionine residue;
Y₁₇ is a methionine, norleucine, or phenylalanine residue; and
Y₁₈ is a phenylalanine or isoleucine residue.
37. The compound of Claim 36, wherein
25 Y₁₅ is a lysine residue;
Y₁₆ is a tryptophan residue;
Y₁₇ is a methionine residue; and
Y₁₈ is a phenylalanine residue.
- 30 38. The compound of any one of Claim 34-37, wherein Y₁₉ is an isoleucine or alanine residue.

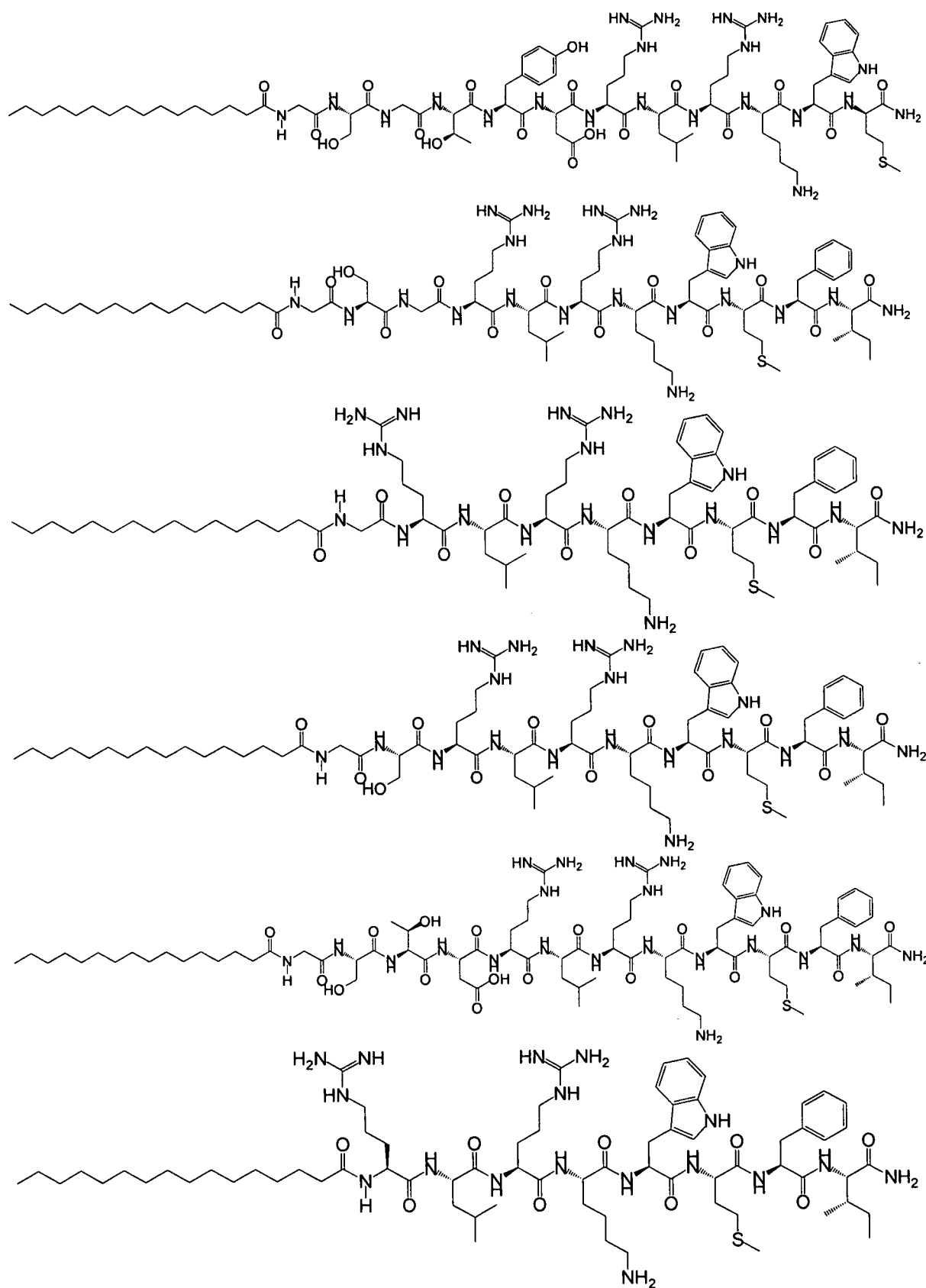
39. The compound of any one of Claim 34-37, wherein Y₁₉ is an isoleucine residue.

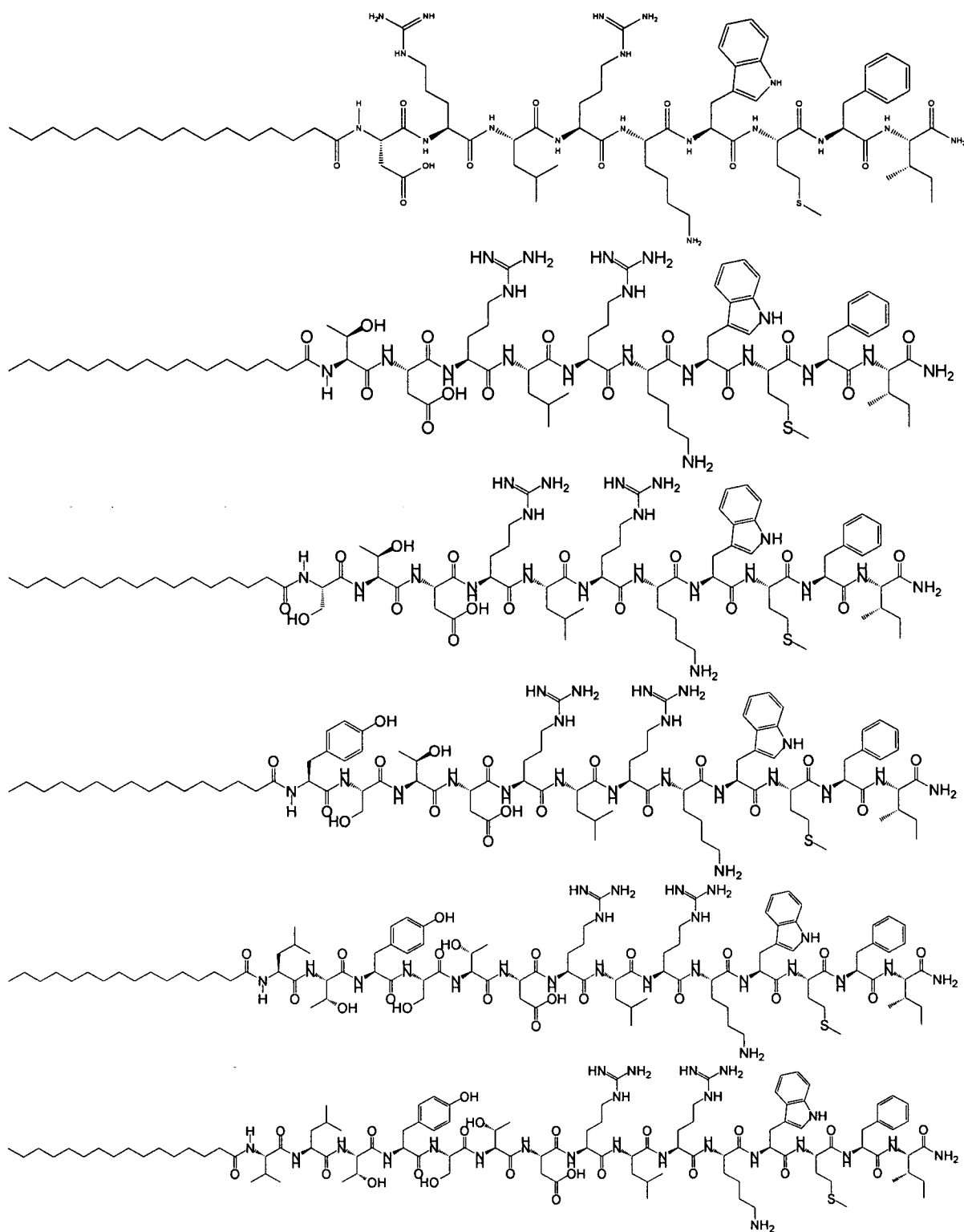
40. The compound of Claim 14, selected from:

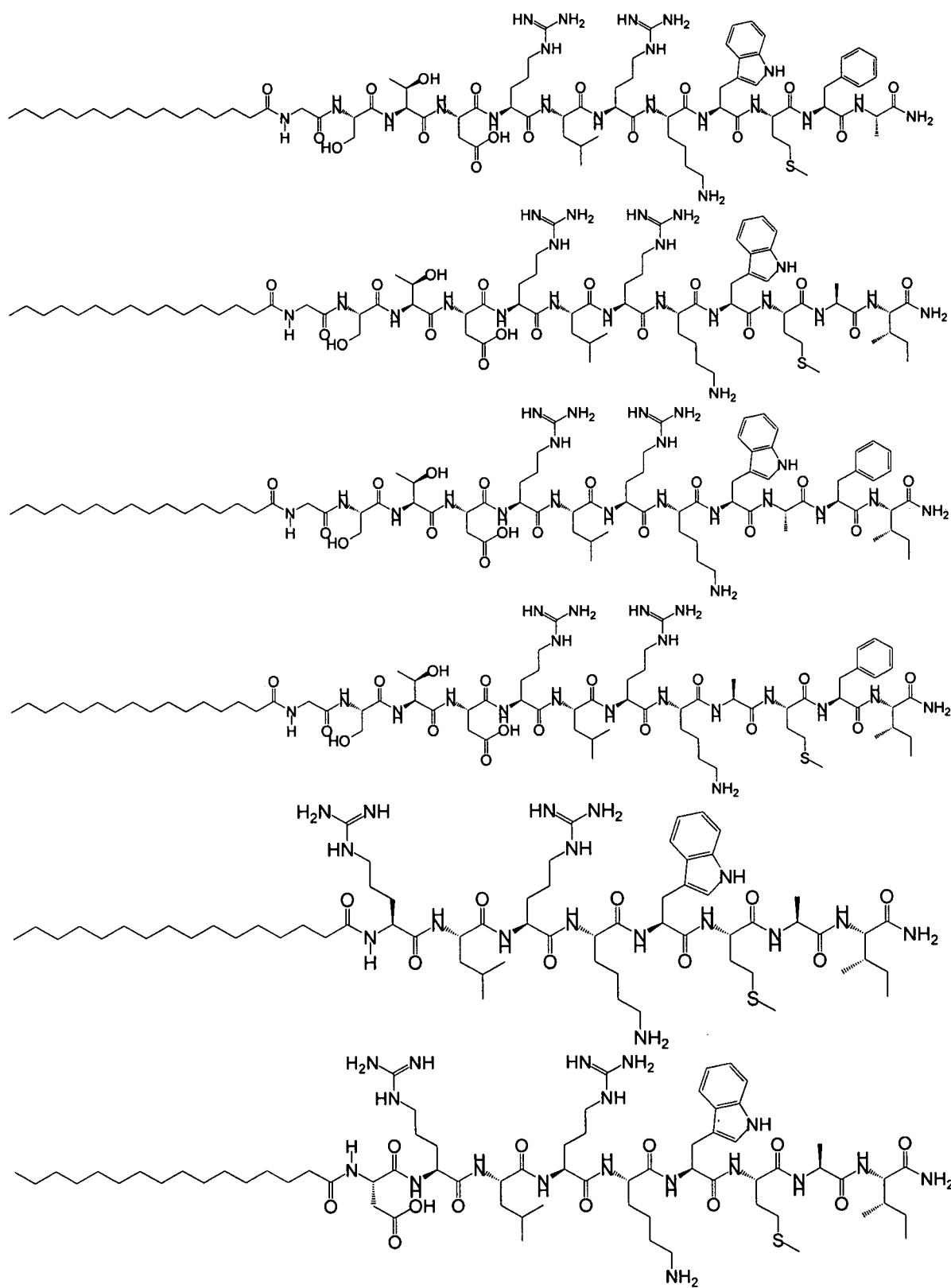
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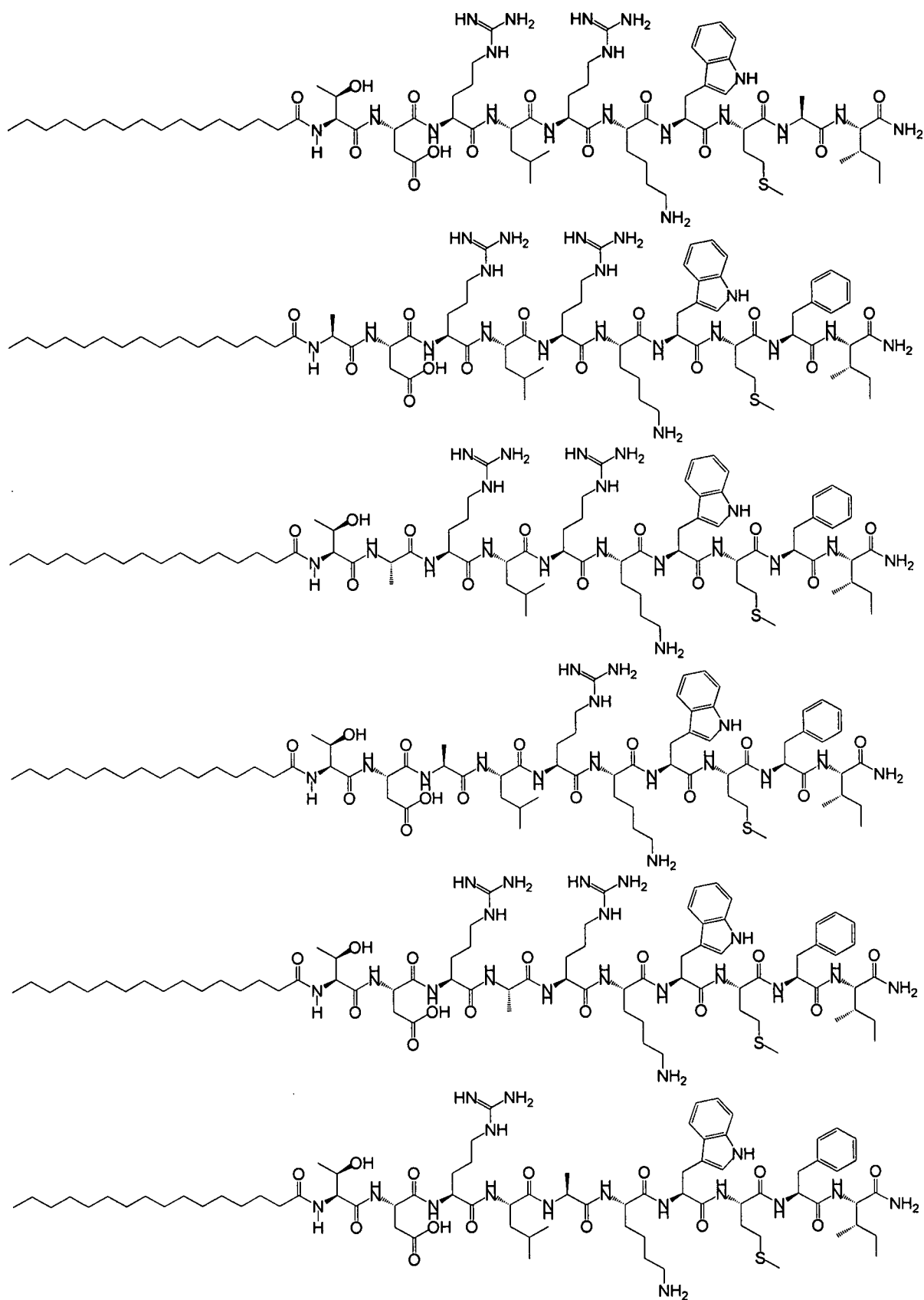


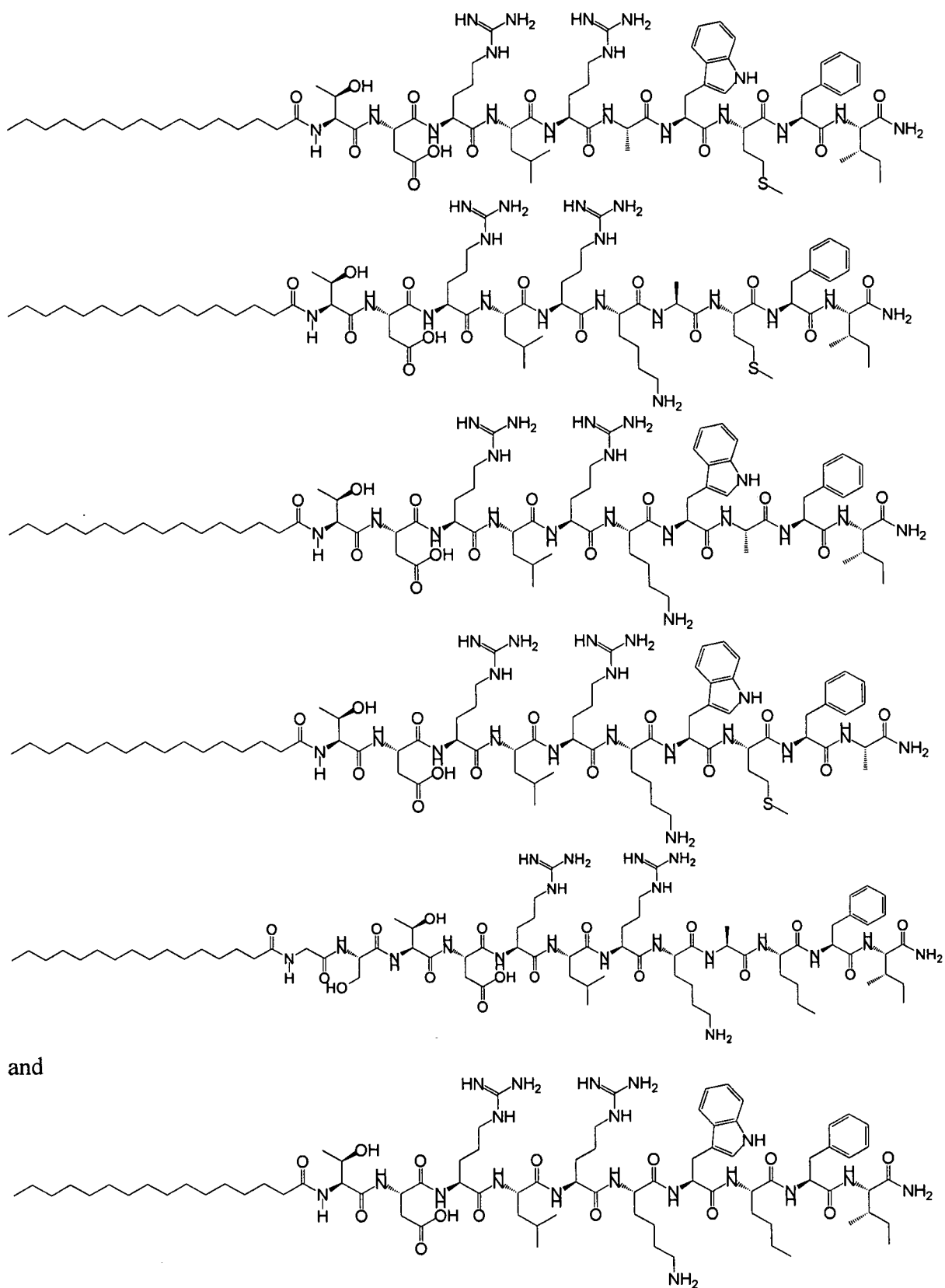












or a pharmaceutically acceptable salt of any of the foregoing.

41. The compound of Claim 1, wherein P comprises at least three contiguous amino acid residues of the i2 loop.

42. The compound of Claim 41, wherein P is derived from the following sequence:

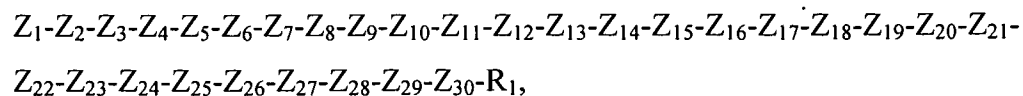
5 HTAIVLTYSTDRLRKWMFI (SEQ ID NO: 24).

43. The compound of Claim 42, wherein P is a sequence selected from:

	HTAIVLTYSTDRLRKWMFI	(SEQ ID NO: 24);
	HTAIVLTYSTDRLRKWM	(SEQ ID NO: 25);
10	AIVLTYSTDRLRKWMFI	(SEQ ID NO: 26);
	GSGTYSTDRLRKWMFI	(SEQ ID NO: 27);
	HTAIVLTYSTDRLRK	(SEQ ID NO: 28);
	GSGTYSTDRLRKWMF	(SEQ ID NO: 29);
	VLTYSTDRLRKWMFI	(SEQ ID NO: 30);
15	HTAIVLTYSTDRLR	(SEQ ID NO: 31);
	LTYSTDLRKWMFI	(SEQ ID NO: 32);
	TYSTDRLRKWMFI	(SEQ ID NO: 33);
	HTAIVLTYSTD	(SEQ ID NO: 34);
	GSGTYDRLRKWM	(SEQ ID NO: 35);
20	GSGTYSTDRLRK	(SEQ ID NO: 36);
	GSTDRLRKWMFI	(SEQ ID NO: 37);
	GSTDRLRKWMFA	(SEQ ID NO: 38);
	GSTDRLRKWMAI	(SEQ ID NO: 39);
	GSTDRLRKWAFI	(SEQ ID NO: 40);
25	GSTDRLRKAMFI	(SEQ ID NO: 41);
	GSTDRLRKAXFI	(SEQ ID NO: 42);
	YSTDRLRKWMFI	(SEQ ID NO: 43);
	GSTDRLRKMF	(SEQ ID NO: 44);
	GSGRLRKWMFI	(SEQ ID NO: 45);
30	STDRLRKWMFI	(SEQ ID NO: 46);
	YSTDRLRKWMF	(SEQ ID NO: 47);
	STDRLRKWMF	(SEQ ID NO: 48);

	ADRLRKWMFI	(SEQ ID NO: 49);
	GSRLRKWMFI	(SEQ ID NO: 50);
	TDRLRKWMFI	(SEQ ID NO: 51);
	TDRLRKWXFI	(SEQ ID NO: 52);
5	TARLRKWMFI	(SEQ ID NO: 53);
	TDALRKWMFI	(SEQ ID NO: 54);
	TDRARKWMFI	(SEQ ID NO: 55);
	TDRLAKWMFI	(SEQ ID NO: 56);
	TDRLRAWMFI	(SEQ ID NO: 57);
10	TDRLRKAMFI	(SEQ ID NO: 58);
	TDRLRKWAFI	(SEQ ID NO: 59);
	TDRLRKWMAI	(SEQ ID NO: 60);
	TDRLRKWMFA	(SEQ ID NO: 61);
	TYSTDRLRK	(SEQ ID NO: 62);
15	STDRLRKMF	(SEQ ID NO: 63);
	GSGRLRKWM	(SEQ ID NO: 64);
	GRLRKWMFI	(SEQ ID NO: 65);
	DRLRKWMFI	(SEQ ID NO: 66);
	DRLRKWMAI	(SEQ ID NO: 67);
20	GSTDRLRK	(SEQ ID NO: 68);
	RLRKWMFI	(SEQ ID NO: 69); and
	RLRKWMAI	(SEQ ID NO: 70).

44. The compound of Claim 1, wherein P is derived from the i3 loop and is represented
 25 by the following structural formula or a pharmaceutically acceptable salt thereof:



wherein :

- 30 Z_1 is absent or a phenylalanine residue;
 Z_2 is absent or an asparagine residue;
 Z_3 is absent or an isoleucine residue;
 Z_4 is absent or a valine residue;

- 5 Z_5 is absent or an arginine residue;
 Z_6 is absent or an isoleucine residue;
 Z_7 is absent or a leucine residue;
 Z_8 is absent or a methionine residue;
 Z_9 is absent or a threonine residue;
 Z_{10} is absent or a lysine residue;
 Z_{11} is absent or a leucine residue;
 Z_{12} is absent or an arginine residue;
 Z_{13} is absent or an alanine residue;
10 Z_{14} is absent or a serine residue;
 Z_{15} is absent or a threonine residue;
 Z_{16} is absent or a threonine residue;
 Z_{17} is absent or a serine residue;
 Z_{18} is absent or a glutamic acid residue;
15 Z_{19} is absent or a threonine residue;
 Z_{20} is absent or an isoleucine residue;
 Z_{21} is absent or a glutamine residue;
 Z_{22} is absent or a tyrosine residue;
 Z_{23} is absent or an arginine residue;
20 Z_{24} is absent or a lysine residue;
 Z_{25} is absent or an alanine residue;
 Z_{26} is absent or a valine residue;
 Z_{27} is absent or a lysine residue;
 Z_{28} is absent or an alanine or serine residue;
25 Z_{29} is absent or a threonine residue; and
 Z_{30} is absent or a leucine residue;
 provided that at least five of Z_1 - Z_{30} are present;
 R_1 is OR_2 or $N(R_2)_2$;
 each R_2 is independently hydrogen or (C_1-C_{10}) alkyl; and
30 from 0 to 5 amino acid residues are present in the D configuration.

45. The compound of Claim 44, wherein at least three of Z₅, Z₆, Z₇, Z₈, and Z₉ are present.
46. The compound of Claim 45, wherein
5 Z₅ is an arginine residue;
Z₆ is an isoleucine residue; and
Z₇ is a leucine residue.
47. The compound of Claim 45, wherein
10 Z₇ is a leucine residue;
Z₈ is a methionine residue; and
Z₉ is a threonine residue.
48. The compound of Claim 46, wherein
15 Z₅ is an arginine residue;
Z₆ is an isoleucine residue;
Z₇ is a leucine residue; and
Z₈ is a methionine residue.
49. The compound of Claim 47, wherein
20 Z₆ is an isoleucine residue;
Z₇ is a leucine residue;
Z₈ is absent or a methionine residue; and
Z₉ is a threonine residue.
50. The compound of Claim 48 or 49, wherein
25 Z₅ is an arginine residue;
Z₆ is an isoleucine residue;
Z₇ is a leucine residue;
30 Z₈ is a methionine residue; and
Z₉ is a threonine residue.

51. The compound of Claim 44, wherein at least three of Z₁₀, Z₁₁, Z₁₂, and Z₁₃ are present.

52. The compound of Claim 51, wherein

Z₁₀ is a lysine residue;

5 Z₁₁ is a leucine residue; and

Z₁₂ is an arginine residue.

53. The compound of Claim 51, wherein

Z₁₁ is a leucine residue;

10 Z₁₂ is an arginine residue; and

Z₁₃ is an alanine residue.

54. The compound of Claim 52 or 53, wherein

Z₁₀ is a lysine residue;

15 Z₁₁ is a leucine residue;

Z₁₂ is an arginine residue; and

Z₁₃ is an alanine residue.

55. The compound of Claim 44, wherein at least three of Z₁₄, Z₁₅, Z₁₆, and Z₁₇ are present.

56. The compound of Claim 55, wherein

Z₁₄ is a serine residue;

Z₁₅ is a threonine residue; and

Z₁₆ is a threonine residue.

57. The compound of Claim 55, wherein

Z₁₅ is a threonine residue;

Z₁₆ is a threonine residue; and

Z₁₇ is a serine residue;

58. The compound of Claim 56 or 57, wherein

Z₁₄ is a serine residue;

Z₁₅ is a threonine residue;
Z₁₆ is a threonine residue; and
Z₁₇ is a serine residue;

- 5 59. The compound of Claim 44, wherein at least three of Z₁₉, Z₂₀, Z₂₁, Z₂₂, and Z₂₃ are present.
60. The compound of Claim 59, wherein
 Z₁₉ is a threonine residue;
10 Z₂₀ is an isoleucine residue; and
 Z₂₁ is a glutamine residue.
61. The compound of Claim 59, wherein
 Z₂₁ is a glutamine residue;
15 Z₂₂ is a tyrosine residue; and
 Z₂₃ is an arginine residue.
62. The compound of Claim 60, wherein
 Z₁₉ is a threonine residue;
20 Z₂₀ is an isoleucine residue;
 Z₂₁ is a glutamine residue; and
 Z₂₂ is a tyrosine residue.
63. The compound of Claim 61, wherein
25 Z₂₀ is an isoleucine residue;
 Z₂₁ is a glutamine residue;
 Z₂₂ is a tyrosine residue; and
 Z₂₃ is an arginine residue.
- 30 64. The compound of Claim 62 or 63, wherein
 Z₁₉ is a threonine residue;
 Z₂₀ is an isoleucine residue;

Z₂₁ is a glutamine residue;
Z₂₂ is a tyrosine residue; and
Z₂₃ is an arginine residue.

- 5 65. The compound of Claim 44, wherein at least three of Z₂₄, Z₂₅, Z₂₆, Z₂₇, and Z₂₈ are present.
66. The compound of Claim 65, wherein
10 Z₂₄ is a lysine residue;
 Z₂₅ is an alanine residue; and
 Z₂₆ is a valine residue.
67. The compound of Claim 65, wherein
15 Z₂₆ is a valine residue;
 Z₂₇ is a lysine residue; and
 Z₂₈ is an alanine or serine residue.
68. The compound of Claim 66, wherein
20 Z₂₄ is a lysine residue;
 Z₂₅ is an alanine residue;
 Z₂₆ is a valine residue; and
 Z₂₇ is a lysine residue.
69. The compound of Claim 67, wherein
25 Z₂₅ is an alanine residue;
 Z₂₆ is a valine residue;
 Z₂₇ is a lysine residue; and
 Z₂₈ is an alanine or serine residue.
- 30 70. The compound of Claim 68 or 69, wherein
 Z₂₄ is a lysine residue;
 Z₂₅ is an alanine residue;

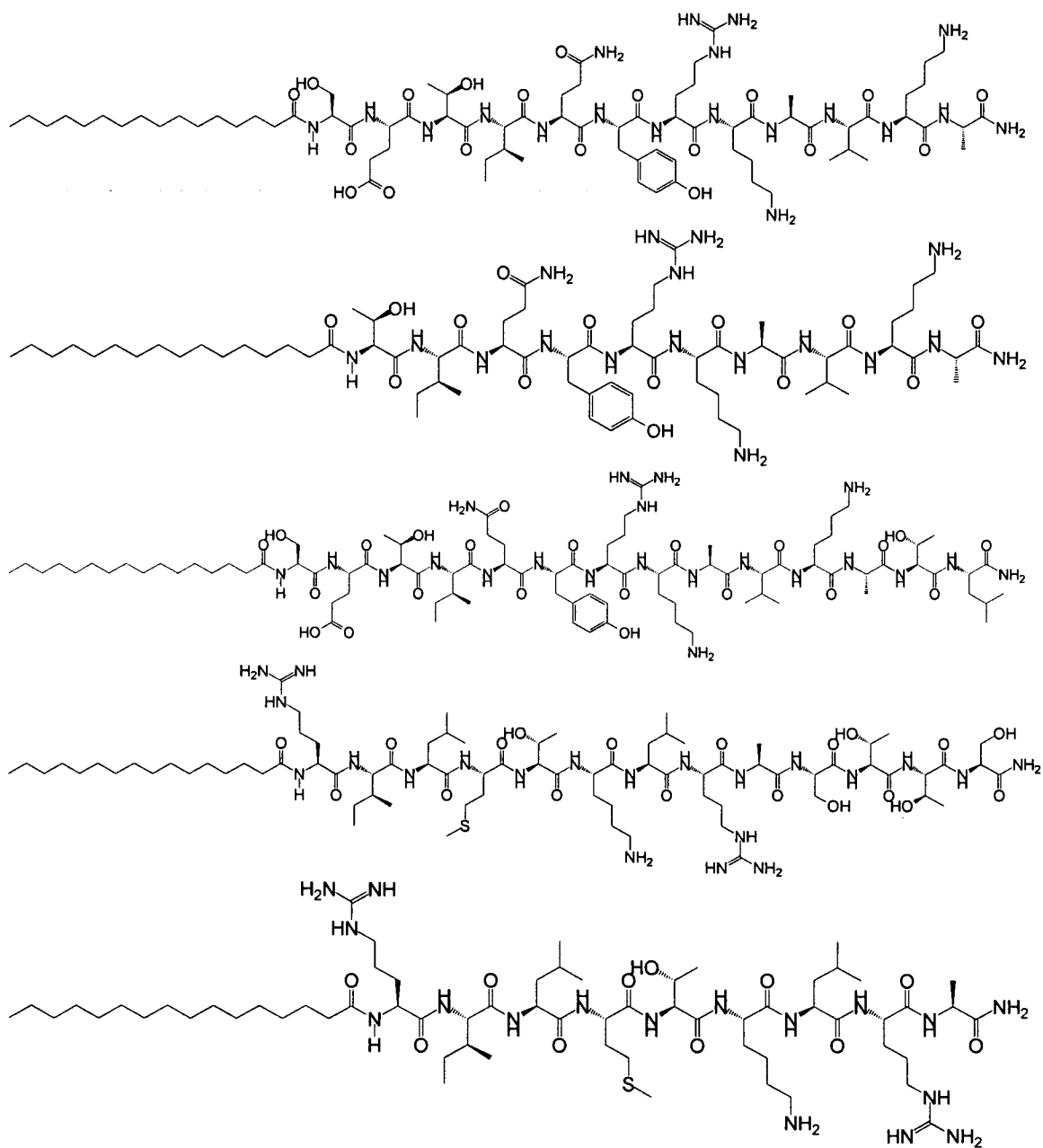
Z₂₆ is a valine residue;

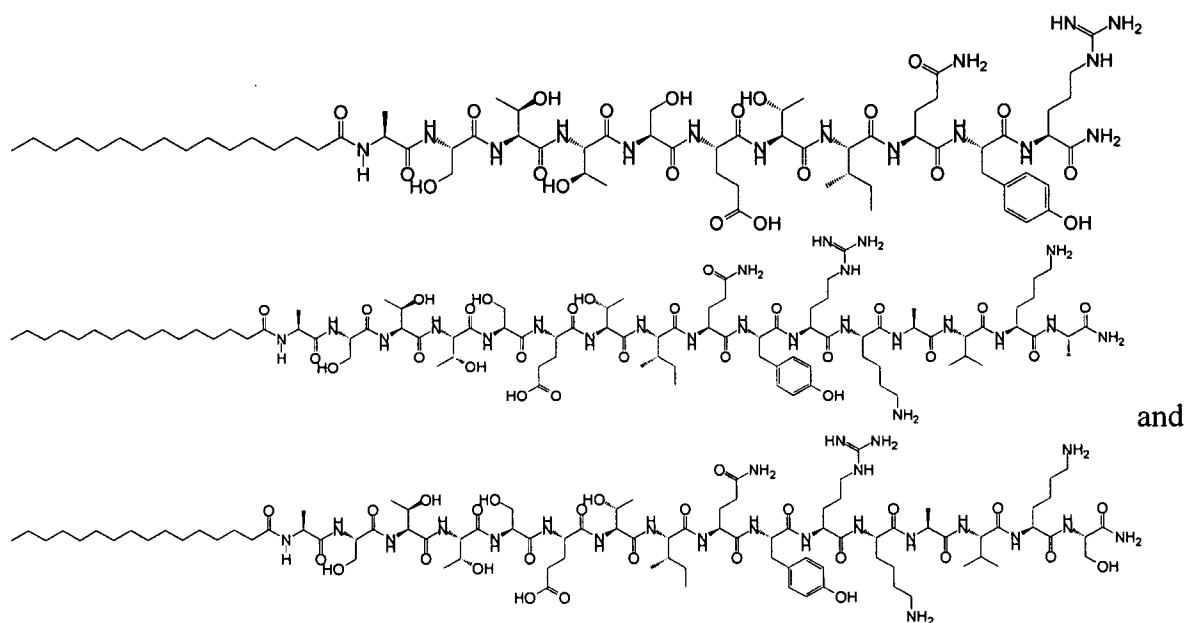
Z₂₇ is a lysine residue; and

Z₂₈ is an alanine or serine residue.

5 71. The compound of Claim 70, wherein Z₂₈ is an alanine residue.

72. The compound of Claim 44, selected from:





- 5 or a pharmaceutically acceptable salt of any of the foregoing.
73. The compound of Claim 1, wherein P comprises at least three contiguous amino acid residues of the i3 loop.
- 10 74. The compound of Claim 73, wherein P is derived from the following sequence:
FNIVRILMTKLRAS~~T~~TTSETIQYRKAVKA (SEQ ID NO: 71).
75. The compound of Claim 74, wherein P is a sequence selected from:
- | | | |
|----|--|------------------|
| | FNIVRILMTKLRAS ~~T~~ TTSETIQYRKAVKA | (SEQ ID NO: 71); |
| 15 | IVRILMTKLRAS ~~T~~ TTSETIQYRKAVKA | (SEQ ID NO: 72); |
| | FNIVRILMTKLRAS ~~T~~ TTSETIQYRKAV | (SEQ ID NO: 73); |
| | RILMTKLRAS ~~T~~ TTSETIQYRKAVKA | (SEQ ID NO: 74); |
| | FNIVRILMTKLRAS ~~T~~ TTSETIQYRK | (SEQ ID NO: 75); |
| | FNIVRILMTKLRAS ~~T~~ TTSETIQYR | (SEQ ID NO: 76); |
| 20 | LMTKLRAS ~~T~~ TTSETIQYRKAVKA | (SEQ ID NO: 77); |
| | FNIVRILMTKLRAS ~~T~~ TTSETIQY | (SEQ ID NO: 78); |
| | TKLRAS ~~T~~ TTSETIQYRKAVKA | (SEQ ID NO: 79); |
| | LMTKLRAS ~~T~~ TTSETIQYRKAV | (SEQ ID NO: 80); |

	LRASTTSETIQYRKAVKA	(SEQ ID NO: 81);
	LMTKLRASTTSETIQYRK	(SEQ ID NO: 82);
	LMTKLRASTTSETIQYR	(SEQ ID NO: 83);
	ASTTSETIQYRKAVKA	(SEQ ID NO: 84);
5	ASTTSETIQYRKAVKS	(SEQ ID NO: 85);
	LMTKLRASTTSETIQ	(SEQ ID NO: 86);
	SETIQYRKAVKATL	(SEQ ID NO: 87);
	LMTKLRASTTSETI	(SEQ ID NO: 88);
	RILMTKLRASTTS	(SEQ ID NO: 89);
10	SETIQYRKAVKA	(SEQ ID NO: 90);
	TKLRASTTSETI	(SEQ ID NO: 91);
	ASTTSETIQYR	(SEQ ID NO: 92);
	TKLRASTTSET	(SEQ ID NO: 93);
	KLRASTTSETI	(SEQ ID NO: 94);
15	TIQYRKAVKA	(SEQ ID NO: 95);
	KLRASTTSET	(SEQ ID NO: 96);
	RILMTKLRA	(SEQ ID NO: 97); and
	KLRASTTSE	(SEQ ID NO: 98).

- 20 76. The compound of Claim 1, wherein P derived from the i4 domain and is represented by the following structural formula or a pharmaceutically acceptable salt thereof
- $M_1-M_2-M_3-M_4-M_5-M_6-M_7-M_8-M_9-M_{10}-M_{11}-M_{12}-M_{13}-M_{14}-M_{15}-M_{16}-M_{17}-M_{18}-M_{19}-M_{20}-M_{21}-M_{22}-M_{23}-M_{24}-M_{25}-M_{26}-M_{27}-M_{28}-M_{29}-M_{30}-M_{31}-M_{32}-M_{33}-M_{34}-M_{35}-M_{36}-M_{37}-M_{38}-M_{39}-M_{40}-M_{41}-M_{42}-M_{43}-M_{44}-M_{45}-M_{46}-M_{47}-R_1$,
- 25 wherein:
- M_1 is absent or a glutamic acid residue;
- M_2 is absent or a valine residue;
- M_3 is absent or an arginine residue;
- M_4 is absent or a serine residue;
- 30 M_5 is absent or an alanine residue;
- M_6 is absent or an isoleucine residue;
- M_7 is absent or an arginine residue;

- M₈ is absent or a lysine residue;
M₉ is absent or an arginine residue;
M₁₀ is absent or a tryptophan residue;
M₁₁ is absent or a histidine residue;
5 M₁₂ is absent or an arginine residue;
M₁₃ is absent or a tryptophan residue;
M₁₄ is absent or a glutamine residue;
M₁₅ is absent or an aspartic acid residue;
M₁₆ is absent or a lysine residue;
10 M₁₇ is absent or a histidine or glycine residue;
M₁₈ is absent or a serine residue;
M₁₉ is absent or an isoleucine residue;
M₂₀ is absent or an arginine residue;
M₂₁ is absent or an alanine residue;
15 M₂₂ is absent or an arginine residue;
M₂₃ is absent or a valine residue;
M₂₄ is absent or an alanine residue;
M₂₅ is absent or an arginine residue;
M₂₆ is absent or an alanine residue;
20 M₂₇ is absent or a methionine residue;
M₂₈ is absent or a serine residue;
M₂₉ is absent or an isoleucine residue;
M₃₀ is absent or a proline residue;
M₃₁ is absent or a threonine residue;
25 M₃₂ is absent or a serine residue;
M₃₃ is absent or a proline residue;
M₃₄ is absent or a threonine residue;
M₃₅ is absent or an arginine residue;
M₃₆ is absent or a valine residue;
30 M₃₇ is absent or a serine residue;
M₃₈ is absent or a phenylalanine residue;
M₃₉ is absent or a histidine residue;

- M₄₀ is absent or a serine residue;
M₄₁ is absent or an isoleucine residue;
M₄₂ is absent or a lysine residue;
M₄₃ is absent or a glutamine residue;
5 M₄₄ is absent or a serine residue;
M₄₅ is absent or a threonine residue;
M₄₆ is absent or an alanine residue; and
M₄₇ is absent or a valine residue; provided that at least five of M₁-M₄₇ are present;
R₁ is OR₂ or N(R₂)₂;
10 each R₂ is independently hydrogen or (C₁-C₁₀)alkyl; and
from 0 to 5 amino acid residues are present in the D configuration.
77. The compound of Claim 76, wherein at least three of M₂-M₇ are present.
- 15 78. The compound of Claim 77, wherein
M₂ is a valine residue;
M₃ is an arginine residue; and
M₄ is a serine residue.*
- 20 79. The compound of Claim 77, wherein
M₅ is an alanine residue;
M₆ is an isoleucine residue; and
M₇ is an arginine residue.
- 25 80. The compound of Claim 78, wherein
M₂ is a valine residue;
M₃ is an arginine residue;
M₄ is a serine residue; and
M₅ is an alanine residue.
- 30 81. The compound of Claim 79, wherein
M₄ is a serine residue;

M₅ is an alanine residue;
M₆ is an isoleucine residue; and
M₇ is an arginine residue.

5 82. The compound of Claim 80, wherein
 M₂ is a valine residue;
 M₃ is an arginine residue;
 M₄ is a serine residue;
 M₅ is an alanine residue;
10 M₆ is an isoleucine residue.

 83. The compound of Claim 81, wherein
 M₃ is an arginine residue;
 M₄ is a serine residue;
15 M₅ is an alanine residue;
 M₆ is an isoleucine residue; and
 M₇ is an arginine residue.

 84. The compound of Claim 82 or 83, wherein
20 M₂ is a valine residue;
 M₃ is an arginine residue;
 M₄ is a serine residue;
 M₅ is an alanine residue;
 M₆ is an isoleucine residue; and
25 M₇ is an arginine residue.

85. The compound of Claim 76, wherein at least three of M₉-M₁₃ are present.

 86. The compound of Claim 85, wherein
30 M₉ is an arginine residue;
 M₁₀ is a tryptophan residue;
 M₁₁ is a histidine residue;

M₁₂ is an arginine residue.

87. The compound of Claim 85, wherein

M₁₀ is a tryptophan residue;

5 M₁₁ is a histidine residue;

M₁₂ is an arginine residue; and

M₁₃ is a tryptophan residue.

88. The compound of Claim 86 or 87, wherein

10 M₉ is an arginine residue;

M₁₀ is a tryptophan residue;

M₁₁ is a histidine residue;

M₁₂ is an arginine residue; and

M₁₃ is a tryptophan residue.

15

89. The compound of Claim 76, wherein at least three of M₁₈-M₂₂ are present.

90. The compound of Claim 89, wherein

M₁₈ is a serine residue;

20 M₁₉ is an isoleucine residue;

M₂₀ is an arginine residue; and

M₂₁ is an alanine residue.

91. The compound of Claim 89, wherein

25 M₁₉ is an isoleucine residue;

M₂₀ is an arginine residue;

M₂₁ is an alanine residue; and

M₂₂ is an arginine residue.

30 92. The compound of Claim 90 or 91, wherein

M₁₈ is a serine residue;

M₁₉ is an isoleucine residue;

M₂₀ is an arginine residue;
M₂₁ is an alanine residue; and
M₂₂ is an arginine residue.

5 93. The compound of Claim 76, wherein at least three of M₂₃-M₂₇ are present.

94. The compound of Claim 93, wherein
M₂₃ is a valine residue;
M₂₄ is an alanine residue;
10 M₂₅ is an arginine residue; and
M₂₆ is an alanine residue.

95. The compound of Claim 93, wherein
M₂₄ is an alanine residue;
15 M₂₅ is an arginine residue;
M₂₆ is an alanine residue;
M₂₇ is a methionine residue.

96. The compound of Claim 94 or 95, wherein
20 M₂₃ is a valine residue;
M₂₄ is an alanine residue;
M₂₅ is an arginine residue;
M₂₆ is an alanine residue;
M₂₇ is a methionine residue.

25 97. The compound of Claim 76, wherein at least three of M₂₅-M₂₉ are present.

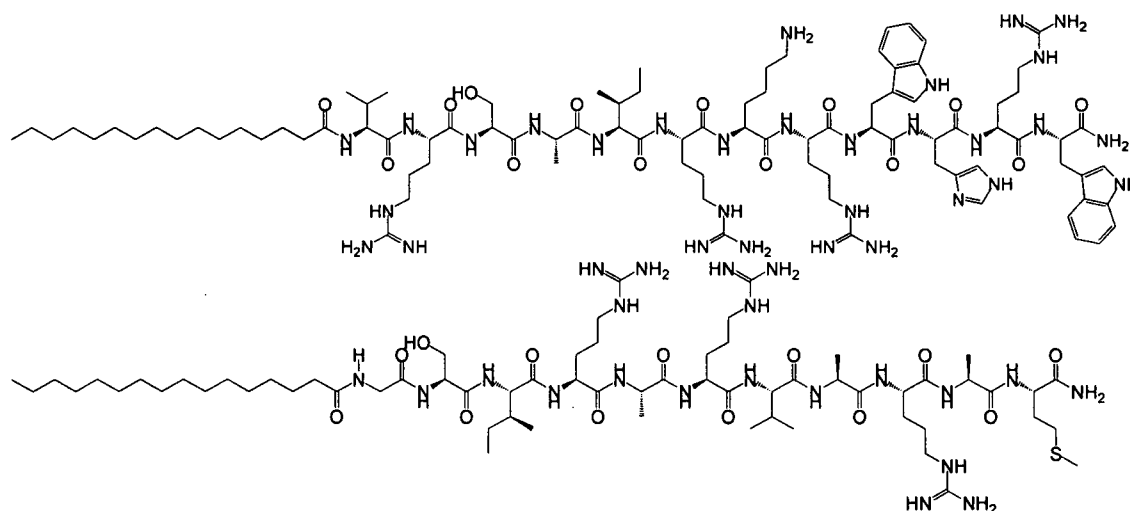
98. The compound of Claim 97, wherein
M₂₅ is an arginine residue;
30 M₂₆ is an alanine residue;
M₂₇ is a methionine residue; and
M₂₈ is a serine residue.

99. The compound of Claim 97, wherein
M₂₆ is an alanine residue;
M₂₇ is a methionine residue;
5 M₂₈ is a serine residue; and
M₂₉ is an isoleucine residue.
100. The compound of Claim 98 or 99, wherein
M₂₅ is an arginine residue;
10 M₂₆ is an alanine residue;
M₂₇ is a methionine residue;
M₂₈ is a serine residue; and
M₂₉ is an isoleucine residue.
- 15 101. The compound of Claim 76, wherein at least three of M₃₂-M₃₆ are present.
102. The compound of Claim 101, wherein
M₃₂ is a serine residue;
M₃₃ is a proline residue;
20 M₃₄ is a threonine residue; and
M₃₅ is an arginine residue.
103. The compound of Claim 101, wherein
M₃₃ is a proline residue;
25 M₃₄ is a threonine residue;
M₃₅ is an arginine residue; and
M₃₆ is a valine residue.
104. The compound of Claim 102 or 103, wherein
30 M₃₂ is a serine residue;
M₃₃ is a proline residue;
M₃₄ is a threonine residue;

M₃₅ is an arginine residue; and

M₃₆ is a valine residue.

105. The compound of Claim 76, selected from:



or a pharmaceutically acceptable salt of any of the foregoing.

106. The compound of Claim 1, wherein P comprises at least three contiguous amino acid residues of the i4 domain.

107. The compound of Claim 106, wherein P is derived from the following sequence:
EVRSAIRKRWHRWQDKHSIRARVARAMSIPTSPTRVSFHSIKQSTAV (SEQ ID NO: 99).

108. The compound of Claim 107, wherein P is a sequence selected from

RAMSIPTSPTRVSFHSIKQSTAV	(SEQ ID NO: 100);
HSIRARVARAMSIPTSPTRV	(SEQ ID NO: 101);
RWQDKHSIRARVARAMSI	(SEQ ID NO: 102);
EVRSAIRKRWHRWQD	(SEQ ID NO: 103);
RWHRWQDKHSIRAR	(SEQ ID NO: 104);
VRSAIRKRWHRW	(SEQ ID NO: 105); and
GSIRARVARAM	(SEQ ID NO: 106).

109. The compound of any one of Claims 1-9, 11-39, 41-71, 73-104, and 106-108, wherein T is an optionally substituted (C₆-C₃₀)alkyl, (C₆-C₃₀)alkenyl, (C₆-C₃₀)alkynyl, wherein 0-3 carbon atoms are replaced with oxygen, sulfur, nitrogen or a combination thereof.
- 5 110. The compound of Claim 109, wherein T is selected from the group consisting of:
CH₃(CH₂)₁₆, CH₃(CH₂)₁₅, CH₃(CH₂)₁₄, CH₃(CH₂)₁₃, CH₃(CH₂)₁₂, CH₃(CH₂)₁₁,
CH₃(CH₂)₁₀, CH₃(CH₂)₉, CH₃(CH₂)₈, CH₃(CH₂)₉OPh-, CH₃(CH₂)₆C=C(CH₂)₆,
CH₃(CH₂)₁₁O(CH₂)₃, and CH₃(CH₂)₉O(CH₂)₂.
- 10 111. The compound of any one of Claims 1-9, 11-39, 41-71, 73-104, and 106-108, wherein T is a fatty acid derivative.
112. The compound of Claim 111, wherein the fatty acid is selected from the group
consisting of: butyric acid, caproic acid, caprylic acid, capric acid, lauric acid,
15 myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid,
myristoleic acid, palmitoleic acid, oleic acid, linoleic acid, α-linolenic acid,
arachidonic acid, eicosapentaenoic acid, erucic acid, docosahexaenoic acid.
113. The compound of any one of Claims 1-9, 11-39, 41-71, 73-104, and 106-108, wherein
20 T is a bile acid derivative.
114. The compound of Claim 113, wherein the bile acid is selected from the group
consisting of: lithocholic acid, chenodeoxycholic acid, deoxycholic acid, cholanic
acid, cholic acid, ursocholic acid, ursodeoxycholic acid, isoursodeoxycholic acid,
25 lagodeoxycholic acid, dehydrocholic acid, hyocholic acid, and hyodeoxycholic acid.
115. The compound of any one of Claims 1-9, 11-39, 41-71, 73-104, and 106-108, wherein
T is selected from sterols; progestagens; glucocorticoids; mineralcorticoids;
androgens; and estrogens.
30
116. The compound of any one of Claims 1-9, 11-39, 41-71, 73-104, and 106-108, wherein
TL is selected from:

$\text{CH}_3(\text{CH}_2)_{15}-\text{C}(\text{O});$

$\text{CH}_3(\text{CH}_2)_{13}-\text{C}(\text{O});$

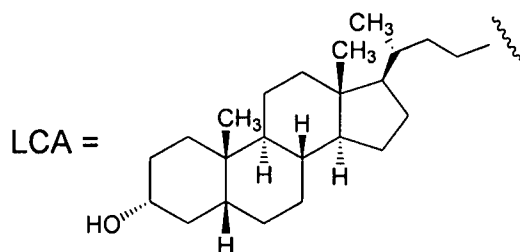
$\text{CH}_3(\text{CH}_2)_9\text{O}(\text{CH}_2)_2\text{C}(\text{O});$

$\text{CH}_3(\text{CH}_2)_{10}\text{O}(\text{CH}_2)_2\text{C}(\text{O});$

5 $\text{CH}_3(\text{CH}_2)_6\text{C}=\text{C}(\text{CH}_2)_6-\text{C}(\text{O});$

$\text{LCA}-\text{C}(\text{O});$ and

$\text{CH}_3(\text{CH}_2)_9\text{OPh}-\text{C}(\text{O})$ wherein



- 10 117. A method of treating diseases and conditions associated with CRF1 modulation.
in a patient in need thereof comprising administering to said patient and effective
amount of a compound of Claim 1.
- 15 118. The method of Claim 117, wherein the disease or condition is selected from:
peripherally acting inflammatory bowel disease, irritable bowel syndrome, stress
response, anxiety, sleep disorder, addictive behavior, acute and chronic
neurodegeneration, preterm labor and pain.
- 20 119. A pharmaceutical composition comprising a compound of any one of Claims 1-116
and a pharmaceutically acceptable carrier.