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(54) **Title**: CXCR4 RECEPTOR COMPOUNDS

(57) **Abstract**: The invention relates generally to compounds which are allosteric modulators (e.g., positive and negative allosteric modulators, and allosteric agonists) of the G protein coupled receptor for stromal derived factor 1 (SDF-I), also known as the CXCR4 receptor. The CXCR4 receptor compounds are derived from the intracellular loops and domains of the CXCR4 receptor. The invention also relates to the use of these CXCR4 receptor compounds and pharmaceutical compositions comprising the CXCR4 receptor compounds in the treatment of diseases and conditions associated with CXCR4 modulation such as bone marrow transplantation, chemosensitization, cancer, metastatic disease, inflammatory diseases, HIV infection and stem cell-based regenerative medicine.

CXCR4 RECEPTOR COMPOUNDS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/198,254, filed on November 4, 2008 and U.S. Provisional Application No. 61/240,176, filed on September 4, 2009. The entire teachings of the above applications are incorporated 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 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. 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).

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 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 allosteric modulators of GPCRs (e.g., negative and positive allosteric modulators, allosteric agonists, and ago-allosteric modulators).

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 stromal derived factor 1 (SDF-1, CXCL12), also known as the CXCR4 receptor. The CXCR4 receptor compounds are derived from the intracellular loops and domains of the CXCR4 receptor. The invention also relates to the use of these CXCR4 receptor compounds and pharmaceutical compositions comprising the CXCR4 receptor compounds in the treatment of diseases and conditions associated with CXCR4 receptor modulation such as bone marrow transplantation, chemosensitization, cancer, metastatic disease, inflammatory diseases, HIV infection and stem cell-based regenerative medicine.

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

TLP,

or a pharmaceutically acceptable salt 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 CXCR4 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.

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 (inhibition or activation) of the CXCR4 receptor.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing will be apparent from the following more particular description of example embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating embodiments of the present invention.

FIGs. 1A-1V are a series of graphical representations of compounds of the invention derived from the i1 loop in a chemotaxis assay as compared with vehicle.

FIGs.2A-2D are a series of graphical representations of compounds of the invention derived from the i2 loop in a chemotaxis assay as compared with vehicle.

FIGs.3A-3G are a series of graphical representations of compounds of the invention derived from the i3 loop in a chemotaxis assay as compared with vehicle.

FIGs. 4A-4D are a series of graphical representations of compounds of the invention derived from the i4 domain in a chemotaxis assay as compared with vehicle.

FIG. 5 is a graphical representation of SDF1-a dependent calcium mobilization in CEM cells upon testing with compounds of the invention.

FIG. 6 is a graphical representation of agonist activity of compounds of the invention in a CEM chemotaxis assay.

FIGs. 7A-7C is a series of graphs showing WBC mobilization of CXCR4 modulators in response to testing with compounds of the invention.

FIGs. 8A-8B is a series of graphs showing results of CXCR4 modulators in a PMN mobilization assay.

FIGs. 9A-9C is a series of graphs showing results of CXCR4 modulators in a lymphocyte mobilization assay.

FIG. 10 is a series of graphs showing the effects of CXCR-4 receptor compounds: 43, 88, 90 and 92 on burst forming unit-erythroid cells (BFU-E) and Colonly-forming unit granulocyte macrophages (CFU-GM).

FIG. 11 is a bar graph showing the effects of 10 μmol/kg CXCR-4 receptor Compound No. 43 and AMD3100 on PMN recuitment in BALB/c mice following subcutaneous injection.

FIG. 12 is is a bar graph showing the effects of 10 μmol/kg CXCR-4 receptor Compound No. 43 and AMD3100 on lymphocyte recruitment in BALB/c mice following subcutaneous injection.

DETAILED DESCRIPTION OF THE INVENTION

A description of example embodiments of the invention follows.

G PROTEIN COUPLED RECEPTORS (GPCRs)

G protein coupled receptors (GPCRs) constitute one of the largest superfamilies of genes in the human genome; these transmembrane proteins enable the cell the 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 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); Dorsham & Gutkind, *Nature Reviews 7*: 79-94 (2007).

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 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.

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, 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 intrisic 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/Smoothened 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.

Class A GPCRs, also called family A or rhodopsin-like, are the largest class of receptors and characteristically have relatively small extracellular loops that form the basis for selectivity vs. endogenous agonists and small-molecule drugs. In addition, Class A receptors also have relatively small intracellular loops. Class A receptors include amine family members such as dopamine and serotonin, peptide members such as chemokine and opioid, the visual opsins, odorant receptors and an array of hormone receptors.

The CXCR4 receptor (SDF-1) is a Class A receptor that has been implicated in conditions such as cancer, metastatic disease, leukocyte homeostasis, hematopoietic stem cell homing to the bone marrow, hematopoietic cell engraftment, inflammatory diseases and HIV tropism.

PEPTIDES

As defined herein, P is a peptide comprising at least three contiguous amino-acid residues (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16) of an intracellular i1, i2 or i3 loop or intracellular i4 domain of the CXCR4 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.

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.

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 least thirteen, at least fourteen, at least fifteen, at least sixteen contiguous amino acid residues of the intracellular i1, i2 or i3 loop or intracellular i4 domain of the CXCR4 receptor.

In certain embodiment, P is cyclized. The amino acids can be cyclized via their side chains or end to end.

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, or 16) are derived from the intracellular i1, i2 or i3 loop or intracellular i4 domain of the CXCR4 receptor, wherein the amino acid sequence of each loop and the i4 domain is as described in Table 1.

Table 1:

Intracellular Loop or Domain	CXCR4 Receptor
i1	MGYQKKLRSMTDKYRLH (SEQ ID NO:370)
i2	DRYLAIVHATNSQRPRKLLAEK (SEQ ID NO:371)
i3	IIISKLSHSKGHQKRKALKTTVI (SEQ ID NO:372)
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS (SEQ ID NO:373)

It is understood that in addition to the amino acids listed in the sequences in Table 1, the intracellular loop for the i1 loop, i2 loop, i3 loop and i4 domain can also include the 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 a Serine residue, or a Serine-Alanine residue at the C-terminus, SEQ ID NOS: 370 and 371 respectively.. Similarly, the N-teminus of the i1 loop sequence described in Table 1 can also be extended to include a Valine residue (SEQ ID NO: 372) or –Valine-Leucine residues (SEQ ID

NO: 373), or by –Valine-Leucine-Isoleucine residues (SEQ ID NO: 374) or by – Valine-Leucine-Isoleucine-Valine residues (SEQ ID NO 375).

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, or at least sixteen contiguous amino acid residues of the i1 intracellular loop of the CXCR4 receptor.

In an even more specific embodiment, P is selected from the group consisting of SEQ ID NOS:1-148 as listed in Table 2 below. Amino acids designated as lower case letters indicate D-amino acids.

Table 2:

CXCR4 i-Loop	Sequence	SEQ ID NO:
i1	SGYQKKLRSSTD	1
i1	MGYQKKLRSSTD	2
i1	SGYQKKLRSMTD	3
i1	JGYQKKLRSJTD	4
i1	LGYQKKLRSLTD	5
i1	IGYQKKLRSITD	6
i1	JGYQKKLRSSTD	7
i1	JGYQKKLRSMTD	8
i1	LGYQKKLRSMTD	9
i1	IGYQKKLRSMTD	10
i1	AGYQKKLRSMTD	11
i1	MAYQKKLRSMTD	12
i1	MGAQKKLRSMTD	13
i1	MGYAKKLRSMTD	14
i1	MGYQKKLRAMTD	15
i1	MGYQKKLRSATD	16
i1	MGYQKKLRSMAD	17
i1	MGYQKKLRSMTA	18
i1	MGYQAKLRSMTD	19
i1	MGYQKKLASMTD	20
i1	MGYQKALRSMTD	21
i1	MGYQKKARSMTD	22
i1	mGYQKKLRSMTD	23
i1	MGyQKKLRSMTD	24
i1	MGYqKKLRSMTD	25
i1	MGYQkKLRSMTD	26
i1	MGYQKkLRSMTD	27

il	MGYQKKlRSMTD	28
il	MGYQKKLrSMTD	29
il	MGYQKKLRsMTD	30
il	MGYQKKLRSmTD	31
il	MGYQKKLRSMtD	32
il	MGYQKKLRSMTd	33
il	GSHYQKKLRSSTD	34
il	GSGYQKKLRSSTD	35
il	YQKKLRSSTD	36
il	GYQKKLRSJTD	37
il	GYQKKLRSLTD	38
il	GYQKKLRSMTDKYRLH	39
il	YQKKLRSMTDKYRLH	40
il	QKKLRSMTDKYRLH	41
il	KKLRSMTDKYRLH	42
il	KLRSMTDKYRLH	43
il	LRSMTDKYRLH	44
il	RSMTDKYRLH	45
il	SMTDKYRLH	46
il	MTDKYRLH	47
il	TDKYRLH	48
il	GYQKKLRSMTDKYRL	49
il	GYQKKLRSMTDKYR	50
il	GYQKKLRSMTDKY	51
il	GYQKKLRSMTDK	52
il	GYQKKLRSMTD	53
il	GYQKKLRSITD-	54
il	GYQKKLRSMT	55
il	GYQKKLRSM	56
il	GYQKKLRS	57
il	GYQKKLR	58
il	YQKKLRS	59
il	QKKLRSM	60
il	KKLRSMT	61
il	KLRSMTD	62
il	LRSMTDK	63
il	RSMTDKY	64
il	SMTDKYR	65
il	MTDKYRL	66
il	KRMKTSLYDGRMQYLK	67
il	sGYQKKLRSSTD	68
il	KKLRSMTDKY	69
il	KKLRSMTDKYR	70
il	KKLRSMTDKYRL	71
il	KKLRSXTDKYRLH (X= Norluceine (Nle))	72

il	KKLRSMTDKYRLHL	73
il	KKLRSMTDKYRLHLSV	74
il	QKKLRSMTDKYRI	75
il	QKKLRSMTDKYRLHL	76
il	YQKKLRSMTDKYRLHLSV	77
il	LVMGYQKKLRSMTD	78
il	MGYQKKLRSMTDK	79
il	MGYQKKLRSMTDKY	80
il	MGYQKKLRSMTDKYRI	81
il	MGYQKKLRSMTDKYRL	82
il	MGYQKKLRSMTDKYRLHL	83
il	MGYQKKLRSMTDKYRLHLSV	84
il	YTKRLDSHRKLKM	85
il	VMGYQKKLRSMTD	86
il	KKLCRSMTDKCYRL	87
il	KKLRCSMTDCKYRL	88
il	kKLRSMTDKYRLH	89
il	KkLRSMTDKYRLH	90
il	KKlRSMTDKYRLH	91
il	KKLrSMTDKYRLH	92
il	KKLRsMTDKYRLH	93
il	KKLRSmTDKYRLH	94
il	AKLRSMTDKYRLH	95
il	KALRSMTDKYRLH	96
il	KKARSMTDKYRLH	97
il	KKLASMTDKYRLH	98
il	KKLRAMTDKYRLH	99
il	KKLRSATDKYRLH	100
il	AGYQKKLRSMTDKYRL	101
il	MAYQKKLRSMTDKYRL	102
il	MGAQKKLRSMTDKYRL	103
il	MGYAKKLRSMTDKYRL	104
il	MGYQAKLRSMTDKYRL	105
il	MGYQKALRSMTDKYRL	106
il	MGYQKKARSMTDKYRL	107
il	MGYQKKLASMTDKYRL	108
il	KKLRSMADKYRLH	109
il	KKLRSMTAKYRLH	110
il	KKLRSMTDAYRLH	111
il	KKLRSMTDKARLH	112
il	KKLRSMTDKYALH	113
il	KKLRSMTDKYRAH	114
il	KKLRSMTDKYRLA	115
il	MGYQKKLRAMTDKYRL	116
il	MGYQKKLRSATDKYRL	117
il	MGYQKKLRSMADKYRL	118

i1	MGYQKKLRSMTAKYRL	119
i1	MGYQKKLRSMTDAYRL	120
i1	MGYQKKLRSMTDKARL	121
i1	MGYQKKLRSMTDKYAL	122
i1	MGYQKKLRSMTDKYRA	123
i1	KKLRSMtDKYRLH	124
i1	KKLRSMTdKYRLH	125
i1	KKLRSMTDKYrLH	126
i1	KKLRSMTDKYRlH	127
i1	KKLRSMTDKYRLh	128
i1	MGYQKKLRSMTDKYrL	129
i1	MGYQKKLRSMTDKyRL	130
i1	MGYQKKLRSMTDkYRL	131
i1	MGYQKKLRSMTdKYRL	132
i1	MGYQKKLRSMtDKYRL	133
i1	mGYQKKLRSMTDKYRL	134
i1	MGyQKKLRSMTDKYRL	135
i1	MGYqKKLRSMTDKYRL	136
i1	MGYQkKLRSMTDKYRL	137
i1	MGYQKkLRSMTDKYRL	138
i1	MGYQKKlRSMTDKYRL	139
i1	MGYQKKLrSMTDKYRL	140
i1	MGYQKKLRsMTDKYRL	141
i1	MGYQKKLRSmTDKYRL	142
i1	KKLRSMTDKYRlS	143
i1	MGYQKKLRSpTDKYRL	144
i1	MGYQKKLRpMTDKYRL	145
i1	MGYQKKLpSMTDKYRL	146
i1	MGYQKKpRSMTDKYRL	147
i1	MGYQKKLRSMPDKYRL	148

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, or 16) are derived from the i2 intracellular loopof the CXCR4 receptor.

In a more specific embodiment, P is selected from the group consisting of SEQ ID NOS: 149-199 as listed in Table 3 below.

Table 3:

CXCR4 i-Loop	Sequence	SEQ ID NO:
i2	DRYLAIVHATNSQRPRKLLAEK	149
i2	DRYLAIVHATNSQRPRKLLAE	150
i2	DRYLAIVHATNSQRPRKLLA	151
i2	DRYLAIVHATNSQRPRKLL	152
i2	DRYLAIVHATNSQRPRKL	153
i2	DRYLAIVHATNSQRPRK	154
i2	DRYLAIVHATNSQRPR	155
i2	DRYLAIVHATNSQRP	156
i2	DRYLAIVHATNSQR	157
i2	DRYLAIVHATNSQ	158
i2	DRYLAIVHATNS	159
i2	DRYLAIVHATN	160
i2	DRYLAIVHAT	161
i2	DRYLAIVHA	162
i2	DRYLAIVH	163
i2	DRYLAIV	164
i2	RYLAIVHATNSQRPRKLLAEK	165
i2	YLAIVHATNSQRPRKLLAEK	166
i2	LAIVHATNSQRPRKLLAEK	167
i2	AIVHATNSQRPRKLLAEK	168
i2	IVHATNSQRPRKLLAEK	169
i2	VHATNSQRPRKLLAEK	170
i2	HATNSQRPRKLLAEK-	171
i2	ATNSQRPRKLLAEK	172
i2	TNSQRPRKLLAEK	173
i2	NSQRPRKLLAEK	174
i2	SQRPRKLLAEK	175
i2	QRPRKLLAEK	176
i2	RPRKLLAEK	177
i2	PRKLLAEK	178
i2	RKLLAEK	179
i2	RYLAIVH-	180
i2	YLAIVHA	181
i2	LAIVHAT	182
i2	AIVHATN-	183
i2	IVHATNS-	184
i2	VHATNSQ	185
i2	HATNSQR	186
i2	ATNSQRP	187
i2	TNSQRPR-	188
i2	NSQRPRK	189
i2	SQRPRKL	190

i2	QRPRKLL	191
i2	RPRKLLA	192
i2	PRKLLAE	193
i2	VHATNSQRPRKLLAEKVVY	194
i2	VHATNSQRPRKLLA	195
i2	HATNSQRPRKL	196
i2	HATNSQRPRKLLA	197
i2	HATNSQRPRKLLAE	198
i2	HATNSQRPRKLLAEKV	199

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, or 16) of the i3 intracellular loopof the CXCR4 receptor.

In a more specific embodiment, P is selected from the group consisting of SEQ ID NOS:200-254 as listed in Table 4 below.

Table 4:

CXCR4 i-Loop	Sequence	SEQ ID:
i3	HSKKGHQKRKALK	200
i3	JGYQKKLRSJTD	201
i3	IIISKLSHSKGHQKRKALKT	202
i3	IIISKLSHSKGHQKRKALK	203
i3	IIISKLSHSKGHQKRKAL	204
i3	IIISKLSHSKGHQKRKA	205
i3	IIISKLSHSKGHQKRK	206
i3	IIISKLSHSKGHQKR	207
i3	IIISKLSHSKGHQK	208
i3	IIISKLSHSKGHQ	209
i3	IIISKLSHSKGH	210
i3	IIISKLSHSKG	211
i3	IIISKLSHSK	212
i3	IIISKLSHS	213
i3	IIISKLSH	214
i3	IIISKLS	215
i3	IISKLSHSKGHQKRKALKT	216
i3	ISKLSHSKGHQKRKALKT	217
i3	SKLSHSKGHQKRKALKT	218
i3	KLSHSKGHQKRKALKT	219
i3	LSHSKGHQKRKALKT	220
i3	SHSKGHQKRKALKT	221
i3	HSKGHQKRKALKT	222
i3	SKGHQKRKALKT	223
i3	KGHQKRKALKT	224

i3	GHQKRKALKT	225
i3	HQKRKALKT	226
i3	QKRKALKT	227
i3	KRKALKT	228
i3	IISKLSH	229
i3	ISKLSHS	230
i3	SKLSHSK	231
i3	KLSHSKG	232
i3	LSHSKGH	233
i3	SHSKGHQ	234
i3	HSKGHQK	235
i3	SKGHQKR	236
i3	KGHQKRK	237
i3	GHQKRKA	238
i3	HQKRKAL	239
i3	QKRKALK	240
i3	HSKGHQKRKALKTT	241
i3	HSKGHQKRKALKTTV	242
i3	HSKGHQKRKALKTTVI	243
i3	HSKGHQKRKQALK	244
i3	KLSHSKGHQKRKA	245
i3	KLSHSKGHQKRKAL	246
i3	KLSHSKGHQKRKALK	247
i3	KLSHSKGHQKRKALKTTV	248
i3	KLSHSKGHQKRKALKTTVIL	249
i3	LSHSKGHQKRKALK	250
i3	SHSKGHQKRKALK	251
i3	SKLSHSKGHQKRKALK	252
i3	SKLSHSKGHQKRKALKTTVIL	253
i3	QHLHIALKKSTSRKVKSGTLK	254

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 or 16) of the i4 intracellular domain of the CXCR4 receptor.

In a more specific embodiment, P is selected from the group consisting of SEQ ID NOS: 255- 368 as listed in Table 5 below.

Table 5:

CXCR4 i-Loop	Sequence	SEQ ID NO:
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFH	255
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSF	256
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSS	257

i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESS	258
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESES	259
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESE	260
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTES	261
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTE	262
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVST	263
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVS	264
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSV	265
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSS	266
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHS	267
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGH	268
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGG	269
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRG	270
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKR	271
i4	GAKFKTSAQHALTSVSRGSSLKILSKGK	272
i4	GAKFKTSAQHALTSVSRGSSLKILSKG	273
i4	GAKFKTSAQHALTSVSRGSSLKILSK	274
i4	GAKFKTSAQHALTSVSRGSSLKILS	275
i4	GAKFKTSAQHALTSVSRGSSLKIL	276
i4	GAKFKTSAQHALTSVSRGSSLKI	277
i4	GAKFKTSAQHALTSVSRGSSLK	278
i4	GAKFKTSAQHALTSVSRGSSL	279
i4	GAKFKTSAQHALTSVSRGSS	280
i4	GAKFKTSAQHALTSVSRGS	281
i4	GAKFKTSAQHALTSVSRG	282
i4	GAKFKTSAQHALTSVSR	283
i4	GAKFKTSAQHALTSVS	284
i4	GAKFKTSAQHALTSV	285
i4	GAKFKTSAQHALTS	286
i4	GAKFKTSAQHALT	287
i4	GAKFKTSAQHAL	288
i4	GAKFKTSAQHA	289
i4	GAKFKTSAQH	290
i4	AKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	291
i4	KFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	292
i4	FKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	293
i4	KTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	294
i4	TSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	295
i4	SAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	296
i4	AQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	297
i4	QHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	298
i4	HALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	299
i4	ALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	300
i4	LTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	301
i4	TSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	302
i4	SVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	303

i4	VSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	304
i4	SRGSSLKILSKGKRGGHSSVSTESESSSFHSS	305
i4	RGSSLKILSKGKRGGHSSVSTESESSSFHSS	306
i4	GSSLKILSKGKRGGHSSVSTESESSSFHSS	307
i4	SSLKILSKGKRGGHSSVSTESESSSFHSS	308
i4	SLKILSKGKRGGHSSVSTESESSSFHSS	309
i4	LKILSKGKRGGHSSVSTESESSSFHSS	310
i4	KILSKGKRGGHSSVSTESESSSFHSS	311
i4	ILSKGKRGGHSSVSTESESSSFHSS	312
i4	LSKGKRGGHSSVSTESESSSFHSS	313
i4	SKGKRGGHSSVSTESESSSFHSS	314
i4	KGKRGGHSSVSTESESSSFHSS	315
i4	GKRGGHSSVSTESESSSFHSS	316
i4	KRGGHSSVSTESESSSFHSS	317
i4	RGGHSSVSTESESSSFHSS	318
i4	GGHSSVSTESESSSFHSS	320
i4	GHSSVSTESESSSFHSS	321
i4	HSSVSTESESSSFHSS	322
i4	SSVSTESESSSFHSS	323
i4	SVSTESESSSFHSS	324
i4	VSTESESSSFHSS	325
i4	STESESSSFHSS	326
i4	TESESSSFHSS	327
i4	ESESSSFHSS	328
i4	AKFKTSAQHA	329
i4	KFKTSAQHAL	330
i4	FKTSAQHALT	331
i4	KTSAQHALTS	332
i4	TSAQHALTSV	333
i4	SAQHALTSVS	334
i4	AQHALTSVSR	335
i4	QHALTSVSRG	336
i4	HALTSVSRGS	337
i4	ALTSVSRGSS	338
i4	LTSVSRGSSL	339
i4	TSVSRGSSLK	340
i4	SVSRGSSLKI	341
i4	VSRGSSLKIL	342
i4	SRGSSLKILS	343
i4	RGSSLKILSK	345
i4	GSSLKILSKG	346
i4	SSLKILSKGK	347
i4	SLKILSKGKR	348
i4	LKILSKGKRG	349
i4	KILSKGKRGG	350
i4	ILSKGKRGGH	351

i4	LSKGKRGGHS	352
i4	SKGKRGGHSS	353
i4	KGKRGGHSSV	354
i4	GKRGGHSSVS	355
i4	KRGGHSSVST	356
i4	RGGHSSVSTE	357
i4	GGHSSVSTES	358
i4	GHSSVSTESE	359
i4	HSSVSTESES	360
i4	SSVSTESESS	361
i4	SVSTESESSS	362
i4	VSTESESSSF	363
i4	STESESSSFH	364
i4	TESESSSFHS	365
i4	ESESSSFHSS	366
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHS	367
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSCFH	368

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 an alkyl group, for example a (C_1-C_{10}) alkyl group and R_3 is an alkyl group, for example, a (C_1-C_{10}) alkyl group.

In another embodiment, the C-terminus of P has a lipophilic tether moiety. In certain embodiments, the lipophilic tether moiety is attached to a NH capped C-terminus of P.

It is understood that as long as P comprises the indicated number of contiguous amino acids residues from the CXCR4 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:

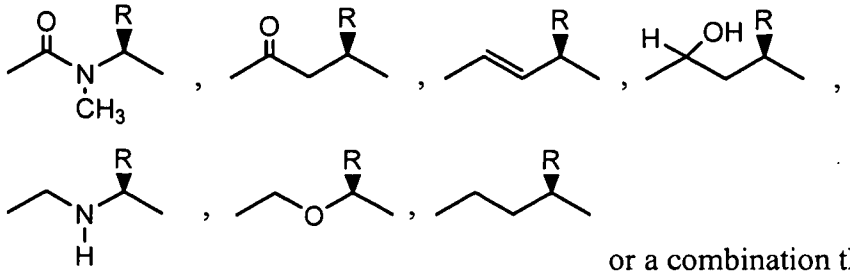
(a) any natural amino acid residue, unnatural amino acid residue or a combination thereof;

(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;

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



or a combination thereof;

(f) a peptide sequence according to (c) comprising one or more depsipeptide 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 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; despsipeptide linkages; conformational restrictions; or a combination thereof.

It is noted that P of Formula I can 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 an alkyl group, for example a (C_1-C_{10}) alkyl group and R_3 is an alkyl group, for example a (C_1-C_{10}) alkyl group. Functionalization of the C-terminus can result from the methods used to prepare.

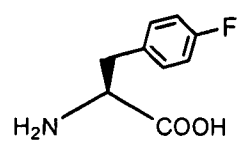
Peptidomimetic as used herein refers to a compound comprising non-peptidic structural elements in place of a peptide sequence.

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 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., 

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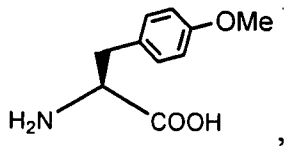

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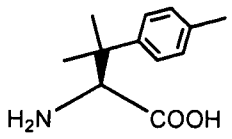

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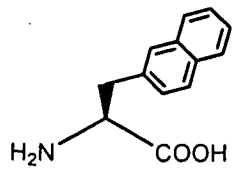
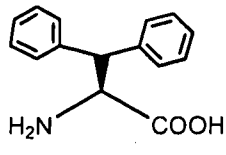


, and



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-diaminobutryic acid), α-aminopimelic acid, TMSA (trimethylsilyl-Ala), aIle (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^{α}-alkylated amino acids such as MeGly (N^{α}-methylglycine), EtGly (N^{α}-ethylglycine) and EtAsn (N^{α}-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 lipohilic tether moiety which imparts lipophilicity to the CXCR4 receptor compounds of the invention. The lipophilicity which T imparts, can promote penetration of the CXCR4 receptor compounds into the cell membrane and tethering of the CXCR4 receptor compounds to the cell membrane. As such, the lipophilicity imparted by T can facilitate interaction between the CXCR4 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 = $[compound]_{octanol}/[compound]_{aqueous}$). 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 ($-CH_2-$) onto to an existing alkyl group, the trend in log P can be calculated using, for example, ChemDraw (CambridgeSoft, Inc).

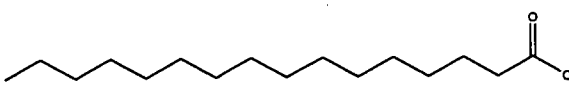
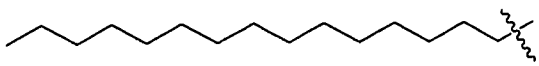
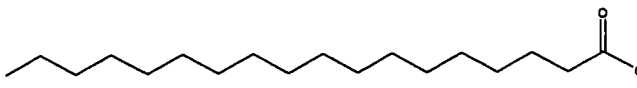
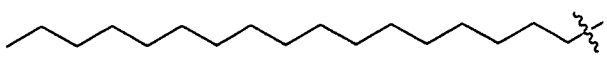
In one embodiment, T is an optionally substituted (C_6-C_{30})alkyl, (C_6-C_{30})alkenyl, (C_6-C_{30})alkynyl wherein 0-3 carbon atoms are replaced with oxygen, sulfur, nitrogen or a combination thereof.

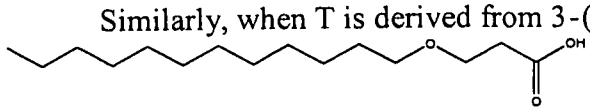
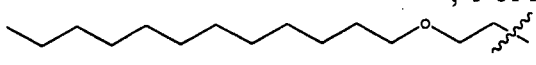
In a specific embodiment, the (C_6-C_{30})alkyl, (C_6-C_{30})alkenyl, (C_6-C_{30})alkynyl are substituted at one or more substitutable carbon atoms with halogen, -CN, -OH, $-NH_2$, NO_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, aryloxy, (C_1-C_6)alkoxycarbonyl, $-CONH_2$, $-OCONH_2$, $-NHCONH_2$, -N(C_1-C_6)alkylCONH$_2$, -N(C_1-C_6)alkylCONH(C_1-C_6)alkyl, -NHCONH(C_1-C_6)alkyl, -NHCON((C_1-C_6)alkyl)$_2$, -N(C_1-C_6)alkylCON((C_1-C_6)alkyl)$_2$, -NHC(S)NH$_2$, -N(C_1-C_6)alkylC(S)NH$_2$, -N(C_1-C_6)alkylC(S)NH(C_1-C_6)alkyl, -NHC(S)NH(C_1-C_6)alkyl, -NHC(S)N((C_1-C_6)alkyl)$_2$, -N(C_1-C_6)alkylC(S)N((C_1-C_6)alkyl)$_2$, -CONH(C_1-C_6)alkyl, -OCONH(C_1-C_6)alkyl -CON((C_1-C_6)alkyl)$_2$, -C(S)(C_1-C_6)alkyl, -S(O)$_p$(C_1-C_6)alkyl, -S(O)$_p$NH$_2$, -S(O)$_p$NH(C_1-C_6)alkyl, -S(O)$_p$N((C_1-C_6)alkyl)$_2$, -CO(C_1-C_6)alkyl, -OCO(C_1-C_6)alkyl, -C(O)O(C_1-C_6)alkyl, -OC(O)O(C_1-C_6)alkyl, -C(O)H or $-CO_2H$; and p is 1 or 2.

In a specific embodiment, T is selected from the group consisting of: $CH_3(CH_2)_9OPh$-, $CH_3(CH_2)_6C{=}C(CH_2)_6$, $CH_3(CH_2)_{11}O(CH_2)_3$, $CH_3(CH_2)_9O(CH_2)_2$ and $CH_3(CH_2)_{13}$.

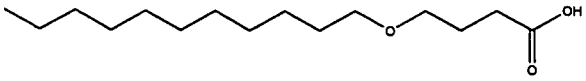
In a specific embodiment, T is selected from the group consisting of: $CH_3(CH_2)_{16}$, $CH_3(CH_2)_{15}$, $CH_3(CH_2)_{14}$, $CH_3(CH_2)_{13}$, $CH_3(CH_2)_{12}$, $CH_3(CH_2)_{11}$, $CH_3(CH_2)_{10}$, $CH_3(CH_2)_9$, $CH_3(CH_2)_8$, $CH_3(CH_2)_9OPh$-, $CH_3(CH_2)_6C{=}C(CH_2)_6$, $CH_3(CH_2)_{11}O(CH_2)_3$, and $CH_3(CH_2)_9O(CH_2)_2$ and $CH_3(CH_2)_{13}$.

It is understood that the lipophilic moiety (T) of Formula I can be derived from precursor liphophilic 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 APJ 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.

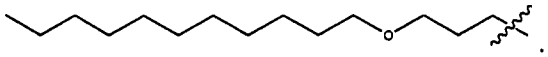
For example, the lipophilic tether moiety, T of Formula I, can be derived from a fatty acid or a bile acid. It is understood that in accordance with Formula I, when T is derived from a fatty acid (i.e., a fatty acid derivative) it is attached to L-P at the carbon atom alpha to the carbonyl carbon of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

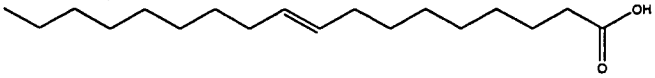
Similarly, when T is derived from 4-(undecyloxy)butanoic acid,



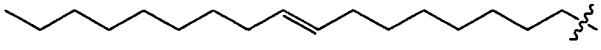
, T of Formula I has the following structure:



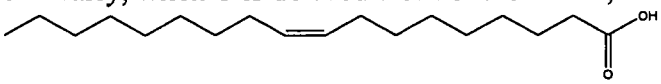
Similarly, when T is derived from elaidic acid,



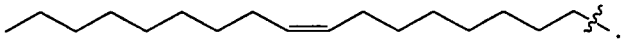
, T of Formula I has the following structure:



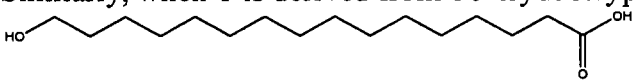
Similarly, when T is derived from oleic acid,



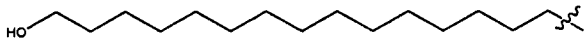
, T of Formula I has the following structure:



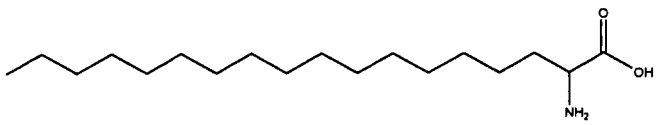
Similarly, when T is derived from 16-hydroxypalmitic acid,



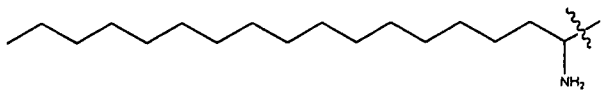
, T of Formula I has the following structure:



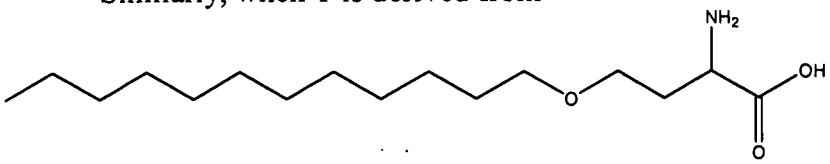
Similarly, when T is derived from 2-aminooctadecanoic acid



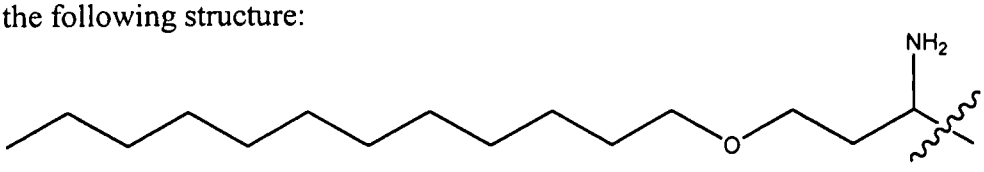
, T of Formula I has the following structure:



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



, T of Formula I has the following structure:

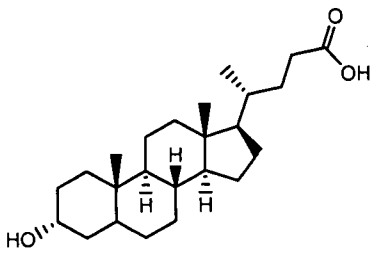


In a further embodiment, T is derived from a fatty acid. In a specific embodiment, T is derived from a fatty acid selected from the group consisting of:

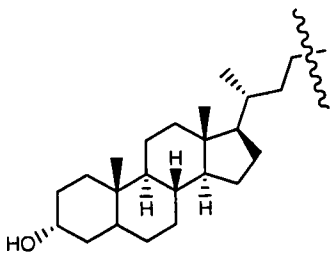
butyric acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, and lignoceric acid.

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.

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

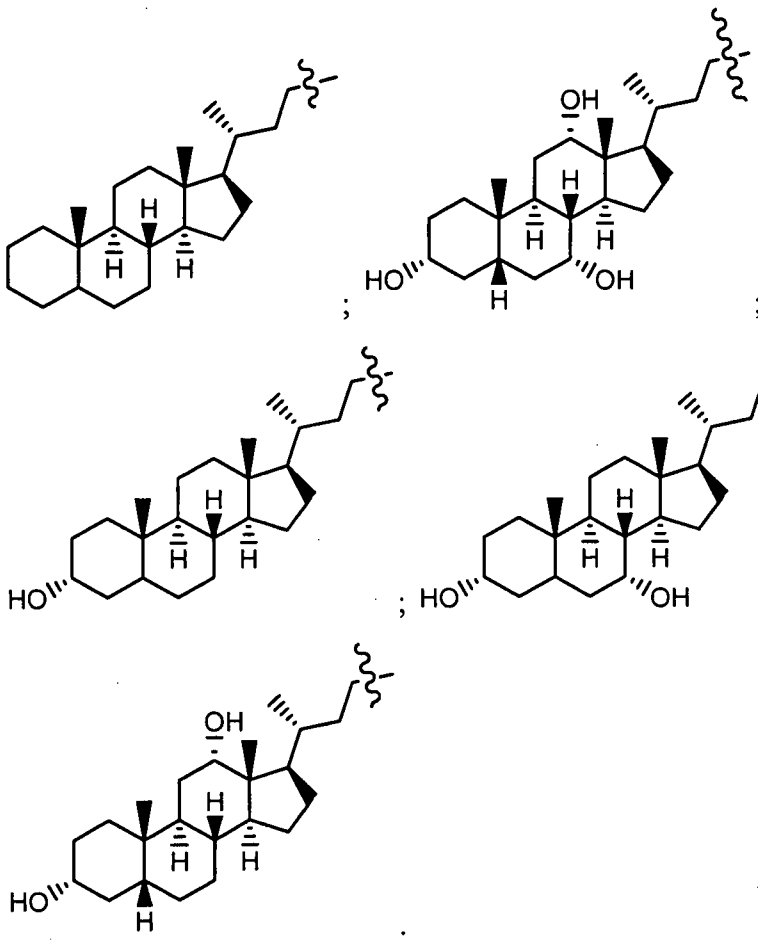


lithocholic acid, , T of Formula I has the following structure:

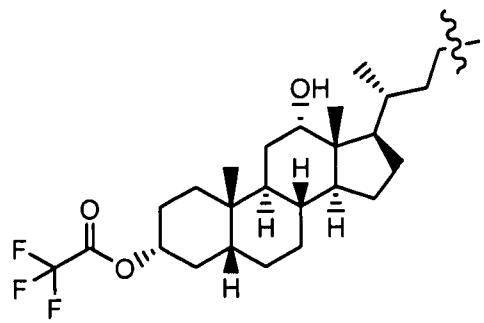


In a further embodiment, T is derived from a bile acid. In a specific embodiment, T is derived from a bile acid selected from the group consisting of: lithocholic acid, chenodeoxycholic acid, deoxycholic acid, cholanic acid, cholic acid, ursocholic acid, ursodeoxycholic acid, isoursodeoxycholic acid,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



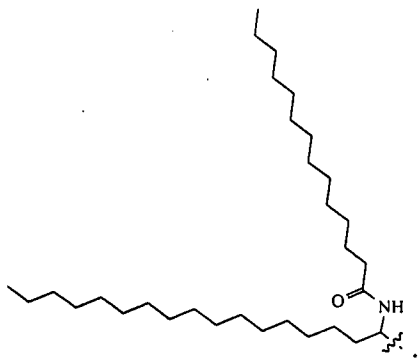
Other lipophilic moieties suitable for use as the lipophilic membrane tether, T, of Formula I, include but are not limited to steroids. Suitable steroids include, but are not limited to, sterols; progestagens; glucocorticoids; mineralcorticoids; androgens; and estrogens. Generally any steroid capable 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.

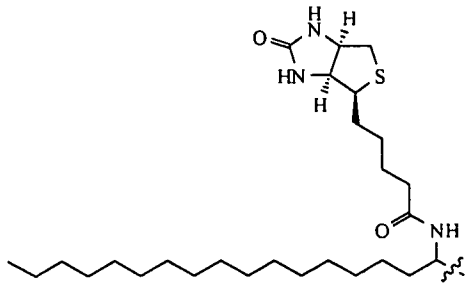
Suitable sterols for use in the invention at T, include but are not limited to: cholestanol, coprostanol, cholesterol, epicholesterol, ergosterol, ergocalciferol, and the like. Preferred sterols are those that provide a balance of lipophilicity with water solubility.

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.

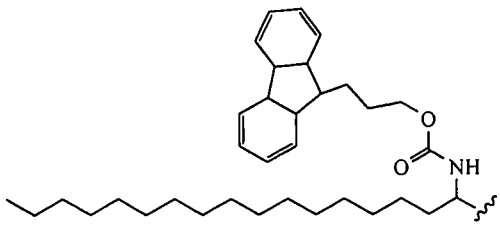
In another specific embodiment, T can be derived from 2-tetradecanamideooctadecanoid acid. Similar to the embodiment where T is a fatty acid derivative, it is understood that in accordance with Formula I, when T is derived from 2-tetradecanamideooctadecanoid acid it is attached to L-P at the carbon atom 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-tetradecanamideooctadecanoid 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 of 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 a pharmaceutically acceptable salt 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 CXCR4 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, the i1 loop of the CXCR4 receptor from which P is derived has the following sequence:

MGYQKKLRSMTDKYRLH (SEQ ID NO:370).

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

CXCR4 i-Loop	Sequence	SEQ ID NO:
i1	SGYQKKLRSSTD	1
i1	MGYQKKLRSSTD	2
i1	SGYQKKLRSMTD	3
i1	JGYQKKLRSJTD	4
i1	LGYQKKLRSLTD	5
i1	IGYQKKLRSITD	6
i1	JGYQKKLRSSTD	7
i1	JGYQKKLRSMTD	8
i1	LGYQKKLRSMTD	9
i1	IGYQKKLRSMTD	10
i1	AGYQKKLRSMTD	11
i1	MAYQKKLRSMTD	12
i1	MGAQKKLRSMTD	13
i1	MGYAKKLRSMTD	14
i1	MGYQKKLRAMTD	15
i1	MGYQKKLRSATD	16
i1	MGYQKKLRSMAD	17
i1	MGYQKKLRSMTA	18
i1	MGYQAKLRSMTD	19
i1	MGYQKKLASMTD	20
i1	MGYQKALRSMTD	21
i1	MGYQKKARSMTD	22
i1	mGYQKKLRSMTD	23
i1	MGyQKKLRSMTD	24
i1	MGYqKKLRSMTD	25
i1	MGYQkKLRSMTD	26
i1	MGYQKkLRSMTD	27
i1	MGYQKKlRSMTD	28
i1	MGYQKKLrSMTD	29
i1	MGYQKKLRsMTD	30
i1	MGYQKKLRSmTD	31
i1	MGYQKKLRSMtD	32
i1	MGYQKKLRSMTd	33
i1	GSHYQKKLRSSTD	34

il	GSGYQKKLRSSTD	35
il	YQKKLRSSTD	36
il	GYQKKLRSJTD	37
il	GYQKKLRSLTD	38
il	GYQKKLRSMTDKYRLH	39
il	YQKKLRSMTDKYRLH	40
il	QKKLRSMTDKYRLH	41
il	KKLRSMTDKYRLH	42
il	KLRSMTDKYRLH	43
il	LRSMTDKYRLH	44
il	RSMTDKYRLH	45
il	SMTDKYRLH	46
il	MTDKYRLH	47
il	TDKYRLH	48
il	GYQKKLRSMTDKYRL	49
il	GYQKKLRSMTDKYR	50
il	GYQKKLRSMTDKY	51
il	GYQKKLRSMTDK	52
il	GYQKKLRSMTD	53
il	GYQKKLRSITD-	54
il	GYQKKLRSMT	55
il	GYQKKLRSM	56
il	GYQKKLRS	57
il	GYQKKLR	58
il	YQKKLRS	59
il	QKKLRSM	60
il	KKLRSMT	61
il	KLRSMTD	62
il	LRSMTDK	63
il	RSMTDKY	64
il	SMTDKYR	65
il	MTDKYRL	66
il	KRMKTSLYDGRMQYLK	67
il	sGYQKKLRSSTD	68
il	KKLRSMTDKY	69
il	KKLRSMTDKYR	70
il	KKLRSMTDKYRL	71
il	KKLRSXTDKYRLH (X= Norluceine (Nle))	72
il	KKLRSMTDKYRLHL	73
il	KKLRSMTDKYRLHLSV	74
il	QKKLRSMTDKYRI	75
il	QKKLRSMTDKYRLHL	76
il	YQKKLRSMTDKYRLHLSV	77
il	LVMGYQKKLRSMTD	78
il	MGYQKKLRSMTDK	79

il	MGYQKKLRSMTDKY	80
il	MGYQKKLRSMTDKYRI	81
il	MGYQKKLRSMTDKYRL	82
il	MGYQKKLRSMTDKYRLHL	83
il	MGYQKKLRSMTDKYRLHLSV	84
il	YTKRLDSHRKLKM	85
il	VMGYQKKLRSMTD	86
il	KKLCRSMTDKCYRL	87
il	KKLRCSMTDCKYRL	88
il	kKLRSMTDKYRLH	89
il	KkLRSMTDKYRLH	90
il	KKlRSMTDKYRLH	91
il	KKLrSMTDKYRLH	92
il	KKLRsMTDKYRLH	93
il	KKLRSmTDKYRLH	94
il	AKLRSMTDKYRLH	95
il	KALRSMTDKYRLH	96
il	KKARSMTDKYRLH	97
il	KKLASMTDKYRLH	98
il	KKLRAMTDKYRLH	99
il	KKLRSATDKYRLH	100
il	AGYQKKLRSMTDKYRL	101
il	MAYQKKLRSMTDKYRL	102
il	MGAQKKLRSMTDKYRL	103
il	MGYAKKLRSMTDKYRL	104
il	MGYQAKLRSMTDKYRL	105
il	MGYQKALRSMTDKYRL	106
il	MGYQKKARSMTDKYRL	107
il	MGYQKKLASMTDKYRL	108
il	KKLRSMADKYRLH	109
il	KKLRSMTAKYRLH	110
il	KKLRSMTDAYRLH	111
il	KKLRSMTDKARLH	112
il	KKLRSMTDKYALH	113
il	KKLRSMTDKYRAH	114
il	KKLRSMTDKYRLA	115
il	MGYQKKLRAMTDKYRL	116
il	MGYQKKLRSATDKYRL	117
il	MGYQKKLRSMADKYRL	118
il	MGYQKKLRSMTAKYRL	119
il	MGYQKKLRSMTDAYRL	120
il	MGYQKKLRSMTDKARL	121
il	MGYQKKLRSMTDKYAL	122
il	MGYQKKLRSMTDKYRA	123
il	KKLRSMtDKYRLH	124
il	KKLRSMTdKYRLH	125

il	KKLRSMTDKYrLH	126
il	KKLRSMTDKYRlH	127
il	KKLRSMTDKYRLh	128
il	MGYQKKLRSMTDKYrL	129
il	MGYQKKLRSMTDKyRL	130
il	MGYQKKLRSMTDkYRL	131
il	MGYQKKLRSMTdKYRL	132
il	MGYQKKLRSMtDKYRL	133
il	mGYQKKLRSMTDKYRL	134
il	MGyQKKLRSMTDKYRL	135
il	MGYqKKLRSMTDKYRL	136
il	MGYQkKLRSMTDKYRL	137
il	MGYQKkLRSMTDKYRL	138
il	MGYQKKlRSMTDKYRL	139
il	MGYQKKLrSMTDKYRL	140
il	MGYQKKLRsMTDKYRL	141
il	MGYQKKLRSmTDKYRL	142
il	KKLRSMTDKYRlS	143
il	MGYQKKLRSpTDKYRL	144
il	MGYQKKLRpMTDKYRL	145
il	MGYQKKLpSMTDKYRL	146
il	MGYQKKpRSMTDKYRL	147
il	MGYQKKLRSMPDKYRL	148

It is understood that for the embodiments presented herein, that when the amino acid residues of P are represented by X, W, 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-terminla residue includes –OH as well as other moieties defined herein.

In a more specific embodiment, the compounds is represented by Formula A:

T-L-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}- X_{20}- X_{21}- X_{22}-X_{23}- X_{24}-R_1; or a pharmaceutically acceptable salt thereof, wherein: L is a linking moiety represented by C(O) and bonded to the N terminal nitrogen of X_1 or the next present amino acid residue if X_1 is absent; T is a lipophilic tether moiety bonded to L; and R_1 is OR_2 or $N(R_2)_2$, each R_2 is independently H or alkyl,

wherein at least three contiguous X_1-X_{24} amino acid residues are present, and wherein:

X_1 is a valine residue or absent

X_2 is a isoleucine residue or absent,

X_3 is a leucine residue or absent,
X_4 is a valine residue, a glycine residue or absent,
X_5 is a methionine residue, a isoleucine residue, a leucine residue, a norleucine residue, a serine residue, an alanine residue, a d-methionine residue, a d-serine residue, or absent,
X_6 is a glycine residue, an alanine residue, a histidine residue, a lysine residue or absent,
X_7 is a tyrosine residue, an alanine residue, a d-tyrosine residue, an arginine residue or absent
X_8 is a glutamine residue, an alanine residue, a d-glutamine residue, a methionine residue, a threonine residue, or a lysine residue or absent,
X_9 is a lysine residue, a d-lysine residue, a alanine residue or absent,
X_{10} is a lysine residue, a d-lysine residue, a leucine residue, a threonine residue, an alanine residue or absent,
X11 is a leucine residue, a d-leucine residue, an alanine residue, an isoleucine residue, a serine residue, a cysteine residue, an arginine residue or absent,
X_{12} is an arginine residue, a d-arginine residue, an alanine residue, a leucine residue, an aspartic acid residue, a cysteine residue, or absent,
X_{13} is a serine residue, a d-serine residue, an alanine residue, a tyrosine residue or absent,
X_{14} is a methionine residue, a serine residue, a leucine residue, an isoleucine residue, a norleucine residue, an alanine residue, a d-methionine residue, an aspartic acid residue, or absent,
X_{15} is a threonine residue, a d-threonine residue, a arginine residue, a glycine residue, an alanine residue or absent,
X_{16} is an aspartic acid residue, and-aspartic acid residue, an alanine residue, an arginine residue, a lysine residue or absent,
X_{17} is a methionine residue, a lysine residue, a histidine residue, a leucine residue, a cysteine residue or absent,
X_{18} is a tyrosine residue, a glutamine residue , a leucine residue, a lysine residue, a cysteine residue or absent,

X_{19} is an arginine residue, a tyrosine residue, a serine residue, a methionine residue or absent,

X_{20} is a leucine residue, a isoleucine residue, an arginine residue, or a valine residue or absent,

X_{21} is a histidine residue, a lysine residue, a leucine residue or absent,

X_{22} is a leucine residue, a tyrosine residue or absent,

X_{23} is an arginine residue, a serine residue or absent, and

X_{24} is a valine residue, a leucine residue or absent;

wherein when X_1-X_4 and X_{17}-X_{24} are absent and X_5 is a methionine residue, then at least one of the amino acids of X_6-X_{16} is an alanine residue or a d-amino acid, and wherein when X_1-X_6 and X_{17}-X_{24} are absent and X_7 is a tyrosine residue then at least one of the amino acids of X_8-X_{16} is an alanine residue, d-amino acid or a serine residue.

In another apsect, the compound is represented wherein, X_1-X_4 and X_{17}-X_{24} are absent and

wherein:

X_5 is a methionine residue, a d-methionine residue, an isoleucine residue, a leucine residue, a serine residue, an alanine residue, or d-a methionine residue,

X_6 is a glycine residue or an alanine residue,

X_7 is a tyrosine residue, an alanine residue, or a d-tyrosine residue,

X_8 is a glutamine residue, an alanine residue or a d-glutamine residue,

X_9 is a lysine residue, a d-lysine residue, or an alanine residue,

X_{10} is a lysine residue, a d-lysine residue, or an alanine residue,

X_{11} is a leucine residue, a d-leucine residue, or an alanine residue,

X_{12} is an arginine residue, a d-arginine residue, or an alanine residue,

X_{13} is a serine residue, a d-serine residue, or an alanine residue,

X_{14} is a methionine residue, a serine residue, a leucine residue, an isoleucine residue, an alanine residue, or a d-methionine residue,

X_{15} is a threonine residue, a d-threonine residue, or an alanine residue, and

X_{16} is aspartic acid residue, a d-aspartic acid residue, or an alanine residue, or an arginine residue.

In yet another aspect, when X_1-X_4 and X_{21}-X_{24} are absent, and wherein:

X_5 is a methionine residue, a d-methionine residue an alanine residue or a glycine residue,

X_6 is a glycine residue or an alanine residue,

X_7 is a tyrosine residue, a d-tyrosine residue, or an alanine residue,

X_8 is a glutamine residue, d-glutamine residue, or an alanine residue,

X_9 is a lysine residue, a d-lysine residue or an alanine residue,

X_{10} is a lysine residue, a d-lysine residue or an alanine residue,

X_{11} is a leucine residue, a d-leucine residue, an alanine residue, a proline residue or a d-proline residue,

X_{12} is an arginine residue, a d-arginine residue, an alanine residue, a proline residue or d-proline residue,

X_{13} is a serine residue, a d-serine residue, an alanine residue, a proline residue or a d-proline residue,

X_{14} is a methionine residue, an alanine residue, a d-methionine residue, a d-proline residue, a glycine residue, a histidine residue, or noreleucine residue

X_{15} is a threonine residue, a d-threonine residue, a d-proline residue, a proline residue or an alanine residue,

X_{16} is an aspartic acid residue, a d-aspartic acid residue, or an alanine residue,

X_{17} is a lysine residue, a d-lysine residue or an alanine residue,

X_{18} is a tyrosine residue, a d-tyrosine residue, or an alanine residue,

X_{19} is an arginine residue, a lysine residue, or a d-arginine residue, and

X_{20} is a leucine residue, a d-leucine residue, an alanine residue, a noreleucine residue, an isoleucine residue or a valine residue.

In another aspect, when X_1-X_8 are absent, and wherein:

X_9 is a lysine residue, a d-lysine residue or an alanine residue,

X_{10} is a lysine residue, a d-lysine residue or an alanine residue,

X_{11} is a leucine residue, a d-leucine residue or an alanine residue,

X_{12} is an arginine residue, a d-arginine residue or an alanine residue,

X_{13} is a serine residue, a d-serine residue or an alanine residue,

X_{14} is a methionine residue, a d-methionine residue, a norleucine residue or an alanine residue,

X_{15} is a threonine residue, a d-threonine residue, or an alanine residue,

X_{16} is an aspartic acid residue, a d-aspartic acid residue, or an alanine residue,

X_{17} is a lysine residue, a d-lysine residue or an alanine residue,

X_{18} is a tyrosine residue, a d-tyrosine residue, an alanine residue or absent,

X_{19} is an arginine residue, a d-arginine, an alanine residue or absent,

X_{20} is leucine residue, a d-leucine, an alanine or absent,

X_{21} is a histidine residue, a d- histidine residue, a d-serine residue, an alanine residue or absent,

X_{22} is leucine residue, isoleucine residue or absent,

X_{23} is a serine residue or absent, and

X_{24} is a valine residue or absent. In another embodiment, X_{22}, X_{23} and X_{24} are absent.

In yet another specific aspect, X_1-X_5 and X_{22}-X_{24} are absent, and wherein:

X_6 is a glycine residue or absent,

X_7 is a tyrosine residue or absent,

X_8 is a glutamine residue or absent,

X_9 is a lysine residue or absent,

X_{10} is a lysine residue or absent,

X_{11} is a leucine residue or absent,

X_{12} is an arginine residue or absent,

X_{13} is a serine residue or absent,

X_{14} is a methionine residue or absent,

X_{15} is a threonine residue,

X_{16} is an aspartic acid residue,

X_{17} is a lysine residue,

X_{18} is a tyrosine residue,

X_{19} is an arginine residue,

X_{20} is a leucine residue, and

X_{21} is a histidine residue.

In another specific aspect, X_1-X_5 and X_{22}-X_{24} are absent, and wherein:

X_6 is a glycine residue,

X_7 is a tyrosine residue,

X_8 is a glutamine residue,

X_9 is a lysine residue,

X_{10} is a lysine residue,

X_{11} is a leucine residue,

X_{12} is an arginine residue,

X_{13} is a serine residue or absent,

X_{14} is a methionine residue or absent,

X_{15} is threonine residue or absent,

X_{16} is an aspartic acid residue or absent,

X_{17} is a lysine residue or absent,

X_{18} is a tyrosine residue or absent,

X_{19} is an arginine residue or absent,

X_{20} is a leucine residue or absent, and

X_{21} is a histidine residue or absent.

In another embodiment, compounds wherein X_1-X_5 and X_{21}-X_{24} are absent, wherein at least seven contiguous amino acid residues are present, and wherein:

X_6 is a glycine residue or absent,

X_7 is a tyrosine residue or absent,

X_8 is a glutamine residue or absent,

X_9 is a lysine residue or absent,

X_{10} is a lysine residue or absent,

X_{11} is a leucine residue or absent,

X_{12} is a an arginine residue or absent,

X_{13} is a serine residue or absent,

X_{14} is a methionine residue or absent

X_{15} is a threonine residue or absent,

X_{16} is an aspartic acid residue or absent,

X_{17} is a lysine residue or absent,

X_{18} is a tyrosine residue or absent,

X_{19} is an arginine residue or absent, and

X_{20} is a leucine residue or absent.

In a futher embodiment,

X_3 is a leucine residue or absent,

X_4 is a glycine residue or absent,

X_5 is a serine residue, a d-serine residue or absent,

X_6 is a glycine residue, a histidine residue, a lysine residue or absent,

X_7 is a tyrosine residue or an arginine residue,

X_8 is a glutamine residue, or a methionine residue,

X_9 is a lysine residue,

X_{10} is a lysine residue or a threonine residue,

X_{11} is a leucine residue or a serine residue,

X_{12} is an arginine residue, or a leucine residue,

X_{13} is a serine residue, or a tyrosine residue,

X_{14} is a serine residue, a leucine residue, an isoleucine residue, or an aspartic acid residue,

X_{15} is a threonine residue or a glycine residue,

X_{16} is an aspartic acid residue or an arginine residue,

X_{17} is a methionine residue or absent,

X_{18} is a glutamine residue or absent,

X_{19} is, a tyrosine residue or absent,

X_{20} is a leucine residue, a isoleucine residue, an arginine residue, a valine residue or absent,

X_{21} is a histidine residue, a lysine residue, or absent,

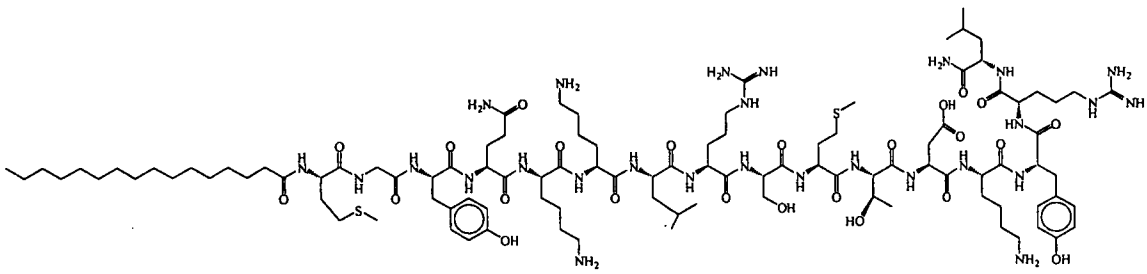
X_{22} is a leucine residue or absent,

X_{23} is a serine residue or absent, and

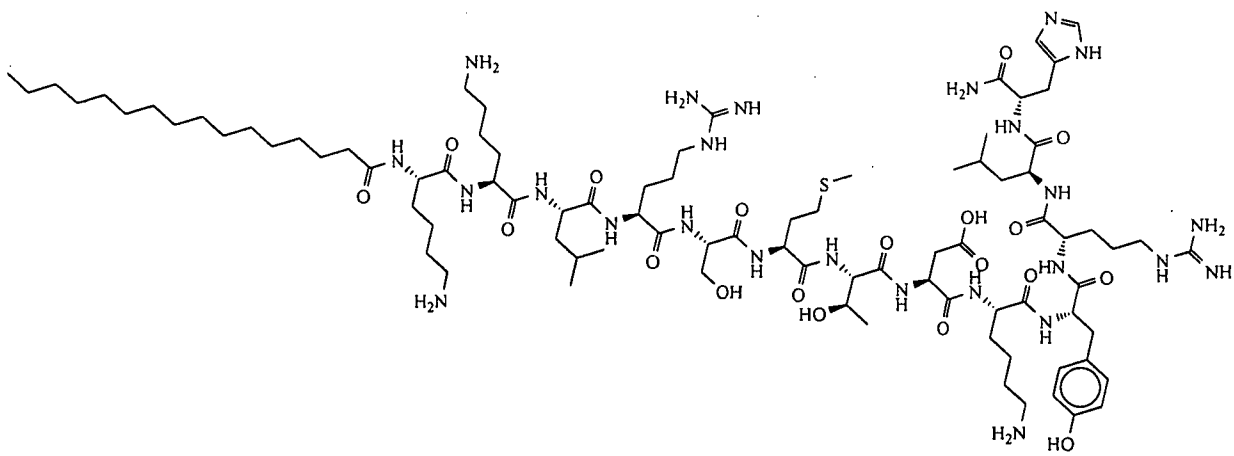
X_{24} is a valine residue or absent.

In a more specific embodiment, the compounds are selected from any one of Compound Nos. 1-73 and 117-194 or a pharmaceutically acceptable salt thereof. For example, the compound is selected from any one of Compounds Nos. 1-73 or a pharmaceutically acceptable salt thereof. In another example the compound is selected from any one of Compound Nos. 117-194 or a pharmaceutically acceptable salt thereof.

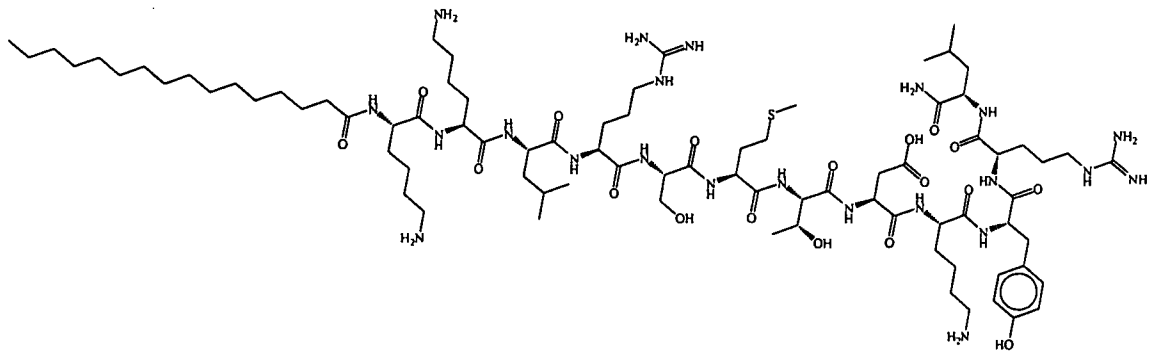
In a more specific embodiment, the compound is selected from: Compound No. 38,



Compound No. 43,



and Compound No. 44,



or a pharmaceutically acceptable salt thereof.

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

In a specific embodiment of the fourth aspect, the i2 loop of the CXCR4 receptor from which P is derived has the following sequence: DRYLAIVHATNSQRPRKLLAEK (SEQ ID NO:371).

In another embodiment of the fourth aspect, P is a sequence selected from SEQ ID NOS:149-199:

CXCR4 i-Loop	Sequence	SEQ ID NO:
i2	DRYLAIVHATNSQRPRKLLAEK	149
i2	DRYLAIVHATNSQRPRKLLAE	150
i2	DRYLAIVHATNSQRPRKLLA	151
i2	DRYLAIVHATNSQRPRKLL	152
i2	DRYLAIVHATNSQRPRKL	153
i2	DRYLAIVHATNSQRPRK	154
i2	DRYLAIVHATNSQRPR	155
i2	DRYLAIVHATNSQRP	156
i2	DRYLAIVHATNSQR	157
i2	DRYLAIVHATNSQ	158
i2	DRYLAIVHATNS	159
i2	DRYLAIVHATN	160
i2	DRYLAIVHAT	161
i2	DRYLAIVHA	162
i2	DRYLAIVH	163
i2	DRYLAIV	164
i2	RYLAIVHATNSQRPRKLLAEK	165
i2	YLAIVHATNSQRPRKLLAEK	166
i2	LAIVHATNSQRPRKLLAEK	167
i2	AIVHATNSQRPRKLLAEK	168
i2	IVHATNSQRPRKLLAEK	169
i2	VHATNSQRPRKLLAEK	170

i2	HATNSQRPRKLLAEK-	171
i2	ATNSQRPRKLLAEK	172
i2	TNSQRPRKLLAEK	173
i2	NSQRPRKLLAEK	174
i2	SQRPRKLLAEK	175
i2	QRPRKLLAEK	176
i2	RPRKLLAEK	177
i2	PRKLLAEK	178
i2	RKLLAEK	179
i2	RYLAIVH-	180
i2	YLAIVHA	181
i2	LAIVHAT	182
i2	AIVHATN-	183
i2	IVHATNS-	184
i2	VHATNSQ	185
i2	HATNSQR	186
i2	ATNSQRP	187
i2	TNSQRPR-	188
i2	NSQRPRK	189
i2	SQRPRKL	190
i2	QRPRKLL	191
i2	RPRKLLA	192
i2	PRKLLAE	193
i2	VHATNSQRPRKLLAEKVVY	194
i2	VHATNSQRPRKLLA	195
i2	HATNSQRPRKL	196
i2	HATNSQRPRKLLA	197
i2	HATNSQRPRKLLAE	198
i2	HATNSQRPRKLLAEKV	199

In a more specific embodiment, a compound of the invention is represented by Formula B or a pharmaceutically acceptable salt thereof: wherein

T-L-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}-Y_{20}-Y_{21}-Y_{22}-Y_{23}-Y_{24}-Y_{25}-R_1;

wherein L is a linking moiety represented by C(O) and bonded to the N terminal nitrogen of Y_1 or the next present amino acid residue if Y_1 is absent; T is a lipophilic tether moiety bonded to L; and R_1 is OR_2 or $N(R_2)_2$, each R_2 is independently H or alkyl, wherein at least three contiguous Y_1-Y_{25} amino acid residues are present and wherein at least one of Y_1-Y_{22} is absent, a d-amino acid residue or an alanine residue, and wherein:

Y_1 is an aspartic acid residue, a d-aspartic acid residue, an alanine residue or absent,

Y_2 is an arginine residue, a d-arginine residue, an alanine residue or absent,

Y_3 is a tyrosine residue, a d-tyrosine residue, an alanine residue or absent,

Y_4 is a leucine residue, a d-leucine residue, an alanine residue or absent,

Y_5 is an alanine residue, a d-alanine residue or absent,

Y_6 is an isoleucine residue, a d-isoleucine residue, an alanine residue or absent,

Y_7 is a valine residue, a d-valine acid residue, an alanine residue or absent,

Y_8 is a histidine residue a d-histidine residue, an alanine residue or absent,

Y_9 is an alanine residue, a d-alanine residue or absent,

Y_{10} is a threonine residue, a d-threonine residue, an alanine residue or absent,

Y_{11} is an asparagine residue, a d-asparagine residue, an alanine residue or absent,

Y_{12} is a serine residue, a d-serine residue, an alanine residue or absent,

Y_{13} is a glutamine residue, a d-glutamine residue, an alanine residue or absent,

Y_{14} is an arginine residue, a d-arginine residue, an alanine residue or absent,

Y_{15} is a proline residue, a d-proline residue, an alanine residue or absent,

Y_{16} is an arginine residue, a d-arginine residue, an alanine residue or absent,

Y_{17} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Y_{18} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Y_{19} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Y_{20} is an alanine residue, a d-alanine, an isoleucine residue, a d-isoleucine residue, an arginine residue, a d-arginine residue, a valine residue, a d-valine or absent,

Y_{21} is a glutamic acid residue, a d-glutamic acid residue, an alanine residue, a d-alanine residue or absent,

Y_{22} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Y_{23} is a valine residue, a d-valine residue or absent,

Y_{24} is a valine residue, a d-valine residue or absent, and

Y_{25} is a tyrosine residue, a d-tyrosine residue or absent.

In another embodiment of Formula B, the compound is represented by wherein Y_{23}-Y_{25} are absent, and wherein:

Y_1 is an aspartic acid residue,

Y_2 is an arginine residue,

Y_3 is a tyrosine residue,

Y_4 is a leucine residue,

Y_5 is an alanine,

Y_6 is an isoleucine residue,

Y_7 is a valine residue,

Y_8 is a histidine residue,

Y_9 is an alanine or absent,

Y_{10} is a threonine or absent,

Y_{11} is an asparagine or absent,

Y_{12} is a serine residue or absent,

Y_{13} is a glutamine residue or absent,

Y_{14} is an arginine residue or absent,

Y_{15} is a proline residue or absent,

Y_{16} is an arginine residue or absent,

Y_{17} is a lysine residue or absent,

Y_{18} is a leucine residue,

Y_{19} is a leucine residue,

Y_{20} is an alanine residue or absent,

Y_{21} is a glutamic acid residue or absent, and

Y_{22} is a lysine residue or absent.

In yet another aspect, the compound of Formula B comprises, when Y_1 and Y_{23}-Y_{25} are absent, and wherein:

Y_2 is an arginine residue or absent,

Y_3 is a tyrosine residue or absent,

Y_4 is a leucine residue or absent,

Y_5 is an alanine residue or absent,

Y_6 is an isoleucine residue or absent,

Y_7 is a valine residue or absent,

Y_8 is a histidine residue or absent,
Y_9 is an alanine or absent,
Y_{10} is a threonine or absent,
Y_{11} is an asparagine or absent,
Y_{12} is a serine residue or absent,
Y_{13} is a glutamine residue or absent,
Y_{14} is an arginine residue or absent,
Y_{15} is a proline residue or absent,
Y_{16} is an arginine residue or absent,
Y_{17} is a lysine residue,
Y_{18} is a leucine residue,
Y_{19} is a leucine residue,
Y_{20} is an alanine residue,
Y_{21} is a glutamic acid residue, and
Y_{22} is a lysine residue.

In another specific embodiment of a compound represented by Formula B, comprises when Y_{23}-Y_{25} are absent and wherein seven contiguous Y_1-Y_{22} amino acid residues are present, and wherein,

Y_1 is an aspartic acid residue or absent,
Y_2 is an arginine residue or absent,
Y_3 is a tyrosine residue or absent,
Y_4 is a leucine residue or absent,
Y_5 is an alanine residue or absent,
Y_6 is an isoleucine residue or absent,
Y_7 is a valine residue or absent,
Y_8 is a histidine residue or absent,
Y_9 is an alanine residue or absent,
Y_{10} is a threonine residue or absent,
Y_{11} is an asparagine residue or absent,
Y_{12} is a serine residue or absent,
Y_{13} is a glutamine residue or absent,
Y_{14} is an arginine residue or absent;

Y_{15} is a proline residue or absent,
Y_{16} is an arginine residue or absent,
Y_{17} is a lysine residue or absent,
Y_{18} is a isoleucine residue or absent,
Y_{19} is a leucine residue or absent,
Y_{20} is an alanine residueor absent,
Y_{21} is a glutamic acid residue or absent, and
Y_{22} is a lysine residue or absent.

In a more specific embodiment of a compound represented by Formula B, when Y_1-Y_6 are absent and wherein:

Y_7 is a valine residue or absent,
Y_8 is a histidine residue,
Y_9 is a alanine residue,
Y_{10} is a threonine residue,
Y_{11} is an asparagine residue ,
Y_{12} is a serine residue,
Y_{13} is a glutamine residue,
Y_{14} is an arginine residue,
Y_{15} is a proline residue,
Y_{16} is an arginine residue,
Y_{17} is a lysine residue,
Y_{18} is a leucine residue,
Y_{19} is a leucine residue or absent,
Y_{20} is an alanine residue or absent,
Y_{21} is a glutamic acid or absent,
Y_{22} is a lysine residue or absent,
Y_{23} is a valine lysine residue or absent,
Y_{24} is a valine residue or absent, and
Y_{25} is a tyrosine residue or absent.

In a more specific embodiment of Fomula B, the CXCR4 compound is selected from any one of the Compound Nos. 74-83 or a pharmaceutically acceptable salt thereof.

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

In a specific embodiment of the fifth aspect, the i3 loop of the CXCR4 receptor from which P is derived has the following sequence: IIISKLSHSKGHQKRKALKTTVI (SEQ ID NO:372).

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

CXCR4 i-Loop	Sequence	SEQ ID:
i3	HSKKGHQKRKALK	200
i3	JGYQKKLRSJTD	201
i3	IIISKLSHSKGHQKRKALKT	202
i3	IIISKLSHSKGHQKRKALK	203
i3	IIISKLSHSKGHQKRKAL	204
i3	IIISKLSHSKGHQKRKA	205
i3	IIISKLSHSKGHQKRK	206
i3	IIISKLSHSKGHQKR	207
i3	IIISKLSHSKGHQK	208
i3	IIISKLSHSKGHQ	209
i3	IIISKLSHSKGH	210
i3	IIISKLSHSKG	211
i3	IIISKLSHSK	212
i3	IIISKLSHS	213
i3	IIISKLSH	214
i3	IIISKLS	215
i3	IISKLSHSKGHQKRKALKT	216
i3	ISKLSHSKGHQKRKALKT	217
i3	SKLSHSKGHQKRKALKT	218
i3	KLSHSKGHQKRKALKT	219
i3	LSHSKGHQKRKALKT	220
i3	SHSKGHQKRKALKT	221
i3	HSKGHQKRKALKT	222
i3	SKGHQKRKALKT	223
i3	KGHQKRKALKT	224
i3	GHQKRKALKT	225
i3	HQKRKALKT	226
i3	QKRKALKT	227
i3	KRKALKT	228
i3	IISKLSH	229
i3	ISKLSHS	230

i3	SKLSHSK	231
i3	KLSHSKG	232
i3	LSHSKGH	233
i3	SHSKGHQ	234
i3	HSKGHQK	235
i3	SKGHQKR	236
i3	KGHQKRK	237
i3	GHQKRKA	238
i3	HQKRKAL	239
i3	QKRKALK	240
i3	HSKGHQKRKALKTT	241
i3	HSKGHQKRKALKTTV	242
i3	HSKGHQKRKALKTTVI	243
i3	HSKGHQKRKQALK	244
i3	KLSHSKGHQKRKA	245
i3	KLSHSKGHQKRKAL	246
i3	KLSHSKGHQKRKALK	247
i3	KLSHSKGHQKRKALKTTV	248
i3	KLSHSKGHQKRKALKTTVIL	249
i3	LSHSKGHQKRKALK	250
i3	SHSKGHQKRKALK	251
i3	SKLSHSKGHQKRKALK	252
i3	SKLSHSKGHQKRKALKTTVIL	253
i3	QHLHIALKKSTSRKVKSGTLK	254

In another aspect, a CXCR4 compound of the invention is represented by Formula C or a pharmaceutically acceptable salt thereof,:

T-L-W_1-W_2-W_3-W_4-W_5-W_6-W_7-W_8-W_9-W_{10}-W_{11}-W_{12}-W_{13}-W_{14}-W_{15}-W_{16}-W_{17}-W_{18}-W_{19}-W_{20}-W_{21}-W_{22}-W_{23}-W_{24}-W_{25}-W_{26}-W_{27}-W_{28}-W_{29}-W_{30}-W_{31}-W_{32}-R_1;

wherein L is a linking moiety represented by C(O) and bonded to W_1 at an N terminal nitrogen of W_1 or the next present amino acid residue if W_1 is absent; T is a lipophilic tether moiety bonded to L; R_1 is OR_2 or $N(R_2)_2$, each R_2 is independently H or alkyl, wherein at least three contiguous W_1-W_{32} are present, and wherein:W_1 is an isoleucine residue, a d-isoleucine residue, an alanine residue or absent, W_2 is isoleucine residue, a d-isoleucine residue, an alanine residue or absent, W_3 is isoleucine residue, a d-isoleucine residue, an alanine residue or absent,W_4 is a serine residue, a d-serine residue, an alanine residue or absent, W_5 is a lysine residue, a d-lysine residue, an alanine residue or absent, W_6 is a leucine residue, a histidine residue, a d-leucine residue, an alanine residue or absent, W_7 is a serine residue, a d-serine residue, an alanine residue or absent, W_8 is a histidine residue, a d-histidine

residue, an alanine residue or absent, W_9 is a serine residue, a d-serine residue, an alanine residue a lysine residue, or absent, W_{10} is a lysine residue, a d-lysine residue, an alanine residue, a leucine residue, an isoleucine residue or absent, W_{11} is glycine residue, a d-glycine residue, an alanine residue or absent, W_{12} is a histidine residue, a d-histidine residue, an alanine residue a tyrosine residue or absent, W_{13} is a glutamine residue, a d-glutamine residue, an alanine residue or absent, W_{14} is a lysine residue, a d-lysine residue, an alanine residue or absent; W_{15} is an arginine residue, a d-arginine residue, an alanine residue, a lysine residue or absent, W_{16} is a lysine residue, a d-lysine residue, an alanine residue, a leucine residue or absent, W_{17} is an alanine, d-alanine, an arginine residue or absent, W_{18} is a leucine residue, a d-leucine residue, an alanine residue, a serine residue or absent, W_{19} is a lysine residue, a d-lysine residue, an alanine residue, a leucine residue, an isoleucine residue or absent, W_{20} is threonine, a d-threonine residue, an alanine residue leucine residue or absent, W_{21} is threonine, a d-threonine residue, an alanine residue a lysine residue or aspartic acid or absent, W_{22} is a valine, a d-valine residue, an alanine residue or absent, W_{23} is isoleucine residue, a d-isoleucine residue, an alanine residue a serine residue or absent, W_{24} is leucine residue, a d-leucine residue, an alanine residue an arginine residue or absent, W_{25} is a lysine residue, a d-lysine residue, an alanine residue or absent, W_{26} is a valine residue, a d-valine residue, an alanine residue or absent, W_{27} is a lysine residue, a d-lysine residue, an alanine residue or absent, W_{28} is a serine residue a d-serine residue, an alanine residue or absent, W_{29} is a glycine residue, a d-glycine residue, an alanine residue or absent, W_{30} is a threonine residue, a d-threonine residue, an alanine residue or absent, W_{31} is a leucine residue, a d-leucine residue, an alanine residue or absent, W_{32} is a lysine residue, a d-lysine residue, an alanine residue or absent, wherein when W_{20}-W_{32} is absent at least one of W_1-W_{23} is also absent and wherein when W_1-W_7 and W_{20}-W_{32} is absent, at least one of W_8-W_{19} is absent, a d-amino acid or alanine.

In another aspect, a CXCR4 compound is represented by W_{24}-W_{32} are absent and wherein:

W_1 is an isoleucine residue,

W_2 is an isoleucine residue,

W_3 is an isoleucine residue,

W_4 is a serine residue,

W_5 is a lysine residue,
W_6 is a leucine residue,
W_7 is a serine residue,
W_8 is a histidine residue or absent,
W_9 is a serine residue, or absent,
W_{10} is a lysine residue or absent,
W_{11} is a glycine residue or absent,
W_{12} is a histidine residue, or absent,
W_{13} is a glutamine residue or absent,
W_{14} is a lysine residue or absent,
W_{15} is an arginine residue or absent,
W_{16} is a lysine residue or absent,
W_{17} is an alanine residue or absent,
W_{18} is a leucine residue or absent,
W_{19} is a lysine residue or absent,
W_{20} is a threonine residue or absent,
W_{21} is a threonine residue or absent,
W_{22} is a valine residue or absent, and
W_{23} is an isoleucine residue or absent.

In another aspect, the CXCR 4 compounds of the invention are represented when W_1, W_{21}-W_{32} are absent and wherein:

W_2 is an isoleucine residue or absent,
W_3 is an isoleucine residue or absent,
W_4 is a serine residue or absent,
W_5 is a lysine residue or absent,
W_6 is a leucine residue or absent,
W_7 is a serine residue or absent,
W_8 is a histidine residue or absent,
W_9 is a serine residue, or absent,
W_{10} is a lysine residue or absent,
W_{11} is a glycine residue or absent,
W_{12} is a histidine residue, or absent,

W_{13} is a glutamine residue or absent,
W_{14} is a lysine residue,
W_{15} is an arginine residue,
W_{16} is a lysine residue,
W_{17} is an alanine residue,
W_{18} is a leucine residue,
W_{19} is a lysine residue, and
W_{20} is a threonine residue.

In yet another embodiment, the CXCR4 compounds of the invention comprise seven contiguous amino acid residues of W_1-W_{19} are present and wherein:

W_1 is an isoleucine residue or absent,
W_2 is an isoleucine residue or absent,
W_3 is an isoleucine residue or absent,
W_4 is a serine residue or absent,
W_5 is a lysine residue or absent,
W_6 is a leucine residue or absent,
W_7 is a serine residue or absent,
W_8 is a histidine residue or absent,
W_9 is a serine residue, or absent,
W_{10} is a lysine residue or absent,
W_{11} is a glycine residue or absent,
W_{12} is a histidine residue, or absent,
W_{13} is a glutamine residue or absent,
W_{14} is a lysine residue or absent,
W_{15} is an arginine residue or absent,
W_{16} is a lysine residue or absent,
W_{17} is an alanine residue or absent,
W_{18} is a leucine residue or absent, and
W_{19} is a lysine residue or absent,

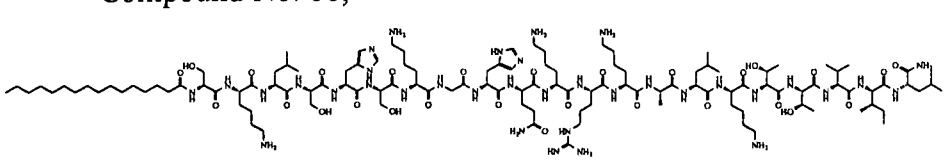
In yet another embodiment, the CXCR4 compounds are reprented when W_1-W_3 are absent and W_{25}-W_{32} are absent, and wherein:

W_4 is a serine residue or absent,
W_5 is a lysine residue or absent,
W_6 is a leucine residue or absent,
W_7 is a serine residue or absent,
W_8 is a histidine residue,
W_9 is a serine residue,
W_{10} is a lysine residue,
W_{11} is a glycine residue,
W_{12} is a histidine residue,
W_{13} is a glutamine residue,
W_{14} is a lysine residue,
W_{15} is an arginine residue,
W_{16} is a lysine residue,
W_{17} is alanine or a glutamine residue,
W_{18} is leucine residue alanine or absent,
W_{19} is a lysine residue,leucine residue or absent,
W_{20} is threonine or absent,
W_{21} is threonine or absent,
W_{22} is a valine residue or absent,
W_{23} is isoleucine residue or absent,
W_{24} is leucine residue or absent.

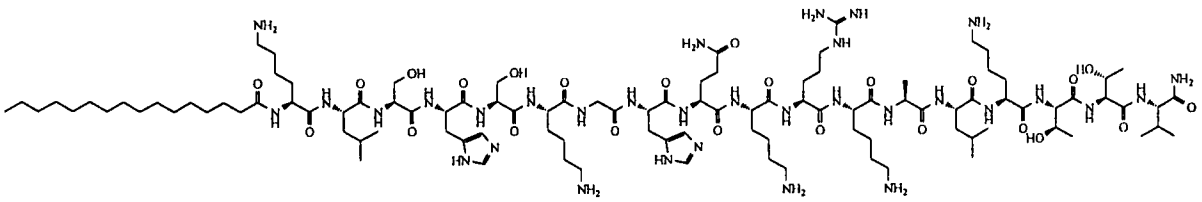
In a more specific embodiment of Fomula C, the compound is selected from any one of the Compound Nos. 84, 87-106 or a pharmaceutically acceptable salt thereof.

In yet another embodiment, a CXCR4 compound of the invention is selected from one of the following compounds or a pharmaceutically acceptable salt thereof:

Compound No. 88,

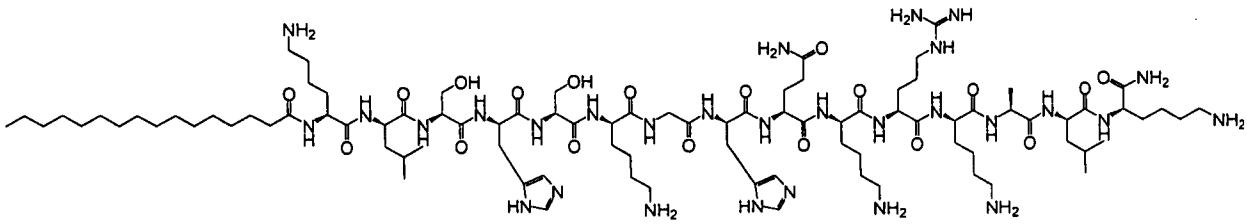


Compound No. 90,



and

Compound No. 92,



or a pharmaceutically acceptable salt thereof.

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

In a specific embodiment of the sixth aspect, the i4 domain of the CXCR4 receptor from which P is derived has the following sequence: GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS (SEQ ID NO:373).

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

CXCR4 i-Loop	Sequence	SEQ ID NO:
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFH	255
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSF	256
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSS	257
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESS	258
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESES	259
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESE	260
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTES	261
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTE	262
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVST	263
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVS	264
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSV	265
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSS	266
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHS	267
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGH	268
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGG	269
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRG	270
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKR	271

i4	GAKFKTSAQHALTSVSRGSSLKILSKGK	272
i4	GAKFKTSAQHALTSVSRGSSLKILSKG	273
i4	GAKFKTSAQHALTSVSRGSSLKILSK	274
i4	GAKFKTSAQHALTSVSRGSSLKILS	275
i4	GAKFKTSAQHALTSVSRGSSLKIL	276
i4	GAKFKTSAQHALTSVSRGSSLKI	277
i4	GAKFKTSAQHALTSVSRGSSLK	278
i4	GAKFKTSAQHALTSVSRGSSL	279
i4	GAKFKTSAQHALTSVSRGSS	280
i4	GAKFKTSAQHALTSVSRGS	281
i4	GAKFKTSAQHALTSVSRG	282
i4	GAKFKTSAQHALTSVSR	283
i4	GAKFKTSAQHALTSVS	284
i4	GAKFKTSAQHALTSV	285
i4	GAKFKTSAQHALTS	286
i4	GAKFKTSAQHALT	287
i4	GAKFKTSAQHAL	288
i4	GAKFKTSAQHA	289
i4	GAKFKTSAQH	290
i4	AKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	291
i4	KFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	292
i4	FKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	293
i4	KTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	294
i4	TSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	295
i4	SAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	296
i4	AQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	297
i4	QHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	298
i4	HALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	299
i4	ALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	300
i4	LTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	301
i4	TSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	302
i4	SVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	303
i4	VSRGSSLKILSKGKRGGHSSVSTESESSSFHSS	304
i4	SRGSSLKILSKGKRGGHSSVSTESESSSFHSS	305
i4	RGSSLKILSKGKRGGHSSVSTESESSSFHSS	306
i4	GSSLKILSKGKRGGHSSVSTESESSSFHSS	307
i4	SSLKILSKGKRGGHSSVSTESESSSFHSS	308
i4	SLKILSKGKRGGHSSVSTESESSSFHSS	309
i4	LKILSKGKRGGHSSVSTESESSSFHSS	310
i4	KILSKGKRGGHSSVSTESESSSFHSS	311
i4	ILSKGKRGGHSSVSTESESSSFHSS	312
i4	LSKGKRGGHSSVSTESESSSFHSS	313
i4	SKGKRGGHSSVSTESESSSFHSS	314
i4	KGKRGGHSSVSTESESSSFHSS	315
i4	GKRGGHSSVSTESESSSFHSS	316
i4	KRGGHSSVSTESESSSFHSS	317

i4	RGGHSSVSTESESSSFHSS	318
i4	GGHSSVSTESESSSFHSS	320
i4	GHSSVSTESESSSFHSS	321
i4	HSSVSTESESSSFHSS	322
i4	SSVSTESESSSFHSS	323
i4	SVSTESESSSFHSS	324
i4	VSTESESSSFHSS	325
i4	STESESSSFHSS	326
i4	TESESSSFHSS	327
i4	ESESSSFHSS	328
i4	AKFKTSAQHA	329
i4	KFKTSAQHAL	330
i4	FKTSAQHALT	331
i4	KTSAQHALTS	332
i4	TSAQHALTSV	333
i4	SAQHALTSVS	334
i4	AQHALTSVSR	335
i4	QHALTSVSRG	336
i4	HALTSVSRGS	337
i4	ALTSVSRGSS	338
i4	LTSVSRGSSL	339
i4	TSVSRGSSLK	340
i4	SVSRGSSLKI	341
i4	VSRGSSLKIL	342
i4	SRGSSLKILS	343
i4	RGSSLKILSK	345
i4	GSSLKILSKG	346
i4	SSLKILSKGK	347
i4	SLKILSKGKR	348
i4	LKILSKGKRG	349
i4	KILSKGKRGG	350
i4	ILSKGKRGGH	351
i4	LSKGKRGGHS	352
i4	SKGKRGGHSS	353
i4	KGKRGGHSSV	354
i4	GKRGGHSSVS	355
i4	KRGGHSSVST	356
i4	RGGHSSVSTE	357
i4	GGHSSVSTES	358
i4	GHSSVSTESE	359
i4	HSSVSTESES	360
i4	SSVSTESESS	361
i4	SVSTESESSS	362
i4	VSTESESSSF	363
i4	STESESSSFH	364
i4	TESESSSFHS	365

i4	ESESSSFHSS	366
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHS	367
i4	GAKFKTSAQHALTSVSRGSSLKILSKGKRGGHSCFH	368

In a another embodiment, CXCR4 compounds of the invention are represented by Formula D or a pharmaceutically acceptable salt thereof, wherein:

T-L-Z_1-Z_2-Z_3-Z_4-Z_5-Z_6-Z_7-Z_8-Z_9-Z_{10}-Z_{11}-Z_{12}-Z_{13}-Z_{14}-Z_{15}-Z_{16}-Z_{17}-Z_{18}-Z_{19}-Z_{20}-Z_{21}-Z_{22}-Z_{23}-Z_{24}-Z_{25}-Z_{26}-Z_{27}-Z_{28}-Z_{29}-Z_{30}-Z_{31}-Z_{32}-Z_{33}-Z_{34}-Z_{35}-Z_{36}-Z_{37}-Z_{38}-Z_{39}-Z_{40}-Z_{41}-Z_{42}-Z_{43}-Z_{44}-Z_{45}-Z_{46}-Z_{47}-R_1; wherein: L is a linking moiety represented by C(O) and bonded to the N terminal nitrogen of Z_1 or the next present amino acid residue if Z_1 is absent;

and T is a lipophilic tether moiety bonded to L; R_1 is OR_2 or $N(R_2)_2$, each R_2 is independently H or alkyl, wherein at least three contiguous Z_1-Z_{32} amino acid residues are present, and wherein:

Z_1 is a glycine residue, a d-glycine residue, an alanine residue or absent,

Z_2 is an alanine residue a d- alanine residue or absent,

Z_3 is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_4 is a phenylalanine residue, a d-phenylalanine residue, an alanine residue or absent,

Z_5 is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_6 is a threonine residue, a d-threonine residue, an alanine residue or absent,

Z_7 is a serine residue a d-serine residue, an alanine residue or absent,

Z_8 is an alanine residue, a d- alanine residue or absent,

Z_9 is a glutamine residue, a d-glutamine residue, an alanine residue or absent,

Z_{10} is a histidine residue, a d-histidine residue, an alanine residue or absent,

Z_{11} is an alanine residue, a d- alanine residue or absent,

Z_{12} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Z_{13} is a threonine residue, a d-threonine residue, an alanine residue or absent,

Z_{14} is a serine residue, a d-serine residue, an alanine residue or absent;

Z_{15} is a valine residue, a d-valine residue, an alanine residue or absent,

Z_{16} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{17} is an arginine residue, a d-arginine residue, an alanine residue or absent,

Z_{18} is a glycine residue, a d-glycine residue, an alanine residue or absent,

Z_{19} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{20} is a serine residue, a d-serine residue, an alanine residue absent,

Z_{21} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Z_{22} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_{23} is a isoleucine residue, a d-isoleucine residue, an alanine residue a serine residue or absent,

Z_{24} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Z_{25} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{26} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_{27} is glycine residue, a d-glycine residue, an alanine residue or absent,

Z_{28} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_{29} is an arginine residue, a d-arginine residue, an alanine residue or absent,

Z_{30} is a glycine residue, a d-glycine residue, an alanine residue or absent,

Z_{31} is a glycine residue, a d-glycine residue, an alanine residue or absent,

Z_{32} is a histidine residue, a d-histidine residue, an alanine residue or absent,

Z_{33} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{34} is a serine residue, a d-serine residue, an alanine residue cysteine, or absent,

Z_{35} is a valine residue, a d-valine residue, an alanine residue a phenylalanine residue, or absent,

Z_{36} is a serine residue, a d-serine residue, an alanine residue a histidine residue or absent,

Z_{37} is a threonine residue, a d-threonine residue, an alanine residue or absent,

Z_{38} is a glutamic acid residue, a d-glutamic acid residue, an alanine residue or absent,

Z_{39} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{40} is a glutamic acid, a d-glutaminc acid residue, an alanine residue or absent

Z_{41} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{42} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{43} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{44} is a phenylalanine residue, a d-phenylalanine residue, an alanine residue or absent,

Z_{45} is a histidine residue, a d-histidine residue, an alanine residue or absent,

Z_{46} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{47} is a serine residue, a d-serine residue, an alanine residue or absent,

wherein at least one of Z_1-Z_{47} is absent.

In a more specific embodiment, the CXCR4 compounds of the invention are represented by the following:

Z_1 is a glycine residue,

Z_2 is an alanine residue,

Z_3 is a lysine residue,

Z_4 is a phenylalanine residue,

Z_5 is a lysine residue,

Z_6 is a threonine residue,

Z_7 is a serine residue,

Z_8 is an alanine residue,

Z_9 is a glutamine residue,

Z_{10} is a histidine residue or absent,

Z_{11} is an alanine residue or absent,

Z_{12} is a leucine residue or absent,

Z_{13} is a threonine residue or absent,

Z_{14} is a serine residue or absent,

Z_{15} is a valine residue or absent,

Z_{16} is a serine residue or absent,

Z_{17} is an arginine residue or absent,

Z_{18} is a glycine residue or absent,

Z_{19} is a serine residue or absent,

Z_{20} is a serine residue or absent,

Z_{21} is a leucine residue or absent,

Z_{22} is a lysine residue or absent,

Z_{23} is an isoleucine residue, a serine residue or absent,

Z_{24} is a leucine residue or absent,

Z_{25} is a serine residue or absent,

Z_{26} is a lysine residue or absent,

Z_{27} is a glycine residue or absent,

Z_{28} is a lysine residue or absent,
Z_{29} is an arginine residue or absent,
Z_{30} is a glycine residue or absent,
Z_{31} is a glycine residue or absent,
Z_{32} is a histidine residue or absent,
Z_{33} is a serine residue or absent,
Z_{34} is a serine residue or absent,
Z_{35} is a valine residue or absent,
Z_{36} is a serine residue or absent,
Z_{37} is a threonine residue or absent,
Z_{38} is a glutamic acid residue or absent,
Z_{39} is a serine residue or absent,
Z_{40} is a glutamic acid residue or absent,
Z_{41} is a serine residue or absent,
Z_{42} is a serine residue or absent,
Z_{43} is a serine residue or absent,
Z_{44} is a phenylalanine residue or absent,
Z_{45} is a histidine residue or absent,
Z_{46} is a serine residue or absent, and
Z_{47} is a serine residue or absent.

In yet another embodiment, the CXCR4 compounds of the invention are represented by:

Z_1 is a glycine residue or absent,
Z_2 is an alanine residue or absent,
Z_3 is a lysine residue or absent,
Z_4 is a phenylalanine residue or absent,
Z_5 is a lysine residue or absent,
Z_6 is a threonine residue or absent,
Z_7 is a serine residue or absent,
Z_8 is an alanine residue or absent,
Z_9 is a glutamine residue or absent,
Z_{10} is a histidine residue or absent,

Z_{11} is an alanine residue or absent,
Z_{12} is a leucine residue or absent,
Z_{13} is a threonine residue or absent,
Z_{14} is a serine residue or absent,
Z_{15} is a valine residue or absent,
Z_{16} is a serine residue or absent,
Z_{17} is an arginine residue or absent,
Z_{18} is a glycine residue or absent,
Z_{19} is a serine residue or absent,
Z_{20} is a serine residue absent,
Z_{21} is a leucine residue or absent,
Z_{22} is a lysine residue or absent,
Z_{23} is an isoleucine residue, or absent,
Z_{24} is a leucine residue or absent,
Z_{25} is a serine residue or absent,
Z_{26} is a lysine residue or absent,
Z_{27} is a glycine residue or absent,
Z_{28} is a lysine residue or absent,
Z_{29} is an arginine residue or absent,
Z_{30} is a glycine residue or absent,
Z_{31} is a glycine residue or absent,
Z_{32} is a histidine residue or absent,
Z_{33} is a serine residue or absent,
Z_{34} is a serine residue or absent,
Z_{35} is a valine residue or absent,
Z_{36} is a serine residue or absent,
Z_{37} is a threonine residue or absent,
Z_{38} is a glutamic acid residue,
Z_{39} is a serine residue,
Z_{40} is a glutamic acid residue,
Z_{41} is a serine residue,
Z_{42} is a serine residue,
Z_{43} is a serine residue,

Z_{44} is a phenylalanine residue,

Z_{45} is a histidine residue,

Z_{46} is a serine residue, and

Z_{47} is a serine residue.

In a more specific embodiment, CXCR4 compounds of the invention are represented when Z_1 is absent, and 10 consecutive Z_2-Z_{47} are present wherein:

Z_2 is an alanine residue or absent,

Z_3 is a lysine residue or absent,

Z_4 is a phenylalanine residue or absent,

Z_5 is a lysine residue or absent,

Z_6 is a threonine residue or absent,

Z_7 is a serine residue or absent,

Z_8 is an alanine residue or absent,

Z_9 is a glutamine residue or absent,

Z_{10} is a histidine residue or absent,

Z_{11} is an alanine residue or absent,

Z_{12} is a leucine residue or absent,

Z_{13} is a threonine residue or absent,

Z_{14} is a serine residue or absent;

Z_{15} is a valine residue or absent,

Z_{16} is a serine residue or absent,

Z_{17} is an arginine residue or absent,

Z_{18} is a glycine residue or absent,

Z_{19} is a serine residue or absent,

Z_{20} is a serine residue absent,

Z_{21} is leucine residue or absent,

Z_{22} is a lysine residue or absent,

Z_{23} is an isoleucine residue, or absent,

Z_{24} is a leucine residue or absent,

Z_{25} is a serine residue or absent,

Z_{26} is a lysine residue or absent,

Z_{27} is a glycine or absent,

Z_{28} is a lysine residue or absent,
Z_{29} is an arginine residue or absent,
Z_{30} is a glycine residue or absent,
Z_{31} is a glycine residue or absent,
Z_{32} is a histidine residue or absent,
Z_{33} is a serine residue or absent,
Z_{34} is a serine residue or absent,
Z_{35} is a valine residue or absent,
Z_{36} is a serine residue or absent,
Z_{37} is a threonine residue or absent,
Z_{38} is a glutamic acid residue,
Z_{39} is a serine residue,
Z_{40} is glutamic acid residue,
Z_{41} is a serine residue,
Z_{42} is a serine residue,
Z_{43} is a serine residue,
Z_{44} is a phenylalanine residue,
Z_{45} is a histidine residue,
Z_{46} is a serine residue, and
Z_{47} is a serine residue.

In a more specific embodiment of Fomula D, the CXCR4 compound is selected from any one of the Compound Nos. 107-116 or a pharmaceutically acceptable salt thereof.

In a seventh aspect, T is an optionally substituted $(C_6\text{-}C_{30})$alkyl, $(C_6\text{-}C_{30})$alkenyl, $(C_6\text{-}C_{30})$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 same.

In a specific embodiment of the seventh aspect, T is selected from: $CH_3(CH_2)_{16}$, $CH_3(CH_2)_{15}$, $CH_3(CH_2)_{14}$, $CH_3(CH_2)_{13}$, $CH_3(CH_2)_{12}$, $CH_3(CH_2)_{11}$,

$CH_3(CH_2)_{10}$, $CH_3(CH_2)_9$, $CH_3(CH_2)_8$, $CH_3(CH_2)_9OPh$-, $CH_3(CH_2)_6C=C(CH_2)_6$, $CH_3(CH_2)_{11}O(CH_2)_3$, and $CH_3(CH_2)_9O(CH_2)_2$.

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, 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 consisting of: lithocholic acid, chenodeoxycholic acid, deoxycholic acid, cholanic acid, cholic acid, ursocholic 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, 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:

$CH_3(CH_2)_{15}$–C(O);

$CH_3(CH_2)_{13}$– C(O);

$CH_3(CH_2)_9O(CH_2)_2C(O)$;

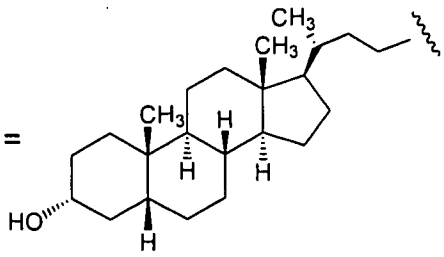
$CH_3(CH_2)_{10}O(CH_2)_2C(O)$;

$CH_3(CH_2)_6C=C(CH_2)_6$-C(O);

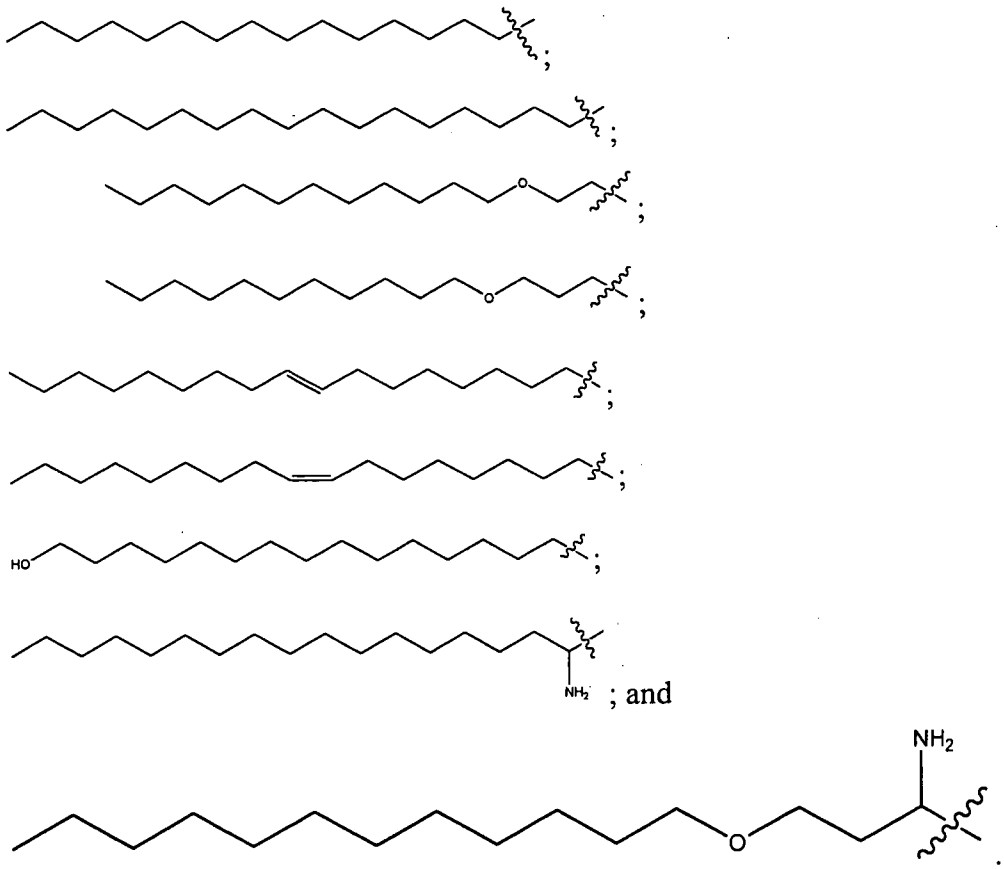
LCA-C(O); and

$CH_3(CH_2)_9OPh$-C(O) wherein

LCA =



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



; and

In a twelth aspect, the CXCR4 receptor compounds are selected from the compounds represented in Tables 6-13, excluding controls and those compounds not with the structure of Formula 1 or a pharmaceutically acceptable salt thereof.

Table 6. CXCR4 i1 loop compounds

No.:	Loop	Sequence	Lipid	Comments	MW
1	i1	AGYQKKLRSMTD (SEQ ID NO. 11)	Pal		1635.024
2	i1	MAYQKKLRSMTD (SEQ ID NO.12)	Pal		1709.168

3	il	MGAQKKLRSMTD (SEQ ID NO. 13)	Pal		1603.046
4	il	MGYAKKLRSMTD (SEQ ID NO. 14)	Pal		1638.09
5	il	MGYQKKLRAMTD (SEQ ID NO.15)	Pal		1679.142
6	il	MGYQKKLRSATD (SEQ ID NO. 16)	Pal		1635.024
7	il	MGYQKKLRSMAD (SEQ ID NO.17)	Pal		1665.116
8	il	MGYQKKLRSMTA(SEQ ID NO.18)	Pal		1651.132
9	il	MGYQAKLRSMTD (SEQ ID NO. 19)	Pal		1638.047
10	il	MGYQKKLASMTD (SEQ ID NO.20)	Pal		1610.034
11	il	MGYQKALRSMTD (SEQ ID NO.21)	Pal		1638.047
12	il	MGYQKKARSMTD (SEQ ID NO. 22)	Pal		1653.062
13	il	mGYQKKLRSMTD (SEQ ID NO.23)	Pal	D-Methionine	1695.142
14	il	MGyQKKLRSMTD (SEQ ID NO.24)	Pal	D-Tyrosine	1695.142
15	il	MGYqKKLRSMTD (SEQ ID NO.25)	Pal	D-Glutamine	1695.142
16	il	MGYQkKLRSMTD (SEQ ID NO.26)	Pal	D-Lysine	1695.142
17	il	MGYQKkLRSMTD (SEQ ID NO. 27)	Pal	D-Lysine	1695.142
18	il	MGYQKKlRSMTD (SEQ ID NO.28)	Pal	D-Leucine	1695.142
19	il	MGYQKKLrSMTD (SEQ ID NO. 29)	Pal	D-Arginine	1695.142
20	il	MGYQKKLRsMTD (SEQ ID NO. 30)	Pal	D-Serine	1695.142
21	il	MGYQKKLRSmTD (SEQ ID NO. 31)	Pal	D-Methionine	1695.142
22	il	MGYQKKLRSMtD (SEQ ID NO. 32)	Pal	D-Threonine	1695.142
23	il	MGYQKKLRSMTd (SEQ ID NO.33)	Pal	D-Aspartic acid	1695.142
24	il	GSHYQKKLRSSTD (SEQ ID NO.34)	Pal		1744.043
25	il	SGYQKKLRSSTD (SEQ ID NO.1)	Elaidic		1632.942
26	il	SGYQKKLRSSTD (SEQ ID NO. 1)	Oleic		1618.915

27	i1	sGYQKKLRSSTD (SEQ ID NO. 64)	Pal	D-Serine	1606.904
28	i1	GSGYQKKLRSST D (SEQ ID NO. 35)	Pal		1663.955
29	i1	YQKKLRSSTD (SEQ ID NO.36)	Pal		1462.776
30	i3	JGYQKKLRSJTD (SEQ ID NO.4)	Pal		1659.065
31	i3	JGYQKKLRSJTD (SEQ ID NO. 4)	Pal		1645.038
32 (control)	i1	MGYQKKLRSMT D (SEQ ID NO. 376)	None	capped peptide	1498.77
33	i1	MGYQKKLRSMT D (SEQ ID NO. 4)	C16H33 backbon e	Pentadecyla lanine with Biotin	1964.505
34	i1	LVMGYQKKLRS MTD (SEQ ID NO. 78)	Pal		1907.43
35	i1	VMGYQKKLRSM TD (SEQ ID NO. 86)	Pal		1794.273
36	i1	MGYQKKLRSMT DK (SEQ ID NO. 79)	Pal		1823.314
37	i1	MGYQKKLRSMT DKY (SEQ ID NO. 80)	Pal		1986.487
38	i1	MGYQKKLRSMT DKYRL (SEQ ID NO. 82)	Pal		2255.831
39	i1	MGYQKKLRSMT DKYRLHL (SEQ ID NO. 83)	Pal		2506.127
40	i1	YQKKLRSMTDK YRLHLSV (SEQ ID NO. 77)	Pal		2504.088
41	i1	KKLRSMTDKYR LHLSV (SEQ ID NO. 74)	Pal		2212.786
42	i1	KKLRSMTDKYR LHL (SEQ ID NO. 73)	Pal		2026.578
43	i1	KKLRSMTDKYR LH (SEQ ID NO.)	Pal		1913.42
44	i1	KKLRSMTDKYR L (SEQ ID NO.)	Pal		1776.281
45	i1	KKLRSMTDKYR (SEQ ID NO.)	Pal		1663.123
46	i1	KKLRSMTDKY (SEQ ID NO.)	Pal		1506.937
47	i1	MGYQKKLRSMT DKYRI (SEQ ID NO.)	Pal	lipid on both termini	2480.256

48	il	MGYQKKLRSMT DKYRI (SEQ ID NO.)	Myr	also on backbone	2509.254
49	il	MGYQKKLRSMT DKYRI (SEQ ID NO.)	Pal		2255.831
50	il	SGYQKKLRSSTD (SEQ ID NO.)	Myr	also backbone lipid	1860.328
51	il	MGYQKKLRSMT D (SEQ ID NO.)	Myr	backbone lipid also	1948.565
52	il	QKKLRSMTDKY RI (SEQ ID NO.)	NH(CH 2)15-CH3		1932.463
53	il	MGYQKKLRSMT DKYRLHL (SEQ ID NO.)	Pal	C-terminus also	2730.553
54	il	MGYQKKLRSMT DKYRLHL (SEQ ID NO.)	Myr	dual lipid backbone	2759.551
55	il	MGYQKKLRSMT DKYRLHLSV (SEQ ID NO.)	Pal		2692.336
56	il	MGYQKKLRSMT DKYRLHLSV (SEQ ID NO.)	Myr	dual lipid backbone	2945.759
58	il	MGYQKKLRSMT DK (SEQ ID NO.)		capped peptide	1626.942
59	il	MGYQKKLRSMT DK (SEQ ID NO.)	NH(CH_2)15-CH3		1851.367
60	il	MGYQKKLRSMT DK (SEQ ID NO.)	Myr	Dual peptide Myr and C16 backbone	2076.737
61	il	KKLCRSMTDKC YRL (SEQ ID NO.)	Pal	4, 11 Cys cyclization	1980.551
62	il	KKLRCSMTDCK YRL (SEQ ID NO.)	Pal	5, 10 Cys cyclization	1980.551
63	il	KKLRSMTDKYR L (SEQ ID NO.)	Pal	head to tail cyclized	1802.318
64	il	KKLRSMTDKYR L (SEQ ID NO.)	Pal		1820.333
65	il	KRMKTSLYDGR MQYLK (SEQ ID NO.)	Pal	scrambled No.:39	2255.831
66	il	YTKRLDSHRKLK M (SEQ ID NO.)	Pal	scrambled No. 44	1913.42
67	il	MGYQKKLRSMT DKYRL (SEQ ID NO.)			2060.447

68	il	KKLRSXTDKYRL H (SEQ ID NO.)	Pal	X=Norlueci ne substitution	1895.382
69	il	SGYQKKLRSSTD (SEQ ID NO.1)	Pal		1606.904
70	il	SGYQKKLRSSTD (SEQ ID NO.1)	Myr		1565.852
71	il	SGYQKKLRSSTD (SEQ ID NO.1)	Lca		1727.053
72	il	MGYQKKLRSST D (SEQ ID NO.)	Pal		1651.023
73	il	SGYQKKLRSMT D (SEQ ID NO.)	Pal		1651.023
117	il	kKLRSMTDKYRL H (SEQ ID NO.89)	Pal		
118	il	KkLRSMTDKYRL H (SEQ ID NO. 90)	Pal		
119	il	KKlRSMTDKYRL H (SEQ ID NO.91)	Pal		
120	il	KKLrSMTDKYRL H (SEQ ID NO.92)	Pal		
121	il	KKLRsMTDKYRL H (SEQ ID NO.93)	Pal		
122	il	KKLRSmTDKYR LH (SEQ ID NO.94)	Pal		
123	il	AKLRSMTDKYR LH (SEQ ID NO. 95)	Pal		
124	il	KALRSMTDKYR LH (SEQ ID NO.96)	Pal		
125	il	KKARSMTDKYR LH (SEQ ID NO.97)	Pal		
126	il	KKLASMTDKYR LH (SEQ ID NO. 98)	Pal		
127	il	KKLRAMTDKYR LH (SEQ ID NO. 99)	Pal		
128	il	KKLRSATDKYRL H (SEQ ID NO. 100)	Pal		
129	il	AGYQKKLRSMT DKYRL (SEQ ID NO. 101)	Pal		
130	il	MAYQKKLRSMT DKYRL (SEQ ID NO.102)	Pal		
131	il	MGAQKKLRSMT DKYRL (SEQ ID NO. 103)	Pal		
132	il	MGYAKKLRSMT DKYRL (SEQ ID NO. 104)	Pal		

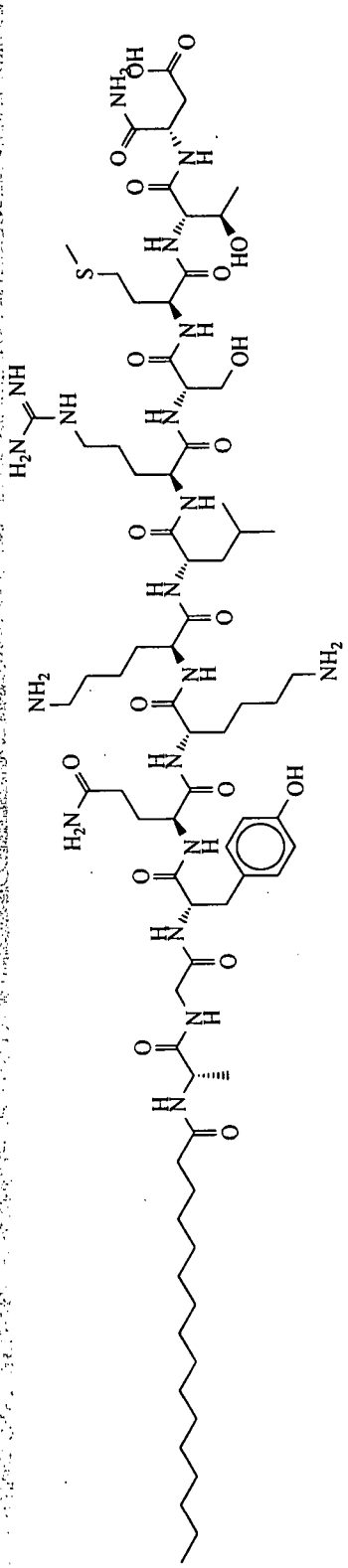
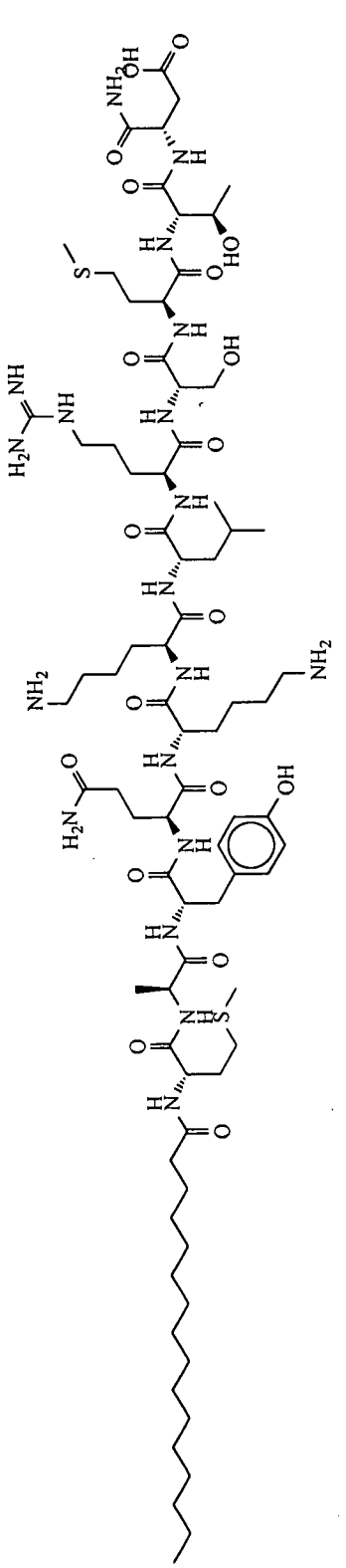
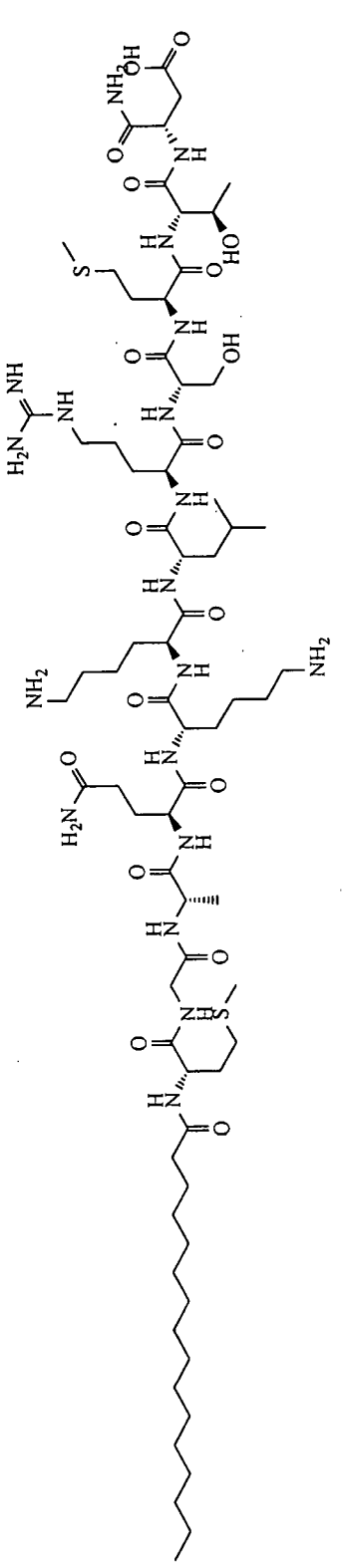
133	i1	MGYQAKLRSMT DKYRL (SEQ ID NO. 105)	Pal		
134	i1	MGYQKALRSMT DKYRL (SEQ ID NO. 106)	Pal		
135	i1	MGYQKKARSMT DKYRL (SEQ ID NO. 107)	Pal		
136	i1	MGYQKKLASMT DKYRL (SEQ ID NO. 108)	Pal		
137	i1	KKLRSMTDKYR LH (SEQ ID NO.42)	Myr		
138	i1	KKLRSMTDKYR LH (SEQ ID NO.42)	Lca		
139	i1	KKLRSMADKYR LH (SEQ ID NO.109)	Pal		
140	i1	KKLRSMTAKYR LH (SEQ ID NO.110)	Pal		
141	i1	KKLRSMTDAYR LH (SEQ ID NO.111)	Pal		
142	i1	KKLRSMTDKAR LH (SEQ ID NO.112)	Pal		
143	i1	KKLRSMTDKYA LH (SEQ ID NO.113)	Pal		
144	i1	KKLRSMTDKYR AH (SEQ ID NO.114)	Pal		
145	i1	KKLRSMTDKYR LA (SEQ ID NO.115)	Pal		
146	i1	MGYQKKLRAMT DKYRL (SEQ ID NO. 116)	Pal		
147	i1	MGYQKKLRSAT DKYRL (SEQ ID NO.)	Pal		
148	i1	MGYQKKLRSMA DKYRL (SEQ ID NO.)	Pal		
149	i1	MGYQKKLRSMT AKYRL (SEQ ID NO.)	Pal		
150	i1	MGYQKKLRSMT DAYRL (SEQ ID NO.)	Pal		
151	i1	MGYQKKLRSMT DKARL(SEQ ID NO.)	Pal		
152	i1	MGYQKKLRSMT DKYAL (SEQ ID NO.)	Pal		

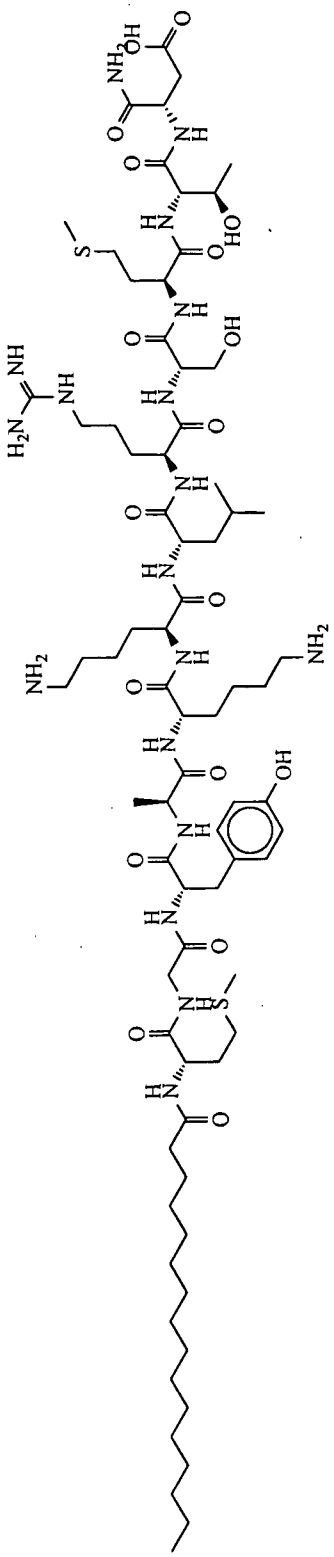
153	i1	MGYQKKLRSMT DKYRA (SEQ ID NO.)	Pal		
154	i1	KKLRSMtDKYRL H (SEQ ID NO.)	Pal		
155	i1	KKLRSMTdKYRL H (SEQ ID NO.)	Pal		
156	i1	KKLRSMTDKYrL H (SEQ ID NO.)	Pal		
157	i1	KKLRSMTDKYRl H (SEQ ID NO.)	Pal		
158	i1	KKLRSMTDKYR Lh (SEQ ID NO.)	Pal		
159	i1	MGYQKKLRSMT DKYRl (SEQ ID NO.)	Pal		
160	i1	MGYQKKLRSMT DKYrL (SEQ ID NO.)	Pal		
161	i1	MGYQKKLRSMT DKyRL (SEQ ID NO.)	Pal		
162	i1	MGYQKKLRSMT DkYRL (SEQ ID NO.)	Pal		
163	i1	MGYQKKLRSMT dKYRL (SEQ ID NO.)	Pal		
164	i1	MGYQKKLRSMt DKYRL (SEQ ID NO.)	Pal		
165	i1	mGYQKKLRSMT DKYRL (SEQ ID NO.)	Pal		
166	i1	MGyQKKLRSMT DKYRL (SEQ ID NO.)	Pal		
167		MGYqKKLRSMT DKYRL (SEQ ID NO.)	Pal		
168	i1	MGYQkKLRSMT DKYRL (SEQ ID NO.)	Pal		
169	i1	MGYQKkLRSMT DKYRL (SEQ ID NO.)	Pal		
170	i1	MGYQKKlRSMT DKYRL (SEQ ID NO.)	Pal		
171	i1	MGYQKKLrSMT DKYRL (SEQ ID	Pal		

		NO.)			
172		MGYQKKLRsMT DKYRL (SEQ ID NO.)	Pal		
173	il	MGYQKKLRSmT DKYRL (SEQ ID NO.)	Pal		
174	il	KKLRSMTDKYRl S (SEQ ID NO.)	Pal		
175	il	MGYQKKLRSMT DKYRL (SEQ ID NO.)	Pal		
176	il	MGYQKKLRSMT DKYRL (SEQ ID NO.)	Elaidic		
177	il	MGYQKKLRSMT DKYRL (SEQ ID NO.)	Oleic		
178	il	MGYQKKLRSMT DKYRL (SEQ ID NO.)	3-(dodecyl oxy)pro panoate		
179	il	MGYQKKLRSMT DKYRL (SEQ ID NO.)	16-hydroxy -Pal		
180	il	KKLRSMTDKYR LH (SEQ ID NO. 42)	Pal		
181	il	KKLRSMTDKYR LH (SEQ ID NO. 42)	3-(dodecyl oxy)pro panoate		
182	il	KKLRSMTDKYR LH (SEQ ID NO.42)	16-hydroxy -Pal		
183	il	KKLRSMTDKYR LH ((SEQ ID NO. 42))			
184	il	KKLRSMTDKYR LH (SEQ ID NO. 42)			
185	il	KKLRSMTDKYR LH (SEQ ID NO. 42)			
186	il	MGYQKKLRSMT DKYRL			
187	il	MGYQKKLRSMT DKYRL			
188	il	MGYQKKLRSMT DKYRL			
189	il	MGYQKKLRSpT DKYRL	Pal		
190	il	MGYQKKLRpMT	Pal		

		DKYRL			
191	il	MGYQKKLpSMT DKYRL	Pal		
192	il	MGYQKKpRSMT DKYRL	Pal		
193	il	MGYQKKLRSMP DKYRL	Pal		
194	il	XGYQKKRLSXT DKYRL X=noreleucine	$C_{15}H_{31}$(CO)		

Table 7. CXCR4 i1 loop compound structures

Comp. #	Structure
1	
2	
3	



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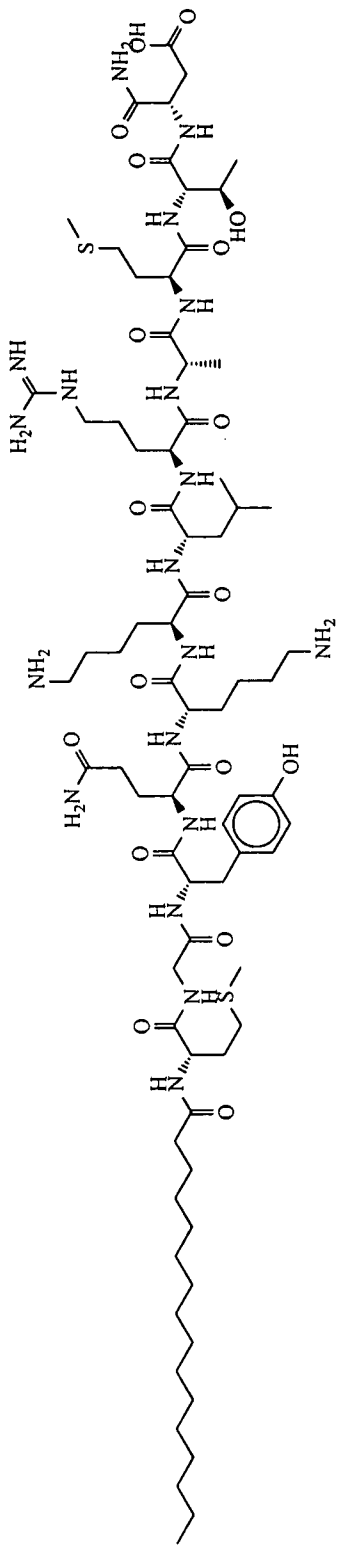

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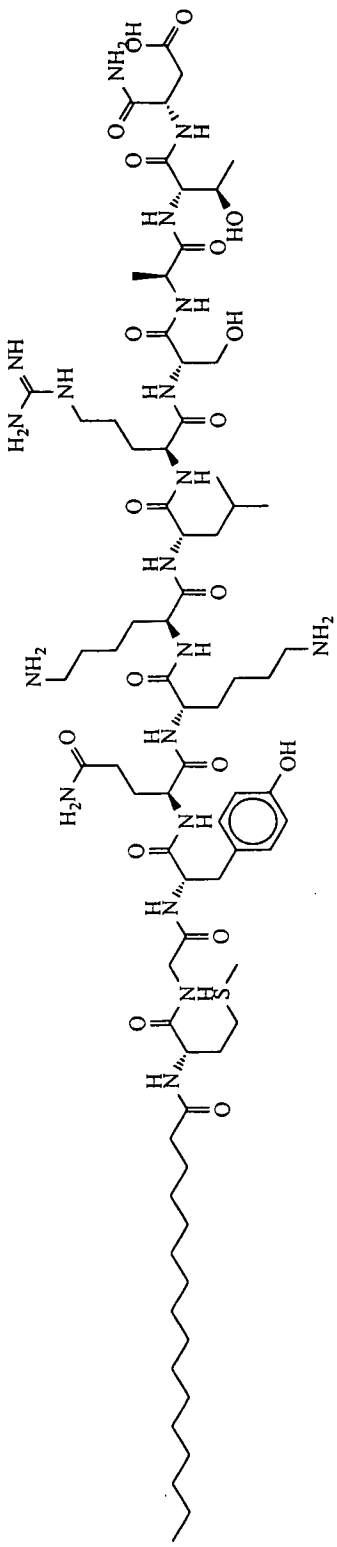

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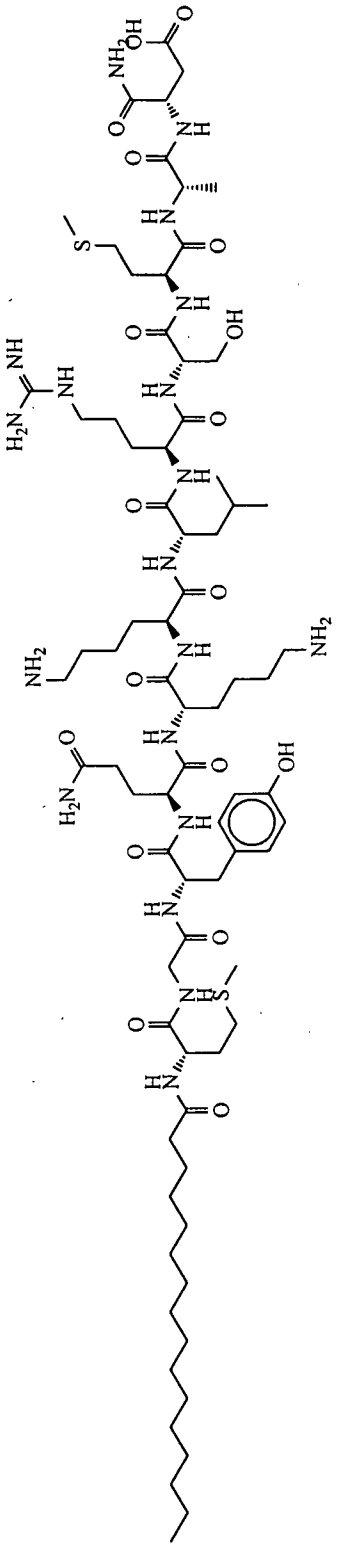

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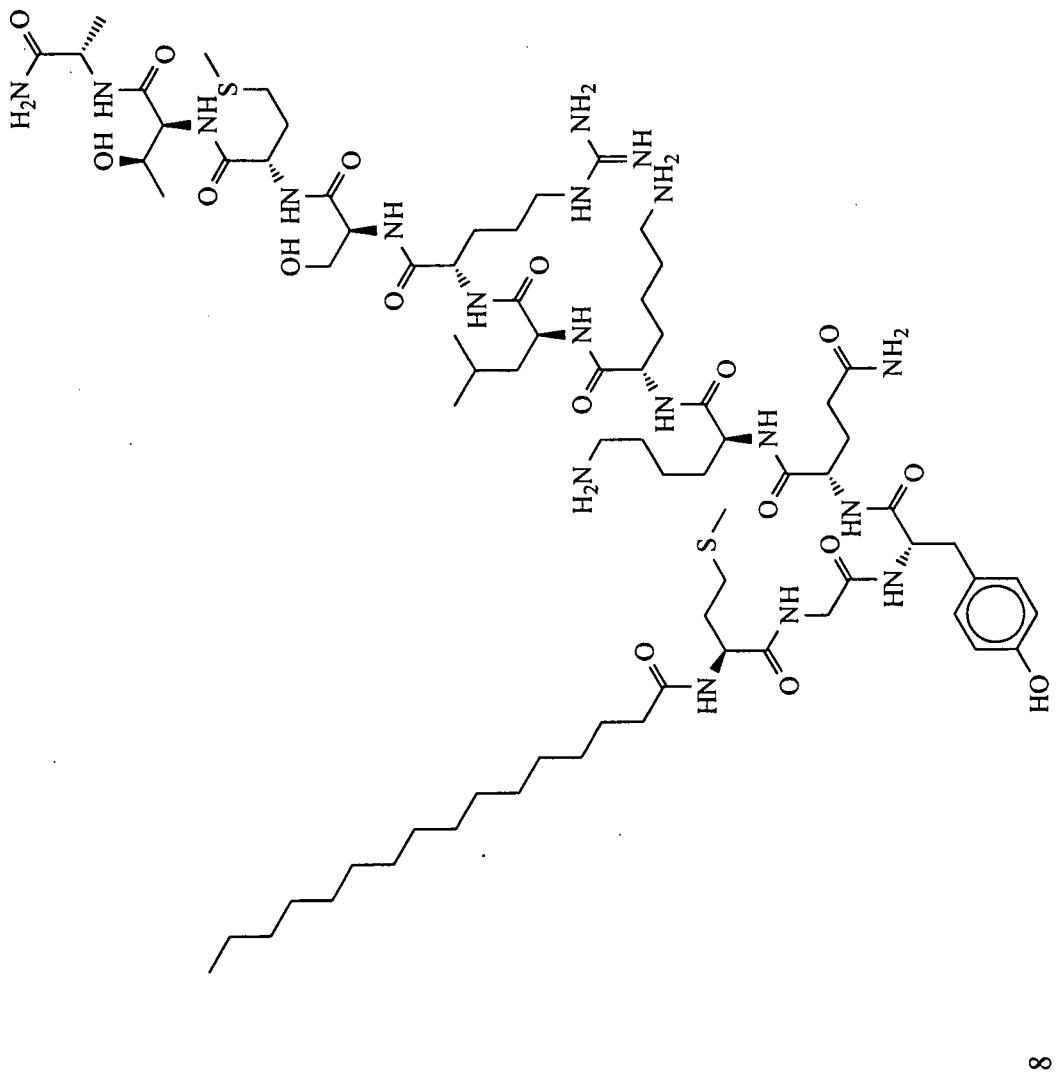

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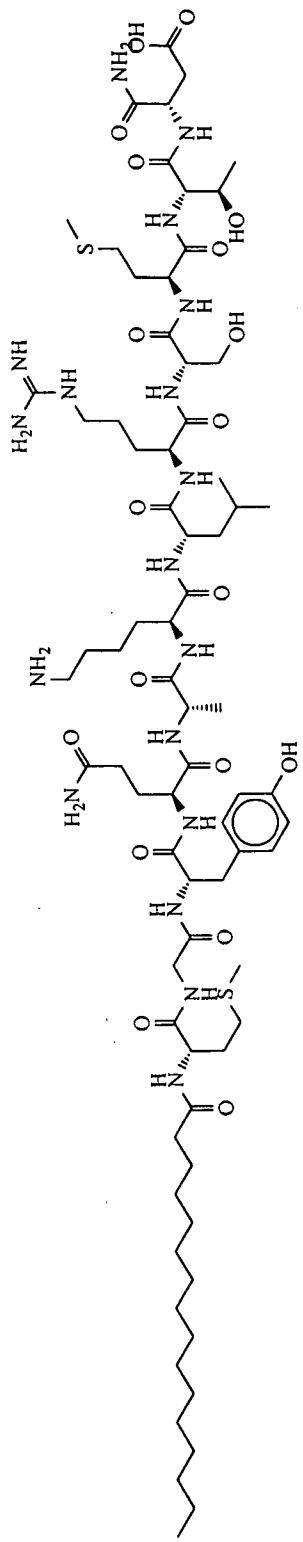

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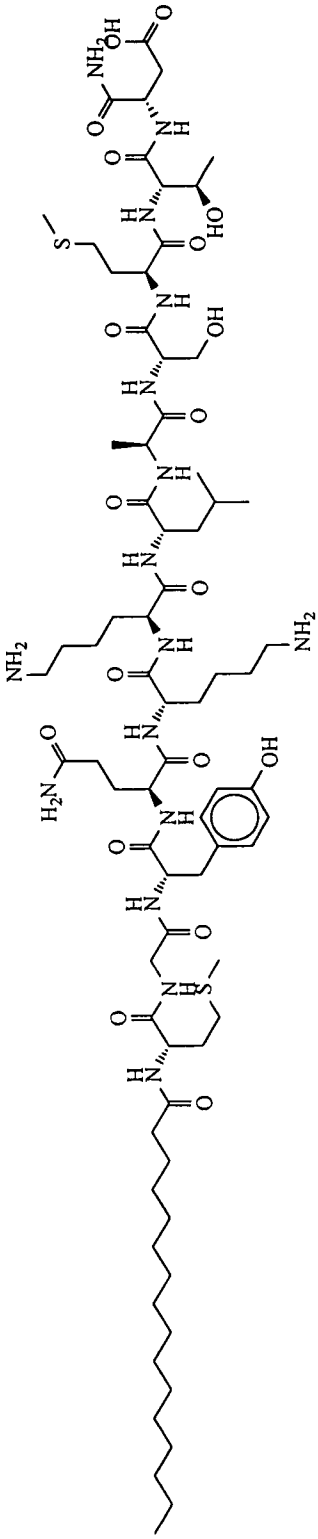

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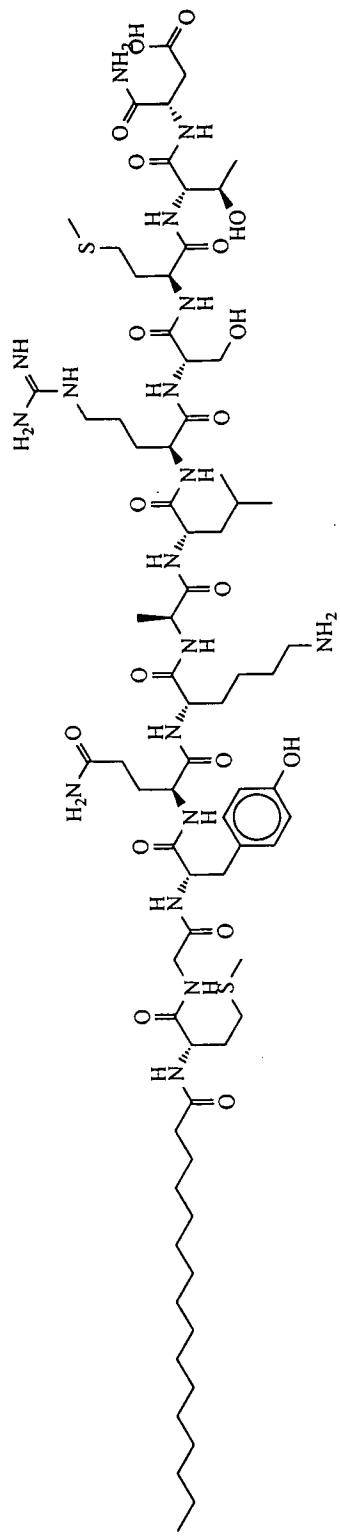

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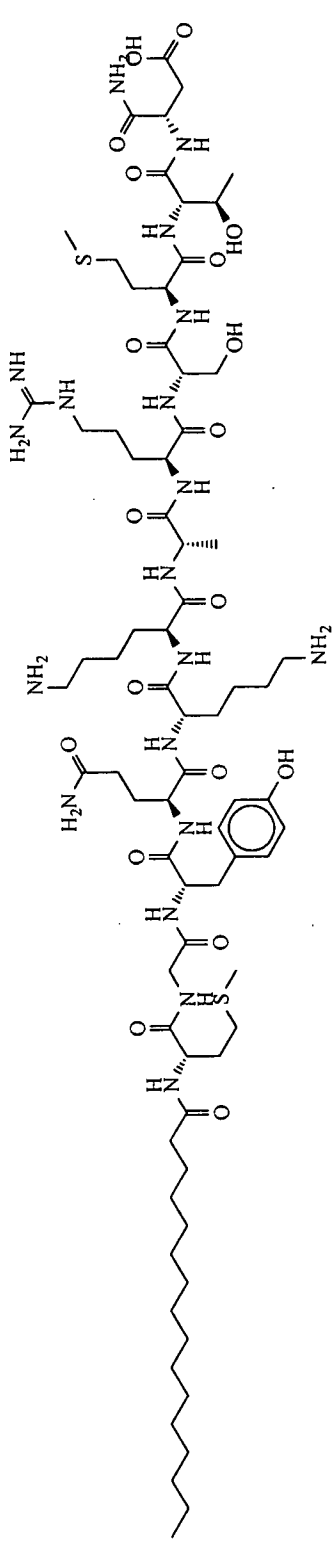

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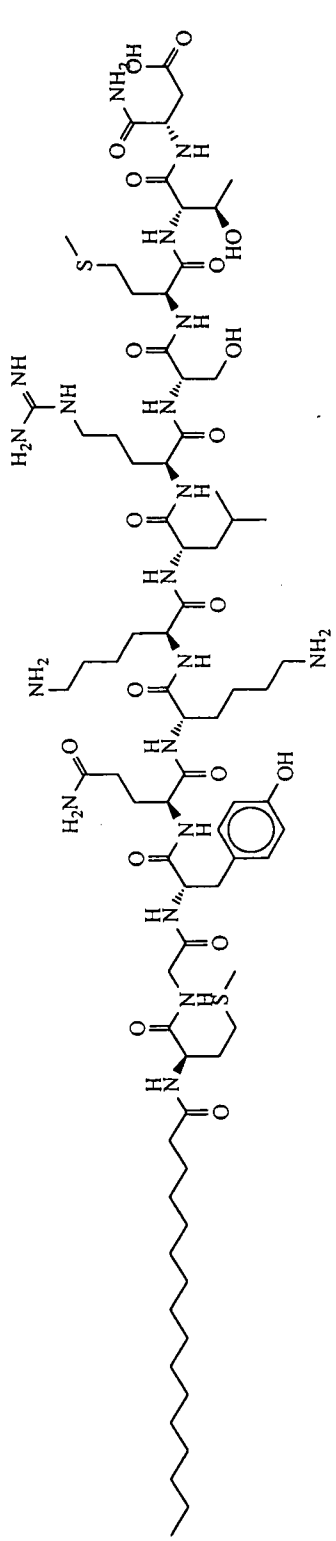

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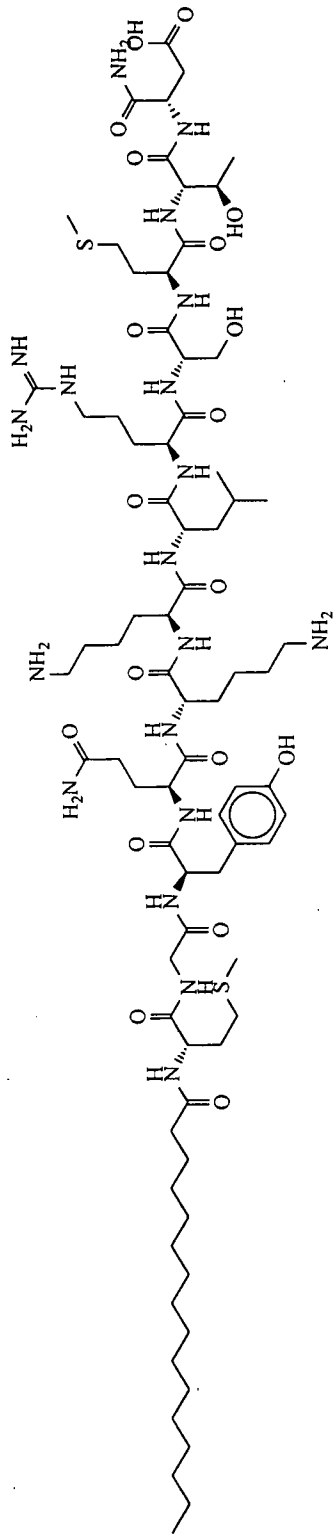

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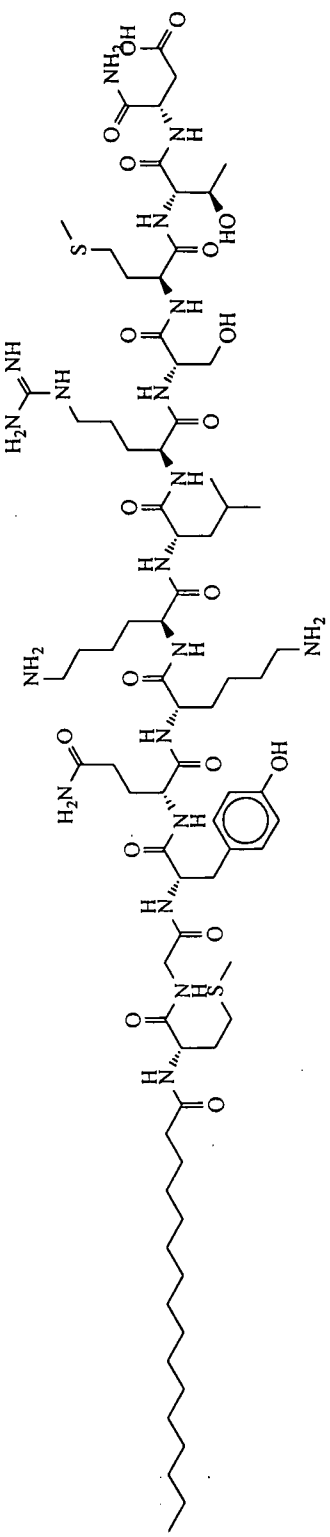

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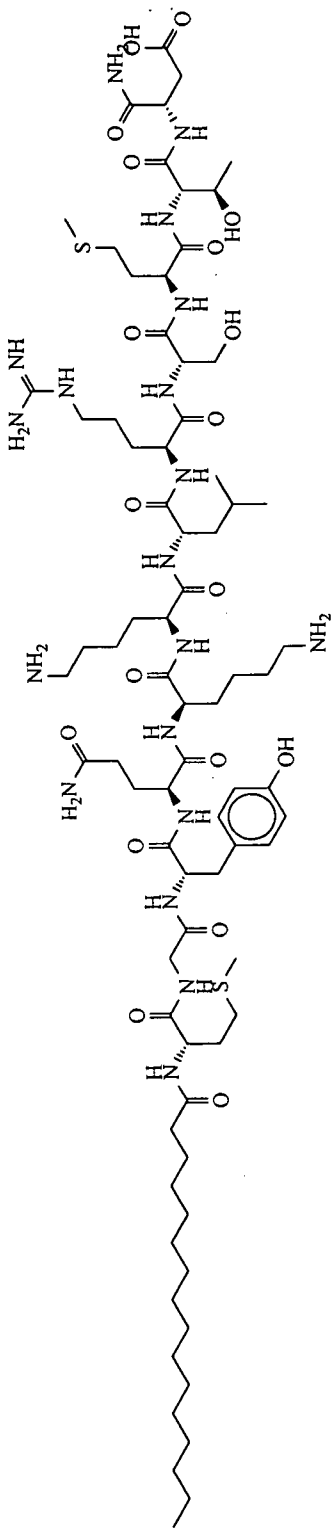

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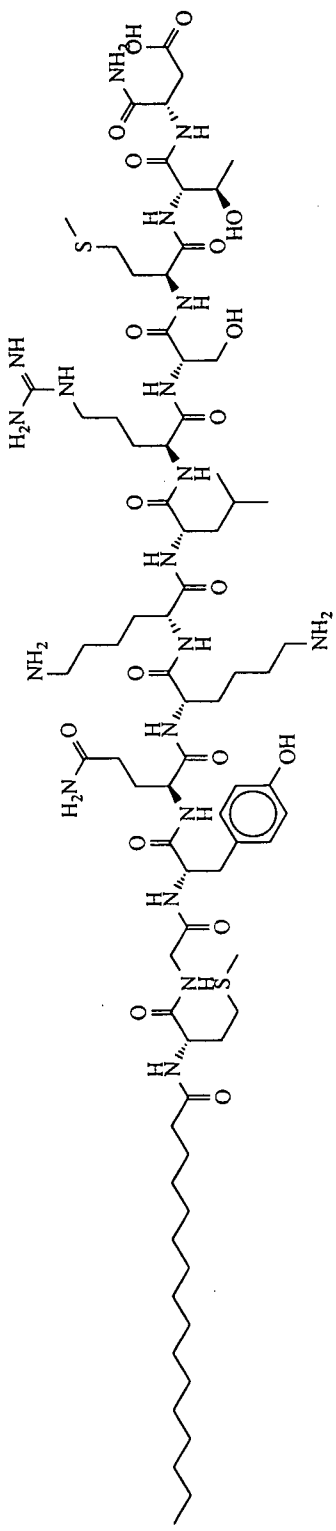

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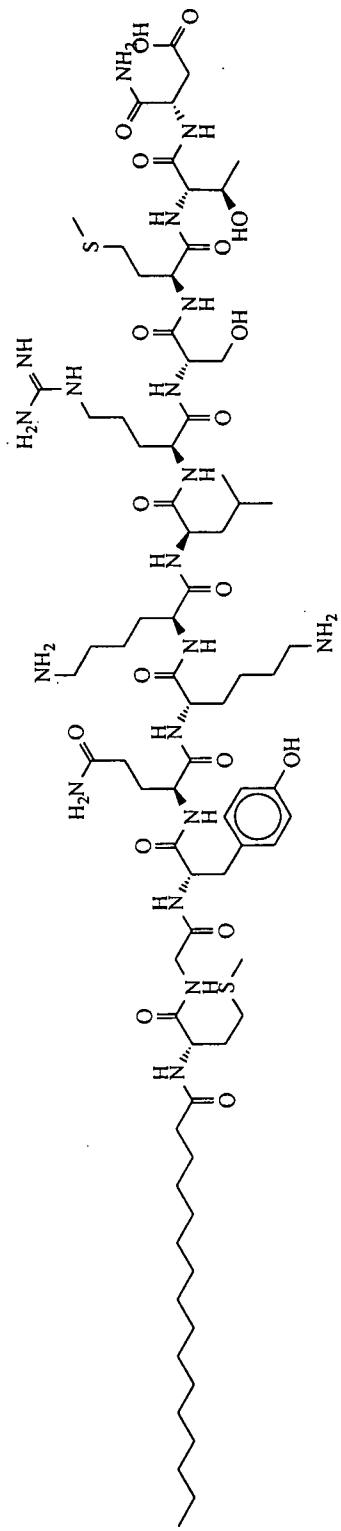

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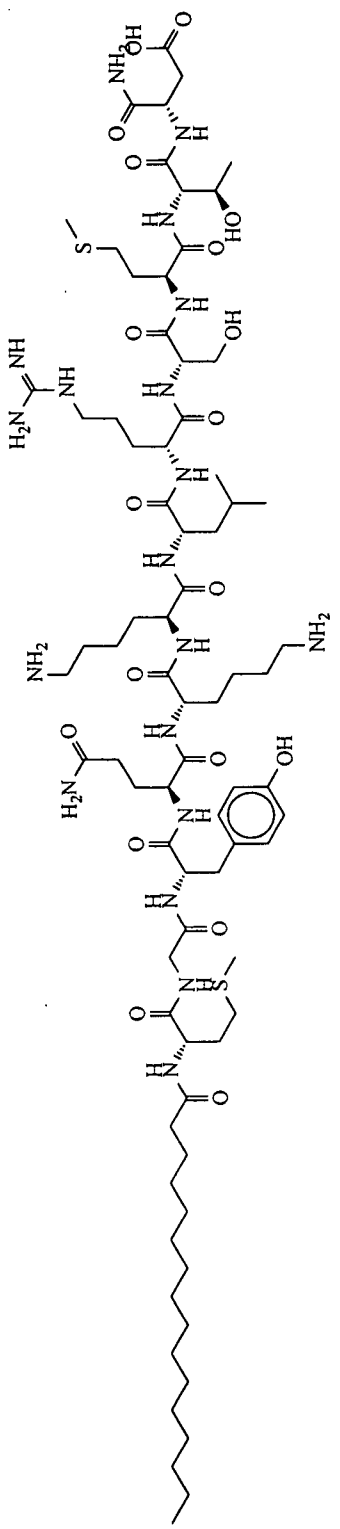

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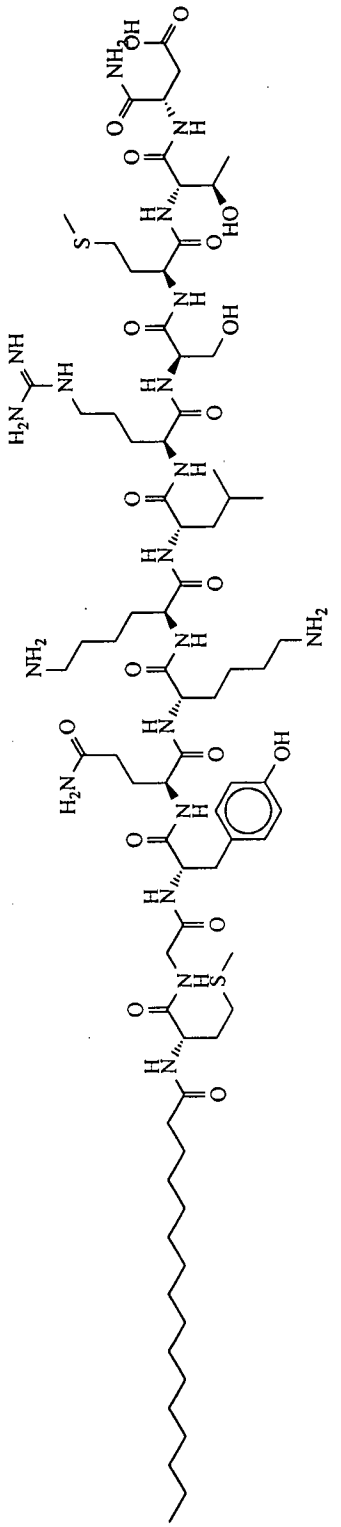

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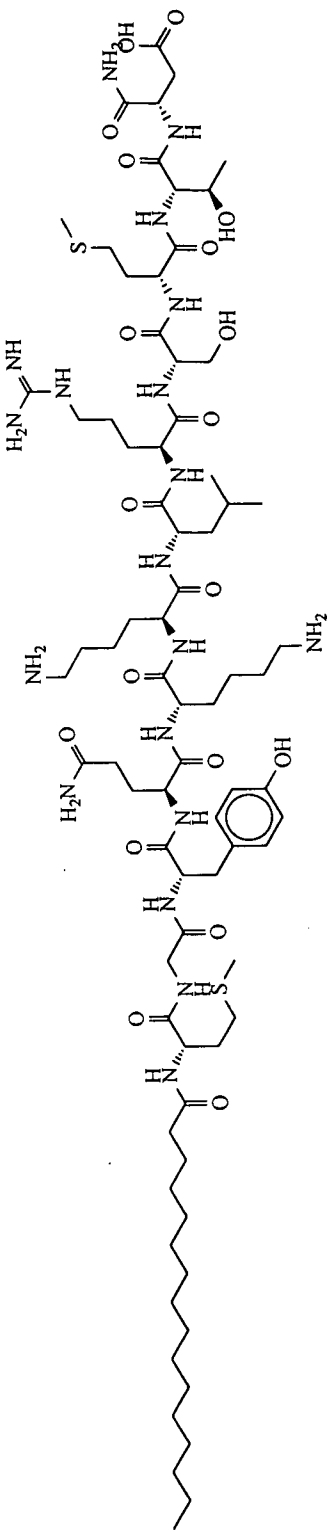

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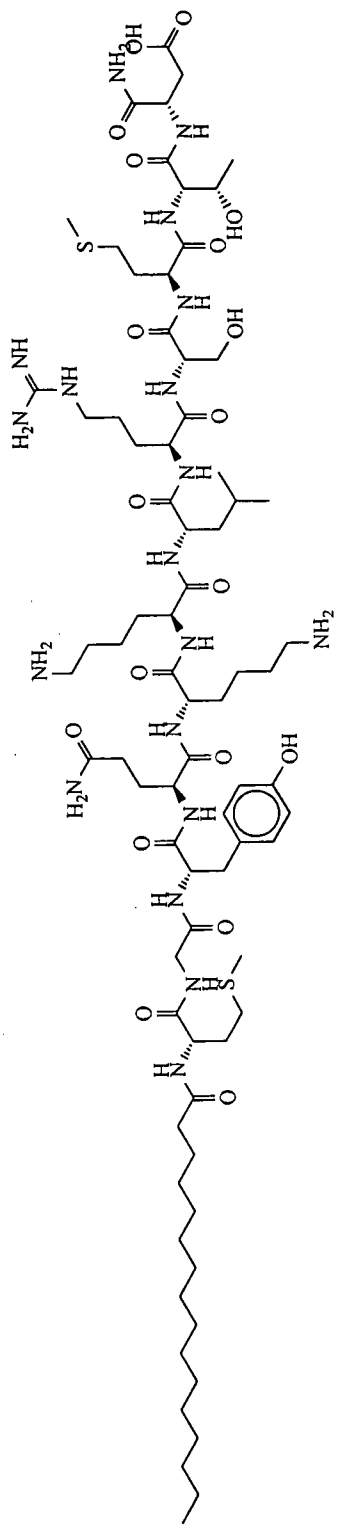

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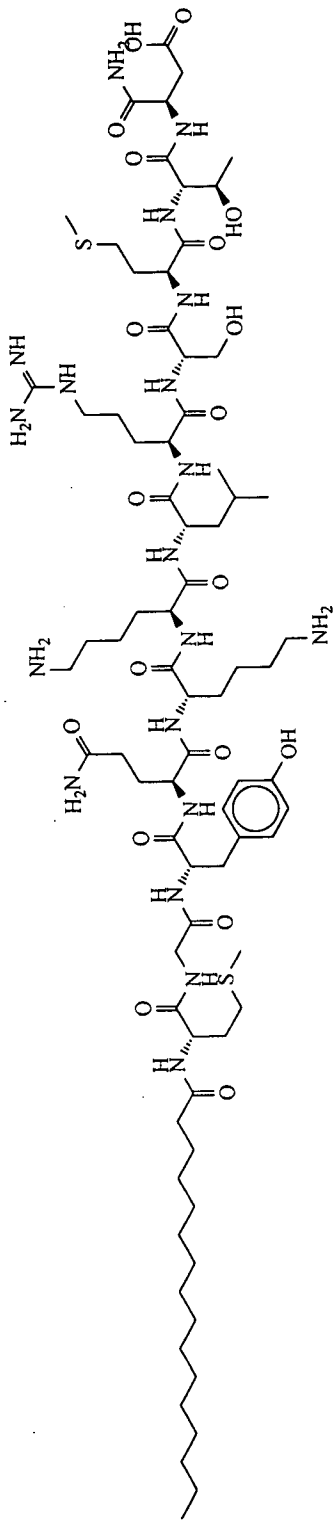

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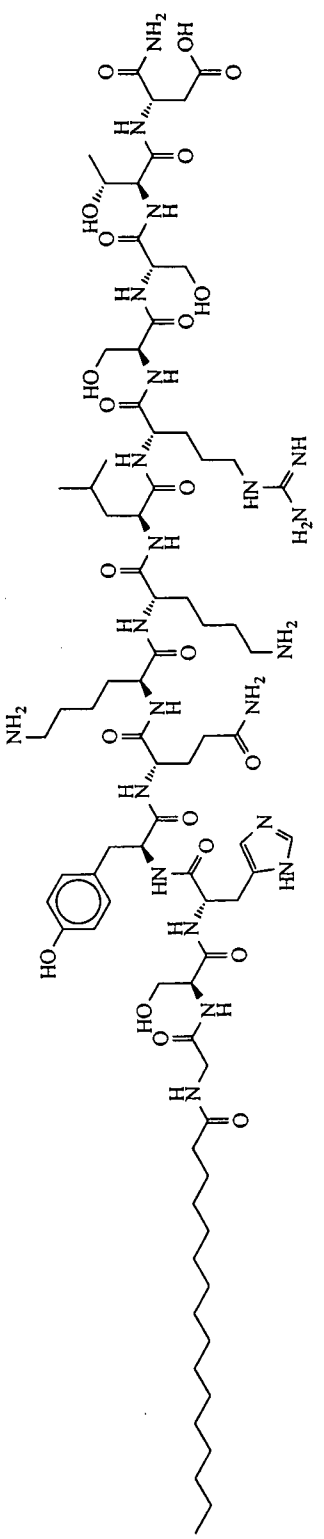

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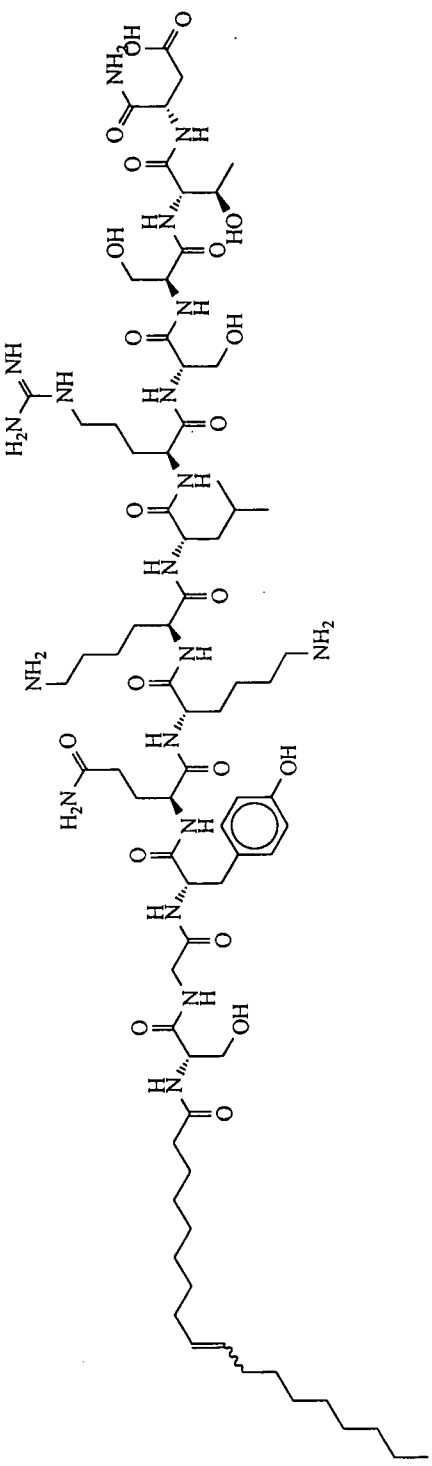

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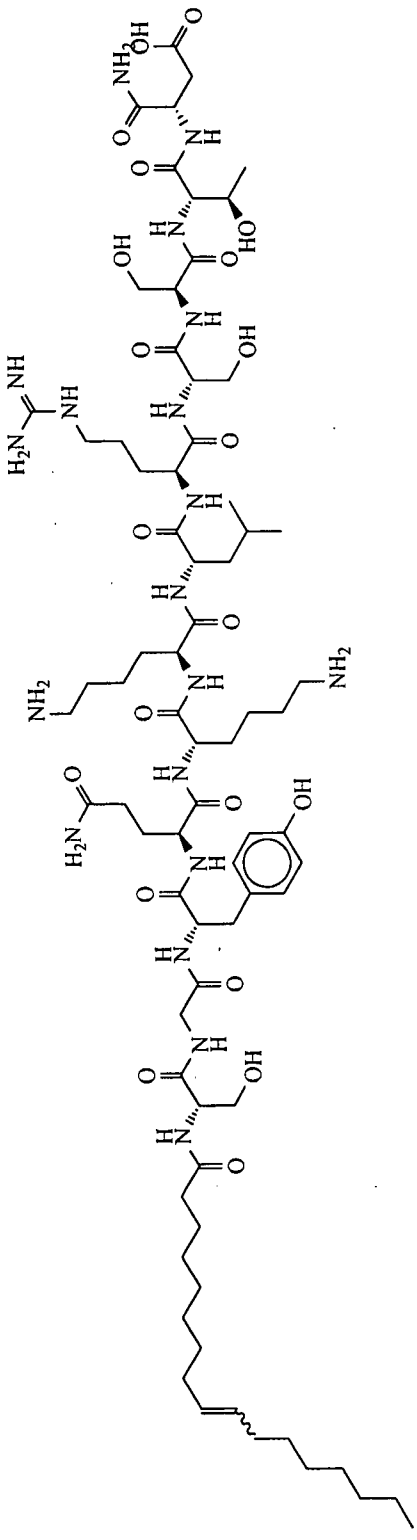

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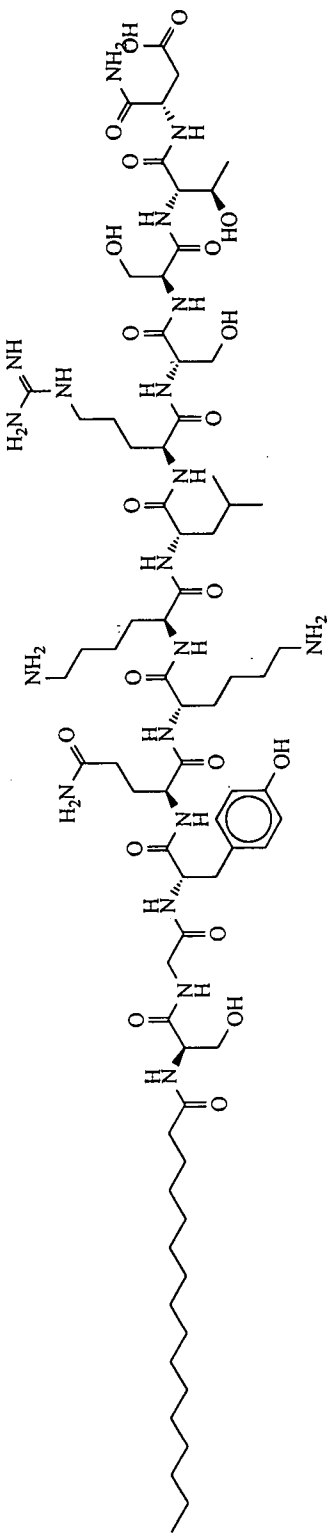

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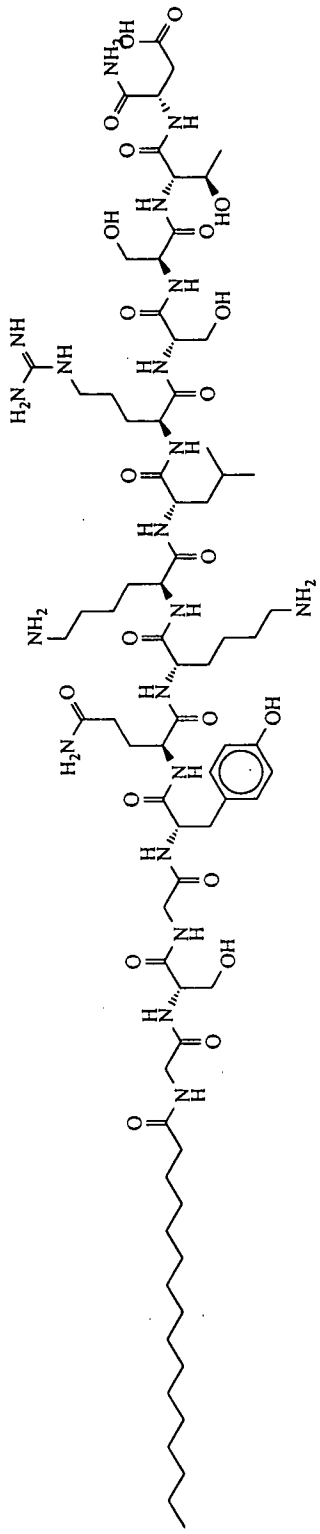

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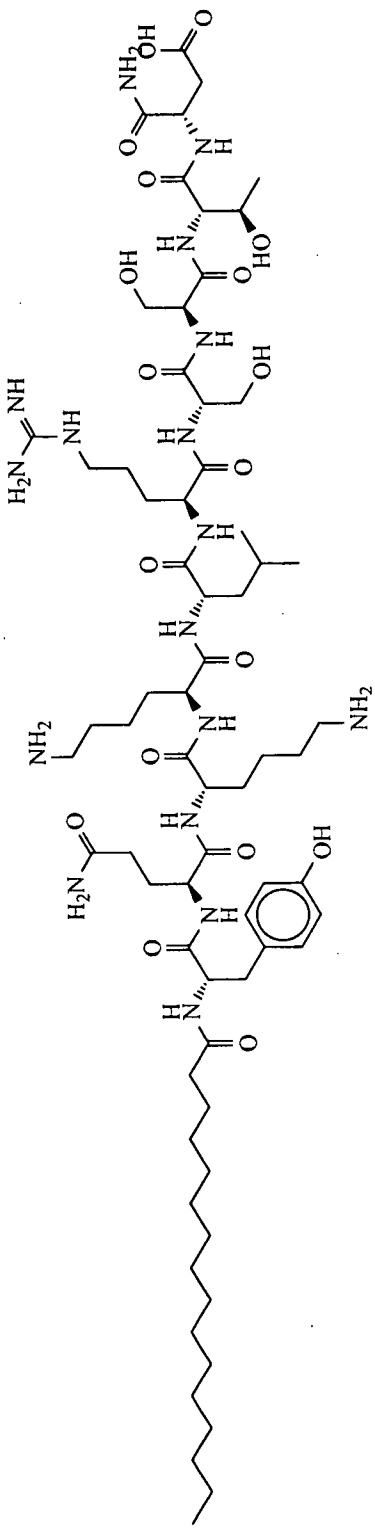

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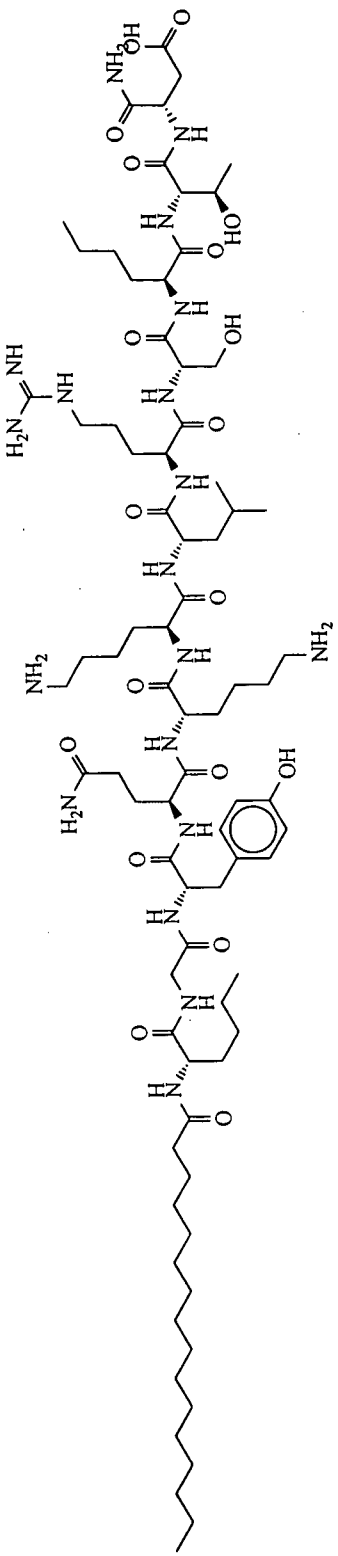

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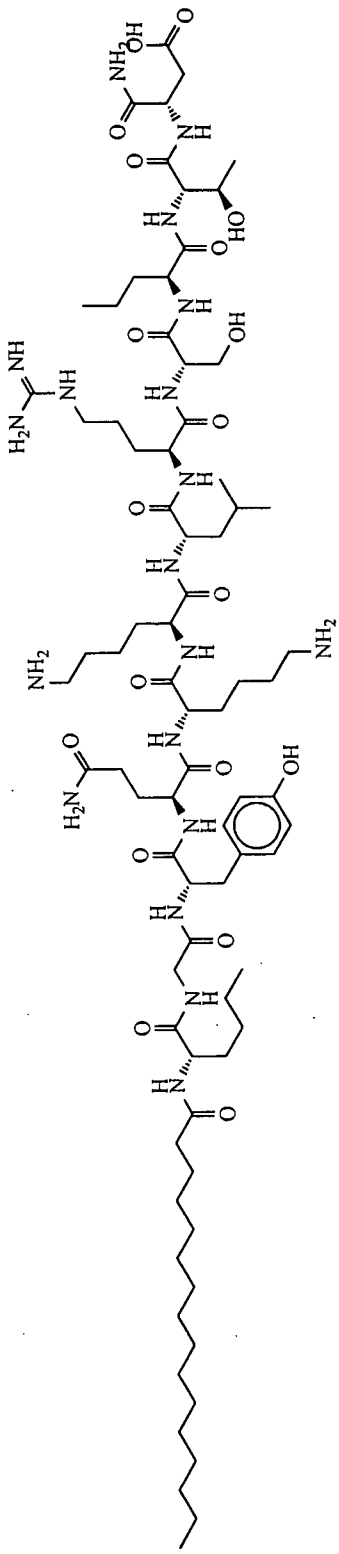

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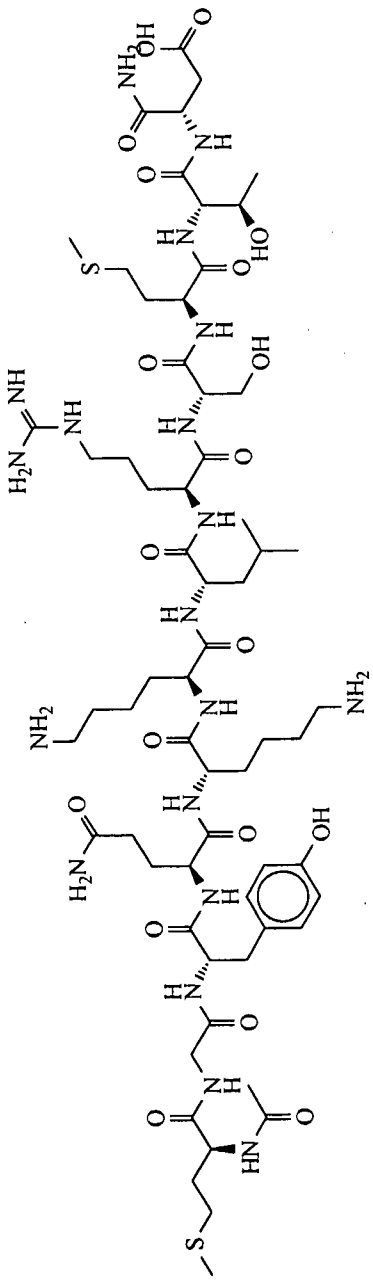

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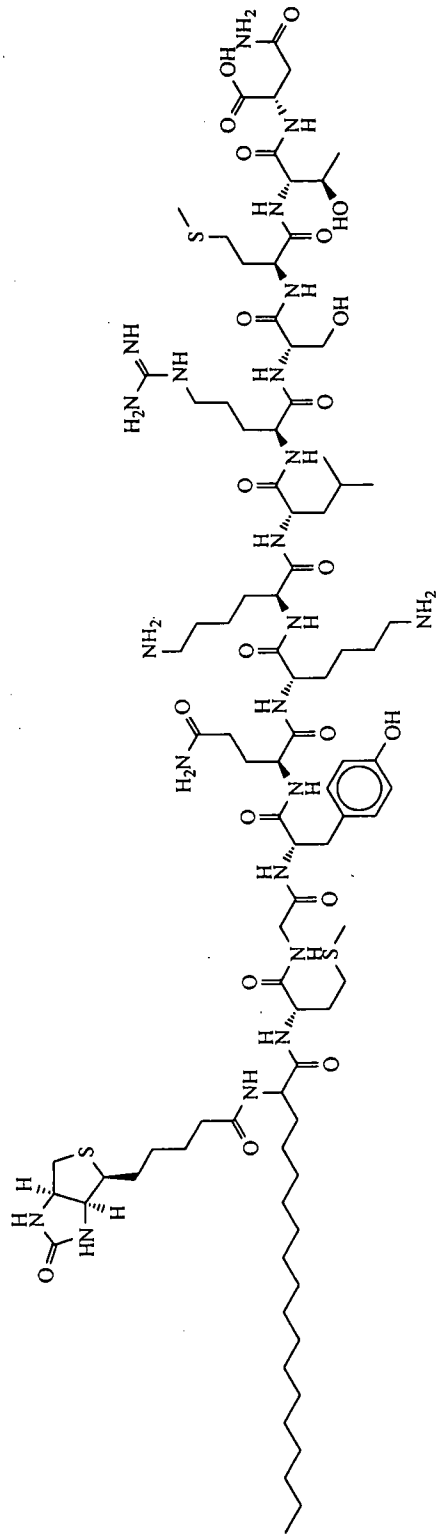

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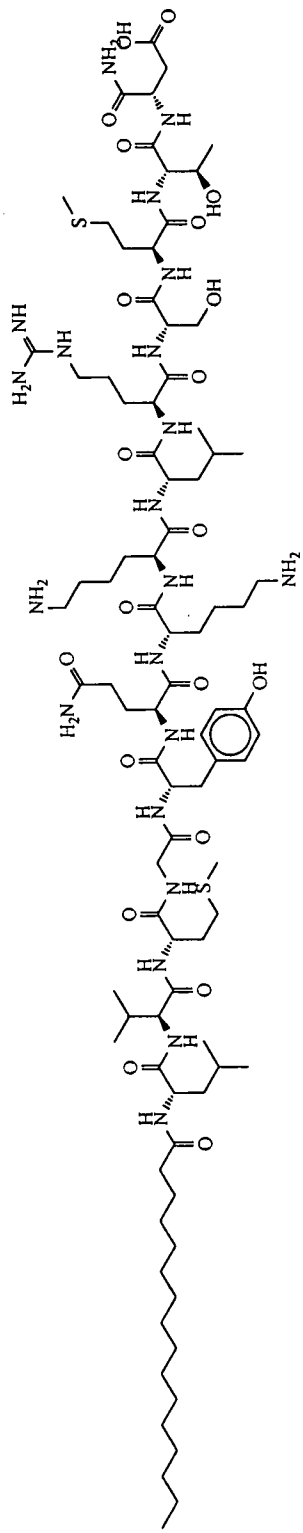

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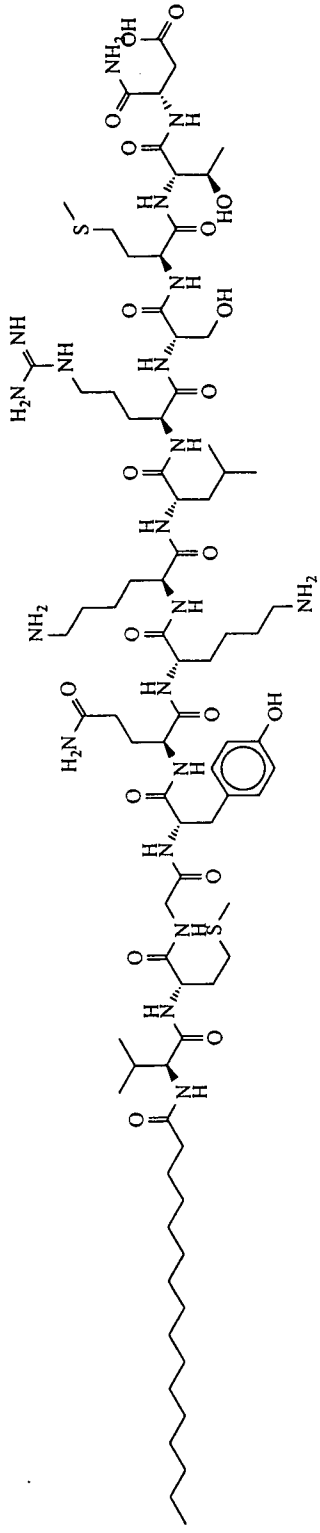

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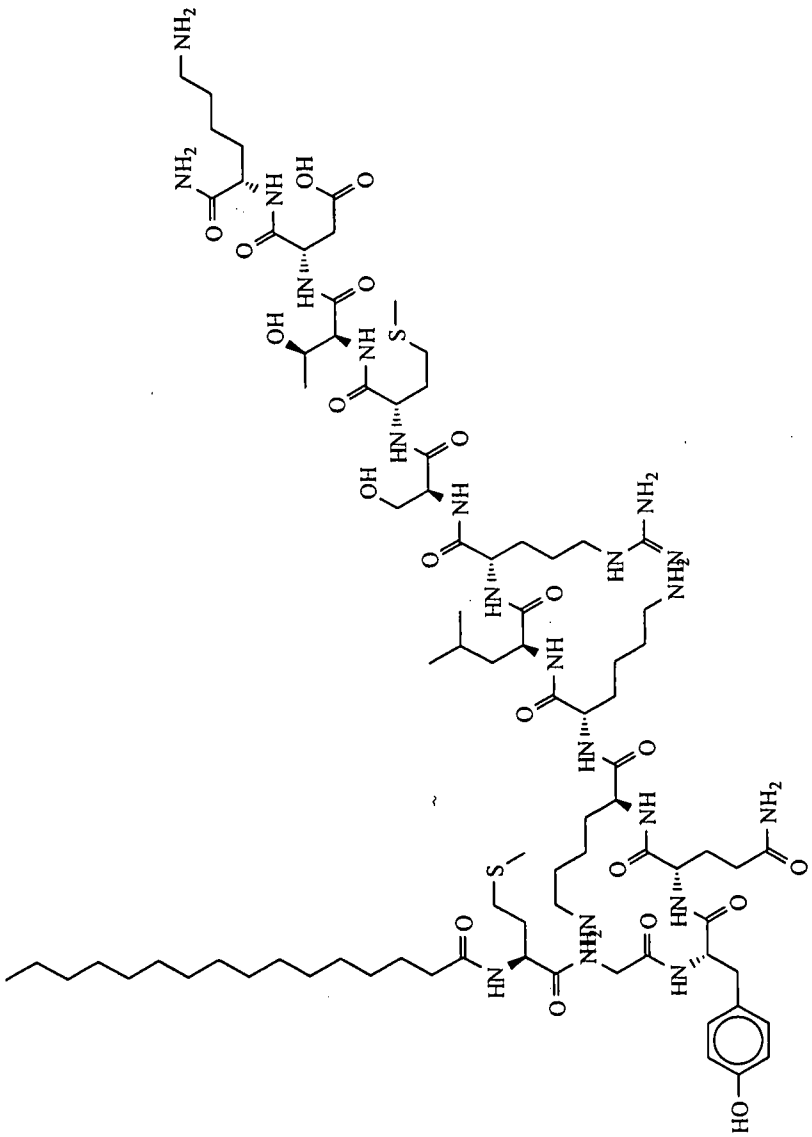

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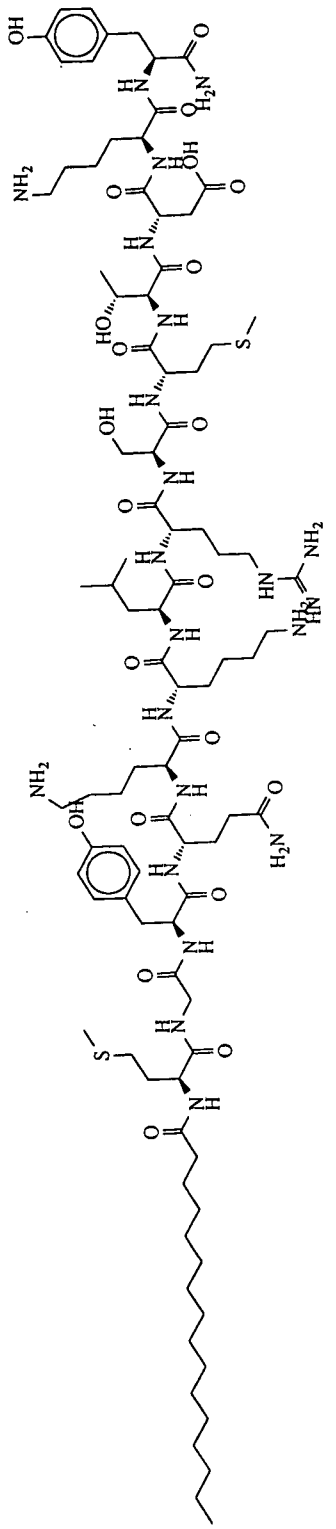

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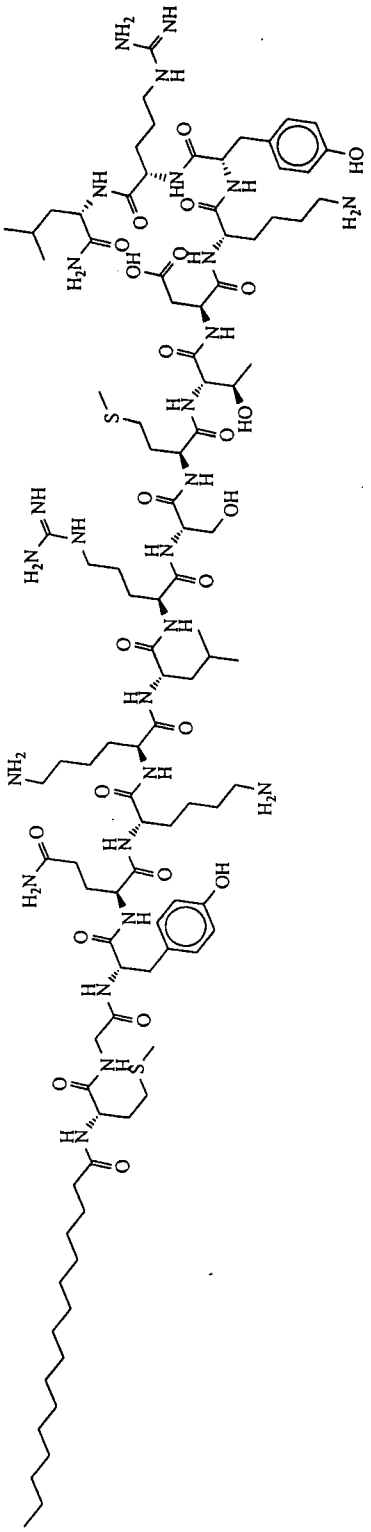

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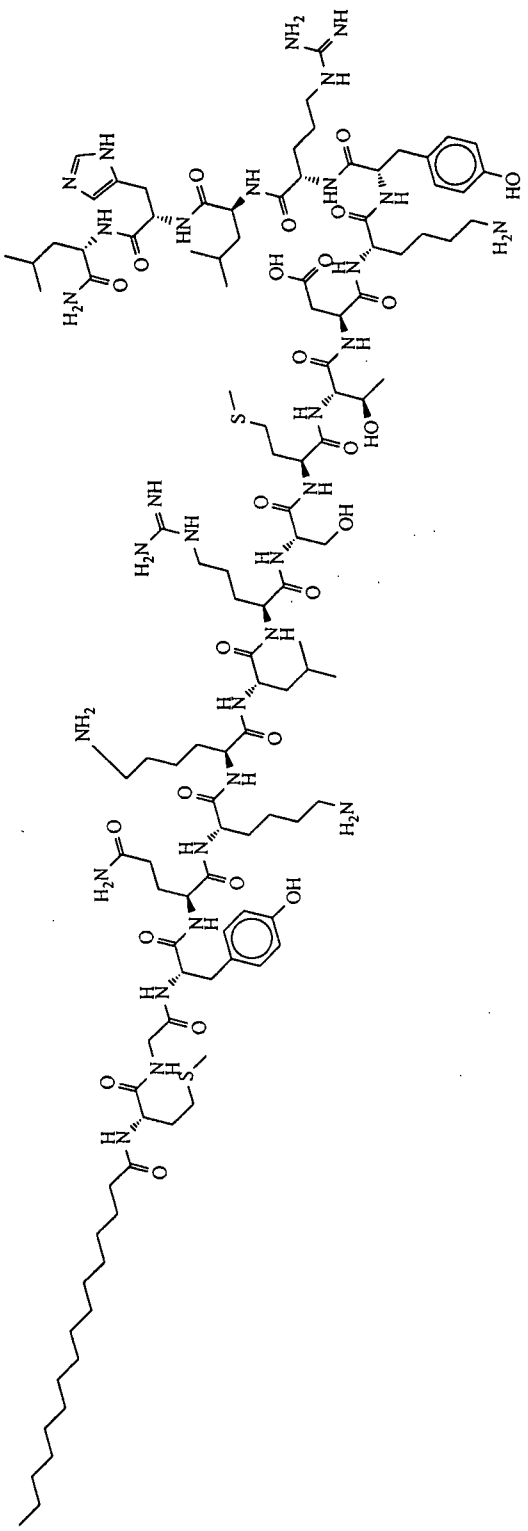

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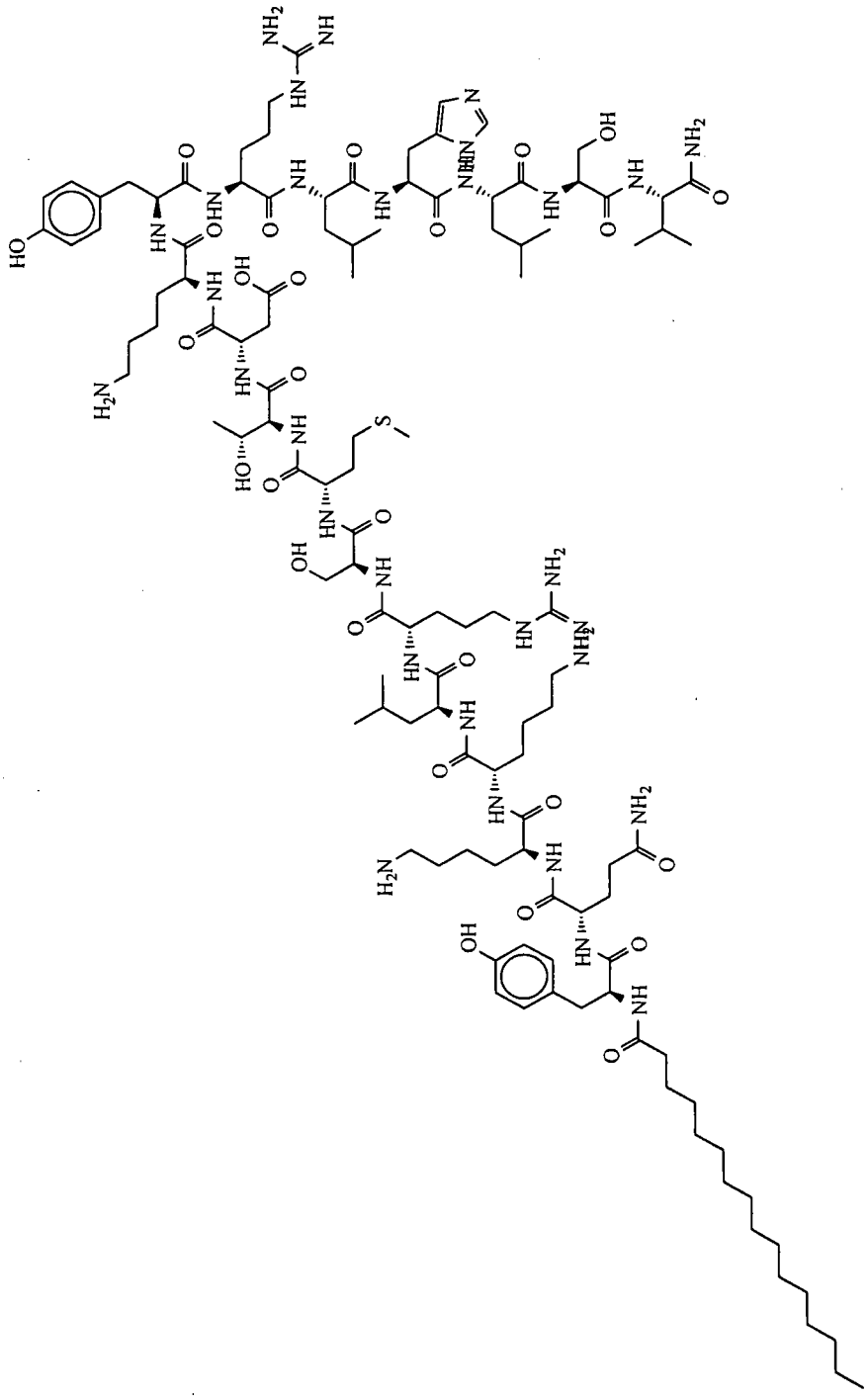

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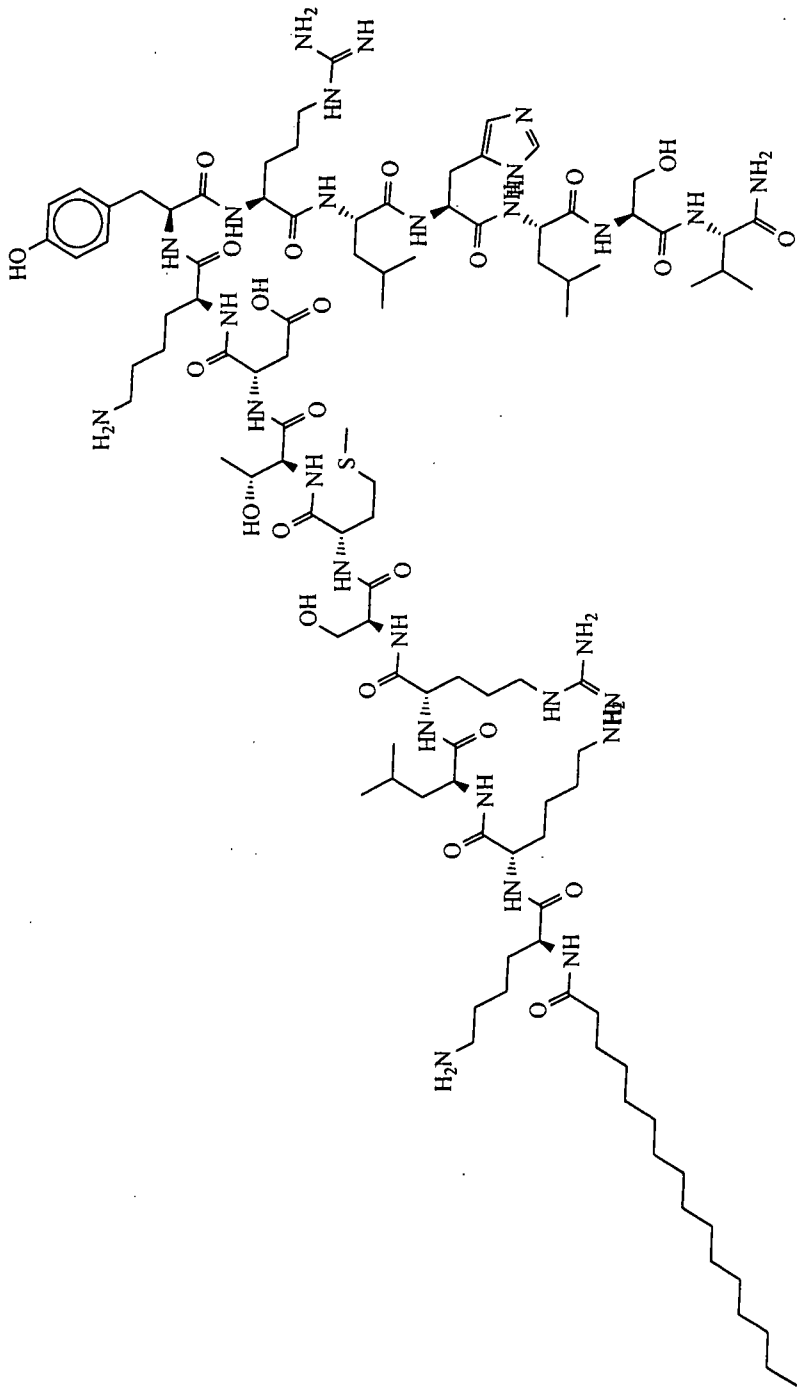

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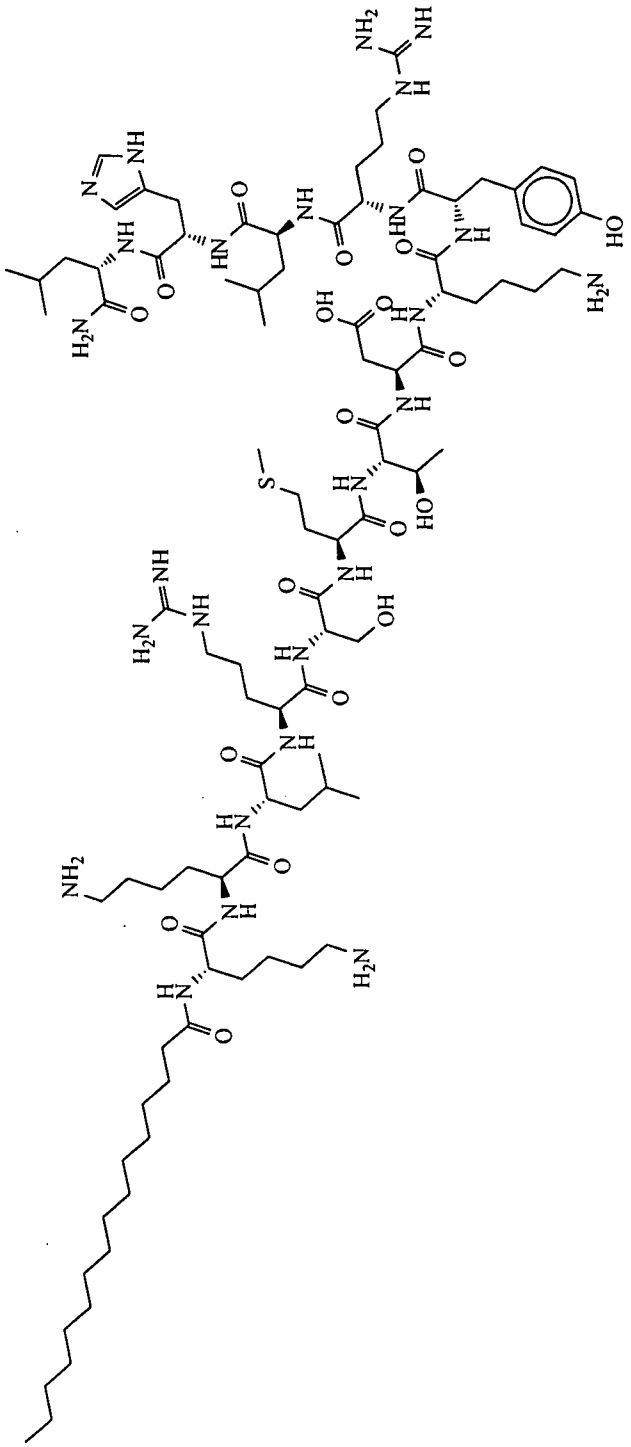

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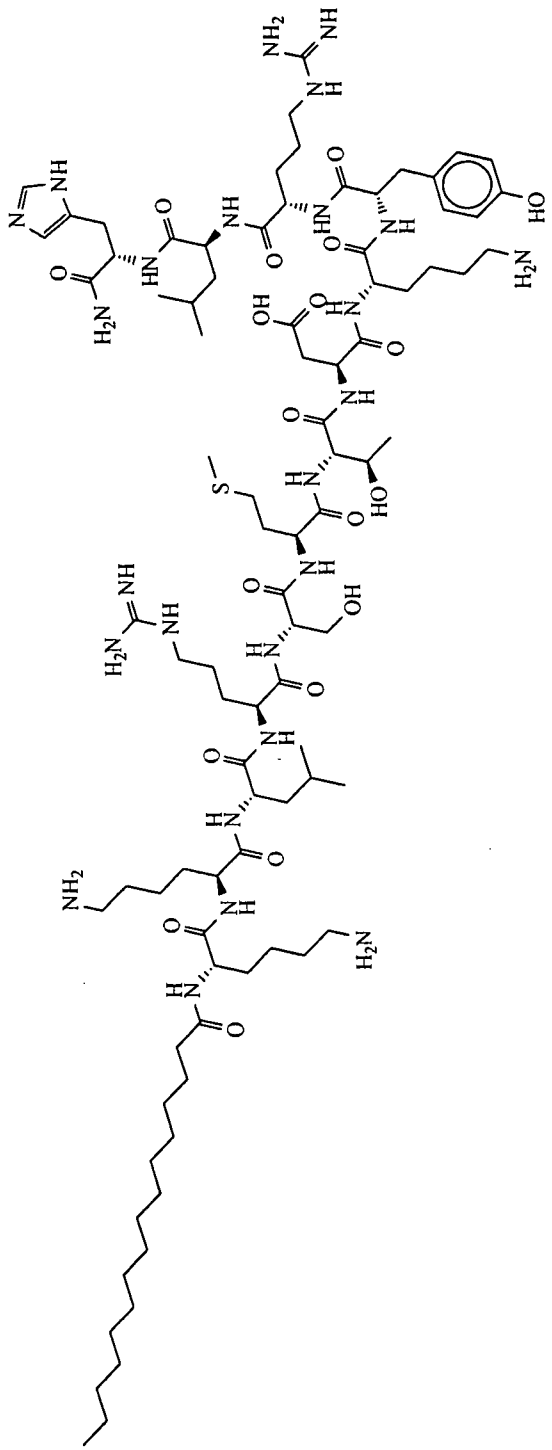

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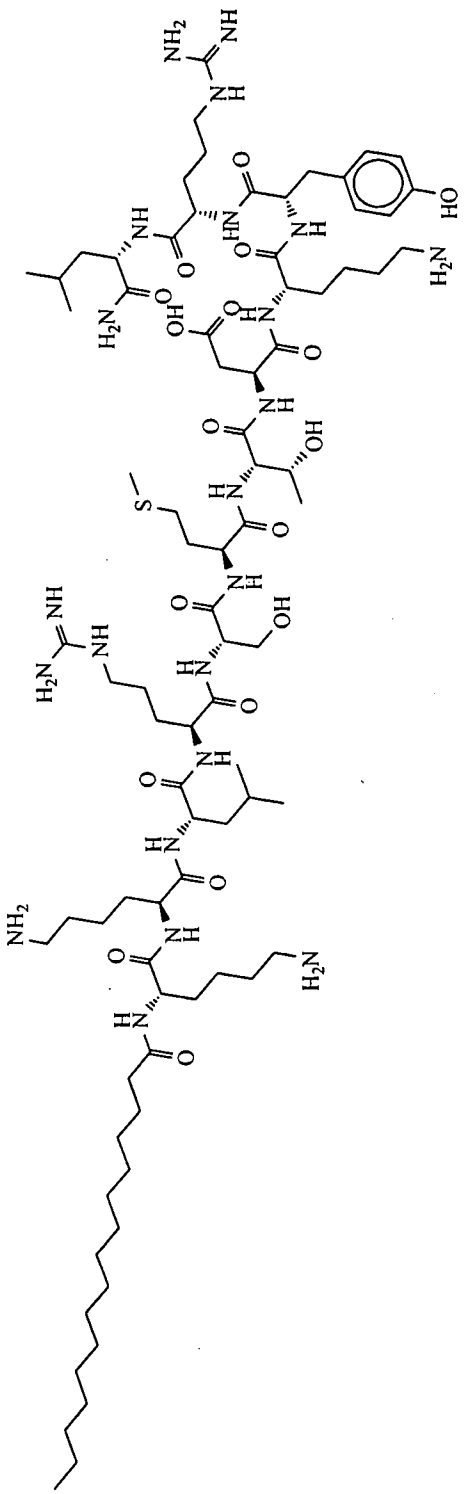

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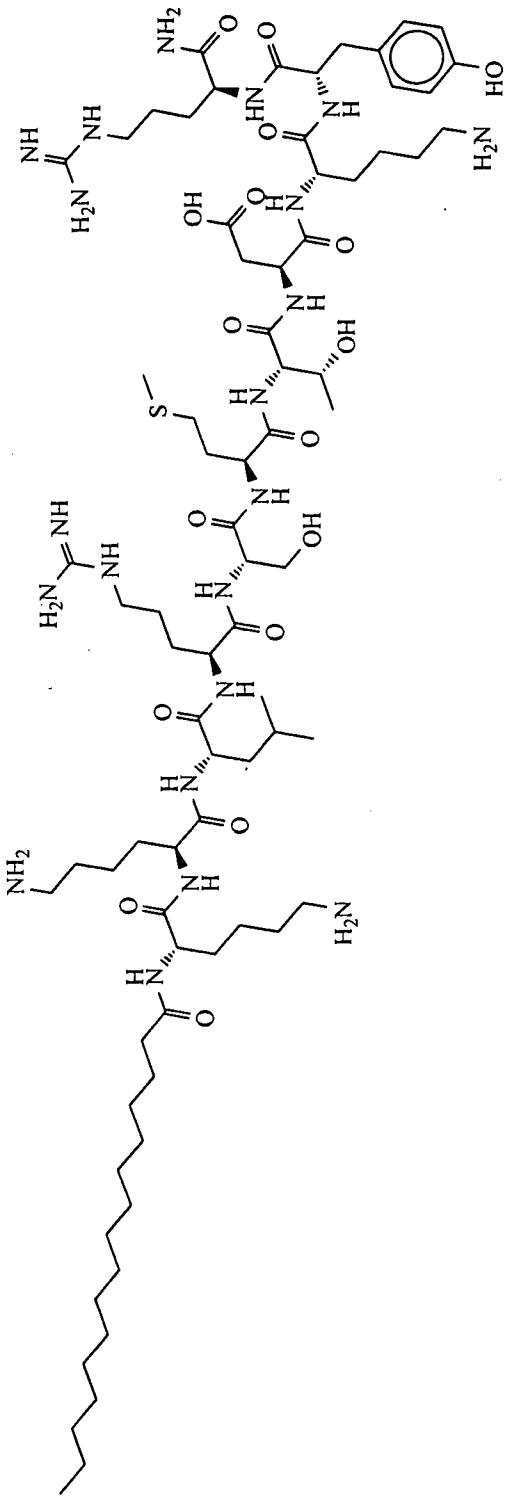

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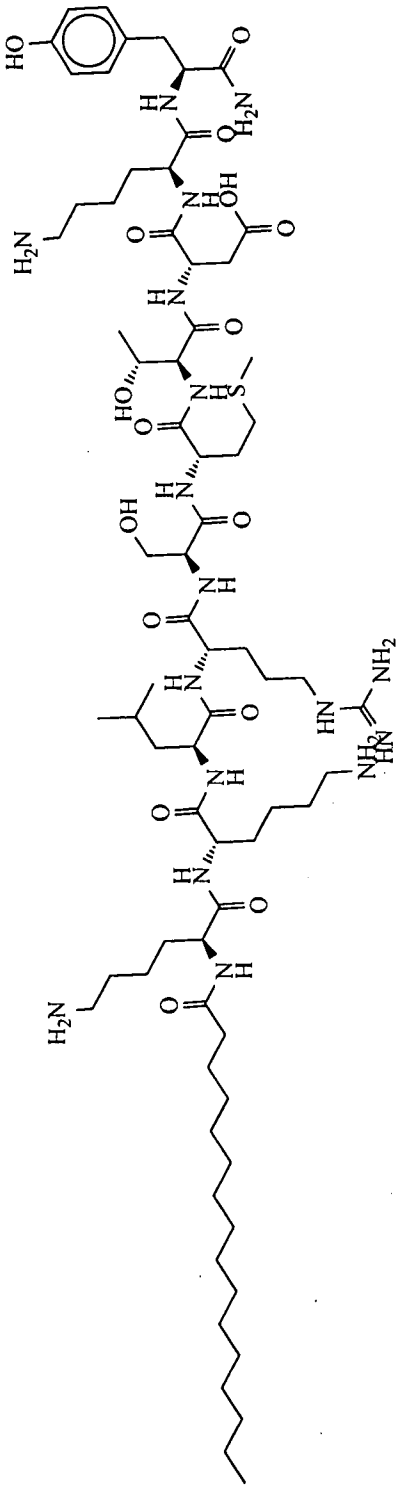

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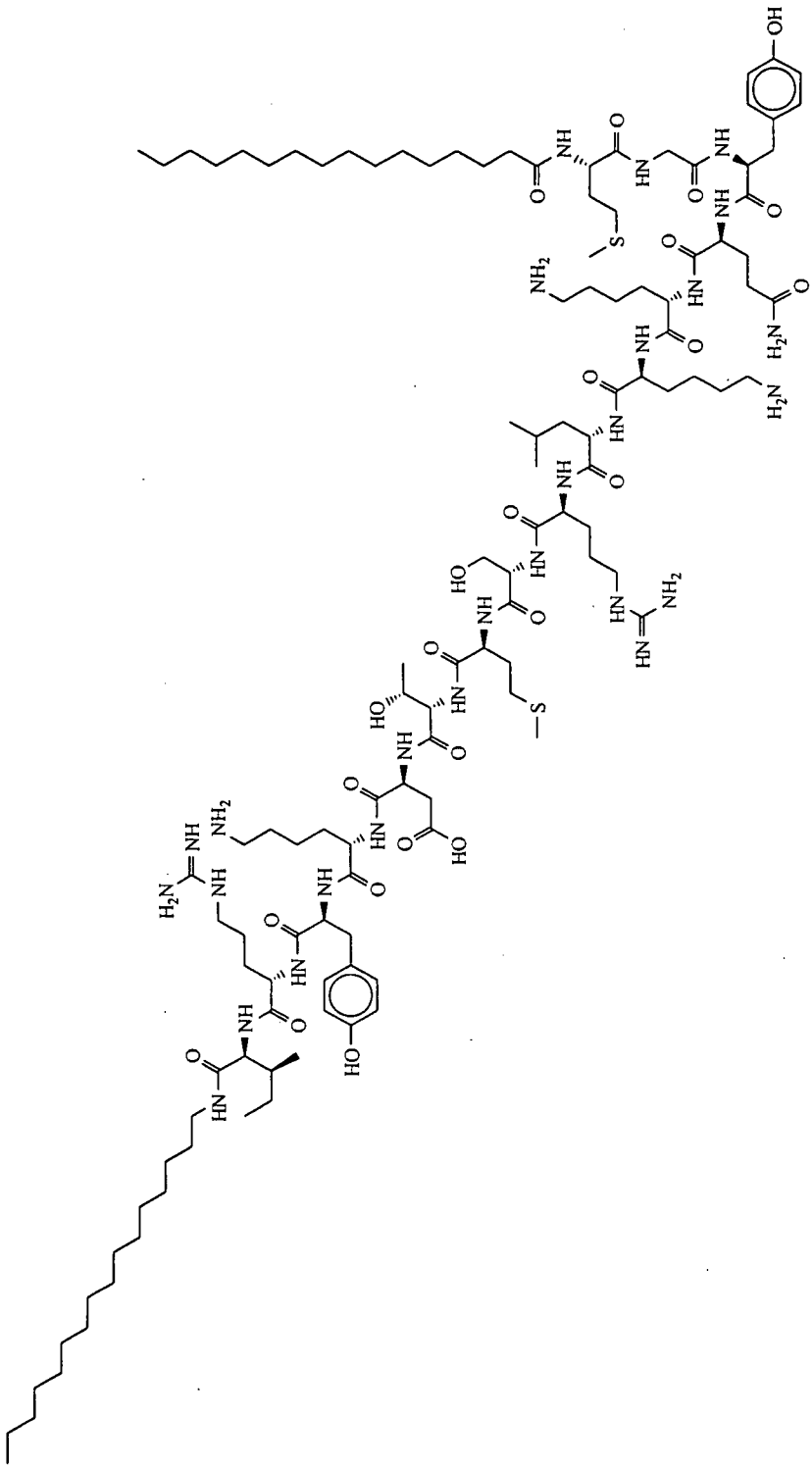

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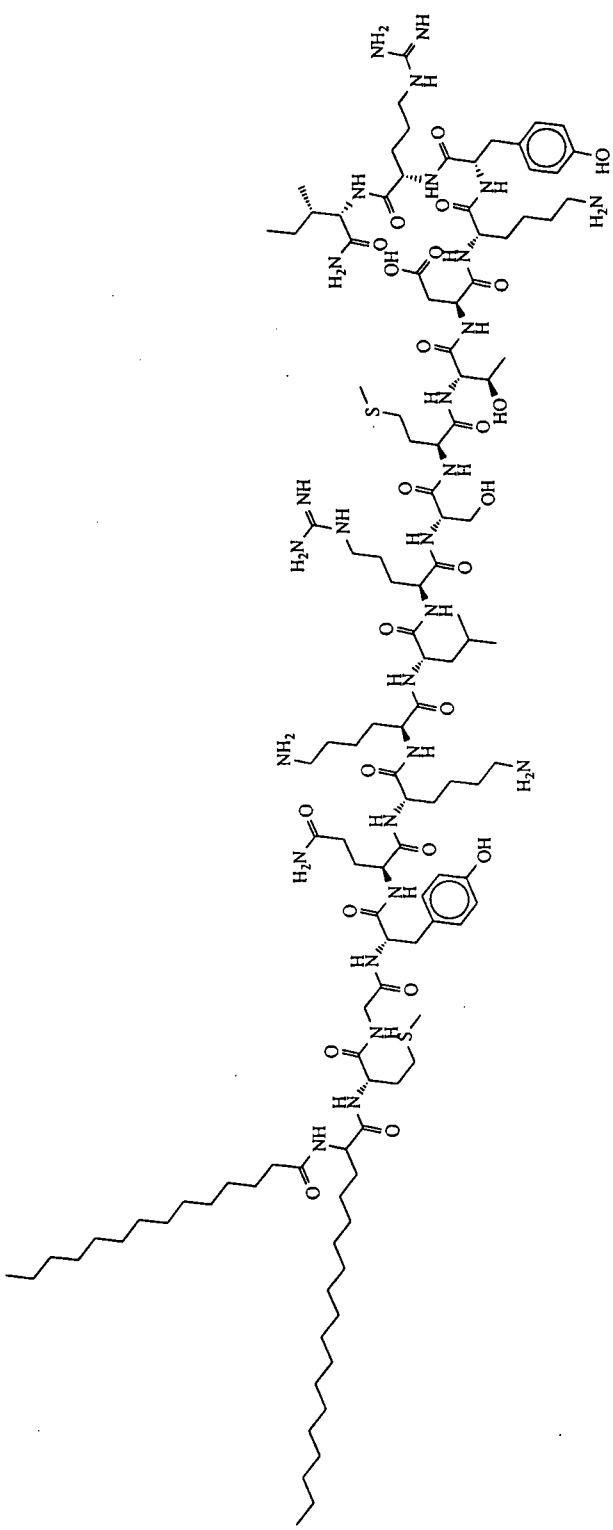

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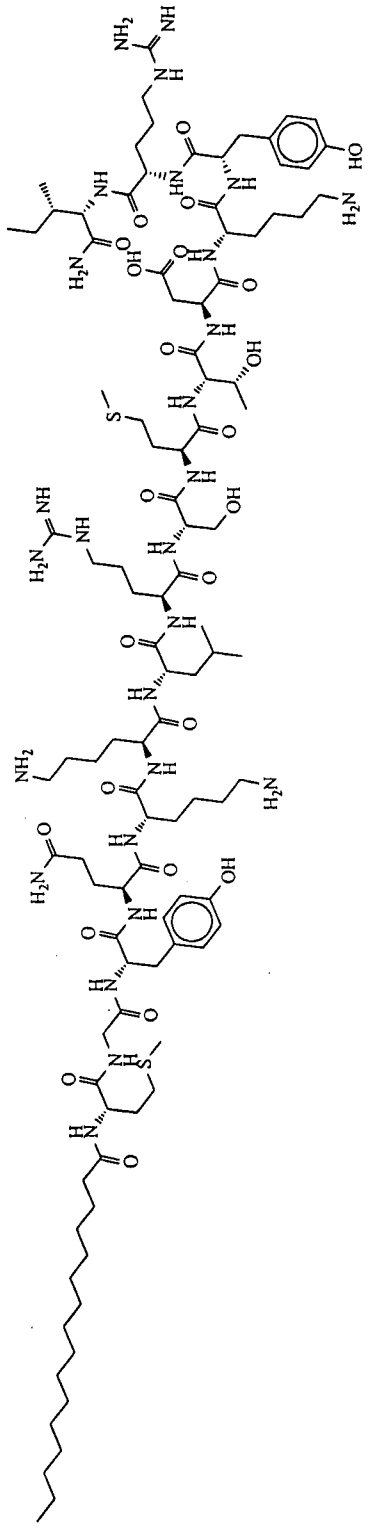

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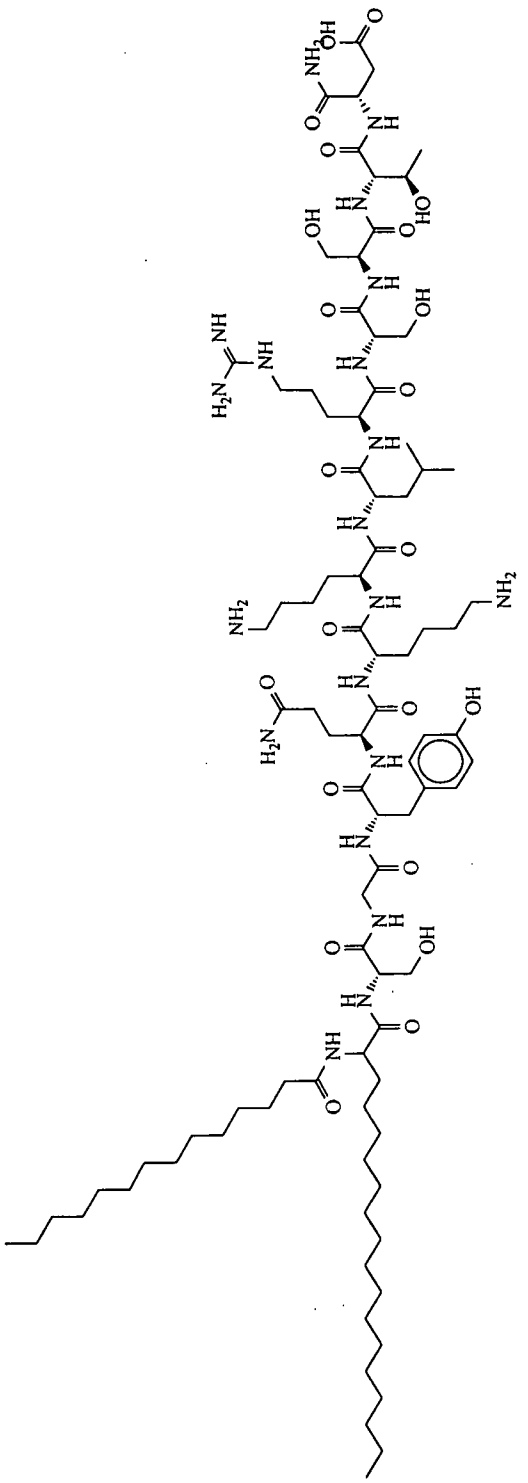

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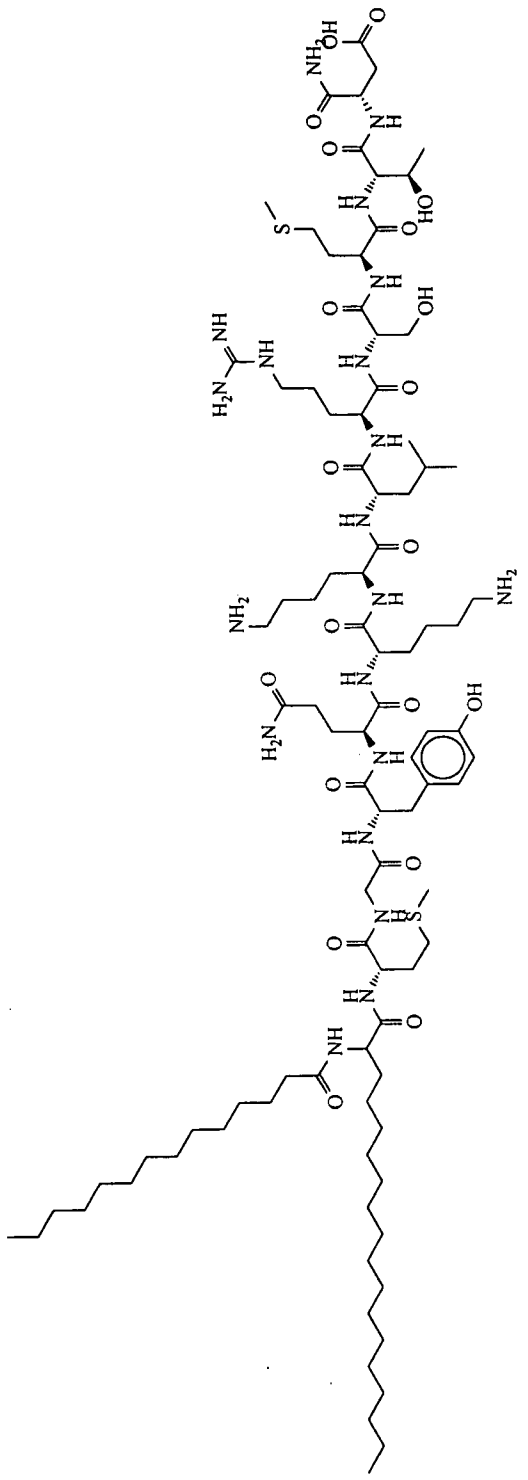

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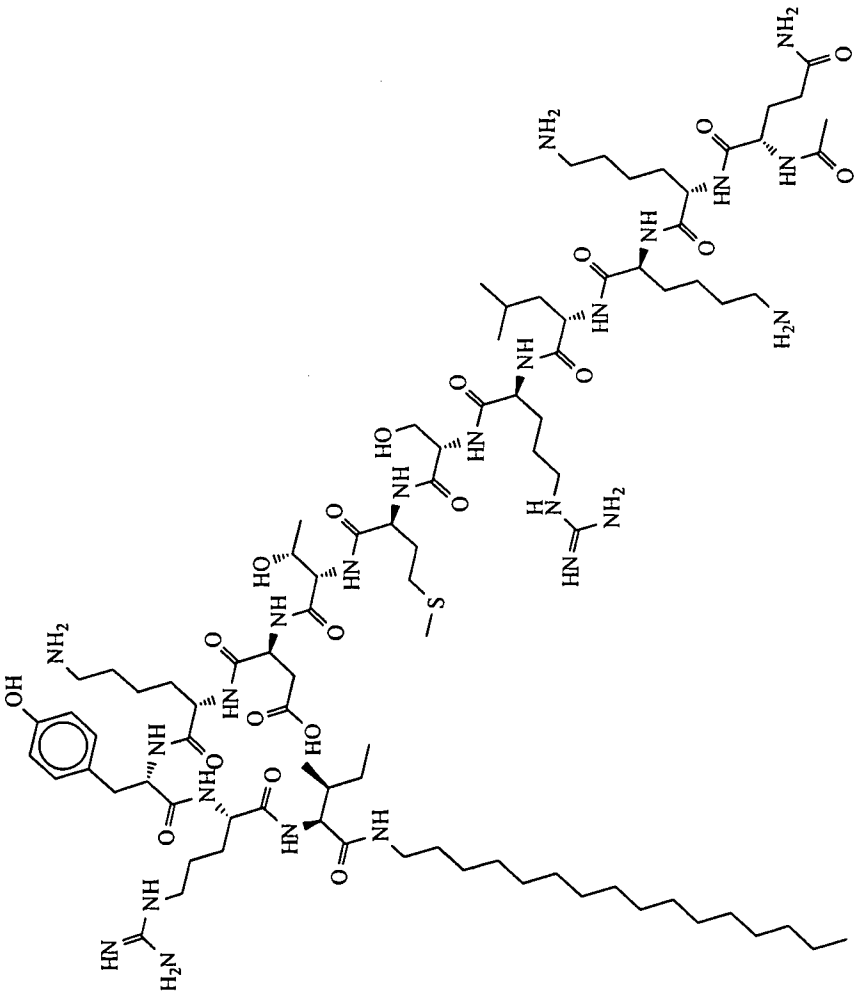

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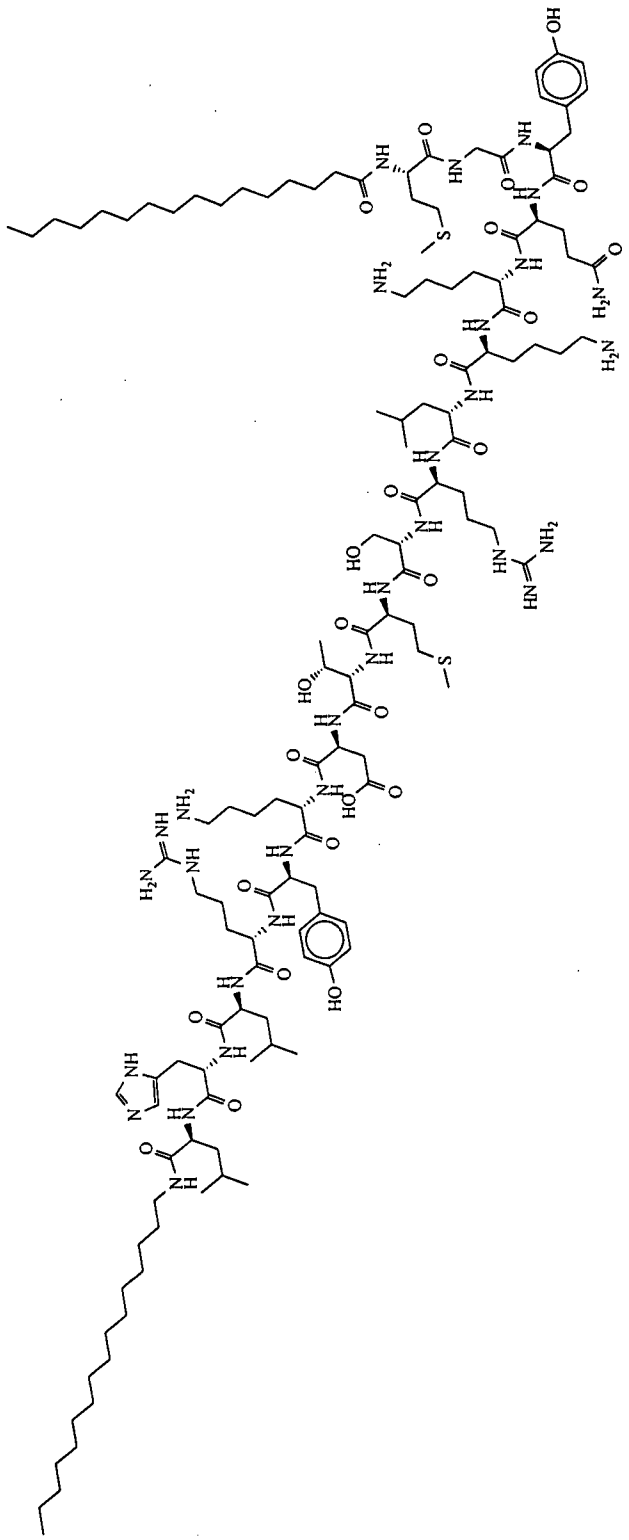

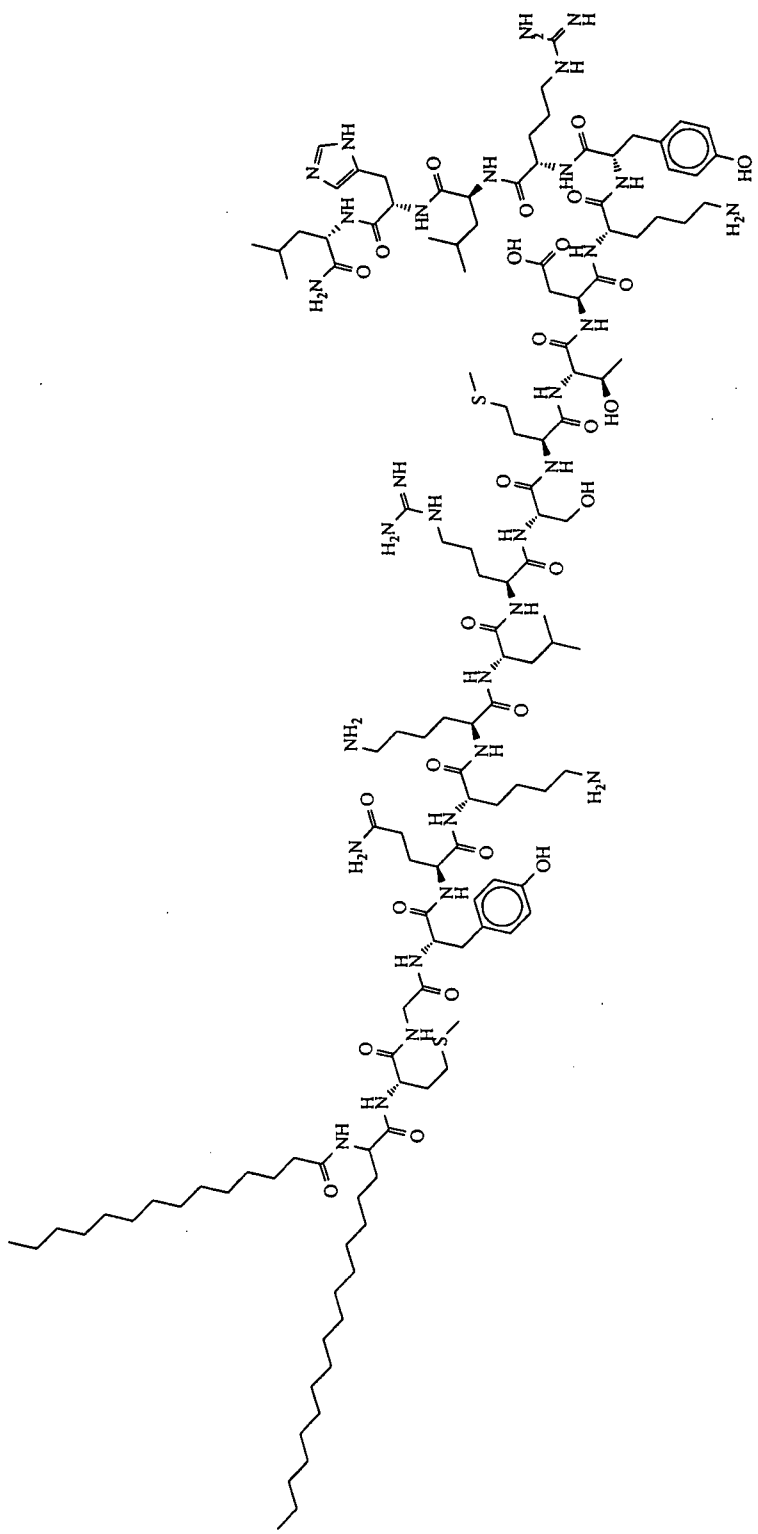

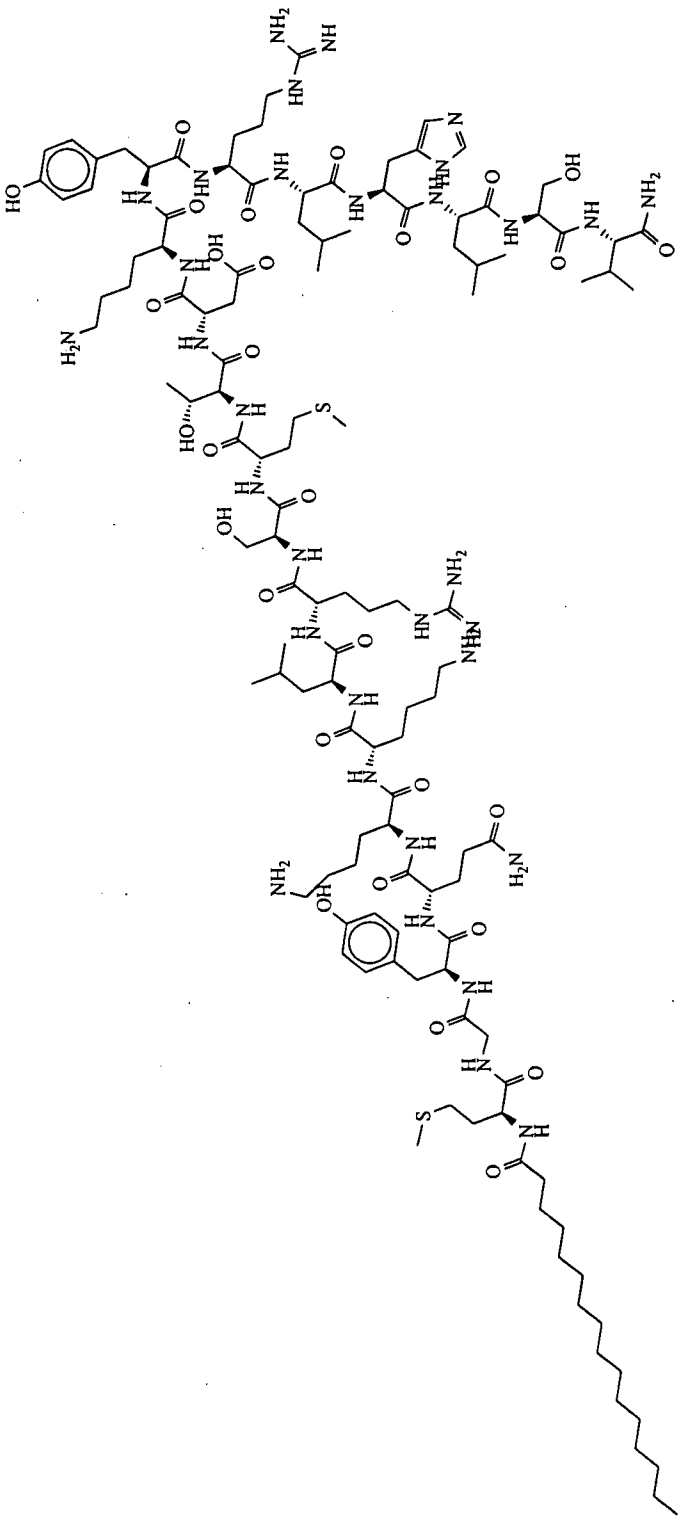

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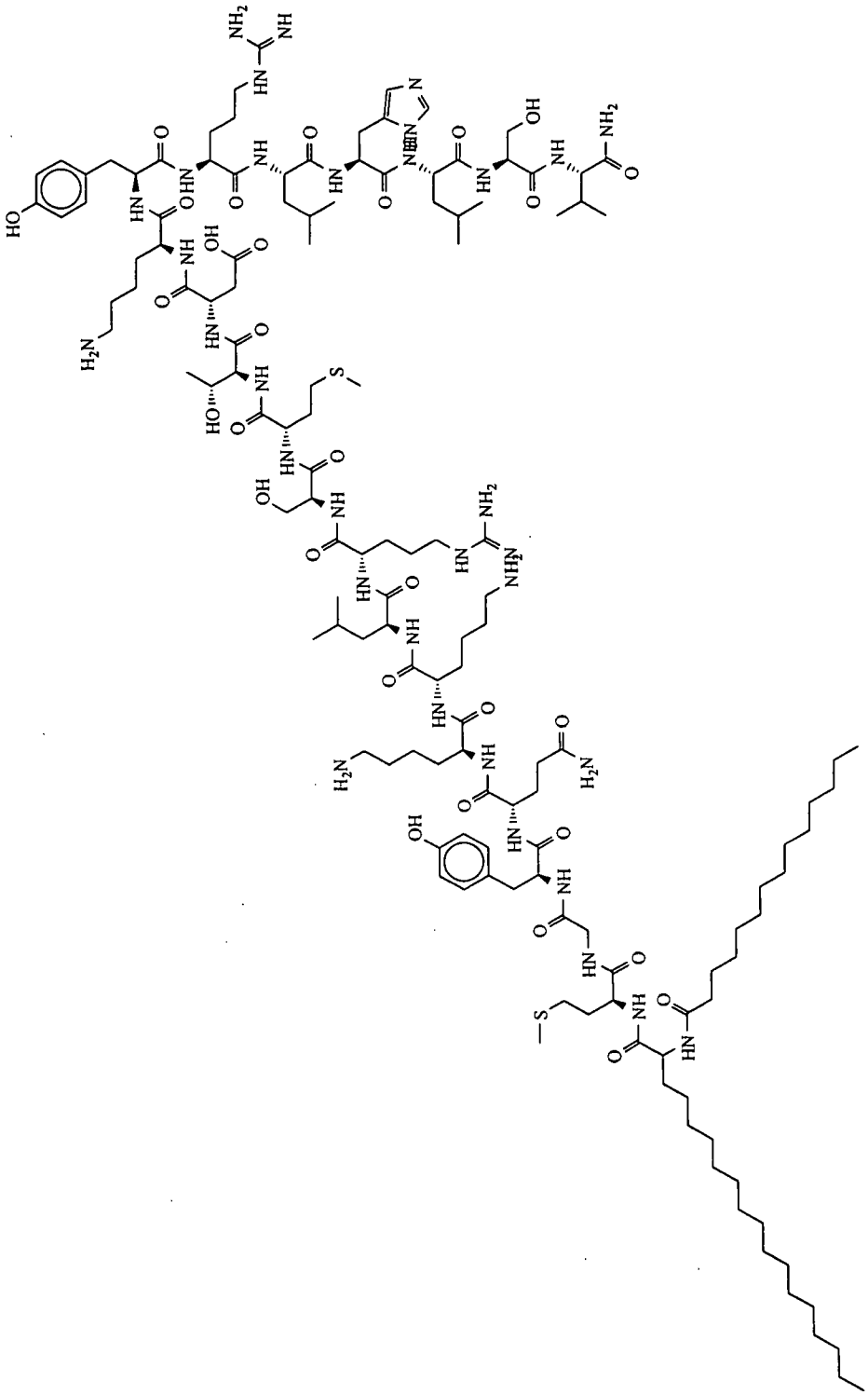

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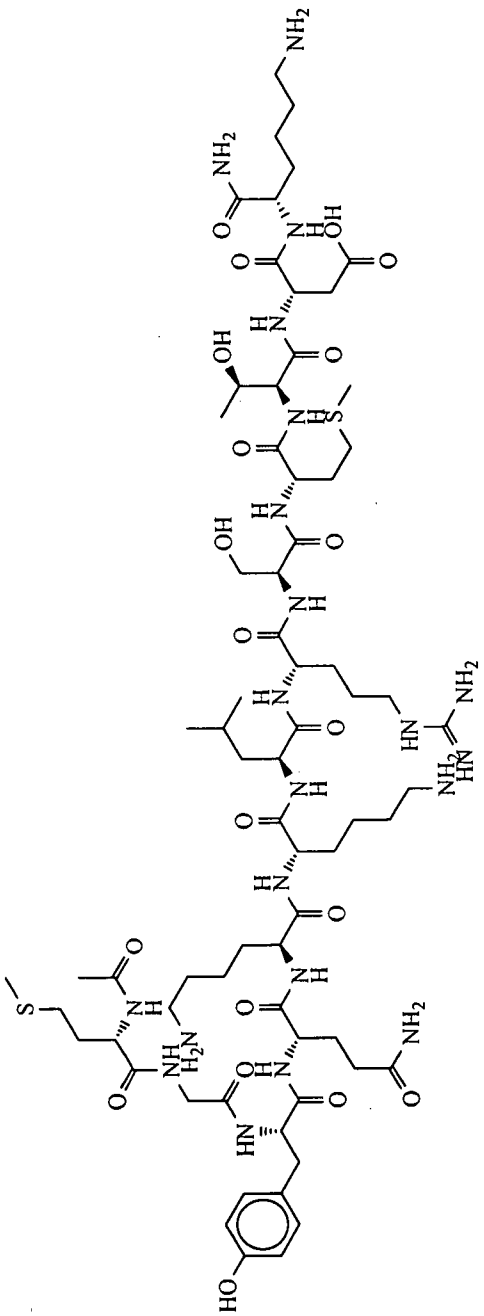

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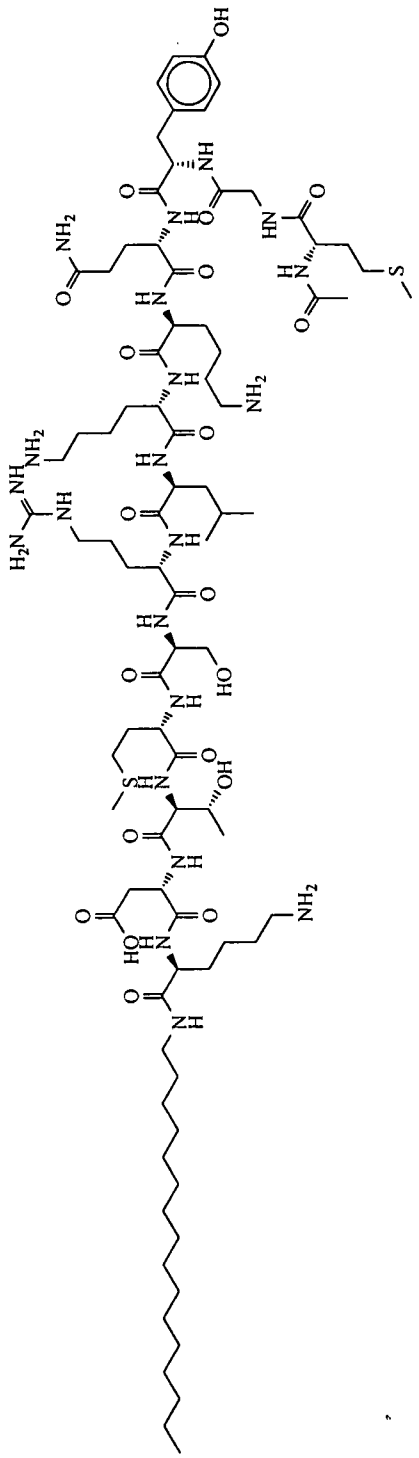

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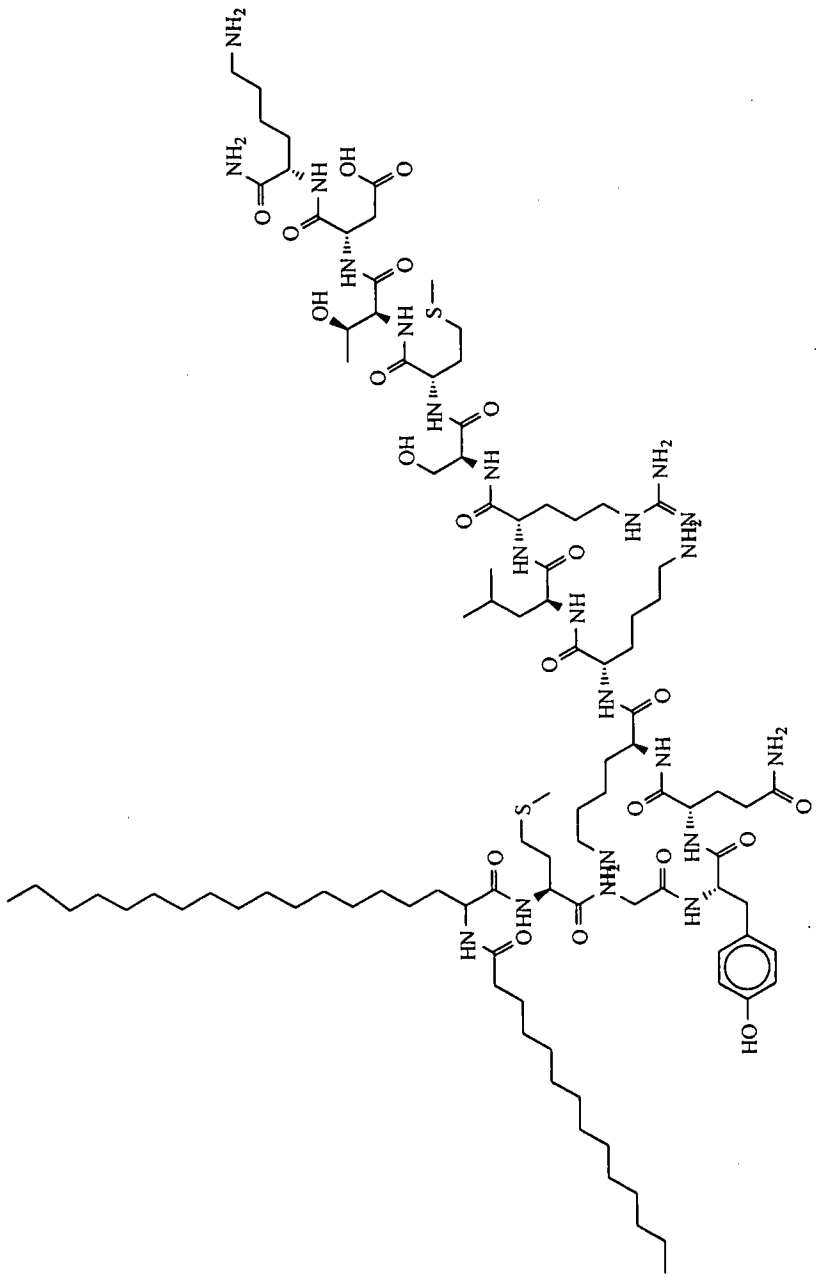

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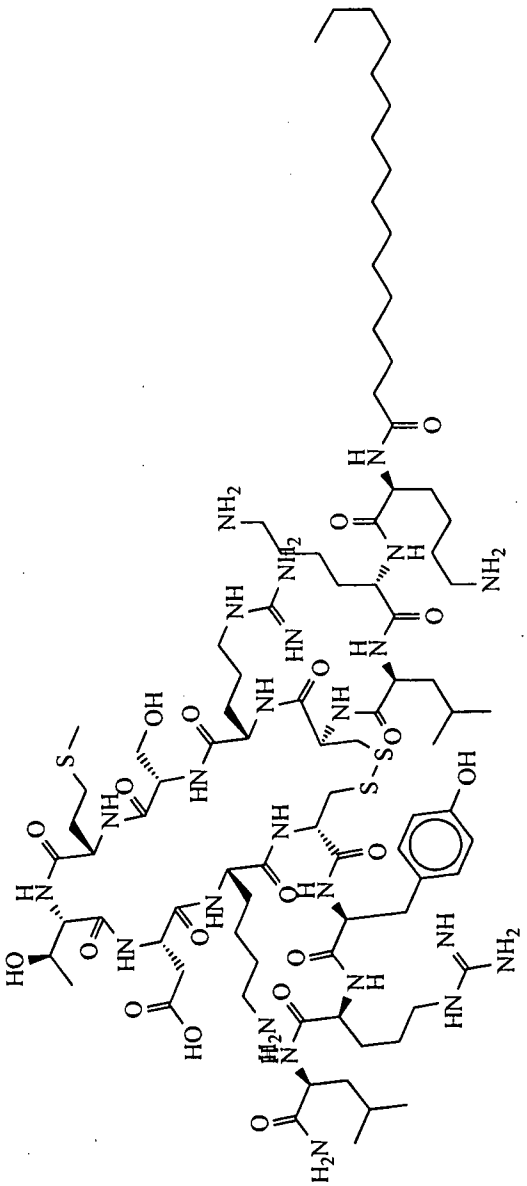

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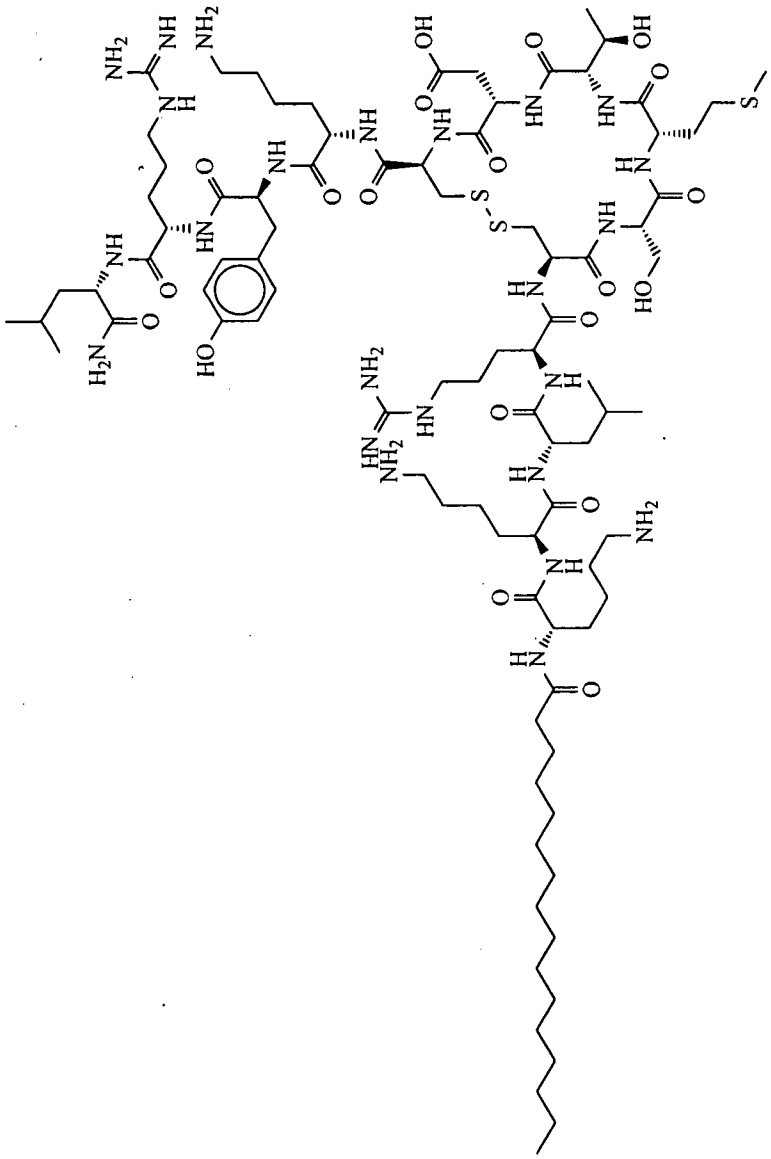

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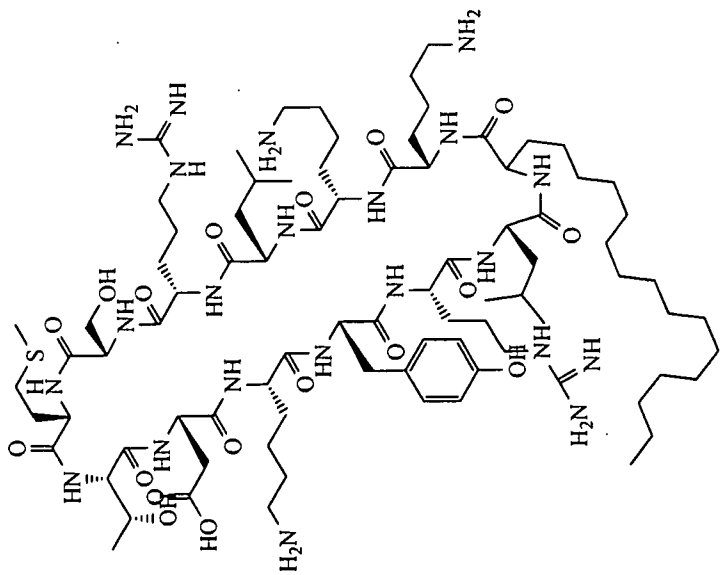

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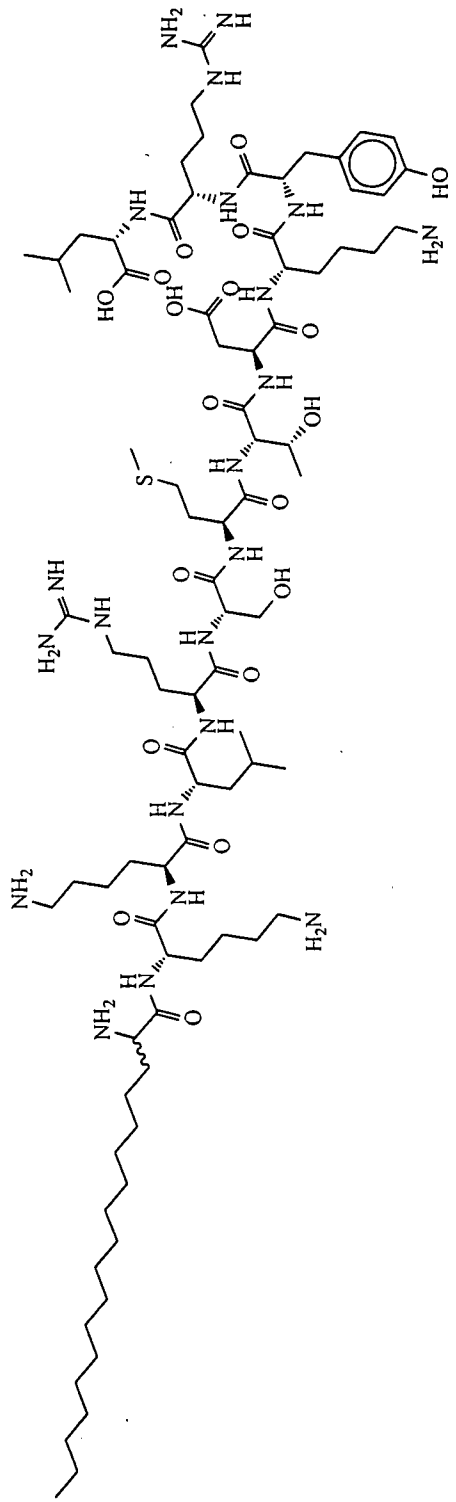

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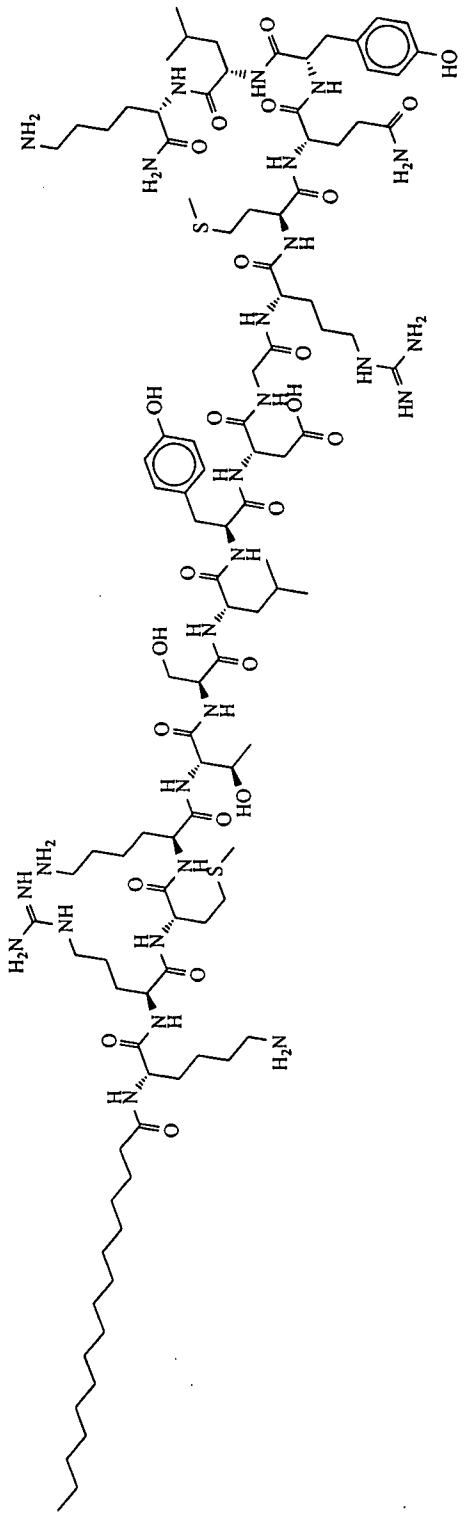

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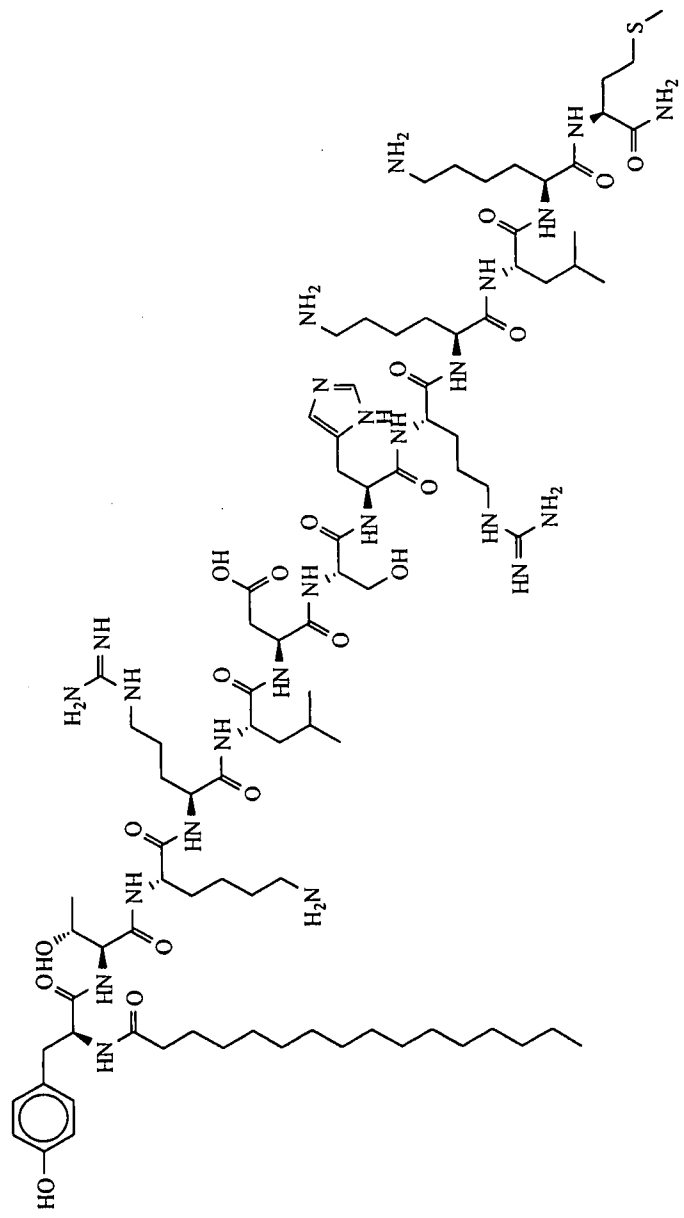

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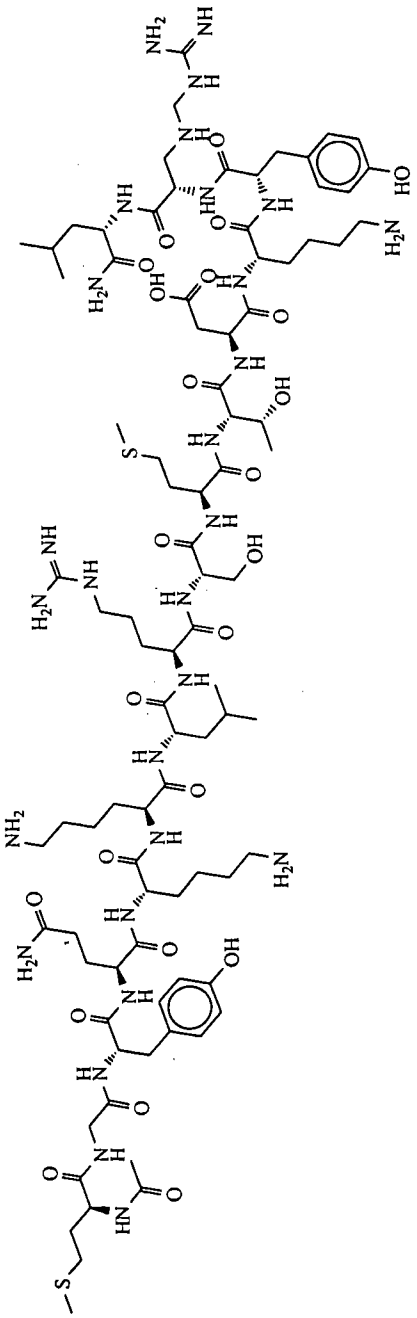

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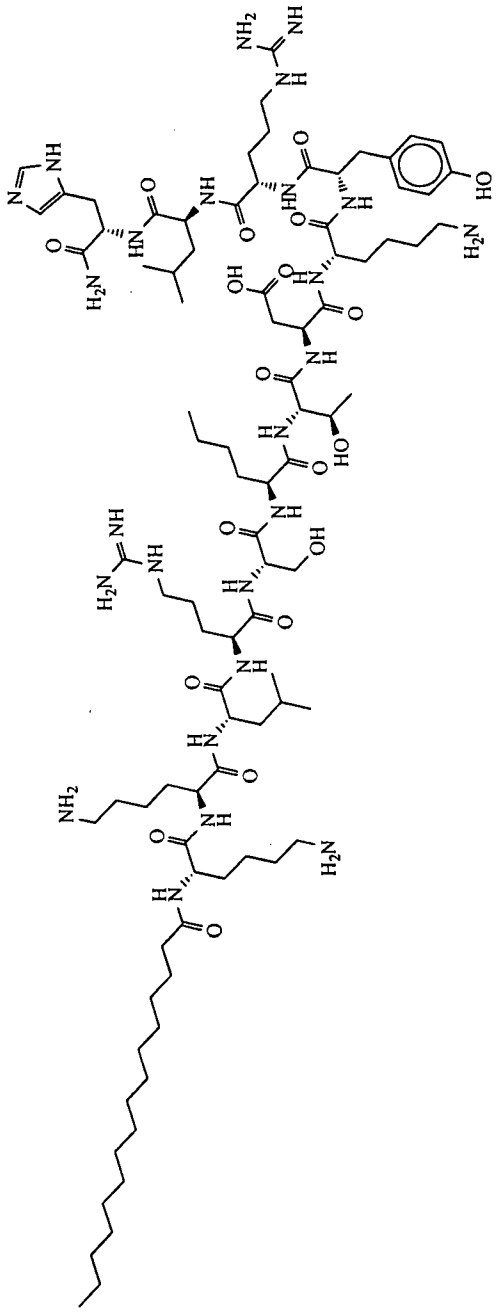

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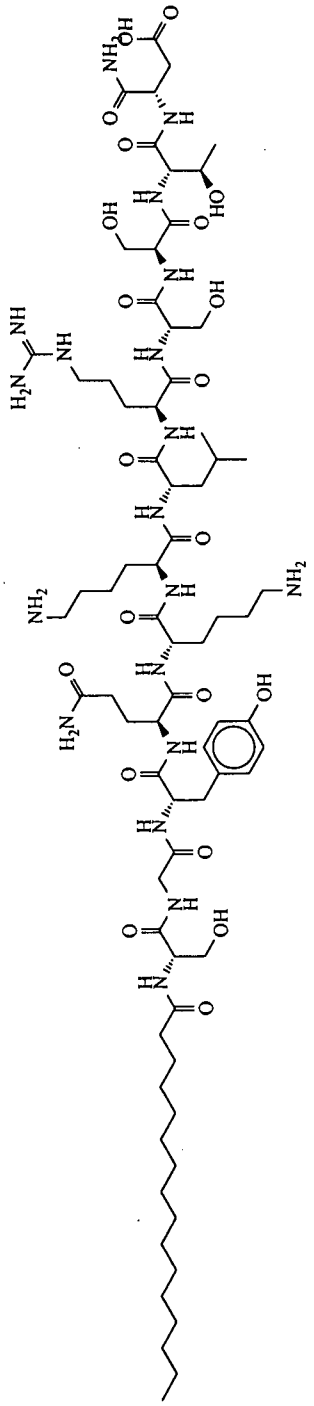

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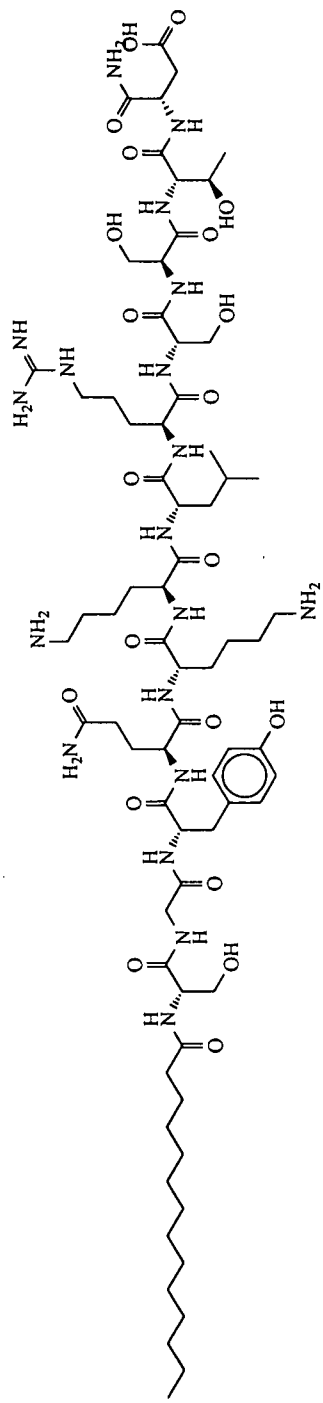

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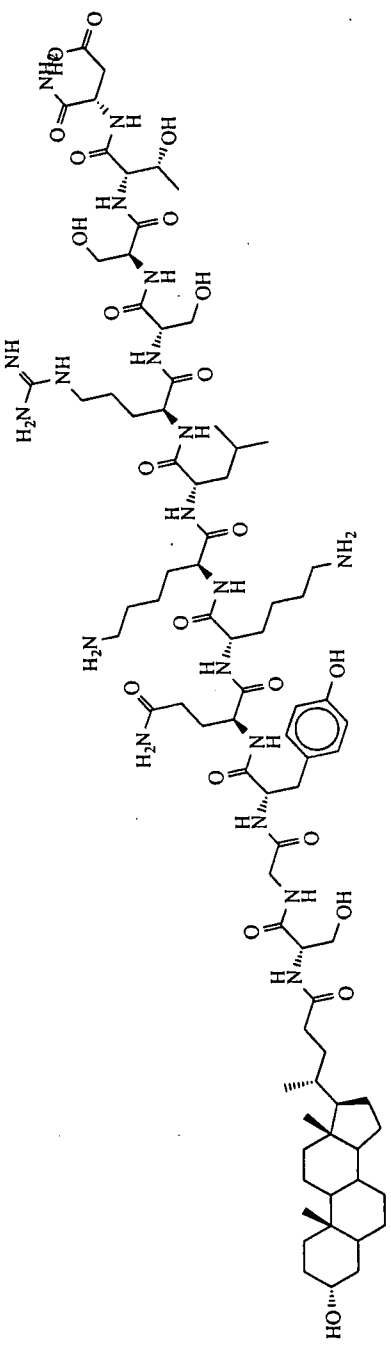

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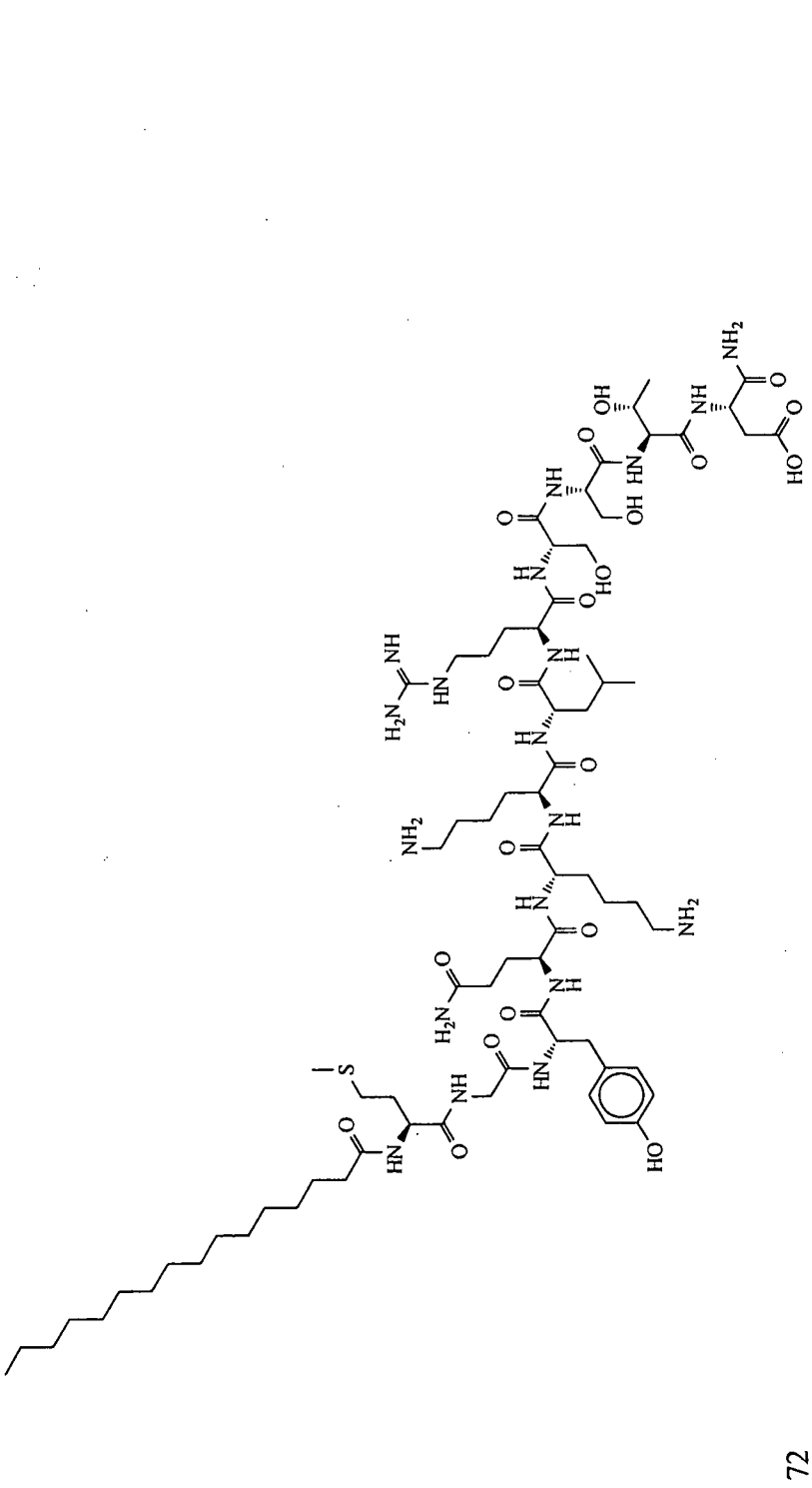

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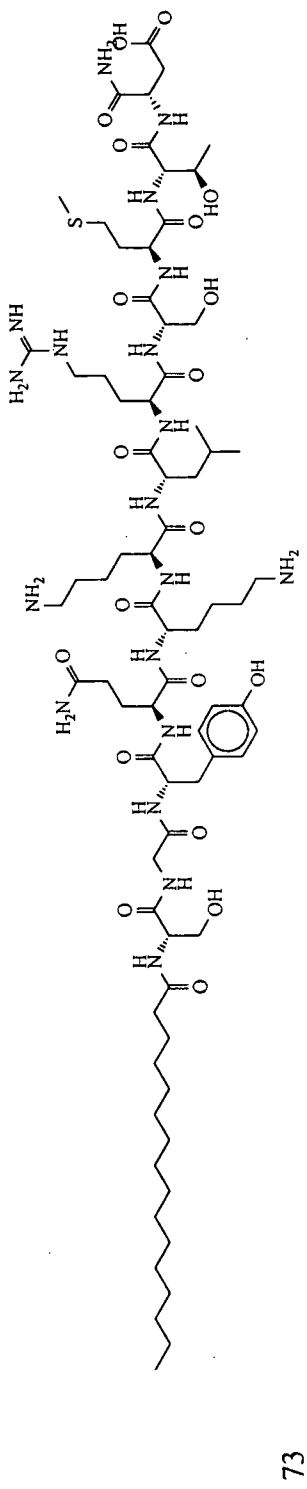

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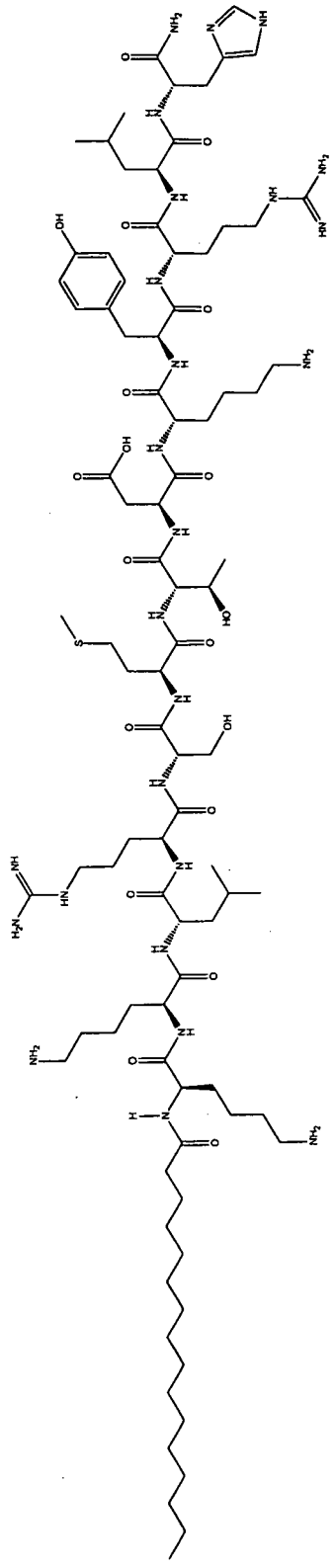

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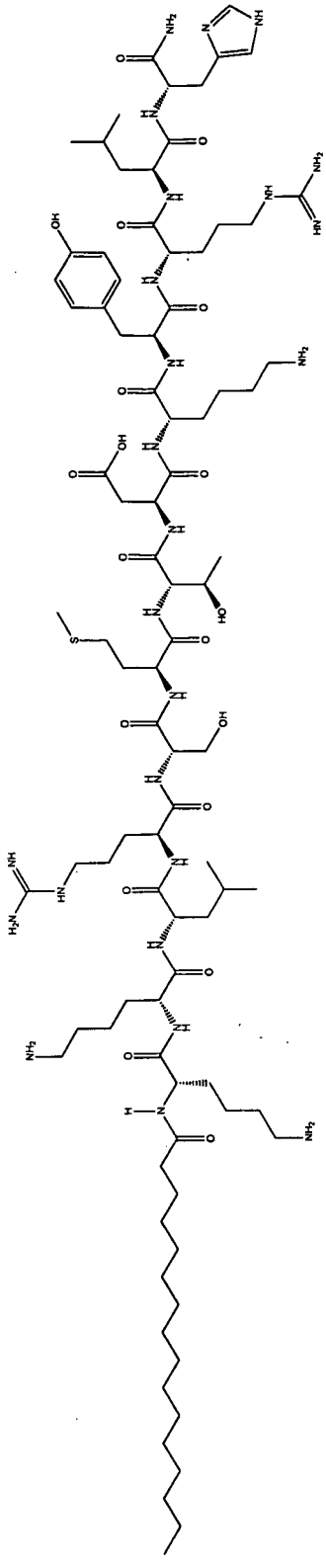

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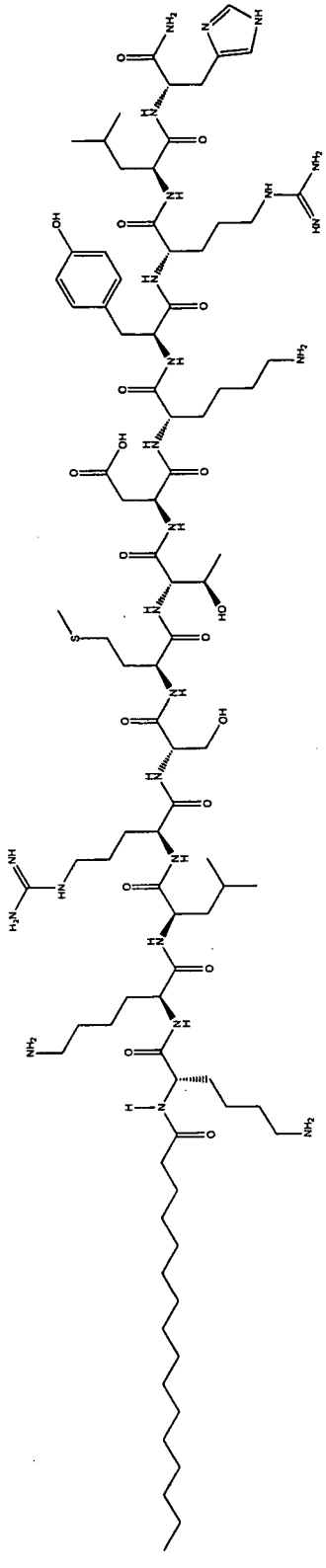

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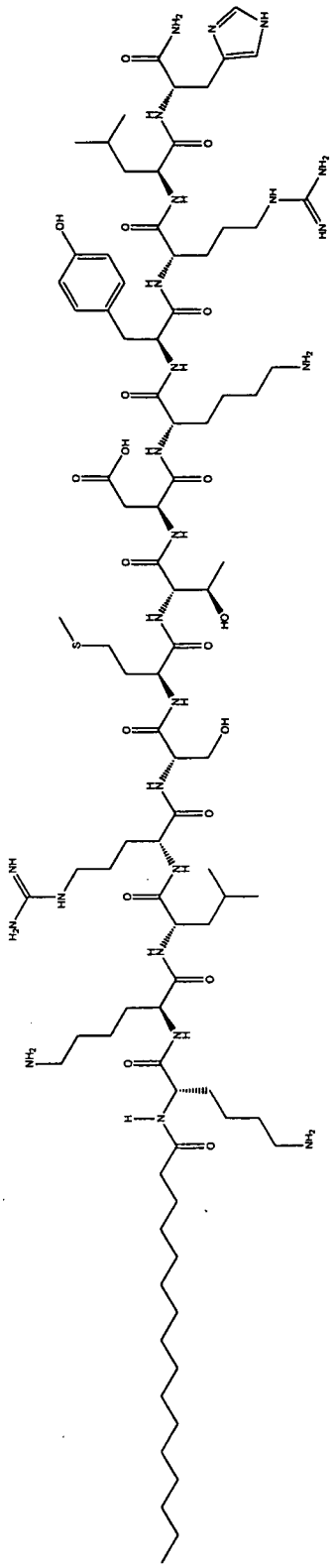

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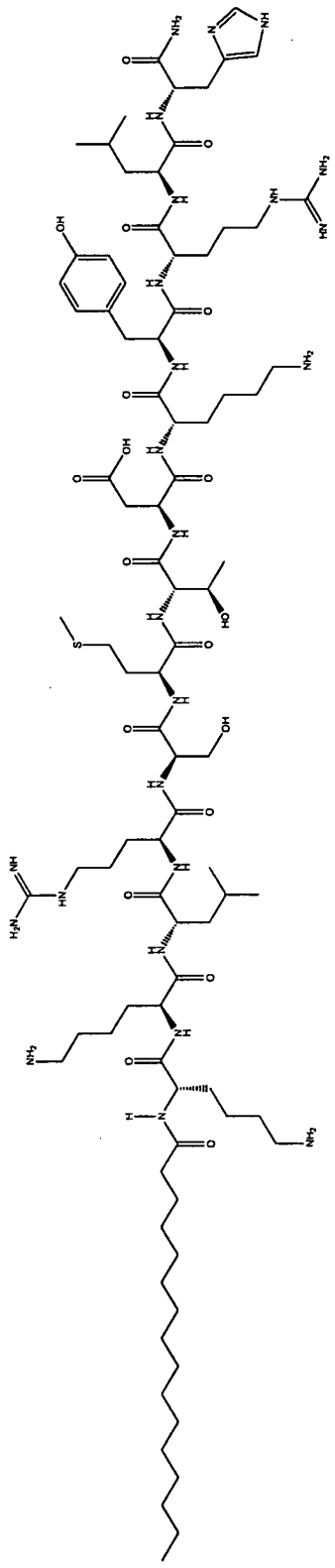

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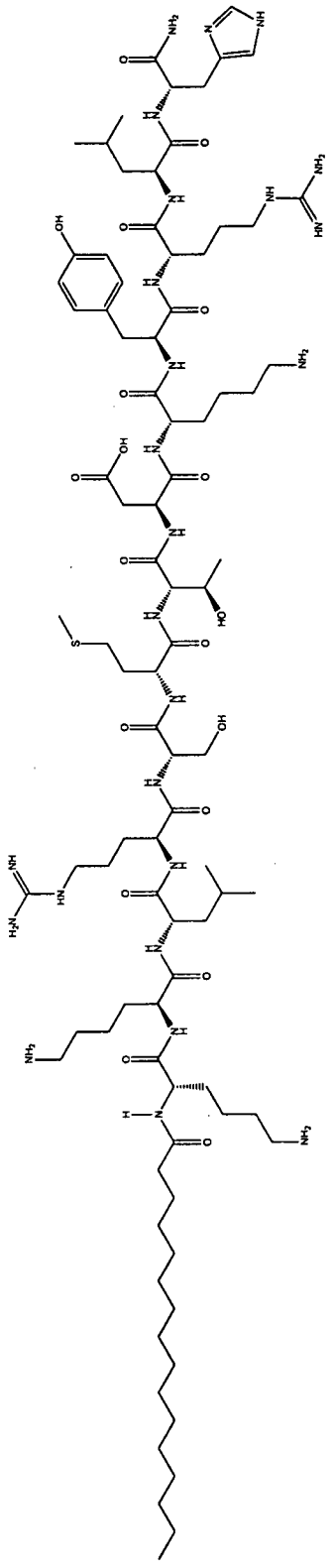

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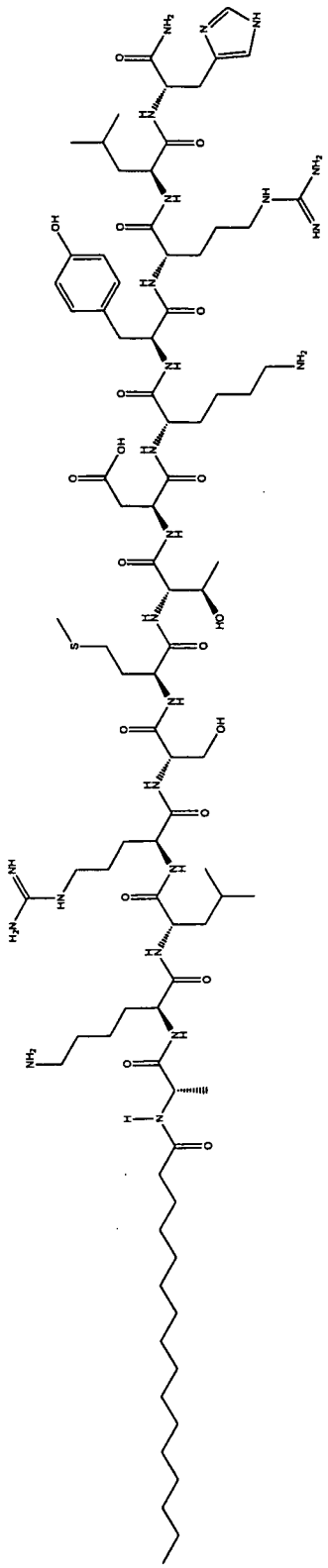

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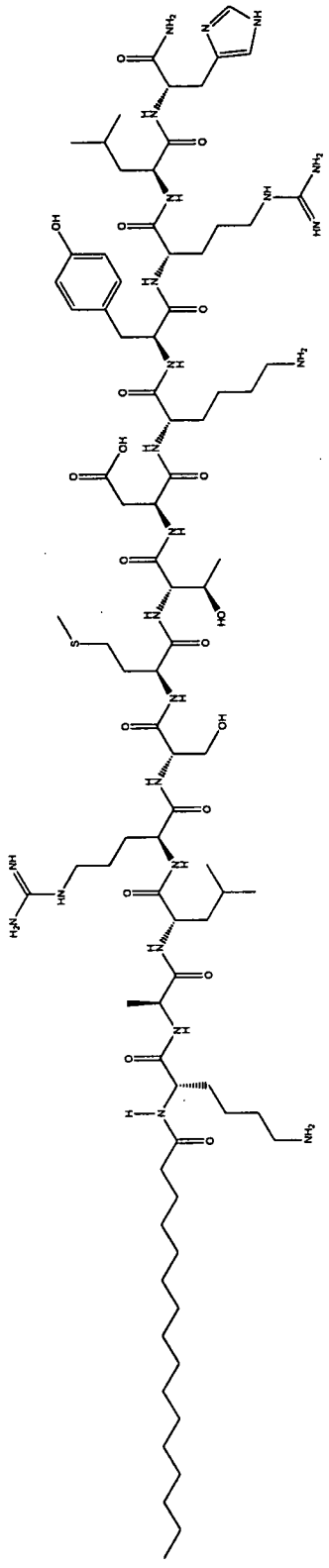

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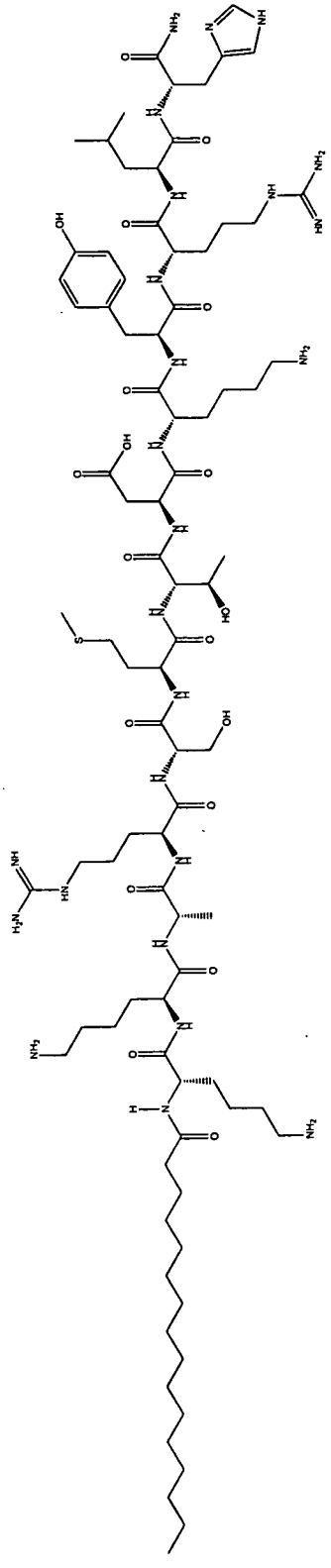

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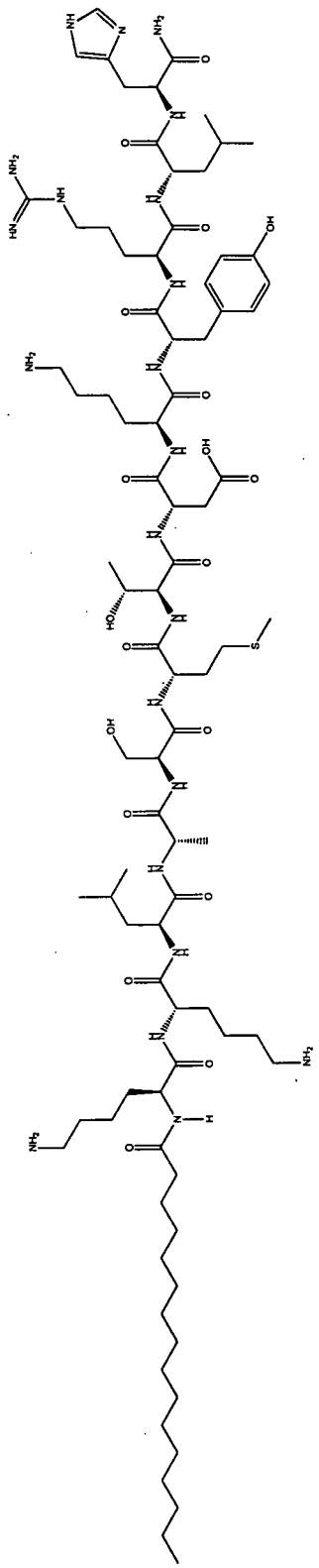

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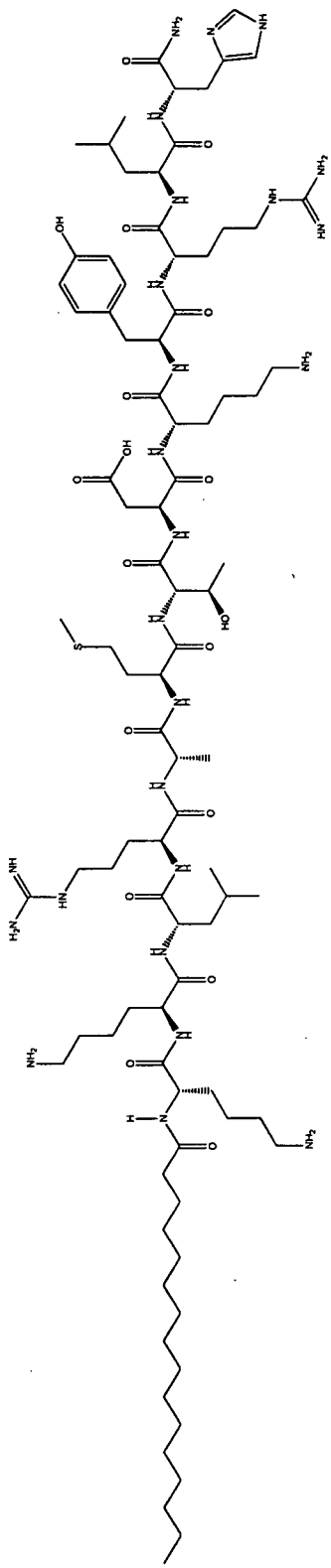

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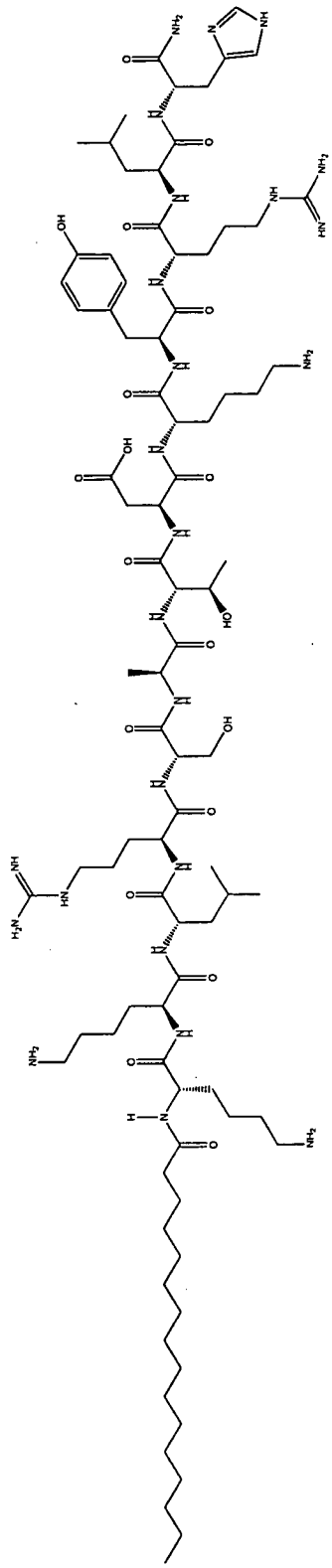

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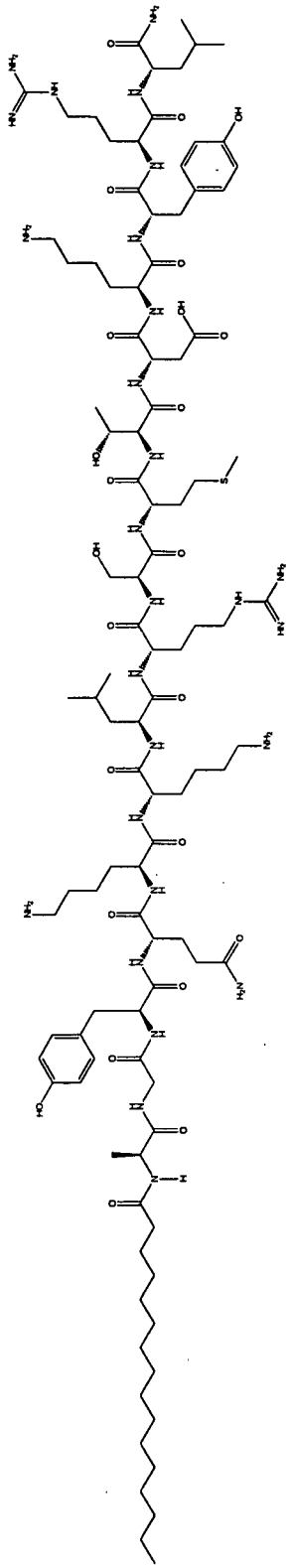

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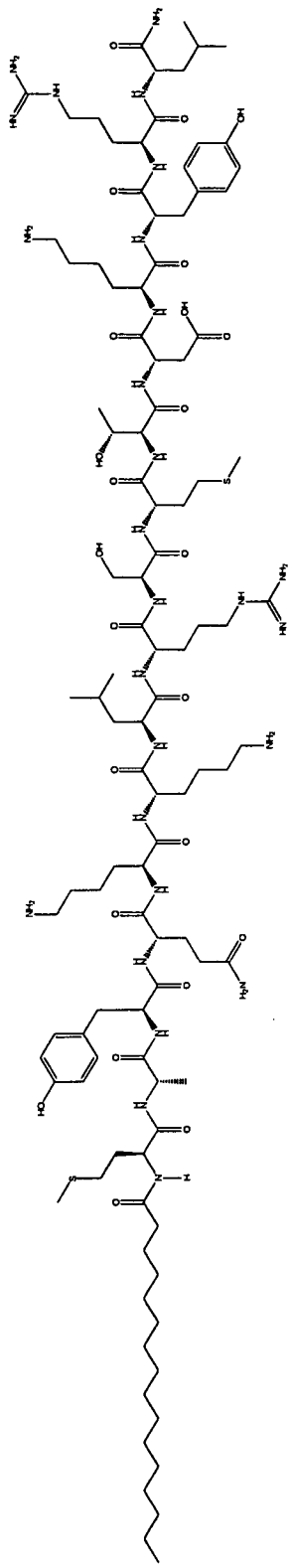

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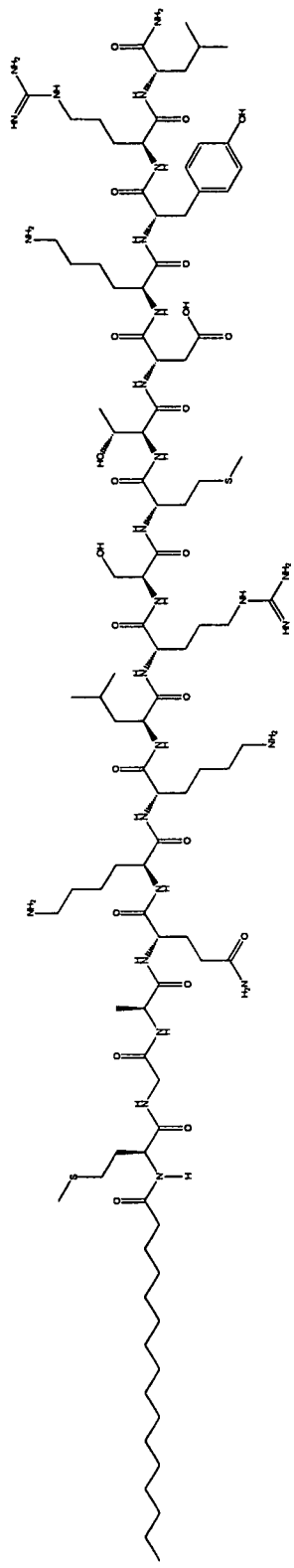

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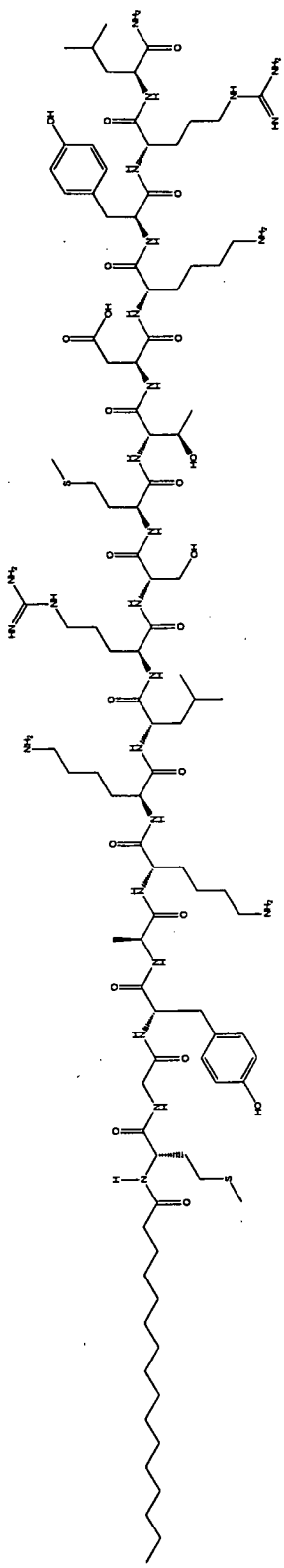

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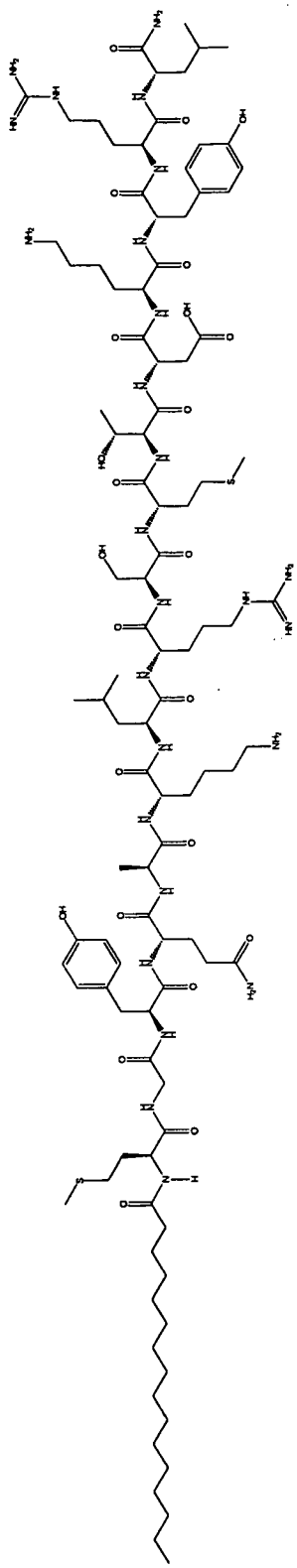

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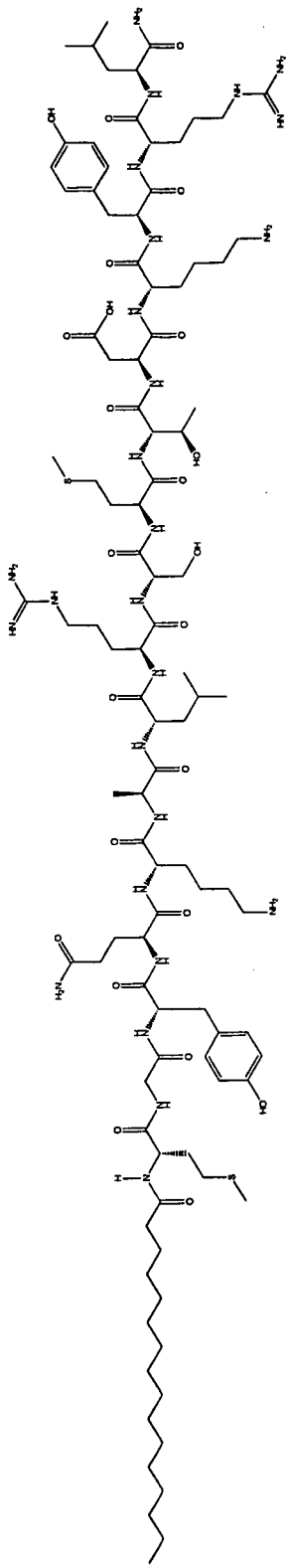

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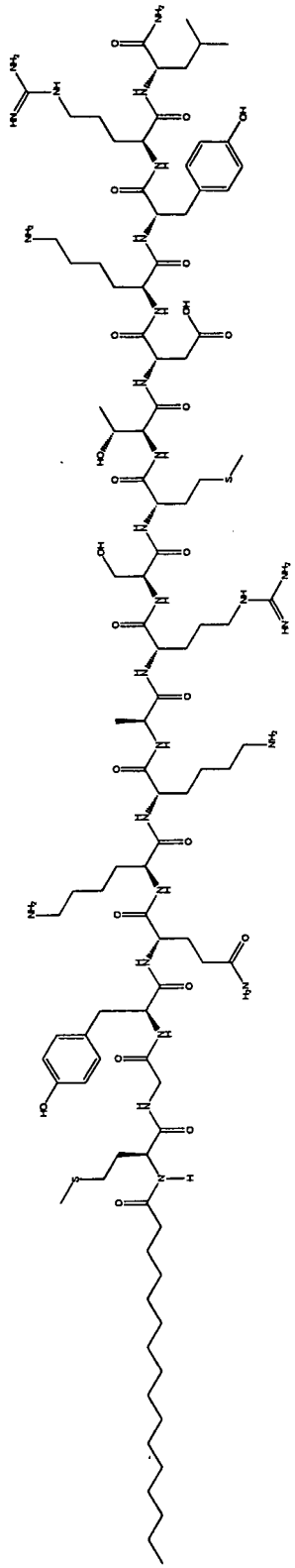

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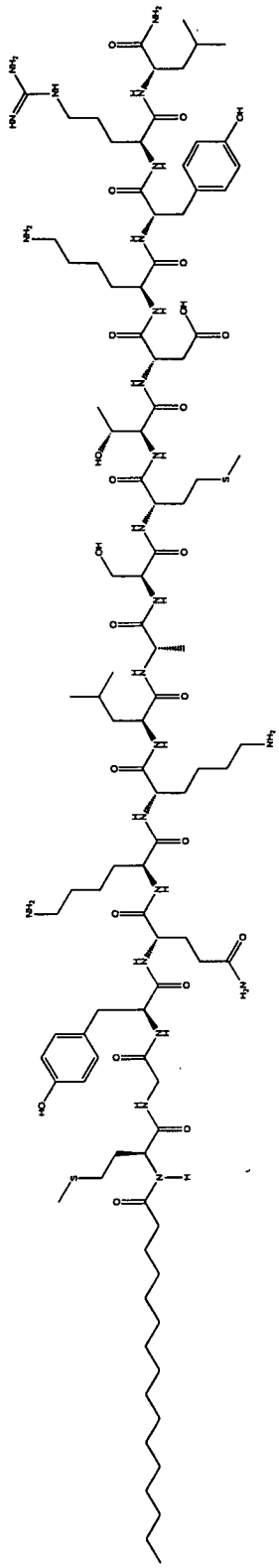

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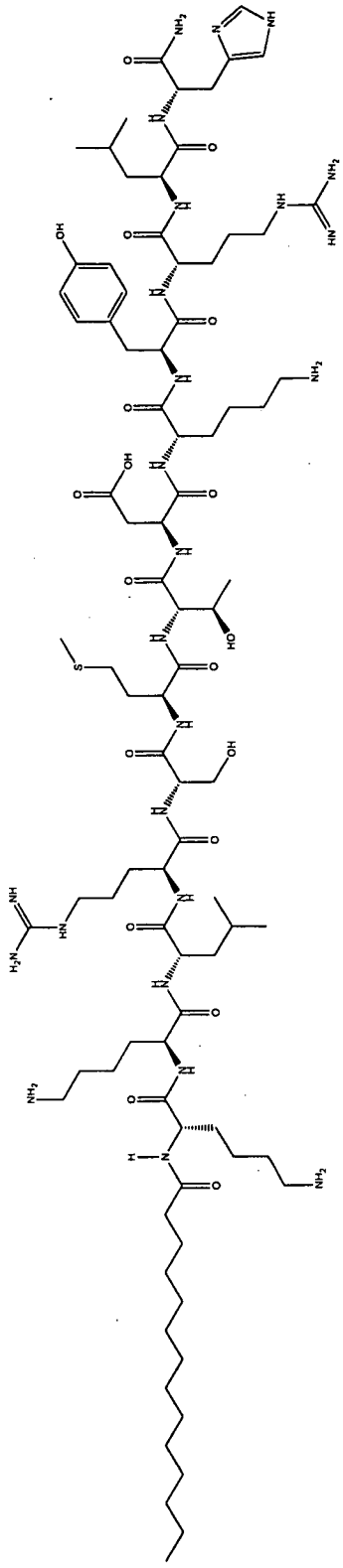

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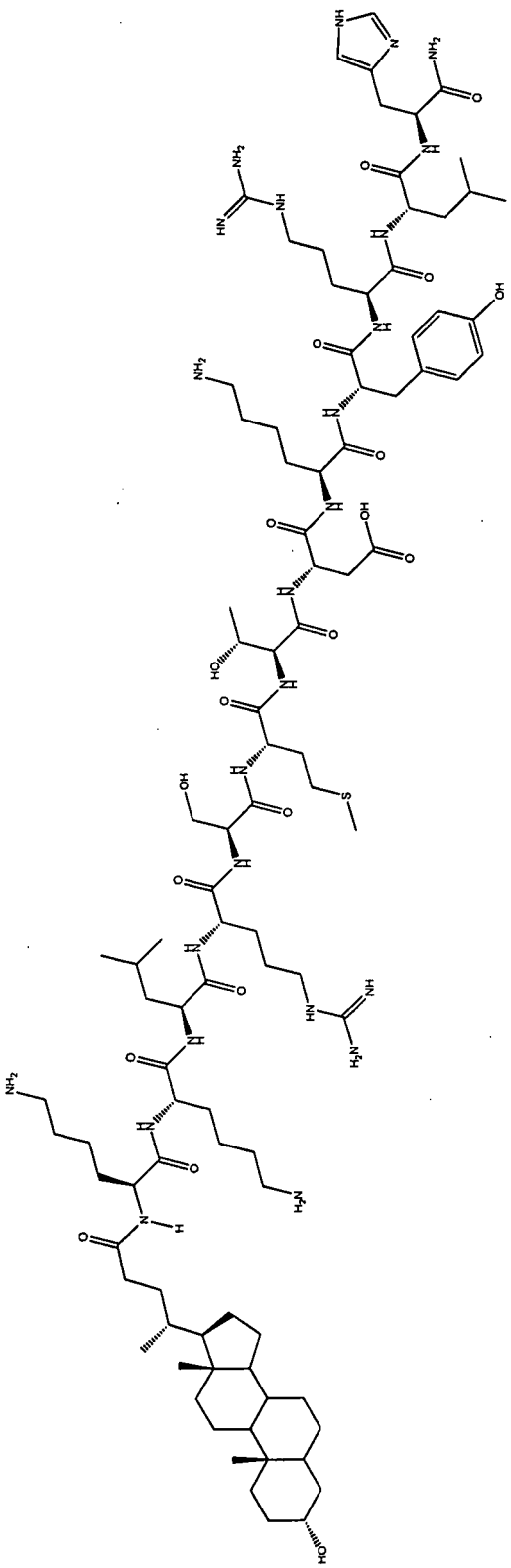

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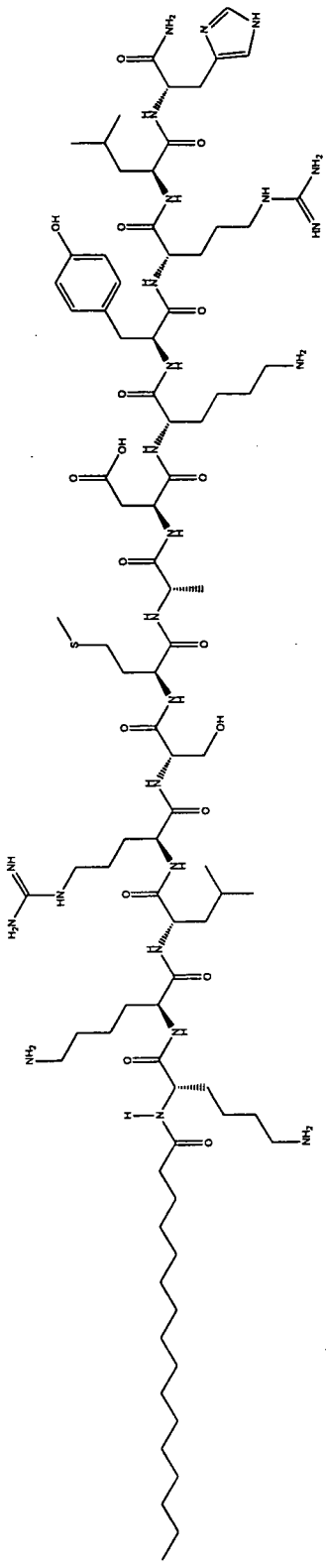

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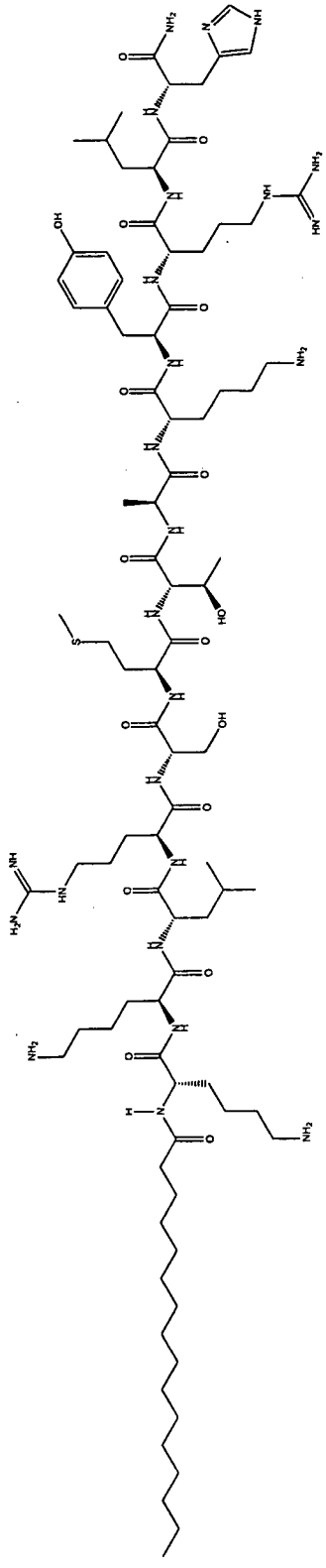

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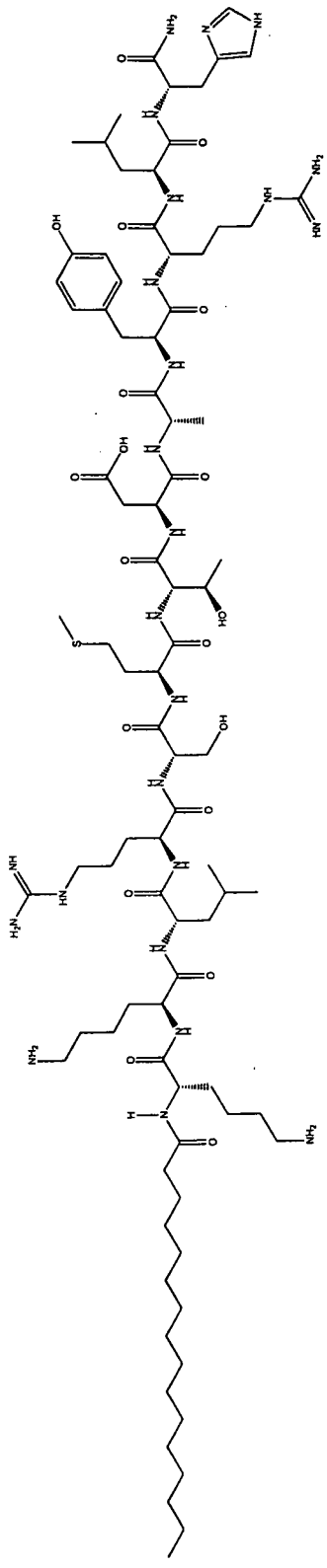

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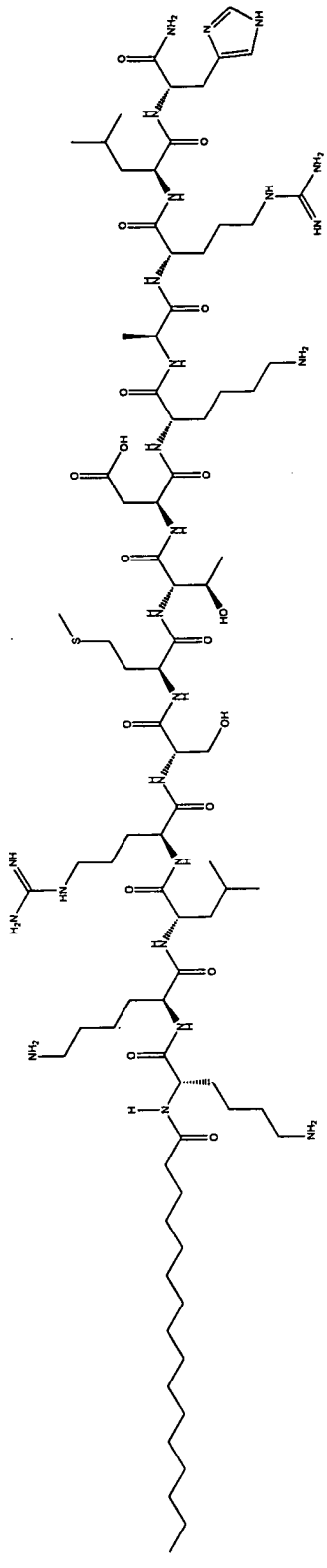

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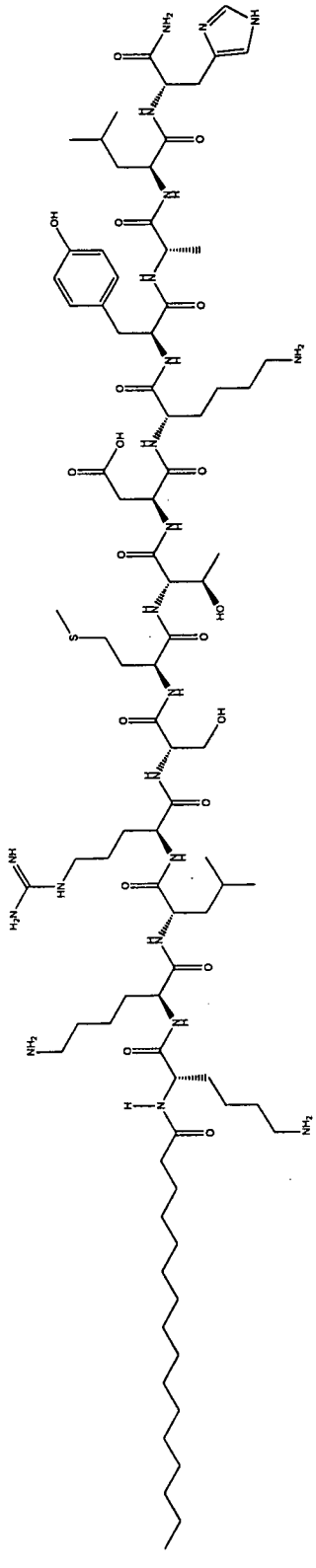

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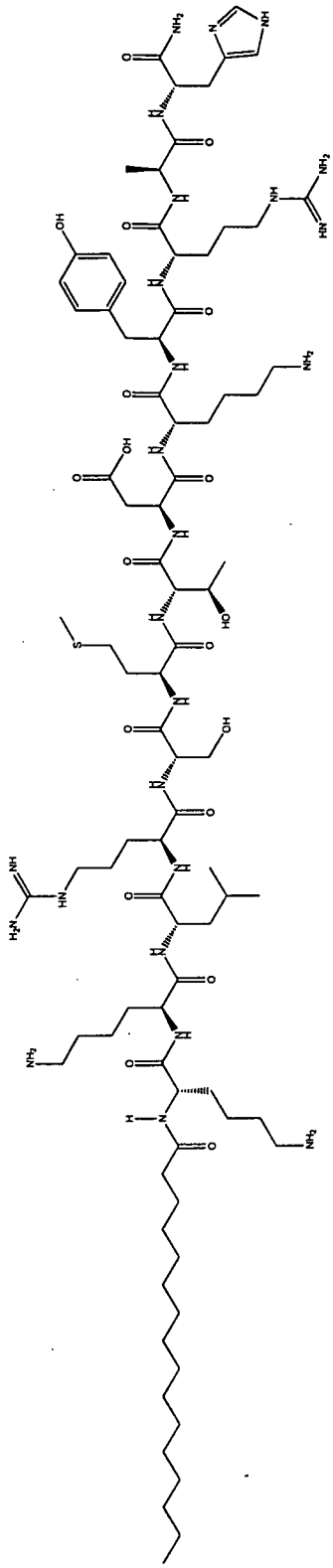

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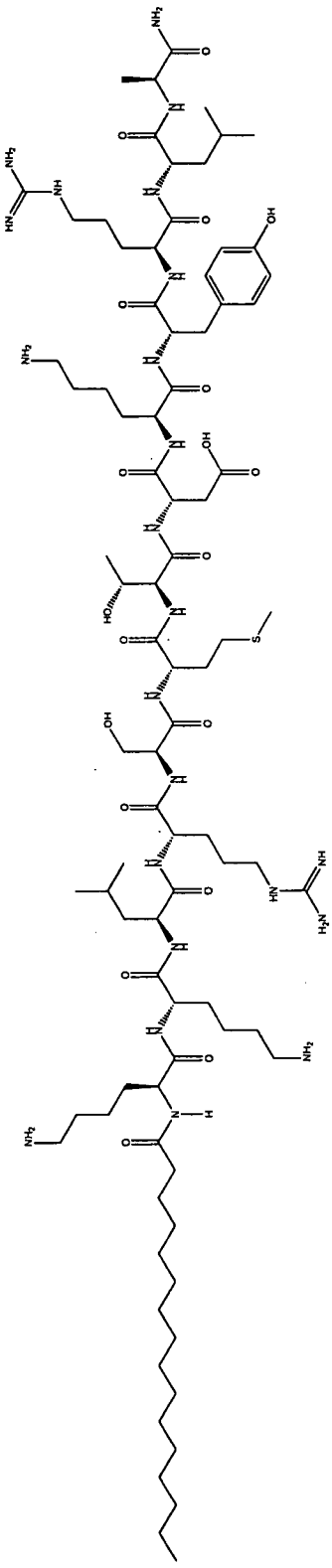

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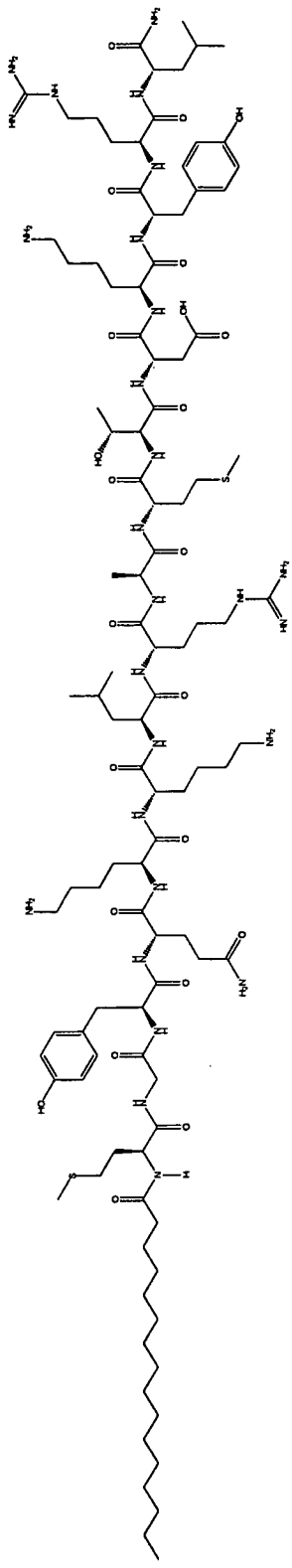

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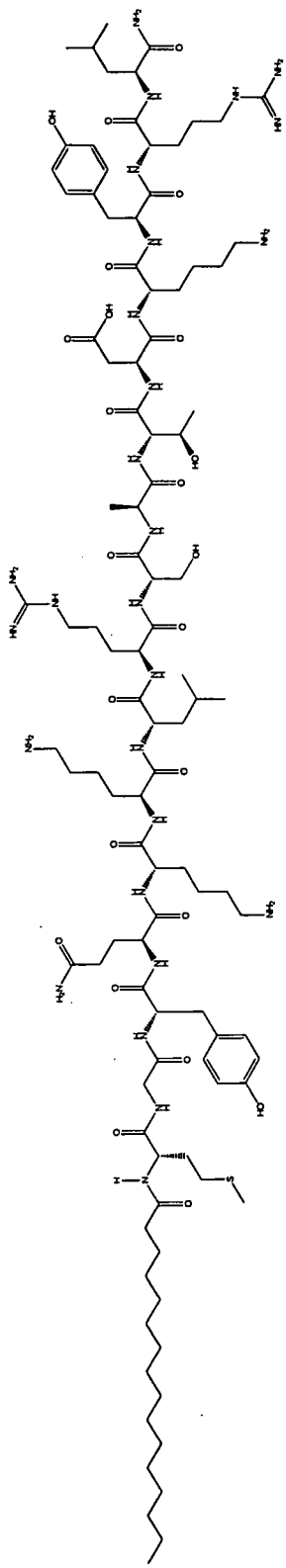

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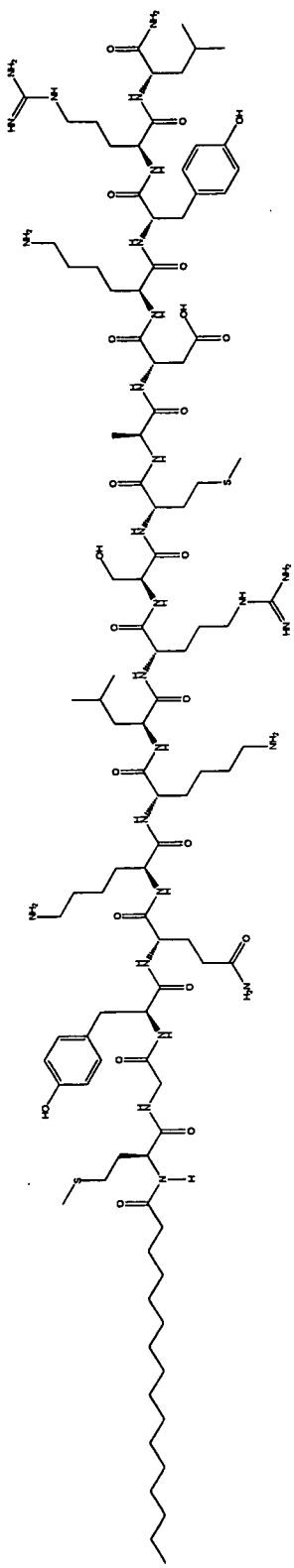

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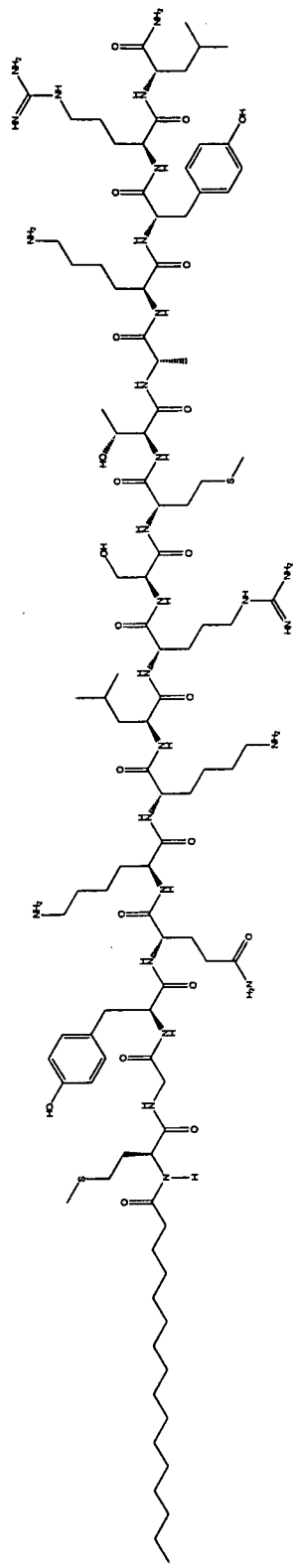

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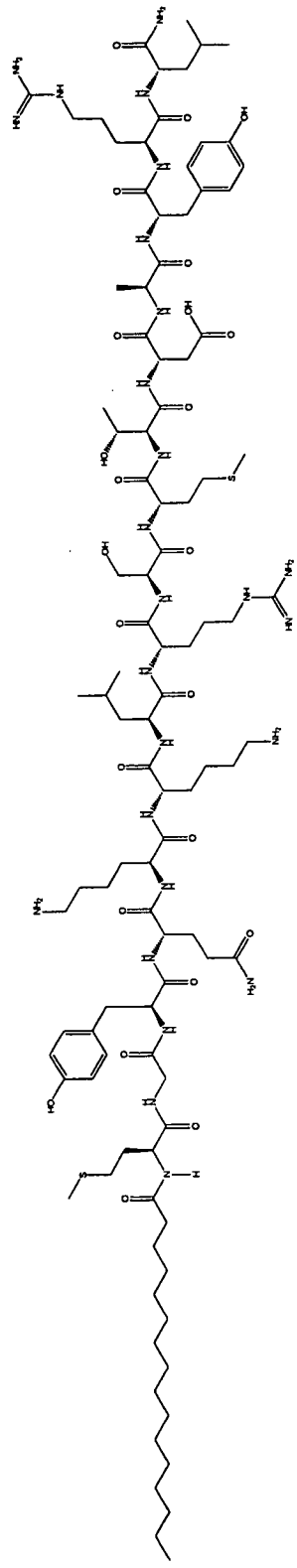

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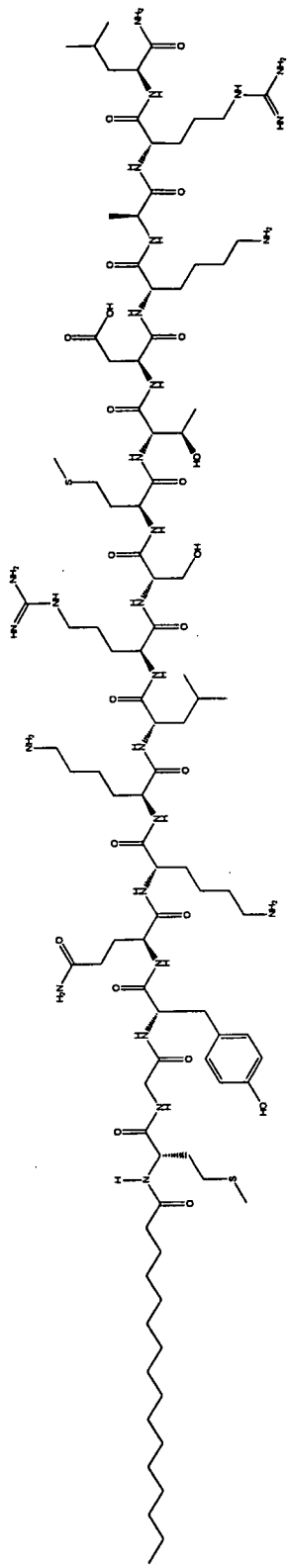

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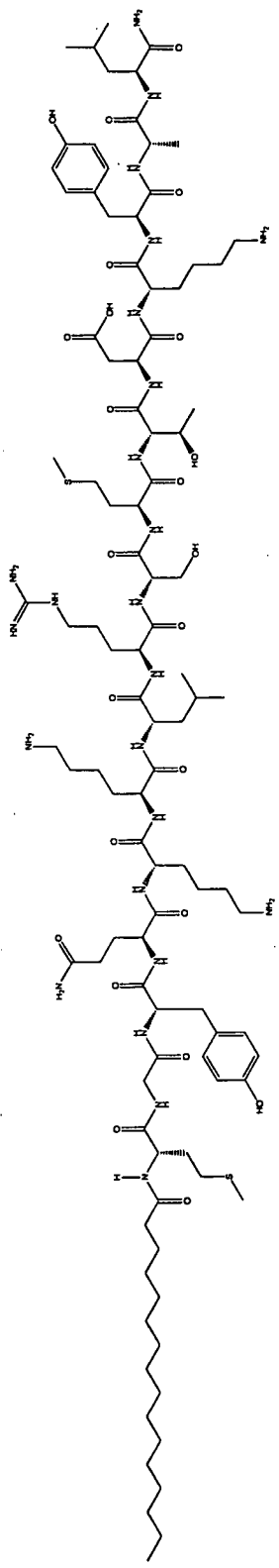

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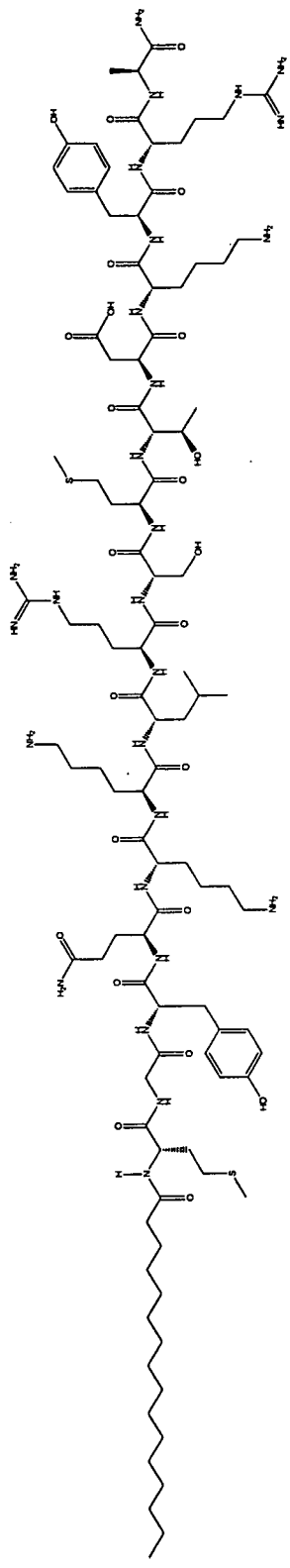

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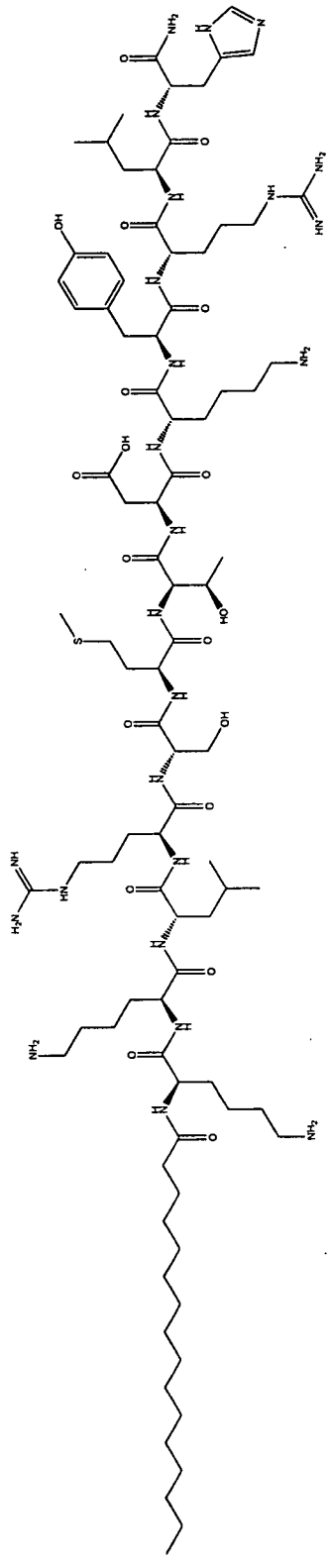

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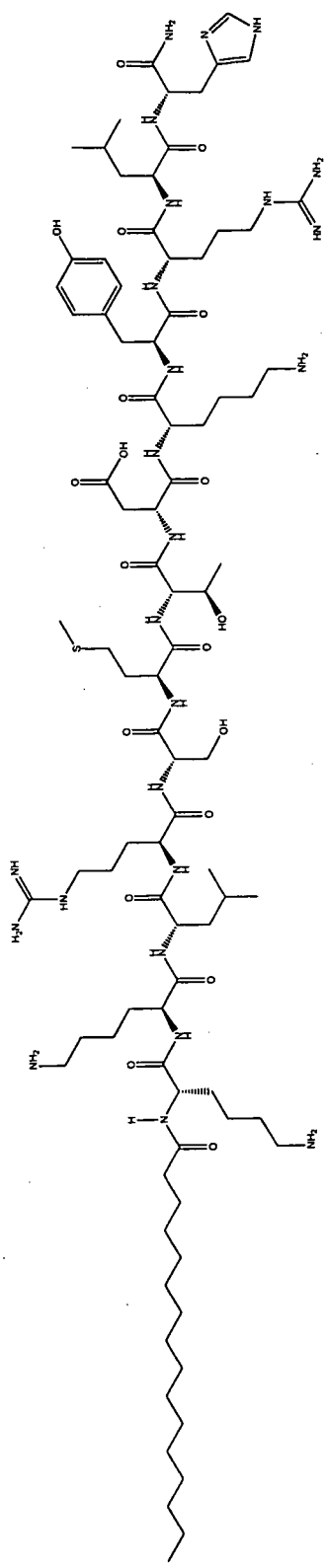

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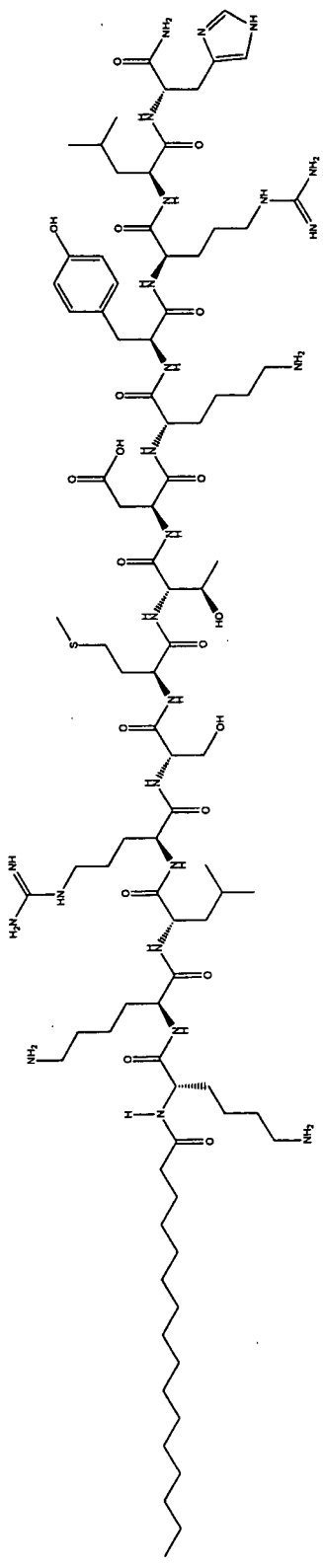

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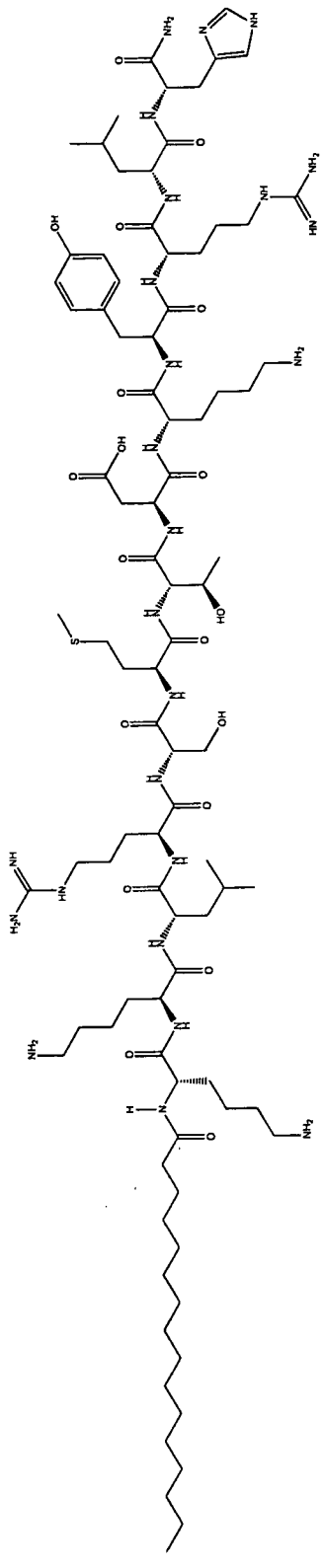

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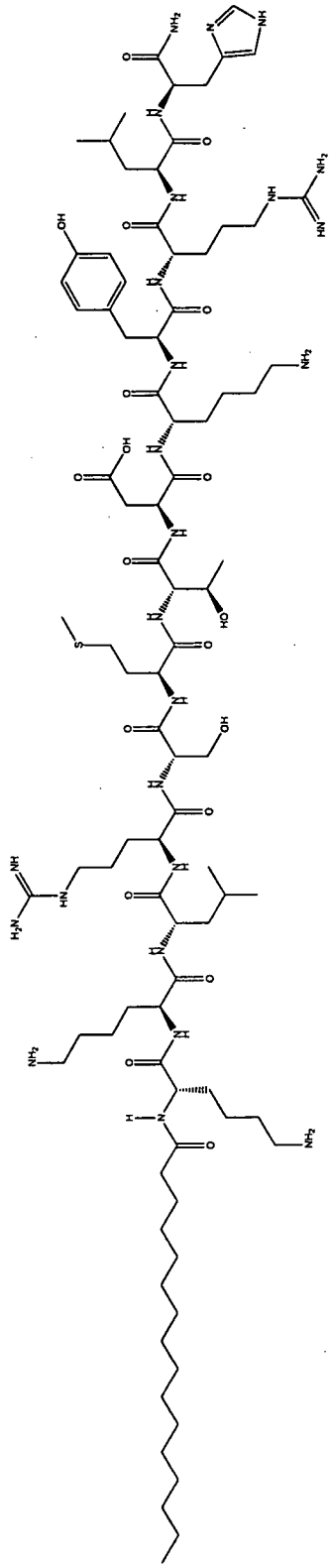

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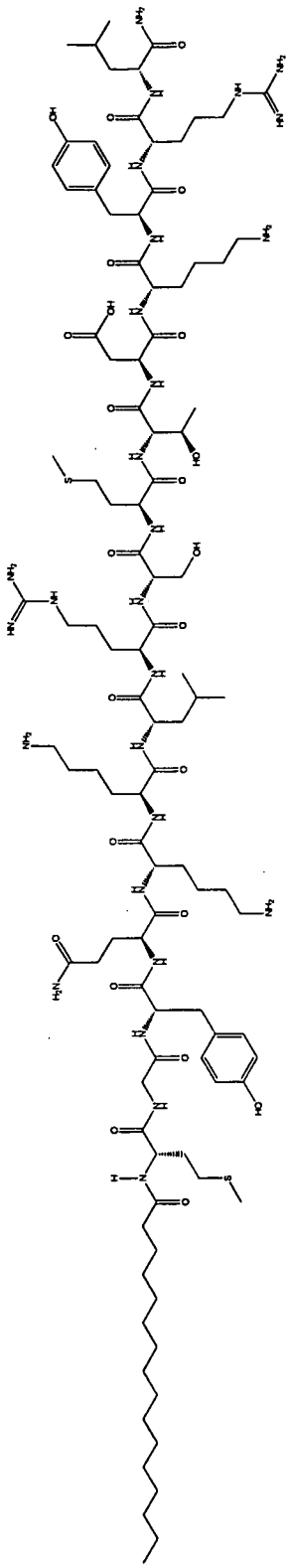

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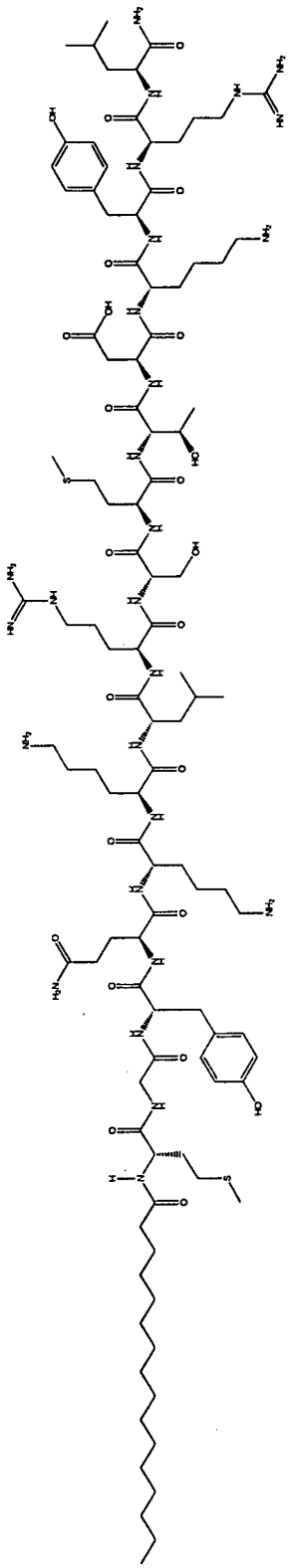

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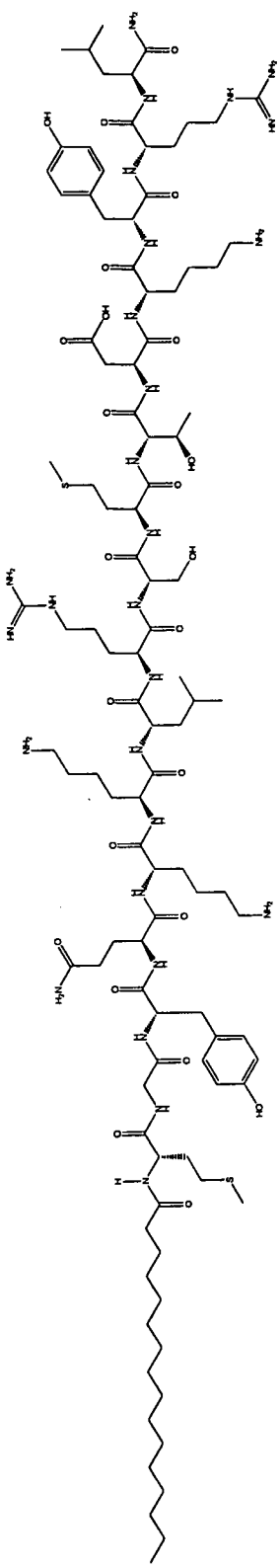

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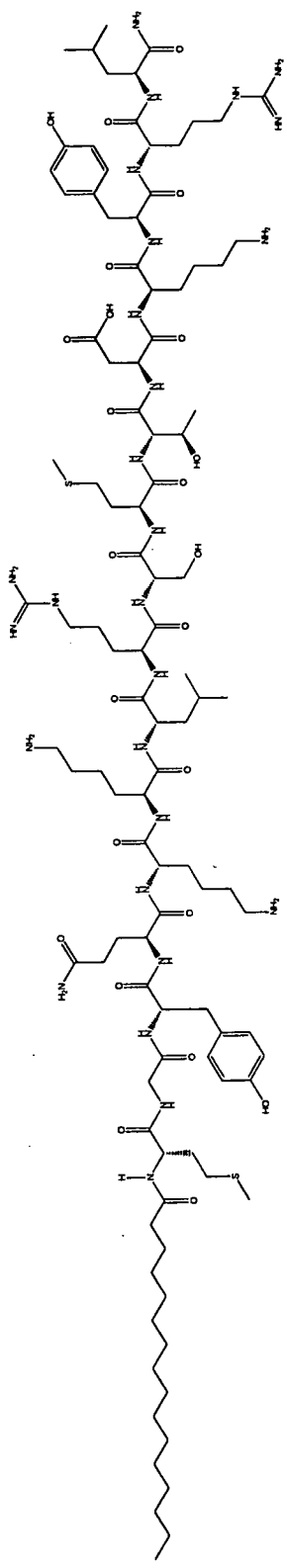

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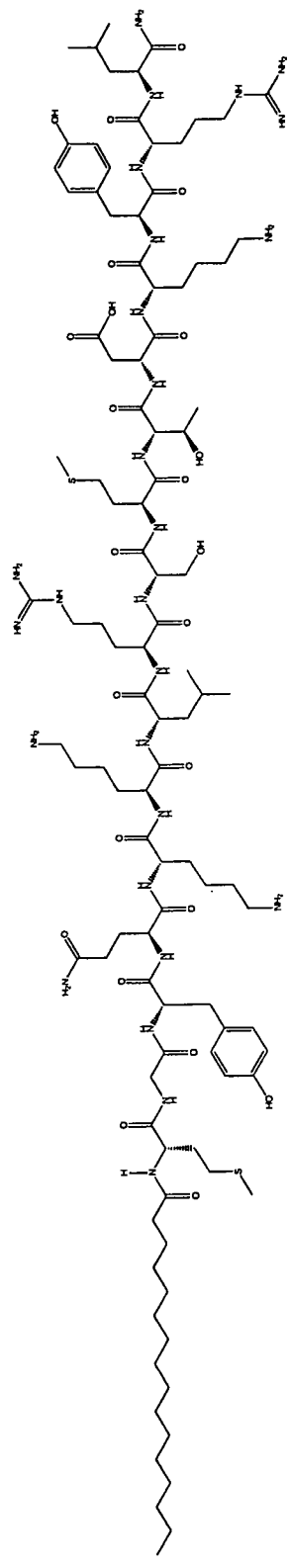

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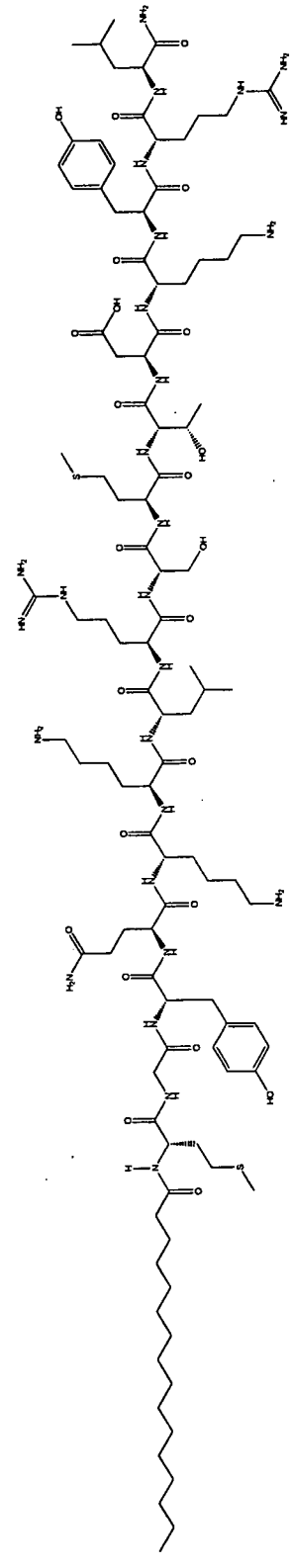

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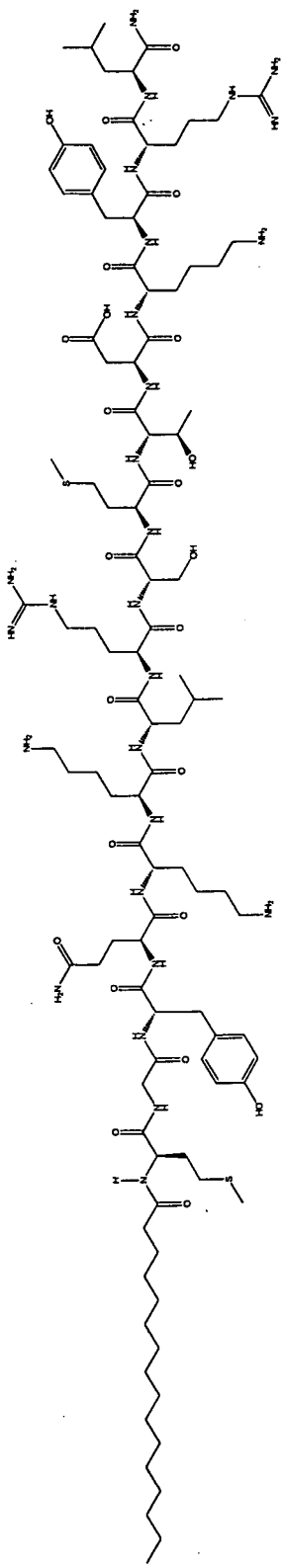

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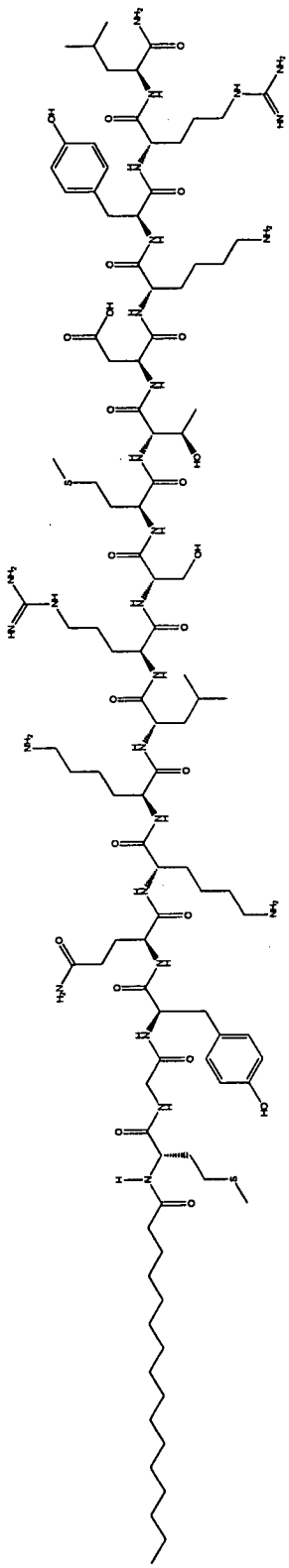

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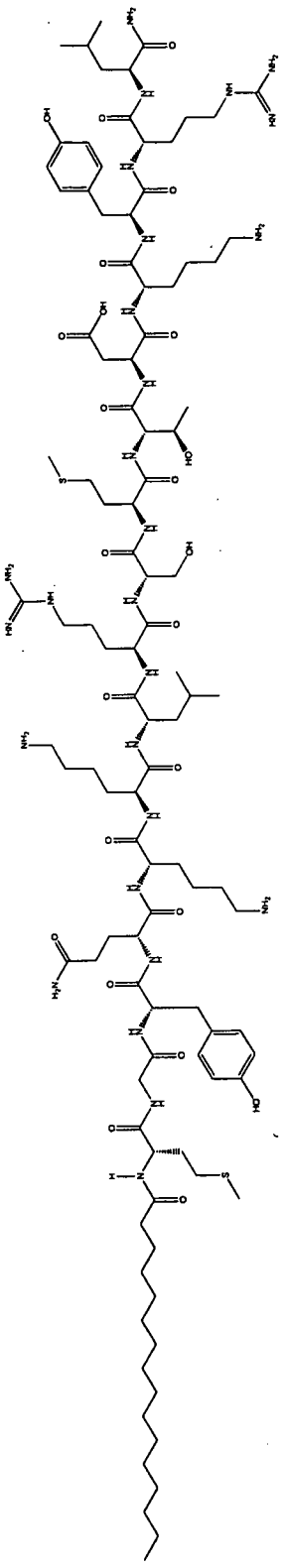

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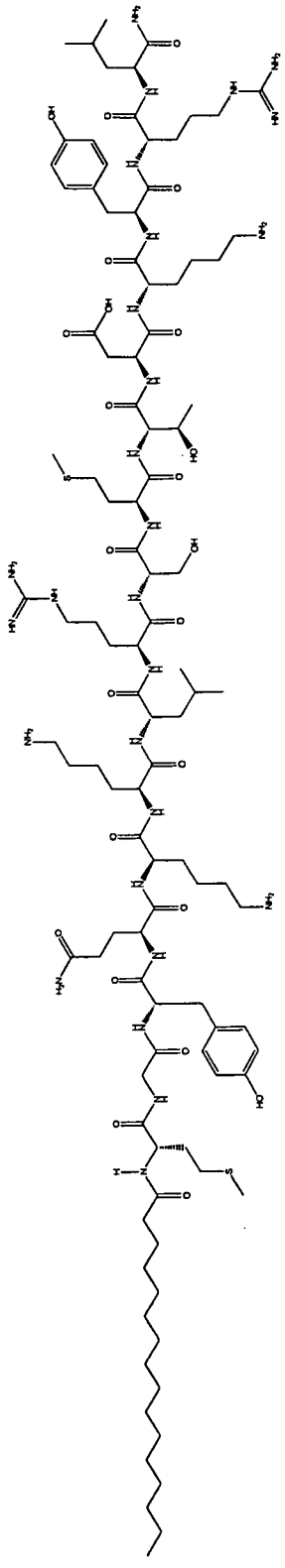

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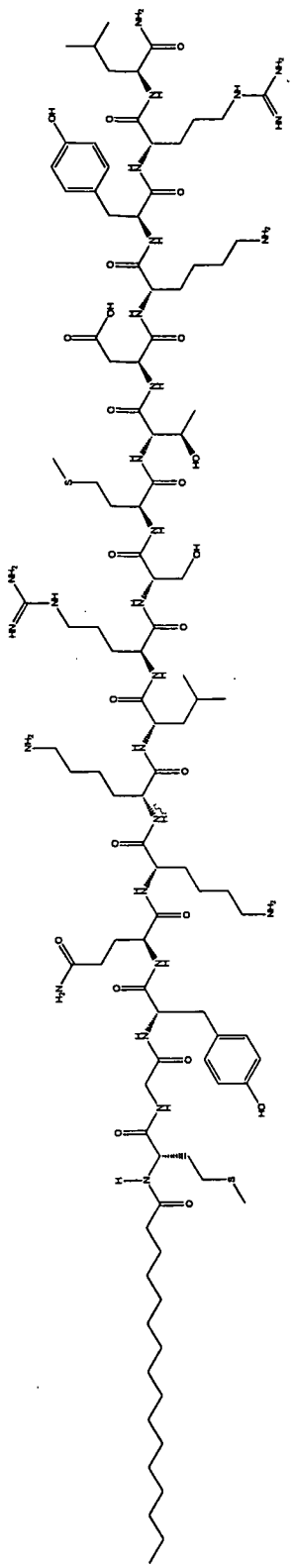

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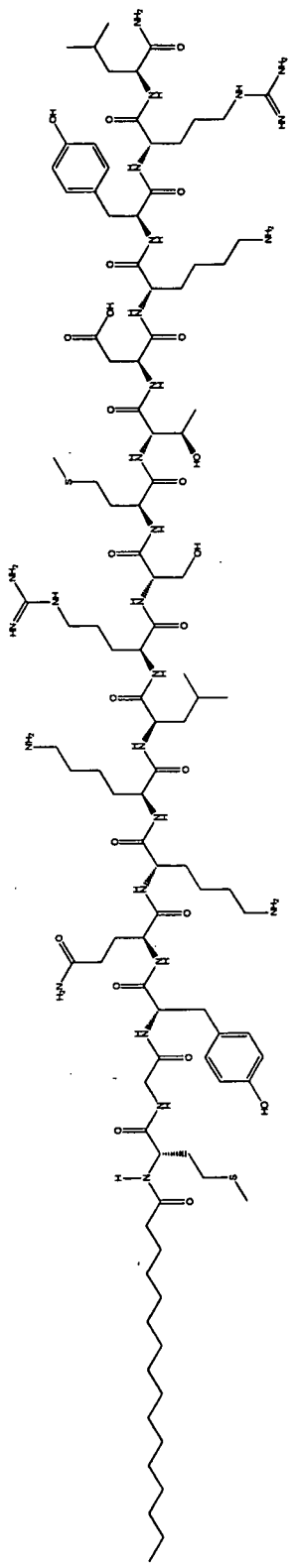

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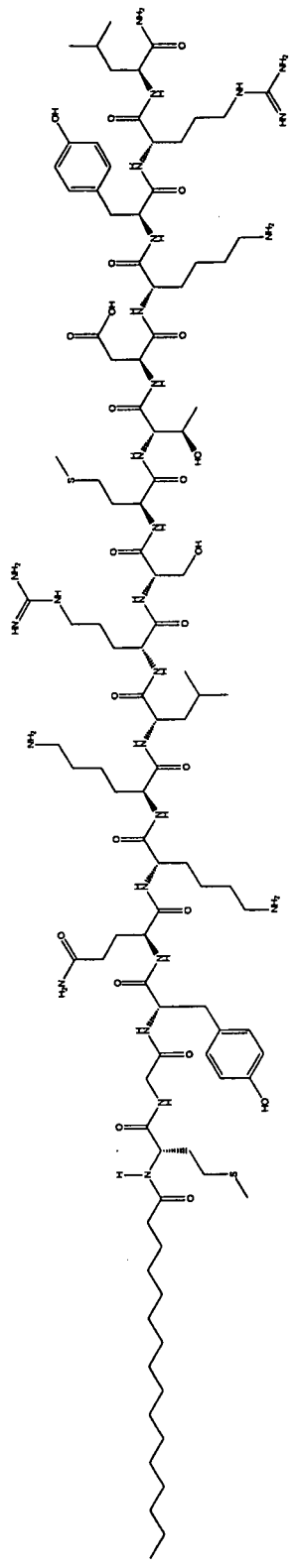

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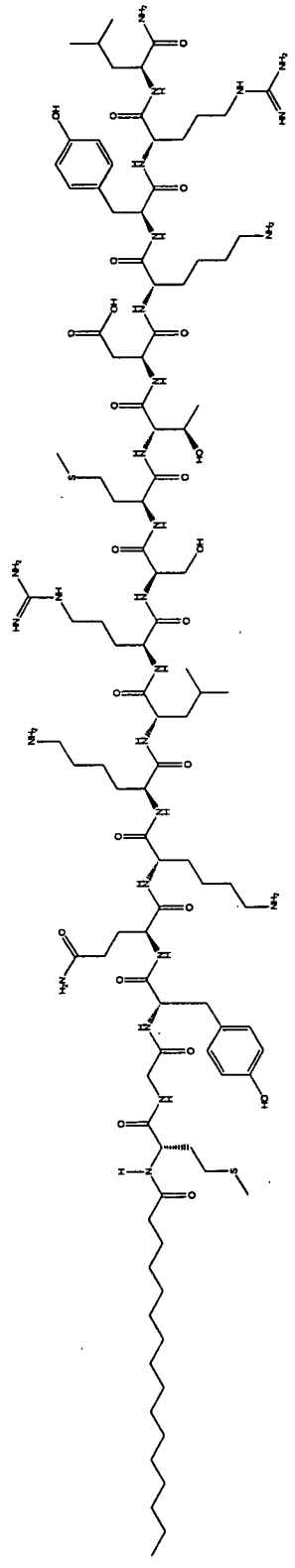

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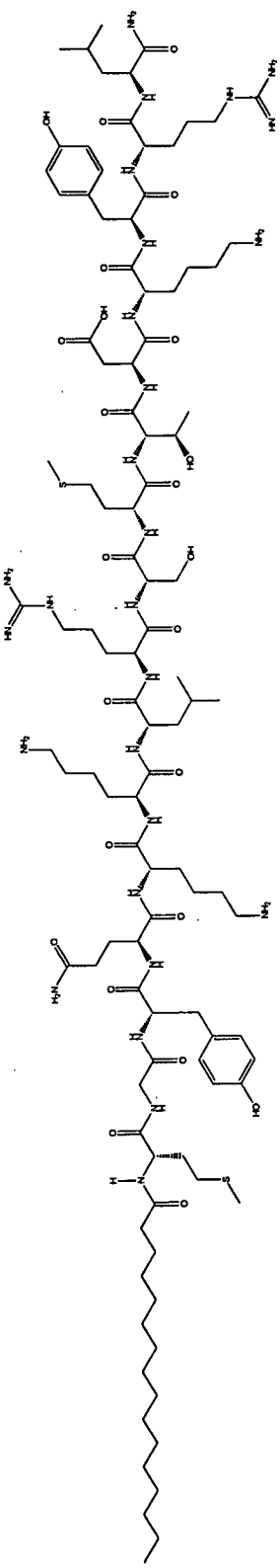

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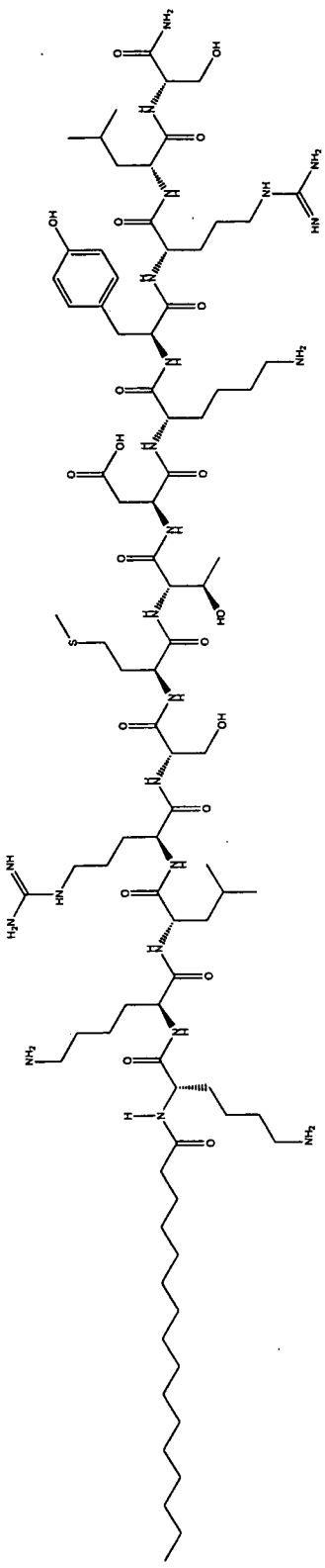

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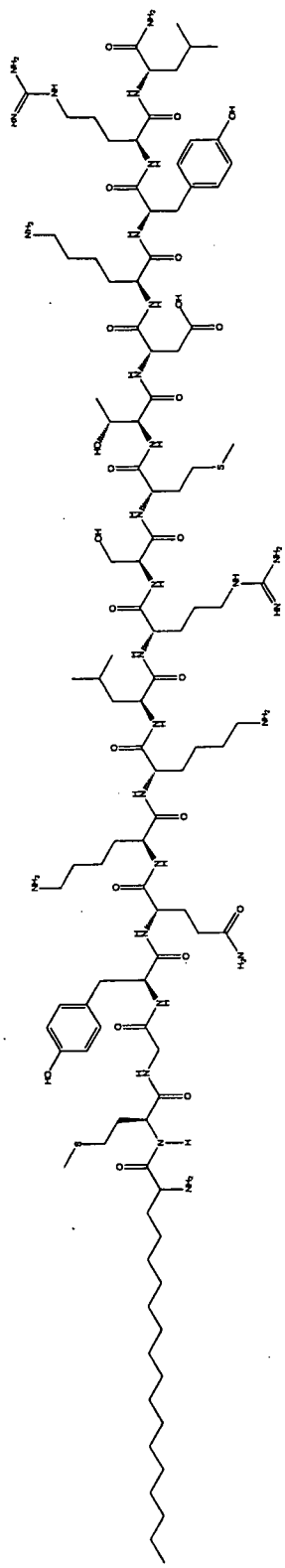

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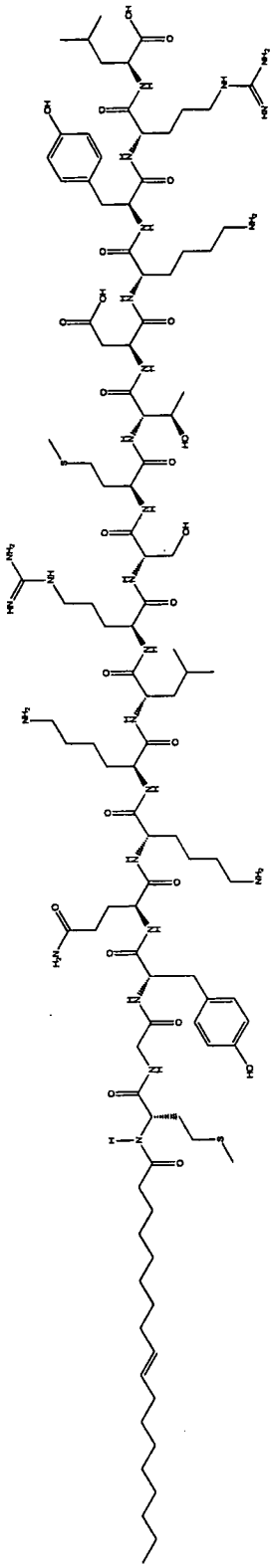

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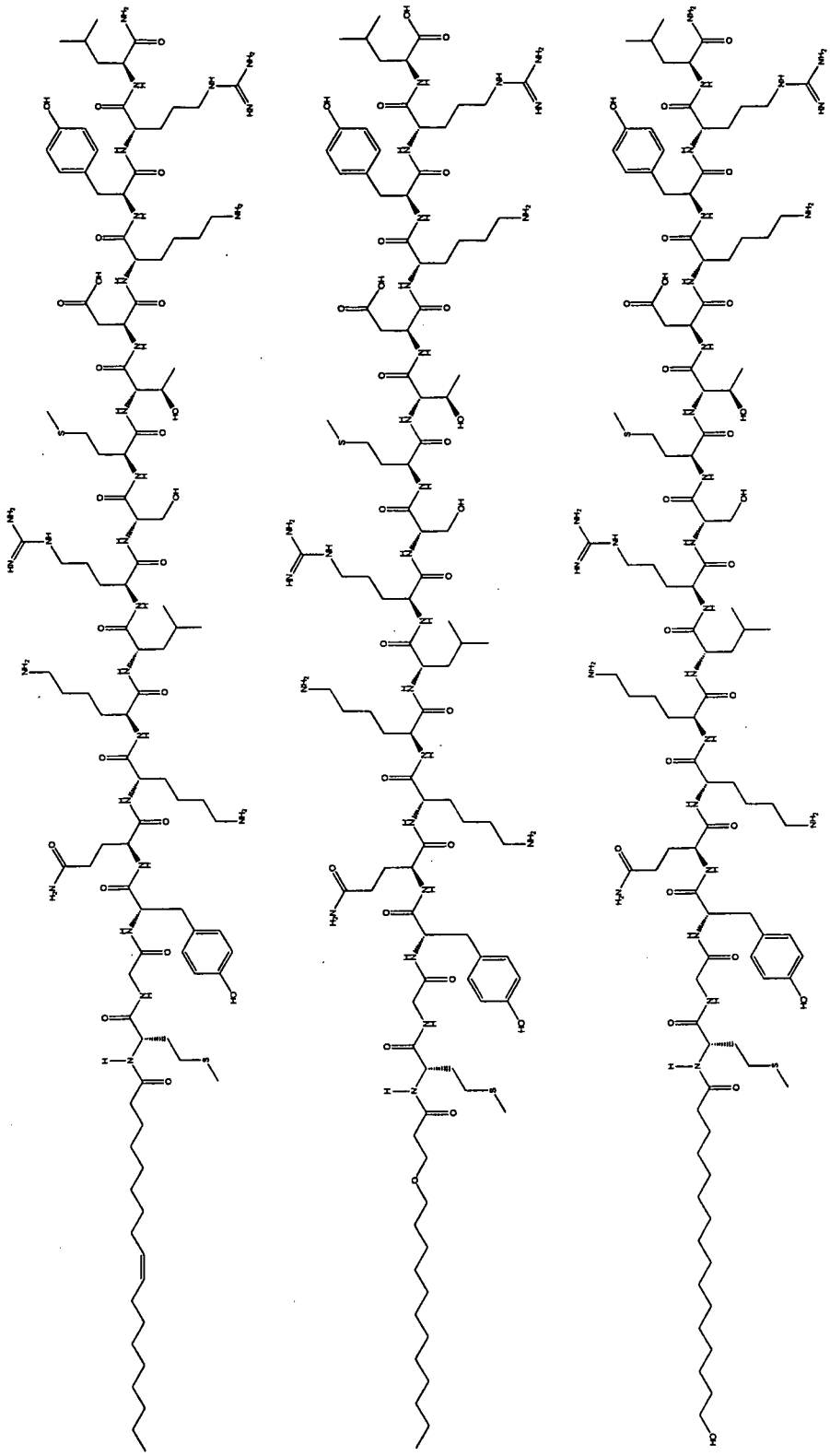

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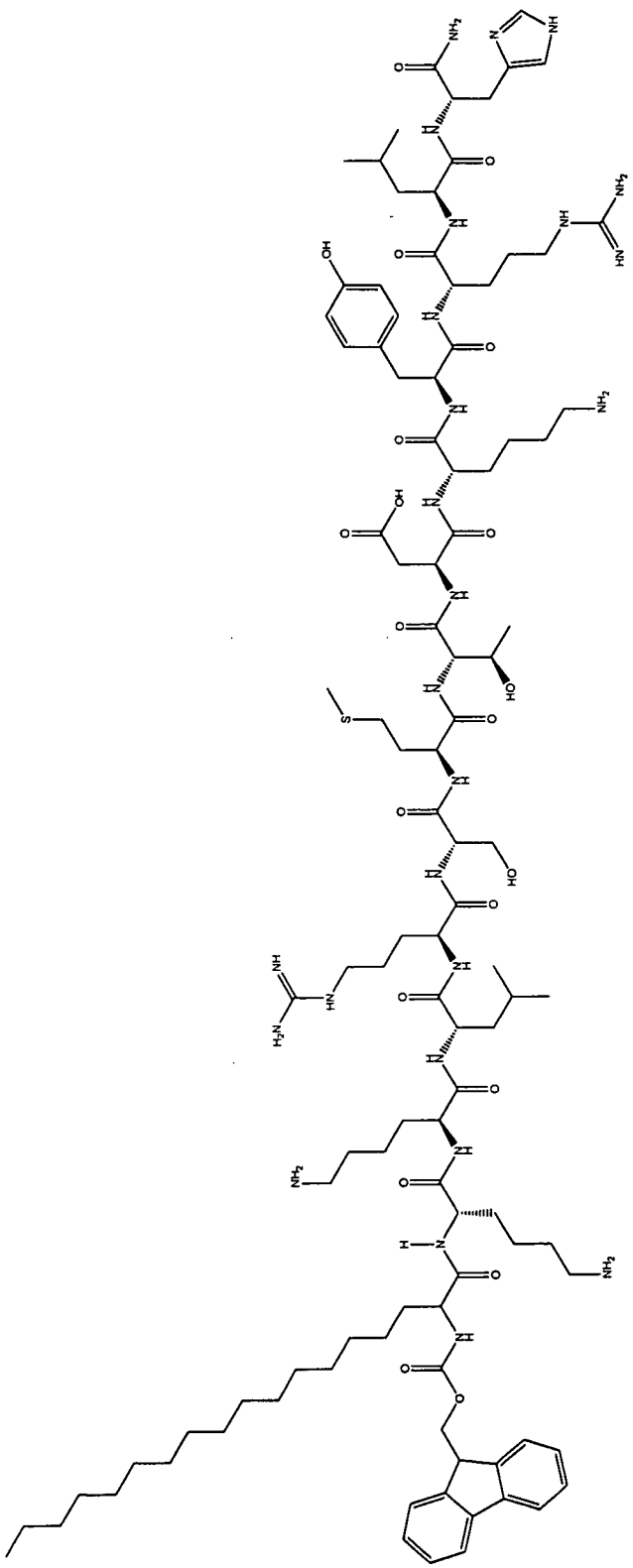

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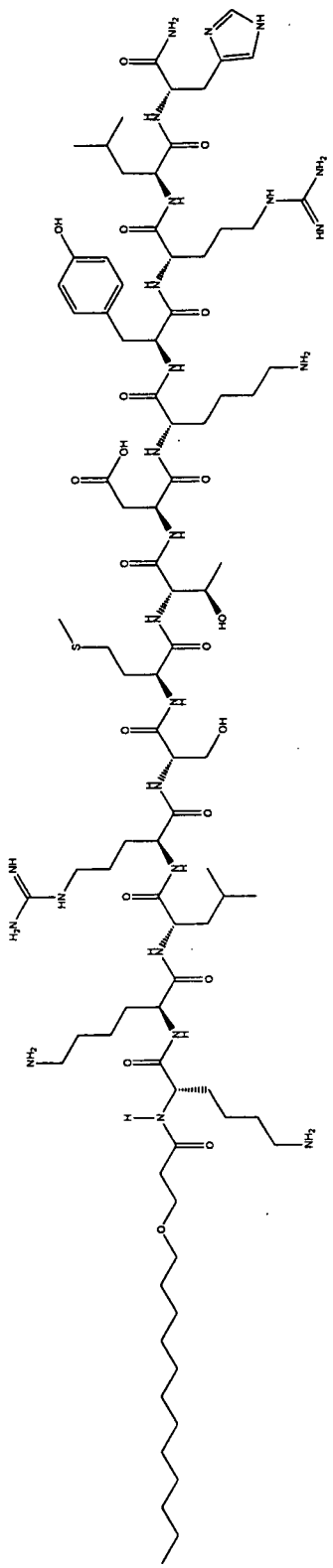

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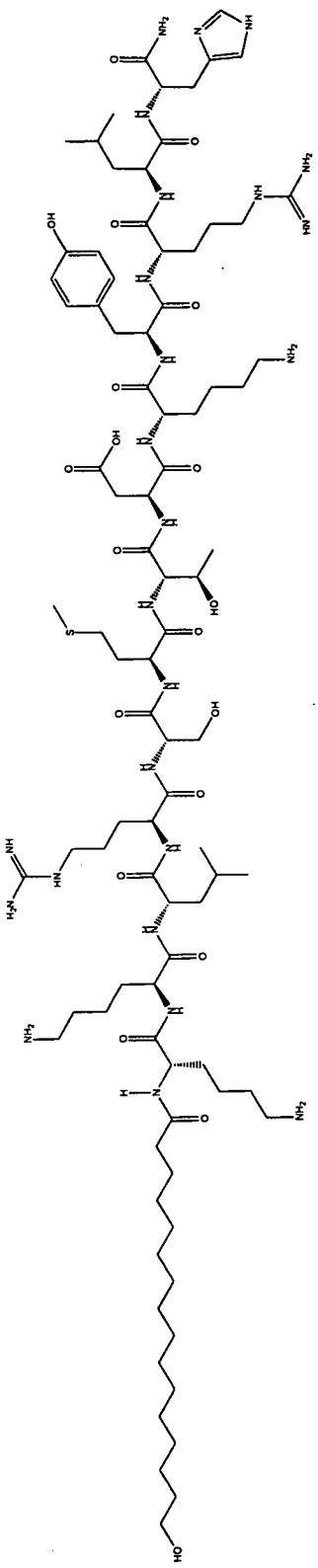

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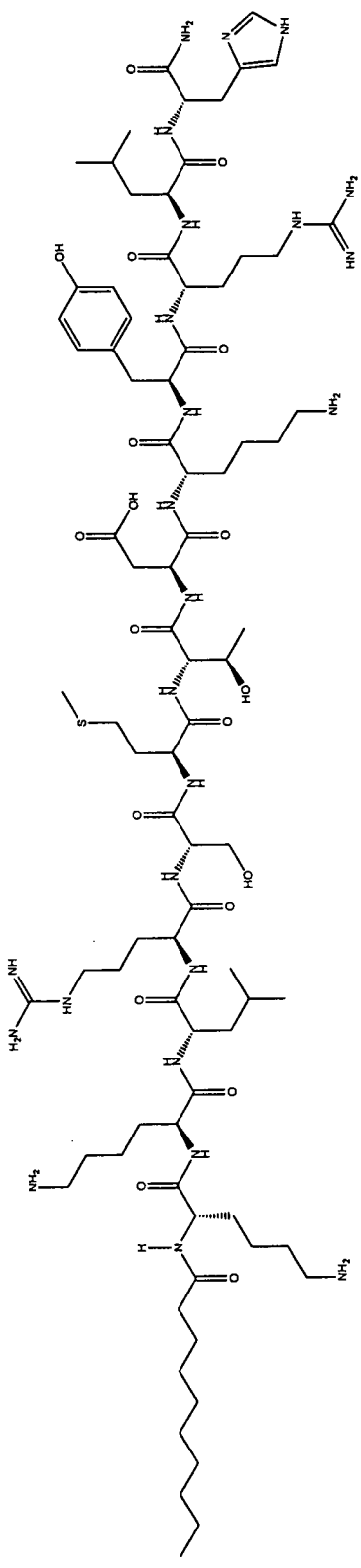

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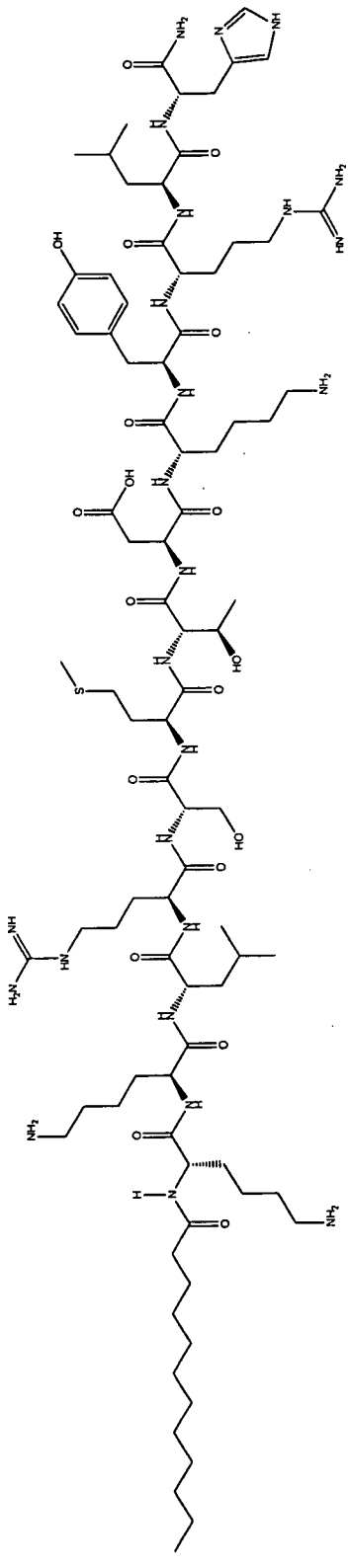

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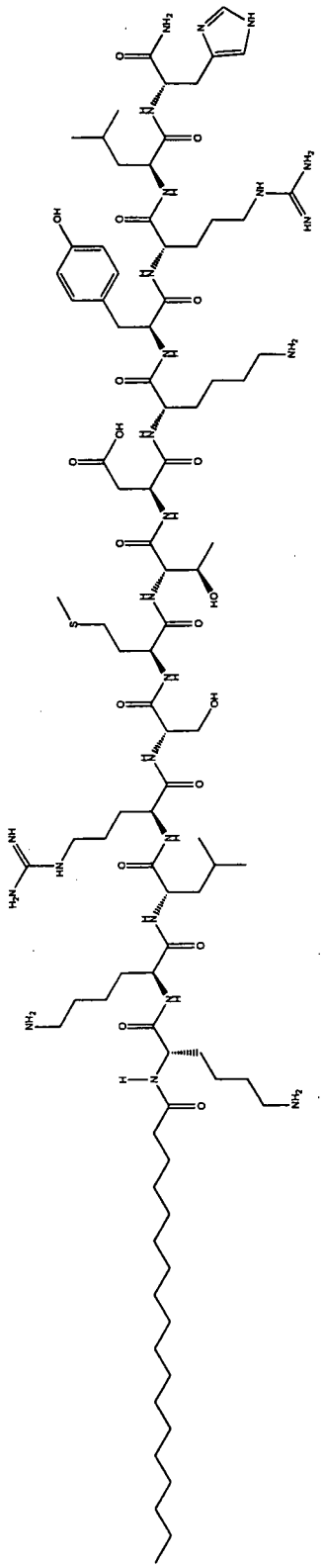

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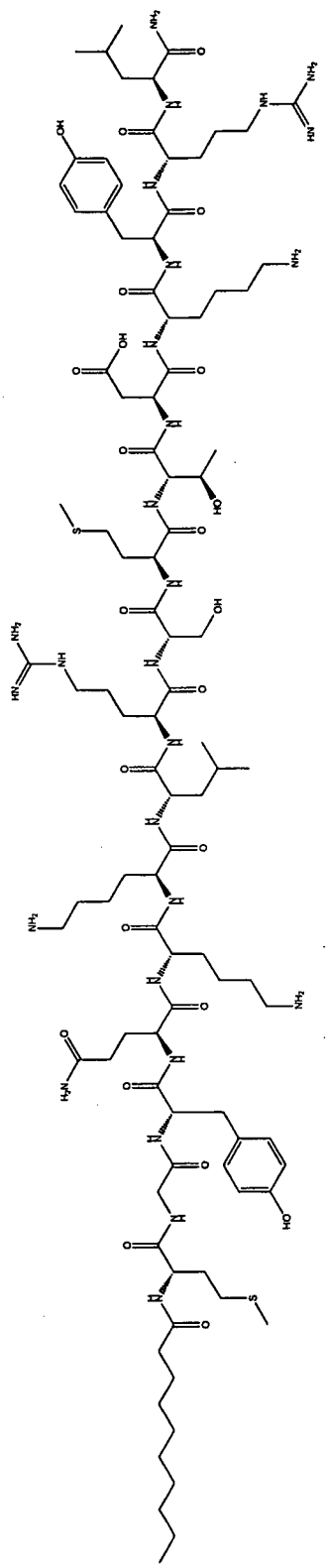

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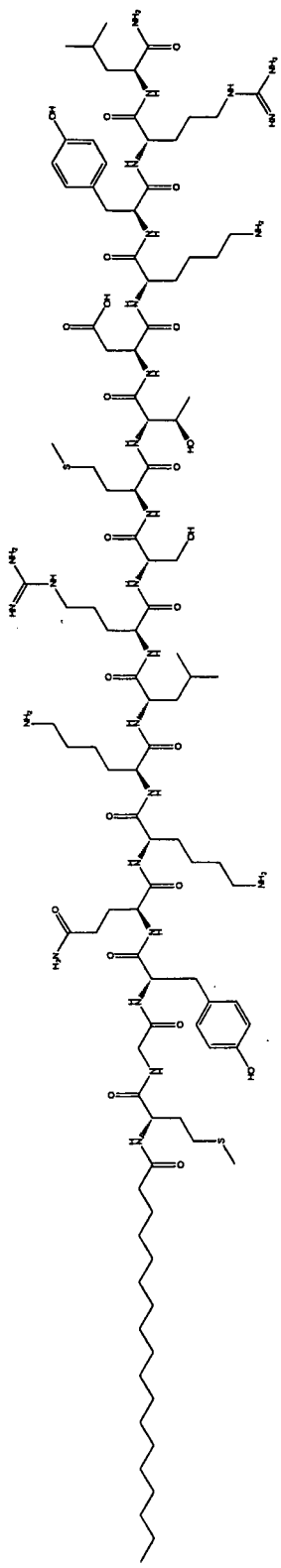

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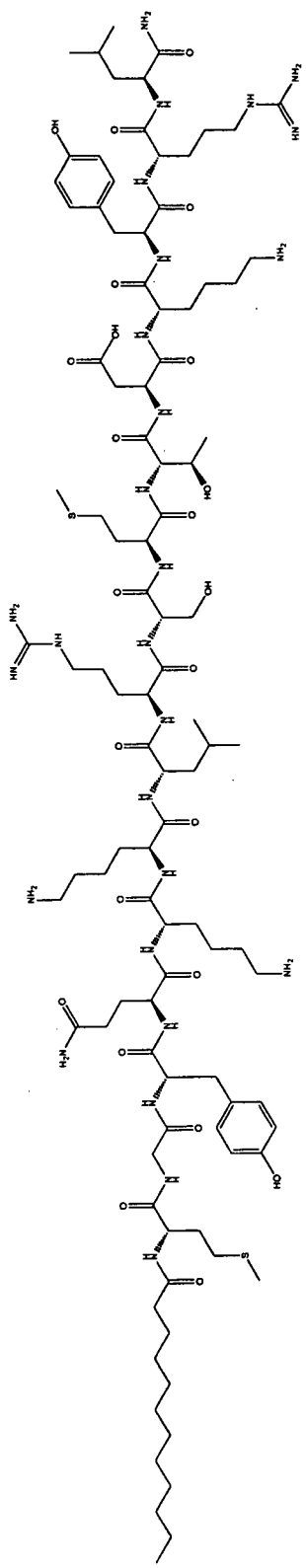

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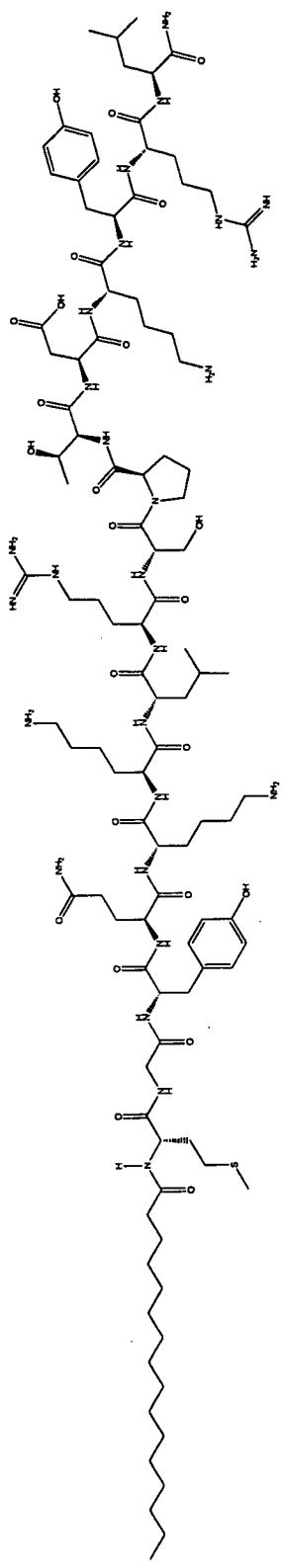

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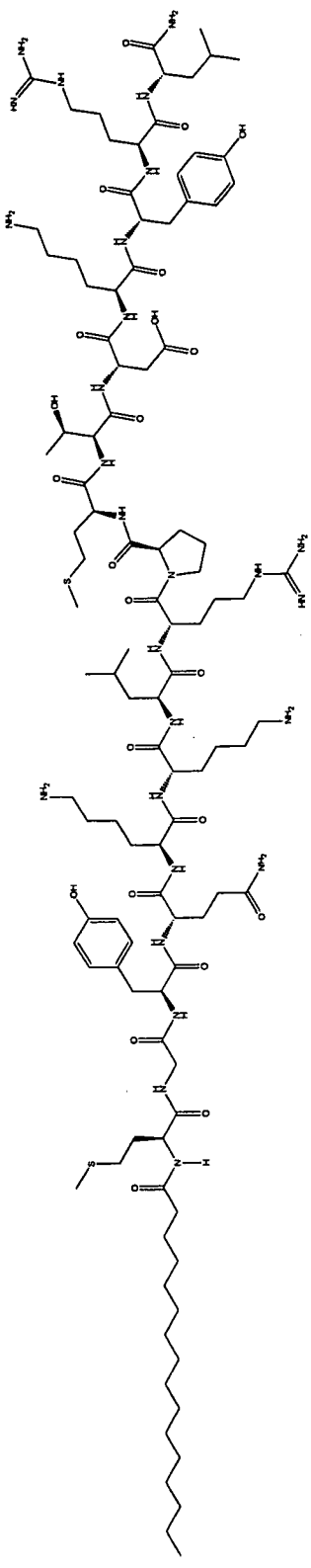

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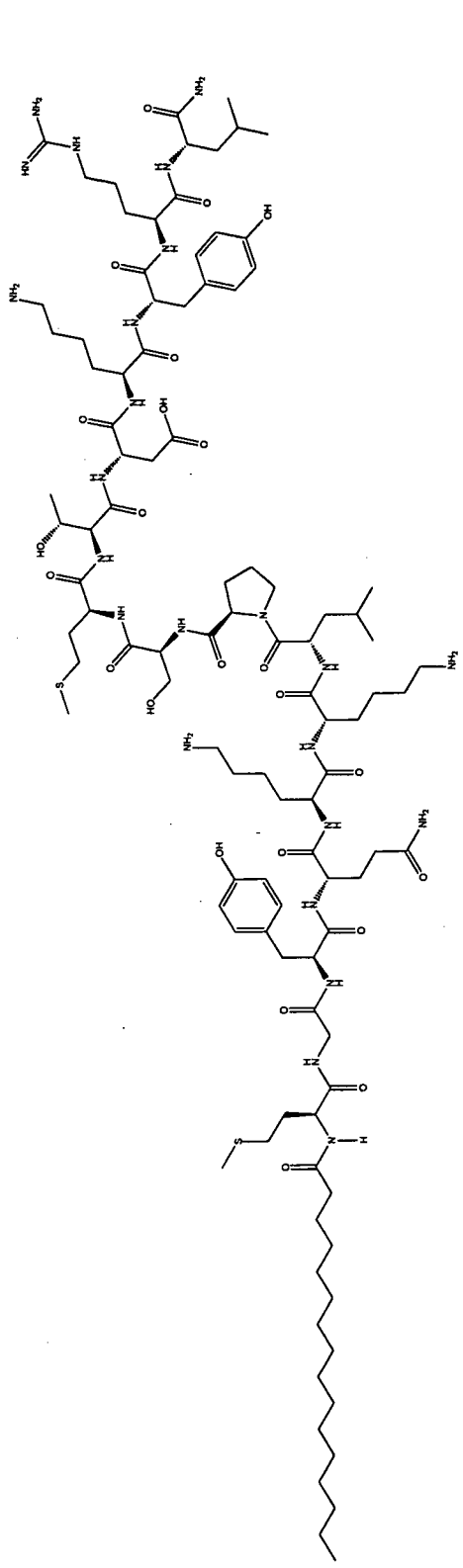

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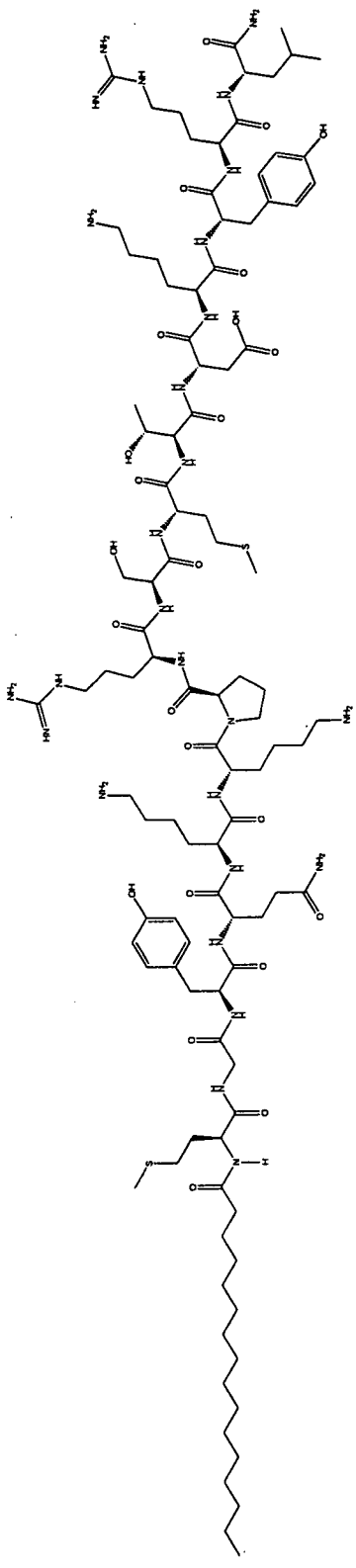

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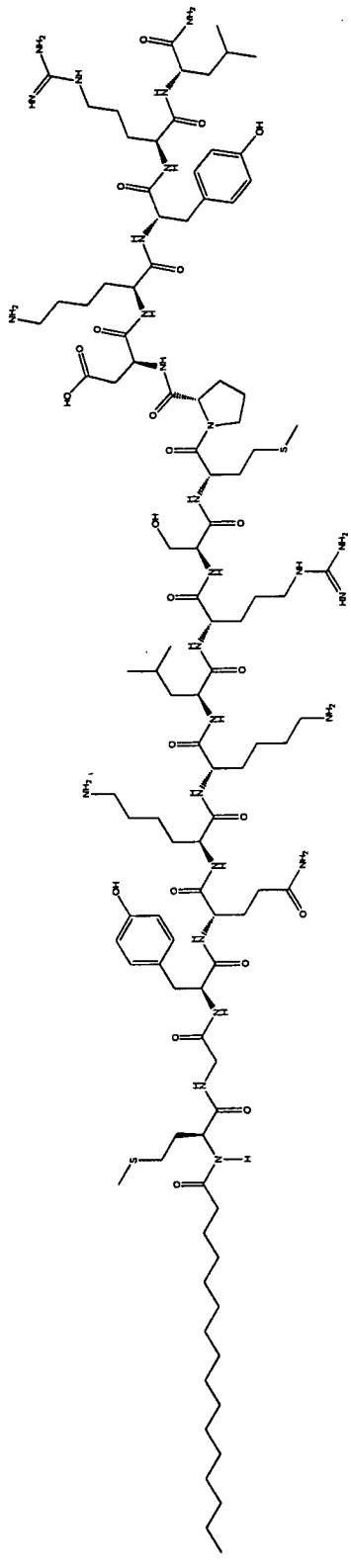

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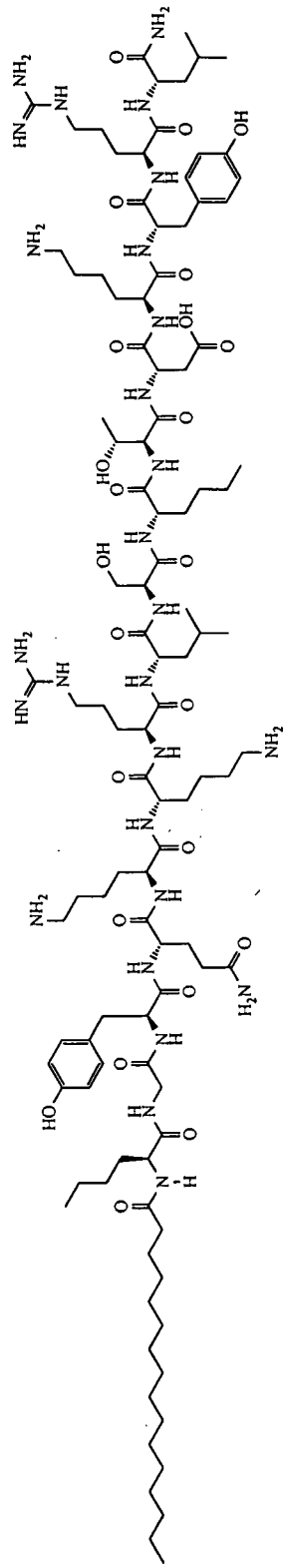

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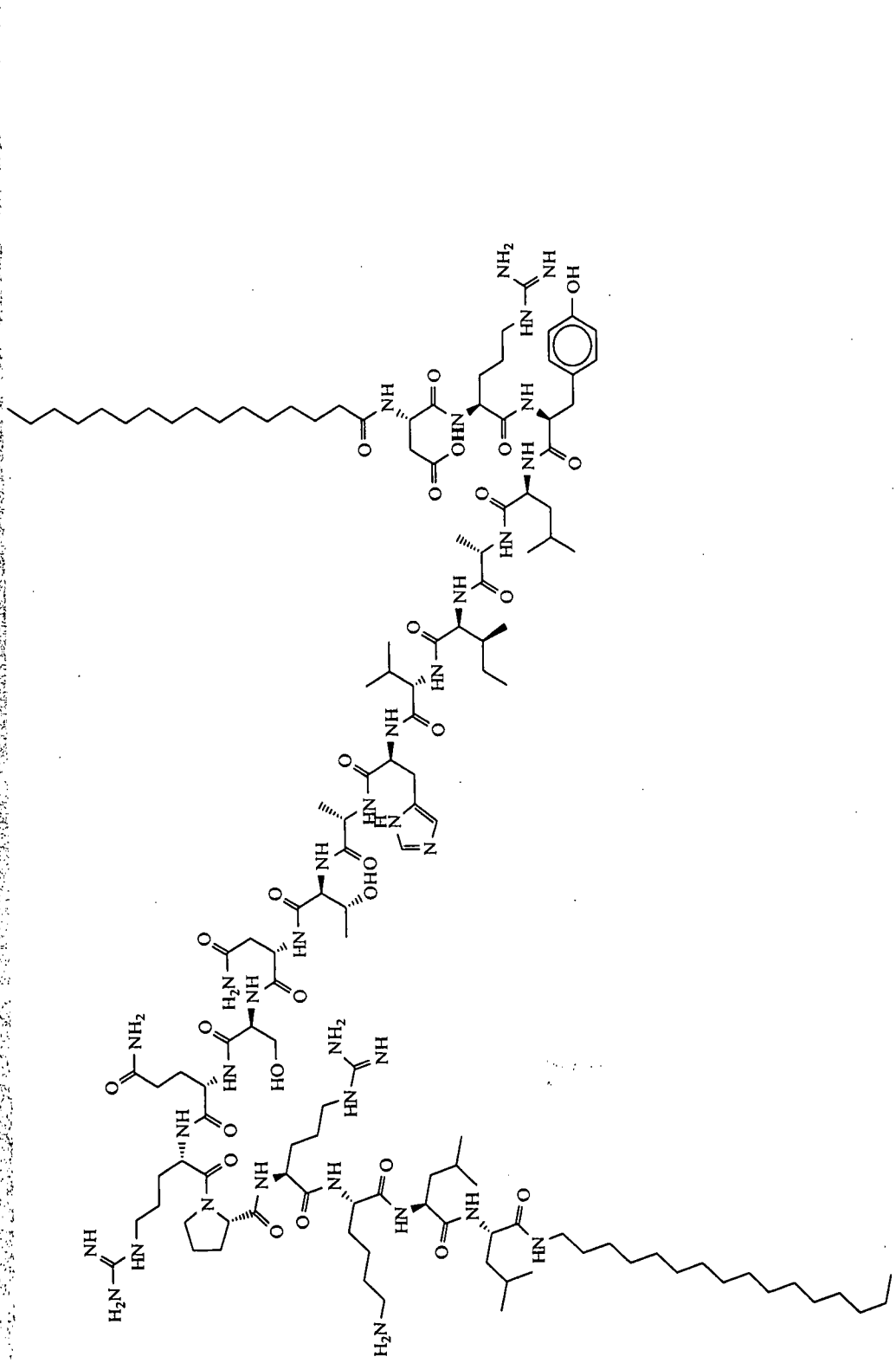
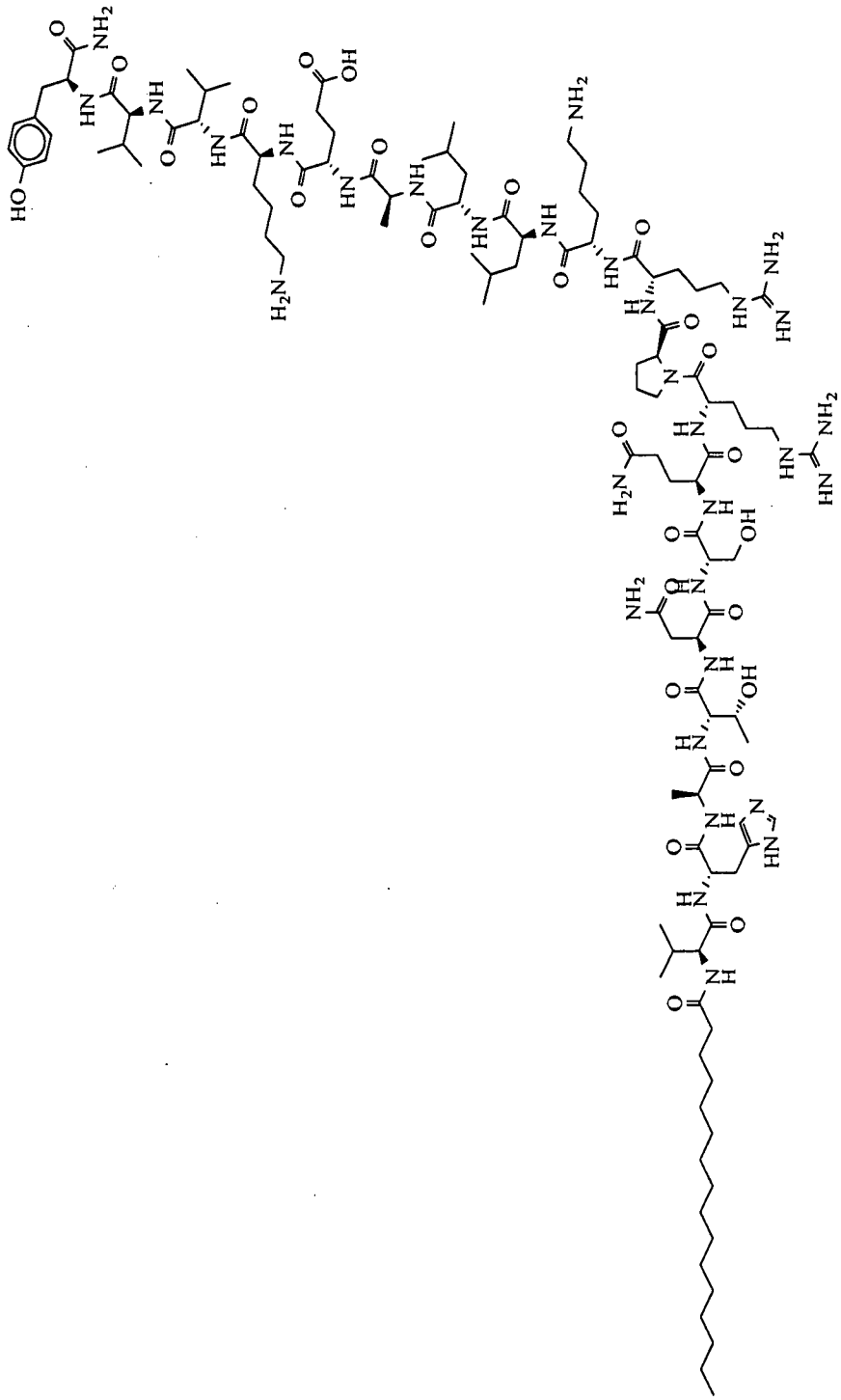
Table 8. CXCR4 i2 loop compounds

Comp. #	Loop	Sequence	Lipid	MW	Comments
74	i2	DRYLAIVHATNSQRPR KLL (SEQ. ID NO),	Pal	2713.439	Dual Lipid
75	i2	VHATNSQRPRKLLAEK VVY (SEQ. ID NO),	Pal	2446.974	
76	i2	DRYLAIVHATNSQRPR KLL (SEQ. ID NO),	Myr	2742.438	second lipid on backbone
77	i2	DRYLAIVHATNSQRPR KLL (SEQ. ID NO),	Pal	2489.014	
78	i2	VHATNSQRPRKLLA (SEQ. ID NO),	Pal	1828.253	
79	i2	HATNSQRPRKL (SEQ. ID NO),	Pal	1544.886	
80	i2	HATNSQRPRKLLA (SEQ. ID NO),	Pal	1729.121	
81	i2	HATNSQRPRKLLAE (SEQ. ID NO),	Pal	1858.235	
82	i2	HATNSQRPRKLLAEK (SEQ. ID NO),	Pal	1986.408	
83	i2	HATNSQRPRKLLAEKV (SEQ. ID NO),	Pal	2085.539	

Table 9. CXCR4 i2 loop compound structures

Comp. #	Structure
74	



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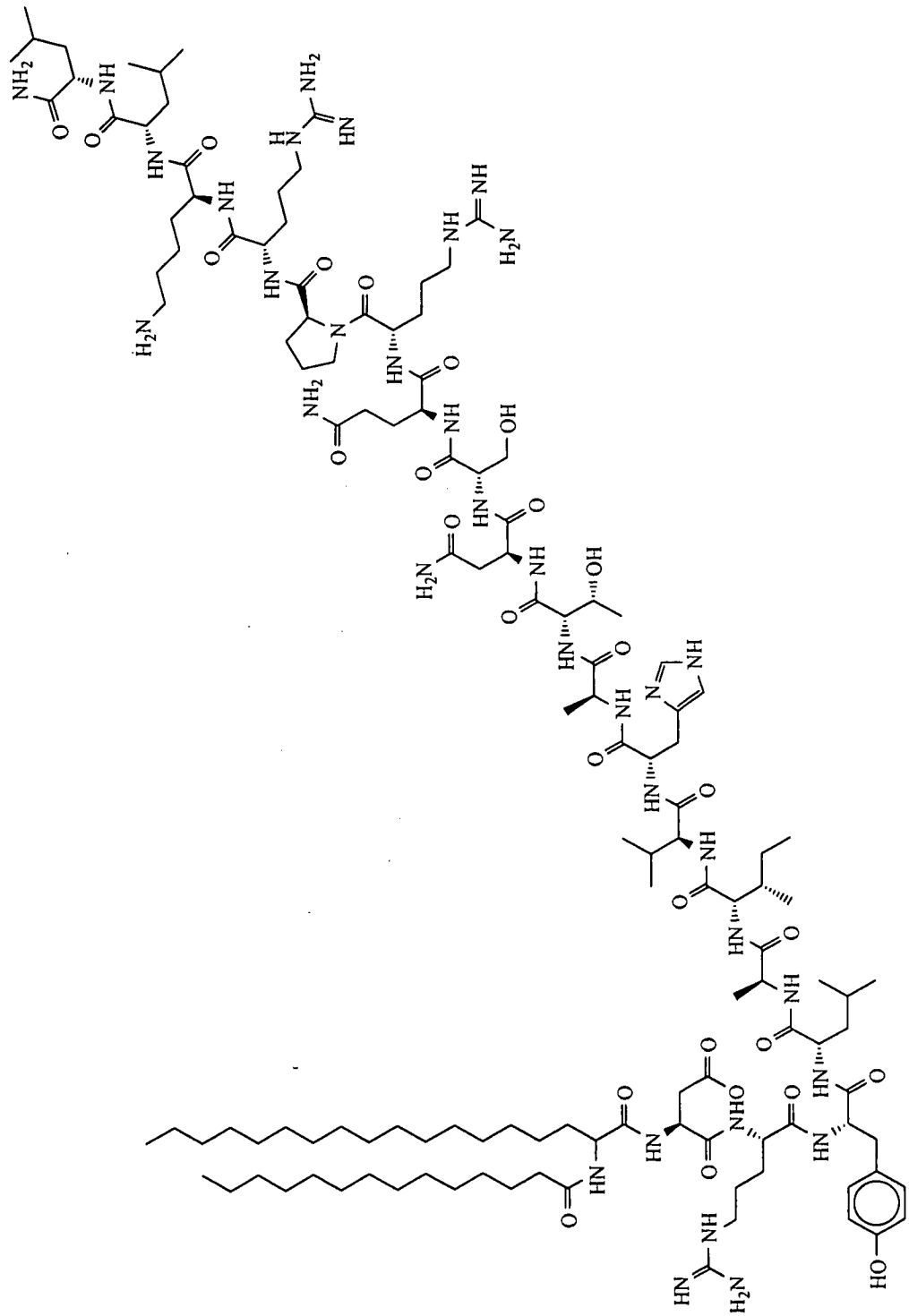

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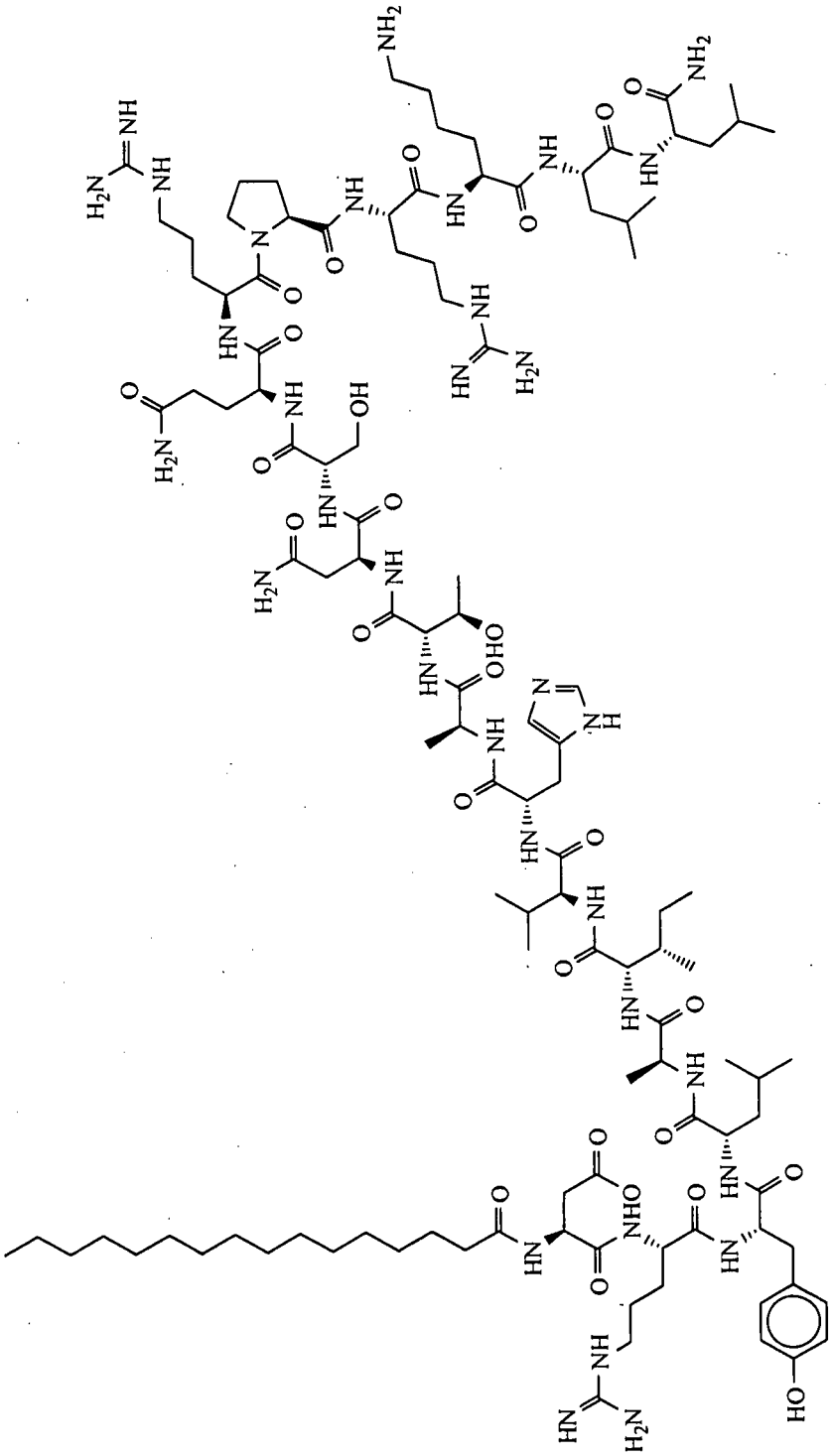

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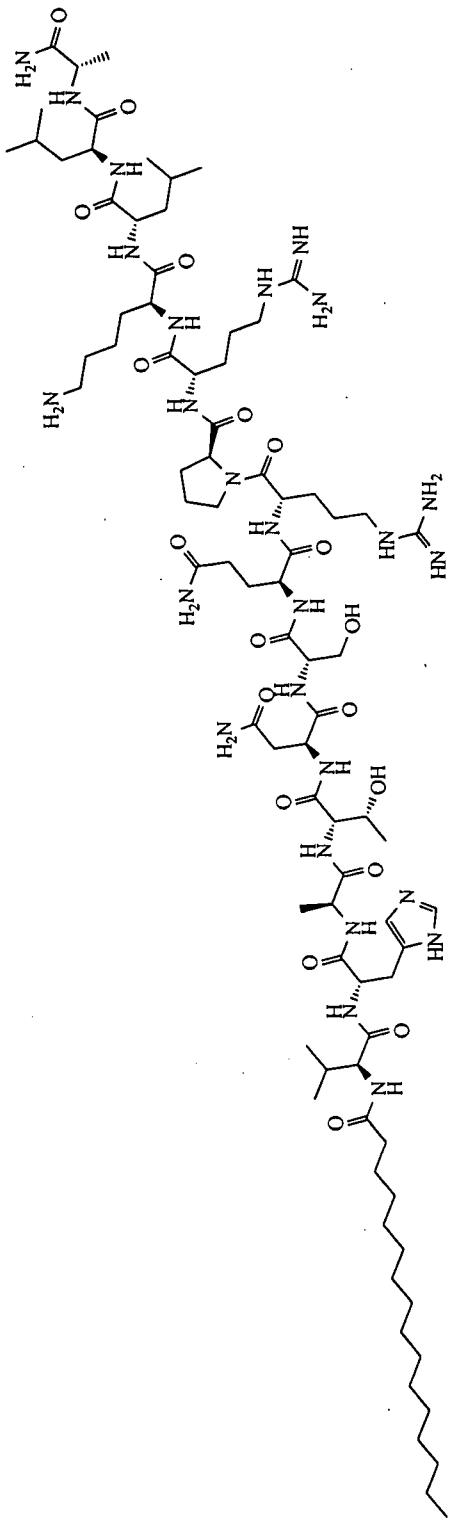

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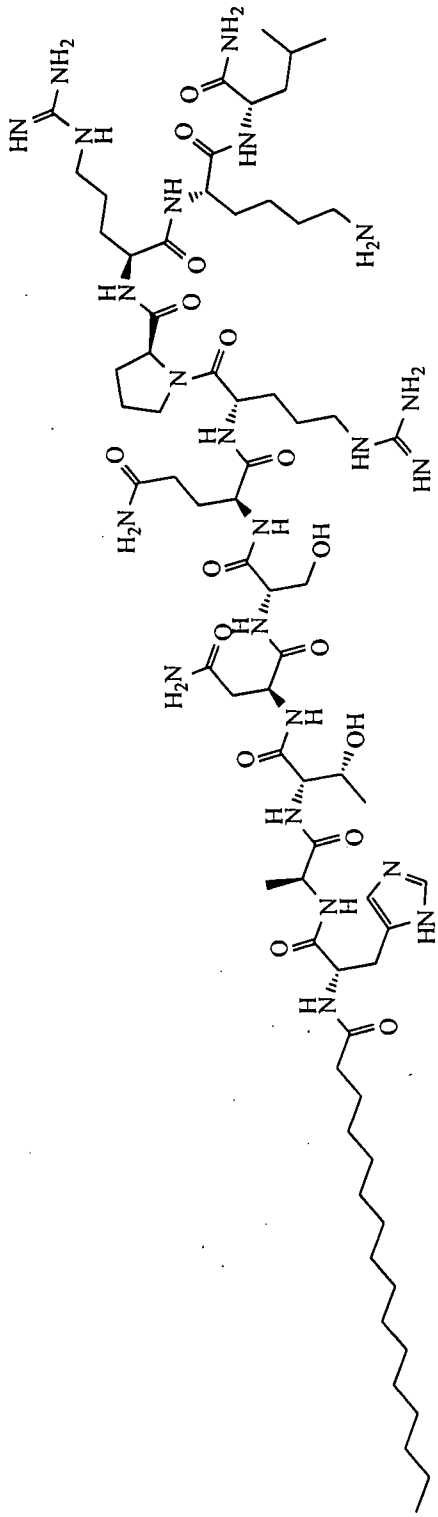

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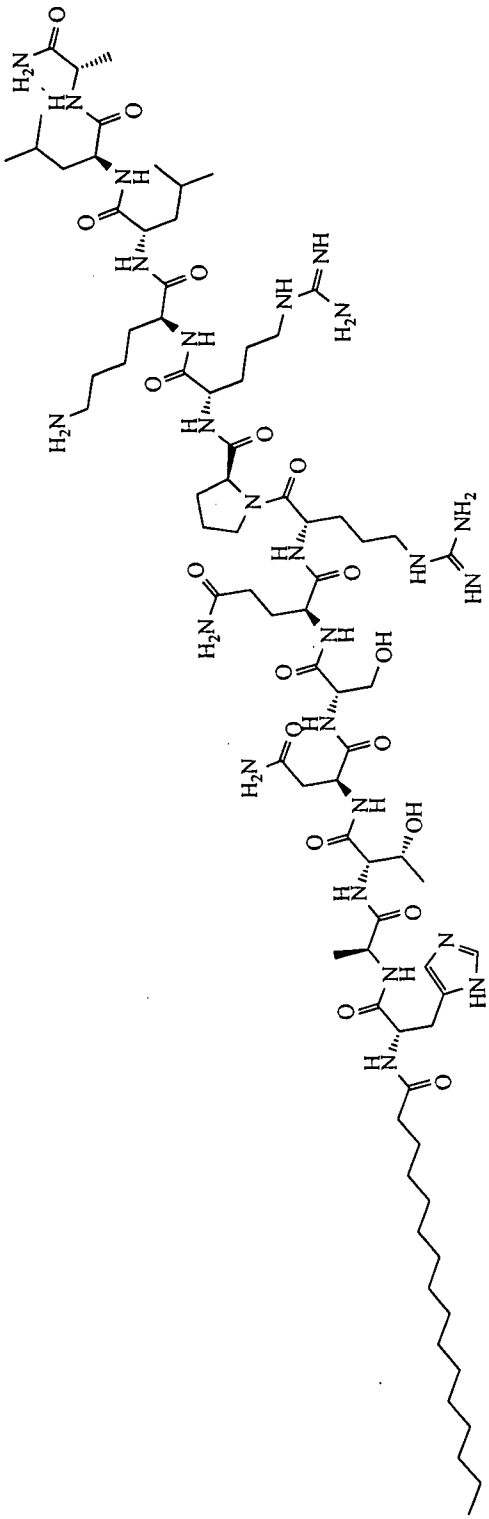

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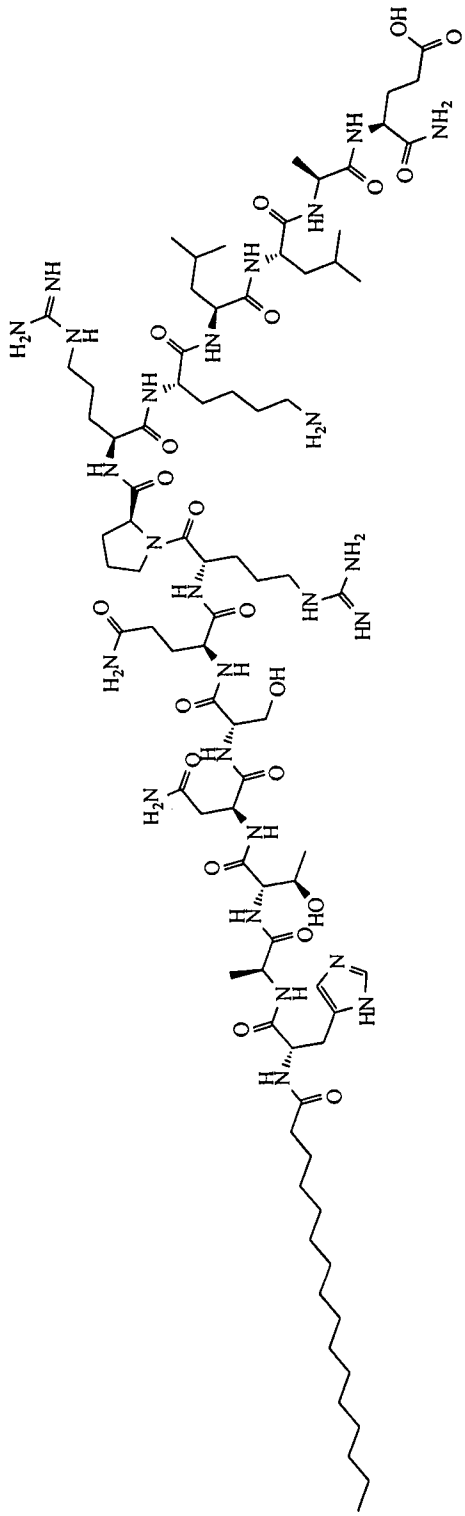

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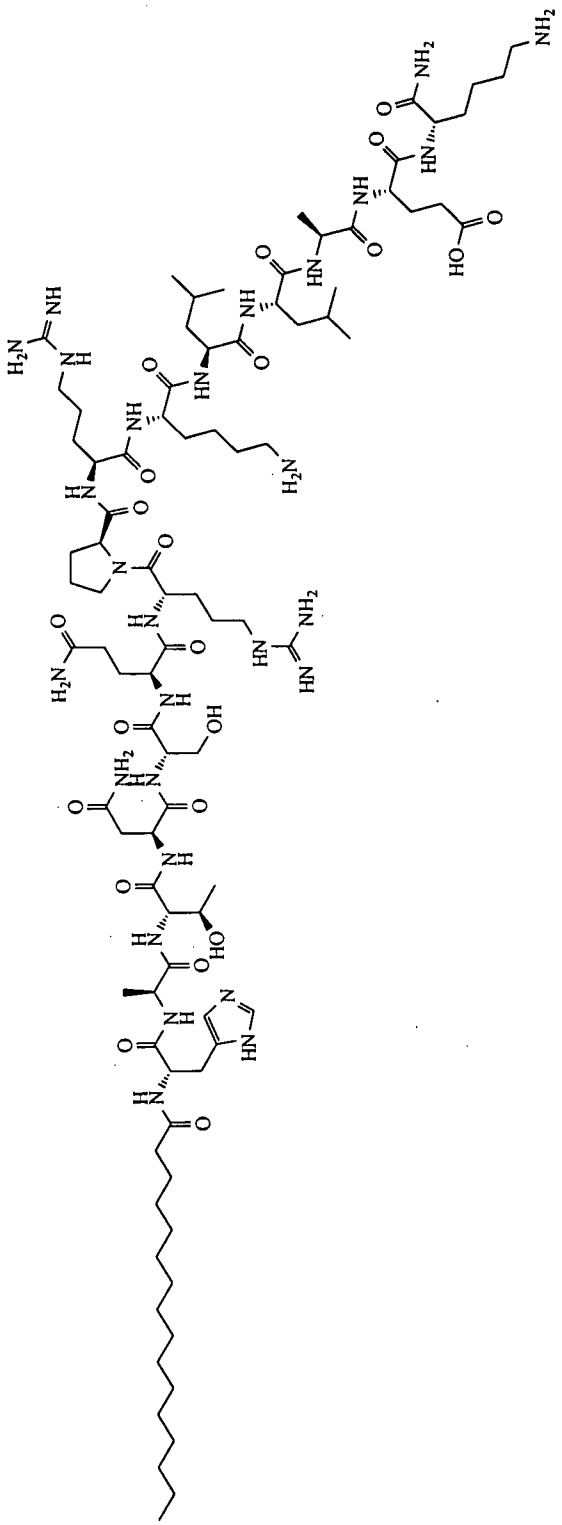

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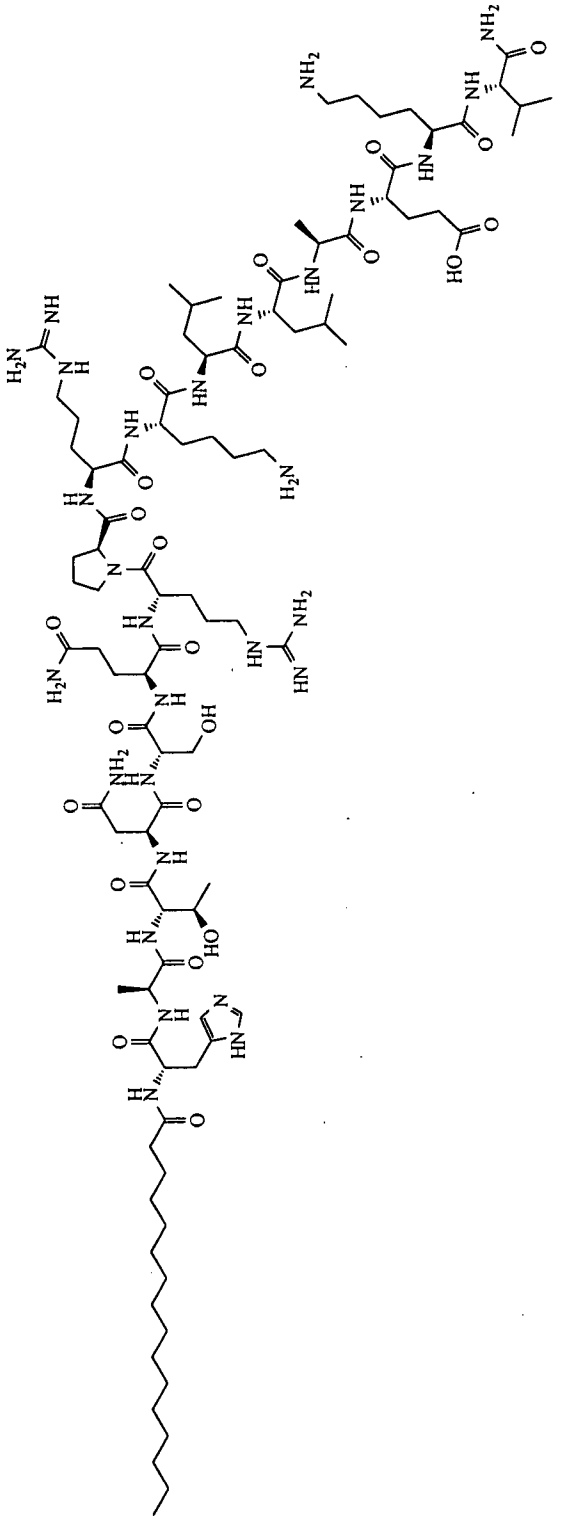


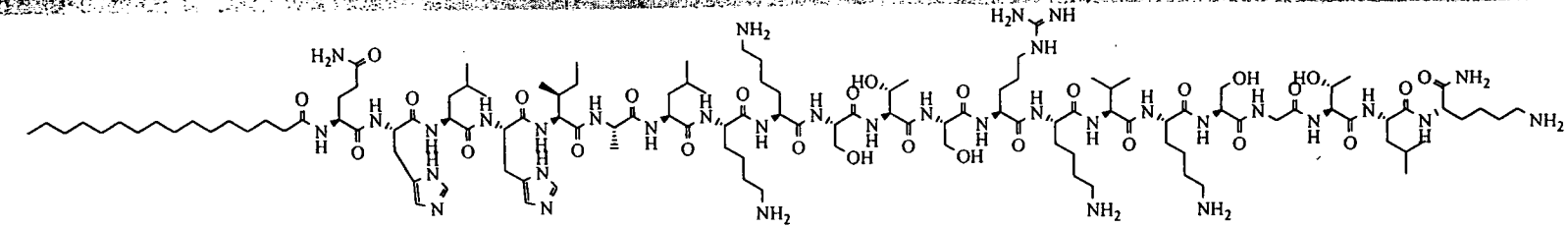
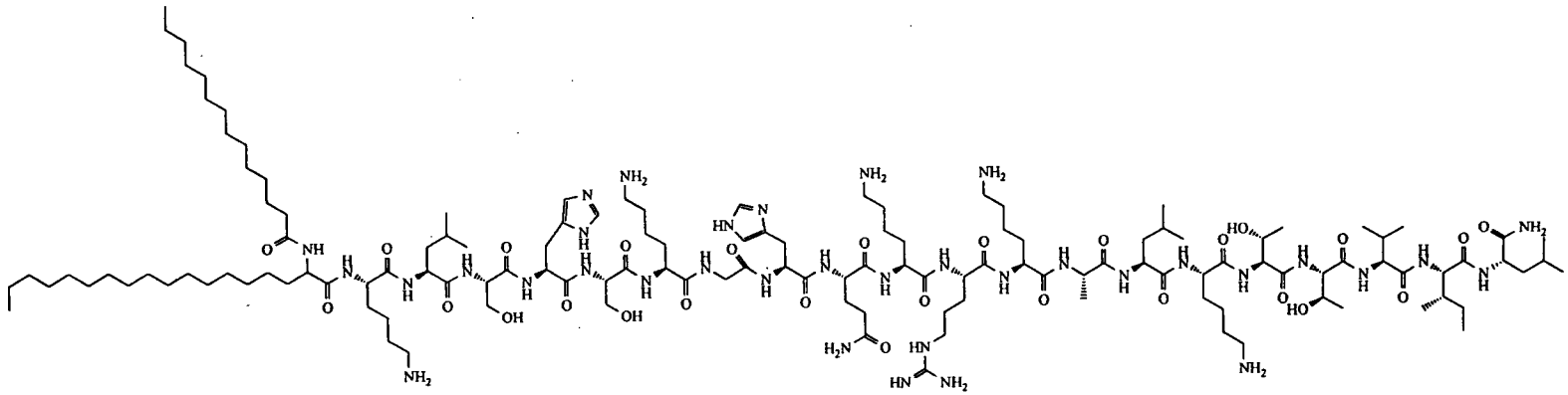
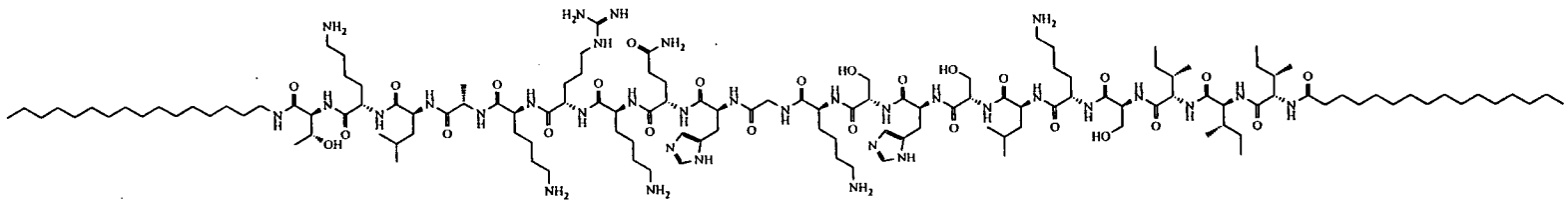
83

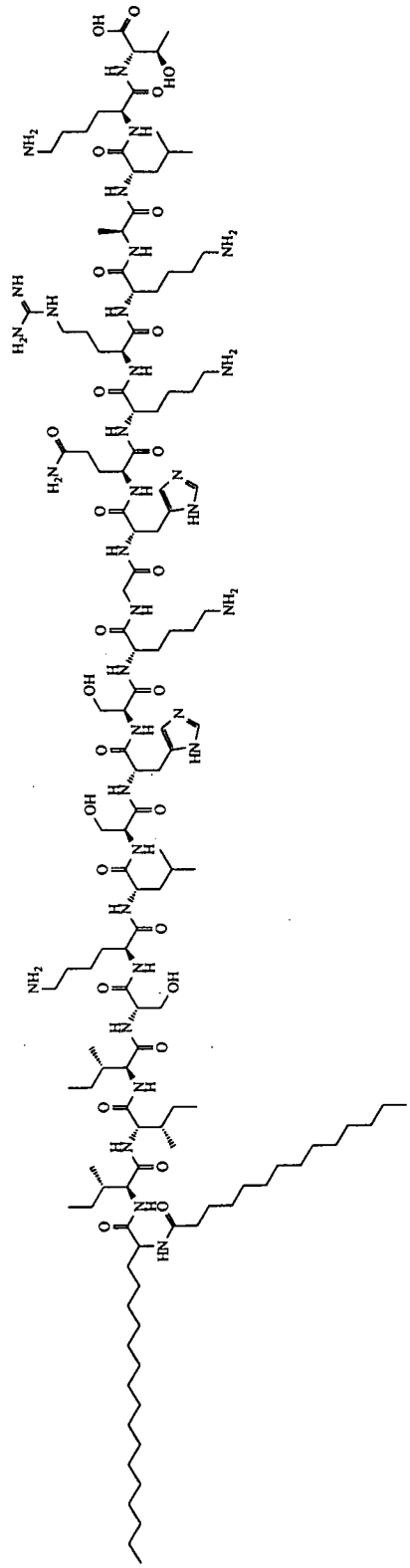
Table 10. CXCR4 i3 loop compounds

	Loop	Sequence	Lipid	Comments	MW
84	i3	HSKKGHQKRKALK (SEQ. ID NO)	Pal		1783.258
85	i3	HSKGHQKRKALK (SEQ. ID NO 369)	Pal		1655.086
87	i3	HSKGHQKRKQALK (SEQ ID NO.)	C16H33	Pentadecyl alanine with Biotin	1924.449
88	i3	SKLSHSKGHQKRKALKTTVIL (SEQ ID NO.)	Pal		2598.225
89	i3	KLSHSKGHQKRKALKTTVIL(SEQ ID NO.)	Pal		2511.147
90	i3	KLSHSKGHQKRKALKTTV(SEQ ID NO.)	Pal		2284.832
91	i3	KLSHSKGHQKRKALKT(SEQ ID NO.)	Pal		2084.597
92	i3	KLSHSKGHQKRKALK (SEQ ID NO.)	Pal		1983.493
93	i3	KLSHSKGHQKRKAL (SEQ ID NO.)	Pal		1855.321
94	i3	KLSHSKGHQKRKA (SEQ ID NO.)	Pal		1742.163
95	i3	LSHSKGHQKRKALK (SEQ ID NO.)	Pal		1855.321
96	i3	SHSKGHQKRKALK (SEQ ID NO.)	Pal		1742.163
97	i3	HSKGHQKRKALKT (SEQ ID NO.)	Pal		1756.19
98	i3	HSKGHQKRKALKTT (SEQ ID NO.)	Pal		1857.294
99	i3	HSKGHQKRKALKTTV (SEQ ID NO.)	Pal		1956.425
100	i3	HSKGHQKRKALKTTVI (SEQ ID NO.)	Pal		2069.583
101	i3	SKLSHSKGHQKRKALK (SEQ ID NO.)	Pal		2070.571
102	i3	IIISKLSHSKGHQKRKALKT (SEQ ID NO.)	Pal		2511.147
103	i3	IIISKLSHSKGHQKRKALKT (SEQ ID NO.)	Myr	dula lipid, backbone	2765.556
104	i3	IIISKLSHSKGHQKRKALKT (SEQ ID NO.)	Pal	dual lipid	2735.573

105	i3	KLSHSKGHQKRKALK TTVIL (SEQ ID NO.)	Myr	Dual lipid, backbone	2764.571
106	i3	QHLHIALKKSTSRKVK SGTLK(SEQ ID NO.)	Pal	scrambled ATI2357	2598.225

Table 11. CXCR4 i3 loop compound structures

Comp. #	Structure
106	
105	
104	



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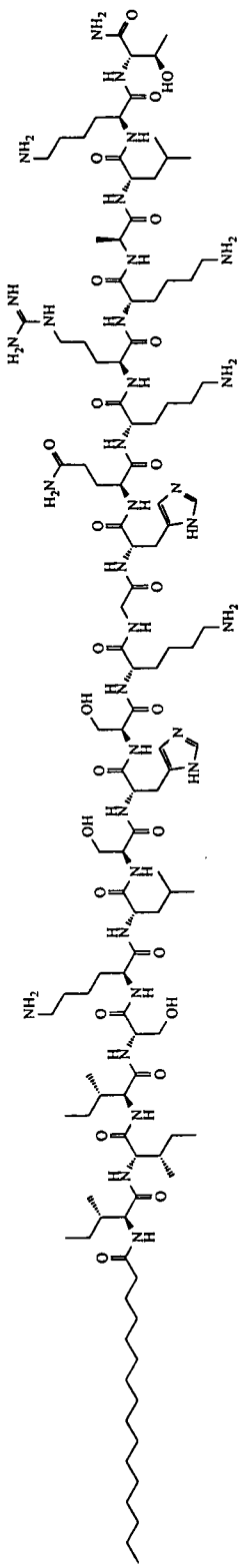

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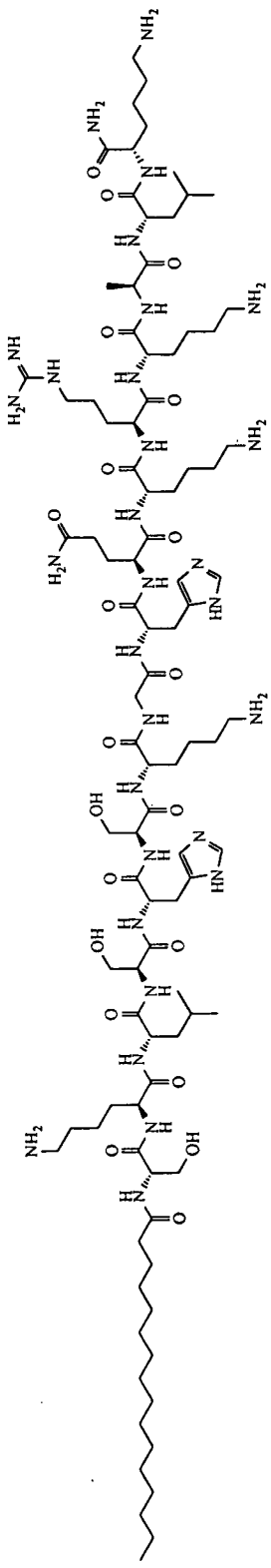

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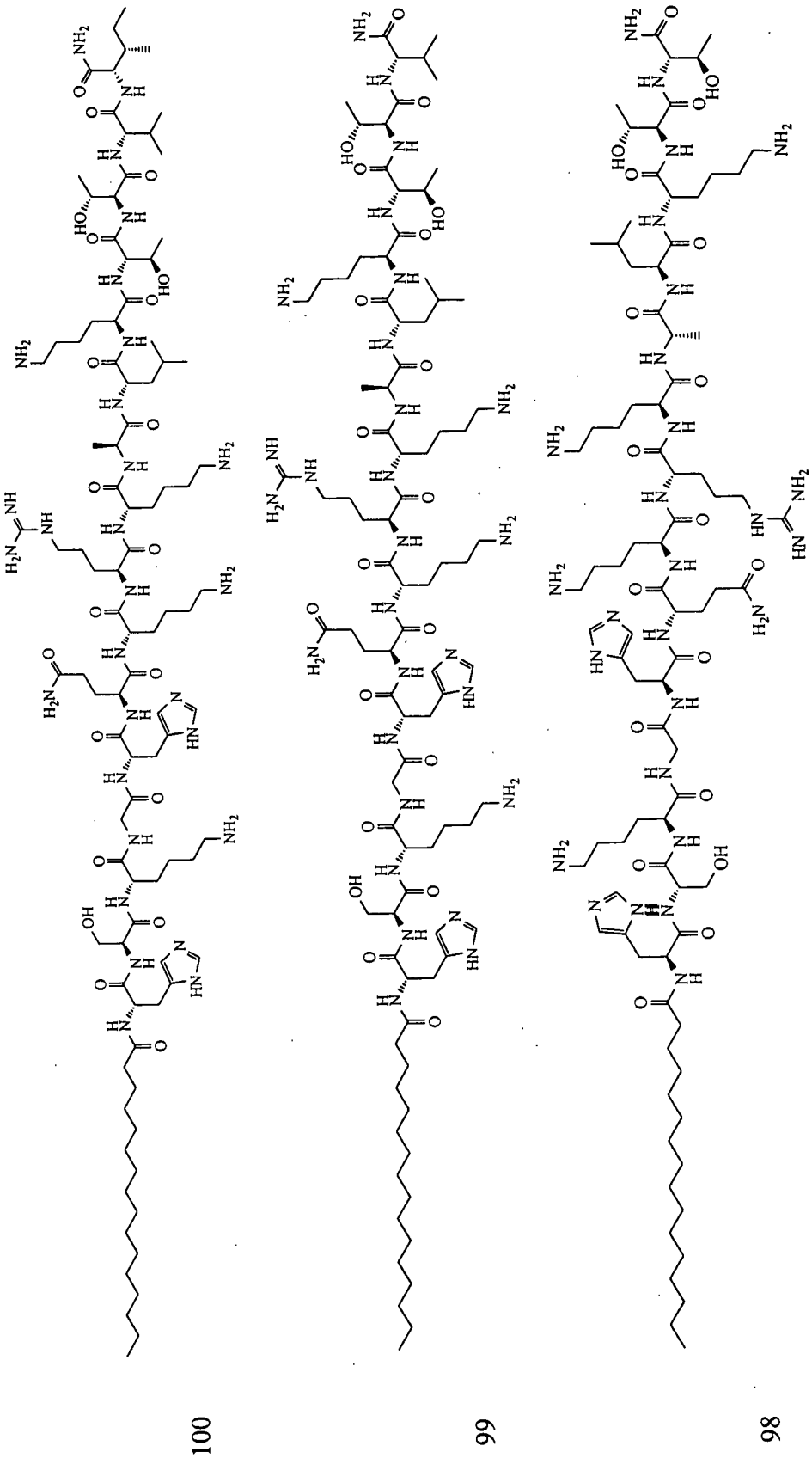
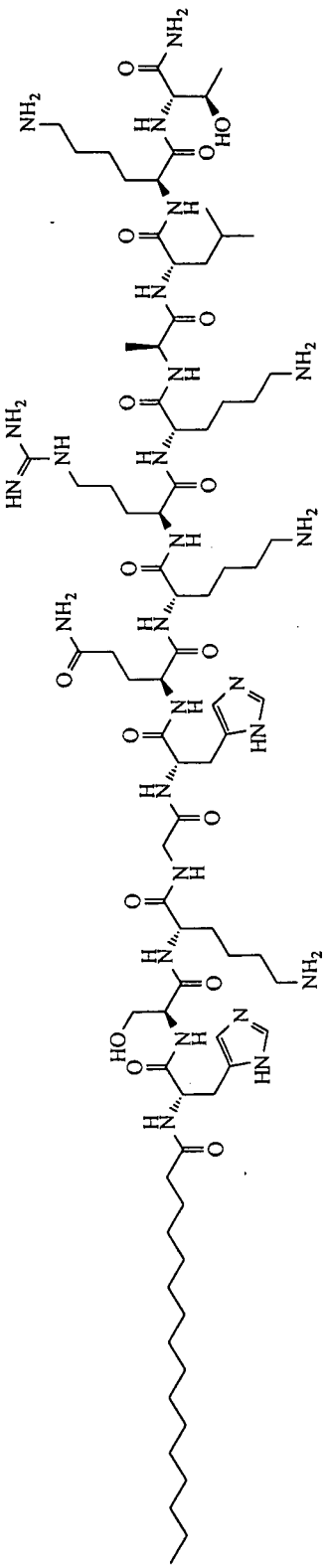


100 99 98



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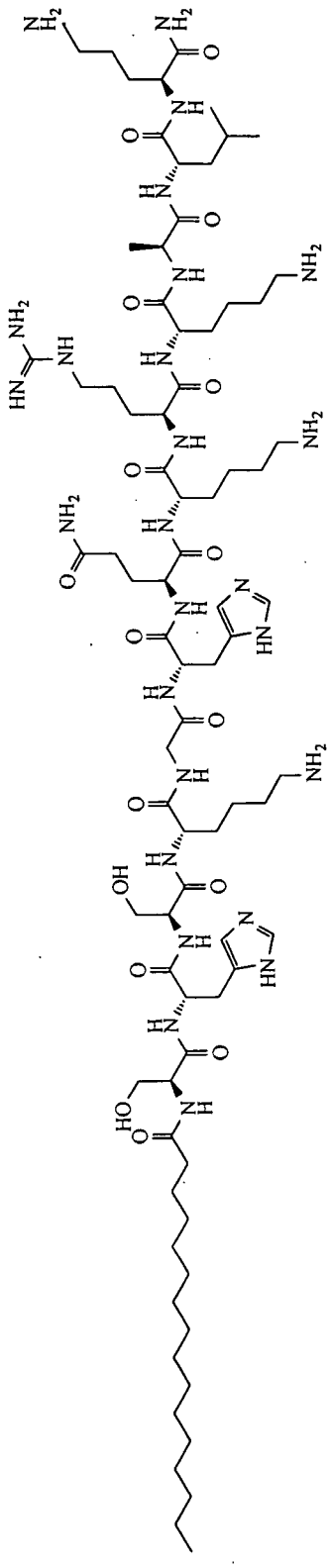

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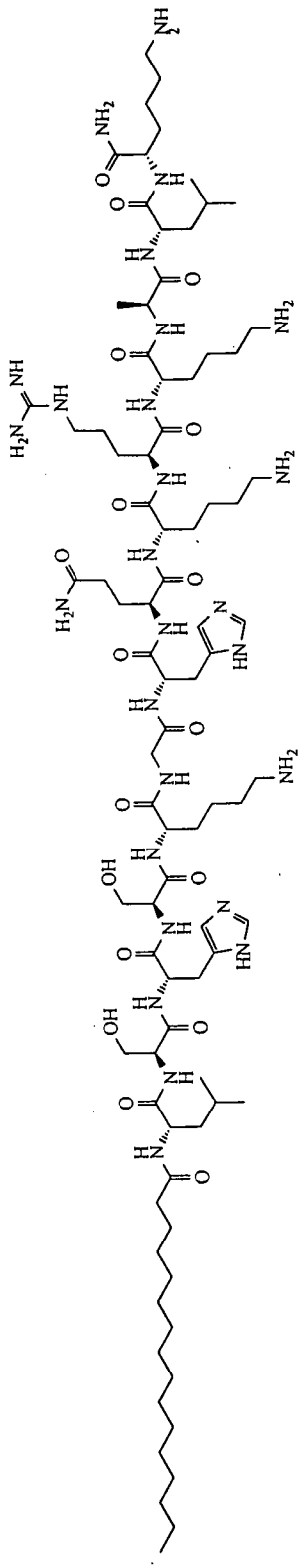

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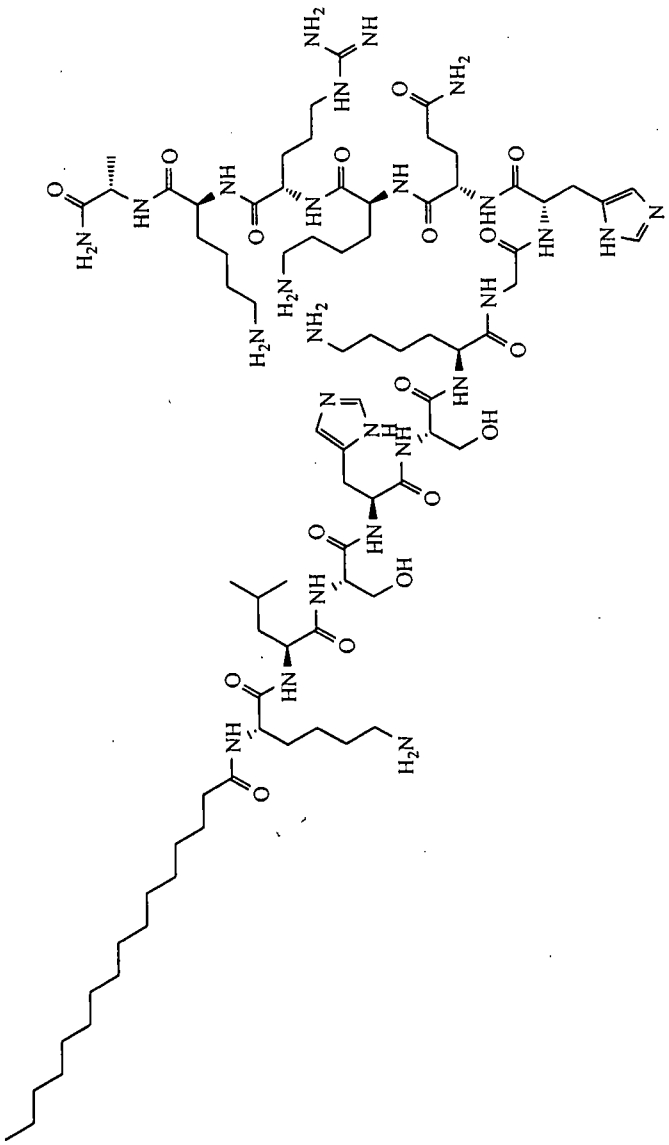

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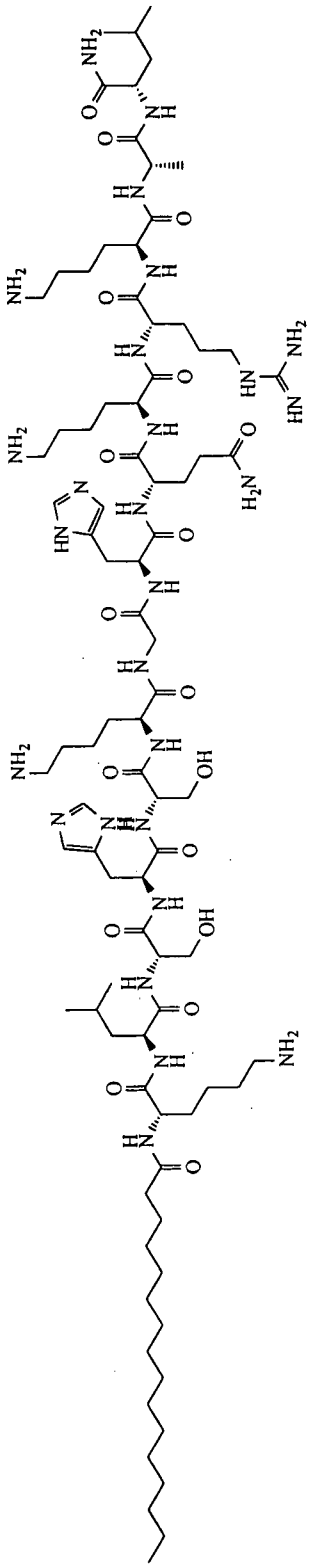

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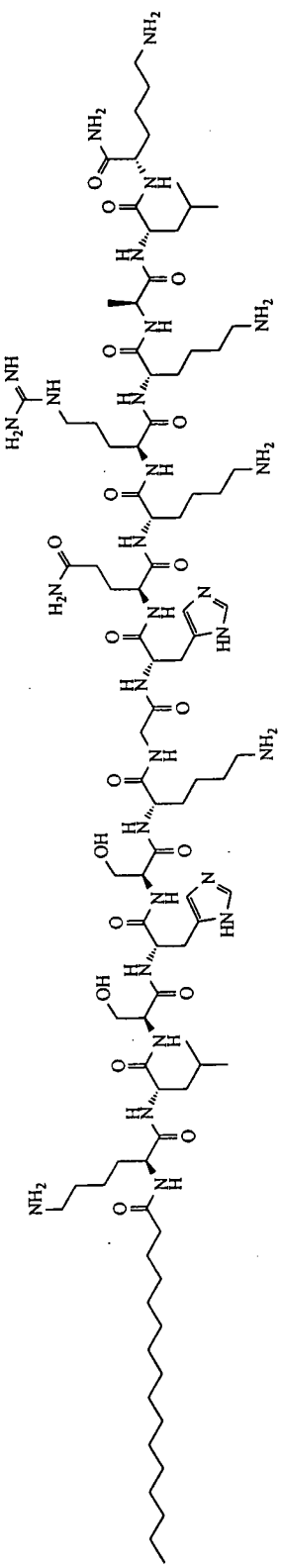

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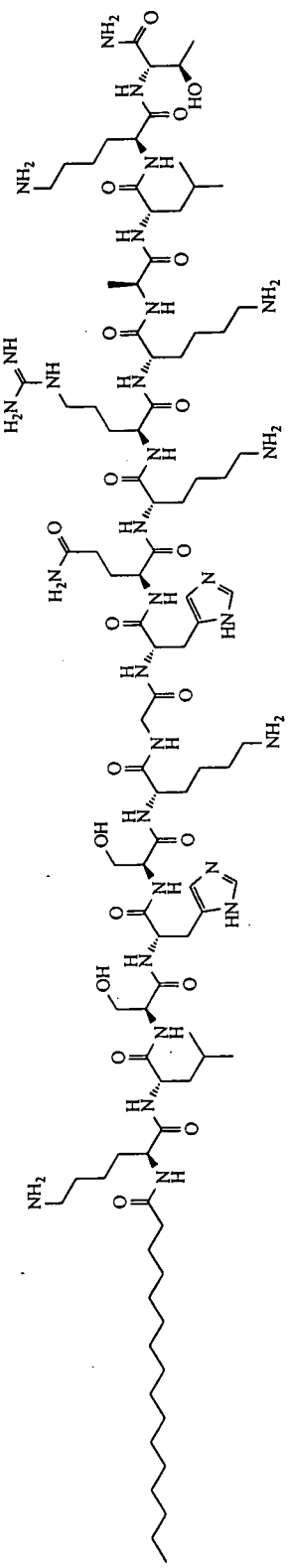

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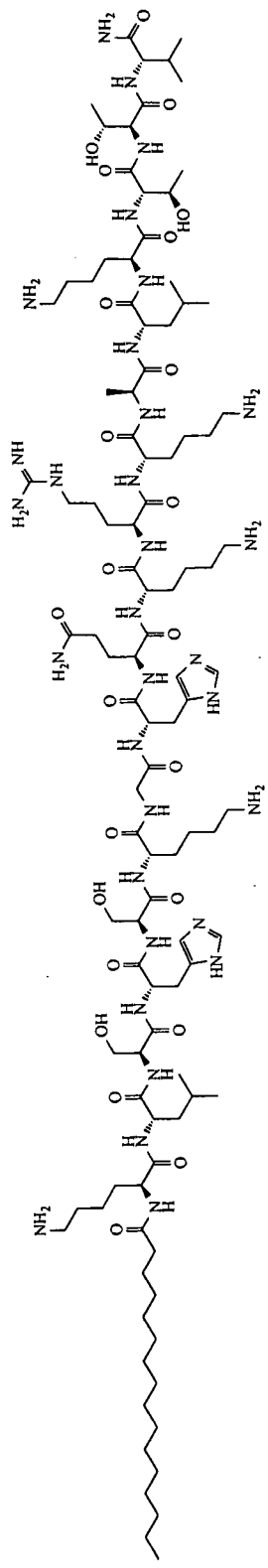

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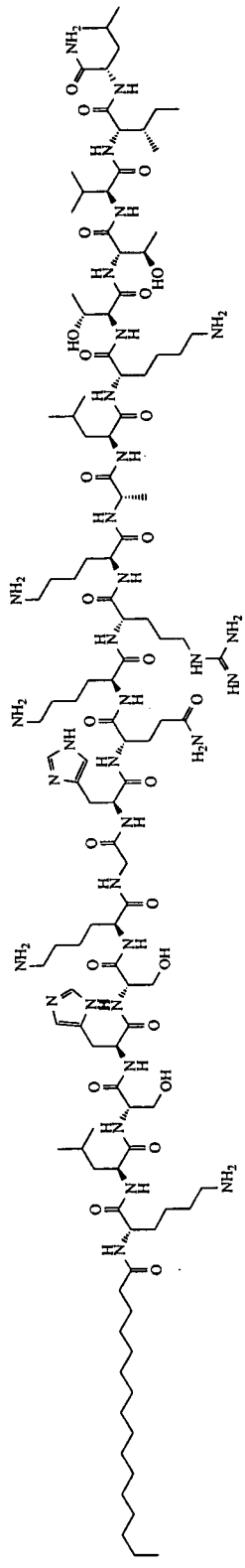

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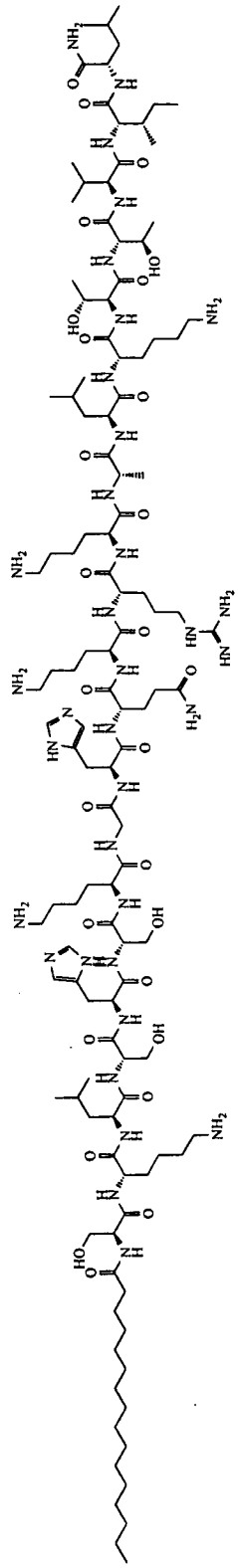

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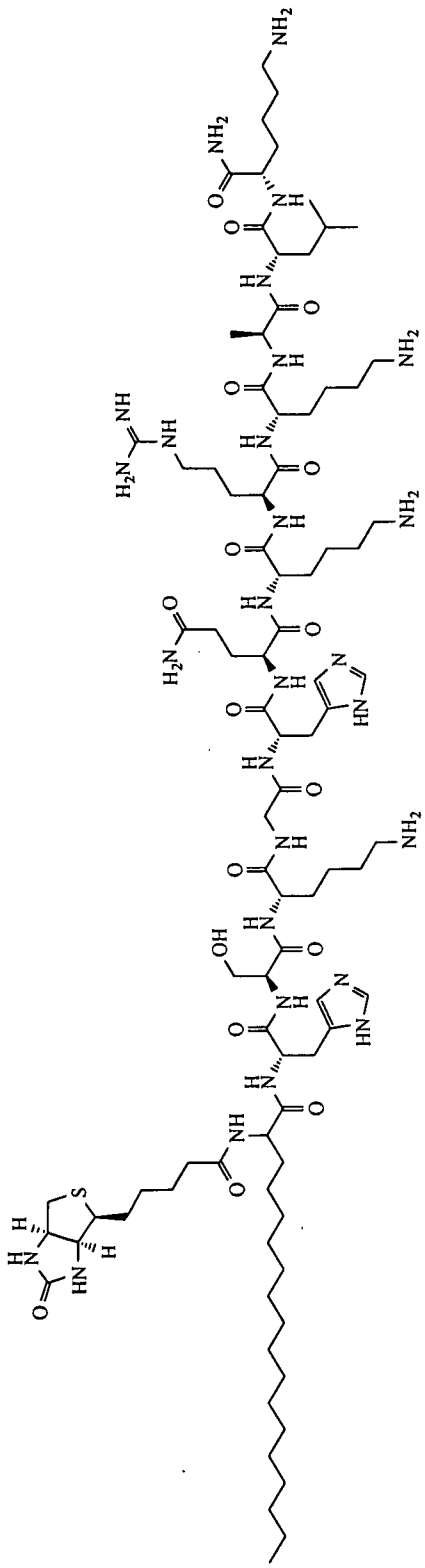

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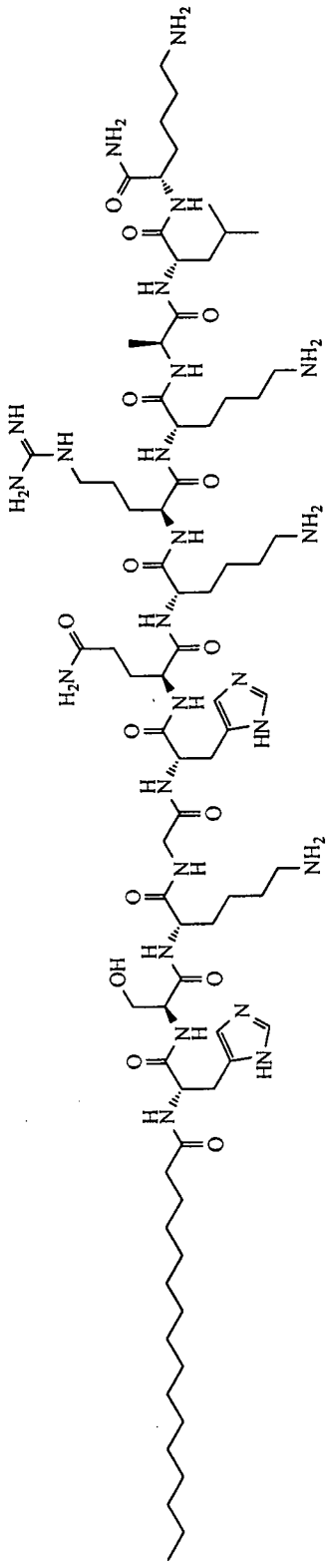

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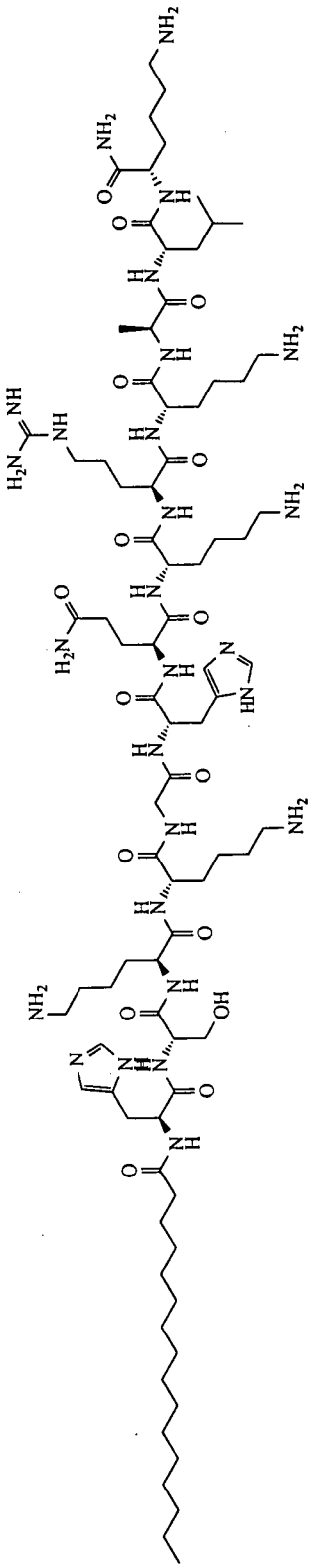
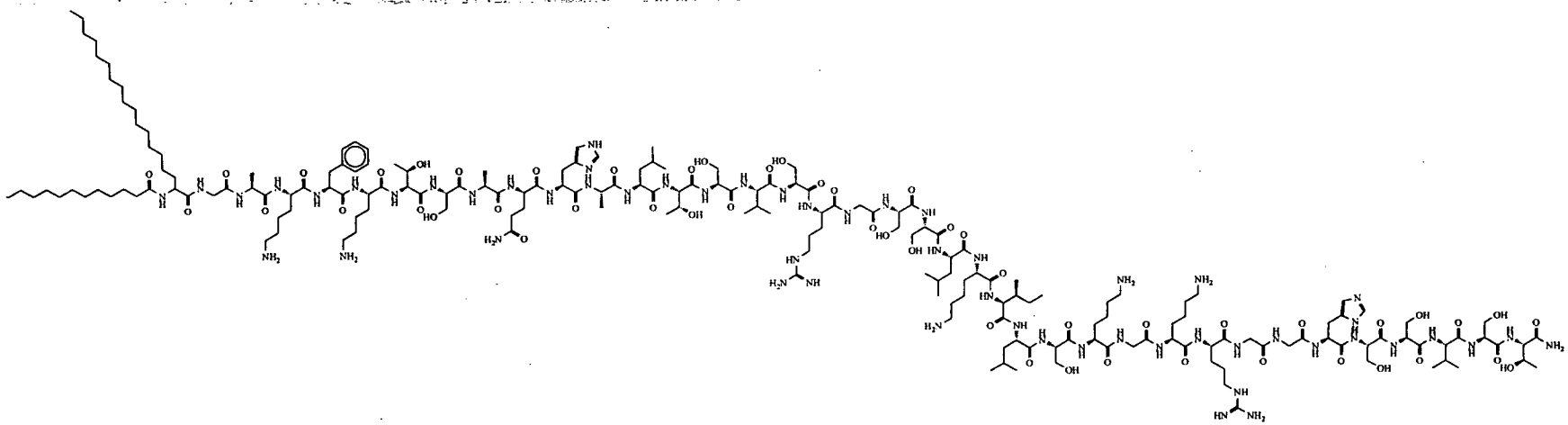


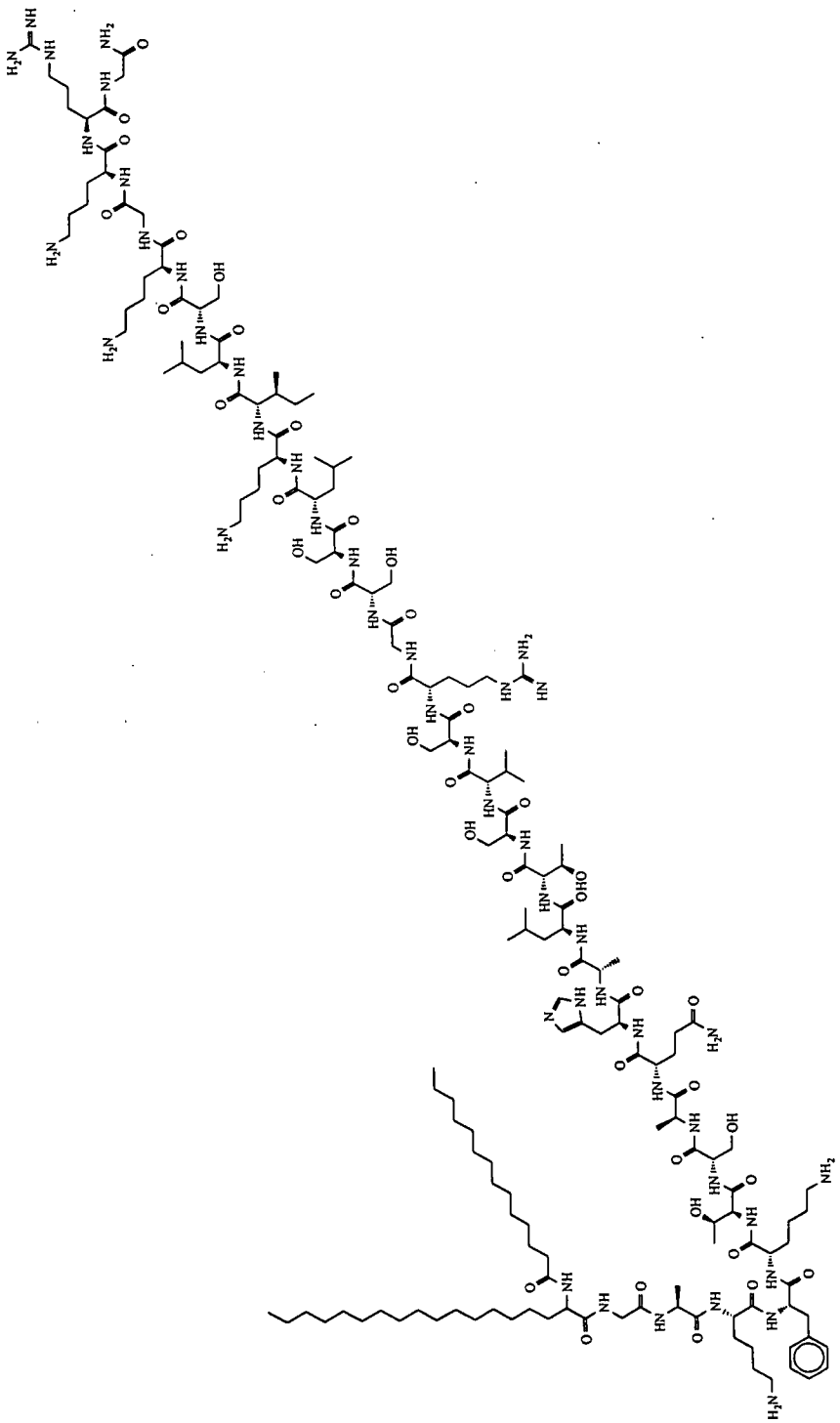
84

Table 12. CXCR4 i4 loop compounds

No.	Loop	Sequence	Lipid	MW	Comments
107	i4	GAKFKTSAQHALTS VSRGSSLKILSKGKR GGHSSVST (SEQ ID NO.)	Myr	4248.067	Backbone lipid - dual lipid
108	i4	GAKFKTSAQHALTS VSRGSSLKILSKGKR G (SEQ ID NO.)	Myr	3592.41	N-terminus and backbone lipid
109	i4	GAKFKTSAQHALTS VSRGSSLKILSKGKR GGHSSVST (SEQ ID NO.)	Pal	3994.644	
110	i4	GAKFKTSAQHALTS VSRGSSLKILSKGKR GGSCFH (SEQ ID NO.)	Pal	3870.571	
111	i4	GAKFKTSAQHALTS VSRGSSLKILSKGKR G (SEQ ID NO.)	Pal	3338.987	
112	i4	GAKFKTSAQHALTS VSRGSSLKILSGGK (SEQ ID NO.)	Pal	3052.8	
113	i4	GAKFKTSAQHALTS VSRG (SEQ ID NO.)	Pal	2083.477	
114	i4	GAKFKTSAQHALTS VSRGSSLKILSK (SEQ ID NO.)	Pal	2940.526	
115	i4	GAKFKTSAQHALTS VSRGSSLK (SEQ ID NO.)	Pal	2498.961	
116	i4	GAKFKTSAQHALTS VR (SEQ ID NO.)	Pal	1938.18	

Table 13. CXCR4 i4 loop compound structures

Comp. #	Structure
107	



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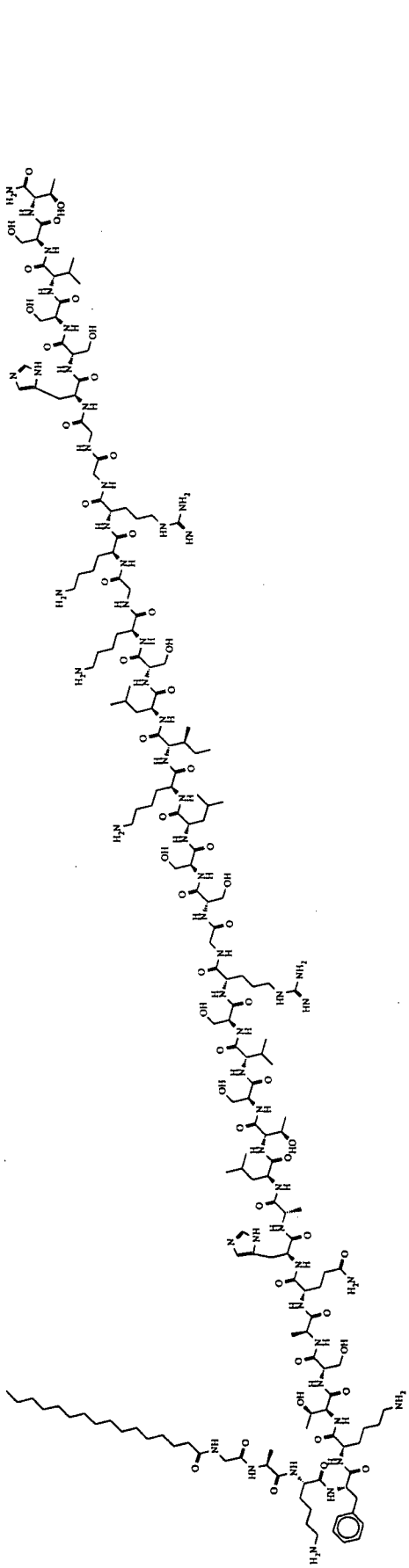

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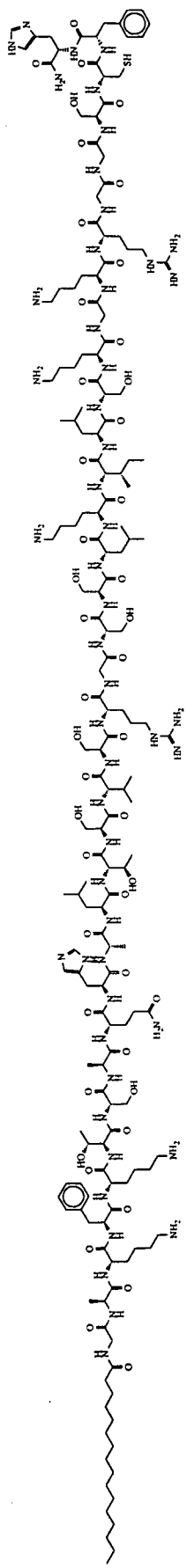

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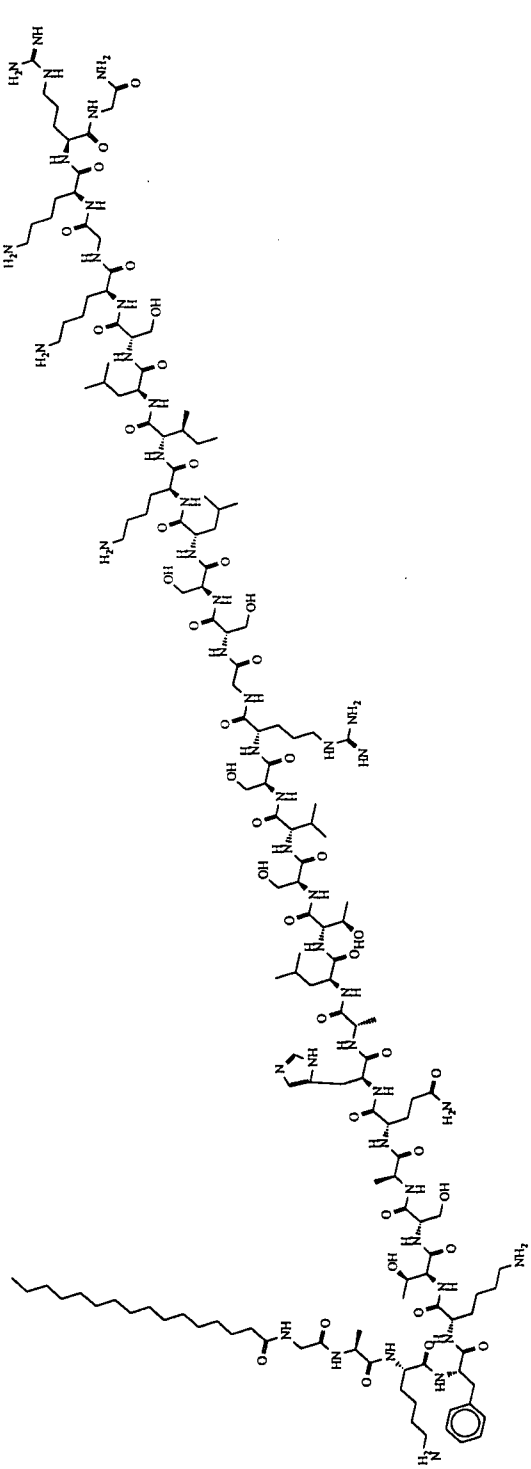
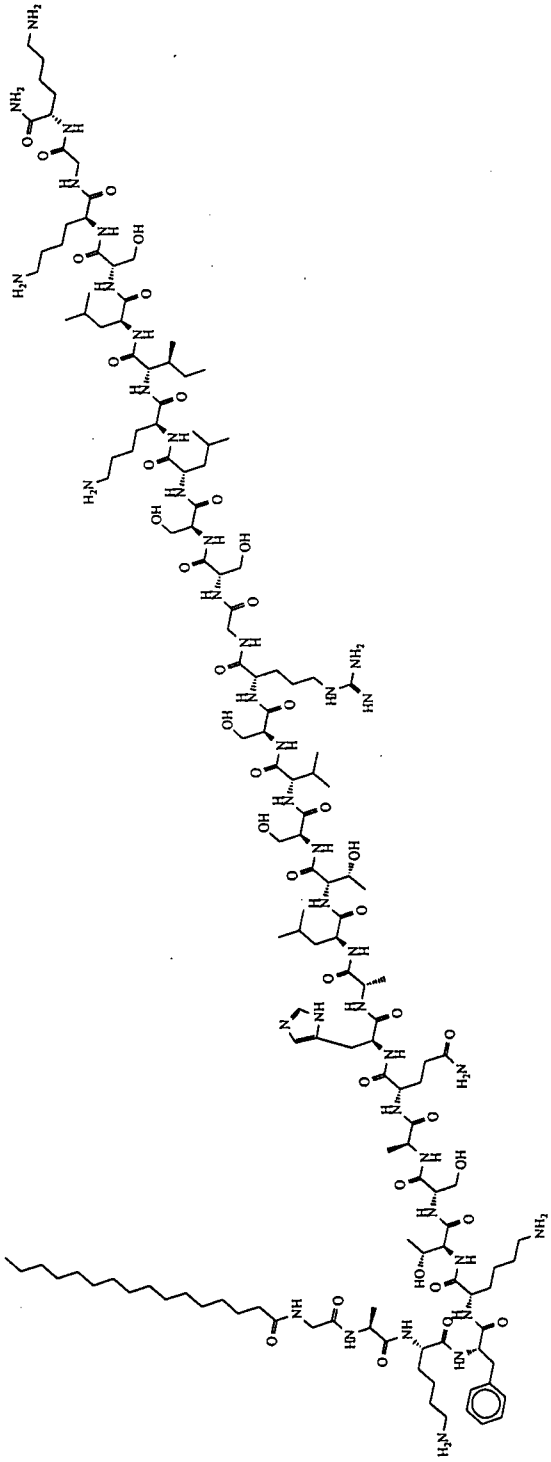


111



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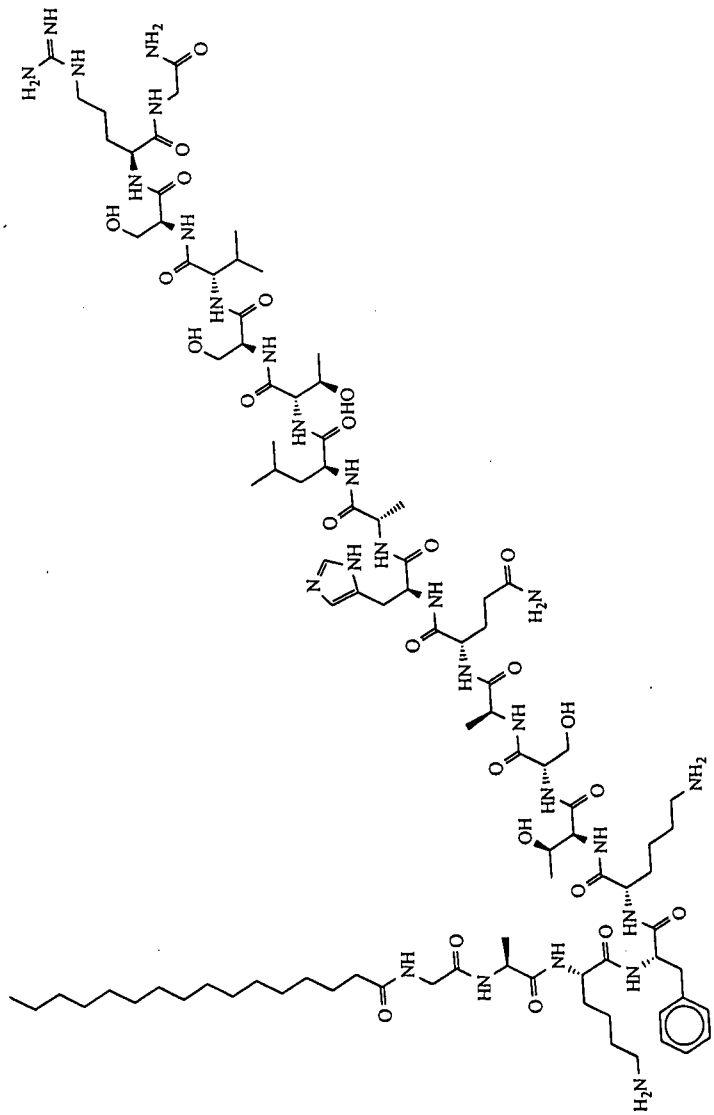

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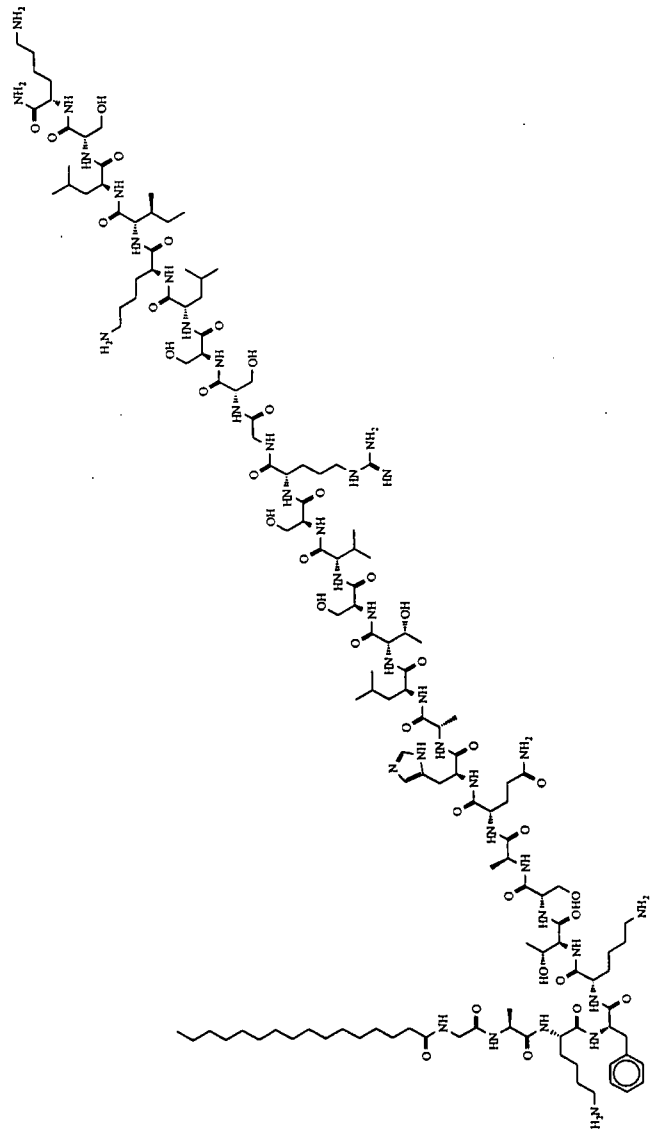

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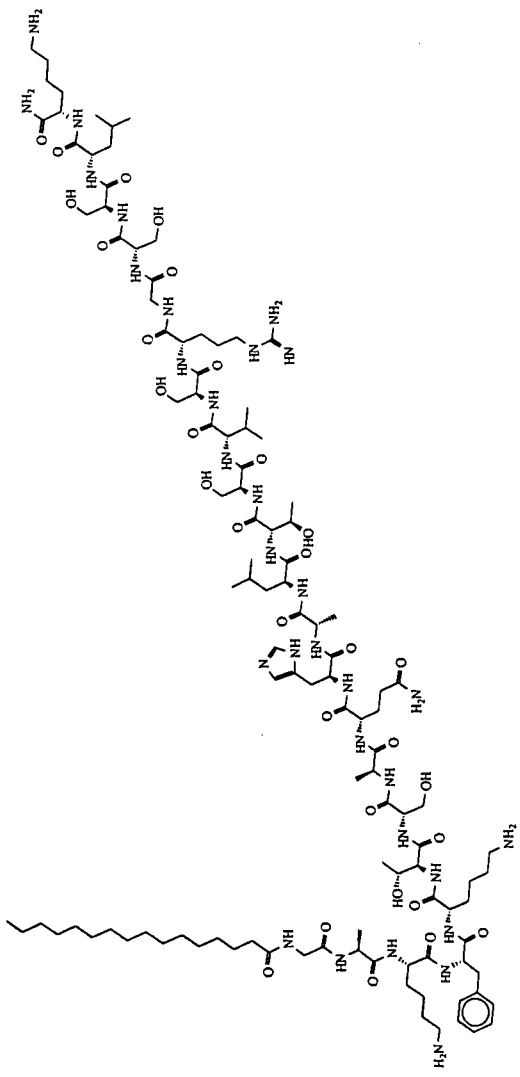

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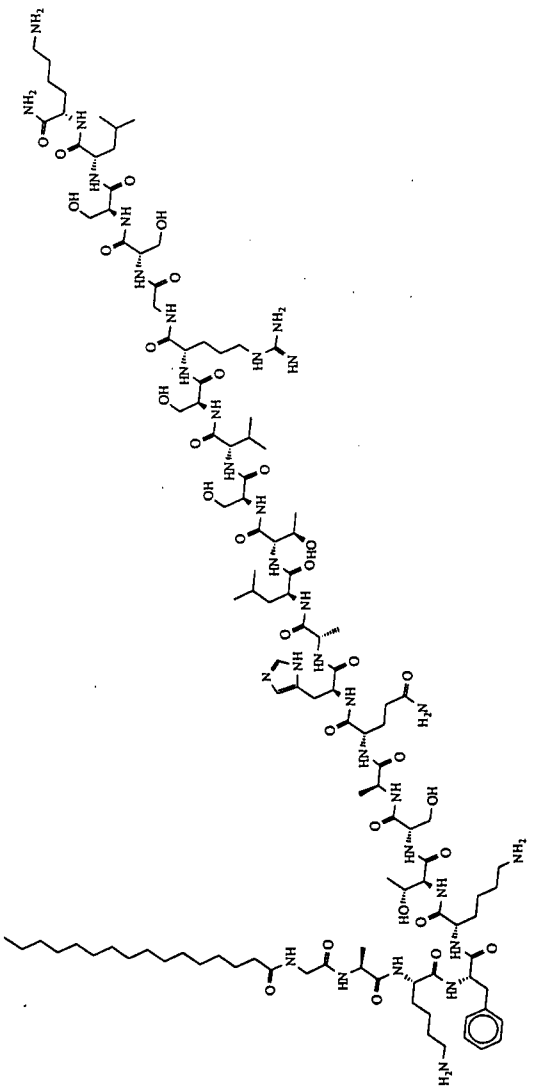
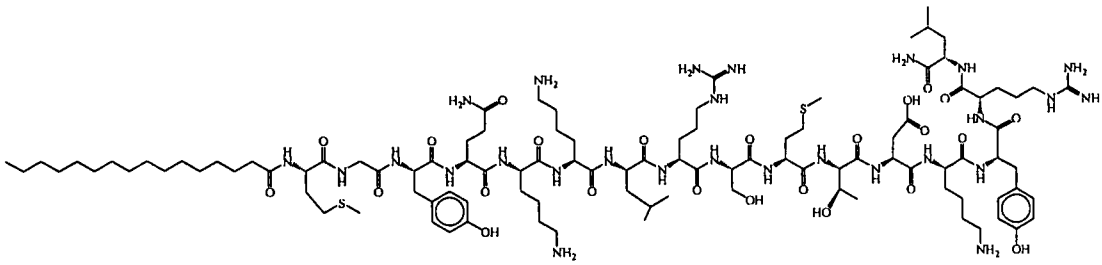


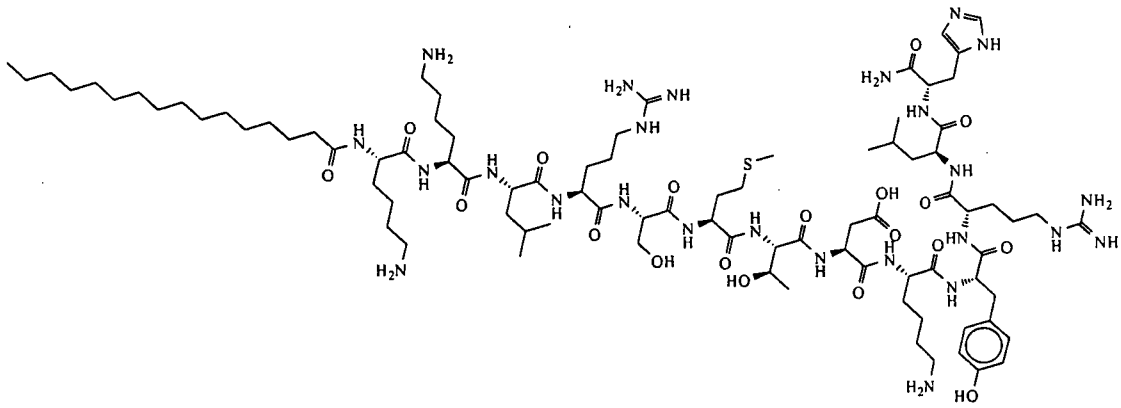
116

In a thirteenth aspect, the compounds are selected from:

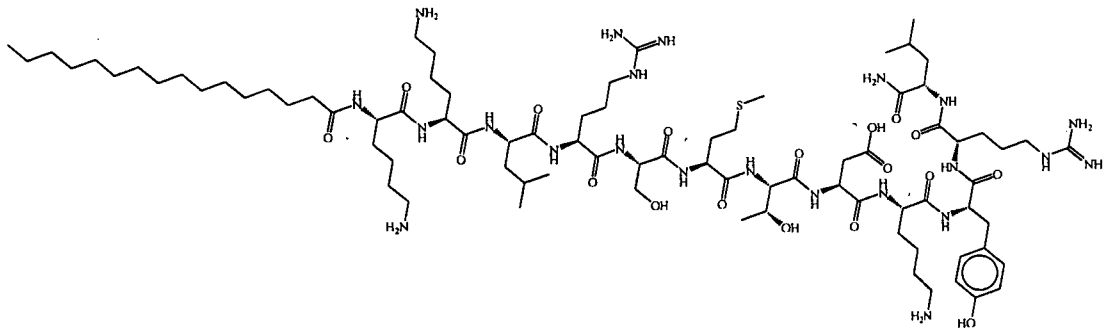
Compound No. 38 (MGYQKKLRSMTDKYRL (SEQ. ID NO),



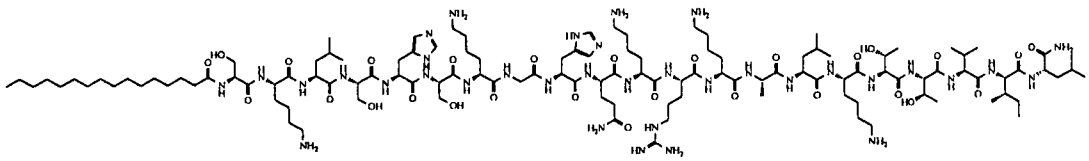
Compound No. 43 (KKLRSMTDKYRLH (SEQ ID NO. 42)),



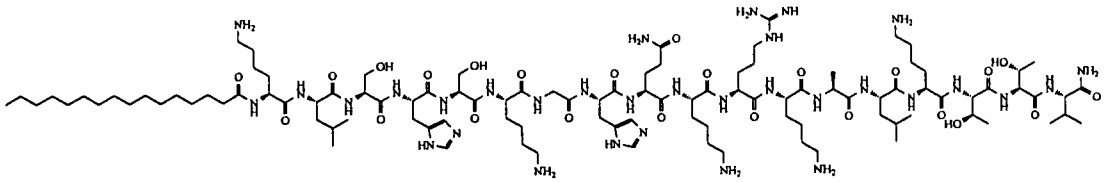
Compound No. 44 (KKLRSMTDKYR (SEQ. ID NO),



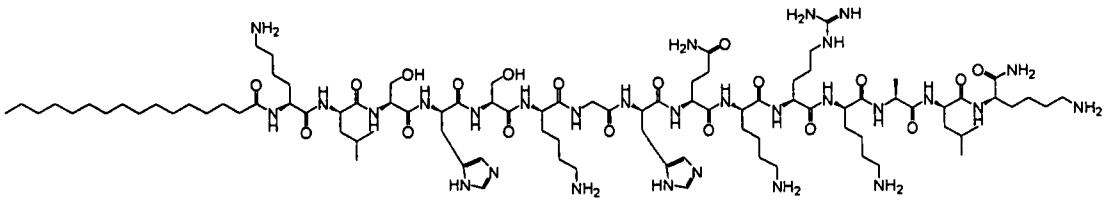
Compound No. 88 (SKLSHSKGHQKRKALKTTVIL (SEQ. ID NO),)



Compound No. 90 (KLSHSKGHQKRKALKTTV (SEQ. ID NO),



Compound No. 92 (KLSHSKGHQKRKALK (SEQ. ID NO),



or a pharmaceutically acceptable salt of any of the foregoing.

"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 atomes.

"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=CH_2), n-2-propenyl (allyl, -CH_2CH=CH_2), 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 (-C≡CH), propargyl (-CH_2C≡CH), pentynyl, hexynyl, and the like.

"Alkylene" refers to a bivalent saturated straight-chained hydrocarbon, e.g., C_1-C_6 alkylene includes –$(CH_2)_6$-, -CH_2-CH-$(CH_2)_3CH_3$, and the like. "Bivalent means that the alkylene group is attached to the remainder of the molecule through two different carbon atoms.

"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.

"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 –OAr group, wherein O is an oxygen atom and Ar is an aryl group as defined above.

"Aralkyl" refers to an alkyl having at least one alkyl hydrogen atom replaced with an aryl moiety, such as benzyl, -$(CH_2)_2$phenyl, -$(CH_2)_3$phenyl, -CH$(phenyl)_2$, and the like.

"Alkyl cycloalkyl" refers to an alkyl having at least one alkyl hydrogen atom replaced with a cycloalkyl moiety, such as $-CH_2$-cyclohexyl, $-CH_2$-cyclohexenyl, and the like.

"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, 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, benzoxa-zolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, 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.

"Heteroaralkyl" refers to an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl moiety, such as $-CH_2$-pyridinyl, $-CH_2$-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.

"Alkyl heterocycloalkyl" refers to an alkyl having at least one alkyl hydrogen atom replaced with a heterocycloalkyl moiety, such as $-CH_2$-morpholino, $-CH_2$-piperidyl and the like.

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

"Hydroxyalkyl" and "alkoxyalkyl" are alky groups substituted with hydroxyl and alkoxy, respectively.

"Amino" means $-NH_2$; "alkylamine" and "dialkylamine" mean –NHR and $-NR_2$, respectively, wherein R is an alkyl group. "Cycloalkylamine" and "dicycloalkylamine" mean –NHR and $-NR_2$, respectively, wherein R is a cycloalkyl group. "Cycloalkylalkylamine" means –NHR wherein R is a cycloalkylalkyl group. "[Cycloalkylalkyl][alkyl]amine" means $-N(R)_2$ 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 of the invention. Examples of suitable substituents are those selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, aryl, heteroaryl, $(C_3$-$C_7)$cycloalkyl, (5-7 membered) heterocycloalkyl, $-NH(C_1$-$C_6)$alkyl, $-N((C_1$-$C_6)$alkyl$)_2$, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, $-CONH_2$, $-OCONH_2$, $-NHCONH_2$, $-N(C_1$-$C_6)$alkylCONH$_2$, $-N(C_1$-$C_6)$alkylCONH$(C_1$-$C_6)$alkyl, $-NHCONH(C_1$-$C_6)$alkyl, $-NHCON((C_1$-$C_6)$alkyl$)_2$, $-N(C_1$-$C_6)$alkylCON$((C_1$-$C_6)$alkyl$)_2$, $-NHC(S)NH_2$, $-N(C_1$-$C_6)$alkylC(S)NH$_2$, $-N(C_1$-$C_6)$alkylC(S)NH$(C_1$-$C_6)$alkyl, $-NHC(S)NH(C_1$-$C_6)$alkyl, $-NHC(S)N((C_1$-$C_6)$alkyl$)_2$, $-N(C_1$-$C_6)$alkylC(S)N$((C_1$-$C_6)$alkyl$)_2$, $-CONH(C_1$-$C_6)$alkyl, $-OCONH(C_1$-$C_6)$alkyl $-CON((C_1$-$C_6)$alkyl$)_2$, $-C(S)(C_1$-$C_6)$alkyl, $-S(O)_p(C_1$-$C_6)$alkyl, $-S(O)_pNH_2$, $-S(O)_pNH(C_1$-$C_6)$alkyl, $-S(O)_pN((C_1$-$C_6)$alkyl$)_2$, $-CO(C_1$-$C_6)$alkyl, $-OCO(C_1$-$C_6)$alkyl, $-C(O)O(C_1$-$C_6)$alkyl, $-OC(O)O(C_1$-$C_6)$alkyl, -C(O)H or $–CO_2H$. More particularly, the substituents are selected from halogen, -CN, -OH, $-NH_2$, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$alkoxy, phenyl, and $(C_3$-$C_7)$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, glycollylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphospate, 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.

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 "pharmaceuticallyacceptable" 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.

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 CXCR4 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 , bone marrow transplantation, chemosensitization, cancer, metastatic disease (e.g., cancer), inflammatory diseases, HIV infection and stem cell-based regenerative medicine, bone marrow transplantation, chemosensitization, cancer, metastatic disease (e.g., cancer), inflammatory diseases, HIV infection and stem cell-based regenerative medicine. For example, the second therapeutic agent is an agent useful in improving the quanity and quality of stem cell harvesting prior to bone marrow ablative cancer therapy.

For example, the second therapeutic agent can be selected from: G-CSF (granulocyte colony-stimulating factor), cyclophosphamide, rituximab and fludaraine. In a particular embodiment, the second therapeutic agent is G-CSF.

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 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 treat (therapeutically or prophylactically) the target disorder. For example, and 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 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 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 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, and 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 CXCR4 receptor comprising administering an effective amount of a CXCR4 receptor compound of the invention to a subject in need thereof. Diseases and conditions which can benefit from modulation (inhibition or activation) of the CXCR4 receptor include, but are not limited to, bone marrow transplantation, chemosensitization, cancer, metastatic disease (e.g., cancer), inflammatory diseases, HIV infection and stem cell-based regenerative medicine. For example, improving the quanity and quality of stem cell harvesting prior to bone marrow ablative cancer therapy.

Bone marrow transplantation can be for treatment of hematological and non hematological malignancies, phagocyte disorders, anemias and myeloproliferative disorders, amyloidoses, radiation poisoning, congenital lysosomal storage disorders and congenital immunodefficiencies.

CXCR4 antagonists are useful for autologous and allogeneic hematopoietic stem cell transplantation (HSCT) to treat acquired as well as congenital diseases. CXCR4 antagonist will be injected into the patients (autologous HSCT) or healthy HLA-matched donor (allogeneic HSCT) before the HSCT procedure. Injection the CXCR4 antagonist induces mobilization of hematopoietc stem cells from bone marrow niche into the peripheral blood. Treatment with the novel CXCR4 antagonist will increase the yield of peripheral hematopoietic stem cells in the amount sufficient for their successful reengraftment or long term storage. HSCs collected during the apheresis procedure will be further reinfused into the patient undergoing HSCT.

The CXCR4 receptor compounds of the invention having antagonist activity are also useful for chemosensitization treatment of patients with hematological malignancies. These patients will be treated with CXCR4 antagonist to induce egress of malignant white blood cells from hematopoietic organs into peripheral circulation. As a result, these abnormal cells will be more readily targeted by chemotherapeutic agents administered intravenously. **b**

Accumulated preclinical data suggests that CXCR4 is essential for the development and progression of inflammatory diseases including but not limited to rheumatoid arthritis and inflammatory bowl disease. Therefore antagonism of CXCR4 can be beneficial for the patients suffering from these disorders. CXCR4 is

also a coreceptor for the entry of several HIV-1 strains. Pharmacological targeting of CXCR4-dependent can potentially modulate HIV-1 tropism and it's infectivity.

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 CXCR4 receptor. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of second therapeutic agents that may be employed in the methods of this invention are those set forth above for use in combination compositions comprising a compound of this invention and a second therapeutic agent.

The term "co-administered" as used herein means that the 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 as described above) 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 CXCR4 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); Spinger-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 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-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 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 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 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 SSPS. Preactivated amino acids such as OSu active ester and acid fluorides also can be used, requiring only a base for completion of the reaction.

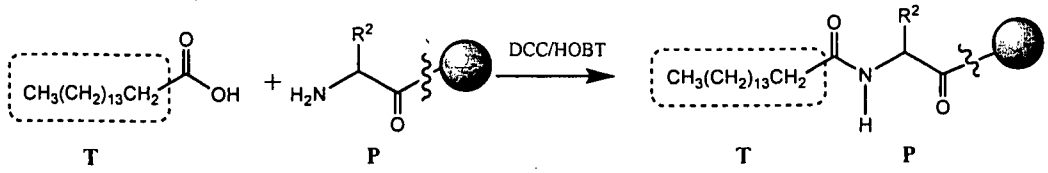
Coupling times require 1.5-2 hours for each step. Two fragments are condensed in solution, giving a larger fragment that then can be further condensed with additional fragments until the desired sequence is complete. The solution phase protocol uses only 1eq of each fragment and will use coupling reagents 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.

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. 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.

Attachment of Tethers

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



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 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*H_2O, 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

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:	2-95%B (10 minutes); 95-2%B (2 minutes); 2% B (2 minutes)

Preparative LC/MS Method

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
Injection:	900 ul
Gradient:	35%B (5 minutes); 35-85%B (13 minutes); 85-35% B (0.5 minutes); 35%B (1.5 minutes)

The compounds listed in Tables 14-17 or pharmaceutically acceptable salts thereof were prepared according to the methods described herein.

Table 14. CXCR4 i1 loop compounds

No.:	Loop	Sequence	N-terminus T-L	C-terminus	MS Theoretical	MS Observed Ion
1	i1	AGYQKKLRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
2	i1	MAYQKKLRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
3	i1	MGAQKKLRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
4	i1	MGYAKKLRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
5	i1	MGYQKKLRAMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
6	i1	MGYQKKLRSATD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
7	i1	MGYQKKLRSMAD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
8	i1	MGYQKKLRSMTA (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
9	i1	MGYQAKLRSMTD	$C_{15}H_{31}C(O)$-	NH_2		
10	i1	MGYQKKLASMTD	$C_{15}H_{31}C(O)$-	NH_2		
11	i1	MGYQKALRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
12	i1	MGYQKKARSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
13	i1	mGYQKKLRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
14	i1	MGyQKKLRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
15	i1	MGYqKKLRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
16	i1	MGYQkKLRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
17	i1	MGYQKkLRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
18	i1	MGYQKKlRSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
19	i1	MGYQKKLrSMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
20	i1	MGYQKKLRsMTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
21	i1	MGYQKKLRSmTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
22	i1	MGYQKKLRSMtD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
23	i1	MGYQKKLRSMTd (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
24	i1	GSHYQKKLRSSTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
25	i1	SGYQKKLRSSTD (SEQ ID NO.)	$C_{17}H_{33}C(O)$-	NH_2		

26	i1	SGYQKKLRSSTD (SEQ ID NO.)	$C_{16}H_{31}C(O)$-	NH_2		
27	i1	sGYQKKLRSSTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
28	i1	GSGYQKKLRSST D (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
29	i1	YQKKLRSSTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
30	i3	JGYQKKLRSJTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
31	i3	JGYQKKLRSJTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
32	i1	MGYQKKLRSMT D (SEQ ID NO.)	$CH_3C(O)$-	NH2		
33	i1	MGYQKKLRSMT D (SEQ ID NO.)	Footnote: 1	NH_2	655.8	655.5
34	i1	LVMGYQKKLRS MTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	954.7, 636.8	954.2, 646.3
35	i1	VMGYQKKLRS MTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	898.1	897.7
36	i1	MGYQKKLRSMT DK (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	912.7	912.2
37	i1	MGYQKKLRSMT DKY (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	994.3	993.7
38	i1	MGYQKKLRSMT DKYRL (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	752.9	753
39	i1	MGYQKKLRSMT DKYRLHL (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	836.4	836
40	i1	YQKKLRSMTDK YRLHLSV (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	1253.0, 835.7, 627.2	1254, 836, 627.50
41	i1	KKLRSMTDKYR LHLSV (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	1107.4, 738.6, 554.2	1107.0, 738.0, 554
42	i1	KKLRSMTDKYR LHL (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	1014.3, 676.5	1014.0, 676.0
43	i1	KKLRSMTDKYR LH (SEQ ID NO. (SEQ ID NO. 42))	$C_{15}H_{31}C(O)$-	NH_2	957.7, 638.8	958.0, 638.0
44	i1	KKLRSMTDKYR L (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	889.2, 592.1	888.0, 592.0
45	i1	KKLRSMTDKYR (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	832.6	833
46	i1	KKLRSMTDKY (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	754.5	754
47	i1	MGYQKKLRSMT DKYRI (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	827.8, 621.0	828.0, 621.0
48	i1	MGYQKKLRSMT DKYRI (SEQ ID NO.)	Footnote: 2	NH_2	837.4	837.4

49	il	MGYQKKLRSMT DKYRI (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	752.9	753
50	il	SGYQKKLRSSTD (SEQ ID NO.)	Footnote: 2	NH_2	931.2	931
51	il	MGYQKKLRSMT D (SEQ ID NO.)	Footnote: 2	NH_2	975.3, 650.5	975.0, 650.5
52	il	QKKLRSMTDKY RI (SEQ ID NO.)	$CH_3C(O)$-	$NHC_{16}H_{33}$	645.2	645
53	il	MGYQKKLRSMT DKYRLHL (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	683.7	684
54	il	MGYQKKLRSMT DKYRLHL (SEQ ID NO.)	Footnote: 2	NH_2	920.9, 690.9	921.0, 691.0
55	il	MGYQKKLRSMT DKYRLHLSV (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	898.4	898
56	il	MGYQKKLRSMT DKYRLHLSV (SEQ ID NO.)	Footnote: 2	NH_2	982.9, 737.5	982.0, 737.0
58	il	MGYQKKLRSMT DK (SEQ ID NO.)	$CH_3C(O)$-	NH_2	814.5	814.5
59	il	MGYQKKLRSMT DK (SEQ ID NO.)	$CH_3C(O)$-	$NHC_{16}H_{33}$	926.7, 618.1	926.5, 618
60	il	MGYQKKLRSMT DK (SEQ ID NO.)	Footnote: 2	NH_2	693.2	693.2
61	il	KKLCRSMTDKC YRL (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	991.2	990
62	il	KKLRCSMTDCK YRL (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
63	il	KKLRSMTDKYR L (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	902.2	901.7
64	il	KKLRSMTDKYR L (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	911.2	910.5
65	il	KRMKTSLYDGR MQYLK (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	752.9	752.3
66	il	YTKRLDSHRKL KM (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	957.7	956.7
67	il	MGYQKKLRSMT DKYRL (SEQ ID NO.)	CH3C(O)-	NH_2	687.8	687
68	il	KKLRSXTDKYR LH (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2	632.8	632.3
69	il	SGYQKKLRSSTD (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
70	il	SGYQKKLRSSTD (SEQ ID NO.)	$C_{16}H_{33}O_2C(O)$-	NH_2		
71	il	SGYQKKLRSSTD (SEQ ID NO.)	$C_{23}H_{39}OC(O)$-	NH_2		
72	il	MGYQKKLRSST D (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		
73	il	SGYQKKLRSMT D (SEQ ID NO.)	$C_{15}H_{31}C(O)$-	NH_2		

117	i1	kKLRSMTDKYR LH (SEQ ID NO. 89)	Pal			
118	i1	KkLRSMTDKYR LH (SEQ ID NO. 90)	Pal			
119	i1	KKlRSMTDKYRL H (SEQ ID NO.91)	Pal			
120	i1	KKLrSMTDKYRL H (SEQ ID NO.92)	Pal			
121	i1	KKLRsMTDKYR LH (SEQ ID NO.93)	Pal			
122	i1	KKLRSmTDKYR LH (SEQ ID NO. 94)	Pal			
123	i1	AKLRSMTDKYR LH (SEQ ID NO. 95)	Pal			
124	i1	KALRSMTDKYR LH (SEQ ID NO.96)	Pal			
125	i1	KKARSMTDKYR LH (SEQ ID NO.97)	Pal			
126	i1	KKLASMTDKYR LH (SEQ ID NO. 98)	Pal			
127	i1	KKLRAMTDKYR LH (SEQ ID NO. 99)	Pal			
128	i1	KKLRSATDKYR LH (SEQ ID NO. 100)	Pal			
129	i1	AGYQKKLRSMT DKYRL (SEQ ID NO101.)	Pal			
130	i1	MAYQKKLRSMT DKYRL (SEQ ID NO.102)	Pal			
131	i1	MGAQKKLRSMT DKYRL (SEQ ID NO. 103)	Pal			
132	i1	MGYAKKLRSMT DKYRL (SEQ ID NO. 104)	Pal			
133	i1	MGYQAKLRSMT DKYRL (SEQ ID NO.105)	Pal			
134	i1	MGYQKALRSMT DKYRL (SEQ ID NO.106)	Pal			
135	i1	MGYQKKARSM TDKYRL (SEQ ID NO.107)	Pal			

136	il	MGYQKKLASMT DKYRL (SEQ ID NO. 108)	Pal			
137	il	KKLRSMTDKYR LH (SEQ ID NO.42)	Myr			
138	il	KKLRSMTDKYR LH (SEQ ID NO.42)	Lca			
139	il	KKLRSMADKYR LH (SEQ ID NO.)	Pal			
140	il	KKLRSMTAKYR LH (SEQ ID NO.)	Pal			
141	il	KKLRSMTDAYR LH (SEQ ID NO.)	Pal			
142	il	KKLRSMTDKAR LH (SEQ ID NO.)	Pal			
143	il	KKLRSMTDKYA LH (SEQ ID NO.)	Pal			
144	il	KKLRSMTDKYR AH (SEQ ID NO.)	Pal			
145	il	KKLRSMTDKYR LA (SEQ ID NO.)	Pal			
146	il	MGYQKKLRAM TDKYRL (SEQ ID NO.)	Pal			
147	il	MGYQKKLRSAT DKYRL (SEQ ID NO.)	Pal			
148	il	MGYQKKLRSM ADKYRL (SEQ ID NO.)	Pal			
149	il	MGYQKKLRSMT AKYRL (SEQ ID NO.)	Pal			
150	il	MGYQKKLRSMT DAYRL (SEQ ID NO.)	Pal			
151	il	MGYQKKLRSMT DKARL (SEQ ID NO.)	Pal			
152	il	MGYQKKLRSMT DKYAL (SEQ ID NO.)	Pal			
153	il	MGYQKKLRSMT DKYRA (SEQ ID NO.)	Pal			
154	il	KKLRSMtDKYRL H (SEQ ID NO.)	Pal			
155	il	KKLRSMTdKYR LH (SEQ ID NO.)	Pal			
156	il	KKLRSMTDKYrL H (SEQ ID NO.)	Pal			
157	il	KKLRSMTDKYRl H (SEQ ID NO.)	Pal			
158	il	KKLRSMTDKYR Lh (SEQ ID NO.)	Pal			

159	i1	MGYQKKLRSMT DKYRl (SEQ ID NO.)	Pal			
160	i1	MGYQKKLRSMT DKYrL (SEQ ID NO.)	Pal			
161	i1	MGYQKKLRSMT DKyRL (SEQ ID NO.)	Pal			
162	i1	MGYQKKLRSMT DkYRL (SEQ ID NO.)	Pal			
163	i1	MGYQKKLRSMT dKYRL (SEQ ID NO.)	Pal			
164	i1	MGYQKKLRSMt DKYRL (SEQ ID NO.)	Pal			
165	i1	mGYQKKLRSMT DKYRL (SEQ ID NO.)	Pal			
166	i1	MGyQKKLRSMT DKYRL (SEQ ID NO.)	Pal			
167		MGYqKKLRSMT DKYRL (SEQ ID NO.)	Pal			
168	i1	MGYQkKLRSMT DKYRL (SEQ ID NO.)	Pal			
169	i1	MGYQKkLRSMT DKYRL (SEQ ID NO.)	Pal			
170	i1	MGYQKKlRSMT DKYRL (SEQ ID NO.)	Pal			
171	i1	MGYQKKLrSMT DKYRL (SEQ ID NO.)	Pal			
172		MGYQKKLRsMT DKYRL (SEQ ID NO.)	Pal			
173	i1	MGYQKKLRSmT DKYRL (SEQ ID NO.)	Pal			
174	i1	KKLRSMTDKYRl S (SEQ ID NO.)	Pal			
175	i1	MGYQKKLRSMT DKYRL (SEQ ID NO.)	Pal			
176	i1	MGYQKKLRSMT DKYRL (SEQ ID NO.)	Elaidic			
177	i1	MGYQKKLRSMT DKYRL (SEQ ID NO.)	Oleic			
178	i1	MGYQKKLRSMT DKYRL (SEQ ID	3-(dodecyloxy)			

		NO.)	propanoate			
179	i1	MGYQKKLRSMT DKYRL (SEQ ID NO.)				
180	i1	KKLRSMTDKYR LH (SEQ ID NO.)	Pal			
181	i1	KKLRSMTDKYR LH (SEQ ID NO.)	3-(dodecyloxy) propanoate			
182	i1	KKLRSMTDKYR LH (SEQ ID NO.)				
183	i1	KKLRSMTDKYR LH (SEQ ID NO.)				
184	i1	KKLRSMTDKYR LH (SEQ ID NO.)				
185	i1	KKLRSMTDKYR LH (SEQ ID NO.)				
186	i1	MGYQKKLRSMT DKYRL (SEQ ID NO.)				
187	i1	MGYQKKLRSMT DKYRL (SEQ ID NO.)				
188	i3	MGYQKKLRSMT DKYRL (SEQ ID NO.)				
189	i1	MGYQKKLRSpT DKYRL (SEQ ID NO.)	Pal			
190	i1	MGYQKKLRpMT DKYRL (SEQ ID NO.)	Pal			
191	i1	MGYQKKLpSMT DKYRL (SEQ ID NO.)	Pal			
192	i1	MGYQKKpRSMT DKYRL (SEQ ID NO.)	Pal			
193	i1	MGYQKKLRSMP DKYRL (SEQ ID NO.)	Pal			

Table 15. CXCR4 i2 loop compounds

Sample Lot	Loop	N-terminus T-L	Sequence	C-terminus	MS Theoretical	MS Observed Ion
74	i2	$C_{15}H_{31}C(O)$-	DRYLAIVHATNSQR PRKLL (SEQ ID NO.)	-(NH)C16H33	679.4, 905.5	679.3, 905.0
75	i2	$C_{15}H_{31}C(O)$-	VHATNSQRPRKLLA EKVVY (SEQ ID NO.)	NH_2	612.8	613.0
76	i2	$C_{31}H_{62}NC(O)$-	DRYLAIVHATNSQR PRKLL (SEQ ID NO.)	NH_2	686.6	686.6

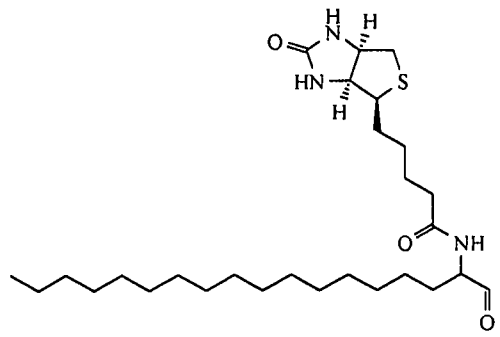
77	i2	$C_{15}H_{31}C(O)$-	DRYLAIVHATNSQRPRKLL (SEQ ID NO.)	NH_2	623.3	623.5
78	i2	$C_{15}H_{31}C(O)$-	VHATNSQRPRKLLA (SEQ ID NO.)	NH_2	915.2	915
79	i2	$C_{15}H_{31}C(O)$-	HATNSQRPRKL (SEQ ID NO.)	NH_2	773.5	773.9
80	i2	$C_{15}H_{31}C(O)$-	HATNSQRPRKLLA (SEQ ID NO.)	NH_2	865.6	865.5
81	i2	$C_{15}H_{31}C(O)$-	HATNSQRPRKLLAE (SEQ ID NO.)	NH_2	930.2	930.5
82	i2	$C_{15}H_{31}C(O)$-	HATNSQRPRKLLAE (SEQ ID NO.)K	NH_2	663.1	663.0
83	i2	$C_{15}H_{31}C(O)$-	HATNSQRPRKLLAE KV (SEQ ID NO.)	NH_2	696.2	696.0

Table 16. CXCR4 i3 loop compounds

	Sequence	C-terminus	N-terminus	MW	MS Theoretical	MS Observed Ion
84	HSKKGHQKR KALK (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	1783.258		
85	**HSKGHQKR KALK** (SEQ ID NO. 369)	NH_2	$C_{15}H_{31}C(O)$-	1655.086		
87	HSKGHQKRK QALK (SEQ ID NO.)	NH_2	C27H50N3 O2SC(O)-	1924.449	963.2	962.0
88	SKLSHSKGHQ KRKALKTTVI L (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	2598.225	867.1, 650.6	866.7, 650.0
89	KLSHSKGHQ KRKALKTTVI L (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	2511.147	838.0, 1256.6	837.5, 1255.8
90	KLSHSKGHQ KRKALKTTV (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	2284.832	762.6	762.0
91	KLSHSKGHQ KRKALKT (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	2084.597	1043.3	1043.0
92	KLSHSKGHQ KRKALK (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	1983.493	992.7	992.0
93	KLSHSKGHQ KRKAL (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	1855.321	619.4, 928.7	619.3, 929.0
94	KLSHSKGHQ KRKA (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	1742.163	581.7, 872.1	582.0, 872.0
95	LSHSKGHQK RKALK (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	1855.321	928.7	928.0

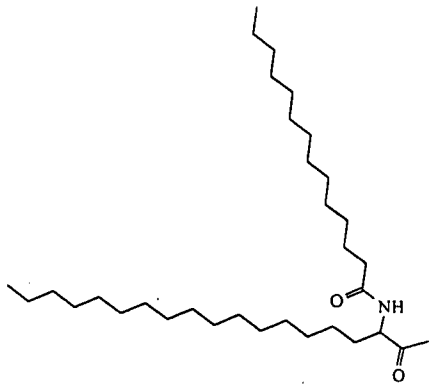
96	SHSKGHQKR KALK (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	1742.163	581.7	585.0
97	HSKGHQKRK ALKT (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	1756.19	879.1	879.0
98	HSKGHQKRK ALKTT (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	1857.294	620.1	619.9
99	HSKGHQKRK ALKTTV (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	1956.425	653.0	653.0
100	HSKGHQKRK ALKTTVI (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	2069.583	733.0	733.6
101	SKLSHSKGHQ KRKALK (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	2070.571	1036.3	1036.0
102	IIISKLSHSKG HQKRKALKT (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	2511.147	628.8	628.7
103	IIISKLSHSKG HQKRKALKT (SEQ ID NO.)	NH_2	$C_{31}H_{62}NC(O)$-	2765.556	692.4	692.4
104	IIISKLSHSKG HQKRKALKT	-(NH)C16H33	$C_{15}H_{31}C(O)$-	2735.573	684.9	684.7
105	KLSHSKGHQ KRKALKTTVI L (SEQ ID NO.)	NH_2	$C_{31}H_{62}NC(O)$-	2764.571	684.9	685.0
106	QHLHIALKKS TSRKVKSGTL K (SEQ ID NO.)	NH_2	$C_{15}H_{31}C(O)$-	2598.225	650.6	650.0

Foot Note 1 of Tables is



1.

Footnote 2 of the tables is:



2.

Table 17. CXCR4 i4 loop compounds

No.	Loop	N-terminus	MW	C-terminus	Sequence	MS Theoretical	MS Observed Ion
107	i4	$C_{31}H_{62}NC(O)$-	4248.067	NH_2	GAKFKTSAQHALTS VSRGSSLKILSKGKR GGHSSVST (SEQ ID NO.)	1063.0	1063.0
108	i4	$C_{31}H_{62}NC(O)$-	3592.41	NH_2	GAKFKTSAQHALTS VSRGSSLKILSKGKR G (SEQ ID NO.)	1198.5	1199
109	i4	$C_{15}H_{31}C(O)$-	3994.644	NH_2	GAKFKTSAQHALTS VSRGSSLKILSKGKR GGHSSVST (SEQ ID NO.)	999.7, 799.2	800.0, 1000.0
110	i4	$C_{15}H_{31}C(O)$-	3870.571	NH_2	GAKFKTSAQHALTS VSRGSSLKILSKGKR GGSCFH (SEQ ID NO.)	775.1	774.7
111	i4	$C_{15}H_{31}C(O)$-	3338.987	NH_2	GAKFKTSAQHALTS VSRGSSLKILSKGKR G (SEQ ID NO.)	835.8, 1114.0	835.8, 1114.0
112	i4	$C_{15}H_{31}C(O)$-	3052.8	NH_2	GAKFKTSAQHALTS VSRGSSLKILSGGK (SEQ ID NO.)	764.2 1018.6	764.6 1019.0
113	i4	$C_{15}H_{31}C(O)$-	2083.477	NH_2	GAKFKTSAQHALTS VSRG (SEQ ID NO.)	695.5, 1042.8	695.0, 1042.0
114	i4	$C_{15}H_{31}C(O)$-	2940.526	NH_2	GAKFKTSAQHALTS VSRGSSLKILSK (SEQ ID NO.)	736.1, 981.2	736.0, 982.0
115	i4	$C_{15}H_{31}C(O)$-	2498.961	NH_2	GAKFKTSAQHALTS VSRGSSLK (SEQ ID NO.)	625.8, 834.0	626.0, 834.0
116	i4	$C_{15}H_{31}C(O)$-	1938.18	NH_2	GAKFKTSAQHALTS VR (SEQ ID NO.)	646.7	647.3

SYNTHESIS OF SELECTED COMPOUNDS

Compound No. 88 (Pal-SKLSHSKGHQKRKALKTTVIL-amide) (SEQ. ID No. 253)

Compound 88 was synthesized as described above on Rink amide resin at 0.1 mmol 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 compound 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 coarse frit Buchner full, triturated with ether and the resulting precipitate collected by centrifugation. Crude peptide was taken up in minimum amount of DMSO and TFA 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.

Lot #	Yield (mg)
1	4
2	2.7
3	6.9

Compound No. 90 (Pal-KLSHSKGHQKRKALKTTV-amide)

Compound 90 was synthesized as described for Compound 88. The yield of representative lots is illustrated in the following table.

Lot #	Yield (mg)
1	8.6

Compound No. 38 (Pal-MGYQKKLRSMTDKYRL-amide)

Compound No. 38 was synthesized as described for Compound 88. The yield of representative lots is illustrated in the following table.

Lot #	Yield (mg)
1	1.8
2	3.4
3	11.0

Compound No. 44 (Pal-KKLRSMTDKYRL-amide)

Compound No. 44 was synthesized as described for Compound No. 88. The yield of representative lots is illustrated in the following table.

Lot #	Yield (mg)
1	7.9
2	7.3
3	9.7

METHODS OF SCREENING

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

Cells expressing the GPCR of interest 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. GPCR expression can be the result of endogenous expression on a cell line or cell type or the result of stable or transient 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.

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. To test for agonist or inverse agonist activity, cells expressing 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. Inverse agonists will suppress levels of reporter to below basal levels in a dose dependent manner. To test for antagonist or inhibitory activity through a stimulatory pathway, cells expressing 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 (e.g., Gi, which couples to CXCR4), 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.

Chemotaxis Assay

Chemotaxis assays were utilized to determine the effect of compound on the directed migration of cells in response to chemokine. Cells that express a receptor of interest were placed in the upper chamber of a Transwell chemotaxis plate (Corning) and allowed to migrate through a polycarbonate membrane to a lower chamber containing the appropriate receptor-specific ligand. To test for antagonist or potentiating activity, cells were mixed with the desired concentration of compound prior to addition to the upper chamber. Conversely, agonist activity was determined by adding compound in the bottom chamber only without endogenous chemokine. The effect of compound is quantified by several parameters, including the extent of maximum response, the shift of agonist dose-response curves, and the area under the curve.

To measure the CXCR4-dependent migration of cells, the appropriate concentration of CXCL12 (SDF1a) or test compound was diluted in phenol red-free RMPI-1640/20mM HEPES/0.5% BSA buffer and placed in the bottom chamber of a transwell apparatus. CCRF-CEM cells, a human T-cell ALL line that endogenously expresses CXCR4, were washed twice in buffer and resuspended at 133,000 cells/ml. A 75µl sample of this suspension is mixed with the test compound of interest and placed in the upper chamber of a 5-micron transwell apparatus.

To initiate cell migration, the assembled transwell plate was placed in a 37°C, 0.5% CO_2 incubator for a specified time interval, typically between 30 and 120 minutes. After incubation, the unit was disassembled and the lower chamber placed at -80°C overnight to facilitate lysis of cells. To quantify migrated cells, plates were thawed at 37°C in a humidified chamber, and then a sample volume was removed from each well and mixed with an equal volume of CyQuant (Invitrogen) working solution in opaque plates. The fluorescence intensity of each well

represents the DNA content and is directly proportional to cell number. Each sample was typically run in duplicate or triplicate and each plate included two separate negative controls. The plate background control, which included no cells in the upper chamber, was subtracted from all values. The negative control had no agonist added in the lower chamber, and served to establish the baseline for random migration. A similar procedure was followed for chemotaxis using SUP B-15 cells.

Calcium Flux Assay

Calcium Flux Assay is one of the most popular 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. Activation of these 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 additional to assess Gq-couple 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.

CXCR4 Testing

The calcium flux assay was used to assess SDF-1α activation of CXCR4 in CCRF-CEM cells (human T lymphoblasts from acute lymphoblastic leukemia). CCRF-CEM cells were seeded into 96-well black plates with clear bottom at 200K/well in RPMI 1640 media with 20 mM HEPES containing 0.2% BSA. After dye loading by incubating with Calcium-4 dye at 37°C for 1 hour, cell plates were read at 37°C using the Flexstation 3 workstation. The addition of test compounds or reference antagonists was accomplished either by manual pipetting or by liquid handling using the Flexstation. The latter allows the assessment of intrinsic agonist activity of the test compounds by measuring initial changes in fluorescent intensity.

After incubation of 24 minutes at 37°C, SDF-1α was added and receptor activation was assessed by measuring changes in fluorescent intensity using the Flexstation.

Representative Results

CXCR4 i1 loop compound Calcium Flux Data

Comp. #	Loop	N-terminus	Sequence	C-terminus	MW	IC50 (nM)
38	i1	Pal	MGYQKKLRSMTD KYRL (SEQ ID NO.)	Amide	2255.831	98
129	i1	Pal	AGYQKKLRSMTD KYRL (SEQ ID NO.)	Amide	2195.712	197
130	i1	Pal	MAYQKKLRSMTD KYRL (SEQ ID NO.)	Amide	2269.857	125
131	i1	Pal	MGAQKKLRSMTD KYRL (SEQ ID NO.)	Amide	2163.735	147
132	i1	Pal	MGYAKKLRSMTD KYRL (SEQ ID NO.)	Amide	2198.779	213
133	i1	Pal	MGYQAKLRSMTD KYRL (SEQ ID NO.)	Amide	2198.736	200
134	i1	Pal	MGYQKALRSMTD KYRL (SEQ ID NO.)	Amide	2198.736	250
135	i1	Pal	MGYQKKARSMTD KYRL (SEQ ID NO.)	Amide	2213.751	175
136	i1	Pal	MGYQKKLASMTD KYRL (SEQ ID NO.)	Amide	2170.723	302
146	i1	Pal	MGYQKKLRAMTD KYRL (SEQ ID NO.)	Amide	2239.831	170
147	i1	Pal	MGYQKKLRSATD KYRL (SEQ ID NO.)	Amide	2195.712	54
148	i1	Pal	MGYQKKLRSMAD KYRL (SEQ ID NO.)	Amide	2225.805	298
149	i1	Pal	MGYQKKLRSMTA KYRL (SEQ ID NO.)	Amide	2211.821	126
150	i1	Pal	MGYQKKLRSMTD AYRL (SEQ ID NO.)	Amide	2198.736	313
151	i1	Pal	MGYQKKLRSMTD KARL (SEQ ID NO.)	Amide	2163.735	>10000
152	i1	Pal	MGYQKKLRSMTD KYAL (SEQ ID NO.)	Amide	2170.723	>10000
153	i1	Pal	MGYQKKLRSMTD KYRA (SEQ ID NO.)	Amide	2213.751	>10000
159	i1	Pal	MGYQKKLRSMTD KYRl (SEQ ID NO.)	Amide	2255.831	>10000
160	i1	Pal	MGYQKKLRSMTD KYrL (SEQ ID NO.)	Amide	2255.831	5731

161	i1	Pal	MGYQKKLRSMTD KyRL (SEQ ID NO.)	Amide	2255.831	>10000
162	i1	Pal	MGYQKKLRSMTDk YRL (SEQ ID NO.)	Amide	2255.831	291
163	i1	Pal	MGYQKKLRSMTdK YRL (SEQ ID NO.)	Amide	2255.831	623
164	i1	Pal	MGYQKKLRSMtDK YRL (SEQ ID NO.)	Amide	2255.831	322
165	i1	Pal	mGYQKKLRSMTD KYRL (SEQ ID NO.)	Amide	2255.831	112
166	i1	Pal	MGyQKKLRSMTDK YRL (SEQ ID NO.)	Amide	2255.831	129
167	i1	Pal	MGYqKKLRSMTDK YRL (SEQ ID NO.)	Amide	2255.831	116
168	i1	Pal	MGYQkKLRSMTDK YRL (SEQ ID NO.)	Amide	2255.831	119
169	i1	Pal	MGYQKkLRSMTDK YRL (SEQ ID NO.)	Amide	2255.831	88
170	i1	Pal	MGYQKKlRSMTDK YRL (SEQ ID NO.)	Amide	2255.831	72
171	i1	Pal	MGYQKKLrSMTDK YRL (SEQ ID NO.)	Amide	2255.831	72
172	i1	Pal	MGYQKKLRsMTD KYRL (SEQ ID NO.)	Amide	2255.831	90
173	i1	Pal	MGYQKKLRSmTD KYRL (SEQ ID NO.)	Amide	2255.831	97

RESULTS

Representative results from the following tables are provided in FIGs. 1- 4.

CXCR4 i1 loop CHTX data

Table 18. CEM and Sup-B-15 cells

Comp. #	Sequence	Drug Conc	Cell Type	AUC (% of)	Max (% of)	Peak Test Comp. (nM)	Peak Control (nM)	Peak Ratio
33	MGYQKKLRSM TD (SEQ ID NO.)	1.0 uM	CEM	68.9	68.09	1	1	1
33	MGYQKKLRSM TD (SEQ ID NO.)	1.0 uM	CEM	54.81	76.06	0.2	0.2	1
35	VMGYQKKLRS MTD (SEQ ID NO.)	1.0 uM	SUP B-15	31.7	49.27	1	5	0.2
35	VMGYQKKLRS MTD (SEQ ID NO.)	1.0 uM	CEM	57.9	56.97	5	5	1
36	MGYQKKLRSM TDK (SEQ ID NO.)	1.0 uM	SUP B-15	49.94	54.8	1	5	0.2
36	MGYQKKLRSM TDK (SEQ ID NO.	1.0 uM	CEM	101.76	119.07	0.2	1	0.2

	)							
37	MGYQKKLRSM TDKY (SEQ ID NO.)	1.0 uM	SUP B-15	63.52	91.09	1	5	0.2
37	MGYQKKLRSM TDKY (SEQ ID NO.)	1.0 uM	CEM	92.31	97.85	1	25	0.04
38	MGYQKKLRSM TDKYRL (SEQ ID NO.)	1.0 uM	SUP B-15	32.38	49.56	1	5	0.2
38	MGYQKKLRSM TDKYRL (SEQ ID NO.)	1.0 uM	CEM	75.53	106.96	5	25	0.2
38	MGYQKKLRSM TDKYRL (SEQ ID NO.)	1.0 uM	CEM	46.27	71.48	0.2	1	0.2
39	MGYQKKLRSM TDKYRLHL (SEQ ID NO.)	1.0 uM	SUP B-15	47.43	37.65	5	25	0.2
39	MGYQKKLRSM TDKYRLHL (SEQ ID NO.)	1.0 uM	CEM	37.55	59.71	1	25	0.04
40	YQKKLRSMTDK YRLHLSV (SEQ ID NO.)	1.0 uM	SUP B-15	71.92	71.22	5	25	0.2
41	KKLRSMTDKYR LHLSV (SEQ ID NO.)	1.0 uM	SUP B-15	51.69	41.71	1	25	0.04
41	KKLRSMTDKYR LHLSV (SEQ ID NO.)	1.0 uM	CEM	66.71	76.8	0.2	25	0.01
42	KKLRSMTDKYR LHL (SEQ ID NO.)	1.0 uM	SUP B-15	43.82	33.47	5	25	0.2
46	KKLRSMTDKYR LHL (SEQ ID NO.)	1.0 uM	CEM	69.74	115.97	0.2	25	0.01
43	KKLRSMTDKYR LH (SEQ ID NO.)	1.0 uM	SUP B-15	70.8	55.84	1	25	0.04
43	KKLRSMTDKYR LH (SEQ ID NO.)	1.0 uM	CEM	32.08	77.15	0.2	1	0.2
43	KKLRSMTDKYR LH (SEQ ID NO.)	3.0 uM	CEM	79.43	76.32	0.2	0.2	0.2
43	KKLRSMTDKYR LH (SEQ ID NO.)	1.0 uM	CEM	84.82	66.81	0	0	0.04
43	KKLRSMTDKYR LH (SEQ ID NO.)	0.3 uM	CEM	92.91	80.68	0	0	0.04
43	KKLRSMTDKYR LH (SEQ ID NO.)	0.1 uM	CEM	113.68	96.86	0.2	0.2	0.2
43	KKLRSMTDKYR LH (SEQ ID NO.)	0.03 uM	CEM	101.82	91.16	0.8	0.8	1
43	KKLRSMTDKYR LH (SEQ ID NO.)	0.01 uM	CEM	98.09	93.17	0.8	0.8	1
43	KKLRSMTDKYR LH (SEQ ID NO.)	3.0 uM	CEM	79.17	72.73	0	0.2	0.2
43	KKLRSMTDKYR LH (SEQ ID NO.)	1.0 uM	CEM	85.24	78.94	0	0	0.04
43	KKLRSMTDKYR	0.3 uM	CEM	97.93	84.51	0	0	0.04

	LH (SEQ ID NO.)							
43	KKLRSMTDKYR LH (SEQ ID NO.)	0.1 uM	CEM	108.05	93.58	0	0.2	0.2
43	KKLRSMTDKYR LH (SEQ ID NO.)	0.03 uM	CEM	109.76	92.65	0.8	0.8	1
43	KKLRSMTDKYR LH (SEQ ID NO.)	0.01 uM	CEM	109.93	114.2	0.8	0.8	1
44	KKLRSMTDKYR L (SEQ ID NO.)	1.0 uM	SUP B-15	25.94	31.52	1	5	0.2
44	KKLRSMTDKYR L (SEQ ID NO.)	1.0 uM	CEM	15.86	54.8	0.2	1	0.2
44	KKLRSMTDKYR L (SEQ ID NO.)	1.0 uM	CEM	92.31	97.85	1	25	0.04
45	KKLRSMTDKYR (SEQ ID NO.)	1.0 uM	SUP B-15	178.4	193.55	5	5	1
46	KKLRSMTDKY (SEQ ID NO.)	1.0 uM	SUP B-15	87.24	82.87	1	5	0.2
48	MGYQKKLRSM TDKYRI (SEQ ID NO.)	1.0 uM	CEM	53.03	53.48	25	5	5
49	MGYQKKLRSM TDKYRI (SEQ ID NO.)	1.0 uM	CEM	50.9	62.66	1	5	0.2
50	SGYQKKLRSST D (SEQ ID NO.)	1.0 uM	CEM	102.07	121.17	0.2	1	0.2
50	SGYQKKLRSST D (SEQ ID NO.)	1.0 uM	CEM	52.16	59.19	1	0.2	5
52	QKKLRSMTDKY RI (SEQ ID NO.)	1.0 uM	CEM	111.49	97.78	1	5	0.2
52	QKKLRSMTDKY RI (SEQ ID NO.)	1.0 uM	CEM	76.62	92.8	0.2	1	0.2
52	QKKLRSMTDKY RI (SEQ ID NO.)	1.0 uM	CEM	45.5	63.35	0.2	0.2	1
53	MGYQKKLRSM TDKYRLHL (SEQ ID NO.)	1.0 uM	CEM	60.98	68.45	1	0.2	5
53	MGYQKKLRSM TDKYRLHL (SEQ ID NO.)	1.0 uM	CEM	91.1	89.56	1	1	1
54	MGYQKKLRSM TDKYRLHL (SEQ ID NO.)	1.0 uM	CEM	83.08	77.31	1	1	1
54	MGYQKKLRSM TDKYRLHL (SEQ ID NO.)	1.0 uM	CEM	110.43	114.34	1	1	1
55	MGYQKKLRSM TDKYRLHLSV (SEQ ID NO.)	1.0 uM	CEM	18.58	39.83	0.2	1	0.2
55	MGYQKKLRSM TDKYRLHLSV (SEQ ID NO.)	1.0 uM	CEM	43.3	72.73	0.2	1	0.2
56	MGYQKKLRSM TDKYRLHLSV (SEQ ID NO.)	1.0 uM	CEM	33.7	31.5	0.2	1	0.2
56	MGYQKKLRSM TDKYRLHLSV (SEQ ID NO.)	1.0 uM	CEM	64.22	70.2	1	1	1

59	MGYQKKLRSM TDK (SEQ ID NO.)	1.0 uM	CEM	51.62	59.79	1	1	1
59	MGYQKKLRSM TDK (SEQ ID NO.)	1.0 uM	CEM	68.96	84.52	1	1	1
69	SGYQKKLRSST D (SEQ ID NO.)	1.0 uM	CEM	100	93.13	25	25	1

Table 19. CXCR4 i2 loop Chemotaxis data
SUPB-15 cells

Comp. #	Sequence	Conc	AUC (% of vehicle)	Max (% of vehicle)	Peak Test Comp. (nM)	Peak Control (nM)	Peak Ratio
83	HATNSQRPRK LLAEKV (SEQ ID NO.)	1.0 uM	126.36	110.06	5	5	1
82	HATNSQRPRK LLAEK (SEQ ID NO.)	1.0 uM	124.56	126.31	1	5	0.2
81	HATNSQRPRK LLAE (SEQ ID NO.)	1.0 uM	79.85	76.46	5	25	0.2
80	HATNSQRPRK LLA (SEQ ID NO.)	1.0 uM	102.2	69.02	5	25	0.2
79	HATNSQRPRK L (SEQ ID NO.)	1.0 uM	109.36	109.68	5	25	0.2
78	VHATNSQRPR KLLA (SEQ ID NO.)	1.0 uM	71.85	72.31	5	25	0.2
77	DRYLAIVHAT NSQRPRKLL (SEQ ID NO.)	1.0 uM	42.24	56.21	0.2	1	0.2
77	DRYLAIVHAT NSQRPRKLL (SEQ ID NO.)	1.0 uM	31.64	55.59	0.2	0.2	1
76	DRYLAIVHAT NSQRPRKLL (SEQ ID NO.)	1.0 uM	52.16	54.04	0.2	0.2	1
76	DRYLAIVHAT NSQRPRKLL (SEQ ID NO.)	1.0 uM	8.95	9.03	1	1	1
75	VHATNSQRPR KLLAEKVVY (SEQ ID NO.)	1.0 uM	46.73	52.32	1	0.2	5
75	VHATNSQRPR KLLAEKVVY (SEQ ID NO.)	1.0 uM	47.91	64.15	0.2	1	0.2

74	DRYLAIVHAT NSQRPRKLL (SEQ ID NO.)	1.0 uM	90.39	91.29	5	5	1
74	DRYLAIVHAT NSQRPRKLL (SEQ ID NO.)	1.0 uM	77.13	75.81	5	1	5

Table 20. CXCR4 i3 loop Chemotaxis data
CEM cells

Comp. #	Sequence	Conc	AUC (% of vehicle)	Max (% of vehicle)	Peak Test Compound (nM)	Peak Control (nM)	Peak Ratio
87	HSKGHQKR KQALK (SEQ ID NO.)	1.0 uM	52.64	76.1	0.2	1	0.2
88	SKLSHSKGH QKRKALKT TVIL (SEQ ID NO.253)	3.0 uM	116.49	114.49	0.8	0.8	1
88	SKLSHSKGH QKRKALKT TVIL (SEQ ID NO. 253)	1.0 uM	143.61	131.59	0.8	0.8	1
88	SKLSHSKGH QKRKALKT TVIL (SEQ ID NO.253)	0.3 uM	131.2	113.68	0.2	0.8	0.2
88	SKLSHSKGH QKRKALKT TVIL (SEQ ID NO.253)	0.1 uM	183.19	157.79	0.03	0.8	0.04
88	SKLSHSKGH QKRKALKT TVIL (SEQ ID NO.253)	0.03 uM	226.59	202.16	0.03	0.8	0.04
88	SKLSHSKGH QKRKALKT TVIL (SEQ ID NO.253)	0.01 uM	172.33	156.08	0.03	0.8	0.04
89	KLSHSKGHQ KRKALKTT VIL (SEQ ID NO. 249)	1.0 uM	37.55	59.71	1	25	0.04
90	KLSHSKGHQ KRKALKTT V (SEQ ID NO.248)	3.0 uM	152.75	114.49	0.16	0.16	1
90	KLSHSKGHQ KRKALKTT V (SEQ ID NO.248)	1.0 uM	153.95	131.59	0.16	0.16	1

90	KLSHSKGHQ KRKALKTT V (SEQ ID NO.248)	0.3 uM	129.83	113.68	0.16	0.16	1
90	KLSHSKGHQ KRKALKTT V (SEQ ID NO.248)	0.1 uM	175.95	157.79	0.03	0.16	0.2
90	KLSHSKGHQ KRKALKTT V (SEQ ID NO.248)	0.03 uM	217.53	202.16	0.16	0.16	1
90	KLSHSKGHQ KRKALKTT V (SEQ ID NO.248)	0.01 uM	171.8	156.08	0.16	0.16	1
90	KLSHSKGHQ KRKALKTT V (SEQ ID NO.248)	1.0 uM	66.71	76.8	0.2	25	0.01
92	KLSHSKGHQ KRKALK (SEQ ID NO.)	3.0 uM	183.65	175.7	0.8	0.8	1
92	KLSHSKGHQ KRKALK (SEQ ID NO.)	1.0 uM	196.33	163.91	0.16	0.8	0.2
92	KLSHSKGHQ KRKALK (SEQ ID NO.)	0.3 uM	179.77	165.35	0.16	0.8	0.2
92	KLSHSKGHQ KRKALK (SEQ ID NO.)	0.1 uM	173.69	169.49	0.16	0.8	0.2
92	KLSHSKGHQ KRKALK (SEQ ID NO.)	0.03 uM	200.49	198.29	0.16	0.8	0.2
92	KLSHSKGHQ KRKALK(SEQ ID NO.)	0.01 uM	157.79	155.72	0.16	0.8	0.2
92	KLSHSKGHQ KRKALK (SEQ ID NO.)	1.0 uM	32.08	77.15	0.2	1	0.2
93	KLSHSKGHQ KRKAL (SEQ ID NO.)	1.0 uM	15.86	54.8	0.2	1	0.2
94	KLSHSKGHQ KRKA (SEQ ID NO.)	1.0 uM	65.28	80.48	1	1	1
95	LSHSKGHQK RKALK (SEQ ID NO.)	1.0 uM	77.47	92.11	1	1	1
96	SHSKGHQK	1.0 uM	34.22	63.12	1	1	1

	RKALK (SEQ ID NO.)						
97	HSKGHQKR KALKT (SEQ ID NO.)	1.0 uM	48.9	54.67	1	5	0.2
99	HSKGHQKR KALKTTV (SEQ ID NO.)	1.0 uM	44.95	64.52	0.2	1	0.2
100	HSKGHQKR KALKKTTVI (SEQ ID NO.)	1.0 uM	49.31	49.84	0.2	5	0.04
101	SKLSHSKGH QKRKALK (SEQ ID NO.)	1.0 uM	75.55	74.92	1	1	1
102	IIISKLSHSK GHQKRKAL KT (SEQ ID NO.)	1.0 uM	0	0.24		1	
103	IIISKLSHSK GHQKRKAL KT (SEQ ID NO.)	1.0 uM	26.32	24.45	1	1	1
104	IIISKLSHSK GHQKRKAL KT (SEQ ID NO.)	1.0 uM	36.4	56.39	0.2	1	0.2
105	KLSHSKGHQ KRKALKTT VIL (SEQ ID NO.249)	1.0 uM	23.79	42.91	0.2	1	0.2

Table 21. CXCR4 i4 Loop CHTX data

CEM cells

Cmpd #	Sequence	Conc	AUC (% of Vehicle)	Max (% of Vehicle)	Peak Test Comp. (nM)	Peak Control (nM)	Peak Ratio
116	GAKFKTSAQH ALTSVR (SEQ ID NO.)	1.0 uM	65.28	80.48	1	1	1
115	GAKFKTSAQH ALTSVSRGSSL K (SEQ ID NO.)	1.0 uM	77.47	92.11	1	1	1
114	GAKFKTSAQH ALTSVSRGSSL KILSK (SEQ ID NO.)	1.0 uM	34.22	63.12	1	1	1

112	GAKFKTSAQH ALTSVSRGSSL KILSGGK (SEQ ID NO.)	1.0 uM	48.9	54.67	1	5	0.2
110	GAKFKTSAQH ALTSVSRGSSL KILSKGKRGG SCFH (SEQ ID NO.)	1.0 uM	40.98	42.08	5	5	1
109	GAKFKTSAQH ALTSVSRGSSL KILSKGKRGG HSSVST (SEQ ID NO.)	1.0 uM	49.31	49.84	0.2	5	0.04
108	GAKFKTSAQH ALTSVSRGSSL KILSKGKRG (SEQ ID NO.)	1.0 uM	89.47	83.94	25	5	5
108	GAKFKTSAQH ALTSVSRGSSL KILSKGKRG (SEQ ID NO.)	1.0 uM	89.47	83.94	25	5	5
107	GAKFKTSAQH ALTSVSRGSSL KILSKGKRGG HSSVST (SEQ ID NO.)	1.0 uM	57.34	49.48	25	5	5

Compounds with varying biological activities at the CXCR4 receptor have been identified. These include positive allosteric modulating activity, negative allosteric modulating activity, and allosteric agonists. Compounds exhibiting negative allosteric modulating activity at the CXCR4 receptor are evidenced by their ability to inhibit chemoattraction in response to SDF1-a induced chemoattraction. Compound receptor modulators are capable of modifying CXCR4 dependent activity in several characteristic patterns. In FIGs. 1-4, these activities are present.

One such phenotype is left- or right- shifting of the SDF1-a dependent chemotactic response. An example of this response is shown by Compound 43. In this case, 1 uM of Compound 43 induces a left shift of the SDF1-a mediated chemotactic response.

Another phenotype is positive allosteric modulation of the SDF1-a dependent chemotactic response. An example of this response is shown with Compound No. 44. In this case, 30 nM of Compound 88 induces a positive SDF1-a

mediated chemotactic response (i.e., the larger RFU response indicates that a greater number of cells migrate toward SDF1a in the presence of Compound 44).

In another example, Compound 44 negatively modulates the SDF1-a induced chemotactic response in CEM cells as evidenced by the lower raw relative fluorescent units (RFU) which reflects the number of cells migrating toward an SDF1a gradient. The lower RFU response, the fewer migrating cells.

Compounds with allosteric agonist activity are evidenced by their ability to induce CXCR4 dependent calcium mobilization (FIG. 5) and/or chemoattraction of leukocytes expressing CXCR4 (FIG. 6). Like the endogenous agonist SDF1-a activity, these CXCR4 agonists exhibit a bell-shaped activity curve with respect to chemoattraction.

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

AlphaScreen cellular kinase assays.

GPCR activation results in modulation of downstream kinase systems and is often used to probe GPCR function and regulation. TGR Bioscience and PerkinElmer have developed Surefire cellular kinase assay kits that are HTS capable and useful in screening kinase regulation. Such kits enable the monitoring of Gi regulated downstream kinases like ERK1/2. The assay allows the measurement of increases in ERK1/2 kinase phosphorylation upon Gi coupled receptor (e.g., CXCR4) activation and this signal in turn can be used to assay Gi coupled receptor modulator. Similar kits are also available to assay other pathway dependent signaling kinases such as MAP and BAD.

IN VIVO ASSAYS

Animal models are currently available for in vivo validation of novel therapeutics targeting the CXCR4/SDF-1 signaling axis include the mouse air pouch WBCs recruitment model, the PMN mobilization model, the HPCs mobilization model and BM transplantation models including NOD/SCID mice repopulation model.

In the mouse air pouch WBCs recruitment model, the air pouch is formed by 2 subcutaneous injections (on day 0 and day 3) of 3 ml of sterile air. On day 6 mice receive an injection of 1 ml of SDF-1 solution into the formed air pouch. Six or 24 hours later WBCs recruited to the air pouch are recovered and WBCs subsets are analyzed using differential cell count and Flow Cytometry. In this model the concentration of SDF-1 in air pouch is controlled by an investigator.

The other animal models that are widely used for the *in vivo* validation of novel CXCR4 antagonists are PMNs mobilization model and hematopoietic progenitor's cells (HPCs) mobilization models. These two models are very similar and they exploit the fact that bone marrow niche express high level of SDF-1. Bone marrow SDF-1 interacts with the CXCR4 on bone marrow cells and constitutively activates it. This SDF-1/CXCR4 interaction is critical for the retention of HPCs and immature PMNs within the bone marrow. Disruption of this interaction causes release of PMNs and HPCs into peripheral blood where they can be readily detected and counted using differential cell counter (for PMNs), Flow Cytometry and colony forming units assay (for HPCs). In contrast to the air pouch model, in this model

the concentration of SDF-1 is physiological. In addition, PMNs/HPCs mobilization models do not require preliminary preparation of animals for actual experiment as is the case in air pouch WBCs recruitment model.

Bone marrow transplantation models allow assessing long term engraftment potential of mobilized into peripheral blood hematopoietic stem cells (HSCs). The donor cells can be of either mouse or human origin like in the NOD/SCID mice repopulation model. In long term repopulation model dilutions of donor blood cells compete with the recipient marrow cells for engraftment in lethally irradiated recipients. This model is relatively long and takes up to 4 months to accomplish.

Recently hematological malignancies such as Acute Myeloid Leukemia (AML) were recognized as potential indications for anti-CXCR4 therapy. Preclinical data suggests that dislodging of malignant cells from bone marrow environment using CXCR4 antagonists significantly improves survival of animals and outcome of chemotherapy. Several animal models of chemosensitization were developed. They are based on the induction of AML following adoptive transfer of malignant cells such APL cells from mCG-PML-PARα mice, A20 cells, or Ba/F3 cells. To facilitate the detection of malignant cells genes encoding fluorescent proteins or luciferase are introduced into them. The progression of AML and efficacy of anti-AML chemotherapy is assessed using FACS analysis of cells from peripheral blood, spleen and bone marrow. In addition, whole body in vivo bioluminescence imaging allows quantitatation of the effect of CXCR4 antagonists on anti-AML therapy in individual animal over time.

RESULTS

Results are shown in FIG. 7-12.

CXCR-4 compound antagonists/modulators mobilize white blood cells in vivo (mouse model) with efficacy similar to AMD3100 (Mozobil) See FIG. 7. Upon analysis of cell types in peripheral blood it was found that CXCR4 receptor compounds are predominately mobilizing polymorphonuclear lymphocytes (See FIG. 9).

CXCR-4 compound antagonists/modulators are active in mobilizing bone marrow progenitor cells with efficacy similar to AMD3100 (Mozobil). This was demonstrated in a mouse model of progenitor cell mobilization. See FIG. 10. In

this assay, DBA/2 mice, male, 10 weeks old, n=4/group; vehicle (10% PEG, 0.1 ml; AMD3100 (2 μmol/kg, in PBS); ATI-2346 (2 μmol/kg, 10% PEG, 0.1 ml). WBCs harvested from 150 ml of blood, premixed with 3 ml of Methocult medium. CFU-GM colonies were scored at day 12.

CXCR-4 compound agonists are also active in mobilizing both neutrophils and bone marrow progenitor cells. The CXCR4 agonist SDF1a has similarly been shown to mobilize bone marrow progenitor cells and hypothesized to occur by establishing an additional chemotactant gradient in the blood following intravenous injection to oppose the natural retentive function of SDF1a in the bone marrow. CXCR4 compound agonists also likely function in this way to mobilize BMPC. An example of Compound 38 agonist data are shown in FIG. 8.

The effects of 10 μmol/kg CXCR-4 receptor compound 43 and CXCR4 compound AMD3100 on PMN recuitment in BALB/c mice following subcutaneous injection are shown in FIG. 11.

The effects of 10 μmol/kg CXCR-4 receptor compound 43 and CXCR4 compound AMD3100 on lymphocyte recruitment in BALB/c mice following subcutaneous injection are shown in FIG.12.

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 A:

$T\text{-}L\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_7\text{-}X_8\text{-}X_9\text{-}X_{10}\text{-}X_{11}\text{-}X_{12}\text{-}X_{13}\text{-}X_{14}\text{-}X_{15}\text{-}X_{16}\text{-}X_{17}\text{-}X_{18}\text{-}X_{19}\text{-}X_{20}\text{-}X_{21}\text{-}X_{22}\text{-}X_{23}\text{-}X_{24}\text{-}R_1$;

or a pharmaceutically acceptable salt thereof, wherein: L is a linking moiety represented by C(O) and bonded to the N terminal nitrogen of X_1 or the next present amino acid residue if X_1 is absent; T is a lipophilic tether moiety bonded to L; and R_1 is OR_2 or $N(R_2)_2$, each R_2 is independently H or alkyl,

wherein at least three contiguous X_1-X_{24} amino acid residues are present, and wherein:

X_1 is a valine residue or absent

X_2 is a isoleucine residue or absent,

X_3 is a leucine residue or absent,

X_4 is a valine residue, a glycine residue or absent,

X_5 is a methionine residue, a isoleucine residue, a leucine residue, a norleucine residue, a serine residue, an alanine residue, a d-methionine residue, a d-serine residue, or absent,

X_6 is a glycine residue, an alanine residue, a histidine residue, a lysine residue or absent,

X_7 is a tyrosine residue, an alanine residue, a d-tyrosine residue, an arginine residue or absent

X_8 is a glutamine residue, an alanine residue, a d-glutamine residue, a methionine residue, a threonine residue, or a lysine residue or absent,

X_9 is a lysine residue, a d-lysine residue, a alanine residue or absent,

X_{10} is a lysine residue, a d-lysine residue, a leucine residue, a threonine residue, an alanine residue or absent,

X_{11} is a leucine residue, a d-leucine residue, an alanine residue, an isoleucine residue, a serine residue, a cysteine residue, an arginine residue or absent,

X_{12} is an arginine residue, a d-arginine residue, an alanine residue, a leucine residue, an aspartic acid residue, a cysteine residue, or absent,

X_{13} is a serine residue, a d-serine residue, an alanine residue, a tyrosine residue or absent,

X_{14} is a methionine residue, a serine residue, a leucine residue, an isoleucine residue, a norleucine residue, an alanine residue, a d-methionine residue, an aspartic acid residue, or absent,

X_{15} is a threonine residue, a d-threonine residue, a arginine residue, a glycine residue, an alanine residue or absent,

X_{16} is an aspartic acid residue, and-aspartic acid residue, an alanine residue, an arginine residue, a lysine residue or absent,

X_{17} is a methionine residue, a lysine residue, a histidine residue, a leucine residue, a cysteine residue or absent,

X_{18} is a tyrosine residue, a glutamine residue , a leucine residue, a lysine residue , a cysteine residue or absent,

X_{19} is an arginine residue , a tyrosine residue, a serine residue, a methionine residue or absent,

X_{20} is a leucine residue, a isoleucine residue, an arginine residue, or a valine residue or absent,

X_{21} is a histidine residue, a lysine residue, a leucine residue or absent,

X_{22} is a leucine residue, a tyrosine residue or absent,

X_{23} is an arginine residue, a serine residue or absent, and

X_{24} is a valine residue, a leucine residue or absent;

wherein when X_1-X_4 and X_{17}-X_{24} are absent and X_5 is a methionine residue, then at least one of the amino acids of X_6-X_{16} is an alanine residue or a d-amino acid, and wherein when X_1-X_6 and X_{17}-X_{24} are absent and X_7 is a tyrosine residue then at least one of the amino acids of X_8-X_{16} is an alanine residue, d-amino acid or a serine residue.

2. The compound of Claim 1, wherein X_1-X_4 and X_{17}-X_{24} are absent and wherein:

X_5 is a methionine residue, a d-methionine residue, an isoleucine residue, a leucine residue, a serine residue, an alanine residue, or d-a methionine residue,

X_6 is a glycine residue or an alanine residue,

X_7 is a tyrosine residue, an alanine residue, or a d-tyrosine residue,

X_8 is a glutamine residue, an alanine residue or a d-glutamine residue,

X_9 is a lysine residue, a d-lysine residue, or an alanine residue,

X_{10} is a lysine residue, a d-lysine residue, or an alanine residue,

X_{11} is a leucine residue, a d-leucine residue, or an alanine residue,

X_{12} is an arginine residue, a d-arginine residue, or an alanine residue,

X_{13} is a serine residue, a d-serine residue, or an alanine residue,

X_{14} is a methionine residue, a serine residue, a leucine residue, an isoleucine residue, an alanine residue, or a d-methionine residue,

X_{15} is a threonine residue, a d-threonine residue, or an alanine residue, and

X_{16} is aspartic acid residue, a d-aspartic acid residue, or an alanine residue, or an arginine residue.

3. The compound of Claim 1, wherein X_1-X_4 and X_{21}-X_{24} are absent, and wherein:

X_5 is a methionine residue, a d-methionine residue an alanine residue or a glycine residue,

X_6 is a glycine residue or an alanine residue,

X_7 is a tyrosine residue, a d-tyrosine residue, or an alanine residue,

X_8 is a glutamine residue, d-glutamine residue, or an alanine residue,

X_9 is a lysine residue, a d-lysine residue or an alanine residue,

X_{10} is a lysine residue, a d-lysine residue or an alanine residue,

X_{11} is a leucine residue, a d-leucine residue, an alanine residue, a proline residue or a d-proline residue,

X_{12} is an arginine residue, a d-arginine residue, an alanine residue, a proline residue or d-proline residue,

X_{13} is a serine residue, a d-serine residue, an alanine residue, a proline residue or a d-proline residue,
X_{14} is a methionine residue, an alanine residue, a d-methionine residue, a d-proline residue, a glycine residue, a histidine residue, or noreleucine residue
X_{15} is a threonine residue, a d-threonine residue, a d-proline residue, a proline residue or an alanine residue,
X_{16} is an aspartic acid residue, a d-aspartic acid residue, or an alanine residue,
X_{17} is a lysine residue, a d-lysine residue or an alanine residue,
X_{18} is a tyrosine residue, a d-tyrosine residue, or an alanine residue,
X_{19} is an arginine residue, a lysine residue, or a d-arginine residue, and
X_{20} is a leucine residue, a d-leucine residue, an alanine residue, a noreleucine residue, an isoleucine residue or a valine residue.

4. The compound of Claim 1, wherein X_1-X_8 are absent, and wherein:
X_9 is a lysine residue, a d-lysine residue or an alanine residue,
X_{10} is a lysine residue, a d-lysine residue or an alanine residue,
X_{11} is a leucine residue, a d-leucine residue or an alanine residue,
X_{12} is an arginine residue, a d-arginine residue or an alanine residue,
X_{13} is a serine residue, a d-serine residue or an alanine residue,
X_{14} is a methionine residue, a d-methionine residue, a norleucine residue or an alanine residue,
X_{15} is a threonine residue, a d-threonine residue, or an alanine residue,
X_{16} is an aspartic acid residue, a d-aspartic acid residue, or an alanine residue,
X_{17} is a lysine residue, a d-lysine residue or an alanine residue,
X_{18} is a tyrosine residue, a d-tyrosine residue, an alanine residue or absent,
X_{19} is an arginine residue, a d-arginine, an alanine residue or absent,
X_{20} is leucine residue, a d-leucine, an alanine or absent,

X_{21} is a histidine residue, a d- histidine residue, a d-serine residue, an alanine residue or absent,
X_{22} is leucine residue, isoleucine residue or absent,
X_{23} is a serine residue or absent, and
X_{24} is a valine residue or absent.

5. The compound of Claim 4, wherein X_{22}, X_{23} and X_{24} are absent.

6. The compound of Claim 1, wherein X_1-X_5 and X_{22}-X_{24} are absent, and wherein:
X_6 is a glycine residue or absent,
X_7 is a tyrosine residue or absent,
X_8 is a glutamine residue or absent,
X_9 is a lysine residue or absent,
X_{10} is a lysine residue or absent,
X_{11} is a leucine residue or absent,
X_{12} is an arginine residue or absent,
X_{13} is a serine residue or absent,
X_{14} is a methionine residue or absent,
X_{15} is a threonine residue,
X_{16} is an aspartic acid residue,
X_{17} is a lysine residue,
X_{18} is a tyrosine residue,
X_{19} is an arginine residue,
X_{20} is a leucine residue, and
X_{21} is a histidine residue.

7. The compound of Claim 1, wherein X_1-X_5 and X_{22}-X_{24} are absent, and wherein:
X_6 is a glycine residue,
X_7 is a tyrosine residue,
X_8 is a glutamine residue,
X_9 is a lysine residue,

X_{10} is a lysine residue,
X_{11} is a leucine residue,
X_{12} is an arginine residue,
X_{13} is a serine residue or absent,
X_{14} is a methionine residue or absent,
X_{15} is threonine residue or absent,
X_{16} is an aspartic acid residue or absent,
X_{17} is a lysine residue or absent,
X_{18} is a tyrosine residue or absent,
X_{19} is an arginine residue or absent,
X_{20} is a leucine residue or absent, and
X_{21} is a histidine residue or absent.

8. The compound of Claim 1, wherein X_1-X_5 and X_{21}-X_{24} are absent, wherein at least seven contiguous amino acid residues are present, and wherein:

X_6 is a glycine residue or absent,
X_7 is a tyrosine residue or absent,
X_8 is a glutamine residue or absent,
X_9 is a lysine residue or absent,
X_{10} is a lysine residue or absent,
X_{11} is a leucine residue or absent,
X_{12} is a an arginine residue or absent,
X_{13} is a serine residue or absent,
X_{14} is a methionine residue or absent
X_{15} is a threonine residue or absent,
X_{16} is an aspartic acid residue or absent,
X_{17} is a lysine residue or absent,
X_{18} is a tyrosine residue or absent,
X_{19} is an arginine residue or absent, and
X_{20} is a leucine residue or absent.

9. The compound of Claim 1, wherein X_1 and X_2 are absent,

X_3 is a leucine residue or absent,

X_4 is a glycine residue or absent,
X_5 is a serine residue, a d-serine residue or absent,
X_6 is a glycine residue, a histidine residue, a lysine residue or absent,
X_7 is a tyrosine residue or an arginine residue,
X_8 is a glutamine residue, or a methionine residue,
X_9 is a lysine residue,
X_{10} is a lysine residue or a threonine residue,
X_{11} is a leucine residue or a serine residue,
X_{12} is an arginine residue, or a leucine residue,
X_{13} is a serine residue, or a tyrosine residue,
X_{14} is a serine residue, a leucine residue, an isoleucine residue, or an aspartic acid residue,
X_{15} is a threonine residue or a glycine residue,
X_{16} is an aspartic acid residue or an arginine residue,
X_{17} is a methionine residue or absent,
X_{18} is a glutamine residue or absent,
X_{19} is, a tyrosine residue or absent,
X_{20} is a leucine residue, a isoleucine residue, an arginine residue, a valine residue or absent,
X_{21} is a histidine residue, a lysine residue, or absent,
X_{22} is a leucine residue or absent,
X_{23} is a serine residue or absent, and
X_{24} is a valine residue or absent.

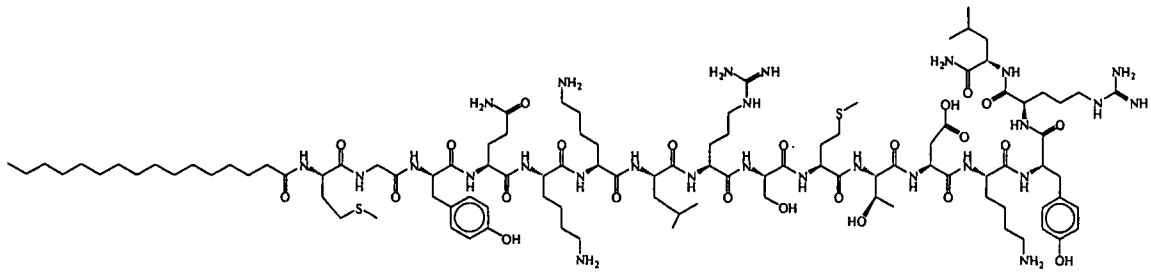
10. The compound of Claim 1 selected from any one of Compound Nos. 1-73 and 117-194.

11. The compound of Claim 10 selected from any one of Compound Nos. 1-73.

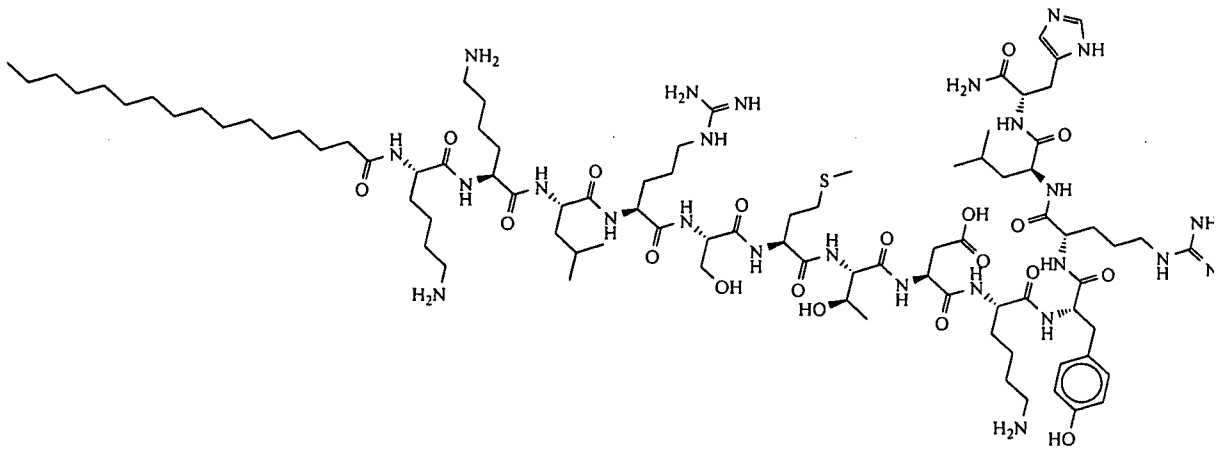
12. The compound of Claim 10 selected from any one of Compound Nos. 117-194.

13. A compound of Claim 1 selected from:

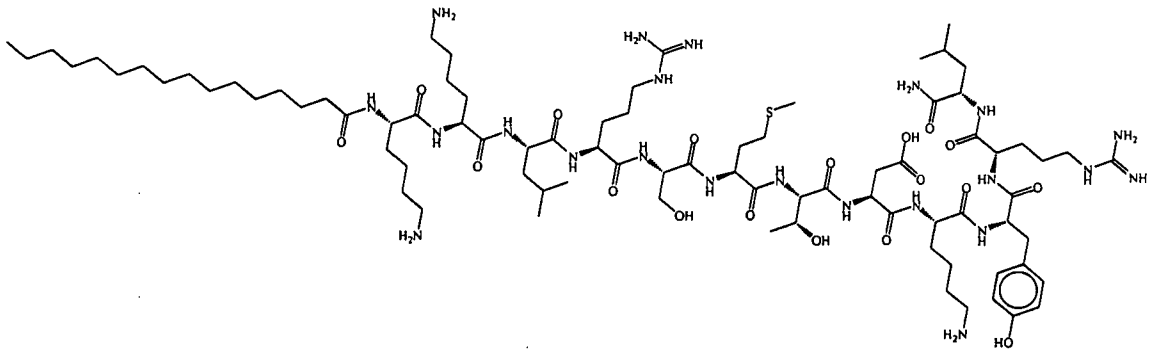
Compound No. 38,



Compound No. 43,

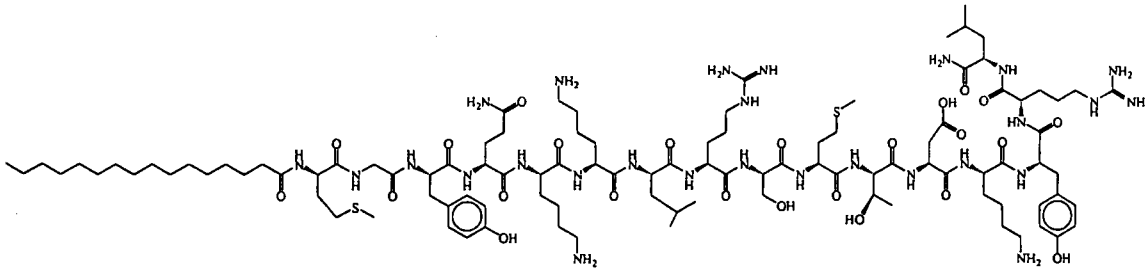


Compound No. 44,



or a pharmaceutically acceptable salt thereof.

14: A compound of Claim 1 having the following structural formula:



or a pharmaceutically acceptable salt thereof .

15. A compound represented by Formula B or a pharmaceutically acceptable salt thereof:

T-L-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}- Y_{20}- Y_{21}- Y_{22}-Y_{23}- Y_{24}-Y_{25}-R_1;

wherein L is a linking moiety represented by C(O) and bonded to the N terminal nitrogen of Y_1 or the next present amino acid residue if Y_1 is absent; T is a lipophilic tether moiety bonded to L; and R_1 is OR_2 or $N(R_2)_2$, each R_2 is independently H or alkyl, wherein at least three contiguous Y_1- Y_{25} amino acid residues are present and wherein at least one of Y_1- Y_{22} is absent, a d-amino acid residue or an alanine residue, and wherein:

Y_1 is an aspartic acid residue, a d-aspartic acid residue, an alanine residue or absent,

Y_2 is an arginine residue, a d-arginine residue, an alanine residue or absent,

Y_3 is a tyrosine residue, a d-tyrosine residue, an alanine residue or absent,

Y_4 is a leucine residue a d-leucine residue, an alanine residue or absent,

Y_5 is an alanine residue, a d-alanine residue or absent,

Y_6 is an isoleucine residue, a d-isoleucine residue, an alanine residue or absent,

Y_7 is a valine residue, a d-valine acid residue, an alanine residue or absent,

Y_8 is a histidine residue a d-histidine residue, an alanine residue or absent,

Y_9 is an alanine residue, a d-alanine residue or absent,

Y_{10} is a threonine residue, a d-threonine residue, an alanine residue or absent,

Y_{11} is an asparagine residue, a d-asparagine residue, an alanine residue or absent,

Y_{12} is a serine residue, a d-serine residue, an alanine residue or absent,

Y_{13} is a glutamine residue, a d-glutamine residue, an alanine residue or absent,

Y_{14} is an arginine residue, a d-arginine residue, an alanine residue or absent,

Y_{15} is a proline residue, a d-proline residue, an alanine residue or absent,

Y_{16} is an arginine residue, a d-arginine residue, an alanine residue or absent,

Y_{17} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Y_{18} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Y_{19} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Y_{20} is an alanine residue, a d-alanine, an isoleucine residue, a d-isoleucine residue, an arginine residue, a d-arginine residue, a valine residue, a d-valine or absent,

Y_{21} is a glutamic acid residue, a d-glutamic acid residue, an alanine residue, a d-alanine residue or absent,

Y_{22} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Y_{23} is a valine residue, a d-valine residue or absent,

Y_{24} is a valine residue, a d-valine residue or absent, and

Y_{25} is a tyrosine residue, a d-tyrosine residue or absent.

16. The compound of Claim 15, wherein Y_{23}-Y_{25} are absent, and wherein:

Y_1 is an aspartic acid residue,

Y_2 is an arginine residue,
Y_3 is a tyrosine residue,
Y_4 is a leucine residue,
Y_5 is an alanine,
Y_6 is an isoleucine residue,
Y_7 is a valine residue,
Y_8 is a histidine residue,
Y_9 is an alanine or absent,
Y_{10} is a threonine or absent,
Y_{11} is an asparagine or absent,
Y_{12} is a serine residue or absent,
Y_{13} is a glutamine residue or absent,
Y_{14} is an arginine residue or absent,
Y_{15} is a proline residue or absent,
Y_{16} is an arginine residue or absent,
Y_{17} is a lysine residue or absent,
Y_{18} is a leucine residue,
Y_{19} is a leucine residue,
Y_{20} is an alanine residue or absent,
Y_{21} is a glutamic acid residue or absent, and
Y_{22} is a lysine residue or absent.

17. The compound of Claim 15, wherein Y_1 and Y_{23}-Y_{25} are absent, and wherein:
Y_2 is an arginine residue or absent,
Y_3 is a tyrosine residue or absent,
Y_4 is a leucine residue or absent,
Y_5 is an alanine residue or absent,
Y_6 is an isoleucine residue or absent,
Y_7 is a valine residue or absent,
Y_8 is a histidine residue or absent,
Y_9 is an alanine or absent,
Y_{10} is a threonine or absent,
Y_{11} is an asparagine or absent,

Y_{12} is a serine residue or absent,
Y_{13} is a glutamine residue or absent,
Y_{14} is an arginine residue or absent,
Y_{15} is a proline residue or absent,
Y_{16} is an arginine residue or absent,
Y_{17} is a lysine residue,
Y_{18} is a leucine residue,
Y_{19} is a leucine residue,
Y_{20} is an alanine residue,
Y_{21} is a glutamic acid residue, and
Y_{22} is a lysine residue.

18. The compound of Claim 15, wherein Y_{23}-Y_{25} are absent and wherein seven contiguous Y_1-Y_{22} amino acid residues are present, and wherein,

Y_1 is an aspartic acid residue or absent,
Y_2 is an arginine residue or absent,
Y_3 is a tyrosine residue or absent,
Y_4 is a leucine residue or absent,
Y_5 is an alanine residue or absent,
Y_6 is an isoleucine residue or absent,
Y_7 is a valine residue or absent,
Y_8 is a histidine residue or absent,
Y_9 is an alanine residue or absent,
Y_{10} is a threonine residue or absent,
Y_{11} is an asparagine residue or absent,
Y_{12} is a serine residue or absent,
Y_{13} is a glutamine residue or absent,
Y_{14} is an arginine residue or absent;
Y_{15} is a proline residue or absent,
Y_{16} is an arginine residue or absent,
Y_{17} is a lysine residue or absent,
Y_{18} is a isoleucine residue or absent,
Y_{19} is a leucine residue or absent,

Y_{20} is an alanine residueor absent,
Y_{21} is a glutamic acid residue or absent, and
Y_{22} is a lysine residue or absent.

19. The compound of Claim 15, wherein Y_1-Y_6 are absent and wherein:
Y_7 is a valine residue or absent,
Y_8 is a histidine residue,
Y_9 is a alanine residue,
Y_{10} is a threonine residue,
Y_{11} is an asparagine residue ,
Y_{12} is a serine residue,
Y_{13} is a glutamine residue,
Y_{14} is an arginine residue,
Y_{15} is a proline residue,
Y_{16} is an arginine residue,
Y_{17} is a lysine residue,
Y_{18} is a leucine residue,
Y_{19} is a leucine residue or absent,
Y_{20} is an alanine residue or absent,
Y_{21} is a glutamic acid or absent,
Y_{22} is a lysine residue or absent,
Y_{23} is a valine lysine residue or absent,
Y_{24} is a valine residue or absent, and
Y_{25} is a tyrosine residue or absent.

20. The compound of Claim 11 selected from any one of Compound Nos. 74-83.

21. A compound represented by Formula C or a pharmaceutically acceptable salt thereof,:
T-L-W_1- W_2- W_3- W_4- W_5- W_6- W_7 -W_8 -W_9 -W_{10} -W_{11}- W_{12}- W_{13}-W_{14}-W_{15}- W_{16}- W_{17}- W_{18}- W_{19}- W_{20}- W_{21}- W_{22}-W_{23}-W_{24}-W_{25}-W_{26}-W_{27}-W_{28}-W_{29}- W_{30}-W_{31}- W_{32}-R_1; wherein L is a linking moiety represented by C(O) and bonded to W_1 at an N terminal nitrogen of W_1 or the next present amino

acid residue if W_1 is absent; T is a lipophilic tether moiety bonded to L; R_1 is OR_2 or $N(R_2)_2$, each R_2 is independently H or alkyl, wherein at least three contiguous

W_1-W_{32} are present, and wherein:

W_1 is an isoleucine residue, a d-isoleucine residue, an alanine residue or absent,

W_2 is isoleucine residue, a d-isoleucine residue, an alanine residue or absent,

W_3 is isoleucine residue, a d-isoleucine residue, an alanine residue or absent,

W_4 is a serine residue, a d-serine residue, an alanine residue or absent,

W_5 is a lysine residue, a d-lysine residue, an alanine residue or absent,

W_6 is a leucine residue, a histidine residue, a d-leucine residue, an alanine residue or absent,

W_7 is a serine residue, a d-serine residue, an alanine residue or absent,

W_8 is a histidine residue, a d-histidine residue, an alanine residue or absent,

W_9 is a serine residue, a d-serine residue, an alanine residue a lysine residue, or absent,

W_{10} is a lysine residue, a d-lysine residue, an alanine residue, a leucine residue, an isoleucine residue or absent,

W_{11} is glycine residue, a d-glycine residue, an alanine residue or absent,

W_{12} is a histidine residue, a d-histidine residue, an alanine residue a tyrosine residue or absent,

W_{13} is a glutamine residue, a d-glutamine residue, an alanine residue or absent,

W_{14} is a lysine residue, a d-lysine residue, an alanine residue or absent;

W_{15} is an arginine residue, a d-arginine residue, an alanine residue, a lysine residue or absent,

W_{16} is a lysine residue, a d-lysine residue, an alanine residue, a leucine residue or absent,

W_{17} is an alanine, d-alanine, an arginine residue or absent,

W_{18} is a leucine residue, a d-leucine residue, an alanine residue, a serine residue or absent,

W_{19} is a lysine residue, a d-lysine residue, an alanine residue, a leucine residue, an isoleucine residue or absent,

W_{20} is threonine, a d-threonine residue, an alanine residue leucine residue or absent,

W_{21} is threonine, a d-threonine residue, an alanine residue a lysine residue or aspartic acid or absent,

W_{22} is a valine, a d-valine residue, an alanine residue or absent,

W_{23} is isoleucine residue, a d-isoleucine residue, an alanine residue a serine residue or absent,

W_{24} is leucine residue, a d-leucine residue, an alanine residue an arginine residue or absent,

W_{25} is a lysine residue, a d-lysine residue, an alanine residue or absent,

W_{26} is a valine residue, a d-valine residue, an alanine residue or absent,

W_{27} is a lysine residue, a d-lysine residue, an alanine residue or absent,

W_{28} is a serine residue a d-serine residue, an alanine residue or absent,

W_{29} is a glycine residue, a d-glycine residue, an alanine residue or absent,

W_{30} is a threonine residue, a d-threonine residue, an alanine residue or absent,

W_{31} is a leucine residue, a d-leucine residue, an alanine residue or absent,

W_{32} is a lysine residue, a d-lysine residue, an alanine residue or absent,

wherein when W_{20}-W_{32} is absent at least one of W_1-W_{23} is also absent and wherein when W_1-W_7 and W_{20}-W_{32} is absent, at least one of W_8-W_{19} is absent, a d-amino acid or alanine.

22. The compound of Claim 21, wherein, W_{24}-W_{32} are absent and wherein:

W_1 is an isoleucine residue,

W_2 is an isoleucine residue,

W_3 is an isoleucine residue,

W_4 is a serine residue,

W_5 is a lysine residue,

W_6 is a leucine residue,

W_7 is a serine residue,

W_8 is a histidine residue or absent,

W_9 is a serine residue, or absent,

W_{10} is a lysine residue or absent,

W_{11} is a glycine residue or absent,

W_{12} is a histidine residue, or absent,

W_{13} is a glutamine residue or absent,

W_{14} is a lysine residue or absent,

W_{15} is an arginine residue or absent,

W_{16} is a lysine residue or absent,

W_{17} is an alanine residue or absent,

W_{18} is a leucine residue or absent,

W_{19} is a lysine residue or absent,

W_{20} is a threonine residue or absent,

W_{21} is a threonine residue or absent,

W_{22} is a valine residue or absent, and

W_{23} is an isoleucine residue or absent.

23. The compound of Claim 21, wherein W_1, W_{21}-W_{32} are absent and wherein:

W_2 is an isoleucine residue or absent,

W_3 is an isoleucine residue or absent,
W_4 is a serine residue or absent,
W_5 is a lysine residue or absent,
W_6 is a leucine residue or absent,
W_7 is a serine residue or absent,
W_8 is a histidine residue or absent,
W_9 is a serine residue, or absent,
W_{10} is a lysine residue or absent,
W_{11} is a glycine residue or absent,
W_{12} is a histidine residue, or absent,
W_{13} is a glutamine residue or absent,
W_{14} is a lysine residue,
W_{15} is an arginine residue,
W_{16} is a lysine residue,
W_{17} is an alanine residue,
W_{18} is a leucine residue,
W_{19} is a lysine residue, and
W_{20} is a threonine residue.

24. The compound of Claim 21, wherein seven contiguous amino acid residues of W_1-W_{19} are present and wherein:

W_1 is an isoleucine residue or absent,
W_2 is an isoleucine residue or absent,
W_3 is an isoleucine residue or absent,
W_4 is a serine residue or absent,
W_5 is a lysine residue or absent,
W_6 is a leucine residue or absent,
W_7 is a serine residue or absent,
W_8 is a histidine residue or absent,
W_9 is a serine residue, or absent,
W_{10} is a lysine residue or absent,
W_{11} is a glycine residue or absent,
W_{12} is a histidine residue, or absent,

W_{13} is a glutamine residue or absent,
W_{14} is a lysine residue or absent,
W_{15} is an arginine residue or absent,
W_{16} is a lysine residue or absent,
W_{17} is an alanine residue or absent,
W_{18} is a leucine residue or absent, and
W_{19} is a lysine residue or absent,

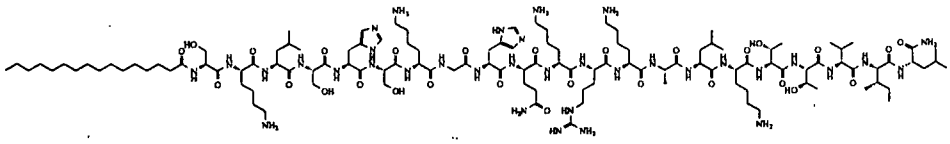
25. The compound of Claim 21, wherein, W_1-W_3 are absent and W_{25}-W_{32} are absent, and wherein:

W_4 is a serine residue or absent,
W_5 is a lysine residue or absent,
W_6 is a leucine residue or absent,
W_7 is a serine residue or absent,
W_8 is a histidine residue,
W_9 is a serine residue,
W_{10} is a lysine residue,
W_{11} is a glycine residue,
W_{12} is a histidine residue,
W_{13} is a glutamine residue,
W_{14} is a lysine residue,
W_{15} is an arginine residue,
W_{16} is a lysine residue,
W_{17} is alanine or a glutamine residue,
W_{18} is leucine residue alanine or absent,
W_{19} is a lysine residue,leucine residue or absent,
W_{20} is threonine or absent,
W_{21} is threonine or absent,
W_{22} is a valine residue or absent,
W_{23} is isoleucine residue or absent,
W_{24} is leucine residue or absent.

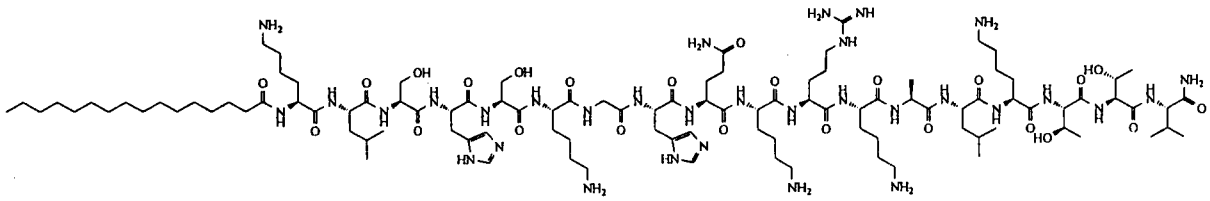
26. The compound of Claim 21 selected from any one of Compound Nos. 84-96.

27. The compound of Claim 21 selected from:

Compound No. 88,

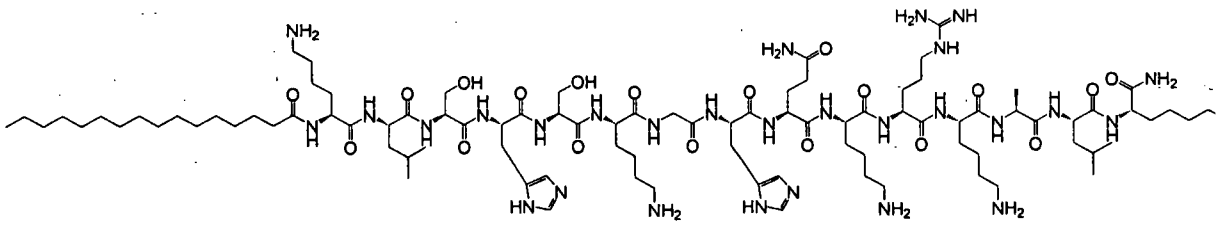


Compound No. 90,



and

Compound No. 92,



or a pharmaceutically acceptable salt thereof.

28. A compound represented by Formula D or a pharmaceutically acceptable salt thereof, wherein:

T-L-Z_1- Z_2- Z_3- Z_4- Z_5- Z_6- Z_7 -Z_8 -Z_9 -Z_{10} -Z_{11}- Z_{12}- Z_{13}-Z_{14}- Z_{15}- Z_{16}- Z_{17}- Z_{18}- Z_{19}- Z_{20}- Z_{21}- Z_{22}-Z_{23}-Z_{24}-Z_{25}-Z_{26}-Z_{27}-Z_{28}- Z_{29}- Z_{30}-Z_{31}- Z_{32}- Z_{33}-Z_{34}-Z_{35}-Z_{36}-Z_{37}-Z_{38}-Z_{39}-Z_{40}- Z_{41}-Z_{42}-Z_{43}-Z_{44}-Z_{45}-Z_{46} -Z_{47}-R_1; wherein:

L is a linking moiety represented by C(O) and bonded to the N terminal nitrogen of Z_1 or the next present amino acid residue if Z_1 is absent;

and T is a lipophilic tether moiety bonded to L; R_1 is OR_2 or $N(R_2)_2$, each R_2 is independently H or alkyl, wherein at least three contiguous Z_1- Z_{32} amino acid residues are present, and wherein

Z_1 is a glycine residue, a d-glycine residue, an alanine residue or absent,

Z_2 is an alanine residue a d- alanine residue or absent,

Z_3 is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_4 is a phenylalanine residue, a d-phenylalanine residue, an alanine residue or absent,

Z_5 is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_6 is a threonine residue, a d-threonine residue, an alanine residue or absent,

Z_7 is a serine residue a d-serine residue, an alanine residue or absent,

Z_8 is an alanine residue, a d- alanine residue or absent,

Z_9 is a glutamine residue, a d-glutamine residue, an alanine residue or absent,

Z_{10} is a histidine residue, a d-histidine residue, an alanine residue or absent,

Z_{11} is an alanine residue, a d- alanine residue or absent,

Z_{12} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Z_{13} is a threonine residue, a d-threonine residue, an alanine residue or absent,

Z_{14} is a serine residue, a d-serine residue, an alanine residue or absent;

Z_{15} is a valine residue, a d-valine residue, an alanine residue or absent,

Z_{16} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{17} is an arginine residue, a d-arginine residue, an alanine residue or absent,

Z_{18} is a glycine residue, a d-glycine residue, an alanine residue or absent,

Z_{19} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{20} is a serine residue, a d-serine residue, an alanine residue absent,

Z_{21} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Z_{22} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_{23} is a isoleucine residue, a d-isoleucine residue, an alanine residue a serine residue or absent,

Z_{24} is a leucine residue, a d-leucine residue, an alanine residue or absent,

Z_{25} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{26} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_{27} is glycine residue, a d-glycine residue, an alanine residue or absent,

Z_{28} is a lysine residue, a d-lysine residue, an alanine residue or absent,

Z_{29} is an arginine residue, a d-arginine residue, an alanine residue or absent,

Z_{30} is a glycine residue, a d-glycine residue, an alanine residue or absent,

Z_{31} is a glycine residue, a d-glycine residue, an alanine residue or absent,

Z_{32} is a histidine residue, a d-histidine residue, an alanine residue or absent,

Z_{33} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{34} is a serine residue, a d-serine residue, an alanine residue cysteine, or absent,

Z_{35} is a valine residue, a d-valine residue, an alanine residue a phenylalanine residue, or absent,

Z_{36} is a serine residue, a d-serine residue, an alanine residue a histidine residue or absent,

Z_{37} is a threonine residue, a d-threonine residue, an alanine residue or absent,

Z_{38} is a glutamic acid residue, a d-glutamic acid residue, an alanine residue or absent,

Z_{39} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{40} is a glutamic acid, a d-glutaminc acid residue, an alanine residue or absent

Z_{41} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{42} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{43} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{44} is a phenylalanine residue, a d-phenylalanine residue, an alanine residue or absent,

Z_{45} is a histidine residue, a d-histidine residue, an alanine residue or absent,

Z_{46} is a serine residue, a d-serine residue, an alanine residue or absent,

Z_{47} is a serine residue, a d-serine residue, an alanine residue or absent, wherein at least one of Z_1-Z_{47} is absent.

29. The compound of Claim 28, wherein:

Z_1 is a glycine residue,

Z_2 is an alanine residue,

Z_3 is a lysine residue,

Z_4 is a phenylalanine residue,

Z_5 is a lysine residue,

Z_6 is a threonine residue,

Z_7 is a serine residue,

Z_8 is an alanine residue,

Z_9 is a glutamine residue,

Z_{10} is a histidine residue or absent,

Z_{11} is an alanine residue or absent,

Z_{12} is a leucine residue or absent,

Z_{13} is a threonine residue or absent,

Z_{14} is a serine residue or absent,

Z_{15} is a valine residue or absent,

Z_{16} is a serine residue or absent,

Z_{17} is an arginine residue or absent,

Z_{18} is a glycine residue or absent,

Z_{19} is a serine residue or absent,

Z_{20} is a serine residue or absent,

Z_{21} is a leucine residue or absent,

Z_{22} is a lysine residue or absent,

Z_{23} is an isoleucine residue, a serine residue or absent,

Z_{24} is a leucine residue or absent,

Z_{25} is a serine residue or absent,

Z_{26} is a lysine residue or absent,

Z_{27} is a glycine residue or absent,

Z_{28} is a lysine residue or absent,

Z_{29} is an arginine residue or absent,

Z_{30} is a glycine residue or absent,

Z_{31} is a glycine residue or absent,

Z_{32} is a histidine residue or absent,

Z_{33} is a serine residue or absent,

Z_{34} is a serine residue or absent,

Z_{35} is a valine residue or absent,

Z_{36} is a serine residue or absent,

Z_{37} is a threonine residue or absent,

Z_{38} is a glutamic acid residue or absent,

Z_{39} is a serine residue or absent,

Z_{40} is a glutamic acid residue or absent,

Z_{41} is a serine residue or absent,

Z_{42} is a serine residue or absent,

Z_{43} is a serine residue or absent,

Z_{44} is a phenylalanine residue or absent,

Z_{45} is a histidine residue or absent,

Z_{46} is a serine residue or absent, and

Z_{47} is a serine residue or absent.

30. The compound of Claim 28, wherein

Z_1 is a glycine residue or absent,

Z_2 is an alanine residue or absent,

Z_3 is a lysine residue or absent,

Z_4 is a phenylalanine residue or absent,

Z_5 is a lysine residue or absent,

Z_6 is a threonine residue or absent,

Z_7 is a serine residue or absent,

Z_8 is an alanine residue or absent,

Z_9 is a glutamine residue or absent,

Z_{10} is a histidine residue or absent,

Z_{11} is an alanine residue or absent,

Z_{12} is a leucine residue or absent,

Z_{13} is a threonine residue or absent,

Z_{14} is a serine residue or absent,

Z_{15} is a valine residue or absent,

Z_{16} is a serine residue or absent,

Z_{17} is an arginine residue or absent,

Z_{18} is a glycine residue or absent,

Z_{19} is a serine residue or absent,

Z_{20} is a serine residue absent,

Z_{21} is a leucine residue or absent,

Z_{22} is a lysine residue or absent,

Z_{23} is an isoleucine residue, or absent,

Z_{24} is a leucine residue or absent,

Z_{25} is a serine residue or absent,

Z_{26} is a lysine residue or absent,

Z_{27} is a glycine residue or absent,

Z_{28} is a lysine residue or absent,

Z_{29} is an arginine residue or absent,

Z_{30} is a glycine residue or absent,

Z_{31} is a glycine residue or absent,
Z_{32} is a histidine residue or absent,
Z_{33} is a serine residue or absent,
Z_{34} is a serine residue or absent,
Z_{35} is a valine residue or absent,
Z_{36} is a serine residue or absent,
Z_{37} is a threonine residue or absent,
Z_{38} is a glutamic acid residue,
Z_{39} is a serine residue,
Z_{40} is a glutamic acid residue,
Z_{41} is a serine residue,
Z_{42} is a serine residue,
Z_{43} is a serine residue,
Z_{44} is a phenylalanine residue,
Z_{45} is a histidine residue,
Z_{46} is a serine residue, and
Z_{47} is a serine residue.

31. The compound of Claim 28, wherein Z_1 is absent, and 10 consecutive Z_2-Z_{47} are present wherein:

Z_2 is an alanine residue or absent,
Z_3 is a lysine residue or absent,
Z_4 is a phenylalanine residue or absent,
Z_5 is a lysine residue or absent,
Z_6 is a threonine residue or absent,
Z_7 is a serine residue or absent,
Z_8 is an alanine residue or absent,
Z_9 is a glutamine residue or absent,
Z_{10} is a histidine residue or absent,
Z_{11} is an alanine residue or absent,
Z_{12} is a leucine residue or absent,
Z_{13} is a threonine residue or absent,
Z_{14} is a serine residue or absent;

Z_{15} is a valine residue or absent,
Z_{16} is a serine residue or absent,
Z_{17} is an arginine residue or absent,
Z_{18} is a glycine residue or absent,
Z_{19} is a serine residue or absent,
Z_{20} is a serine residue absent,
Z_{21} is leucine residue or absent,
Z_{22} is a lysine residue or absent,
Z_{23} is an isoleucine residue, or absent,
Z_{24} is a leucine residue or absent,
Z_{25} is a serine residue or absent,
Z_{26} is a lysine residue or absent,
Z_{27} is a glycine or absent,
Z_{28} is a lysine residue or absent,
Z_{29} is an arginine residue or absent,
Z_{30} is a glycine residue or absent,
Z_{31} is a glycine residue or absent,
Z_{32} is a histidine residue or absent,
Z_{33} is a serine residue or absent,
Z_{34} is a serine residue or absent,
Z_{35} is a valine residue or absent,
Z_{36} is a serine residue or absent,
Z_{37} is a threonine residue or absent,
Z_{38} is a glutamic acid residue,
Z_{39} is a serine residue,
Z_{40} is glutamic acid residue,
Z_{41} is a serine residue,
Z_{42} is a serine residue,
Z_{43} is a serine residue,
Z_{44} is a phenylalanine residue,
Z_{45} is a histidine residue,
Z_{46} is a serine residue, and
Z_{47} is a serine residue.

32. The compound of Claim 28 selected from any one of the compounds 84 and 87-106.

33. A compound represented by Formula I:

T-L-P,

or a pharmaceutically acceptable salt thereof, wherein:

P is a peptide sequence selected from: SEQ ID NOS: 1-368;

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.

34. The compound of Claim 33, wherein the C-terminus of SEQ ID NOS. 1-148; is functionalized with NR_1R_2, wherein R_1 and R_2 are each independently H or alkyl.

35. The compound of Claim 33, wherein the C-terminus of SEQ ID NOS 1-148; is functionalized with NH_2.

36. The compound of Claim 33 or 34, further comprising a lipophilic tether moiety bonded on the C-terminus of P.

37. The compound of Claim 33 or 34, wherein P is selected from SEQ ID NOS: 1-148;.

38. The compound of Claim 33 or 34, wherein P is selected from SEQ ID NOS: 149-199.

39. The compound of Claim 33 or 34, wherein P is selected from SEQ ID NOS: 200-254.

40. The compound of Claim 33 or 34, wherein P is selected from SEQ ID NOS: 255-368.

41. The compound of any one of Claims 1-9, 15-19, 21-25, 28-31 and 33-40, wherein T is an optionally substituted (C_6-C_{30})alkyl, (C_6-C_{30})alkenyl, (C_6-C_{30})alkynyl, wherein 0-3 carbon atoms are replaced with oxygen, sulfur, nitrogen or a combination thereof.

42. The compound of Claim 41, wherein T is selected from the group consisting of: $CH_3(CH_2)_{16}$, $CH_3(CH_2)_{15}$, $CH_3(CH_2)_{14}$, $CH_3(CH_2)_{13}$, $CH_3(CH_2)_{12}$, $CH_3(CH_2)_{11}$, $CH_3(CH_2)_{10}$, $CH_3(CH_2)_9$, $CH_3(CH_2)_8$, $CH_3(CH_2)_9OPh$-, $CH_3(CH_2)_6C{=}C(CH_2)_6$, $CH_3(CH_2)_{11}O(CH_2)_3$, and $CH_3(CH_2)_9O(CH_2)_2$.

43. The compound of any one of Claims 1-9, 15-19, 21-25, 28-31 and 33-40, wherein T is a fatty acid derivative.

44. The compound of Claim 43, wherein 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, eicosapentaenoic acid, erucic acid, docosahexaenoic acid.

45. The compound of any one of Claims 1-9, 15-19, 21-25, 28-31 and 33-40, wherein T is a bile acid derivative.

46. The compound of Claim 45, 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, lagodeoxycholic acid, dehydrocholic acid, hyocholic acid, and hyodeoxycholic acid.

47. The compound of any one of Claims 1-9, 15-19, 21-25, 28-31 and 33-40, wherein T is selected from sterols; progestagens; glucocorticoids; mineralcorticoids; androgens; and estrogens.

48. The compound of any one of Claims 1-9, 15-19, 21-25, 28-31 and 33-40, wherein TL is selected from:

$CH_3(CH_2)_{15}$–C(O);

$CH_3(CH_2)_{13}$– C(O);

$CH_3(CH_2)_9O(CH_2)_2C(O)$;

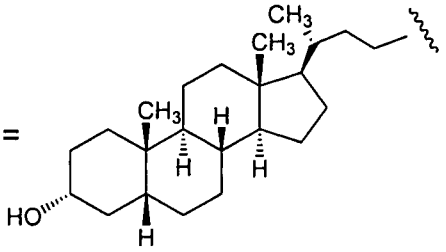
$CH_3(CH_2)_{10}O(CH_2)_2C(O)$;

$CH_3(CH_2)_6C{=}C(CH_2)_6$-C(O);

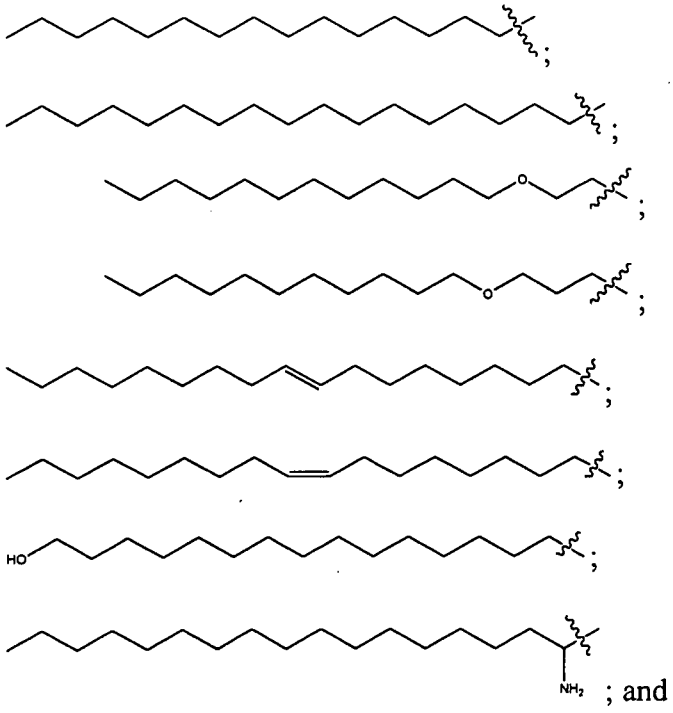
LCA-C(O); and

$CH_3(CH_2)_9OPh$-C(O) wherein

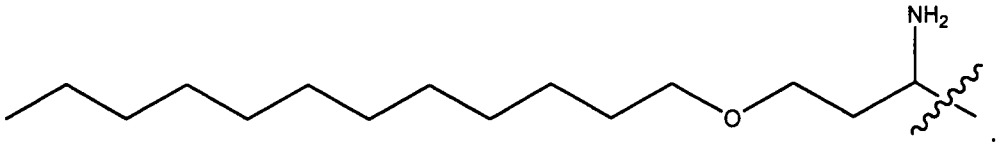
LCA =



49. The compound of any one of Claims 1-9, 15-19, 21-25, 28-31 and 33-40, wherein T is selected from:



; and



50. A method of treating diseases and conditions associated with CXCR4 receptor modulation in a patient in need thereof comprising administering to said patient and effective amount of a compound of any one of Claims 1 to 49.

51. The method of Claim 50, wherein the disease or condition is selected from: bone marrow transplantation, chemosensitization, cancer, metastatic disease, inflammatory diseases, HIV infection and stem cell-based regenerative medicine.

52. A pharmaceutical composition comprising a compound of any one of Claims 1 to 49 and a pharmaceutically acceptable carrier.

CXCR4 i1 loop CHTX data

CEM and Sup-B-15 cells

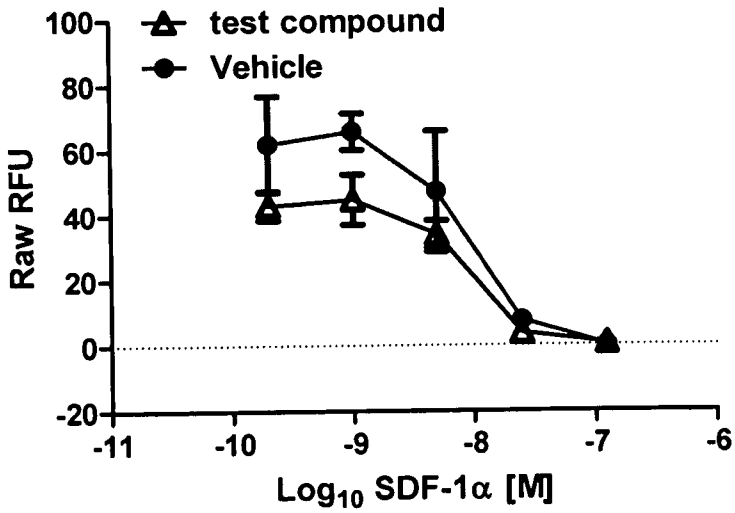
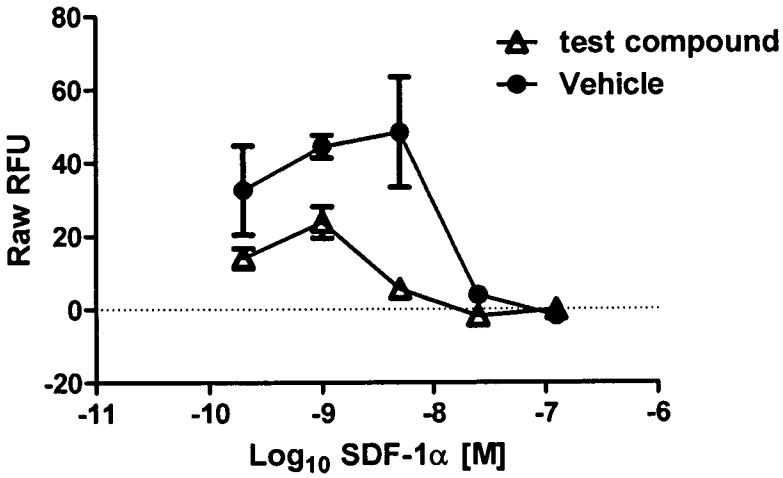
Comp. #	**Sequence**	**Chemotaxis data**
33	MGYQKKLR SMTD	

FIG. 1A

35
SUP B-15

VMGYQKKL
RSMTD



35
CEM

VMGYQKKL
RSMTD

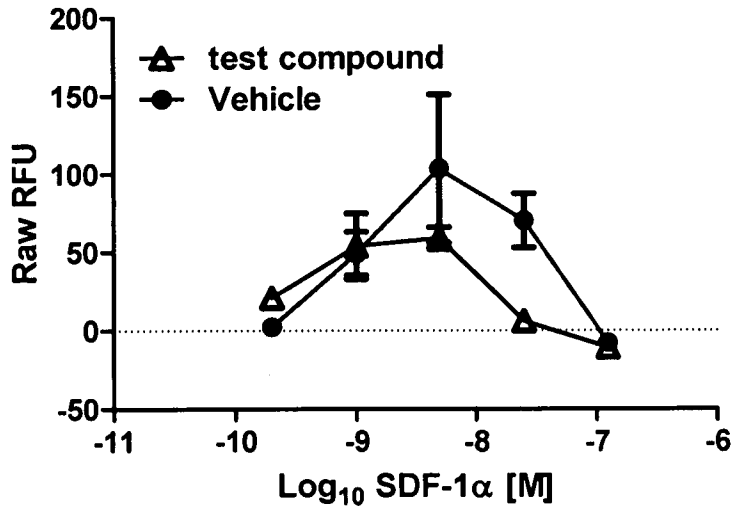


FIG. 1B

36

MGYQKKLR
SMTDK

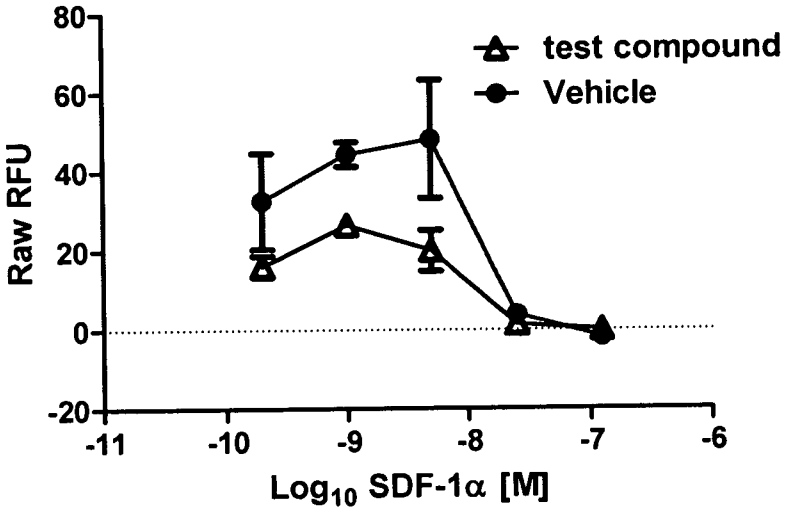
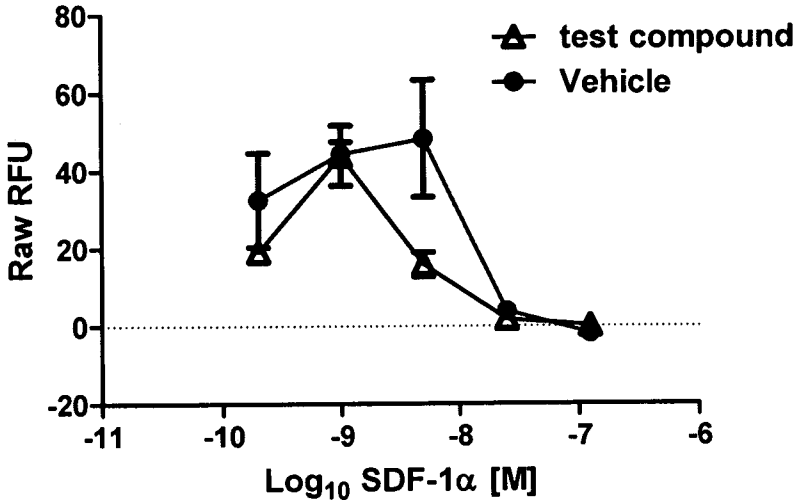


FIG. 1C

37
SUP B-15

MGYQKKLR
SMTDKY



37
CEM

MGYQKKLR
SMTDKY

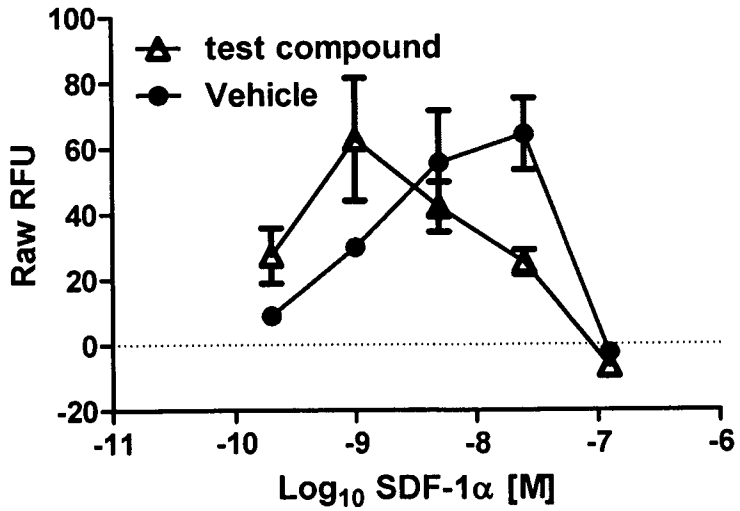
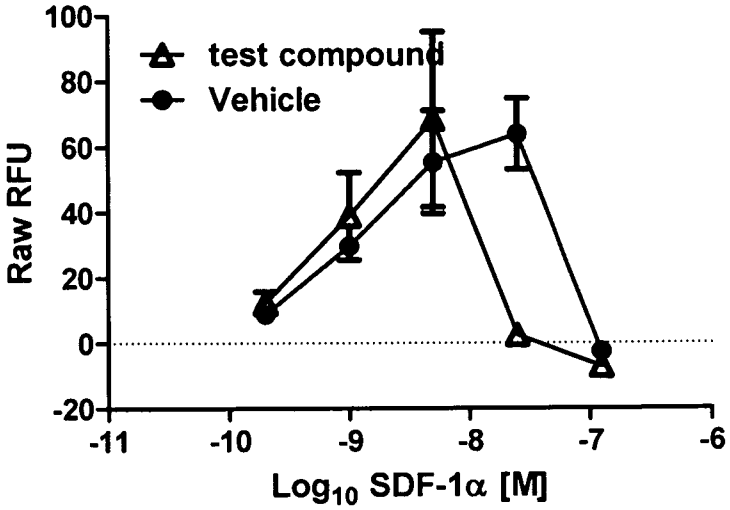


FIG. 1D

38

MGYQKKLR
SMTDKYRL



38

MGYQKKLR
SMTDKYRL

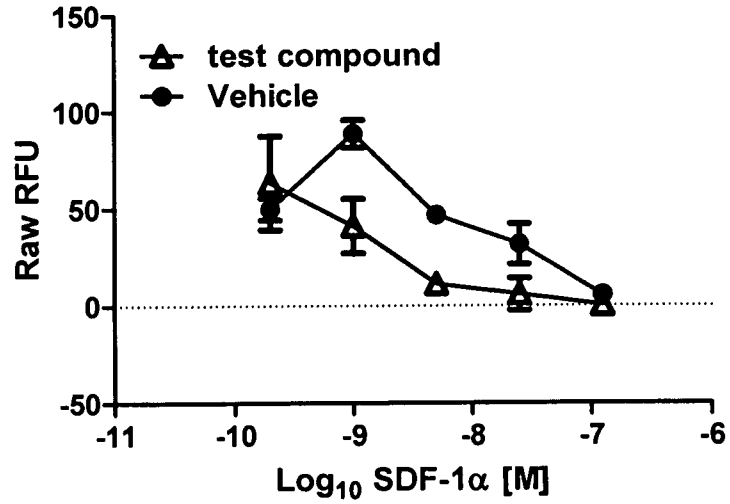
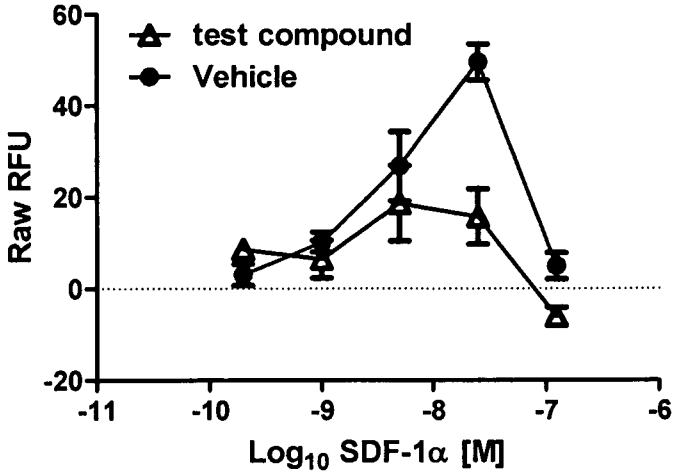


FIG. 1E

39
SUP B-15

MGYQKKLR
SMTDKYRL
HL



39
CEM

MGYQKKLR
SMTDKYRL
HL

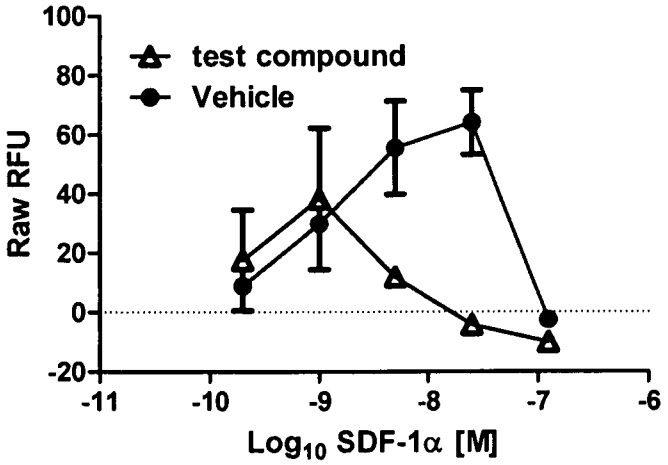


FIG. 1F

40

YQKKLRSM
TDKYRLHL
SV

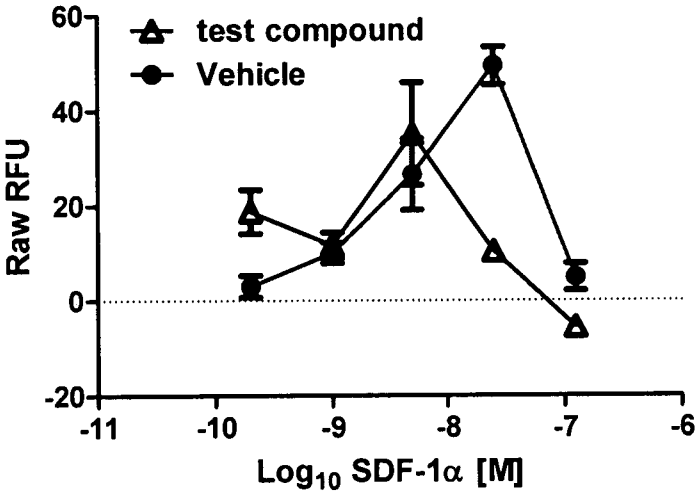
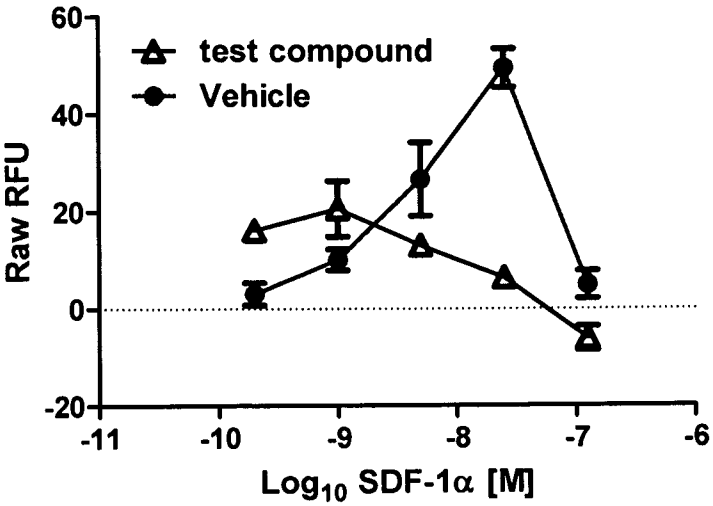


FIG. 1G

41
SUP B-15

KKLRSMTD
KYRLHLSV



41
CEM

KKLRSMTD
KYRLHLSV

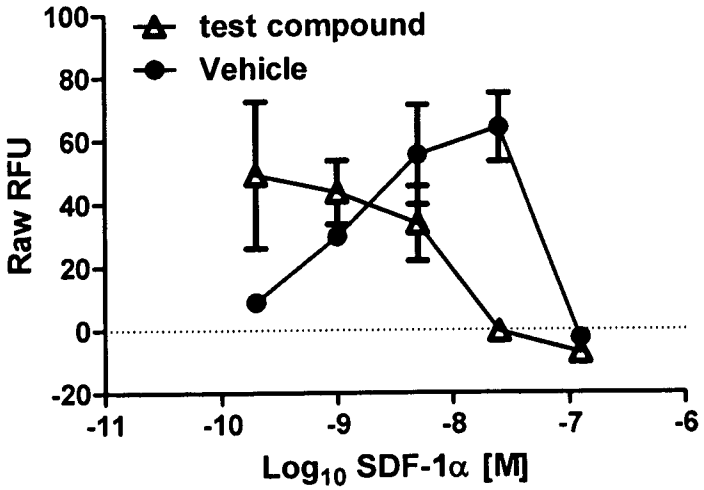
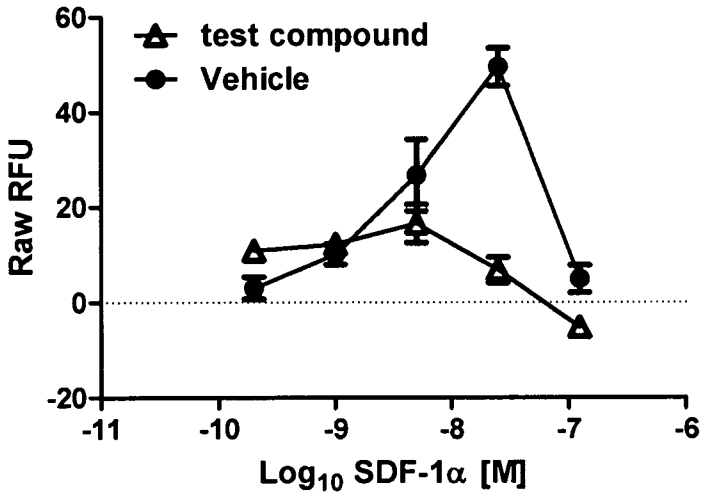


FIG. 1H

42
SUP B-15

KKLRSMTD
KYRLHL



42
CEM

KKLRSMTD
KYRLHL

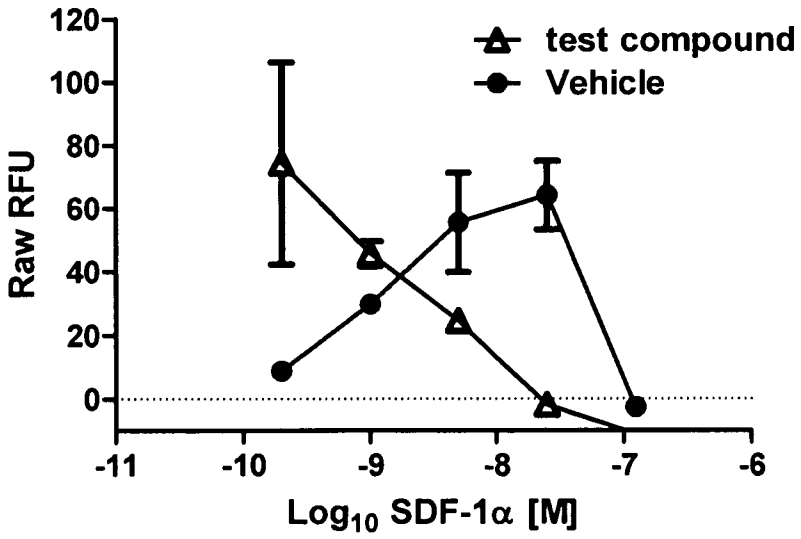
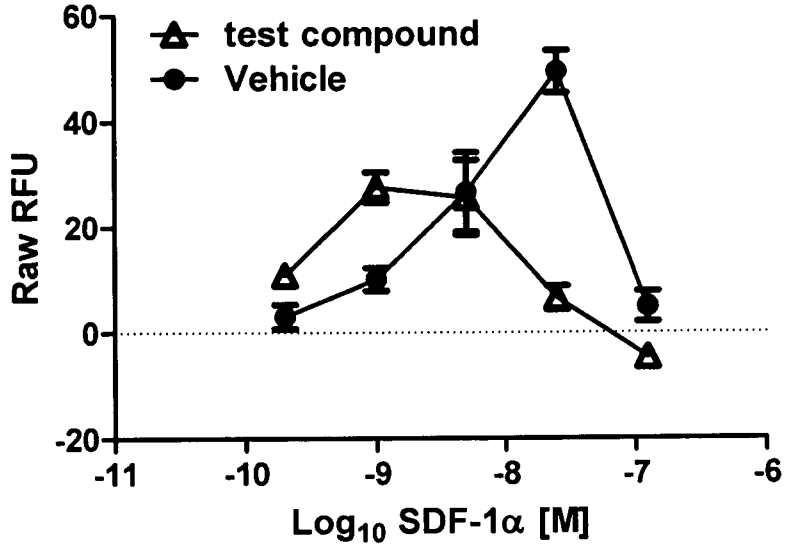


FIG. 1I

43
SUP B-15

KKLRSMTD
KYRLH



43
CEM

KKLRSMTD
KYRLH

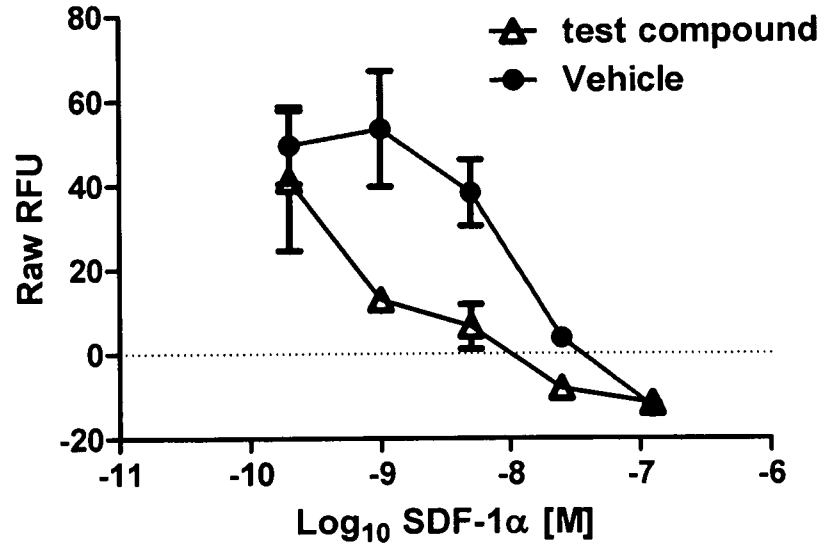
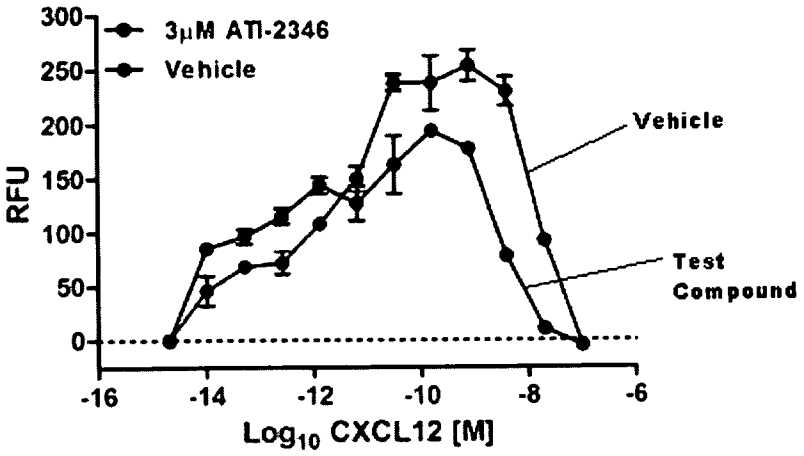


FIG. 1J

43
3.0 μM

KKLRSMTD
KYRLH



43
1.0 μM

KKLRSMTD
KYRLH

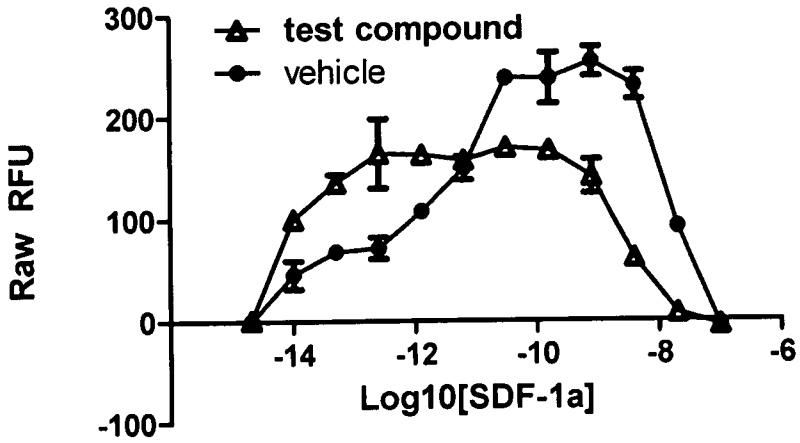
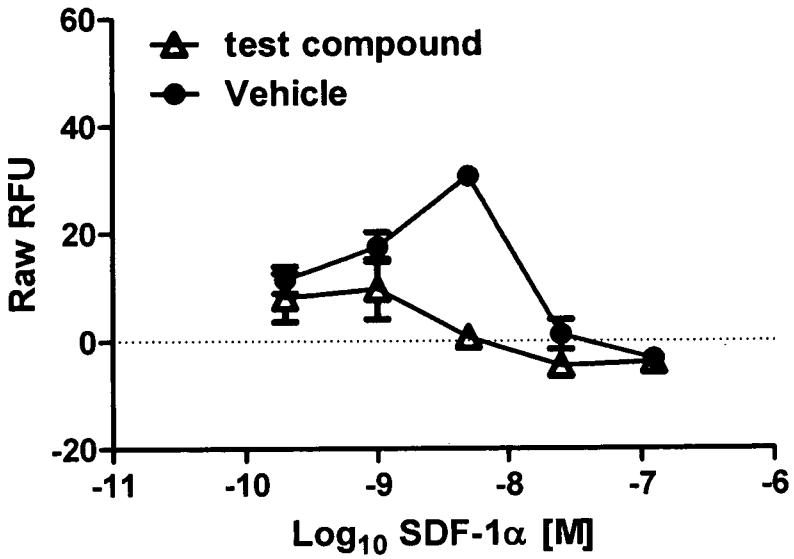


FIG. 1K

44
SUP B-15

KKLRSMTD
KYRL



44
CEM

KKLRSMTD
KYRL

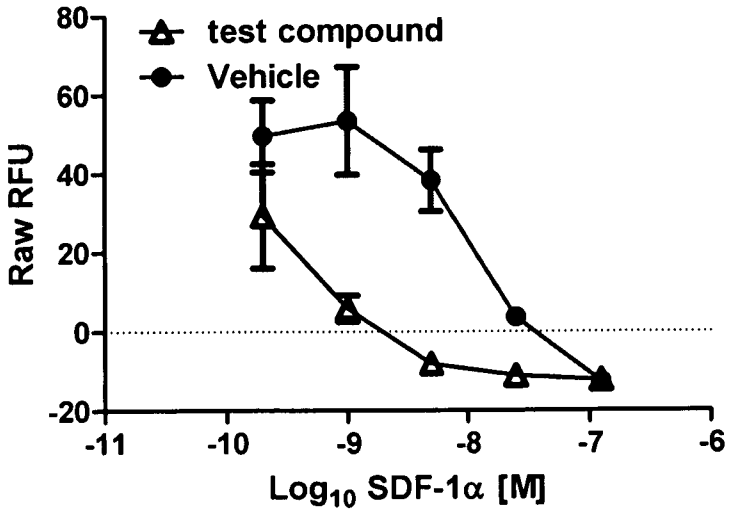


FIG. 1L

44

KKLRSMTD
KYRL

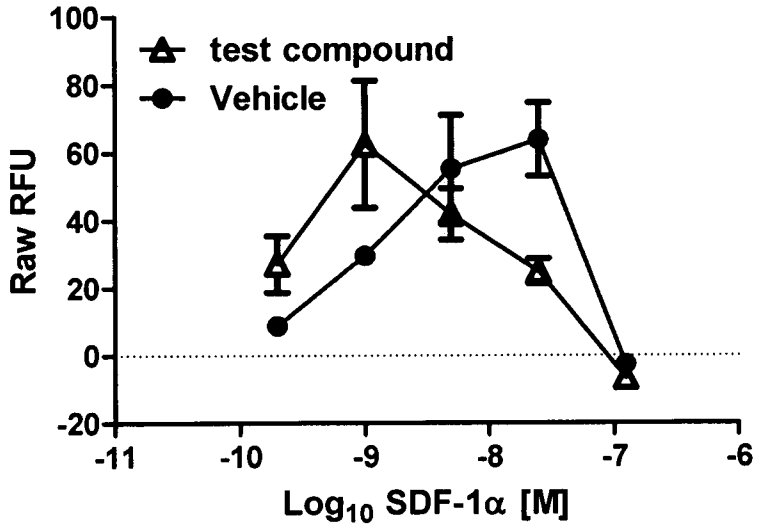
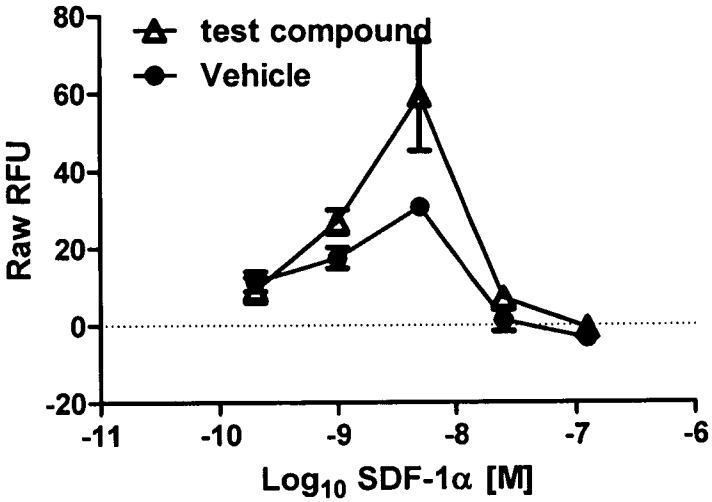


FIG. 1M

45

KKLRSMTD
KYR



46

KKLRSMTD
KY

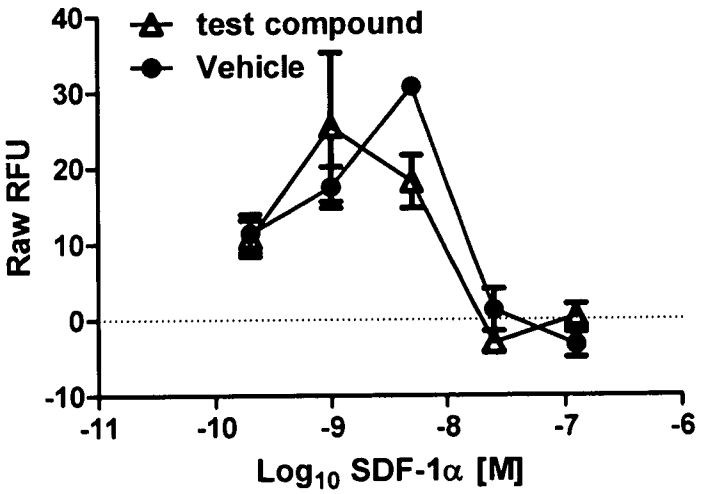
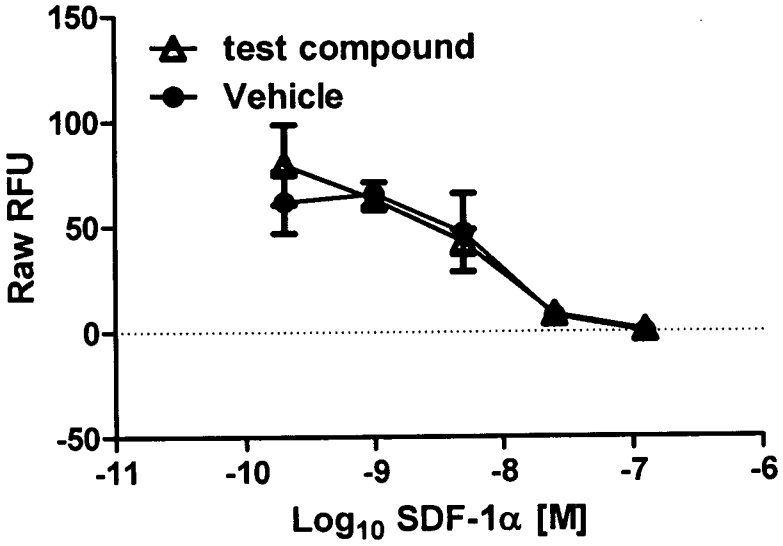


FIG. 1N

50

SGYQKKLR
SSTD



50

SGYQKKLR
SSTD

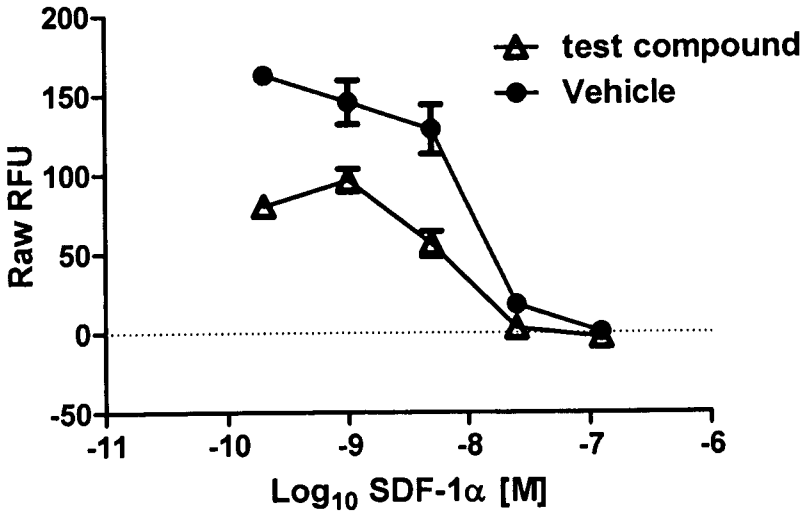


FIG. 1O

52

QKKLRSMT
DKYRI

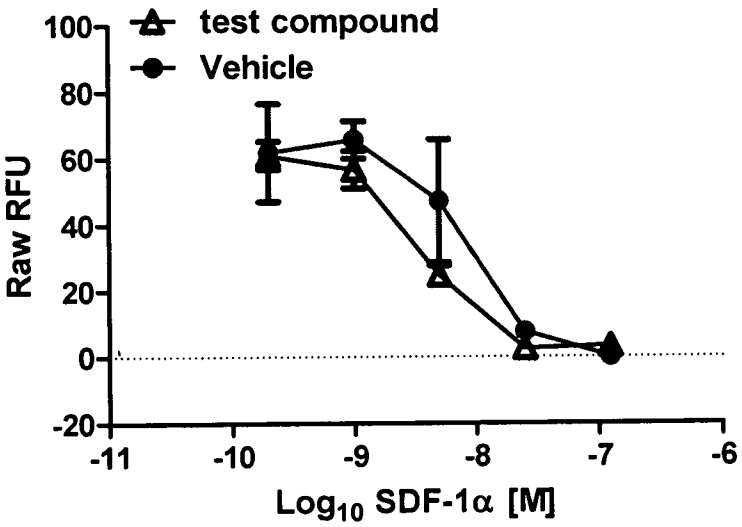
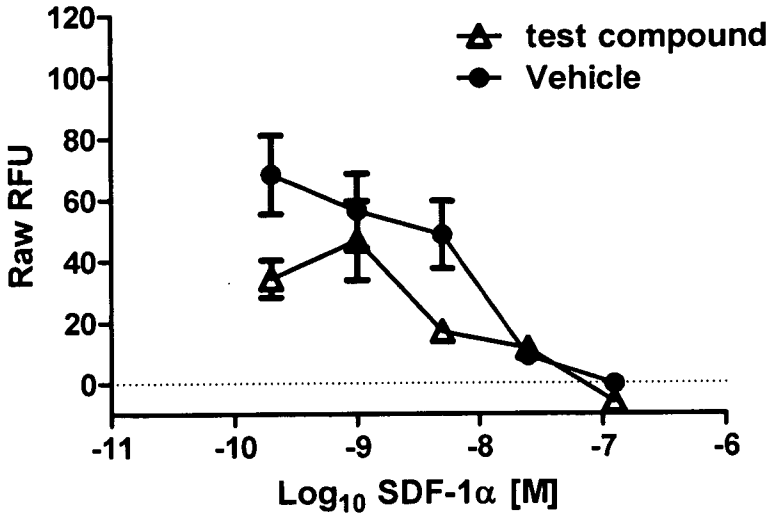


FIG. 1P

53

MGYQKKLR
SMTDKYRL
HL



53

MGYQKKLR
SMTDKYRL
HL

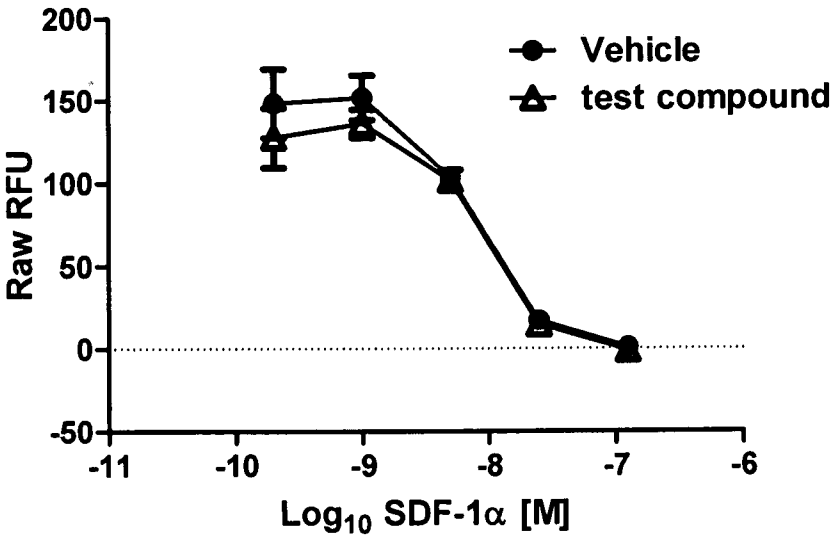
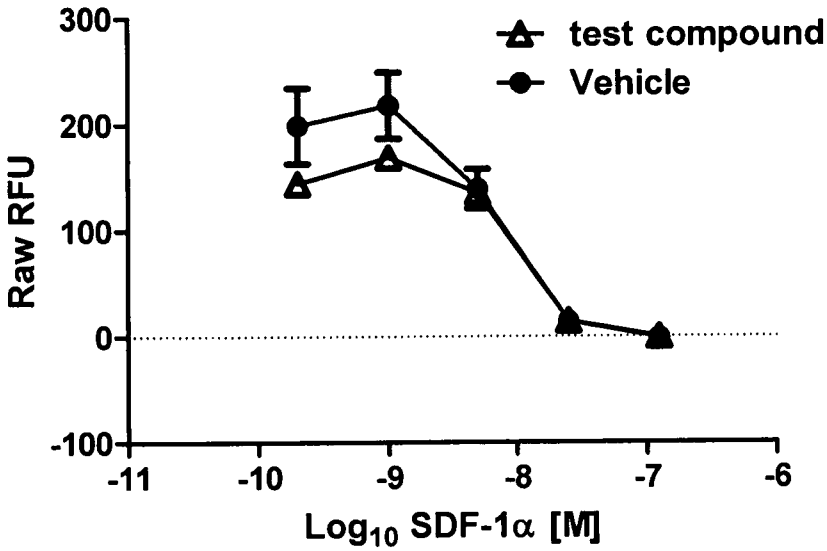


FIG. 1Q

54

MGYQKKLR
SMTDKYRL
HL



54

MGYQKKLR
SMTDKYRL
HL

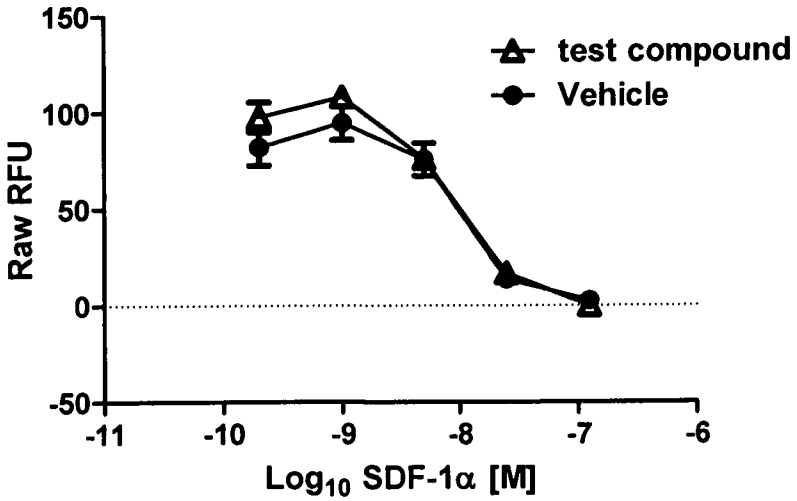
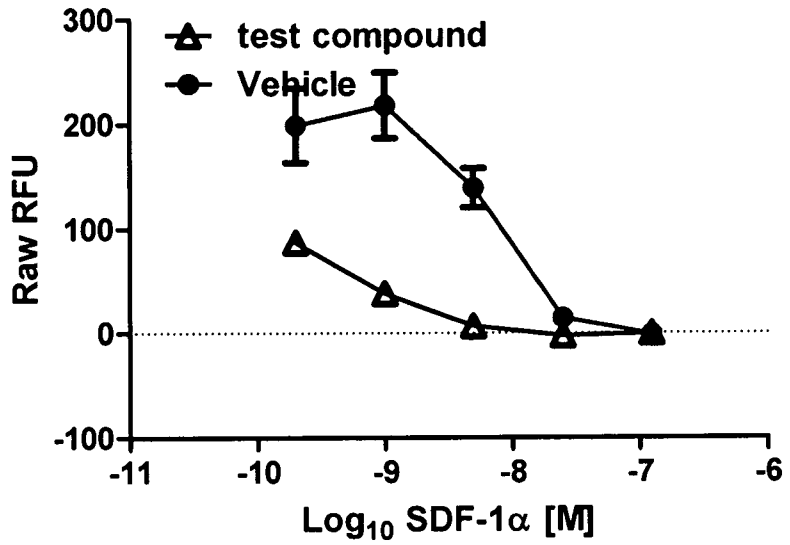


FIG. 1R

55

MGYQKKLR
SMTDKYRL
HLSV



55

MGYQKKLR
SMTDKYRL
HLSV

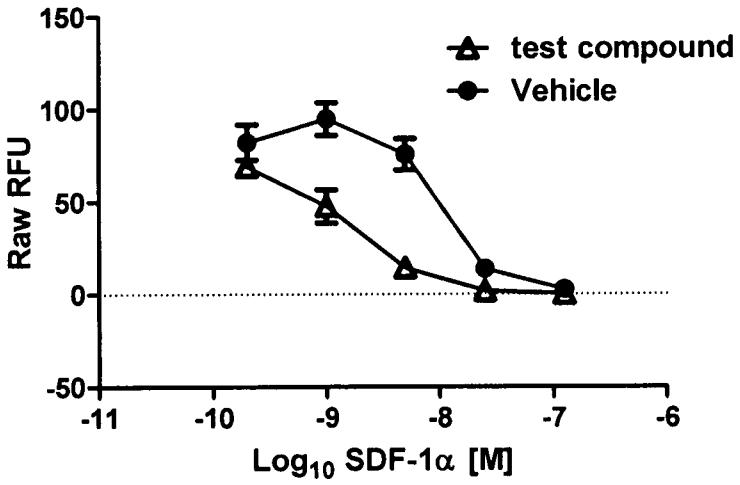


FIG. 1S

56

MGYQKKLR
SMTDKYRL
HLSV

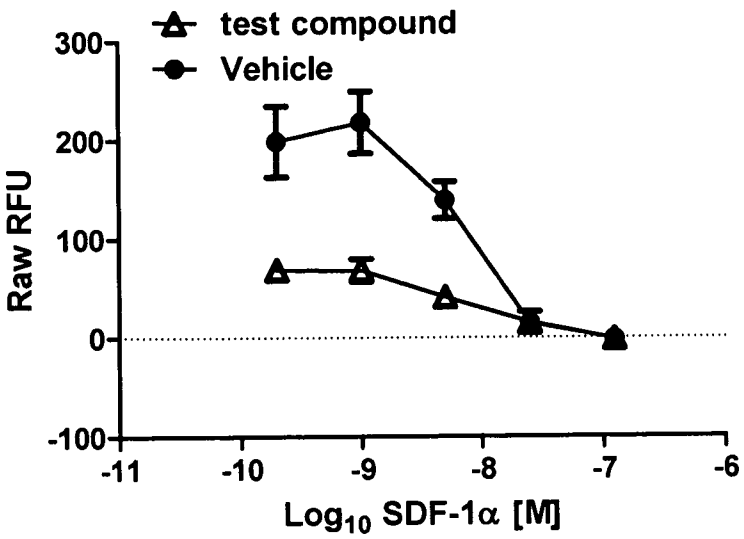


FIG. 1T

56

MGYQKKLR
SMTDKYRL
HLSV

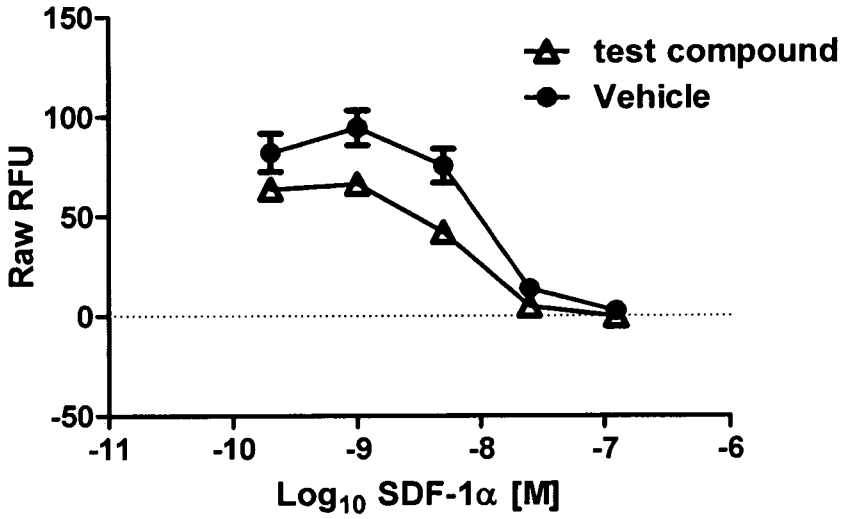
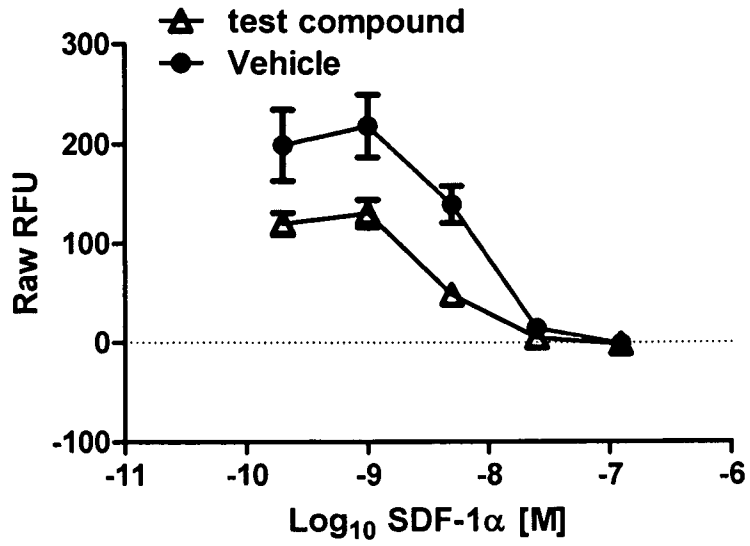


FIG. 1U

59

MGYQKKLR
SMTDK



59

MGYQKKLR
SMTDK

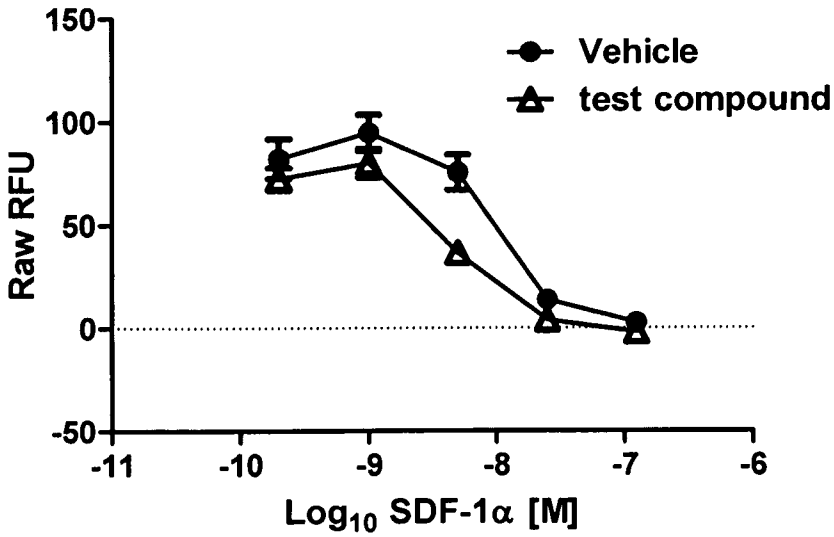


FIG. 1V

CXCR4 i2 loop Chemotaxis data

SUPB-15 cells

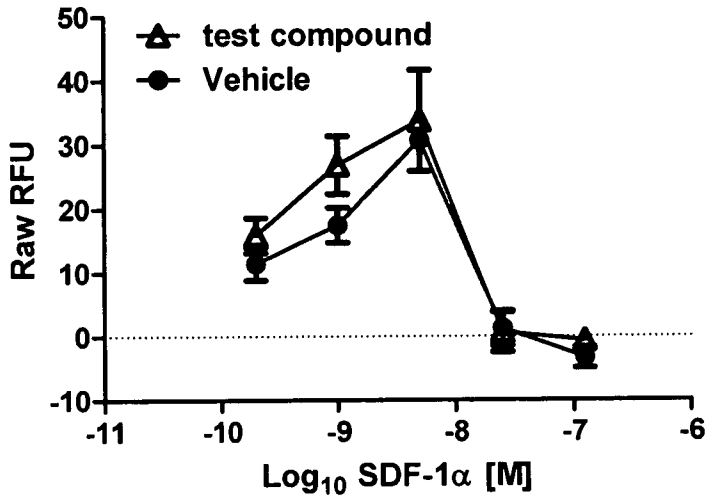
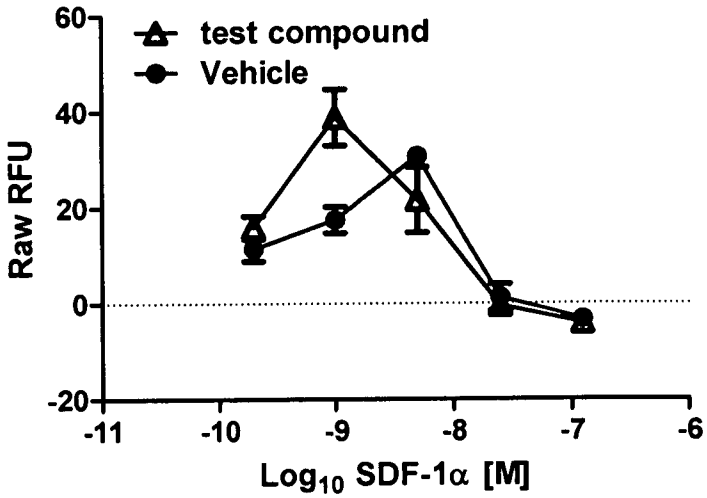
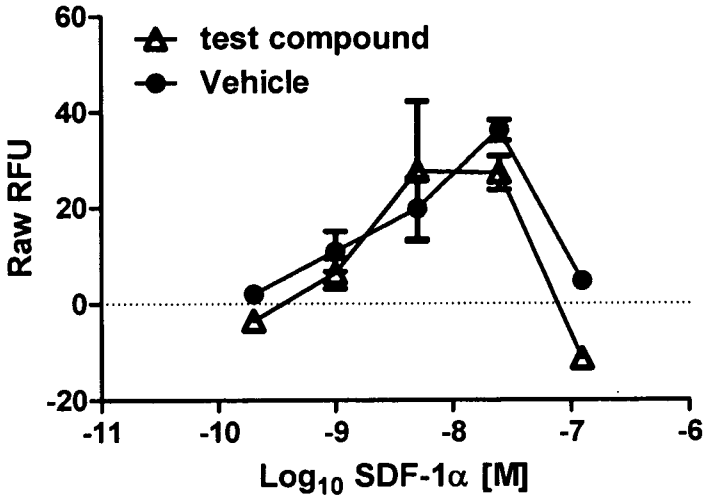
Comp. # Sequence	Chemotaxis Data
83 HATNSQRPRKLLAEKV	
82 HATNSQRPRKLLAEK	

FIG. 2A

81
HATNSQRPRKLLAE



80
HATNSQRPRKLLA

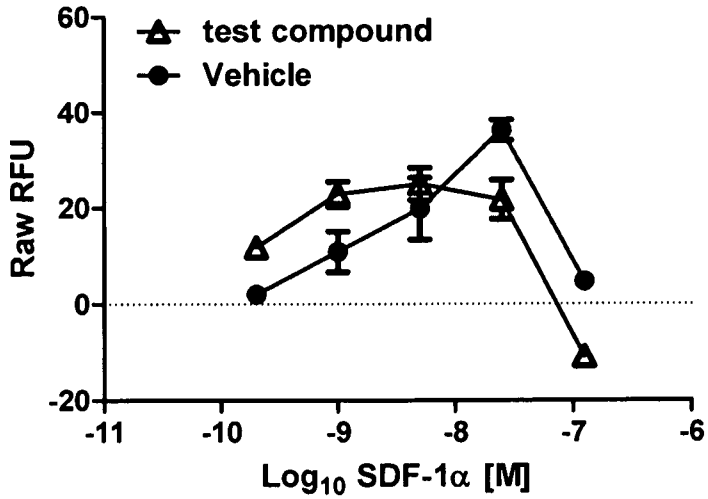
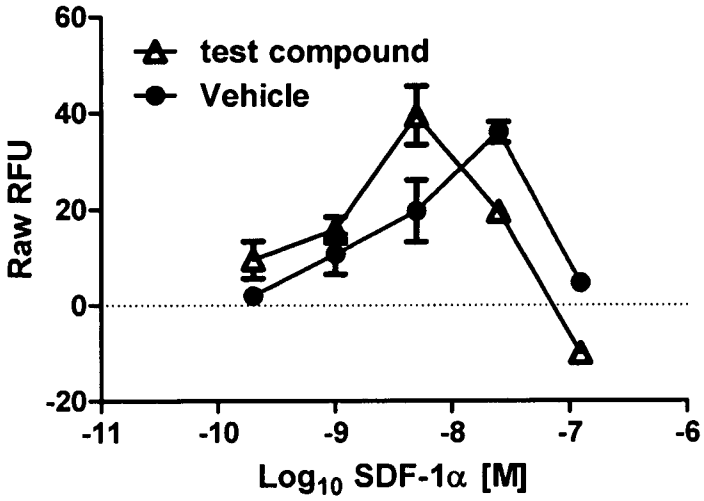


FIG. 2B

79
HATNSQRPRKL



78
VHATNSQRPRKLLA

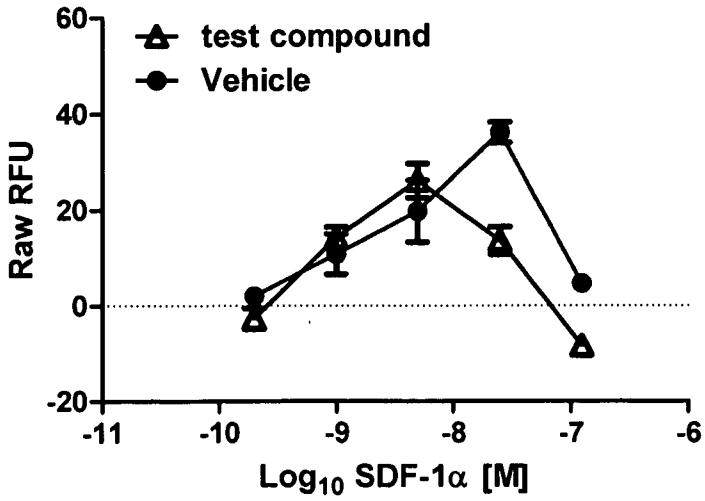
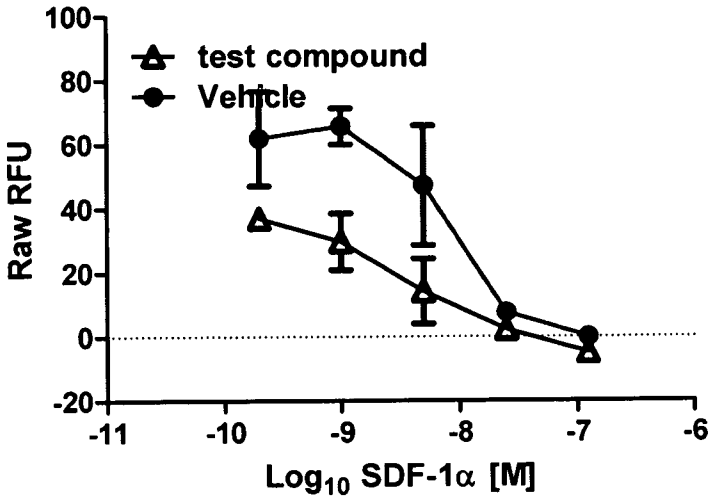


FIG. 2C

77
DRYLAIVHATNSQRPRKLL



76
DRYLAIVHATNSQRPRKLL

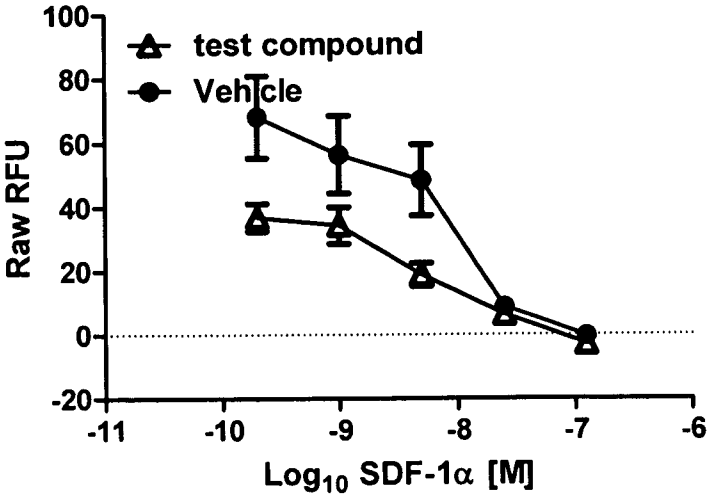


FIG. 2D

CXCR4 i3 loop Chemotaxis data
CEM cells

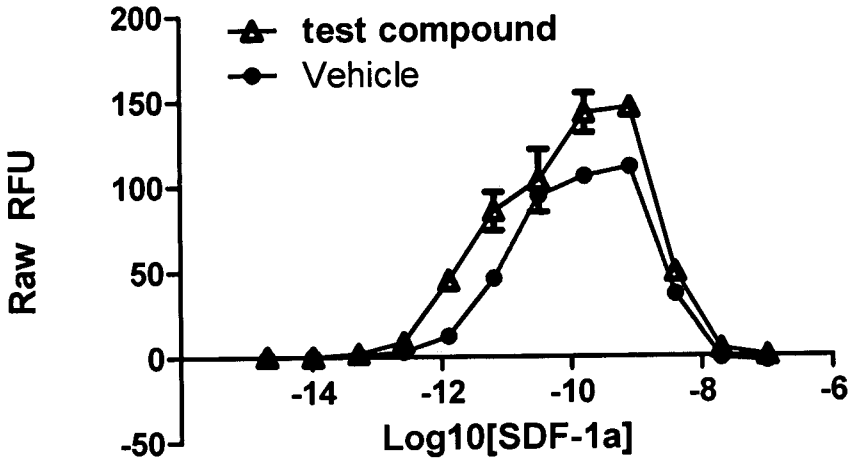
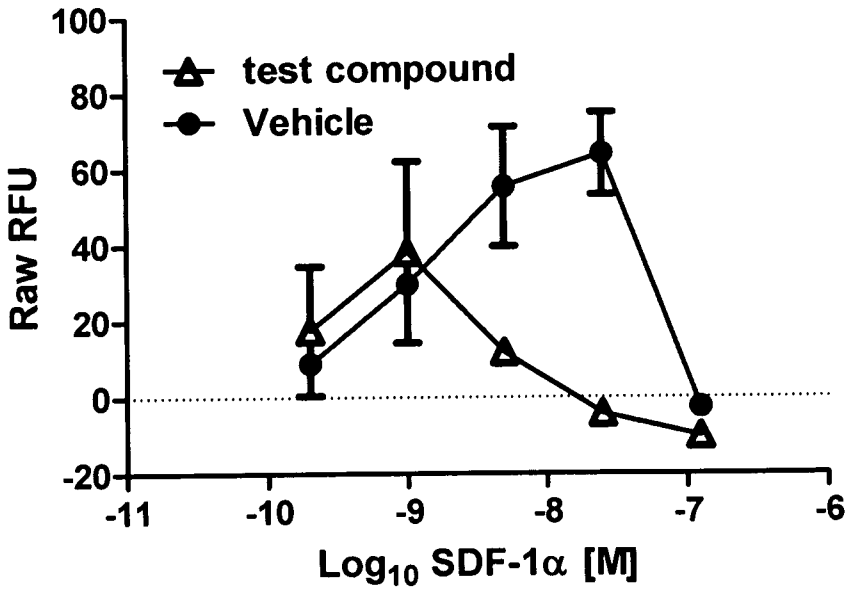
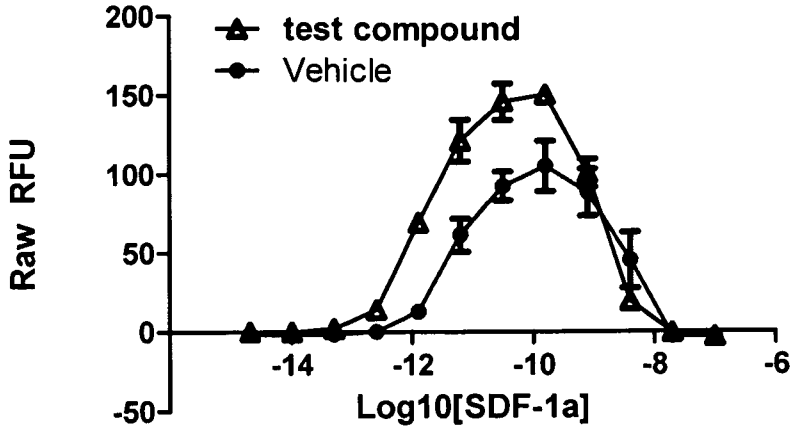
Comp. # Sequence	Chemotaxis data
88 SKLSHSKGHQ KRKALKTTVIL	
89 KLSHSKGHQK RKALKTTVIL	

FIG. 3A

90
KLSHSKGHQK
RKALKTTV



90
KLSHSKGHQK
RKALKTTV

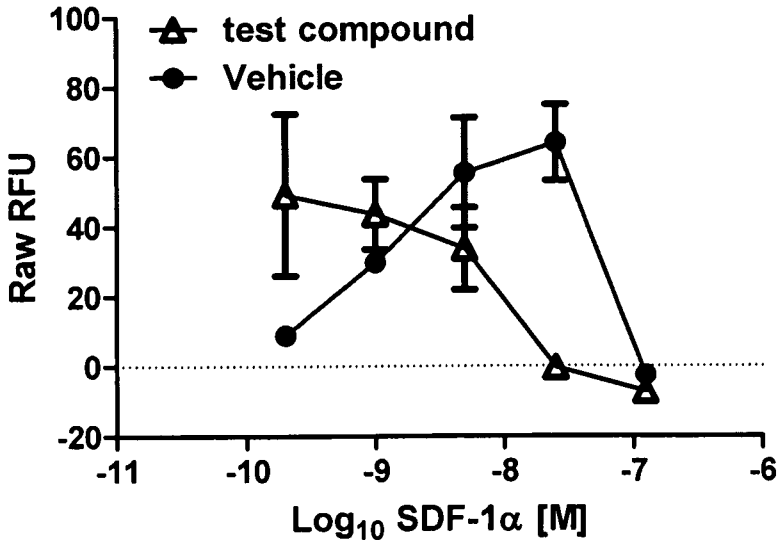
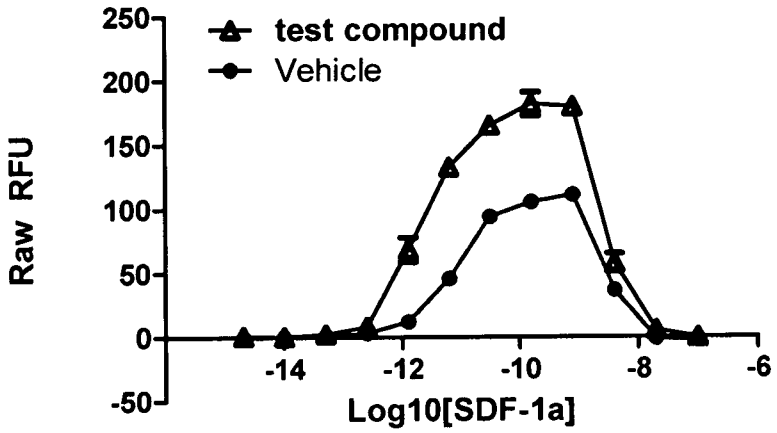


FIG. 3B

92
KLSHSKGHQK
RKALK



92
KLSHSKGHQK
RKALK

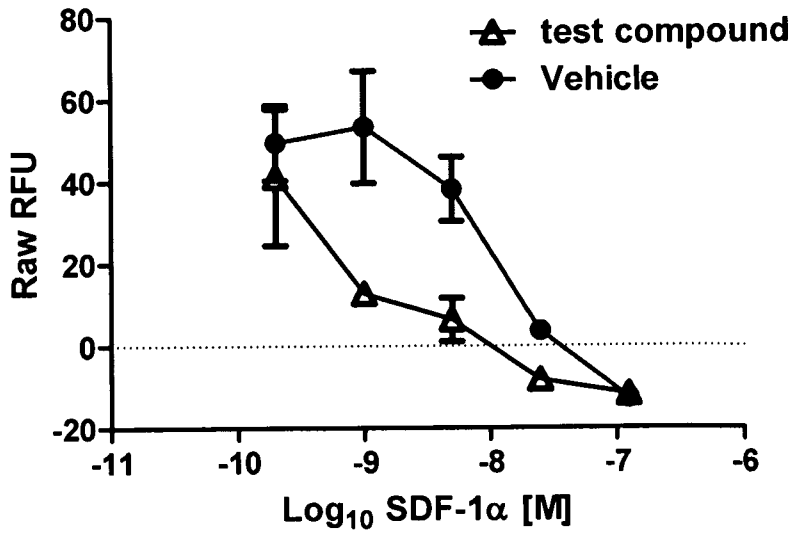
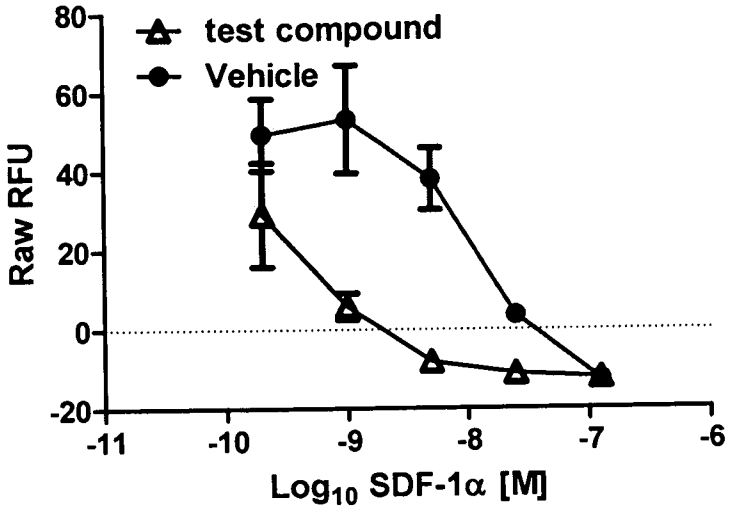


FIG. 3C

93
KLSHSKGHQK
RKAL



94
KLSHSKGHQK
RKA

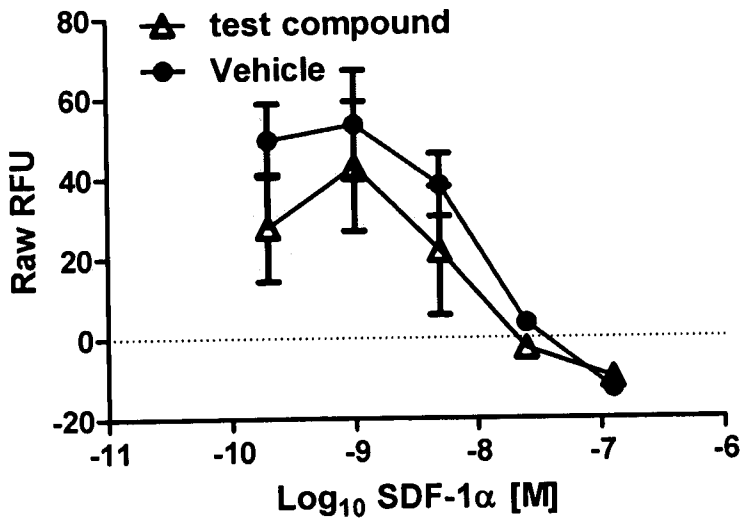
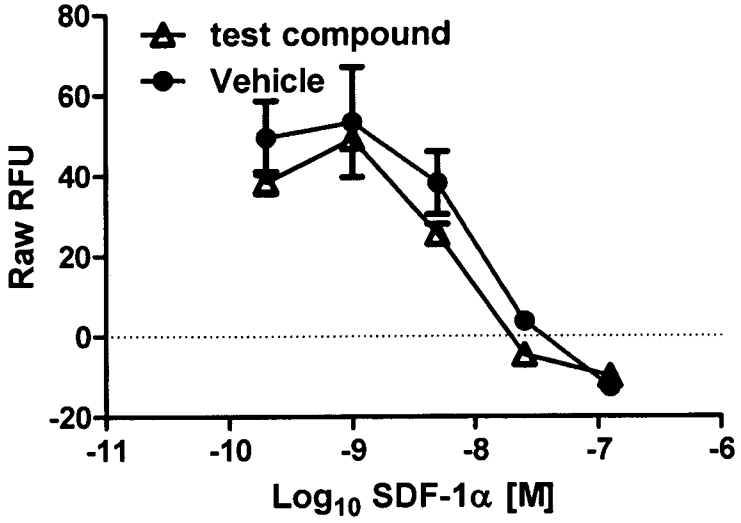


FIG. 3D

95
LSHSKGHQKR
KALK



96
SHSKGHQKRK
ALK

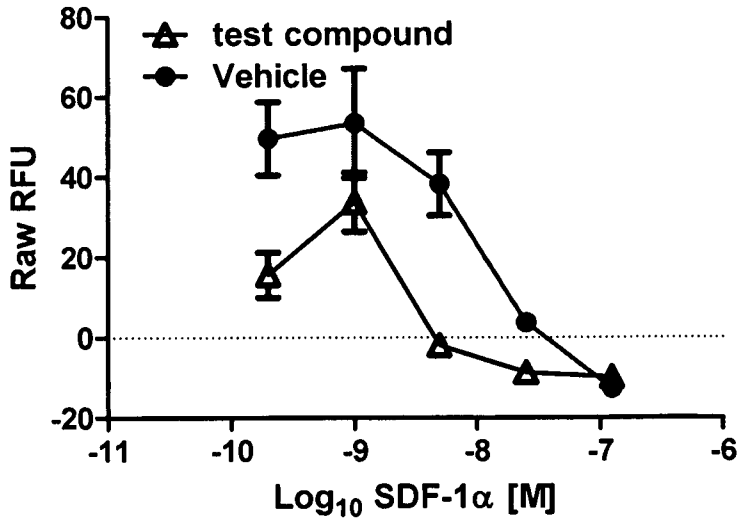
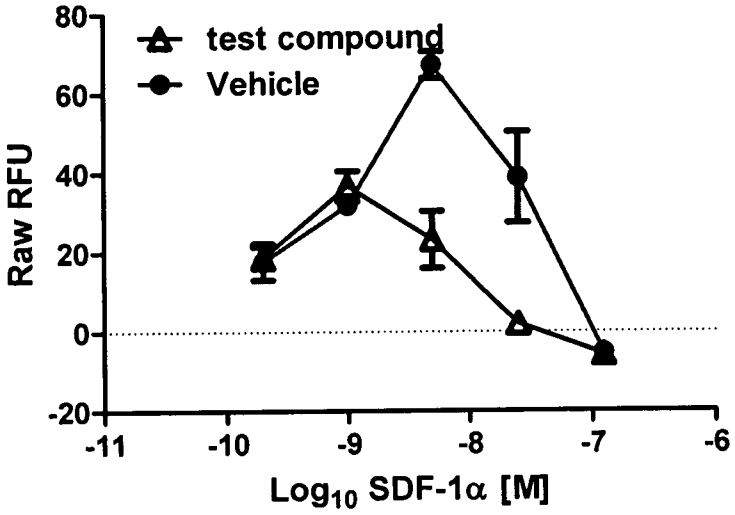


FIG. 3E

97
HSKGHQKRKA
LKT



99
HSKGHQKRKA
LKTTV

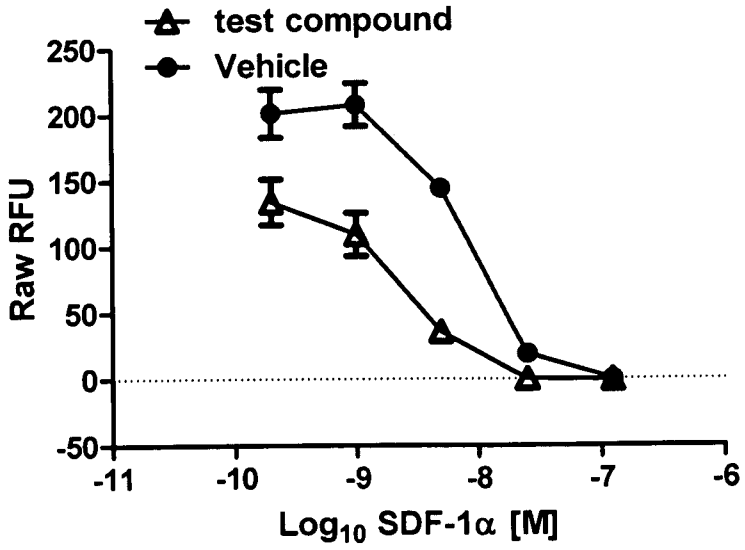
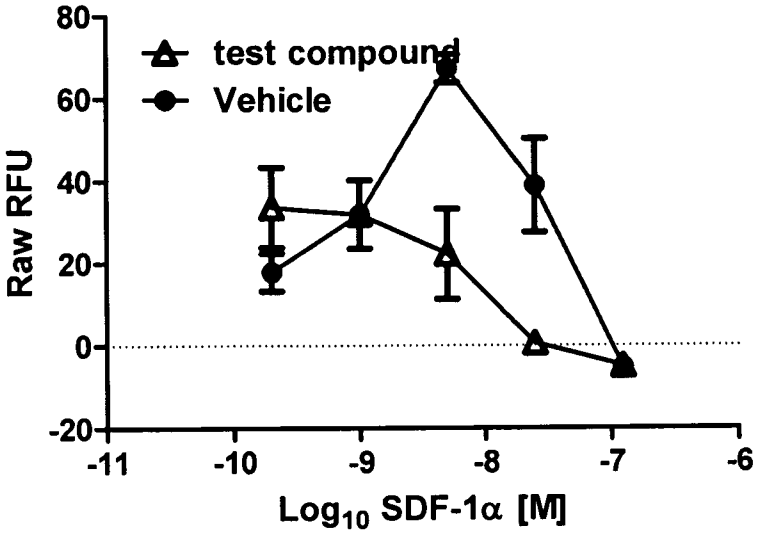


FIG. 3F

100
HSKGHQKRKA
LKKTTVI



101
SKLSHSKGHQ
KRKALK

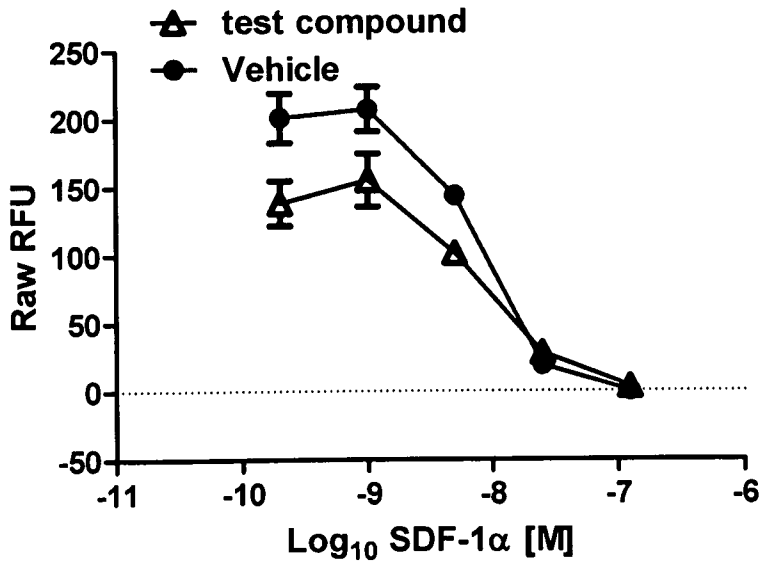


FIG. 3G

CXCR4 i4loop (CEM)

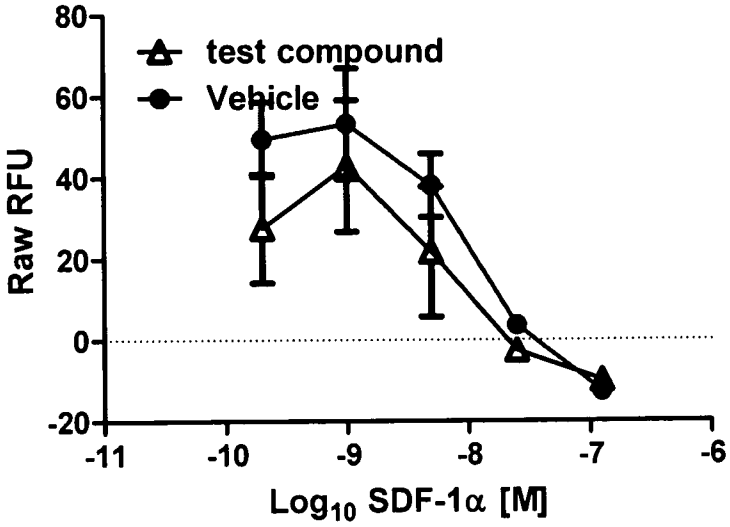
Comp. #

Sequence

Chemotaxis

116

GAKFKTSAQHALTSV
R



115

GAKFKTSAQHALTSV
SRGSSLK

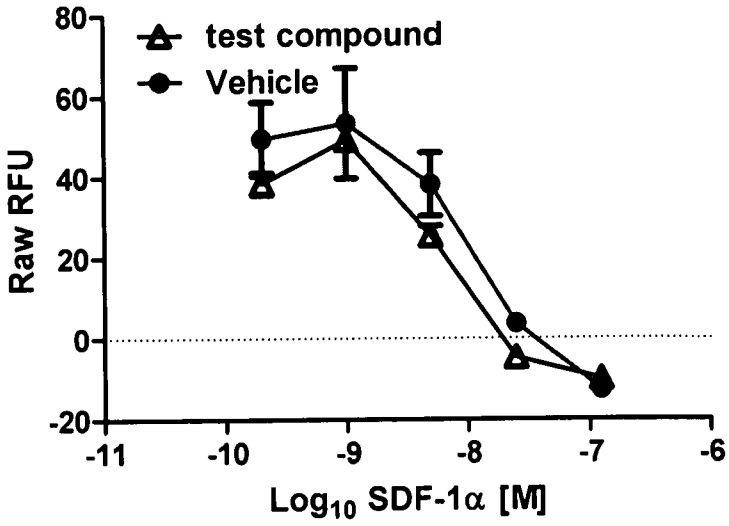
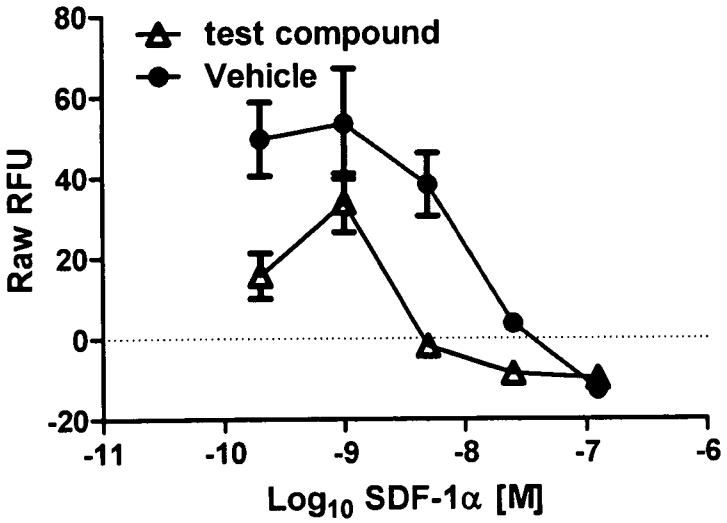


FIG. 4A

114

GAKFKTSAQHALTS
VSRGSSLKILSK



112

GAKFKTSAQHALTS
VSRGSSLKILSGGK

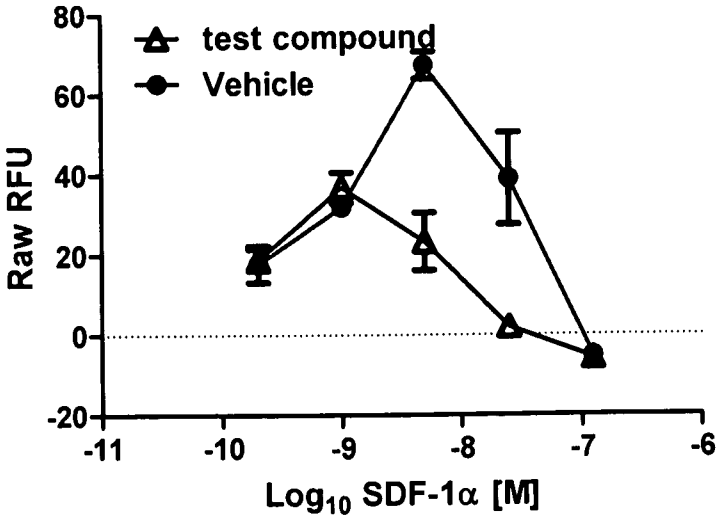
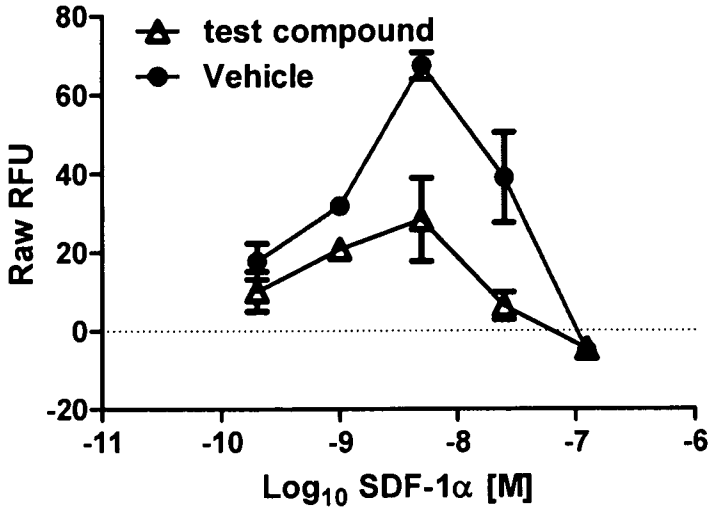


FIG. 4B

110
GAKFKTSAQHALTS
VSRGSSLKILSKGKR
GGSCFH



109
GAKFKTSAQHALTS
VSRGSSLKILSKGKR
GGHSSVST

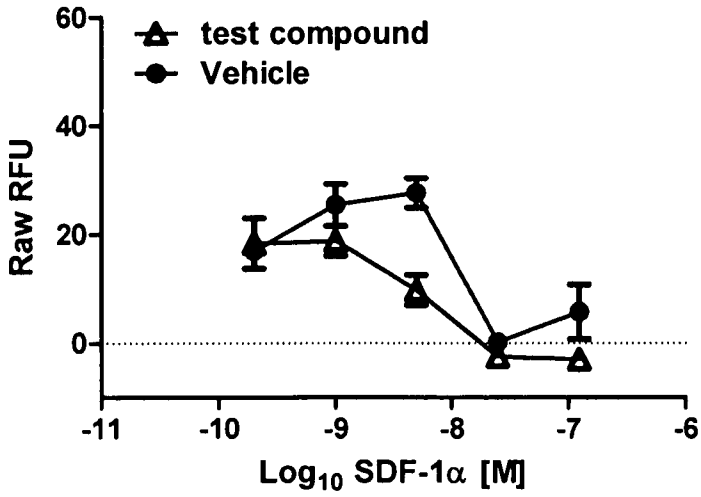
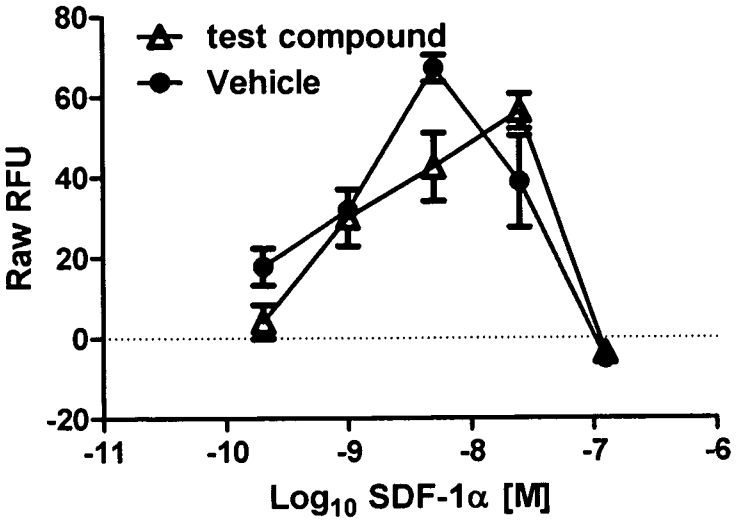


FIG. 4C

108
GAKFKTSAQHALTS
VSRGSSLKILSKGKR
G



107
GAKFKTSAQHALTS
VSRGSSLKILSKGKR
GGHSSVST

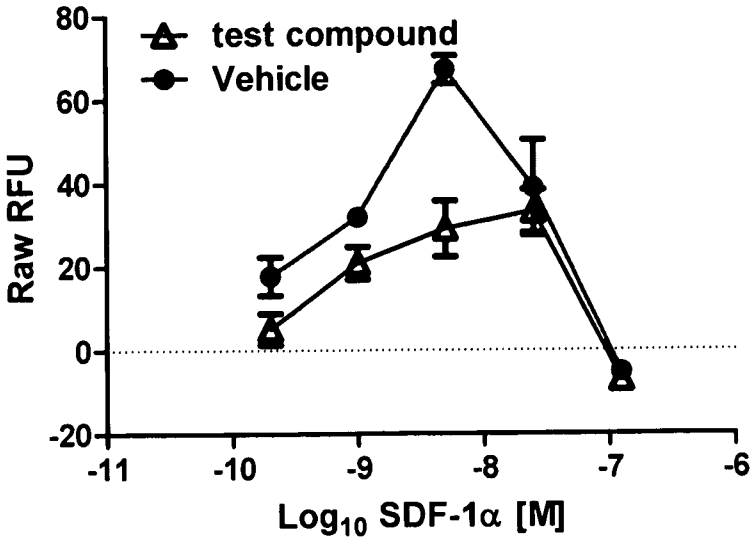


FIG. 4D

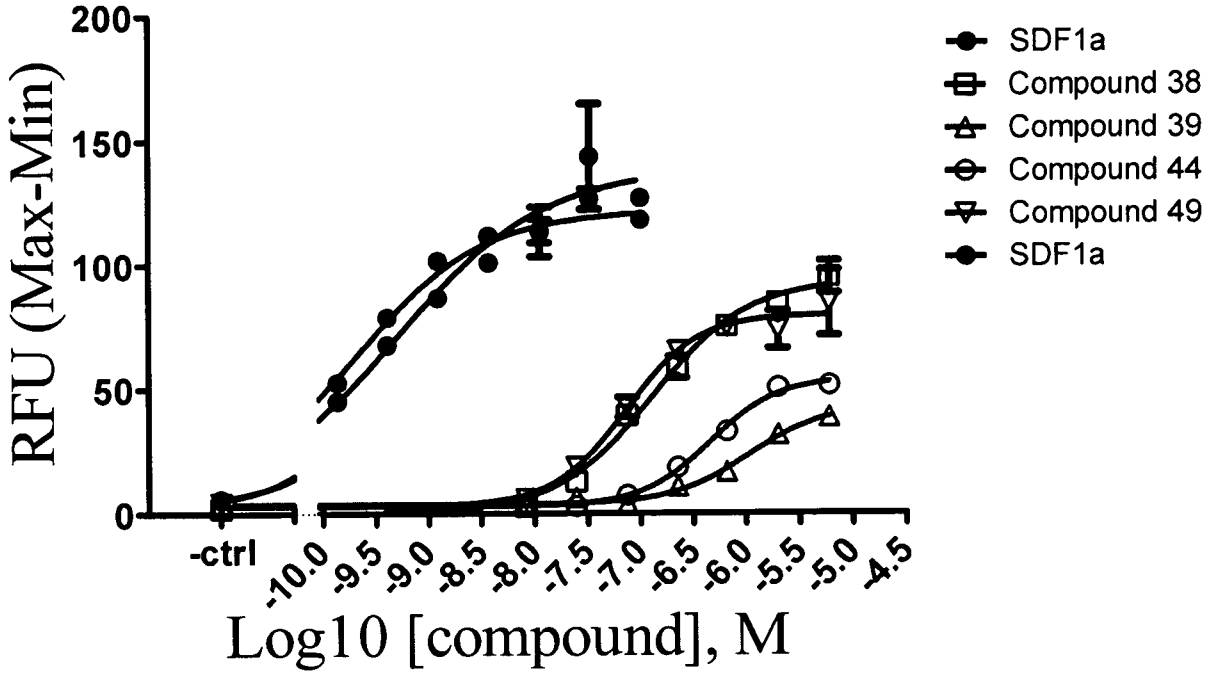

RFU (Max-Min)
200
150
100
50
0
-ctrl
-10.0
-9.5
-9.0
-8.5
-8.0
-7.5
-7.0
-6.5
-6.0
-5.5
-5.0
-4.5
Log10 [compound], M
SDF1a
Compound 38
Compound 39
Compound 44
Compound 49
SDF1a

FIG. 5

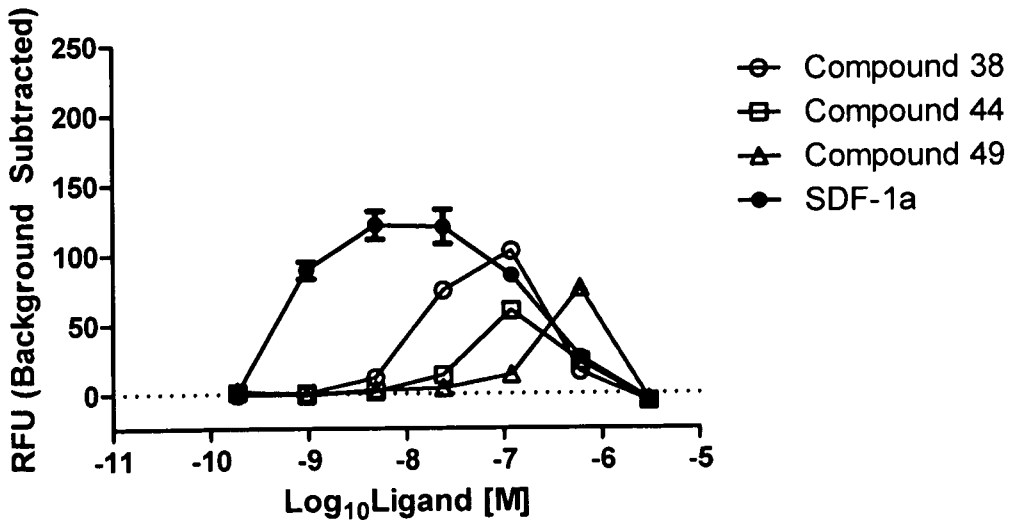

RFU (Background Subtracted)
250
200
150
100
50
0
-11
-10
-9
-8
-7
-6
-5
Log10Ligand [M]
Compound 38
Compound 44
Compound 49
SDF-1a

FIG. 6

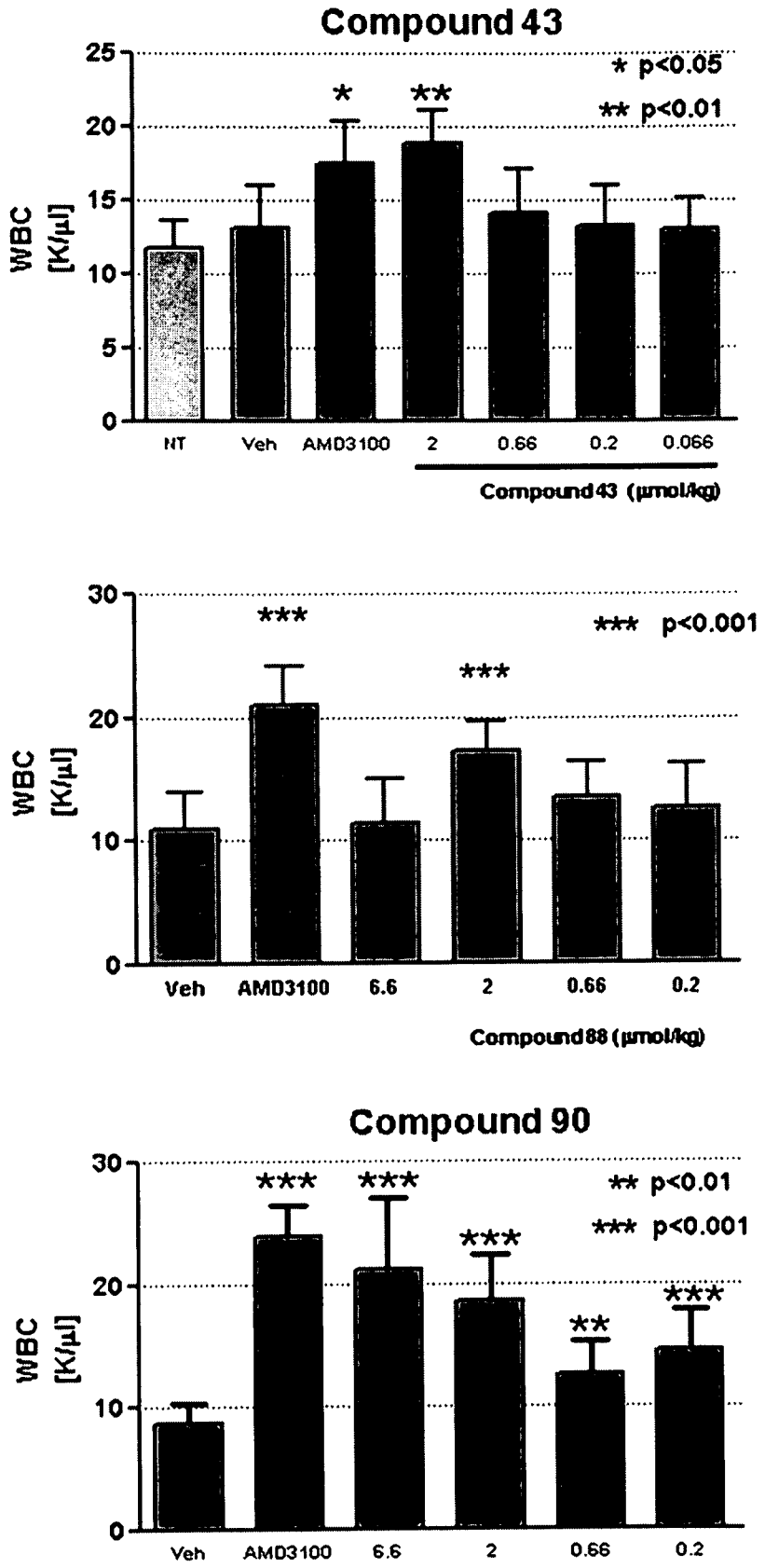

Compound 43
* p<0.05
** p<0.01
WBC [K/µl]
25
20
15
10
5
0
*
**
NT
Veh
AMD3100
2
0.66
0.2
0.066
Compound 43 (µmol/kg)
*** p<0.001
***
***
30
20
10
0
Veh
AMD3100
6.6
2
0.66
0.2
Compound 88 (µmol/kg)
Compound 90
** p<0.01
*** p<0.001
***
***
***
**
***
30
20
10
0
Veh
AMD3100
6.6
2
0.66
0.2

FIG. 7A

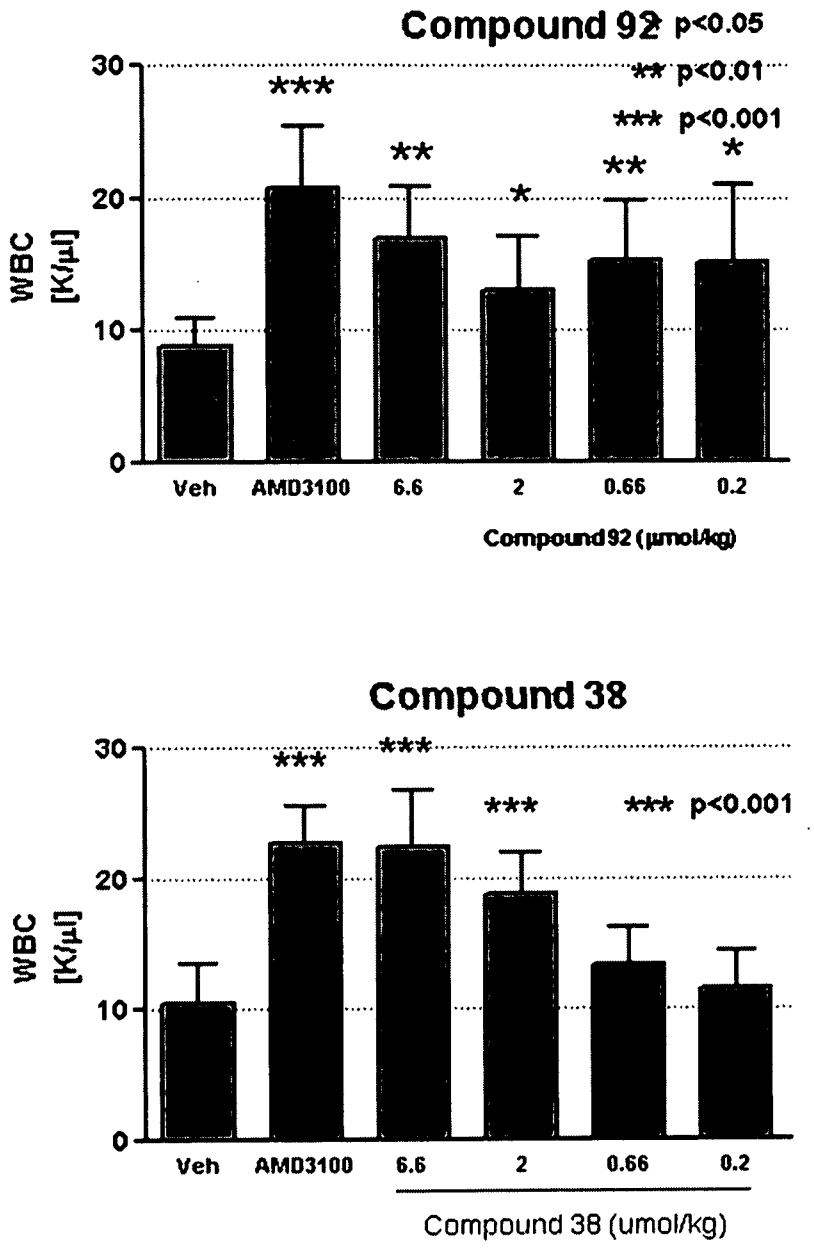

Compound 92
* p<0.05
** p<0.01
*** p<0.001
WBC [K/µl]
30
20
10
0
***
**
*
**
*
Veh
AMD3100
6.6
2
0.66
0.2
Compound 92 (µmol/kg)
Compound 38
***
***
***
***
***
p<0.001
WBC [K/µl]
30
20
10
0
Veh
AMD3100
6.6
2
0.66
0.2
Compound 38 (umol/kg)

FIG. 7B

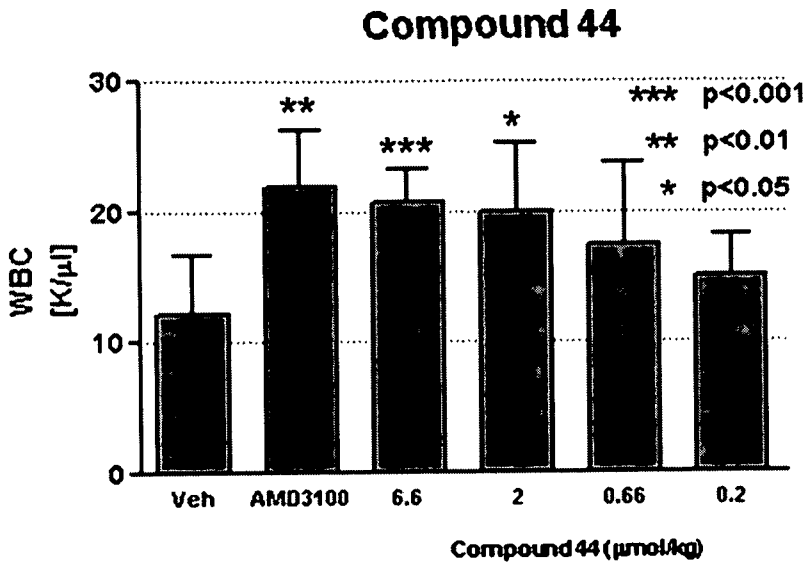
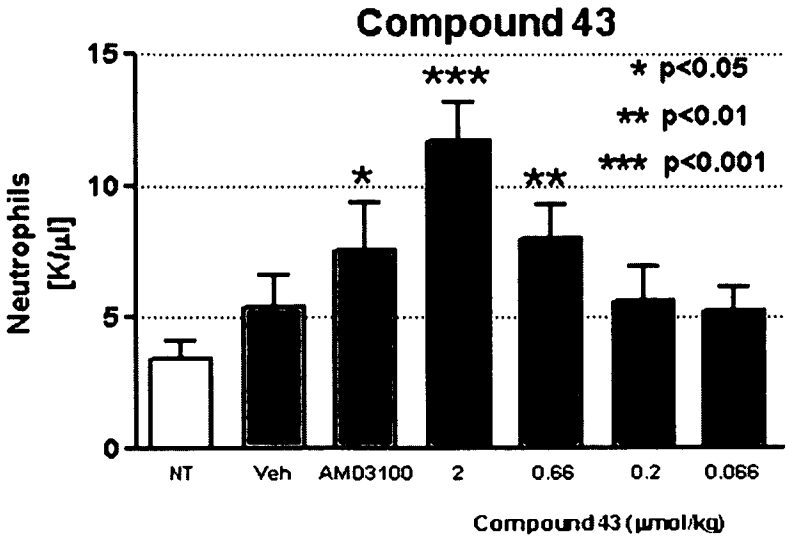
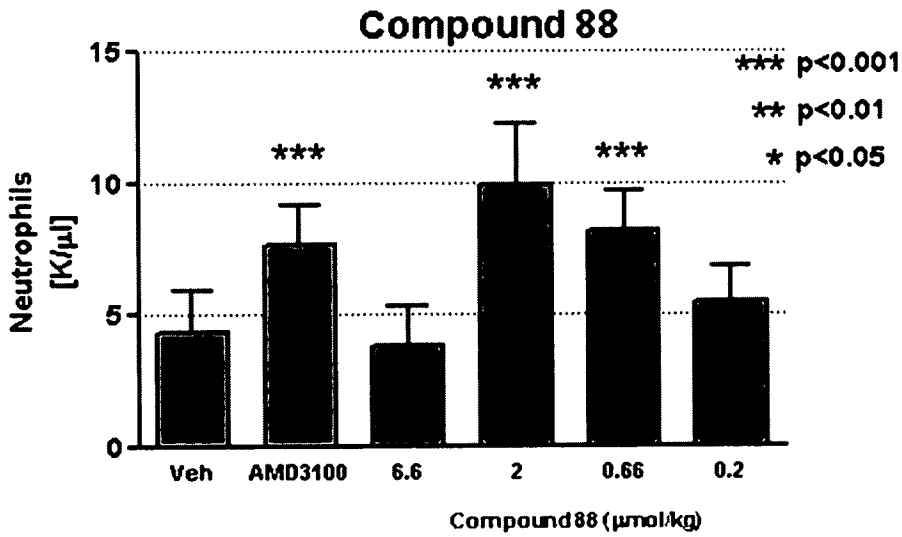

Compound 44
30
20
10
0
WBC [K/µl]
**
***
*
*** p<0.001
** p<0.01
* p<0.05
Veh
AMD3100
6.6
2
0.66
0.2
Compound 44 (µmol/kg)

FIG. 7C


Compound 43
* p<0.05
** p<0.01
*** p<0.001
Neutrophils [K/µl]
15
10
5
0
NT
Veh
AMD3100
2
0.66
0.2
0.066
Compound 43 (µmol/kg)


Compound 88
*** p<0.001
** p<0.01
* p<0.05
Neutrophils [K/µl]
15
10
5
0
Veh
AMD3100
6.6
2
0.66
0.2
Compound 88 (µmol/kg)

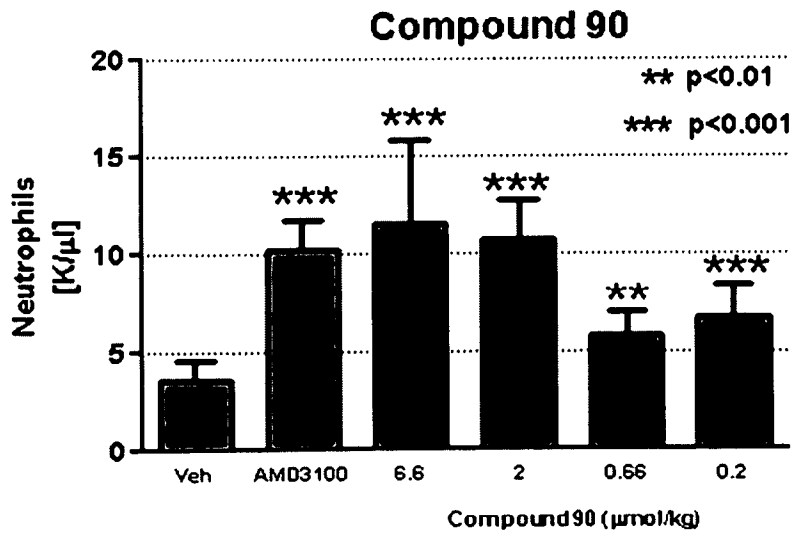

Compound 90
** p<0.01
*** p<0.001
Neutrophils [K/µl]
20
15
10
5
0
Veh
AMD3100
6.6
2
0.66
0.2
Compound 90 (µmol/kg)

FIG. 8A

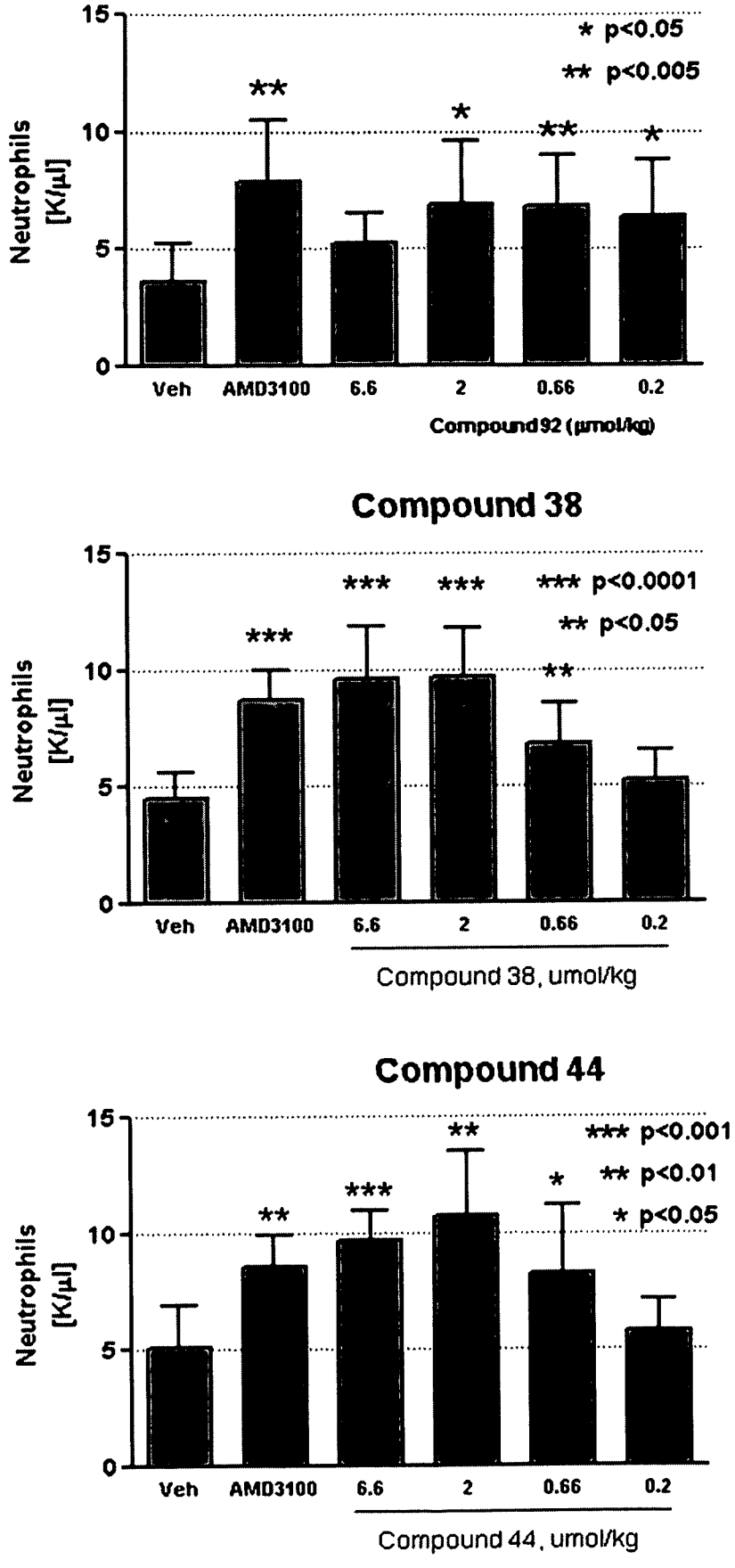
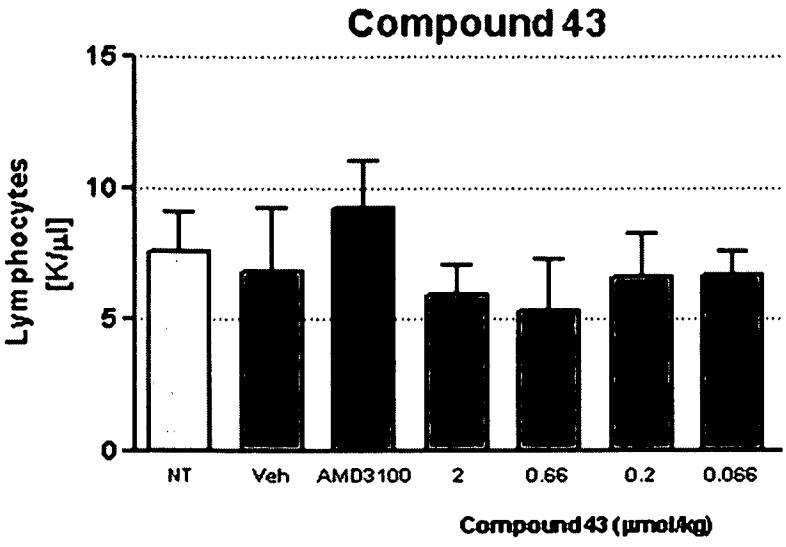
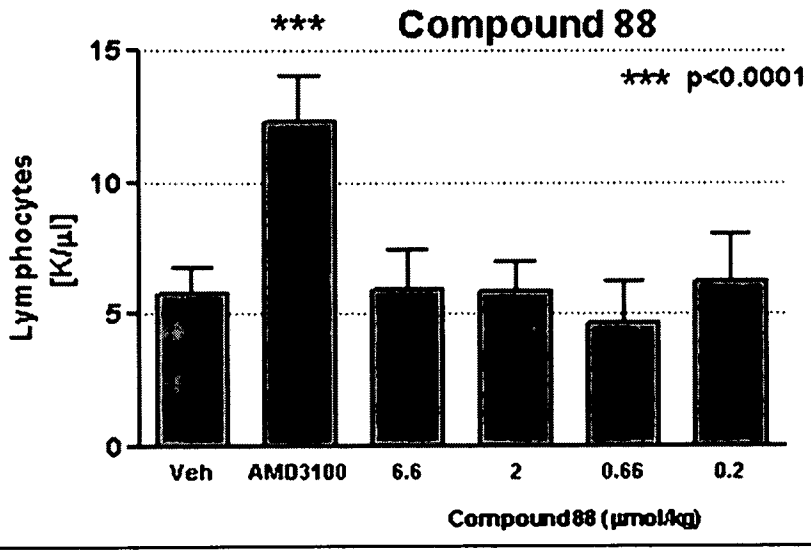

* p<0.05
** p<0.005
Neutrophils [K/µl]
15
10
5
0
Veh
AMD3100
6.6
2
0.66
0.2
Compound 92 (µmol/kg)
Compound 38
*** p<0.0001
** p<0.05
Compound 38, umol/kg
Compound 44
*** p<0.001
** p<0.01
* p<0.05
Compound 44, umol/kg

FIG. 8B


Compound 43
Lymphocytes [K/µl]
15
10
5
0
NT
Veh
AMD3100
2
0.66
0.2
0.066
Compound 43 (µmol/kg)


***
Compound 88
*** p<0.0001
Lymphocytes [K/µl]
15
10
5
0
Veh
AMD3100
6.6
2
0.66
0.2
Compound 88 (µmol/kg)

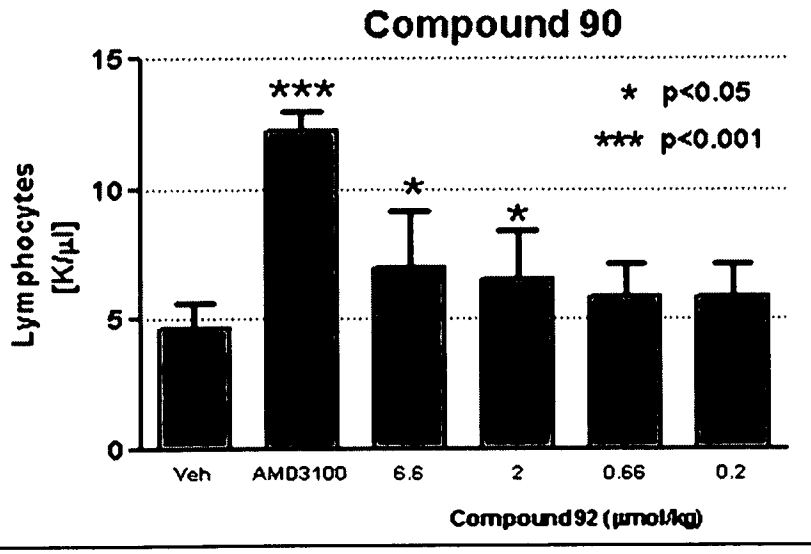

Compound 90
* p<0.05
*** p<0.001
Lymphocytes [K/µl]
15
10
5
0
***
*
*
Veh
AMD3100
6.6
2
0.66
0.2
Compound 92 (µmol/kg)

FIG. 9A

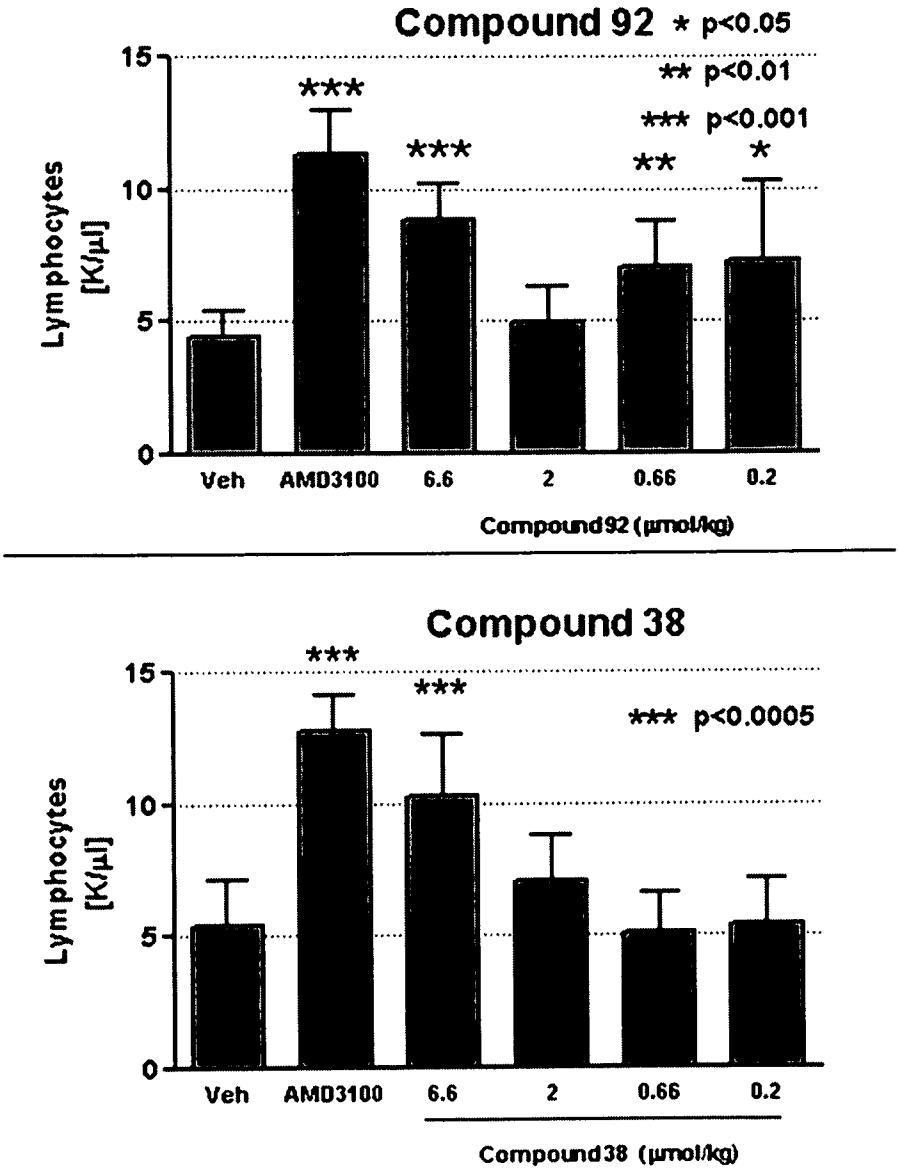

Compound 92 * p<0.05
** p<0.01
*** p<0.001
Lymphocytes [K/µl]
15
10
5
0
***
***
**
*
Veh
AMD3100
6.6
2
0.66
0.2
Compound 92 (µmol/kg)
Compound 38
***
***
*** p<0.0005
Lymphocytes [K/µl]
15
10
5
0
Veh
AMD3100
6.6
2
0.66
0.2
Compound 38 (µmol/kg)

FIG. 9B

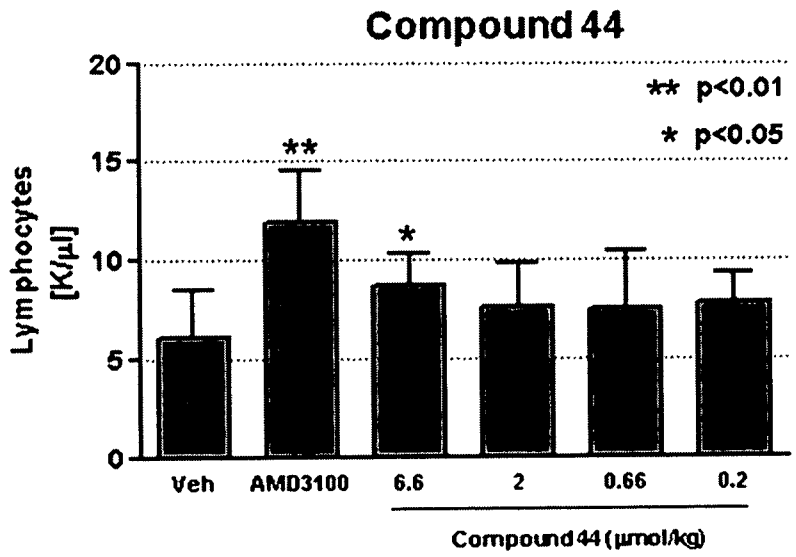
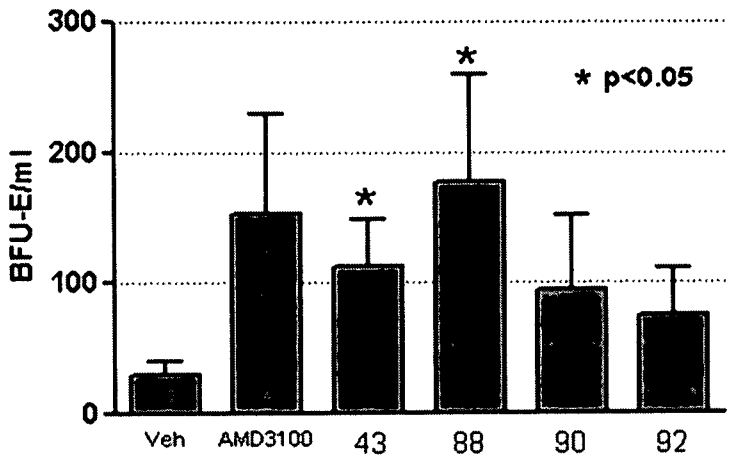

Compound 44
** p<0.01
* p<0.05
Lymphocytes [K/µl]
20
15
10
5
0
**
*
Veh
AMD3100
6.6
2
0.66
0.2
Compound 44 (µmol/kg)

FIG. 9C

BFUE



CFU-GM

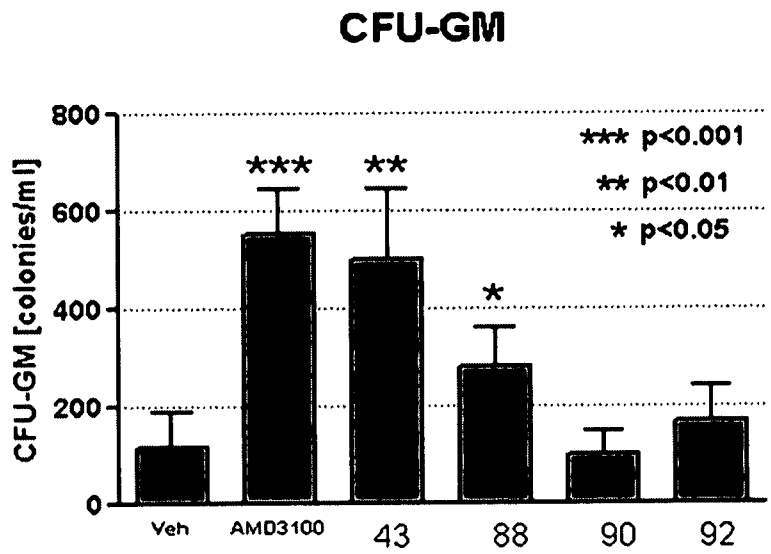


FIG. 10

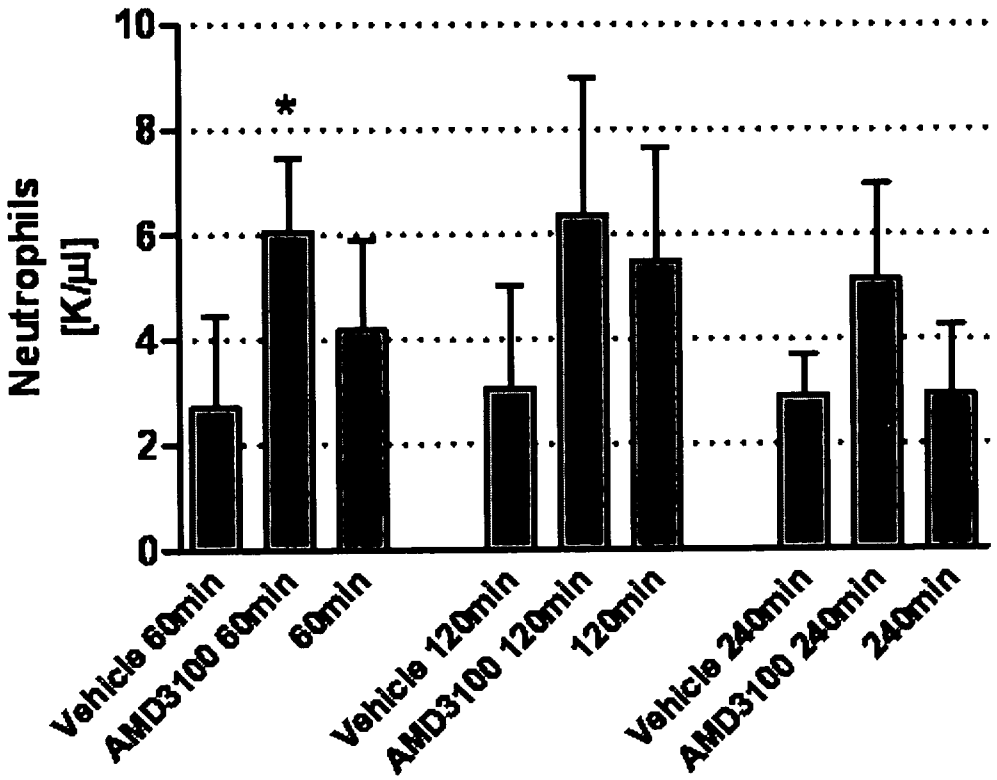

Neutrophils [K/µl]
10
8
6
4
2
0
*
Vehicle 60min
AMD3100 60min
60min
Vehicle 120min
AMD3100 120min
120min
Vehicle 240min
AMD3100 240min
240min

FIG. 11

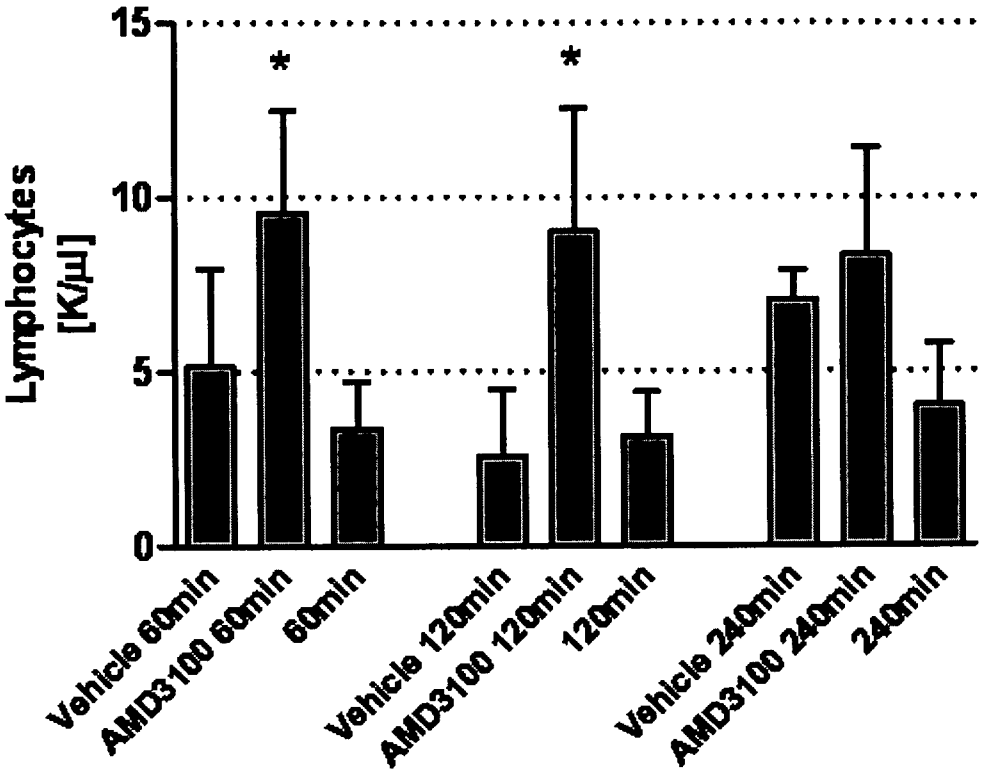

15
10
5
0
Lymphocytes [K/µl]
*
*
Vehicle 60min
AMD3100 60min
60min
Vehicle 120min
AMD3100 120min
120min
Vehicle 240min
AMD3100 240min
240min

FIG. 12