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(54) **Title**: NOVEL NPR-B AGONISTS

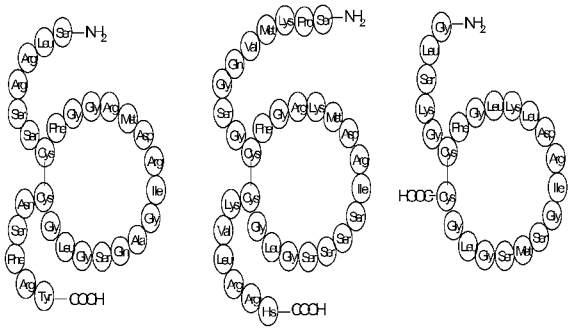

FIG. 1

(57) **Abstract**: Disclosed are novel compounds having NPR-B agonistic activity. Preferred compounds are linear peptides containing 8-13 conventional or non-conventional L- or D- amino acid residues connected to one another via peptide bonds.

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NOVEL NPR-B AGONISTS

BACKGROUND OF THE INVENTION

This application claims priority to U.S. provisional application serial number 61/245,960 filed September 25, 2009.

1. Field of the Invention

The present invention generally relates to novel compounds which are useful in the treatment and prevention of disorders mediated by natriuretic peptides or proteins. More particularly, the present invention relates to novel peptides, pharmaceutical compositions comprising one or more novel peptides described herein, and their use in methods of treating or preventing ocular disorders, such as glaucoma, ocular hypertension, and optic neuropathies, cardiovascular disease, kidney disease, lung disease, and other disorders mediated by natriuretic peptides or proteins.

2. Description of Related Art

The natriuretic peptides (NP's) are a family of cyclic peptide hormones that have first been described by their involvement in the regulation of natriuresis, diuresis and blood pressure control. To date, four natriuretic peptides have been discovered in man, i.e. atrial natriuretic peptide (ANP; SEQ ID NO:1), B-type or brain natriuretic peptide (BNP; SEQ ID NO;2), C-type natriuretic peptide (CNP; SEQ ID NO:3) and urodilatin (SEQ ID NO:4) (see FIG. 1; and Cho *et al.*, 1999, *Heart Dis.* 1:305-328). All NP's are synthesized as prepro-hormones which are activated by proteolytic cleavage before their release into the circulation. The NP's bind to natriuretic peptide receptors (NPR), a group of 3 different membrane bound receptors with guanylyl cyclase activity (Pandey 2005, *Peptides* 26:901-932).

ANP was first discovered as a blood pressure decreasing factor in rat atrial homogenates in 1981 (de Bold 1981, *Life Sci* 28:89-94). Human pre-pro-ANP (SEQ ID NO: 5) contains 151 amino acids and is stored after N-terminal cleavage as 126 amino acid pro-ANP (SEQ ID NO:6), predominantly in atrial granules. Cardiac stretch, due to systemic volume overload induces the rapid release of ANP from these stores. Upon secretion into the circulation, the C-terminal part of pro-ANP is cleaved by the atrial peptidase corin to the

biologically active 28 amino acid form of ANP (SEQ ID NO:1) (Yan 2000, *Proc Natl Acad Sci* 97:8525-8529). The remaining N-terminal part can be further cleaved into 3 different hormones. i.e. Long Acting Natriuretic Peptide (LANP, amino acids 1-30; SEQ ID NO:7), Vessel Dilator (VSDL, amino acids 31-67; SEQ ID NO:8) and Kaliuretic Peptide (KP, amino acids 79-98; SEQ ID NO:9) (Vesely 2004, *Eur J Clin Invest* 34:674-682).

After BNP was discovered in porcine brain as a factor that showed smooth muscle relaxing activity (Sudoh T, 1988, *Nature* 332:78), a much greater tissue expression was found in preparations of cardiac ventricles (Mukoyama 1991, *J Clin Invest* 87:1402-1412), which led to the conclusion that BNP is, similarly to ANP, a cardiac peptide hormone. Although BNP can be found in storage granules in the atria, the expression in ventricles is transcriptionally regulated (Tamura 2000, *Proc Natl Acad Sci* 93:4239-4244). Synthesis of pre-pro-BNP is induced through cardiac wall stretch and leads to a 134 amino acid long peptide (SEQ ID NO:10) which is further cleaved by an unknown protease to yield the 108 amino acid long pro-BNP (SEQ ID NO:11). Additional cleavage liberates the active 32 amino acid C-terminal fragment of BNP (SEQ ID NO:2) and the inactive 76 amino acid N-terminal fragment also referred to as NT-pro-BNP (SEQ ID NO:12). To date, no known splice variants of human BNP exists.

CNP was first isolated from porcine brain almost 10 years after the discovery of ANP (Sudoh 1990, *Biochem Biophys Res Comm* 168:863-870). It is primarily expressed in the central nervous system and endothelial cells. Unlike other NP's, CNP is nearly not present in cardiac tissue, which suggest a more paracrine function on vascular tone and muscle cell growth. The 126 amino acid precursor molecule pro-CNP (SEQ ID NO: 13) is processed by the intracellular endoprotease furin into the mature 53 amino acid peptide CNP-53 (SEQ ID NO:14), which is the most abundant form in the brain (Totsune 1994, *Peptides* 15:37-40), endothelial cells (Stingo, 1992, *Am J Phys* 263:H1318-H1321) and the heart (Minamino 1991, *Biochem Biophys Res Comm* 179:535-542). In both, cerebral spinal fluid (Togashi 1992, *Clin Chem* 38:2136-2139) and human plasma (Stingo 1992, *Am J Phys* 263:H1318-H1321) the most common form is CNP-22 (SEQ ID NO:3), which is generated from CNP-53 by an unknown extracellular protease. Unlike the other NP's CNP-22 lacks the C-terminal extension of the 17 amino acid ring (see FIG. 1).

ANP (SEQ ID NO:1), BNP (SEQ ID NO:2) and CNP (SEQ ID NO:3) show a highly conserved amino acid sequence among different vertebrate species (see FIG. 1; and Cho 1999, *Heart Dis.* 1:305-328). The NP's are inactivated by two distinct mechanisms, i.e. enzymatic cleavage through neutral endopeptidases and binding to the NP clearance receptor (NPR-C; SEQ ID NO:15), which is followed by internalization and intracellular degradation of the NP (Stoupakis 2003, *Heart Dis.* 5:215-223).

The discovery of the natriuretic peptides ANP, BNP and CNP was followed by the description and cloning of their specific receptors, natriuretic peptide receptor -A, -B and -C (NPR-A, -B, -C) (Fuller 1988, *J Biol Chem.* 263:9395-9401; Chang 1989 *Nature* 341:68-72; Chinkers 1989, *Nature* 338:78-83). NPR-A (SEQ ID NO:16) preferentially binds ANP and BNP, while NPR-B (SEQ ID NO:17) is most specific for CNP and NPR-C (SEQ ID NO:15) binds all natriuretic peptides (Koller 1991, *Science* 252:120-123).

The primary structure of NPR-A and NPR-B contain an extracellular ligand binding domain, transmembrane domain, intracellular kinase homology domain containing phosphorylation sites and a C-terminal guanylate cyclase domain (reviewed in Misono 2005, *Peptides* 26:957-68). The latter classifies NPR-A and NPR-B as particulate guanylate cyclases, also known as GC-A and GC-B (E.C.4.6.1.2). In contrast, NPR-C is lacking intracellular homology domains, but evidence is increasing for NPR-C's role not only as a scavenger receptor for natriuretic peptides, but for its' functional coupling to inhibitory G-proteins and phosphoinositide turnover (Maack 1987, *Science* 238:675-678; Murthy and Makhlouf 1999, *J Biol Chem* 274:17587-17592; Anand-Srivastava 2005, *Peptides* 26:1044-1059). Reflecting the grade of sequence homology in natriuretic peptides, natriuretic peptide receptors show a high degree of homology in their extracellular ligand binding domains, with the calculated similarities being 41% between NPR-A and NPR-B and 29% between NPR-A and NPR-C (van den Akker 2001, *J Mol Biol.* 311:923-937).

Ligand binding to NPRs requires a dimer of glycosylated receptor subunits (Fenrick *et al.* 1994, *Mol Cell Biochem.* 137:173-182; Kuhn 2003, *Circ Res.* 93:700-709) and is followed by a conformational change leading to activation of the guanylate cyclase domains. Subsequently, activity of particulate guanylate cyclases is regulated through phosphorylation (reviewed in Kuhn 2003, *Circ Res.* 93:700-709). Phosphorylation of NPRs is maximal in the

basal state, while ligand binding is followed by dephosphorylation and subsequent desensitization of the receptor.

Natriuretic receptors are expressed in many tissues throughout the organism. NPR-A, NPR-B and NPR–C are present in the cardiovascular system and the kidney, with NPR-C being the most abundant receptor subtype accounting for 80% of NPR-expression in some tissues. NPR-B is present in a particularly high level in rat pineal gland, testis and ovaries. NPR-A and NPR-B ligands both induce endothelium-independent vasorelaxation, where ANP and BNP mainly act on arterial vasculature. In contrast, CNP mainly targets the venous system, with the exception of coronary arteries, that relax in response to CNP stimulation (Marton *et al.* 2005, *Vascul Pharmacol* 43:207-212). Importantly, induction of hypotension via NPR-B activation requires 10-fold higher concentrations of ligand compared to blood pressure reduction in response to NPR-A activation (Wei *et al.* 1993, *Am J Physiol.* 264:H71-H73; Woods and Jones 1999, *Am J Physiol.* 276:R1443-R1452). Relaxation of smooth muscle by activation of NPR-B has been shown in a variety of tissues, including blood vessels, seminiferous tubules and uterus. Also contraction of the ocular trabecular meshwork tissue is reduced by activation of natriuretic peptide receptors, confirming functional similarities of trabecular meshwork and smooth muscle cells (Stumpff and Wiederholt 2000, *Ophthalmologica* 214:33-53).

Another main target organ of natriuretic peptides is the kidney. Ligands of NPR-A induce natriuresis and diuresis by a dual mechanism (reviewed in Beltowski and Wojcicka 2002, *Med Sci Monit.* 8:RA39-RA52): (1) increased excretion of sodium by a reduced re-uptake of sodium ions in the distal tubulus, subsequently leading also to higher retention of water in the final urine; and (2) dilation of the affluent and concomitant contraction of the effluent glomerular capillary, increasing glomerular filtration rate, at the cost of reduction of renal perfusion (Endlich and Steinhausen 1997, *Kidney Int.* 52:202-207). In contrast to NPR-A-specific ligands, NPR-B-specific ligands do not induce significant natri- and diuresis, and in addition, show a peculiarity regarding glomerular flow regulation: CNP was shown to dilate both affluent and effluent capillaries in the glomerulus, thus increasing renal blood flow, but not glomerular filtration (Endlich and Steinhausen 1997, *Kidney Int.* 52:202-207).

In addition to effects of NP-receptor (NPR) activation on blood pressure and kidney function, powerful effects of natriuretic peptides on proliferative processes in a variety of cell types have been documented in the literature. Antiproliferative properties of NPR activation

are documented for vascular smooth muscle cells, fibroblasts of different origins, mesangial cells, cancer cells and chondrocytes (reviewed in Schulz 2005, *Peptides* 26:1024-1034). At least for VSMC, evidence for the involvement of the transcription factor GAX in the regulation of proliferation has given an indication as to which intracellular mechanisms might be involved in growth regulation through NPR (Yamashita *et al.* 1997, *Hypertension* 29:381-387). Though tissue growth is mainly regulated by proliferative activity, some organs feature variations in cell size to influence tissue mass. This might be a physiological process, as during endochondral ossification, when chondrocytes mature by undergoing hypertrophy, or a pathological event, as in cardiac hypertrophy, which often precedes chronic heart failure. Both of the above-mentioned events of hypertrophy are regulated by NPR-B. NPR-B deficiency causes dwarfism due to abnormal endochondral ossification, characterized by size reduction of the hypertrophic zone of the epiphyseal growth plate (Bartels *et al.* 2004, *Am J Hum Genet.* 75:27-34; Tamura *et al.* 2004, *Proc Natl Acad Sci.* 101:17300-17305).

Quite different, a partial knock out of NPR-B in rats promoted cardiac hypertrophy, i.e. hypertrophy of cardiomyocytes (Langenickel *et al.* 2006, *Proc Natl Acad Sci.* 103:4735-4740).

Natriuretic peptides, having activity at the natriuretic receptors, were later discovered in various tissues, as well. For example, ANP was discovered in the early 1980s as an endogenous diuretic and vasorelaxant peptide, whose principle circulating form consists of 28 amino acids (SEQ ID NO:1). Subsequently, other natriuretic peptides, such as BNP (SEQ ID NO:2) and CNP (SEQ ID NO:3), were discovered. The presence of natriuretic peptides and their receptors in ocular tissues, especially those involved in the regulation of IOP, have been demonstrated. For example, in rat and rabbit eyes, ANP, BNP, and CNP, as well as NPR-A, NPR-B, and NPR-C mRNA were found in the ciliary processes, retina, and choroid (Mittag *et al.* 1987, *Curr Eye Res.* 6:1189-1196; Nathanson 1987, *Invest Ophthalmol Vis Sci.* 28:1357-1364; Fernandez-Durango *et al.* 1995, *Exp Eye Res.* 61:723-729). Similar results were found in bovine ciliary processes and cultured bovine ciliary epithelial cells. (Millar *et al.* 1997, *J Ocul Pharmacol Ther.* 13:1-11; Shahidullah and Wilson 1999, *Br J Pharmacol.* 127:1438-1446). The presence of the peptides and their receptors in the ciliary epithelium suggests that they may play a role in the production of aqueous humor.

In addition to the ciliary processes, natriuretic peptide receptors were also found in tissues associated with the outflow of aqueous humor. ANP binding sites were localized in the longitudinal ciliary muscle of the guinea pig. (Mantyh *et al.* 1986, *Hypertension*. 8:712-721). In cultured human TM and ciliary muscle cells, CNP is the most potent and efficacious in stimulating the production of cyclic GMP, indicating the presence of functional NPR-B. Activation of this receptor reduces carbachol-induced calcium influx. (Pang *et al.* 1996, *Invest Ophthalmol Vis Sci*. 37:1724-1731). This result predicts that activation of NPR-B should cause relaxation of these tissues. Indeed, CNP significantly decreases the carbachol-induced contraction of monkey and human ciliary muscles. (Ding and Abdel-Latif, 1997, *Invest Ophthalmol Vis Sci*. 38:2629-2638). Change in contractility in TM and ciliary muscle may affect the outflow facility of aqueous humor.

Cyclic GMP and compounds that increase cyclic GMP in ocular tissues, such as nitric oxide donors, have been shown to lower IOP. (Nathanson 1988, *Eur J Pharmacol*. 147:155-156; Becker 1990, *Invest Ophthalmol Vis Sci*. 31:1647-1649; Nathanson 1992, *J Pharmacol Exp Ther*. 260:956-965; Stein and Clack 1994, *Invest Ophthalmol Vis Sci*. 35:2765-2768). Since natriuretic peptides potently increase cyclic GMP production, they were predicted to lower IOP, too. In the past 20 years, the natriuretic peptides have been shown to be highly effective as IOP-lowering agents. For example, various researchers have independently shown that intravitreal injection of ANP in rabbits consistently and significantly lowers IOP. This effect lasts for many hours. (Sugrue and Viader, 1986, *Eur J Pharmacol*. 130:349-350; Mittag *et al.* 1987, *Curr Eye Res*. 6:1189-1196; Nathanson 1987 *Invest Ophthalmol Vis Sci*. 28:1357-1364; Korenfeld and Becker 1989, *Invest Ophthalmol Vis Sci*. 30:2385-2392; Takashima *et al.* 1996, *Invest Ophthalmol Vis Sci*. 37:2671-2677). The IOP effect of ANP correlates with an increase in cyclic GMP production in the iris-ciliary body. (Korenfeld and Becker 1989, *Invest Ophthalmol Vis Sci*. 30:2385-2392). Intravitreal injection of BNP (Takashima *et al.* 1996, *Invest Ophthalmol Vis Sci*. 37:2671-2677) or CNP (Takashima *et al.* 1998, *Exp Eye Res*. 66:89-96) is also highly efficacious in lowering IOP. In addition to intravitreal injection, subconjunctival (Yang *et al.* 1997, *Chin J Ophthalmol*. 33:149-151) or intracameral (Sugrue and Viader 1986, *Eur J Pharmacol*. 130:349-350; Fernandez-Durango *et al.* 1999, *Eur J Pharmacol*. 364:107-113) injection of the natriuretic peptides have been shown to be ocular hypotensive as well. Systemic administration of ANP in the rabbit,

(Tsukahara *et al.* 1988, *Ophthalmologica.* 197:104-109) or human (Diestelhorst and Krieglstein 1989, *Int Ophthalmol.* 13:99-101) also lowers IOP. Unfortunately, it has not been possible to deliver these peptides topically due to their inability to penetrate the cornea. Therefore, these potent and efficacious IOP-lowering compounds have not been developed for such use.

There is a need for novel NPR-B agonists having improved bioavailability, as compared to isolated or synthesized natriuretic peptides, that can be used in the treatment of natriuretic peptide-mediated disorders, such as ocular disorders, diabetes-related disorders, vascular disorders, cardiac and cardiovascular pathologies, inflammation and other disorders described herein. The novel NPR-B agonists, compositions and methods of the present invention meet these needs.

SUMMARY OF THE INVENTION

The present invention provides novel NPR-B agonists, also referred to herein as natriuretic peptide mimics or similars, that are therapeutically useful for lowering intraocular pressure (IOP) and treating other disorders where activation of the type B natriuretic peptide receptor will be beneficial. Specifically, the invention provides novel NPR-B agonists that activate the type B natriuretic peptide receptor (NPR-B). The invention further provides compositions containing such novel NPR-B agonists. The compositions provided herein may be ophthalmic compositions for use in methods of treating or preventing particular ophthalmic diseases such as glaucoma, preferably by lowering intraocular pressure, using such novel NPR-B agonists. Alternatively, the compositions provided herein may be used in methods of treating or preventing cardiovascular disorders, kidney disease, lung disease, skeletal disorders, infertility, and other disorders mediated by natriuretic peptides or proteins.

The invention is in part based on the inventors' finding that the novel NPR-B agonists described herein can provide improved bioavailability, increased chemical stability, and increased metabolic stability in body fluids or tissues, due to their significantly reduced molecular size as compared to the known natriuretic peptides. Certain embodiments of the present application generally pertain to novel peptides containing modified amino acids and that bind to and activate NPR-B with high specificity, as described in more detail herein.

It is specifically contemplated that any limitation discussed with respect to one embodiment of the invention may apply to any other embodiment of the invention. Furthermore, any composition of the invention may be used in any method of the invention, and any method of the invention may be used to produce or to utilize any composition of the invention.

As used herein, the term "NPR-B agonist" refers to the novel molecules described herein that activate the NPR-B with high potency.

The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

Throughout this application, the term "about" is used to indicate that a value includes the standard deviation of error for the device and/or method being employed to determine the value.

As used herein the specification, "a" or "an" may mean one or more, unless clearly indicated otherwise. As used herein in the claim(s), when used in conjunction with the word "comprising," the words "a" or "an" may mean one or more than one. As used herein "another" may mean at least a second or more.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE FIGURES

The following figures form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1. Illustrates the amino acid sequence of ANP (SEQ ID NO;1), BNP (SEQ ID NO:2) and CNP (SEQ ID NO:3).

FIG. 2. Illustrates the effects of CNP, ANP, BNP and mini-ANP (SEQ ID NO:18) on cyclic GMP production in GTM-3 cells. GTM-3 cells have been shown to express NPR-B (Pang et al. 1996, Invest Ophthalmol Vis Sci. 37:1724-1731). The cells were treated with CNP (triangles), ANP (squares), BNP (diamonds) and mini-ANP (circles). The symbols represent mean values and standard deviations. The highest concentration of compounds used was 45 μM for ANP, BNP and mini-ANP and 5 μM for CNP. EC50 values were determined using the 4-Parameter Logistic Equation. CNP EC50 = 38.8 nM, ANP EC50 = 1.63 μM, BNP EC50 = 1.18 μM, mini-ANP EC50 > 45 μM. The Emax (maximum activation) of each compound was determined relative to the maximum activation of CNP, i.e. CNP Emax = 100%, ANP Emax = 15%, BNP Emax = 20% and mini-ANP Emax = 0%.

FIG. 3. Illustrates the effects of CNP, ANP, BNP and mini-ANP on cyclic GMP production in NPR-A transfected 293-T cells. NPR-A transfected 293-T cells were treated with CNP (triangles), ANP (squares), BNP (diamonds), and mini-ANP (circles). The symbols represent mean values and standard deviations. EC_{50} was determined using the 4-Parameter Logistic Equation. EC_{50} of ANP = 73.0 nM, EC_{50} of CNP = 1.60 μM, EC_{50} of BNP = 1.85 μM, EC_{50} of mini-ANP = 1.54 μM.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is in part based on the finding that novel NPR-B agonists having improved bioavailability as compared to known natriuretic peptides are useful for lowering elevated intraocular pressure and treating glaucoma. Thus, the present invention is generally directed to novel NPR-B agonists and their use in methods of treating or preventing disorders mediated by natriuretic peptides or proteins. In one particularly preferred embodiment, the novel NPR-B agonists described herein are formulated for the treatment of ophthalmic diseases such as glaucoma, preferably by lowering the elevated intraocular pressure often associated with glaucoma, using a pharmaceutical composition that comprises one or more novel NPR-B agonists, as described herein. In other preferred embodiments, the novel NPR-B agonists described herein are formulated for the treatment of other natriuretic peptide- or protein-mediated disorders such as cardiovascular disorders, kidney disorders, lung disorders, skeletal disorders, fertility disorders, and fibrosis.

The hallmark feature of all known NP's is the 17 amino acid ring which is formed by an intramolecular cysteine bridge (see FIG. 1). The integrity of the cyclic structure of NP's is believed to be critical for the functional activity, i.e. NP receptor transduced cGMP production. The present inventors have discovered that certain linear peptides, such as the novel peptides described herein, having increased chemical and metabolic stability and the improved bioavailability as compared to known NP's, are useful in the treatment of natriuretic peptide- or protein-mediated disorders.

A. Novel Peptides

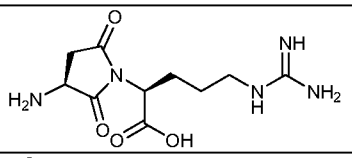
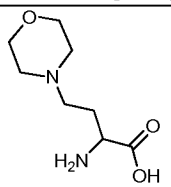
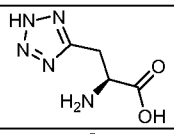
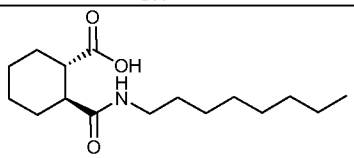
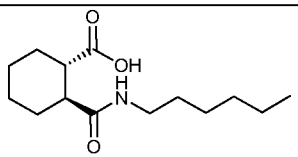
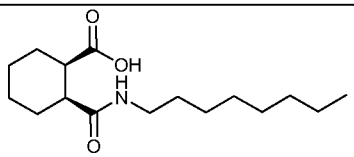
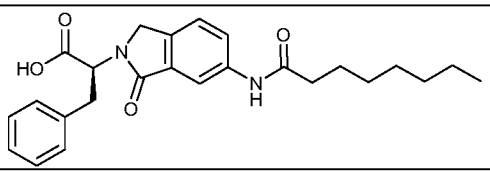
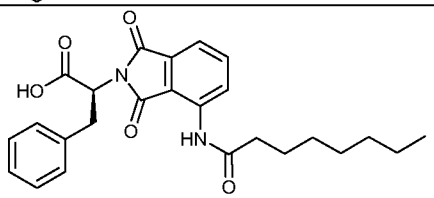
The present invention provides novel NPR-B agonists having biological activity that is improved in certain aspects as compared to that of the known natriuretic peptides. The novel peptides of the invention include conventional and non-conventional amino acids. Conventional amino acids are identified according to their standard, three-letter codes, as set forth in Table 1, below.

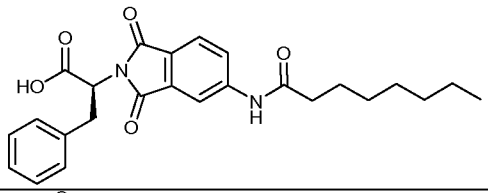
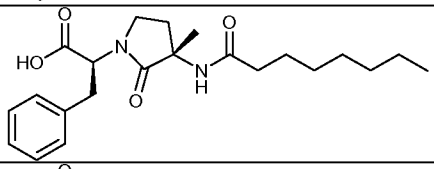
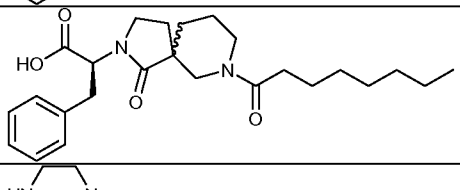
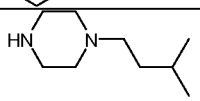
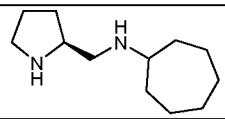
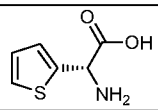
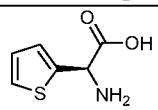
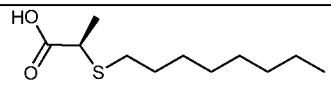
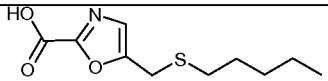
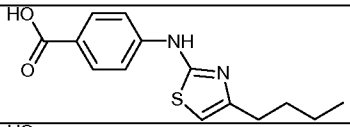
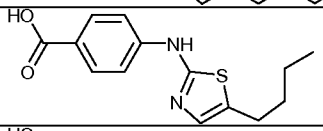
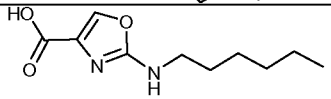
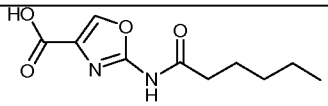
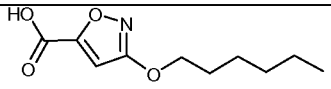
Table 1: For conventional amino acids the 3-letter codes were used:

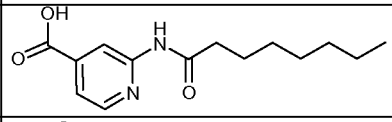
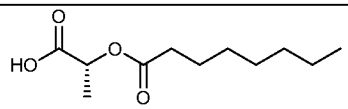
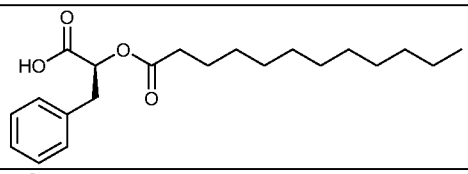
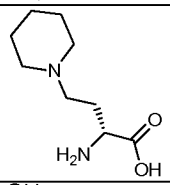
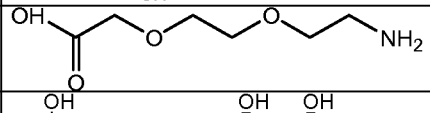
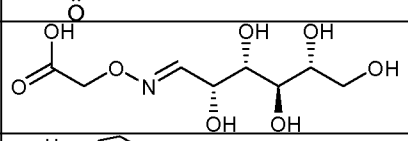
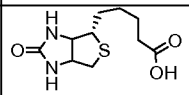
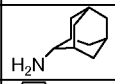
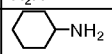
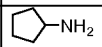
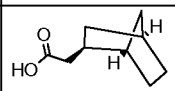
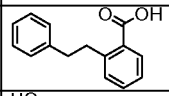
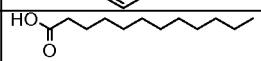
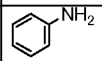
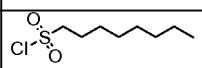
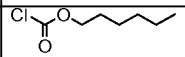
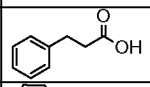
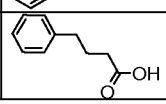
3-letter codes	Amino acids	3-letter codes	Amino acids
Ala	Alanine	Met	Methionine
Cys	Cysteine	Asn	Asparagine
Asp	Aspartic acid	Pro	Proline
Glu	Glutamic acid	Gln	Glutamine
Phe	Phenylalanine	Arg	Arginine
Gly	Glycine	Ser	Serine
His	Histidine	Thr	Threonine
Ile	Isoleucine	Val	Valine
Lys	Lysine	Trp	Tryptophane
Leu	Leucine	Tyr	Tyrosine

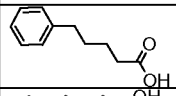
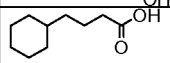
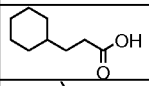
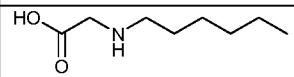
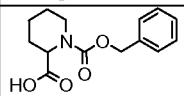
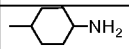
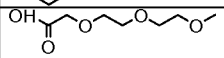
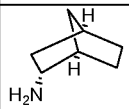
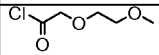
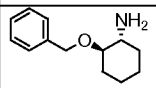
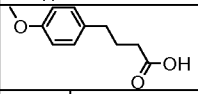
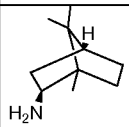
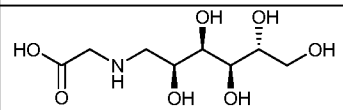
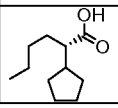
Non-conventional amino acids are identified according to a three-letter code, or other abbreviation, when present in the novel NPR-B agonists of the invention. Table 2, below, provides the full name, three-letter code or abbreviation, and structure of each non-conventional amino acid appearing in the sequences of the novel peptides described herein.

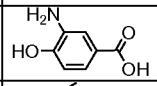
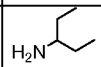
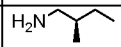
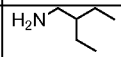
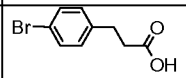
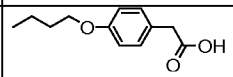
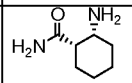
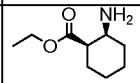
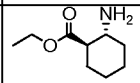
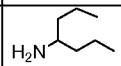
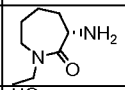
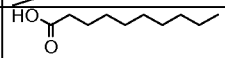
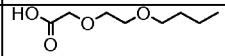
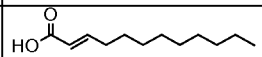
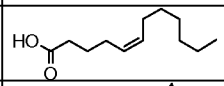
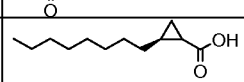
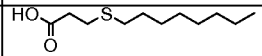
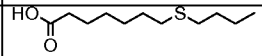
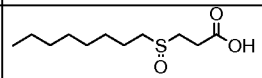
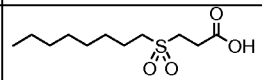
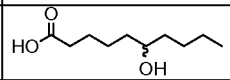
Table 2: List of abbreviations of non-conventional amino acids and other chemical structures.

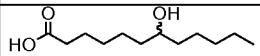
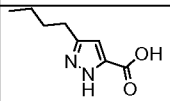
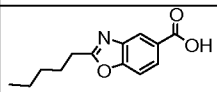
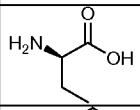
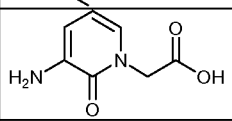
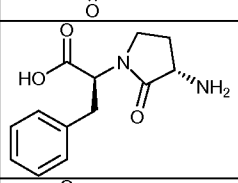
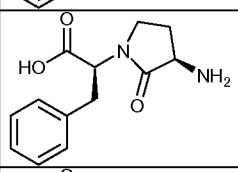
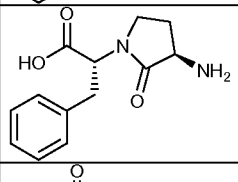
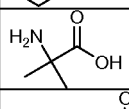
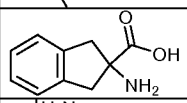
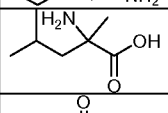
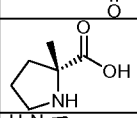
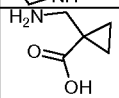
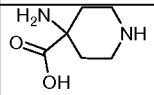
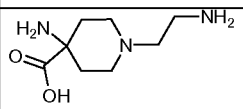
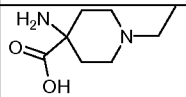
Name	Abbr	Structure
---	---	
rac-2-amino-4-morpholinobutanoic acid	AR-385-017	
(S)-2-amino-3-(2H-tetrazol-5-yl) propanoic acid	AR-314-145	
rac (1S,2S)-2-(octylcarbamoyl)cyclohexane carboxylic acid	AR-314-171	
rac (1S, 2S)-2-(hexylcarbamoyl)cyclohexane carboxylic acid	AR-314-170	
rac (1R, 2S)-2-octylcarbamoyl)cyclohexane carboxylic acid	AR-314-169	
(S)-2-(6-hexanamido-1-oxoisoindolin-2-yl)-3-phenylpropanoic acid	AR-385-008	
(S)-2-(4-octanamido-1,3-dioxoisoindolin-2-yl)-3-phenylpropanoic acid	AR-314-172	

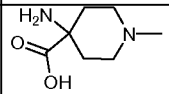
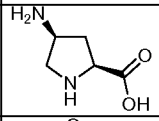
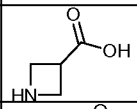
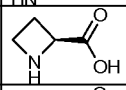
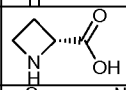
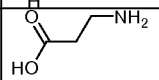
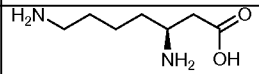
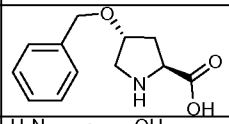
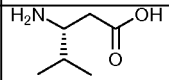
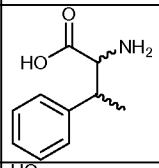
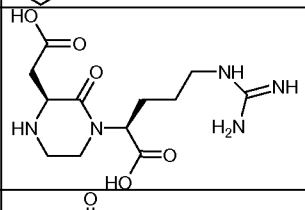
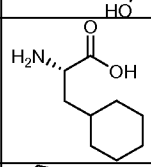
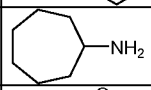
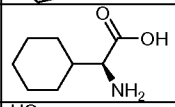
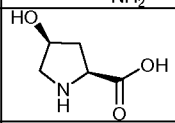
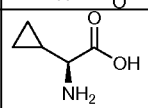
Name	Abbr	Structure
(S)-2-(5-hexanamido-1,3-dioxoisoindolin-2-yl)-3-phenylpropanoic acid	AR-385-042	
(S,S)-2-(3-methyl-3-octanoylamino-2-oxo-pyrrolidin-1-yl)-3-phenyl-propionic acid	AR-314-102	
2-(7-Octanoyl-1-oxo-2,7-diaza-spiro[4.5]dec-2-yl)-3-phenyl-propionic acid	AR-314-087	
1-(3-Methyl-butyl)-piperazine	AR-201-124	
Cycloheptyl-pyrrolidin-2-ylmethyl-amine	ES-283-049	
(S)-Amino-thiophen-2-yl-acetic acid	BB727	
(R)-Amino-thiophen-2-yl-acetic acid	BB726	
2-Octylsulfanyl-propionic acid	AR-201-073	
5-Pentylsulfanylmethyl-oxazole-2-carboxylic acid	AR-201-072	
4-(4-Butyl-thiazol-2-ylamino)-benzoic acid	AR-201-069	
4-(5-Butyl-thiazol-2-ylamino)-benzoic acid	AR-201-068	
2-Hexylamino-oxazole-4-carboxylic acid	AR-201-062	
2-Hexanoylamino-oxazole-4-carboxylic acid	AR-201-059	
3-Hexyloxy-isoxazole-5-carboxylic acid	AR-201-058	

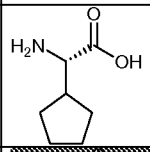
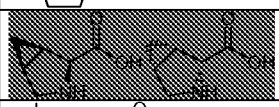
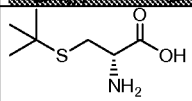
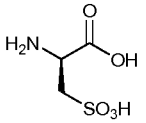
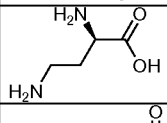
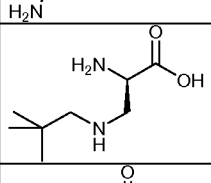
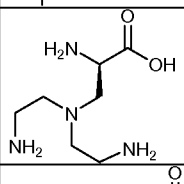
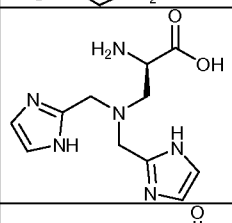
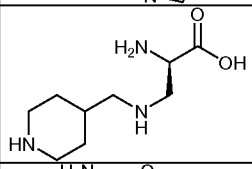
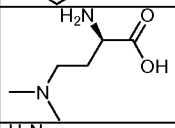
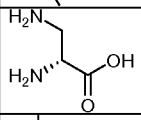
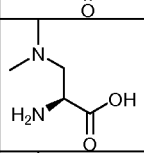
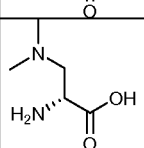
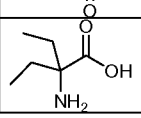
Name	Abbr	Structure
2-Hexanoylamino-isonicotinic acid	AR-201-054	
Octanoic acid 1-carboxy-ethyl ester	AR-201-049	
Dodecanoic acid 1-carboxy-2-phenyl-ethyl ester	AR-201-048	
(R)-2-Amino-4-(piperidin-1-yl) butanoic acid	abu(pip)	
8-amino-3,6-dioxaoctanoic acid	Adx	
(2,3,4,5,6-Pentahydroxy-hexylidenaminooxy)-acetic acid	Gluc-Aoa	
5-((4S)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoic acid	74	
Adamantan-2-yl-amine	504	
Cyclohexylamine	558	
Cyclopentylamine	559	
2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-yl)acetic acid	779	
2-Phenethyl-benzoic acid	785	
Dodecanoic acid	832	
Aniline	873	
Octanesulfonyl chloride	933	
Hexyl chloroformate	1270	
3-Phenyl-propionic acid	1281	
4-Phenyl-butyric acid	1319	

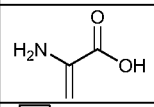
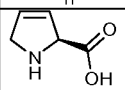
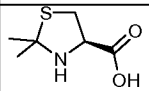
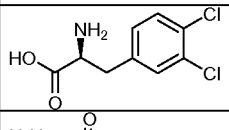
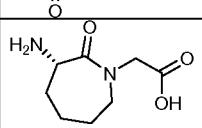
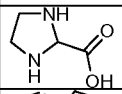
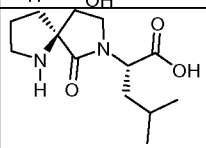
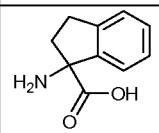
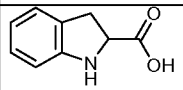
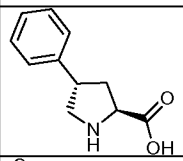
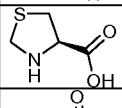
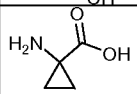
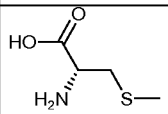
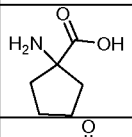
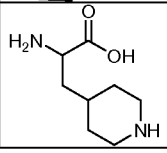
Name	Abbr	Structure
5-Phenyl-pentanoic acid	1320	
4-Cyclohexyl-butyric acid	1339	
3-Cyclohexyl-propionic acid	1340	
(S)-3,3-dimethylbutan-2-amine	1381	
2-(hexylamino)acetic acid	1625-Ac	
Piperidine-1,2-dicarboxylic acid 1-benzyl ester	1695	
4-Methyl-cyclohexyl-amine	1859	
(1R,2R)-2-methylcyclohexanamine	1860	
2-(2-Methoxy-ethoxy)-ethoxy]-acetic acid	1888	
(1R,2R,4R)-bicyclo[2.2.1]heptan-2-amine	1906	
(2-Methoxy-ethoxy)-acetyl chloride	1913	
(1R,2R)-2-(benzyloxy)cyclohexanamine	1934	
(S)-1,2,3,4-tetrahydronaphthalen-1-amine	2118	
(S)-3-methylpiperidine	2137	
4-(4-Methoxy-phenyl)-butyric acid	2553	
(1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine	2797	
2-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexylamino)acetic acid	2857-Ac	
Cyclobutyl-amine	2906	
(S)-2-cyclopentylhexanoic acid	3218	

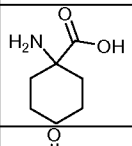
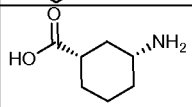
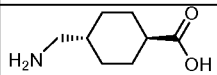
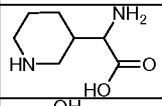
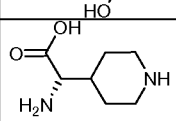
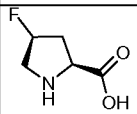
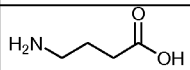
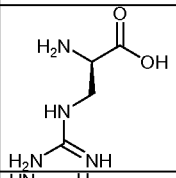
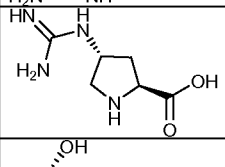
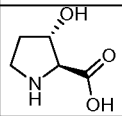
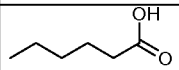
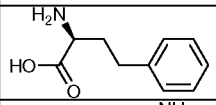
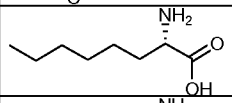
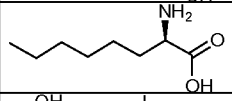
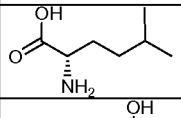
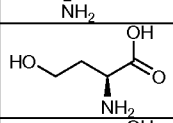
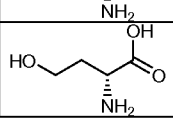
Name	Abbr	Structure
3-Amino-4-hydroxy-benzoic acid	3421	
1-Ethyl-propyl-amine	3791	
(R)-2-methylbutan-1-amine	3806	
2-Ethyl-butyl-amine	3816	
3-(4-Bromo-phenyl)-propionic acid	4703	
(4-Butoxy-phenyl)-acetic acid	4734	
(1S,2R)-2-aminocyclohexanecarboxamide	5116	
(1R,2S)-ethyl 2-aminocyclohexanecarboxylate	5118	
(1R,2R)-ethyl 2-aminocyclohexanecarboxylate	5119	
1-Propyl-butyl-amine	5121	
(S)-3-amino-1-ethylazepan-2-one	5164	
Decanoic acid	5587	
(2-Butoxy-ethoxy)-acetic acid	6013	
(E)-dodec-2-enoic acid	6014	
(Z)-dodec-5-enoic acid	6015	
(2S)-2-octylcyclopropanecarboxylic acid	6056	
3-Octylsulfanyl-propionic acid	6057	
7-Butylsulfanyl-heptanoic acid	6058	
3-(Octane-1-sulfinyl)-propionic acid	6059	
3-(Octane-1-sulfonyl)-propionic acid	6059(O)	
rac-6-Hydroxy-decanoic acid	(6071-OH)	

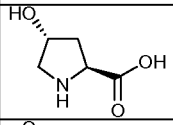
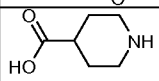
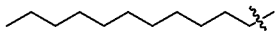
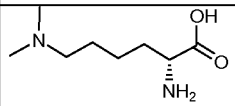
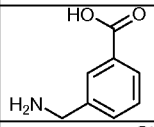
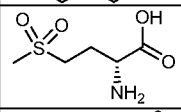
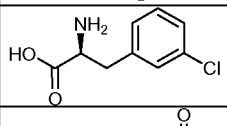
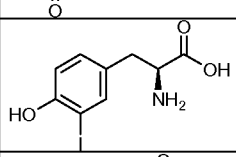
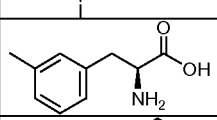
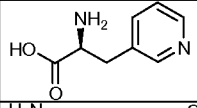
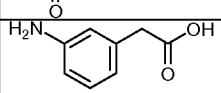
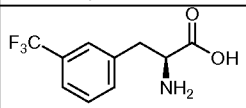
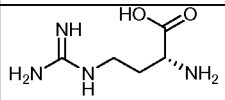
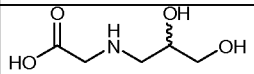
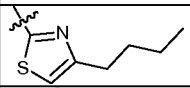
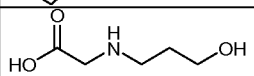
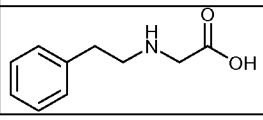
Name	Abbr	Structure
rac-7-Hydroxy-dodecanoic acid	(6072-OH)	
5-Butyl-2H-pyrrazole-3-carboxylic acid	6182	
2-Pentyl-benzooxazole-5-carboxylic acid	6988	
(R)-2-aminobutanoic acid	abu	
3-Amino-1-carboxymethyl-pyridin-2-one	Acp	
(S)-2-((S)-3-amino-2-oxopyrrolidin-1-yl)-3-phenylpropanoic acid	AFL	
(S)-2-((R)-3-amino-2-oxopyrrolidin-1-yl)-3-phenylpropanoic acid	aFL	
(R)-2-((R)-3-amino-2-oxopyrrolidin-1-yl)-3-phenylpropanoic acid	afL	
2-Aminoisobutyric acid	Aib	
2-Aminoindan-2-carboxylic acid	Aic	
rac-α-Methyl-leucine	Aml	
(R)-α-methyl-proline	Amp	
1-Aminomethyl-cyclopropanecarboxylic acid	Amcp	
4-Amino-piperdine-4-carboxylic acid	Apc	
4-Amino-1-(2-amino-ethyl)-piperidine-4-carboxylic acid	Apc(Ae)	
4-Amino-1-ethyl-piperidine-4-carboxylic acid	Apc(Et)	

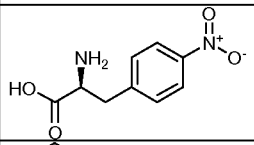
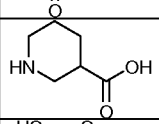
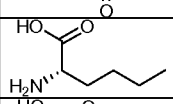
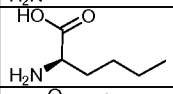
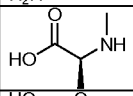
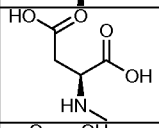
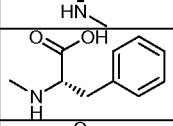
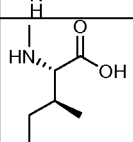
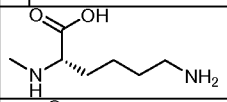
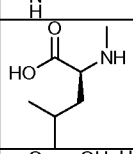
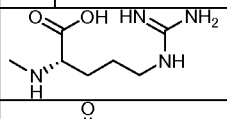
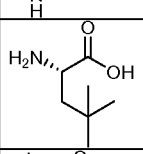
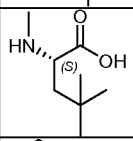
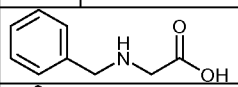
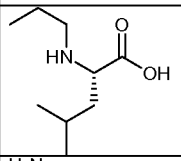
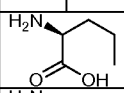
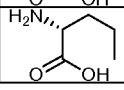
Name	Abbr	Structure
4-Amino-1-methyl-piperidine-4-carboxylic acid	Apc(Me)	
(2S,4S)-4-aminopyrrolidine-2-carboxylic acid	Apr	
Azetidine-3-carboxylic acid	Az3	
(S)-azetidin-2-carboxylic acid	Aze	
(R)-azetidin-2-carboxylic acid	aze	
β-Alanine	Bal	
(S)-β-Homolysine	Bhk	
(2S,4R)-4-(benzyloxy)pyrrolidine-2-carboxylic acid	Bhp	
(R)-β-homoleucine	Ble	
rac-2-amino-3-phenyl-butyric acid	Bmf	
(S)-2-((S)-3-(carboxymethyl)-2-oxopiperazin-1-yl)-5-guanidinopentanoic acid	cDR	
(S)-β-cyclohexylalanine	Cha	
Cycloheptyl-amine	Che	
(S)-Cyclohexylglycine	Chg	
(2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid	Chy	
(S)-2-amino-2-cyclopropylacetic acid	Cpa	

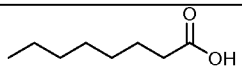
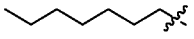
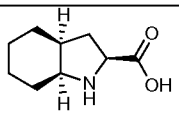
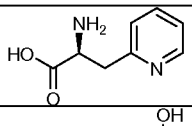
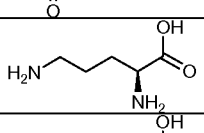
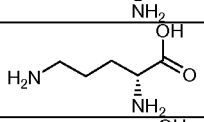
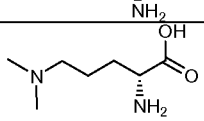
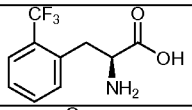
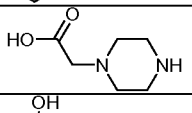
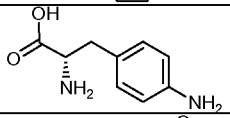
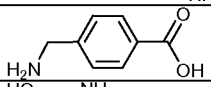
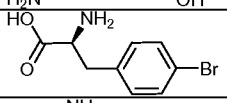
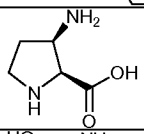
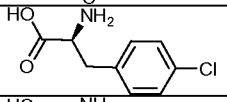
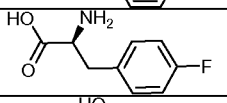
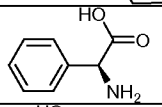
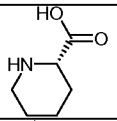
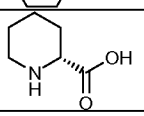
Name	Abbr	Structure
(S)-2-amino-2-cyclopentylacetic acid	Cpg	
rac-(3R,4S)-cis-methanoproline	Cpp	
(S)-2-amino-3-(tert-butylthio) propanoic acid	ctb	
(S)-2-Amino-3-sulfopropanoic acid	Cya	
(R)-2,4-diaminobutanoic acid	dab	
(R)-2-amino-3-(neopentylamino) propanoic acid	dap(1464)	
(R)-2-amino-3-(bis(2-aminoethyl) amino)propanoic acid	dap(6263)2	
(R)-2-amino-3-(bis((1H-imidazol-2-yl)methyl)amino)propanoic acid	dap(3846)2	
(R)-2-amino-3-(piperidin-4-ylmethylamino)propanoic acid	dap(6238)	
((R)-2-amino-4-(dimethylamino) butanoic acid	dab(Me2)	
(R)-2,3-diaminopropanoic acid	dap	
(S)-2-amino-3-(dimethylamino) propanoic acid	Dap(Me2)	
(R)-2-amino-3-(dimethylamino) propanoic acid	dap(Me2)	
2-Amino-2-ethyl-butyric acid	Deg	

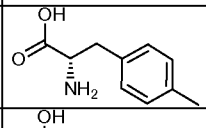
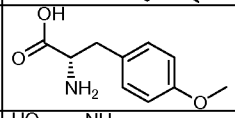
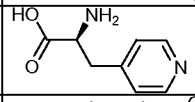
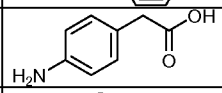
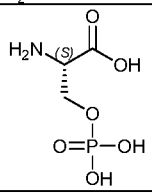
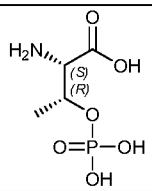
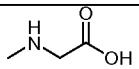
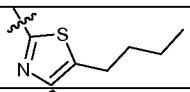
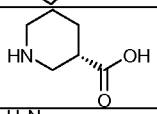
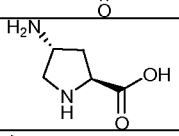
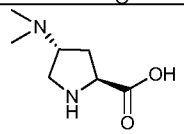
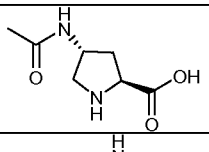
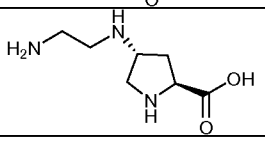
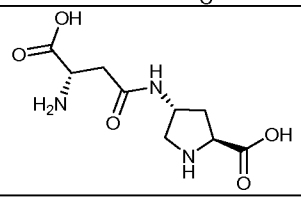
Name	Abbr	Structure
2-Aminoacrylic acid	Dha	
(S)-2,5-dihydro-1H-pyrrole-2-carboxylic acid	Dhp	
(R)-2,2-dimethylthiazolidine-4-carboxylic acid	Dtp	
(S)-3,4-dichloro-phenylalanine	Eaa	
(S)-2-(3-amino-2-oxoazepan-1-yl) acetic acid	Eah	
rac-Imidazolidine-2-carboxylic acid	Eal	
(S)-4-methyl-2-((S)-6-oxo-1,7-diazaspiro[4.4]nonan-7-yl)pentanoic acid	Eam	
rac-1-amino-2,3-dihydro-1H-indene-1-carboxylic acid	Eao	
2,3-Dihydro-1H-indole-2-carboxylic acid	Eat	
(2S,4S)-4-phenylpyrrolidine-2-carboxylic acid	Eay	
(R)-thiazolidine-4-carboxylic acid	Eaz	
1-Aminocyclopropanecarboxylic acid	Ebc	
(R)-2-amino-3-(methylsulfanyl) propanoic acid	Ebe	
1-Amino-cyclopentanecarboxylic acid	Eca	
2-Amino-3-piperidin-4-yl-propionic acid	Egg	

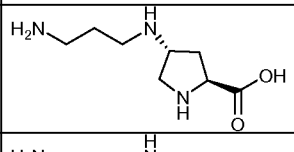
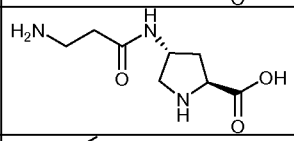
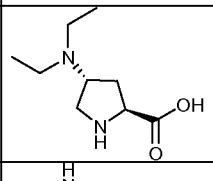
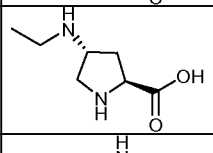
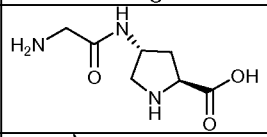
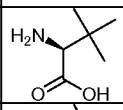
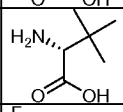
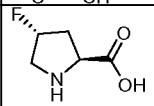
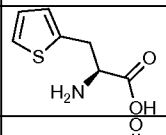
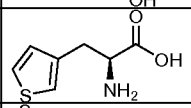
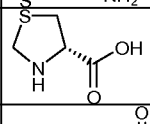
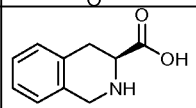
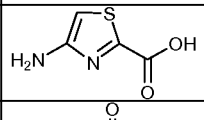
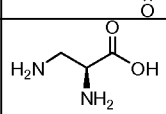
Name	Abbr	Structure
1-aminocyclohexanecarboxylic acid	Egz	
(1S,3R)-3-aminocyclohexane carboxylic acid	Fio	
trans-4-(aminomethyl)cyclohexane carboxylic acid	Fir	
Amino-piperidin-3-yl-acetic acid	Fhy	
(S)-2-amino-2-(piperidin-4-yl)acetic acid	Fhz	
(2S,4S)-4-fluoropyrrolidine-2-carboxylic acid	Fpr	
4-aminobutyric acid	Gab	
(R)-2-amino-3-guanidinopropanoic acid	gdp	
(2S,4R)-4-guanidinopyrrolidine-2-carboxylic acid	Gup	
(2S,3S)-3-hydroxypyrrolidine-2-carboxylic acid	H3p	
Hexanoic acid	Hex	
(S)-homo-phenylalanine	Hfe	
(S)-2-aminooctanoic acid	Hgl	
(R)-2-aminooctanoic acid	hgl	
(S)-2-amino-5-methylhexanoic acid	Hle	
(S)-homo-serine	Hse	
(R)-homo-serine	hse	

Name	Abbr	Structure
(2S,4R)-4-hydroxypyrrolidine-2-carboxylic acid	Hyp	
Piperidine-4-carboxylic acid	Inp	
Dodecane	*Lau*	
(R)-2-amino-6-(dimethylamino) hexanoic acid	lys(Me2)	
3-Aminomethyl-benzoic acid	Mam	
(R)-2-amino-4-(methylsulfonyl) butanoic acid	metO_2	
(S)-meta-chloro-phenylalanine	Mcf	
(S)-4-hydroxy-3-Iodo-phenylalanine	Miy	
(S)-meta-methyl-phenylalanine	Mmf	
(S)-3-(3-Pyridyl)-alanine	Mpa	
(3-Amino-phenyl)-acetic acid	Mpe	
(S)-meta-trifluoromethyl-phenylalanine	Mtf	
(R)-2-amino-4-guanidinobutanoic acid	nar	
rac-(2,3-Dihydroxy-propylamino)-acetic acid	Nbhp	
4-Butyl-thiazole	Nbt	
(3-Hydroxy-propylamino)acetic acid	Nhpr	
Phenethylamino-acetic acid	NHfe	

Name	Abbr	Structure
(S)-para-nitro-phenylalanine	Nif	
rac-Nipecotic acid	Nip	
(S)-Norleucine	Nle	
(R)-Norleucine	nle	
(S)-N-methyl-alanine	Nma	
(S)-N-methyl-aspartic acid	Nmd	
(S)-N-methyl-phenylalanine	Nmf	
(S)-N-methyl-isoleucine	Nmi	
(S)-N-methyl-lysine	Nmk	
(S)-N-methyl-leucine	Nml	
(S)-N-methyl-arginine	Nmr	
(S)-2-amino-4,4-dimethylpentanoic acid	Npg	
4,4-Dimethyl-2-methylamino-pentanoic acid	SH-112-158	
Benzylamino-acetic acid	NPhe	
(S)-4-methyl-2-(propylamino) pentanoic acid	Npl	
(S)-norvaline	Nva	
(R)-norvaline	nva	

Name	Abbr	Structure
Octanoic acid	Occ	
octane	Oct	
(2S,3aS,7aS)-octahydro-1H-indole-2-carboxylic acid	Oic	
(S)-3-(2-pyridyl)-alanine	Opa	
(S)-ornithine	Orn	
(R)-ornithine	orn	
(R)-2-amino-5-(dimethylamino) pentanoic acid	orn(Me2)	
(S)-ortho-trifluoro-phenylalanine	Otf	
Piperazin-1-yl-acetic acid	Paa	
(S)-para-amino-phenylalanine	Paf	
(4-Aminomethyl)-benzoic acid	Pam	
(S)-para-bromo-phenylalanine	Pbf	
(2S,3R)-3-aminopyrrolidine-2-carboxylic acid	Pca	
(S)-para-chloro-phenylalanine	Pcf	
(S)-para-fluoro-phenylalanine	Pff	
(S)-phenylglycine	Phg	
(S)-pipecolinic acid	Pip	
(R)-pipecolinic acid	pip	

Name	Abbr	Structure
(S)-para-methyl-phenylalanine	Pmf	
(S)-para-methoxy-phenylalanine	Pmy	
(S)-3-(4-Pyridyl)-alanine	Ppa	
(4-Amino-phenyl)-acetic acid	Ppe	
(S)-2-amino-3-(phosphonooxy) propanoic acid	Pse	
(2S, 3R)-2-Amino-3-(phosphonooxy) butanoic acid	Pth	
Sarcosine	Sar	
5-Butyl-thiazole	Sbt	
(S)-nipecotic acid	Sni	
(2S,4R)-4-aminopyrrolidine-2-carboxylic acid	Tap	
(2S,4R)-4-(dimethylamino) pyrrolidine-2-carboxylic acid	Tap(2Me)	
(2S,4R)-4-acetamidopyrrolidine-2-carboxylic acid	Tap(Ac)	
(2S,4R)-4-(2-aminoethylamino) pyrrolidine-2-carboxylic acid	Tap(Ae)	
(2S,4R)-4-(S)-3-amino-3-carboxypropaneamido)pyrrolidine-2-carboxylic aicd	Tap(Asp(-))	

Name	Abbr	Structure
4-(3-Amino-propylamino)-pyrrolidine-2-carboxylic acid	Tap(Ap)	
(2S,4R)-4-(3-aminopropanamido) pyrrolidine-2-carboxylic acid	Tap(Bal)	
(2S,4R)-4-(diethylamino)pyrrolidine-2-carboxylic acid	Tap(Et2)	
(2S,4R)-4-(ethylamino)pyrrolidine-2-carboxylic acid	Tap(Et)	
(2S,4R)-4-(2-aminoacetamido) pyrrolidine-2-carboxylic acid	Tap(G)	
(S)-α-tert-butylglycine	Tbg	
(R)-α-tert-butylglycine	tbg	
(2S,4R)-4-fluoropyrrolidine-2-carboxylic acid	Tfp	
(S)-2-thienyl-alanine	Thi	
(S)-3-thienyl-alanine	Thk	
(S)-thiazolidine-4-carboxylic acid	Thz	
(S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	Tic	
4-Amino-thiazol-2-carboxylic acid	Tnc	
(S)-2,3-Diamino-propionic acid (side chain prolongation)	Udp	

The novel NPR-B agonists of the invention comprise the general amino acid sequence of Formula I:

$B\text{-}Xaa_1\text{-}Xaa_2\text{-}Xaa_3\text{-}Xaa_4\text{-}Xaa_5\text{-}Xaa_6\text{-}Xaa_7\text{-}Xaa_8\text{-}Xaa_9\text{-}Xaa_{10}\text{-}Z$ (I)

wherein

B is selected from the group consisting of H, R^{b1}-, R^{b2}-C(O)-, R^{b2}-$S(O_2)$-, R^{b3}-Baa-;

Baa is a conventional α-amino acid, a non-conventional α-amino acid or a β-amino acid;

R^{b1} is selected from C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkenyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkyl aryl optionally substituted by $NR^{b4}R^{b5}$, OH, or OR^{b6}; C_1-C_{12} alkynyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; aryl C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkyl C_3-C_8 cyclic alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, aryl, heteroaryl, or heterocyclyl; C_3-C_6 cyclic alkyl C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylthio C_2-C_{10} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylsulfonyl C_1-C_4 alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylsulfoxyl C_1-C_{10} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; CH_3-$(CH_2)_{qb}$ -O-[-CH_2-$(CH_2)_{nb}O]_{mb}$-CH_2-$(CH_2)_{pb}$-, 2-thiazolo optionally substituted by $C_{1\text{-}8}$ alkyl;

qb = 0-3

nb = 1-3

mb = 1-3

pb = 1-3

R^{b2} is selected from C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkenyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6} C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; aryl C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkynyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6} C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkyl aryl optionally substituted by $NR^{b4}R^{b5}$, OH, or OR^{b6}; C_1-C_{12} alkyl C_3-C_8 cyclic alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_3-C_6 cyclic alkyl C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6} C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9

alkylthio C_1-C_{10} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylsulfonyl C_1-C_{10} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylsulfoxyl C_1-C_4 alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl, CH_3-$(CH_2)_{qb}$-O-[-CH_2-$(CH_2)_{nb}$O]$_{mb}$-CH_2-$(CH_2)_{pb}$-;

qb = 0-3

nb = 1-3

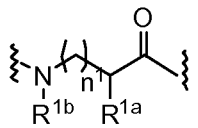
mb = 1-3

pb = 0-3

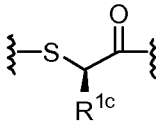
R^{b3} is selected from H, R^{b1}-, R^{b2}-C(O)-, or R^{b2}-S(O_2)-;

R^{b4}, R^{b5} and R^{b6} are, independently, selected from a group consisting of H, or C_1-C_4 alkyl, and

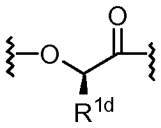
Xaa_1 is selected from the group consisting of a direct bond, a conventional α-amino acid; a non-conventional α-amino acid; a β-amino acid; a γ-amino acid; or a residue of Formula IIa-y:



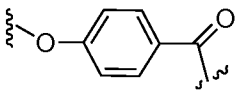
(IIa)



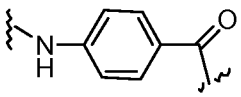
(IIb)



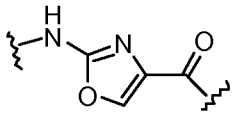
(IIc)



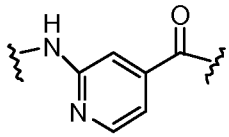
(IId)



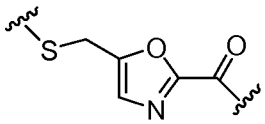
(IIe)



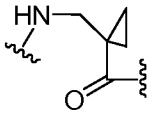
(IIf)



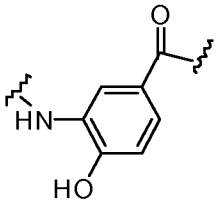
(IIg)



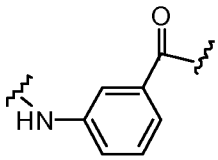
(IIh)



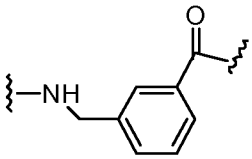
(IIi)



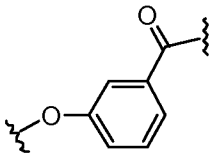
(IIj)



(IIk)



(IIl)



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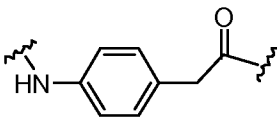
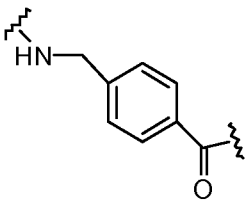
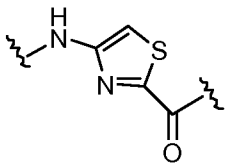


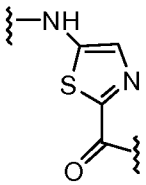
(IIn)



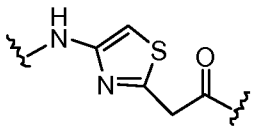
(IIo)



(IIp)



(IIq)



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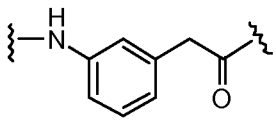
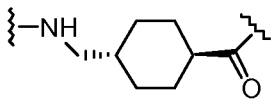


(IIs)



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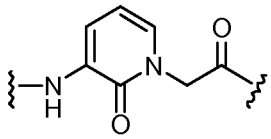

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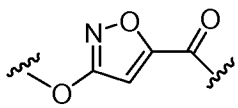

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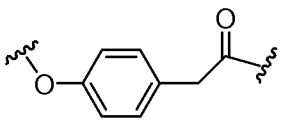
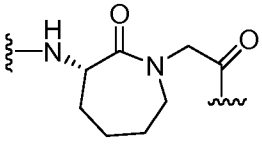
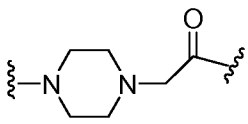


(IIw)



(IIx)



(IIy)

R^{1a} is selected from H, C_1-C_6 alkyl;

R^{1b} is selected from H, C_1-C_6 alkyl optionally substituted by OH, hydroxyC_1-C_6 alkyl optionally substitiuted by OH;

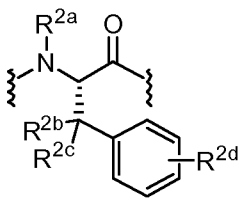
R^{1c} is selected from H, C_1-C_6 alkyl;

R^{1d} is selected from H, C_1-C_6 alkyl;

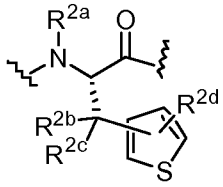
R^{1a} and R^{1b} together may form a heterocyclic ring;

n^1 is 0 to 3;

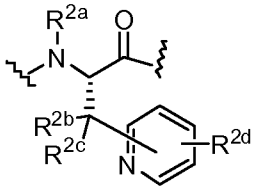
Xaa_2 is an amino acid residue of Formula IIIa-g:



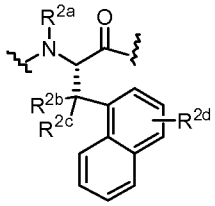
(IIIa)



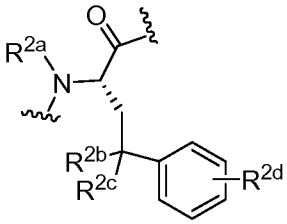
(IIIb)



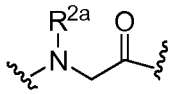
(IIIc)



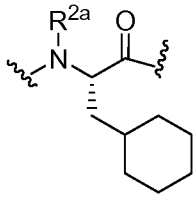
(IIId)



(IIIe)



(IIIf)



(IIIg)

wherein

R^{2a} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, C_1-C_2 alkyl C_3-C_7 cycloalkyl and aryl C_1-C_2 alkyl;

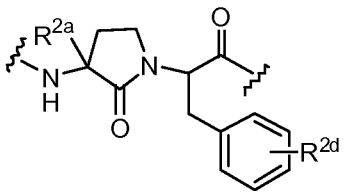
R^{2b} and R^{2c} are, independently, selected from the group consisting of H, methyl, ethyl, propyl; and isopropyl, with the proviso that at least one of R^{2b} and R^{2c} is H;

R^{2d} represents from 0 to 3 substituents, each such substituent being, independently, selected from the group consisting of H, Cl, F, Br, NO_2, NH_2, CN, CF_3, OH, OR^{2e} and C_1-C_4 alkyl;

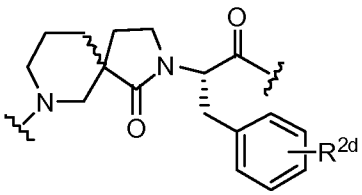
R^{2a} and R^{2b} or R^{2a} and R^{2c} together may form a heterocyclic ring;

R^{2e} is selected from the group consisting of methyl, ethyl, propyl, and isopropyl; or

Xaa_1 and Xaa_2 together may be selected from an amino acid residue of Formula IVa-b

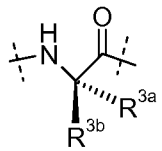


(IVa)



(IVb)

Xaa_3 is selected from the group consisting of Gly, Ala, a conventional D-α-amino acid, a non-conventional D-α-amino acid, and an amino acid residue of Formula Va:



(Va)

wherein R^{3a} is selected from the group consisting of H or C_1-C_4 alkyl;

R^{3b} is selected from the group consisting of H, $-(CH_2)_{n3a}-X^{3a}$;

n3a is 1 to 5;

X^{3a} is selected from the group consisting of H, $NR^{3c}R^{3d}$;

R^{3c} and R^{3d} are independently selected from a group consisting of H, C_1-C_8 alkyl, $-(C=N)-NH_2$ and $-(CH_2)_{n3b}X^{3b}$;

n3b is 1 to 4;

X^{3b} is selected from the group consisting of $NR^{3e}R^{3f}$, C_5-C_6 heteroaryl, C_4-C_7 heterocyclyl, $-NHC(=N)NH_2$;

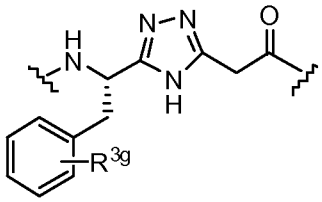
R^{3e} and R^{3f} are independently selected from a group consisting of H, C_1-C_8 alkyl, wherein R^{3e} and R^{3f} can form a cyclic structure;

R^{3a} and R^{3b} can be linked to form a cyclic structure;

or R^{3a} and R^{3b} can be linked with a heteroatom selected from the group consisting of N, O, and S, to form a heterocyclic structure;

or

Xaa_2 and Xaa_3 together may be selected from an amino acid residue of Formula Vb:

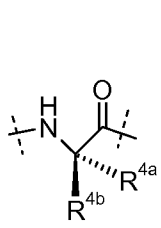


(Vb)

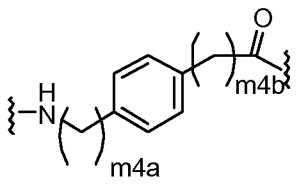
wherein R^{3g} represents from 0 to 3 substituents, each such substituent being, independently, selected from the group consisting of H, Cl, F, Br, NO_2, NH_2, CN; CF_3, OH, OR^{3h} and C_1-C_4 alkyl;

R^{3h} is selected from the group consisting of C_1-C_4 alkyl

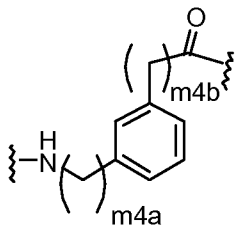
Xaa_4 is an amino acid residue of Formula VIa-h:



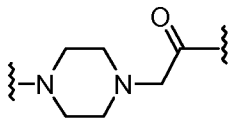
(VIa)



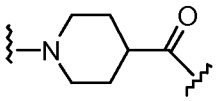
(VIb)



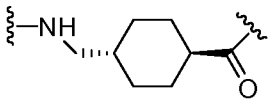
(VIc)



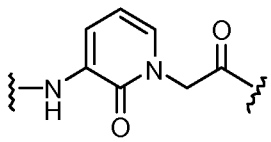
(VId)



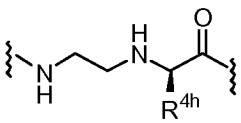
(VIe)



(VIf)



(VIg)



(VIh)

wherein R^{4a} is selected from the group consisting of H, C_1-C_8 alkyl which may be substituted with a moiety selected from the group consisting of OH, CO_2R^{4c}, C(=O)-NH_2, a 5-6 membered heteroaryl, C_1-C_{10} alkyl, C_5-C_8 cycloalkyl C_1-C_{10} alkyl, and C_5-C_8 cycloalkyl, -$(CH_2)_{n4a}$-X^{4a};

n^{4a} is 1 or 2;

R^{4b} is selected from the group consisting of H and methyl;

R^{4c} is selected from the group consisting of H, and C_1-C_3alkyl; and

X^{4a} is OH, CO_2R^{4d}, $NR^{4e}R^{4f}$, SR^{4g}, 4-imidazoyl, 4-hydroxyphenyl;

R^{4d}, R^{4e} and R^{4f} independently are selected from the group consisting of H, and C_1-C_3 alkyl;

R^{4g} is selected from the group consisting of C_1-C_3 alkyl;

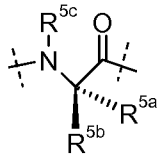
m4a, and m4b are independently selected from 0 or 1;

R^{4h} is C_2-C_6 alkyl;

or

Xaa_3 and Xaa_4 together may be selected from an amino acid residue of Formula VIb-h;

Xaa_5 is an amino acid residue of Formula VII:



(VII)

wherein R^{5a} is $(CH_2)_{n5a}$-X^{5a};

n5a is 1 to 6;

X^{5a} is selected from the group consisting of H, NH_2, and a C_{4-7} amine-containing aliphatic heterocyclic ring;

R^{5b} is selected from the group consisting of H and methyl;

R^{5c} is selected from the group consisting of H and methyl;

and wherein R^{5c} and R^{5a} can combine to form a four to six membered heterocyclic ring or can be linked with a heteroatom selected from the group consisting of N, O, and S to form a monocyclic or bicyclic heterocyclic structure; wherein said heterocyclic ring may have from 0 to 3 substituents, each such substituent being, independently, selected from from the group consisting of OH, OR^{5d}, F, C_1-C_4 alkyl, -NHC(=NH)NH_2, aryl and $NR^{5e}R^{5f}$;

R^{5d} is selected from C_1-C_4 alkyl, C_1-C_4 alkylaryl;

R^{5e} is selected from the group consisting of H, C_1-C_4 alkyl, -C(=O)$(CH_2)_{n5b}$-X^{5b}, -$CH_2(CH_2)_{n5c}$-X^{5b};

R^{5f} is selected from the group consisting of H, C_1-C_4 alkyl, -$CH_2(CH_2)_{n5d}$-X^{5c};

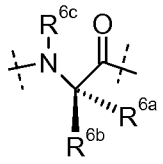
n5b is selected from the group consisting of 1, 2, 3, and 4;

n5c and n5d are independently selected from the group consisting of 2, 3, and 4;

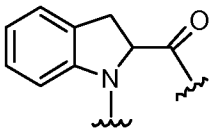
X^{5b} and X^{5c} are independently selected from the group consisting of H, $NR^{5g}R^{5h}$;

R^{5g} and R^{5h} are independently selected from a group consisting of H, C_1-C_4 alkyl;

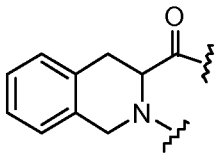
Xaa_6 is an amino acid residue of Formula VIIIa-d:



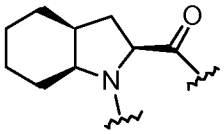
(VIIIa)



(VIIIb)



(VIIIc)



(VIIId)

wherein R^{6a} is selected from the group consisting of C_1-C_8 alkyl, aryl C_1-C_4 alkyl, C_4-C_7 cycloalkyl C_1-C_4 alkyl, C_1-C_4 alkyl S(C_1-C_4alkyl), and C_4-C_7 cycloalkyl, wherein said C_1-C_8 alkyl and C_4-C_7 cycloalkyl may be substituted with a moiety selected from the group consisting of OH, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), and $NR^{6d}R^{6e}$;

R^{6b} is H;

R^{6c} is selected from the group consisting of H, and C_1-C_4alkyl;

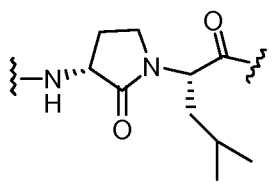
R^{6d}, and R^{6e} are, independently, selected from the group consisting of H, and C_1-C_4 alkyl;

wherein R^{6a} and R^{6c} can form a cyclic structure, which may be substituted with a moiety selected from the group consisting of OH, C_1-C_4 alkyl, NH_2 and F;

or R^{6a} and R^{6c} can be linked with a heteroatom selected from the group consisting of N, O, and S, to form a heterocyclic structure;

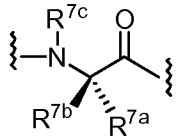
or

Xaa_5 and Xaa_6 together may be an amino acid residue of Formula VIIIe:

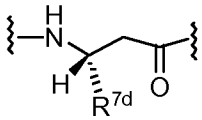


(VIIIe);

Xaa_7 is an amino acid residue of Formula IXa-b:



(IXa)



(IXb)

wherein R^{7a} is selected from the group consisting of C_1-C_4 alkyl, C_3-C_7 cycloalkyl, 2-thienyl, $(CH_2)_{n7a}$-X^{7a}, and C_1-C_4 alkyl substituted with OH;

R^{7b} is H, and 2-thienyl;

R^{7c} is selected from a group consisting of H, and methyl;

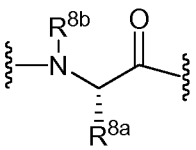
R^{7d} is C_1-C_4 alkyl;

n^{7a} is selected from the group consisting of 1 and 2;

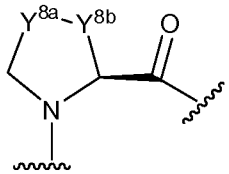
X^{7a} is selected from the group consisting of 2-thienyl, $C(=O)OR^{7e}$, $C(=O)NH_2$, $S(=O)_2OH$, $OS(=O)_2OH$, $B(OH)_2$, $P(=O)(OH)_2$, and $OP(=O)(OH)_2$;

wherein R^{7e} is selected from the group consisting of H, and C_1-C_4 alkyl;

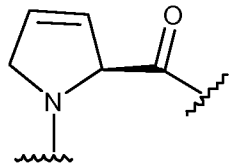
Xaa_8 is an amino acid residue of Formula Xa-g:



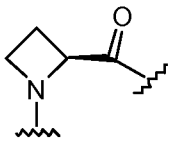
(Xa)



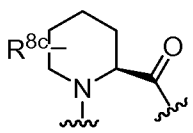
(Xb)



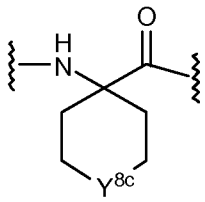
(Xc)



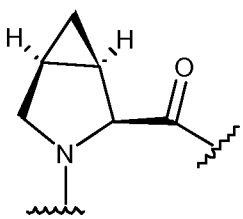
(Xd)



(Xe)



(Xf)



(Xg)

wherein R^{8a} is selected from the group consisting of $(CH_2)_{m8a}$-X^{8a}, and a C_4-C_7 nitrogen-containing aliphatic heterocyclic ring;

m^{8a} = 1-5;

X^{8a} is selected from the group consisting of H, NH_2, and -NHC(=NH)NH_2;

R^{8b} is selected from the group consisting of H and methyl;

R^{8c} is selected from the group consisting of H, NH_2, and OH;

Y^{8a} is selected from the group consisting of $CH(R^{8d})$, and S;

R^{8d} is selected from the group consisting H, aryl, and OH;

Y^{8b} is selected from the group consisting of $CH(R^{8e})$, and NH;

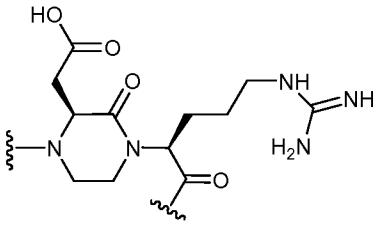
R^{8e} is selected from the group consisting H, NH_2 and OH;

Y^{8c} is selected from the group CH_2 , and NR^{8f};

R^{8f} is selected from the group H, -C(=NH)NH_2, and -C(=O)CH_2NH_2;

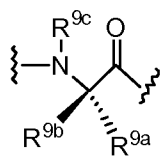
or

Xaa_7 and Xaa_8 together may be an amino acid residue of Formula Xh:

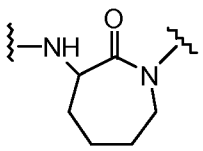


(Xh);

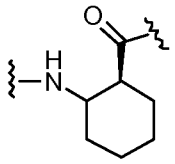
Xaa_9 is selected from the group consisting of a direct bond, and an amino acid residue of Formula XIa-c,



(XIa)



(XIb)



(XIc)

wherein R^{9a} is selected from the group consisting of C_1-C_5 alkyl, and C_4-C_7 cycloalkyl;

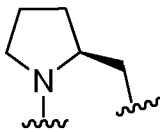
R^{9b} is selected from the group consisting of H, C_1-C_5 alkyl;

and wherein R^{9a} and R^{9b} can form a 5-7 membered cycloalkyl ring;

R^{9c} is selected from the group consisting of H, methyl;

or

Xaa_8 and Xaa_9 together may be a residue of Formula XId:

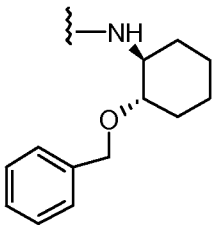


(XId);

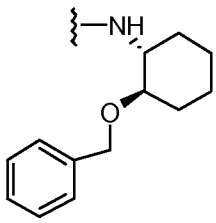
and

Z is selected from the group consisting of H, OR^{11a}, NHR^{11b} a conventional α-amino acid, a non-conventional α-amino acid, a β-amino acid; and a peptide consisting of from 2 to 30 amino acids selected from the group consisting of conventional α-amino acids, non-conventional α-amino acids, and β-amino acids;

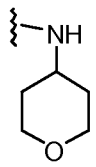
wherein R^{11a} and R^{11b} are independently selected from the group consisting of H, C_1-C_8 alkyl, C_4-C_8 cycloalkyl, C_7-C_{12} bicycloalkyl, C_7-C_{12} cycloalkylaryl, C_1-C_4 alkyl C_4-C_8 cycloalkyl, or a residue of formula XIIa-c:



(XIIa)



(XIIb)



(XIIc).

As used herein, the phrase "optionally substituted" shall be understood by the skilled artisan to mean that the moiety to which the phrase refers may be unsubstituted, or it may be substituted with certain specified additional moieties. For example, the phrase "C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl" refers to a C_1-C_{12} alkyl compound that is either non-substituted or is substituted by a moiety selected from the group consisting of $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, and heterocyclyl. The compound, hexane, would be considered a C_6 alkyl compound that is not substituted, while the compound 3-hexanol is a C_6 alkyl compound that is substituted on the third carbon atom with an OH moiety.

In certain preferred NPR-B agonists of the invention:

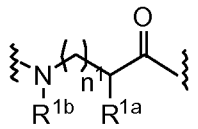
B is selected from the group consisting of R^{b1}-, R^{b2}-C(O)-;

R^{b1} is selected from C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$;

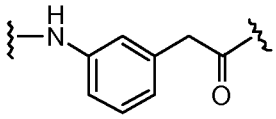
R^{b2} is selected from C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$;

R^{b4}, and R^{b5} are, independently, selected from a group consisting of H, and C_1-C_4 alkyl, and

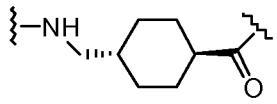
Xaa_1 is selected from the group consisting of a direct bond, a conventional α-amino acid; a non-conventional α-amino acid; a β-amino acid; or a residue selected from the group consisting of Formula IIa, IIs, IIt, IIu, and IIv:



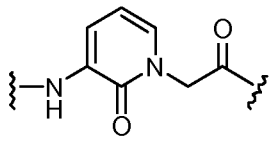
(IIa)



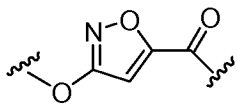
(IIs)



(IIt)



(IIu)



(IIv)

R^{1a} is selected from H, C_1-C_6 alkyl;

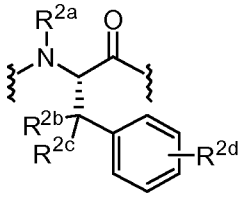
R^{1b} is selected from H, C_1-C_6 alkyl optionally substituted by OH, hydroxyC_1-C_6 alkyl optionally substitiuted by OH;

R^{1c} is selected from H, C_1-C_6 alkyl;

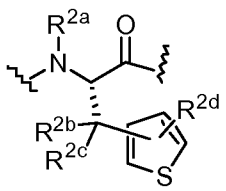
R^{1a} and R^{1b} together may form a heterocyclic ring;

n^1 is 0 to 3; and

Xaa_2 is an amino acid residue of Formula IIIa or Formula IIIb:



(IIIa)



(IIIb)

wherein

R^{2a} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, C_1-C_2 alkyl C_3-C_7 cycloalkyl and aryl C_1-C_2 alkyl;

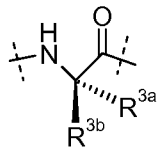
R^{2b} and R^{2c} are, independently, selected from the group consisting of H, methyl, ethyl, propyl; and isopropyl, with the proviso that at least one of R^{2b} and R^{2c} is H;

R^{2d} represents from 0 to 3 substituents, each such substituent being, independently, selected from the group consisting of H, Cl, F, Br, NO_2, NH_2, CN, CF_3, OH, OR^{2e} and C_1-C_4 alkyl;

R^{2a} and R^{2b} or R^{2a} and R^{2c} together may form a heterocyclic ring;

R^{2e} is selected from the group consisting of methyl, ethyl, propyl, and isopropyl; and

Xaa_3 is an amino acid residue of Formula Va:



(Va)

wherein R^{3a} is selected from the group consisting of H or C_1-C_4 alkyl;

R^{3b} is selected from the group consisting of H, $-(CH_2)_{n3a}-X^{3a}$;

n3a is 1 to 5;

X^{3a} is selected from the group consisting of H, $NR^{3c}R^{3d}$;

R^{3c} and R^{3d} are independently selected from a group consisting of H, C_1-C_8 alkyl, -(C=N)-NH_2 and $-(CH_2)_{n3b}X^{3b}$;

n3b is 1 to 4;

X^{3b} is selected from the group consisting of $NR^{3e}R^{3f}$, C_5-C_6 heteroaryl, C_4-C_7 heterocyclyl, $-NHC(=N)NH_2$;

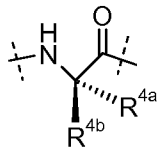
R^{3e} and R^{3f} are independently selected from a group consisting of H, C_1-C_8 alkyl, wherein R^{3e} and R^{3f} can form a cyclic structure;

R^{3a} and R^{3b} can be linked to form a cyclic structure;

or R^{3a} and R^{3b} can be linked with a heteroatom selected from the group consisting of N, O, and S, to form a heterocyclic structure;

and

Xaa_4 is an amino acid residue of Formula VIa:



(VIa)

wherein R^{4a} is selected from the group consisting of H, C_1-C_8 alkyl which may be substituted with a moiety selected from the group consisting of OH, CO_2R^{4c}, C(=O)-NH_2, a 5-6 membered heteroaryl, C_1-C_{10} alkyl, C_5-C_8 cycloalkyl C_1-C_{10} alkyl, and C_5-C_8 cycloalkyl,;

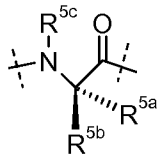
n4a is 1 or 2;

R^{4b} is selected from the group consisting of H and methyl;

R^{4c} is selected from the group consisting of H, and C_{1-3}alkyl; and

and

Xaa_5 is an amino acid residue of Formula VII:



(VII)

wherein R^{5a} is $(CH_2)_{n5a}$-X^{5a};

n5a is 1 to 6;

X^{5a} is selected from the group consisting of H, NH_2, and a C_{4-7} amine-containing aliphatic heterocyclic ring;

R^{5b} is selected from the group consisting of H and methyl;

R^{5c} is selected from the group consisting of H and methyl;

and wherein R^{5c} and R^{5a} can combine to form a four to six membered heterocyclic ring wherein said heterocyclic ring may have from 0 to 2 substituents, each such substituent being, independently, selected from from the group consisting of OH, OR^{5d}, F, C_1-C_4 alkyl, -NHC(=NH)NH_2, aryl and $NR^{5e}R^{5f}$;

R^{5d} is selected from C_1-C_4 alkyl, C_1-C_4 alkylaryl;

R^{5e} is selected from the group consisting of H, C_1-C_4 alkyl, -C(=O)$(CH_2)_{n5b}$-X^{5b}, -$CH_2(CH_2)_{n5c}$-X^{5b};

R^{5f} is selected from the group consisting of H, C_1-C_4 alkyl, -$CH_2(CH_2)_{n5d}$-X^{5c};

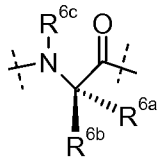
n5b is selected from the group consisting of 1, 2, 3, and 4;

n5c and n5d are independently selected from the group consisting of 2, 3, and 4;

X^{5b} and X^{5c} are independently selected from the group consisting of H, $NR^{5g}R^{5h}$;

R^{5g} and R^{5h} are independently selected from a group consisting of H, C_1-C_4 alkyl and

Xaa_6 is an amino acid residue of Formula VIIIa:



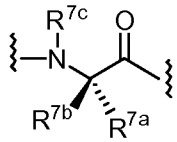
(VIIIa)

wherein R^{6a} is selected from the group consisting of C_1-C_8 alkyl, aryl C_1-C_4 alkyl , C_4-C_7 cycloalkyl C_1-C_4 alkyl, C_1-C_4 alkyl S(C_1-C_4alkyl), and C_4-C_7 cycloalkyl, wherein said C_1-C_8 alkyl and C_4-C_7 cycloalkyl may be substituted with a moiety selected from the group consisting of OH, O(C_1-C_4 alkyl), and S(C_1-C_4 alkyl);

R^{6b} is H;

R^{6c} is selected from the group consisting of H, and C_1-C_4alkyl; and

Xaa_7 is an amino acid residue of Formula IXa:



(IXa)

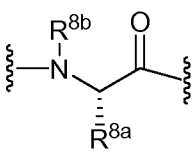
wherein R^{7a} is selected from the group consisting of C_1-C_4 alkyl, C_3-C_7 cycloalkyl, 2-thienyl, and C_1-C_4 alkyl substituted with OH;

R^{7b} is H, and 2-thienyl;

R^{7c} is selected from a group consisting of H, and methyl;

and

Xaa_8 is an amino acid residue of Formula X(a)-(g):



(Xa)

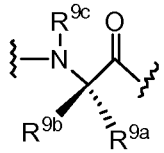
wherein R^{8a} is $(CH_2)_{m8a}$-X^{8a};

m^{8a} = 1-5;

X^{8a} is selected from the group consisting of H, NH_2, and -NHC(=NH)NH_2;

R^{8b} is selected from the group consisting of H and methyl; and

Xaa_9 is selected from the group consisting of a direct bond, and an amino acid residue of Formula XIa-c,



(XIa)

wherein R^{9a} is selected from the group consisting of C_1-C_5 alkyl, and C_4-C_7 cycloalkyl;

R^{9b} is selected from the group consisting of H, and C_1-C_5 alkyl;

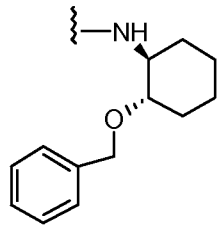
or R^{9a} and R^{9b} can form a 5-7 membered cycloalkyl ring;

R^{9c} is selected from the group consisting of H, and methyl;

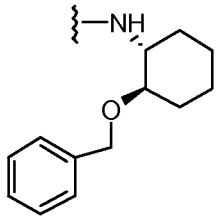
and

Z is NHR^{11b} ;

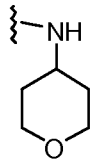
wherein R^{11b} is selected from the group consisting of H, C_1-C_8 alkyl, C_4-C_8 cycloalkyl, C_7-C_{12} bicycloalkyl, C_7-C_{12} cycloalkylaryl, C_1-C_4 alkyl C_4-C_8 cycloalkyl, or a residue of formula XIIa-c



(XIIa)



(XIIb)



(XIIc).

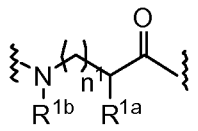
In more preferred embodiments of the present invention, B is selected from the group consisting of R^{b1}-, and R^{b2}-C(O)-;

R^{b1} is selected from the group consisting of C_6-C_{10} alkyl and C_6-C_{10} alkyl substituted by $NR^{b4}R^{b5}$;

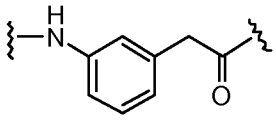
R^{b2} is selected from the group consisting of C_6-C_{10} alkyl and C_6-C_{10} alkyl substituted by $NR^{b4}R^{b5}$;

R^{b4}, and R^{b5} are, independently, selected from a group consisting of H, and C_1-C_4 alkyl, and

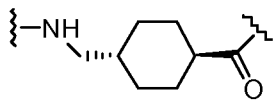
Xaa_1 is selected from the group consisting of a direct bond, a conventional α-amino acid; a non-conventional α-amino acid; a β-amino acid; a residue of Formula IIa, a residue of Formula IIs, a residue of Formula IIt, a residue of Formula IIu, and a residue of Formula IIv



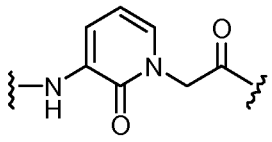
(IIa)



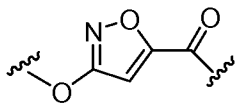
(IIs)



(IIt)



(IIu)



(IIv)

wherein R^{1a} is selected from H, and C_1-C_4 alkyl;

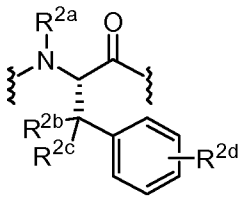
R^{1b} is selected from H, C_1-C_4 alkyl optionally substituted by OH, and hydroxy C_1-C_4 alkyl optionally substitiuted by OH;

R^{1c} is selected from H, C_1-C_6 alkyl;

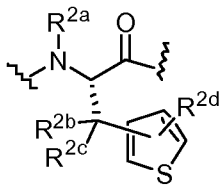
R^{1a} and R^{1b} together may form a heterocyclic ring;

n^1 is 0 , 1; and

Xaa_2 is an amino acid residue of Formula III:



(IIIa)



(IIIb)

wherein

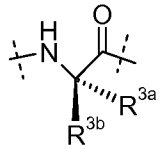
R^{2a} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, C_1-C_2 alkyl C_3-C_7 cycloalkyl and aryl C_1-C_2 alkyl;

R^{2b} and R^{2c} are, independently, selected from the group consisting of H, methyl, ethyl, propyl; and isopropyl, with the proviso that at least one of R^{2b} and R^{2c} is H;

R^{2d} represents from 0 to 3 substituents, each such substituent being, independently, selected from the group consisting of H, Cl, F, Br, CN, CF_3, OH, OR^{2e} and C_1-C_4 alkyl;

R^{2e} is selected from the group consisting of methyl, ethyl, propyl, and isopropyl; and

Xaa_3 is an amino acid residue of Formula Va:



(Va)

wherein R^{3a} is selected from the group consisting of H and C_1-C_4 alkyl;

R^{3b} is selected from the group consisting of H, and $-(CH_2)_{n3a}-X^{3a}$;

n3a is 1 to 5;

X^{3a} is selected from the group consisting of H, and $NR^{3c}R^{3d}$;

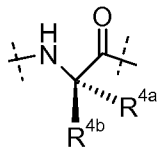
R^{3c} and R^{3d} are independently selected from a group consisting of H, C_1-C_8 alkyl, and $-(C=N)-NH_2$;

R^{3a} and R^{3b} can be linked to form a cyclic structure;

or R^{3a} and R^{3b} can be linked with a heteroatom selected from the group consisting of N, O, and S, to form a heterocyclic structure;

and

Xaa_4 is an amino acid residue of Formula VIa:



(VIa)

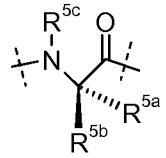
wherein R^{4a} is selected from the group consisting of H, C_1-C_8 alkyl which may be substituted with a moiety selected from the group consisting of OH, and CO_2R^{4c};

R^{4b} is selected from the group consisting of H and methyl;

R^{4c} is selected from the group consisting of H, and C_1-C_3alkyl; and

and

Xaa_5 is an amino acid residue of Formula VII:



(VII)

wherein R^{5a} is $(CH_2)_{n5a}$-X^{5a};

n5a is 1 to 6;

X^{5a} is selected from the group consisting of H, NH_2, and a C_{4-7} amine-containing aliphatic heterocyclic ring;

R^{5b} is selected from the group consisting of H and methyl;

R^{5c} is selected from the group consisting of H and methyl;

and wherein R^{5c} and R^{5a} can combine to form a four to six membered heterocyclic ring wherein said heterocyclic ring may have from 0 to 2 substituents, each such substituent being independently selected from from the group consisting of OH, F, C_1-C_4 alkyl, -NHC(=NH)NH_2, aryl and $NR^{5e}R^{5f}$;

R^{5e} is selected from the group consisting of H, C_1-C_4 alkyl, -C(=O)$(CH_2)_{n5b}$-X^{5b}, and -$CH_2(CH_2)_{n5c}$-X^{5b};

R^{5f} is selected from the group consisting of H, C_1-C_4 alkyl, and -$CH_2(CH_2)_{n5d}$-X^{5c};

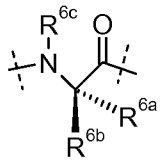
n5b is selected from the group consisting of 1, 2, 3, and 4;

n5c and n5d are independently selected from the group consisting of 2, 3, and 4;

X^{5b} and X^{5c} are independently selected from the group consisting of H, and $NR^{5g}R^{5h}$;

R^{5g} and R^{5h} are independently selected from a group consisting of H, and C_1-C_4 alkyl and

Xaa_6 is an amino acid residue of Formula VIIIa:



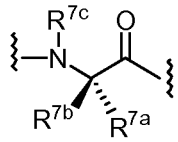
(VIIIa)

wherein R^{6a} is selected from the group consisting of C_1-C_8 alkyl, aryl C_1-C_4 alkyl , C_4-C_7 cycloalkyl C_1-C_4 alkyl, and C_4-C_7 cycloalkyl, wherein said C_1-C_8 alkyl and C_4-C_7 cycloalkyl may be substituted with a moiety selected from the group consisting of OH, and O(C_1-C_4 alkyl);

R^{6b} is H;

R^{6c} is selected from the group consisting of H, and C_1-C_4alkyl; and

Xaa_7 is an amino acid residue of Formula IX:



(IXa)

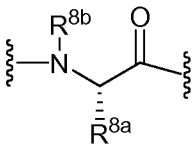
wherein R^{7a} is selected from the group consisting of C_1-C_4 alkyl, C_3-C_7 cycloalkyl, 2-thienyl, and C_1-C_4 alkyl substituted with OH;

R^{7b} is H, and 2-thienyl;

R^{7c} is selected from a group consisting of H, and methyl;

and

Xaa_8 is an amino acid residue of Formula Xa:



(Xa)

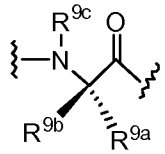
wherein R^{8a} is $(CH_2)_{m8a}$-X^{8a};

m^{8a} = 1-5;

X^{8a} is selected from the group consisting of H, NH_2, and -NHC(=NH)NH_2;

R^{8b} is selected from the group consisting of H and methyl; and

Xaa_9 is selected from the group consisting of a direct bond, and an amino acid residue of Formula XIa,



(XIa)

wherein R^{9a} is selected from the group consisting of C_1-C_5 alkyl, and C_4-C_7 cycloalkyl;

R^{9b} is selected from the group consisting of H, and C_1-C_5 alkyl;

and wherein R^{9a} and R^{9b} can form a 5-7 membered cycloalkyl ring;

R^{9c} is selected from the group consisting of H, and methyl;

and

Z is NHR^{11b};

wherein R^{11b} is selected from the group consisting of H, C_1-C_8 alkyl, C_4-C_8 cycloalkyl, C_7-C_{12} bicycloalkyl, C_7-C_{12} cycloalkylaryl, and C_1-C_4 alkyl C_4-C_8 cycloalkyl.

The sequences of the preferred novel NPR-B agonists of the invention are provided herein in typical peptide sequence format, as would be understood by the ordinary skilled artisan. For example, the three-letter code of a conventional amino acid, or the abbreviation for a non-conventional amino acid, indicates the presence of a particular amino acid in a specified position in the sequence of the molecule, each amino acid being connected to the next and/or previous amino acid by a hyphen. The hyphen, which represents a chemical bond, typically an amide bond, removes OH from the 1- carboxyl group of the amino acid when it is placed right of the abbreviation, and removes H from the 2-amino group (or the only present amino group in case of amino acids lacking a 2-amino group, e.g., Bal) of the amino acid when it is placed on the left of the abbreviation. It is understood that both modifications can apply to one amino acid.

In the case of additional functional groups in the side chains of conventional or non-conventional amino acids, only the 2-amino and/or the 1-carboxy group is used for the formation of peptide bonds.

The C-termini of the novel NPR-B agonists described herein are shown in explicit form by adding either OH, NH2 or an abbreviation for a specific terminating amine separated by a hyphen on the right of the abbreviation of the C-terminal amino acid.

These specific terminating amines are provided in Table 2 as full formulas and similar conventions with regard to hyphens and its structure in a peptide context apply to them, e.g.,

3791 = NH_2-CH(CH_2-CH_3)- CH_2-CH_3

-3791 = - NH-CH(CH_2-CH_3)- CH_2-CH_3

The N-termini of the novel peptides described herein are shown in explicit form by adding either H (for a free N-terminus), or an abbreviation for a specific terminating

carboxylic acid, sulfonic acid or another terminating group in front of the symbol of the N-terminal amino acid.

These specific terminating carboxylic acids, sulfonic acids or other terminating groups like alkyl are provided in Table 2 as full formulas and similar conventions with regard to hyphens and its structure in a peptide context apply to them, e.g.,

Hex = Hexanoic acid
Hex- = Hexanoyl-.

For conventional amino acids and some non-conventional amino acids, a 3-letter code was used where the first letter indicates the stereochemistry of the C-alpha-atom. For example, a capital first letter indicates that the L-form of the amino acid is present in the peptide sequence, while a lower case first letter indicates that the D-form of the correspondent amino acid is present in the peptide sequence.

In preferred embodiments of the present invention, the novel NPR-B agonist is an 8-13 amino acid peptide having a sequence as set forth in Table 3. The agonistic activity of the preferred compounds is also provided in Table 3 and was categorized based upon the following conventions:

NPR-B activation (assayed with GTM-3 Cells)		**Group**
EC_{50}	**Emax (CNP = 100%)**	
≤ 1 μM	> 50%	**A**
≤ 5 μM	> 20%	**B**
≤ 15 μM	> 10%	**C**

The agonistic activity data of each compound was checked first to determine whether it fulfills the criteria for the activity group A. If it did not fulfill the criteria for activity group A, it was checked for group B criteria. If it did not fulfill the criteria for activity group A or activity group B, it was finally checked for group C criteria. If it did not fulfill the criteria for activity group C, it was not included in Table 3.

All examples in Table 3 are linear peptides written in three letter code where applicable. For non-conventional amino acids and other chemical moieties the abbreviations which are listed in Table 2 were used. In vitro activities reported in Table 3 resulted from experiments performed according to the methods described in Example 4.

In certain embodiments of the NPR-B agonists of the invention, in the compound of Formula 1:

B will be selected from a bond, Occ, Oct, Sbt, 1319, 1320, and 5587;

Xaa_1 will be selected from Gly, AR-201-49, AR-201-68, ala, abu, his, aze, pro, pip, thz, thi, asn, ser, His, Ala, Ser, Bal, Sni, Az3, and Gab;

Xaa_2 will be selected from Phe, Pcf, Nmf, Pbf, Pff, Pmf, Eaa. Mcf, Thk, and Mtf;

Xaa_3 will be selected from Gly, Aib, Ebc, a conventional D-α-amino acid, and a non-conventional D-α-amino acid, and will preferably be selected from Gly, Fhy, Apc, Egz, Aib, Ebc, ala, lys, lys(Me2), arg, leu, nle, ctb, abu, AR-385-12, Egg, ser, orn, orn(Me2), and dap(Me_2);

Xaa_4 will be selected from Leu, Nva, Nle, Hle, Npg, Cha, and Ala;

Xaa_5 will be selected from Lys, Orn, Hly, Hpa, Dab, Arg, N(alkyl) derivatives of any of the preceding amino acids, Nmk, Hpr, Pro, Tfp, Apr, Eaz, Hyp, Tap, Tap(G), Tap(Bal), Tap(Et), Tap(Ae), Tap(Ap), Amp, Pip, and Chy;

Xaa_6 will be selected from a bond, Leu, Ile, Nml, Tap, Npg, SH-158, Dap(Me2), Cpg, Val, Tbg, Chg, Hle, Nle, and N(alkyl) derivatives of any of the preceding amino acids;

Xaa_7 will be selected from Asp, Val, BB725, BB727, Ser, Thr, and Cya;

Xaa_8 will be selected from Arg, Nmr, Pro, Eaz, Pca, Orn, Fhz, Har, Nar, Cyr, Mmr, Dmr, Bmr, Opy, and N(alkyl) derivatives of any of the preceding amino acids;

Xaa_9 will be selected from Ile, Tbg, Deg, Egz, Aml, 1860, Che, Nmi, Leu, Val, Ecb, and Eca; and

Xaa_{10} will be selected from a bond, Ser and a N(alkyl) derivative thereof.

Table 3: Preferred compounds according to the present invention and their agonistic activity in in vitro assays.

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Hex-Ebe-pro-Phe-Gly-Leu-Pro-Ile-Asp-Arg-Ile-Ser-Ebe-NH_2;	JAL-0533	19	1446	C
Hex-Ebe-pro-Phe-Gly-Leu-Lys-Ile-Asp-Arg-Ile-Ser-Ebe-NH_2;	JAL-0534	20	1477	C
Hex-Ser-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Ser-Ser-NH_2;	JAL-0535	21	1391	C
Hex-Ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Ser-Ala-NH_2;	JAL-0536	22	1359	B
Hex-Ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Ser-Gly-NH_2;	JAL-0537	23	1345	C
Hex-Gly-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Ser-Ala- NH_2;	JAL-0538	24	1345	B
Hex-Gly-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Ser-Gly- NH_2;	JAL-0539	25	1331	B
Hex-Ebe-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Ser- NH_2;	JAL-0540	26	1334	C
Hex-Ebe-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0541	27	1247	C
Hex-Gab-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Ser-Ebe- NH_2;	JAL-0542	28	1348	C
Hex-Mam-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Ser-Ebe- NH_2;	JAL-0543	29	1396	C
Hex-Gly-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0631	30	1188	C
Hex-Ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0632	31	1202	C
Hex-Ser-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0633	32	1218	C
Hex-Pro-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0634	33	1228	C
Hex-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0635	34	1201	C
Hex-Gly-pro-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0636	35	1213	C
Hex-Ser-pro-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0638	36	1241	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Hex-Mam-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0647	37	1193	C
Hex-Pam-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0648	38	1193	C
Hex-Mpe-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0649	39	1193	C
Hex-Ppe-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0650	40	1193	C
Hex-Inp-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0651	41	1171	C
Hex-Acp-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0652	42	1210	C
Hex-Fir-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0653	43	1199	C
Hex-Nip-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0654	44	1171	C
Hex-Eah-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0656	45	1228	C
Hex-Fio-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0657	46	1185	C
Hex-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Eca-NH_2;	JAL-0692	47	1199	C
1339-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0693	48	1255	C
Occ-pro-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0694	49	1184	C
1339-pro-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0695	50	1210	C
1320-pro-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0696	51	1218	C
Occ-Nip-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0697	52	1198	B
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0701	53	1229	B
1340-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0703	54	1241	C
Hex-Tnc-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0713	55	1186	C
Hex-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Chg-NH_2;	JAL-0718	56	1227	C
Hex-ala-ala-Phe-Paa-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0731	57	1157	C
Occ-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0738	58	1158	C
Occ-thz-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0739	59	1202	C
Occ-aze-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0740	60	1170	C
Occ-Az3-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-NH_2;	JAL-0742	61	1170	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0743	62	1198	B
Occ-Rni-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0744	63	1198	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-2137;	JAL-0748	64	1199	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-3816;	JAL-0749	65	1201	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-3806;	JAL-0751	66	1187	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-565;	JAL-0752	67	1200	B
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-2797 ;	JAL-0754	68	1252	B
Occ-val-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0756	69	1186	C
Occ-tbg-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0758	70	1200	C
Occ-Amcp-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0760	71	1184	C
Occ-Ebc-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0761	72	1170	C
Occ-abu-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0762	73	1171	C
Occ-ser-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0763	74	1174	C
Occ-ala-ala-Phe-Gly-Leu-Lys-leu-Asp-Arg-Ile- NH_2;	JAL-0769	75	1229	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Ile-Asp-Arg-Ile- NH_2;	JAL-0770	76	1229	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Val-Asp-Arg-Ile- NH_2;	JAL-0771	77	1215	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Chg-Asp-Arg-Ile- NH_2;	JAL-0772	78	1255	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Nle-Asp-Arg-Ile- NH_2;	JAL-0775	79	1229	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Nml-Asp-Arg-Ile- NH_2;	JAL-0776	80	1243	C
Occ-ala-ala-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0781_01	81	1214	B
Occ-ala-ala-Phe-Gly-Leu-Nmk-Leu-Asp-Arg-Ile- NH_2;	JAL-0782	82	1243	C
933-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0786	83	1208	C
1270-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0787	84	1160	C
4956-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile- NH_2;	JAL-0788	85	1144	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-1860;	JAL-0789	86	1213	B
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-504;	JAL-0790	87	1251	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-559;	JAL-0791	88	1185	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-3791;	JAL-0792	89	1187	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Che ;	JAL-0797	90	1212	B
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-1859 ;	JAL-0798	91	1211	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-1934 ;	JAL-0799	92	1304	B
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-1906 ;	JAL-0801	93	1209	B
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-873 ;	JAL-0824	94	1192	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-5116 ;	JAL-0825	95	1241	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-5119 ;	JAL-0826	96	1270	B
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-5118 ;	JAL-0831	97	1270	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-5163 ;	JAL-0833	98	1227	C
Occ-ala-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-5164 ;	JAL-0834	99	1255	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0835	100	1127	C
Occ-pro-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0836	101	1153	C
Occ-Sni-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0837	102	1167	C
Occ-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-1860 ;	JAL-0839	103	1141	B
Occ-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Che ;	JAL-0840	104	1141	C
Occ-ala-Phe-Gly-Leu-Lys-Leu-Asp-Arg-5121 ;	JAL-0841	105	1143	C
Occ-ala-Phe-Gly-Leu-Pro-Ile-Asp-Arg-Ile- NH_2;	JAL-0894	106	1127	C
Occ-ala-Phe-Gly-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-0895	107	1141	B
Occ-ala-Phe-Gly-Leu-Pro-Npg-Asp-Arg-Ile- NH_2;	JAL-0896	108	1141	C
Occ-ala-Phe-Gly-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-0898	109	1143	B
Occ-ala-Phe-Gly-Npg-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0903	110	1141	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-ala-Nmf-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0906	111	1141	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-Asp-Nmr-Ile- NH_2;	JAL-0921	112	1141	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-Asn-Arg-Ile- NH_2;	JAL-0924	113	1127	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-Nva-Arg-Ile- NH_2;	JAL-0926	114	1111	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-Val-Arg-Ile- NH_2;	JAL-0927	115	1111	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-Thr-Arg-Ile- NH_2;	JAL-0929	116	1113	C
Occ-ala-Phe-Gly-Cha-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0940	117	1167	C
Occ-ala-Phe-Gly-Nle-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0942	118	1127	C
Occ-ala-Phe-Aib-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0943	119	1155	C
Occ-ala-Phe-ala-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0944	120	1141	C
Occ-ala-Phe-Ebc-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0945	121	1153	C
Occ-ala-Mcf-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0946	122	1161	C
Occ-Sar-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0950	123	1127	C
Occ-Gly-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0951	124	1113	C
Occ-aze-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0953	125	1139	B
Occ-ala-Nmf-Gly-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-0954	126	1155	B
Occ-pro-Phe-Gly-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-0955_01	127	1167	B
Occ-Sni-Phe-Gly-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-0956	128	1181	B
Occ-pro-Nmf-Gly-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-0957	129	1181	C
Occ-Sni-Nmf-Gly-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-0958_01	130	1195	B
Occ-ala-Phe-Gly-Leu-Pro-Hle-Asp-Arg-Ile- NH_2;	JAL-0959	131	1141	C
Occ-ala-Phe-Gly-Leu-Amp-Leu-Asp-Arg-Ile- NH_2;	JAL-0962	132	1141	C
Occ-ala-Phe-Gly-Leu-Chy-Leu-Asp-Arg-Ile- NH_2;	JAL-0964	133	1143	C
Occ-pro-Nmf-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0966	134	1167	C

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Occ-Sni-Nmf-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0967_01	135	1181	C
Occ-ala-Phe-Gly-Leu-Apr-Leu-Asp-Arg-Ile- NH_2;	JAL-0974	136	1142	B
Occ-ala-Phe-Gly-Leu-Eay-Leu-Asp-Arg-Ile- NH_2;	JAL-0975	137	1204	C
Occ-ala-Phe-Gly-Leu-Fpr-Leu-Asp-Arg-Ile- NH_2;	JAL-0978	138	1145	C
Occ-ala-Phe-Gly-Leu-Dtp-Leu-Asp-Arg-Ile- NH_2;	JAL-0979	139	1174	C
Occ-ala-Phe-Gly-Leu-Eaz-Leu-Asp-Arg-Ile- NH_2;	JAL-0980	140	1146	C
Occ-Az3-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0985	141	1139	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Tbg-NH_2;	JAL-0989	142	1127	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-Ser-Arg-Ile- NH_2;	JAL-0992	143	1099	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-Hse-Arg-Ile- NH_2;	JAL-0993	144	1113	C
Occ-ala-Phe-Gly-Ile-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0995	145	1127	C
Occ-ala-Phe-Gly-Nva-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0996	146	1113	C
Occ-ala-Phe-Gly-Hle-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-0998	147	1141	C
Occ-ala-Thi-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1000	148	1133	C
Occ-ala-Pcf-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1002	149	1161	C
Occ-ala-Thk-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1003	150	1133	C
Occ-ala-Mtf-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1005	151	1195	C
Occ-ala-Mmf-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1006	152	1141	C
Occ-ala-Phe-ser-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1010	153	1157	B
Occ-ala-Phe-thr-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1011	154	1171	B
Occ-ala-Phe-val-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1012	155	1169	C
Occ-ala-Phe-leu-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1013	156	1183	B
Occ-ala-Phe-nle-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1014	157	1183	B
Occ-Sni-Phe-Gly-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1015	158	1197	B

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Occ-ala-Phe-Gly-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1016	159	1157	B
Occ-ala-Phe-asn-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1017	160	1184	B
Occ-ala-Phe-met-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1018	161	1201	B
Occ-ala-Phe-abu-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1019	162	1155	B
Occ-ala-Phe-dap-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1020	163	1156	B
Occ-Sni-Phe-nle-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1021	164	1223	B
Occ-Sni-Nmf-nle-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1022	165	1237	B
Occ-Sni-Phe-nle-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1024	166	1239	A
Occ-ala-Phe-nle-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1025	167	1199	B
Occ-ala-Phe-leu-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1026	168	1199	B
Occ-ala-Phe-nva-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1027	169	1185	B
Occ-ala-Phe-phe-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1028	170	1029	B
Occ-ala-Phe-ctb-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1029	171	1244	B
Occ-ala-Phe-lys-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1030	172	1198	B
Occ-ala-Phe-arg-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1031	173	1226	B
Occ-ala-Phe-his-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1032	174	1207	B
Ac-Hgl-ala-ala-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1033	175	1255	B
Ac-hgl-ala-ala-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile-NH_2;	JAL-1034	176	1255	B
Occ-pip-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1035	177	1167	C
Occ-ala-Phe-Gly-Leu-Pro-Leu-cDR-Ile- NH_2;	JAL-1037	178	1153	C
Occ-ala-Phe-Gly-Leu-Bhp-Leu-Asp-Arg-Ile- NH_2;	JAL-1038	179	1234	C
Occ-ala-Phe-leu-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-1039	180	1196	A
Occ-Sni-Phe-leu-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-1040	181	1236	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1041	182	1253	A

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Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1042	183	1213	A
Occ-ala-Pcf-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1043	184	1247	A
Occ-ala-Phe-nle-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1044	185	1213	A
Occ-ala-Phe-Gly-Leu-Pro-Npl-Asp-Arg-Ile- NH_2;	JAL-1045	186	1169	C
Occ-ala-Phe-arg-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1047	187	1242	A
Occ-ala-Phe-asp-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1048	188	1201	C
Occ-ala-Phe-glu-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1049	189	1215	C
Occ-ala-Pcf-leu-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1050	190	1233	A
Occ-ala-Pmf-leu-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1051	191	1213	B
Occ-ala-Nmf-leu-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1052	192	1213	A
Occ-pro-Phe-leu-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1053	193	1225	A
Occ-pip-Phe-leu-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1054	194	1239	A
Occ-ala-Phe-lys-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1060	195	1228	A
Occ-ala-Phe-orn-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1061	196	1214	A
Occ-ala-Phe-lys-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-1065	197	1212	B
Occ-ala-Phe-lys-Leu-Pro-Nml-Ala-Arg-Ile- NH_2;	JAL-1068	198	1168	C
Occ-ala-Phe-arg-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-1075	199	1240	B
Occ-ala-Nmf-arg-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-1076	200	1254	B
Occ-pip-Nmf-arg-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-1077	201	1294	A
Occ-pip-Phe-arg-Leu-Pro-Nml-Asp-Arg-Ile- NH_2;	JAL-1078	202	1280	A
Occ-ala-Nmf-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1085	203	1270	A
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1086	204	1256	A
Occ-pip-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1087	205	1296	A
Occ-ala-Phe-arg-Leu-Tfp-Leu-Asp-Arg-Ile- NH_2;	JAL-1114	206	1244	B

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Occ-ala-Phe-Gly-Leu-Tfp-Leu-Asp-Arg-Ile- NH_2;	JAL-1115	207	1145	B
Occ-ala-Pbf-arg-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1116	208	1321	A
Occ-ala-Phe-dab-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1120	209	1169	B
Occ-ala-Phe-nar-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1121	210	1212	B
Occ-ala-Phe-gdp-Leu-Pro-Leu-Asp-Arg-Ile- NH_2;	JAL-1122	211	1198	B
Oct-ala-Phe-arg-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1156_02	212	1227	B
Oct-pip-Phe-arg-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1157_02	213	1267	C
Occ-ala-Phe-arg-(KM-116-167)-Nml-Asp-Arg-Ile- NH_2;	JAL-1159	214	1226	C
832-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1214	215	1241	B
Occ-ala-Phe-arg-Leu-Hyp-Ile-Asp-Arg-Ile- NH_2;	JAL-1224	216	1242	B
Occ-ala-Phe-arg-Leu-Hyp-Npg-Asp-Arg-Ile- NH_2;	JAL-1225	217	1256	A
Occ-ala-Phe-arg-Leu-Hyp-Tbg-Asp-Arg-Ile- NH_2;	JAL-1226	218	1242	C
Occ-ala-Phe-arg-Leu-Hyp-Ebe-Asp-Arg-Ile- NH_2;	JAL-1227	219	1246	B
Occ-ala-Phe-arg-Leu-Lys-Nml-Asp-Arg-Ile- NH_2;	JAL-1228	220	1271	B
Occ-ala-Phe-arg-Leu-Nmk-Nml-Asp-Arg-Ile- NH_2;	JAL-1229	221	1285	B
Occ-ala-Phe-arg-Leu-Nma-Nml-Asp-Arg-Ile- NH_2;	JAL-1230	222	1228	C
Occ-ala-Phe-arg-Leu-Sar-Nml-Asp-Arg-Ile- NH_2;	JAL-1231	223	1214	B
Occ-ala-Phe-arg-Nva-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1232	224	1242	B
Occ-ala-Phe-arg-Ebe-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1233	225	1260	B
6014-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1237	226	1239	B
6015-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1238	227	1239	B
6054-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1239	228	1241	B
6056-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1240	229	1239	B
6057-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1241	230	1259	B

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6058-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1242	231	1259	B
6059-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1243	232	1274	B
832-Nmf-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1244	233	1255	C
832-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1245	234	1196	B
832-Phe-arg-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1246	235	1225	C
Oct-Sni-FrL-Hyp-Leu-Asp-Arg-Ile- NH_2;	JAL-1248	236	1268	B
Occ-ala-Phe-Gly-Leu-Tap-Leu-Asp-Arg-Ile- NH_2;	JAL-1249	237	1142	A
Occ-ala-Phe-arg-Leu-Tap-Leu-Asp-Arg-Ile- NH_2;	JAL-1250	238	1241	A
Occ-ala-Phe-leu-Leu-Tap-Asp-Arg-Ile- NH_2;	JAL-1251	239	1198	A
Occ-ala-Phe-ser-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1252	240	1187	A
Occ-Sni-Phe-ser-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1253	241	1227	B
Occ-Sni-Phe-lys-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1254	242	1268	A
Occ-Sni-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1255	243	1296	A
Occ-Sni-Mpa-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1256	244	1254	C
Occ-Sni-Ppa-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1257	245	1254	C
(6071-OH)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1259	246	1230	C
(6072-OH)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1260	247	1258	B
5587-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1261	248	1214	C
Occ-ala-Phe-Gly-Leu-Tap(2Me)-Leu-Asp-Arg-Ile- NH_2;	JAL-1262	249	1170	B
Occ-ala-Phe-arg-Leu-Tap(2Me)-Leu-Asp-Arg-Ile- NH_2;	JAL-1263	250	1269	B
Occ-ala-Phe-leu-Leu-Tap(2Me)-Leu-Asp-Arg-Ile- NH_2;	JAL-1264	251	1226	B
Occ-Sni-Phe-orn-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1265	252	1254	A
Occ-Sni-Opa-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1266	253	1254	B
Occ-ala-Nmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1267	254	1227	A

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Occ-ala-Nmf-lys-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1268	255	1242	B
Occ-ala-Nmf-orn-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1269	256	1228	B
Occ-ala-Phe-Gly-Leu-Gup-Leu-Asp-Arg-Ile- NH_2;	JAL-1270	257	1184	B
Occ-ala-Phe-arg-Leu-Gup-Leu-Asp-Arg-Ile- NH_2;	JAL-1271	258	1283	B
Occ-ala-Phe-leu-Leu-Gup-Leu-Asp-Arg-Ile- NH_2;	JAL-1272	259	1240	B
Oct-Sar-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1273	260	1242	B
Oct-aze-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1274	261	1254	B
Oct-Az3-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1275	262	1254	B
Occ-ala-Phe-leu-Leu-Eal-Nml-Asp-Arg-Ile- NH_2;	JAL-1281_01	263	1198	B
Occ-ala-Phe-Gly-Leu-Eal-Nml-Asp-Arg-Ile- NH_2;	JAL-1282	264	1144	C
Occ-ala-Phe-leu-Leu-Hyp-(SH-158)-Asp-Arg-Ile-NH_2;	JAL-1283	265	1227	A
Occ-ala-Phe-arg-Leu-Hyp-(SH-158)-Asp-Arg-Ile-NH_2;	JAL-1284	266	1271	A
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1287	267	1254	A
Occ-ala-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1288	268	1242	A
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1289	269	1282	A
(AR-201-48)-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1291	270	1242	C
(AR-201-49)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1292	271	1257	B
(AR-201-48)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1293	272	1199	C
(AR-201-49)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1294	273	1214	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1295	274	1252	A
Occ-ala-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1296	275	1212	A
Oct-Sni-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1297	276	1282	A
6182-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1298	277	1280	B
Oct-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1302	278	1239	A

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Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Tbg-NH_2;	JAL-1305	279	1256	A
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Eca-NH_2;	JAL-1306	280	1254	B
Occ-ala-Phe-arg-Leu-Hyp-Dap(Me2)-Asp-Arg-Ile-NH_2;	JAL-1314	281	1242	B
Occ-ala-Phe-arg-Dap(Me2)-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1315	282	1257	C
(AR-201-54)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1316	283	1277	B
Occ-Sni-Phe-arg-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1317	284	1295	A
Occ-Sni-Phe-orn-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1318	285	1253	A
Occ-Sni-Phe-nle-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1319	286	1252	B
Occ-Sni-Phe-Gly-Leu-Tap-Nml-Asp-Arg-Ile-NH_2;	JAL-1320	287	1196	A
Occ-Sni-Phe-leu-Leu-Tap(Ac)-Nml-Asp-Arg-Ile-NH_2;	JAL-1321	288	1294	B
Occ-Sni-Phe-leu-Leu-Tap(G)-Nml-Asp-Arg-Ile-NH_2;	JAL-1322	289	1309	A
Occ-Sni-Phe-leu-Leu-Tap(Bal)-Nml-Asp-Arg-Ile-NH_2;	JAL-1323	290	1323	A
6059(O)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1324	291	1291	B
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1325	292	1253	A
Oct-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1326	293	1238	A
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Orn-Ile- NH_2;	JAL-1327	294	1214	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Orn-Ile- NH_2;	JAL-1328	295	1171	B
Occ-ala-Phe-arg-Leu-Hyp-Nml-Glu-Arg-Ile- NH_2;	JAL-1329	296	1270	C
Occ-ala-Phe-leu-Leu-Hyp-Nml-Glu-Arg-Ile- NH_2;	JAL-1330	297	1227	B
Occ-ala-Phe-arg-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	JAL-1331	298	1240	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	JAL-1332	299	1197	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	JAL-1332_02	300	1197	B
Occ-ala-Phe-arg-Leu-Hyp-Nml-Thr-Arg-Ile- NH_2;	JAL-1333	301	1242	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Thr-Arg-Ile- NH_2;	JAL-1334	302	1199	B

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Eca-NH_2;	JAL-1335	303	1211	B
Occ-ala-Phe-Fhy-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1336	304	1240	A
Occ-ala-Phe-Egg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1337	305	1254	B
Occ-ala-Phe-Apc-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1338	306	1226	A
(AR-201-58)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1339	307	1254	C
(AR-201-59)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1340	308	1267	C
(AR-201-62)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1341	309	1253	B
(AR-201-69)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1342	310	1317	B
Sbt-Sni-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1343	311	1309	A
Nbt-Sni-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1344	312	1309	B
Sbt-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1345	313	1269	C
Nbt-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1346	314	1269	C
Occ-ala-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1347	315	1213	B
Occ-Sni-Phe-leu-Leu-Tap(Et2)-Nml-Asp-Arg-Ile-NH_2;	JAL-1348	316	1308	B
Occ-Sni-Phe-leu-Leu-Tap(Et)-Nml-Asp-Arg-Ile-NH_2;	JAL-1349	317	1280	A
Occ-ala-Phe-Apc-Leu-Tap-Nml-Asp-Arg-Ile-NH_2;	JAL-1350	318	1265	A
Occ-Sni-Phe-Apc-Leu-Tap-Nml-Asp-Arg-Ile-NH_2;	JAL-1351	319	1265	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Tbg-NH_2;	JAL-1352	320	1213	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Egz-NH_2;	JAL-1358	321	1225	A
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Egz-NH_2;	JAL-1359	322	1268	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Nle-Ile- NH_2;	JAL-1360	323	1170	C
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Nle-Ile- NH_2;	JAL-1361	324	1213	C
Occ-ala-Phe-arg-Leu-Hyp-Nml-Ile-Arg-Ile- NH_2;	JAL-1362	325	1254	C
Occ-ala-Phe-leu-Leu-Hyp-Nml-Ile-Arg-Ile- NH_2;	JAL-1363	326	1211	B

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-ala-Phe-arg-Leu-Hyp-Oic-Asp-Arg-Ile- NH_2;	JAL-1364	327	1280	B
Occ-ala-Phe-arg-Leu-Hyp-Pip-Asp-Arg-Ile- NH_2;	JAL-1365	328	1240	C
Occ-ala-Phe-leu-Leu-Hyp-Pip-Asp-Arg-Ile- NH_2;	JAL-1366	329	1197	B
Occ-ala-Phe-leu-Leu-Hyp-Dap(Me2)-Asp-Arg-Ile- NH_2;	JAL-1367	330	1200	A
Occ-ala-Phe-leu-Dap(Me2)-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1368	331	1214	B
Oct-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1369	332	1239	A
Occ-Sni-Phe-dap(6263)2-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1370	333	1311	B
Occ-Sni-Phe-leu-Leu-Tap(Ae)-Nml-Asp-Arg-Ile- NH_2;	JAL-1371	334	1295	A
Occ-Sni-Phe-leu-Leu-Tap(Ap)-Nml-Asp-Arg-Ile- NH_2;	JAL-1372	335	1309	A
(AR-201-58)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1373	336	1211	B
(AR-201-62)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1374	337	1210	B
(AR-201-69)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1375	338	1274	B
(AR-201-72)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1376	339	1227	C
(AR-201-72)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1377	340	1270	C
(AR-201-73)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1378	341	1216	B
(AR-201-73)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1379	342	1259	B
(AR-201-68)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1380	343	1274	A
(AR-201-68)-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1381	344	1317	B
Sbt-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1382	345	1266	A
Nbt-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1383	346	1266	B
Occ-ala-Phe-leu-Leu-Hyp-Oic-Asp-Arg-Ile- NH_2;	JAL-1386	347	1237	B
Occ-ala-Phe-arg-Leu-Hyp-Pro-Asp-Arg-Ile- NH_2;	JAL-1387	348	1226	C
Occ-ala-Phe-arg-Leu-Hyp-Aze-Asp-Arg-Ile- NH_2;	JAL-1393	349	1212	C
Occ-ala-Phe-arg-Leu-Hyp-Eat-Asp-Arg-Ile- NH_2;	JAL-1394	350	1244	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-ala-Phe-arg-Leu-Hyp-Eaz-Asp-Arg-Ile- NH_2;	JAL-1395	351	1244	C
Occ-ala-Phe-arg-Leu-Hyp-Tic-Asp-Arg-Ile- NH_2;	JAL-1396	352	1288	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	JAL-1398	353	1237	A
Oct-Sni-Phe-leu-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	JAL-1399	354	1223	B
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	JAL-1400	355	1238	C
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Arg-Ile- NH_2;	JAL-1401	356	1236	A
Oct-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	JAL-1402	357	1224	B
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Val-Arg-Ile- NH_2;	JAL-1403	358	1237	A
Oct-Sni-Phe-leu-Leu-Tap-Nml-Val-Arg-Ile- NH_2;	JAL-1404	359	1222	B
Oct-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Val-Arg-Ile- NH_2;	JAL-1405	360	1223	A
Occ-ala-Phe-Apc(Me)-Met-glu--Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1406	361	1240	A
Occ-ala-Phe-Apc(Et)-Glu-thr--Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1407	362	1254	A
Occ-ala-Phe-Apc(Ae)-Ala-glu--Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1408	363	1269	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Aib-NH_2;	JAL-1413	364	1185	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Aml-NH_2;	JAL-1414	365	1227	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Deg-NH_2;	JAL-1416	366	1213	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Nmr-Ile-NH_2;	JAL-1417	367	1227	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Pro-Ile- NH_2;	JAL-1418	368	1254	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Tbg-Arg-Ile- NH_2;	JAL-1420	369	1211	C
Occ-ala-Phe-leu-Leu-Hyp-Nml-Chg-Arg-Ile- NH_2;	JAL-1421	370	1237	C
Occ-ala-Phe-leu-Leu-Hyp-Nml-Cpa-Arg-Ile- NH_2;	JAL-1424	371	1195	C
Oct-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1429	372	1240	A
Miy-Hgl-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1430	373	1561	A
Miy-Gab-Hgl-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1431	374	1647	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Ac-Miy-Gab-Hgl-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1432	375	1730	C
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Pro-Ile- NH_2;	JAL-1434	376	1198	B
Occ-ala-Phe-Apc-Leu-Hyp-Nml-Asp-Pro-Ile- NH_2;	JAL-1435	377	1167	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-Ile- NH_2;	JAL-1436	378	1194	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Aze-Ile- NH_2;	JAL-1437	379	1140	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Pip-Ile- NH_2;	JAL-1438	380	1168	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Hyp-Ile- NH_2;	JAL-1441	381	1170	C
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Eaz-Ile- NH_2;	JAL-1442	382	1173	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Cpp-Ile- NH_2;	JAL-1443	383	1167	B
Occ-ala-Phe-leu-Leu-Tap-Nml-Asp-Pro-Ile- NH_2;	JAL-1450	384	1153	B
Occ-ala-Phe-Apc-Leu-Hyp-Nml-Asp-Pro-Ile- NH_2;	JAL-1451	385	1207	B
Occ-ala-Phe-Apc-Leu-Tap-Nml-Asp-Pro-Ile- NH_2;	JAL-1452	386	1166	A
Occ-ala-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Pro-Ile- NH_2;	JAL-1453	387	1154	A
Occ-ala-Phe-Egz-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1454	388	1224	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Eay-Ile- NH_2;	JAL-1456	389	1230	C
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Egz-Ile- NH_2;	JAL-1457	390	1182	C
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Apc-Ile- NH_2;	JAL-1458	391	1183	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Tap-Ile- NH_2;	JAL-1459	392	1169	C
Occ-ala-Phe-dap(6238)2-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1460	393	1380	B
Occ-ala-Phe-dap(6238)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1461	394	1282	B
Occ-ala-Phe-dap(3846)2-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1462	395	1345	B
Occ-ala-Phe-dap(1464)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	JAL-1463	396	1255	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-558 ;	JAL-1464	397	1162	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-Ile-OH ;	JAL-1474	398	1194	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-Ile-(NH-CH_3);	JAL-1475	399	1207	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Chy-Ile- NH_2;	JAL-1476	400	1170	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-H3p-Ile- NH_2;	JAL-1477	401	1170	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Dhp-Ile- NH_2;	JAL-1479	402	1152	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Udp-Ile- NH_2;	JAL-1482	403	1143	B
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Bhk-Ile- NH_2;	JAL-1483	404	1199	B
Occ-Sni-Nif-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1486	405	1298	B
Occ-Sni-Pff-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1487	406	1271	A
Occ-Sni-Pmy-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1488	407	1283	B
Occ-Sni-Tyr-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1489	408	1269	C
Occ-Sni-Bmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1490	409	1267	C
Occ-Sni-Eay-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1491	410	1279	B
Occ-Sni-Paf-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1492	411	1268	B
Occ-Sni-Pcf-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1493	412	1287	A
Occ-Sni-Pmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1494	413	1267	A
Occ-Sni-Eaa-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1496	414	1322	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-2118 ;	JAL-1506	415	1210	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-2906 ;	JAL-1508	416	1134	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-1381 ;	JAL-1509	417	1164	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-1381 ;	JAL-1509_02	418	1164	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-1860 ;	JAL-1510	419	1176	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-1906 ;	JAL-1511	420	1174	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-Che ;	JAL-1512_02	421	1176	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-5121 ;	JAL-1513	422	1178	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-Ala-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1553	423	1211	C
Occ-Sni-Phe-Leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1554	424	1253	B
Occ-Sni-Phe-Apc-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1555	425	1266	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-(BB725)-Arg-Ile-NH_2;	JAL-1556	426	1224	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-(BB726)-Arg-Ile-NH_2;	JAL-1557	427	1238	C
Occ-ala-Phe-leu-Leu-Hyp-Nml-(BB727)-Arg-Ile-NH_2;	JAL-1558	428	1238	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Pro-Ile- NH_2;	JAL-1559	429	1194	A
Occ-Sni-Phe-Gly-Leu-Tap-Nml-Asp-Pro-Ile- NH_2;	JAL-1560	430	1138	B
Occ-Sni-Phe-Apc-Leu-Tap-Nml-Asp-Pro-Ile-NH_2;	JAL-1561	431	1207	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Pro-Che;	JAL-1568	432	1176	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Nmi-NH_2;	JAL-1569	433	1267	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Nmr-Ile-NH_2;	JAL-1570	434	1267	B
Occ-Sni-Phe-leu-Nml-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1572	435	1267	C
Occ-Sni-Nmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1573	436	1267	A
Occ-Sni-Phe-nml-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1574	437	1267	C
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Nmi- NH_2;	JAL-1575	438	1268	C
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Nmr-Ile- NH_2;	JAL-1576	439	1268	A
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Nmd-Arg-Ile- NH_2;	JAL-1577	440	1268	C
Occ-Sni-Phe-dap(Me2)-Nml-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1578	441	1268	B
Occ-Sni-Nmf-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1579	442	1268	A
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Pro-Ile- NH_2;	JAL-1580	443	1195	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Val-Pro-Che ;	JAL-1594	444	1160	B
Occ-Sni-Phe-leu-Leu-Hyp-Npg-Asp-Pro-Che ;	JAL-1595	445	1177	A
Occ-Sni-Phe-leu-Leu-Hyp-Ile-Asp-Pro-Che ;	JAL-1596	446	1162	B

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Nmf-leu-Leu-Hyp-Nml-Asp-Pro-Che ;	JAL-1597	447	1191	A
Occ-Sni-Phe-leu-Nml-Hyp-Nml-Asp-Pro-Che;	JAL-1598	448	1190	C
Occ-Sni-Eaa-leu-Leu-Hyp-Nml-Asp-Pro-Che ;	JAL-1599	449	1245	A
Occ-Sni-Phe-Gly-Leu-Hyp-Nml-Asp-Pro-Che;	JAL-1600	450	1120	B
Occ-Sni-Phe-Apc-Leu-Hyp-Nml-Asp-Pro-Che ;	JAL-1601	451	1190	B
Occ-Sni-Phe-Apc-Leu-Tap-Nml-Asp-Pro-Che ;	JAL-1602	452	1190	A
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Pro-Che;	JAL-1603	453	1177	A
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Pro-Che;	JAL-1604	454	1177	A
1319-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1605	455	1272	A
1320-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1606	456	1286	A
2553-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1607	457	1302	C
4734-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1609	458	1316	B
4703-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1612	459	1339	B
6988-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1615	460	1342	C
Hex-(3421)-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1616	461	1360	B
1695-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1617	462	1372	C
Occ-Sni-Mcf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1618	463	1287	A
Occ-Sni-Pbf-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1619	464	1332	A
Occ-Sni-Thk-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1620	465	1259	A
Occ-Sni-Mtf-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1621	466	1321	A
Occ-Sni-Otf-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1622	467	1321	C
Occ-Sni-Phe-ctb-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1623	468	1299	A
Occ-Sni-Phe-leu-Nle-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1624	469	1253	A
Occ-Sni-Phe-leu-Leu-Hyp-Ile-Asp-Arg-Ile- NH_2;	JAL-1625	470	1239	A

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Occ-Sni-Phe-leu-Leu-Hyp-Cpg-Asp-Arg-Ile- NH_2;	JAL-1626	471	1251	A
Occ-Sni-Phe-leu-Leu-Hyp-Chg-Asp-Arg-Ile- NH_2;	JAL-1627	472	1265	B
Occ-Sni-NPhe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1634	473	1253	C
Occ-Sni-NHfe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1635	474	1267	C
Occ-(aFL)-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1636	475	1225	B
Occ-(afL)-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1637	476	1225	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Eaz-Che ;	JAL-1638	477	1195	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Eal-Che ;	JAL-1639	478	1177	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-(ES-283-049) ;	JAL-1646	479	1163	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Glu-Pro-Che ;	JAL-1652	480	1191	B
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Pro-Che ;	JAL-1654	481	1160	A
Occ-Sni-Phe-leu-Nle-Hyp-Nml-Asp-Pro-Che;	JAL-1657	482	1177	A
779-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1659	483	1263	B
785-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1660	484	1335	C
1281-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1661	485	1259	B
3218-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1664	486	1293	C
6013-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1665	487	1285	B
5587-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1666	488	1281	A
1281-G-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1668	489	1316	C
1281-Bal-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1669	490	1330	C
Occ-(AFL)-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1671	491	1225	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Apc-Che ;	JAL-1672	492	1204	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-NP-Che ;	JAL-1673	493	1176	C
Occ-Sni-Phe-leu-Leu-Tap-Nml-(BB726)-Pro-Che ;	JAL-1676	494	1200	B

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pca-Che ;	JAL-1679	495	1192	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Che ;	JAL-1680	496	1236	A
Occ-Sni-Phe-leu-Leu-Tap(Ae)-Nml-Asp-Arg-Che ;	JAL-1681	497	1278	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Che ;	JAL-1682	498	1235	A
Occ-Sni-Phe-leu-Leu-Tap(Ae)-Nml-Val-Arg-Che ;	JAL-1683	499	1262	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Apc(Gua)-Che ;	JAL-1685	500	1248	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Apc(Gly)-Che ;	JAL-1687	501	1263	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-(BB394)-Che ;	JAL-1694	502	1166	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-(BB785)-Che ;	JAL-1697	503	1192	B
Occ-Sni-Hfe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1701	504	1267	C
Occ-ala-Nmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1702	505	1227	C
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Arg-Che ;	JAL-1729	506	1218	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Val-Arg-Che ;	JAL-1730	507	1219	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Ala-Arg-Che ;	JAL-1750	508	1193	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asn-Arg-Che ;	JAL-1751	509	1236	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Ser-Arg-Che ;	JAL-1752	510	1209	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Thr-Arg-Che ;	JAL-1753	511	1223	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Nle-Arg-Che ;	JAL-1755	512	1235	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Ble-Arg-Che ;	JAL-1756	513	1235	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Thi-Arg-Che ;	JAL-1758	514	1275	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Chg-Arg-Che ;	JAL-1763	515	1261	C
(AR-314-87)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1765-2	516	1279	A
(AR-314-102)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1774	517	1239	A
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Che;	JAL-1776	518	1265	A

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-lys(Me2)-Leu-Hyp-Nml-Asp-Arg-Che;	JAL-1777	519	1279	A
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Val-Arg-Che;	JAL-1778	520	1249	B
Occ-Sni-Phe-lys(Me2)-Leu-Hyp-Nml-Val-Arg-Che ;	JAL-1779	521	1263	A
Occ-Sni-Phe-lys(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1781	522	1296	B
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	JAL-1782	523	1266	A
Occ-Sni-Phe-lys(Me2)-Leu-Hyp-Nml-Val-Arg-Ile-NH_2;	JAL-1783	524	1280	C
Occ-Sni-Phe-dab(Me2)-Leu-Hyp-Nml-Val-Arg-Che ;	JAL-1784	525	1235	A
Occ-Sni-Phe-dab(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1785	526	1268	A
Occ-Sni-Phe-dab(Me2)-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	JAL-1786	527	1252	B
Occ-Nhpr-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1798	528	1257	B
Occ-Nbhp-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1799	529	1273	B
Occ-ser-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1800	530	1229	B
Occ-hse-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1801	531	1243	B
Gluc-Aoa-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1802	532	1503	B
Gluc-Aoa-hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1803	533	1503	A
(1913)-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1804	534	1384	B
(1270)-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1805	535	1396	C
(1888)-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1806	536	1428	B
Occ-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1807	537	1394	C
H-Adx-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1808	538	1413	A
1888-hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1837	539	1428	B
H-Adx-hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1838	540	1413	B
Oct-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Che;	JAL-1843	541	1221	A
Oct-Sni-Phe-leu-Leu-Tap-Nml-Val-Pro-Che;	JAL-1844	542	1146	B

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Val-Pro-Che;	JAL-1845	543	1190	B
Occ-Sni-Phe-orn(Me2)-Leu-Tap-Nml-Val-Pro-Che;	JAL-1846	544	1189	B
Oct-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Val-Pro-Che;	JAL-1847	545	1176	C
Oct-Sni-Phe-leu-Leu-Hyp-Nml-Val-Arg-Che ;	JAL-1848	546	1206	B
Oct-Sni-Phe-leu-Leu-Tap-Nml-Val-Arg-Che;	JAL-1849	547	1205	B
Occ-Sni-Phe-orn(Me2)-Leu-Tap-Nml-Val-Arg-Che;	JAL-1850	548	1248	A
Oct-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Val-Arg-Che;	JAL-1851	549	1235	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Bmf-Arg-Ile-NH_2;	JAL-1857	550	1299	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Phg-Arg-Ile- NH_2;	JAL-1858	551	1859	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Cpg-Arg-Ile- NH_2;	JAL-1859	552	1263	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-(AR-314-145)-Arg-Ile- NH_2;	JAL-1864	553	1277	C
(AR-314-169)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1868-2	554	1281	B
(AR-314-170)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1869-2	555	1253	C
(AR-314-171)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1870-2	556	1281	C
(AR-385-008)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1873	557	1273	C
(AR-314-172)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1874	558	1287	B
Occ-Sni-Phe-(AR-385-12)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1877	559	1294	A
Occ-Sni-Phe-hse-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1878	560	1241	B
Occ-Sni-Phe-abu(pip)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1879	561	1308	B
(AR-385-042)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1880	562	1287	B
Occ-Sni-Phe-Fhz-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1881	563	1280	B
Occ-Sni-Phe-Fhy-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1882	564	1280	B
Occ-Sni-Phe-thr-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1883	565	1241	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-his-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1884	566	1277	B
Occ-Sni-Phe-metO2-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1885	567	1303	B
Occ-Sni-Phe-(AR-385-017)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1886	568	1310	B
Occ-Sni-Phe-opa-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1887	569	1288	B
Occ-Sni-Phe-mpa-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1888	570	1288	B
Occ-Sni-Phe-ppa-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1889	571	1288	B
Occ-Sni-Phe-Egg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1890	572	1294	A
Occ-Sni-Phe-Eao-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1892	573	1299	B
Occ-Sni-Phe-Aic-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1893	574	1299	B
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Ser-Arg-Che;	JAL-1894	575	1237	B
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Thr-Arg-Che;	JAL-1895	576	1251	A
H-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1896	577	1268	B
H-hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1897	578	1268	B
H-Lys-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1898	579	1396	B
H-Lys-hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1899	580	1396	B
H-Lys-Pro-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1900	581	1493	A
(2857-Ac)-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1901	582	1489	B
(1625-Ac)-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	JAL-1907	583	1268	B
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Dim-Arg-Ile- NH_2;	JAL-1910	584	1264	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Pse-Arg-Ile- NH_2;	JAL-1912	585	1305	C
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Pth-Arg-Ile-NH_2;	JAL-1913	586	1348	C
Occ-Sni-Phe-Dha-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	JAL-1915_2	587	1209	B
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Pse-Arg-Che;	JAL-1916	588	1316	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Pse-Arg-Che ;	JAL-1917	589	1288	C

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Pth-Arg-Che;	JAL-1918	590	1330	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Pth-Arg-Che ;	JAL-1919	591	1302	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Ser-Arg-Ile- NH_2;	JAL-1920	592	1225	B
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Ser-Arg-Ile-NH_2;	JAL-1921	593	1254	C
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Cya-Arg-Ile- NH_2;	JAL-1922	594	1289	B
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Cya-Arg-Ile- NH_2;	JAL-1923	595	1318	B
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Thr-Arg-Ile- NH_2;	JAL-1924	596	1268	B
Occ-Sni-Phe-leu-Leu-Hyp(Asp(-))-Nml-Asp-Arg-Ile- NH_2;	JAL-1928	597	1368	B
Occ-Sni-Phe-leu-Leu-Hyp(2581)-Nml-Asp-Arg-Ile- NH_2;	JAL-1929	598	1338	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-OH ;	JAL-1930	599	1254	B
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-OH;	JAL-1931	600	1283	B
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Thr-Arg-Ile- NH_2;	JAL-1932	601	1239	A
Occ-Sni-Phe-leu-Leu-Tap(Asp(-))-Nml-Asp-Arg-Ile- NH_2;	JAL-1935	602	1367	B
Occ-Sni-Phe-orn(Me2)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2	JAL-1936	603	1281	A

Preferred NPR-B agonists of the present invention are those peptides within activity group B, as presented in Table 3, above. Most preferred NPR-B agonists of the present invention are those peptides within activity group A, as presented in Table 4, below.

Table 4: Most preferred compounds according to the present invention and their agonistic activity in in vitro assays.

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-nle-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2	JAL-1024	166	1239	A
Occ-ala-Phe-leu-Leu-Pro-Nml-Asp-Arg-Ile-NH_2	JAL-1039	180	1196	A
Occ-Sni-Phe-leu-Leu-Pro-Nml-Asp-Arg-Ile-NH_2	JAL-1040	181	1236	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1041	182	1253	A

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1042	183	1213	A
Occ-ala-Pcf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1043	184	1247	A
Occ-ala-Phe-nle-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1044	185	1213	A
Occ-ala-Phe-arg-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2	JAL-1047	187	1242	A
Occ-ala-Pcf-leu-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2	JAL-1050	190	1233	A
Occ-ala-Nmf-leu-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2	JAL-1052	192	1213	A
Occ-pro-Phe-leu-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2	JAL-1053	193	1225	A
Occ-pip-Phe-leu-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2	JAL-1054	194	1239	A
Occ-ala-Phe-lys-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1060	195	1228	A
Occ-ala-Phe-orn-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1061	196	1214	A
Occ-pip-Nmf-arg-Leu-Pro-Nml-Asp-Arg-Ile-NH_2	JAL-1077	201	1294	A
Occ-pip-Phe-arg-Leu-Pro-Nml-Asp-Arg-Ile-NH_2	JAL-1078	202	1280	A
Occ-ala-Nmf-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1085	203	1270	A
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1086	204	1256	A
Occ-pip-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1087	205	1296	A
Occ-ala-Pbf-arg-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2	JAL-1116	208	1321	A
Occ-ala-Phe-arg-Leu-Hyp-Npg-Asp-Arg-Ile-NH_2	JAL-1225	217	1256	A
Occ-ala-Phe-Gly-Leu-Tap-Leu-Asp-Arg-Ile-NH_2	JAL-1249	237	1142	A
Occ-ala-Phe-arg-Leu-Tap-Leu-Asp-Arg-Ile-NH_2	JAL-1250	238	1241	A
Occ-ala-Phe-leu-Leu-Tap-Asp-Arg-Ile-NH_2	JAL-1251	239	1198	A
Occ-ala-Phe-ser-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1252	240	1187	A
Occ-Sni-Phe-lys-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1254	242	1268	A
Occ-Sni-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1255	243	1296	A
Occ-Sni-Phe-orn-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1265	252	1254	A

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-ala-Nmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1267	254	1227	A
Occ-ala-Phe-leu-Leu-Hyp-(SH-158)-Asp-Arg-Ile-NH_2	JAL-1283	265	1227	A
Occ-ala-Phe-arg-Leu-Hyp-(SH-158)-Asp-Arg-Ile-NH_2	JAL-1284	266	1271	A
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1287	267	1254	A
Occ-ala-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1288	268	1242	A
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1289	269	1282	A
(AR-201-49)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1294	273	1214	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1295	274	1252	A
Occ-ala-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1296	275	1212	A
Oct-Sni-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1297	276	1282	A
Oct-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1302	278	1239	A
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Tbg-NH_2	JAL-1305	279	1256	A
Occ-Sni-Phe-arg-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1317	284	1295	A
Occ-Sni-Phe-orn-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1318	285	1253	A
Occ-Sni-Phe-Gly-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1320	287	1196	A
Occ-Sni-Phe-leu-Leu-Tap(G)-Nml-Asp-Arg-Ile-NH_2	JAL-1322	289	1309	A
Occ-Sni-Phe-leu-Leu-Tap(Bal)-Nml-Asp-Arg-Ile-NH_2	JAL-1323	290	1323	A
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1325	292	1253	A
Oct-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1326	293	1238	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Val-Arg-Ile-NH_2	JAL-1332	299	1197	A
Occ-ala-Phe-Fhy-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1336	304	1240	A
Occ-ala-Phe-Apc-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1338	306	1226	A
Occ-Sni-Phe-leu-Leu-Tap(Et)-Nml-Asp-Arg-Ile-NH_2	JAL-1349	317	1280	A
Occ-ala-Phe-Apc-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1350	318	1265	A

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-Apc-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1351	319	1265	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Tbg-NH_2	JAL-1352	320	1213	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Egz-NH_2	JAL-1358	321	1225	A
Occ-ala-Phe-leu-Leu-Hyp-Dap(Me2)-Asp-Arg-Ile-NH_2	JAL-1367	330	1200	A
Oct-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1369	332	1239	A
Occ-Sni-Phe-leu-Leu-Tap(Ae)-Nml-Asp-Arg-Ile-NH_2	JAL-1371	334	1295	A
Occ-Sni-Phe-leu-Leu-Tap(Ap)-Nml-Asp-Arg-Ile-NH_2	JAL-1372	335	1309	A
(AR-201-68)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1380	343	1274	A
Sbt-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1382	345	1266	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Val-Arg-Ile-NH_2	JAL-1398	353	1237	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Arg-Ile-NH_2	JAL-1401	356	1236	A
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Val-Arg-Ile-NH_2	JAL-1403	358	1237	A
Oct-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Val-Arg-Ile-NH_2	JAL-1405	360	1223	A
Occ-ala-Phe-Apc(Me)-Met-glu--Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1406	361	1240	A
Occ-ala-Phe-Apc(Et)-Glu-thr--Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1407	362	1254	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Aml-NH_2	JAL-1414	365	1227	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Deg-NH_2	JAL-1416	366	1213	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Nmr-Ile-NH_2	JAL-1417	367	1227	A
Oct-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1429	372	1240	A
Miy-Hgl-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1430	373	1561	A
Occ-ala-Phe-Apc-Leu-Tap-Nml-Asp-Pro-Ile-NH_2	JAL-1452	386	1166	A
Occ-ala-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Pro-Ile-NH_2	JAL-1453	387	1154	A
Occ-ala-Phe-Egz-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1454	388	1224	A
Occ-ala-Phe-dap(1464)-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1463	396	1255	A

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Pff-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1487	406	1271	A
Occ-Sni-Pcf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1493	412	1287	A
Occ-Sni-Pmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1494	413	1267	A
Occ-Sni-Eaa-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1496	414	1322	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-1860	JAL-1510	419	1176	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-Che	JAL-1512_02	421	1176	A
Occ-Sni-Phe-Apc-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1555	425	1266	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-(BB725)-Arg-Ile-NH_2	JAL-1556	426	1224	A
Occ-ala-Phe-leu-Leu-Hyp-Nml-(BB727)-Arg-Ile-NH_2	JAL-1558	428	1238	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Pro-Ile-NH_2	JAL-1559	429	1194	A
Occ-Sni-Phe-Apc-Leu-Tap-Nml-Asp-Pro-Ile-NH_2	JAL-1561	431	1207	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Pro-Che	JAL-1568	432	1176	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Nmi-NH_2	JAL-1569	433	1267	A
Occ-Sni-Nmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1573	436	1267	A
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Nmr-Ile-NH_2	JAL-1576	439	1268	A
Occ-Sni-Nmf-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1579	442	1268	A
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Pro-Ile-NH_2	JAL-1580	443	1195	A
Occ-Sni-Phe-leu-Leu-Hyp-Npg-Asp-Pro-Che	JAL-1595	445	1177	A
Occ-Sni-Nmf-leu-Leu-Hyp-Nml-Asp-Pro-Che	JAL-1597	447	1191	A
Occ-Sni-Eaa-leu-Leu-Hyp-Nml-Asp-Pro-Che	JAL-1599	449	1245	A
Occ-Sni-Phe-Apc-Leu-Tap-Nml-Asp-Pro-Che	JAL-1602	452	1190	A
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Pro-Che	JAL-1603	453	1177	A
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Pro-Che	JAL-1604	454	1177	A
1319-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1605	455	1272	A

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
1320-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1606	456	1286	A
Occ-Sni-Mcf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1618	463	1287	A
Occ-Sni-Pbf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1619	464	1332	A
Occ-Sni-Thk-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1620	465	1259	A
Occ-Sni-Mtf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1621	466	1321	A
Occ-Sni-Phe-ctb-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1623	468	1299	A
Occ-Sni-Phe-leu-Nle-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1624	469	1253	A
Occ-Sni-Phe-leu-Leu-Hyp-Ile-Asp-Arg-Ile-NH_2	JAL-1625	470	1239	A
Occ-Sni-Phe-leu-Leu-Hyp-Cpg-Asp-Arg-Ile-NH_2	JAL-1626	471	1251	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Eaz-Che	JAL-1638	477	1195	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Pro-Che	JAL-1654	481	1160	A
Occ-Sni-Phe-leu-Nle-Hyp-Nml-Asp-Pro-Che	JAL-1657	482	1177	A
5587-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1666	488	1281	A
Occ-(AFL)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1671	491	1225	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pca-Che	JAL-1679	495	1192	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Che	JAL-1680	496	1236	A
Occ-Sni-Phe-leu-Leu-Tap(Ae)-Nml-Asp-Arg-Che	JAL-1681	497	1278	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Che	JAL-1682	498	1235	A
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Arg-Che	JAL-1729	506	1218	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Val-Arg-Che	JAL-1730	507	1219	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Ser-Arg-Che	JAL-1752	510	1209	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Thr-Arg-Che	JAL-1753	511	1223	A
(AR-314-87)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1765-2	516	1279	A
(AR-314-102)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1774	517	1239	A

Structure	JAL	SEQ ID NO:	$(M+H)^+$ in MS [amu]	Activity (group)
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Che	JAL-1776	518	1265	A
Occ-Sni-Phe-lys(Me2)-Leu-Hyp-Nml-Asp-Arg-Che	JAL-1777	519	1279	A
Occ-Sni-Phe-lys(Me2)-Leu-Hyp-Nml-Val-Arg-Che	JAL-1779	521	1263	A
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Val-Arg-Ile-NH_2	JAL-1782	523	1266	A
Occ-Sni-Phe-dab(Me2)-Leu-Hyp-Nml-Val-Arg-Che	JAL-1784	525	1235	A
Occ-Sni-Phe-dab(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1785	526	1268	A
H-Adx-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1808	538	1413	A
Oct-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Che	JAL-1843	541	1221	A
Occ-Sni-Phe-orn(Me2)-Leu-Tap-Nml-Val-Arg-Che	JAL-1850	548	1248	A
Occ-Sni-Phe-(AR-385-12)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1877	559	1294	A
Occ-Sni-Phe-Egg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1890	572	1294	A
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Thr-Arg-Che	JAL-1895	576	1251	A
H-Lys-Pro-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2	JAL-1900	581	1493	A
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Thr-Arg-Ile-NH_2	JAL-1932	601	1239	A
Occ-Sni-Phe-orn(Me2)-Leu-Tap-Nml-Asp-Arg-Ile-NH_2	JAL-1936	603	1281	A

B. Diseases to be Treated and/or Prevented

The present invention is also directed to methods of treating or preventing diseases in a subject that involve administering to the subject a therapeutically effective amount of a composition that includes one or more NPR-B agonists as described herein, wherein the disease is one of the following. The subject may be a mammal, such as a human, a primate, a cow, a horse, a dog, a cat, a mouse, or a rat. In particular embodiments, the subject is a human.

1. Definitions

"Treatment" and "treating" refer to administration or application of a drug to a subject or performance of a procedure or modality on a subject for the purpose of obtaining a therapeutic benefit of a disease or health-related condition. The term "therapeutic benefit" used throughout this application refers to anything that promotes or enhances the well-being of the subject with respect to the medical treatment of his condition. This includes, but is not limited to, a reduction in the frequency or severity of the signs or symptoms of a disease. Therapeutic benefit also includes reducing the signs or symptoms associated with glaucoma in a subject with glaucoma. For example, a therapeutic benefit in a patient with glaucoma is obtained where there is no further progression of visual field loss in the affected eye, or a slowing of the rate of progression of visual field loss in the affected eye, or an improvement in vision.

A "disease" or "health-related condition" can be any pathological condition of a body part, an organ, or a system resulting from any cause, such as infection, trauma, genetic defect, age-related deterioration of bodily functions, and/or environmental stress. The cause may or may not be known. Examples of diseases include glaucoma, retinopathies, ocular trauma, and optic neuropathies. Thus, one of skill in the art realizes that a treatment may improve the disease condition, but may not be a complete cure for the disease.

The terms "prevention" and "preventing" are used herein according to their ordinary and plain meaning to mean "acting before" or such an act. In the context of a particular disease or health-related condition, those terms refer to administration or application of an agent, drug, or remedy to a subject or performance of a procedure or modality on a subject for the purpose of blocking or minimizing the onset of a disease or health-related condition. For example, an individual with an eye that is at risk of developing glaucoma (such as an individual with ocular hypertension) can be treated with a NPR-B agonist as set forth herein for the purpose of blocking or minimizing the onset of the signs or symptoms of glaucoma (*i.e.*, prevention of glaucoma). In a specific embodiment, prevention pertains to lowering elevated intraocular pressure, blocking detectable optic nerve damage as a result of glaucoma in a subject, reducing the rate of vision loss in a subject, or halting loss of vision in a subject. The subject can be a subject who is known or suspected of being free of a particular disease or health-related condition at the time the relevant preventive agent is administered. The

subject, for example, can be a subject with no known disease or health-related condition (*i.e.*, a healthy subject). In some embodiments, the subject had a previous disease that has been treated in the past and is now known or suspected to be disease-free.

For those skilled in the art it is easy to understand, that different diseases are summarized under certain terms or generic terms. These summaries are no limitation and each disease can be viewed on its own and can be treated or prevented with the compounds according to the present invention.

2. Glaucoma and Ocular Hypertension

Glaucoma is the second leading cause of blindness world-wide (Thylefors and Negrel 1994, Bull World Health Organ. 72:323-326). Open-angle glaucoma (OAG) and angle closure glaucoma combined represent the second leading cause of blindness worldwide (Quigley and Broman, 2006 Br J Ophthalmol. 90:262-267). Angle-closure glaucoma is more common in the Asian population (Foster et al. 2000, Arch Ophthalmol. 118:1105-11), while open-angle glaucoma is more commonly found in black patients (Leske et al. 2007, Ophthalmic Epidemiol. 14:166-172). Glaucoma is a progressive disease in which the risk of vision loss increases with disease duration. In light of an aging population world-wide, the impact of this blinding disorder can be expected to increase in the future.

The disease state referred to as glaucoma is a family of diseases characterized by a permanent loss of visual function due to irreversible damage to the optic nerve. More specifically, glaucoma results in optic neuropathy leading to the loss of retinal ganglion cell (RGC) function followed by apoptotic cell death and a progressive increase in vision loss. Morphologically or functionally distinct types of glaucoma are typically characterized by elevated intraocular pressure (IOP), which is considered to be an important risk factor of the pathological course of the disease. Disruption of normal aqueous outflow leading to elevated IOP is integral to glaucoma pathophysiology. Ocular hypertension is a condition wherein IOP is elevated but no apparent loss of visual function has occurred; such patients are considered to be at high risk for the eventual development of the visual loss associated with glaucoma. Some patients with glaucomatous field loss have relatively low IOPs. These so called normotension or low tension glaucoma patients can also benefit from agents that lower and control IOP.

Glaucoma is typically identified by changes in IOP, visual field deficits and/or fundus changes at the optic disk. Elevated IOP, found in most glaucoma patients, is a result of morphological and biochemical changes in the trabecular meshwork (TM), an aqueous humor filtering tissue located at the iris-cornea angle of the eye. As glaucoma progresses, there is a loss of TM cells and a buildup of extracellular products which inhibit the normal aqueous humor outflow resulting in IOP elevation. In addition to elevated IOP, other factors, such as genetic defects, may lead to mechanical distortion of the optic nerve head (ONH) ultimately resulting in ONH cupping and loss of RGC and their axons. The exact mechanism of this pathological process is currently unknown. It has been suggested that lowering the IOP of patients diagnosed with glaucoma by at least 20-30% will decrease the progressive worsening of the disease by 50-60% (Quigley 2005 Ophthalmology 112:1642-1643). Without proper diagnosis and treatment, glaucoma can progress to total irreversible blindness.

Initially, most open-angle glaucoma patients are managed with one or more of a wide variety of topical ocular or oral hypotensive medications that act to increase aqueous fluid outflow and/or decrease aqueous fluid production, or with surgical procedures such as laser trabeculoplasty and filtration surgery. Treatment regimens currently available for patients exhibiting elevated IOP, regardless of cause, typically include the topical application, from once daily to multiple times per day, of one or multiple eyedrops or pills containing a small molecule IOP-lowering compound. Also, pills that decrease the amount of aqueous humor created can be given between two and four times daily. Glaucoma medications typically prescribed include cholinergic agonists, adrenergic agonists, beta adrenergic blockers, carbonic anhydrase inhibitors and prostaglandin analogs. Although these classes of medications are effective in controling IOP, each of them has certain limitations in efficacy and untoward effects. For example, beta adrenergic blockers do not lower IOP at night; many glaucoma patients do not respond to a particular drug class; and a majority of glaucoma patients require the use of a combination of drugs. In addition, many of the drugs cause local irritation of the eye, such as burning, stinging, itching, tearing, conjunctival hyperemia, foreign body sensation, blurred vision, and eye pain. Some occasionally induce systemic side effects. Hence, there is a genuine and continuous need for novel and improved glaucoma medications.

"Glaucoma" and "glaucomatous optic neuropathy" and "glaucomatous retinopathy," as used herein, are interchangeable. Glaucoma refers to a disease characterized by the permanent loss of visual function due to irreversible damage to the retinal ganglion cells in the retina and optic nerve. The major risk factor for glaucoma and the related loss of visual function is elevated intraocular pressure. There are different types of glaucoma, including primary open angle glaucoma (POAG), angle closure glaucoma, and congenital/developmental glaucoma.

As used herein, the term "intraocular pressure" or "IOP" refers to the pressure of the content inside the eye. In a normal human eye, IOP is typically in the range of 10 to 21 mm Hg. IOP varies among individuals, for example, it may become elevated due to anatomical problems, inflammation of the eye, as a side-effect from medication or due to genetic factors. "Elevated" intraocular pressure is currently considered to be $\geq$ 21 mm Hg, which is also considered to be a major risk factor for the development of glaucoma.

However, some individuals with an elevated IOP may not develop glaucoma and are considered to have ocular hypertension. "Ocular hypertension" as used herein refers to a condition in which the intraocular pressure in the eye of a subject is higher than normal but the optic nerve and visual fields are within normal limits. These individuals may be susceptible to developing the loss of visual function that is typically associated with glaucoma. As used herein, the terms "susceptible," or "susceptibility" refers to an individual or subject that is or at risk of developing optic nerve damage or retinal damage that is associated with elevated intraocular pressure.

Thus, the present invention is directed to methods of treating or preventing an ophthalmic disease in a subject that involve administering to the subject a therapeutically effective amount of a composition that includes one or more NPR-B agonists as described herein, wherein the ophthalmic disease is glaucoma, elevated intraocular pressure or ocular hypertension. The subject may be a mammal, such as a human, a primate, a cow, a horse, a dog, a cat, a mouse, or a rat. In particular embodiments, the subject is a human.

In preferred aspects, the NPR-B agonists of the invention will lower intraocular pressure associated with glaucoma. The glaucoma may be any type of glaucoma, such as primary open angle glaucoma, angle closure glaucoma, normal tension glaucoma, congenital glaucoma, neovascular glaucoma, steroid-induced glaucoma, or glaucoma related to ocular trauma (e.g., ghost cell glaucoma or glaucoma related to choroidal detachment).

The present invention is also directed to methods of lowering intraocular pressure in a subject, comprising administering to the subject a pharmaceutically effective amount of a composition comprising a NPR-B agonist described herein, wherein intraocular pressed is lowered. In particular embodiments, the subject is a human. For example, in specific embodiments, the human is a patient with ocular hypertension or elevated IOP.

3. CNP deficiencies as in diabetes

Diabetic nephropathy is a progressive kidney disease, resulting from longstanding diabetes mellitus. Experimental evidence shows that natriuretic peptides play a pathophysiological role in the glomerular abnormalities seen in diabetes mellitus. BNP overexpression prevented diabetic nephropathy in a streptozotocin-induced mouse model of diabetes (Makino *et al.* 2006, *Diabetologia.* 49:2514-2524). In another study with streptozotocin-induced diabetic rats, cardiac CNP mRNA concentrations were decreased 2.6-fold (Walther *et al.* 2000, *J Mol Endocrinol.* 24:391-395). In a genetic model of diabetes, the non-obese diabetic mouse, mesangial cells derived from diabetic mice showed constitutive overexpression of NPR-C; this was associated with a reduced response of cGMP production to ANP or CNP treatment (Ardaillou *et al.* 1999, *Kidney Int* 55:1293-1302).

4. Conditions with hyperproliferation of vascular smooth muscle cells

The abnormal growth of vascular smooth muscle cells (VSMC) is a common cause of many vascular diseases. A disturbance of the balance between growth inhibitors and growth promoters results in the hyperproliferation of those cells, and vasoactive substances, including natriuretic peptides, seem to play a major role in this process. Early experimental findings indicate that the guanylyl-cyclase-linked natriuretic peptide receptors mediate anti-proliferative activity of the natriuretic peptides on vascular smooth muscle cell growth (Hutchinson *et al.* 1997, *Cardiovasc Res.* 35:158-167). *Ex vivo* experiments showed a direct inhibition of growth in rat VSMCs by CNP (Furuya *et al.* 1991, *Biochem Biophys Res*

Commun. 177:927-931). Furthermore, migration of rat VSMCs could be inhibited by CNP (Ikeda *et al.* 1997, *Arterioscler Thromb Vasc Biol.* 17:731-736). CNP gene transfer resulted in a reduction of the VSMC proliferation in pig femoral arteries *in vivo*, and the effect was even superior over CNP peptide application (Pelisek *et al.* 2006, *J Gene Med.* 8:835-844). In another report, CNP gene transfer resulted in the suppression of vascular remodelling in porcine coronary arteries *in vivo* (Morishige *et al.* 2000, *J Am Coll Cardiol.* 35:1040-1047), thus further strengthening the rationale of using CNP to offset the hyperproliferation of VSMCs.

5. Cardiac pathologies, especially heart failure and hypertrophy

Considerable evidence supports a central pathophysiological role for natriuretic peptides in cardiovascular diseases, and in particular heart failure. The advantage of focusing on CNP in this indication is the unchanged reactivity of NPR-B, while NPR-A activity was shown to be reduced in this condition (Dickey *et al.* 2007, *Endocrinology.* 148:3518-3522, Nakamura *et al.* 1994, *Circulation.* 90:1210-1214). The fact that plasma CNP is elevated in heart failure patients (Del Ry *et al.* 2005, *Eur J Heart Fail.* 7:1145-1148, Del Ry *et al.* 2007, *Peptides.* 28:1068-1073) is interpreted as part of a compensatory vasodilating response in the peripheral vasculature (Del Ry *et al.* 2005, *Eur J Heart Fail.* 7:1145-1148, Wright *et al.* 2004, *Hypertension.* 43:94-100). Traditional treatment of heart failure aims at the support of cardiac function by preventing cardiomyocyte loss and hypertrophy. CNP is able to support cardiac function via a positive effect on the vitality of cardiomyocytes (Rosenkranz et al. 2003, Cardiovasc Res. 57:515-522, Tokudome et al. 2004, Endocrinology. 145:2131-2140). Also, CNP reduced cardiac fibrosis (Horio et al. 2003, Endocrinology. 144:2279-2284), the effect being stronger than that by ANP or BNP. Results from studies on dogs showed a potential inotropic effect of CNP (Beaulieu et al. 1997, Am J Physiol. 273:H1933-1940), supporting the potential of CNP to treat heart failure.

Hypertrophy of the heart is an enlargement of the organ, due to an increase in the volume of its muscular fibres. Experimental evidence suggests that CNP exhibits important autocrine and paracrine functions within the heart and the coronary circulation (D'Souza et al. 2004, Pharmacol Ther. 101:113-129). In vivo administration of CNP has been shown to improve cardiac function and attenuate cardiac remodelling after myocardial infarction in rats (Soeki et al. 2005, J Am Coll Cardiol 45:608-616). Another recent study shows that CNP is able to reduce reactive hypertrophy of cardiomyocytes after an experimental myocardial

infarction in transgenic mice over-expressing CNP in cardiomyocytes (Wang *et al.* 2007, *Eur J Heart Fail.* 9:548-557).

6. Cardiovascular pathologies, especially atherosclerosis, hypertension, endothelial dysfunction and thrombotic events

Atherosclerosis is a chronic inflammatory response in the walls of arterial blood vessels. In vitro evidence suggests that CNP has an inhibitory role in vascular smooth muscle cell proliferation and migration (Furuya et al. 1991, Biochem Biophys Res Commun. 177:927-931, Shinomiya et al. 1994, Biochem Biophys Res Commun. 205:1051-1056). Type-C natriuretic peptide inhibited neointimal thickening in injured arteries of rabbits and rats in vivo (Furuya et al. 1995, Ann N Y Acad Sci. 748:517-523, Ueno et al. 1997, Circulation. 96:2272-2279). In an experimental model of atherosclerosis in rabbits, local infusion of CNP resulted in the preservation of endothelial function and the prevention of neointimal thickening, which normally results from endothelial injury (Gaspari et al. 2000, Clin Exp Pharmacol Physiol. 27:653-655).

Pulmonary hypertension is a progressive disease, characterized by an elevated pressure in the pulmonary arterial system. Common treatment is the use of vasodilatory substances. The ability of CNP to relax arteries, possibly via direct interaction with the VSMCs, has been show before in isolated pig coronary arteries (Marton et al. 2005, Vascul Pharmacol. 43:207-212). More specifically, CNP was able to ameliorate monocrotaline-induced pulmonary hypertension in rats and improved survival (Itoh et al. 2004, Am J Respir Crit Care Med. 170:1204-1211), even if treatment with CNP started 3 weeks after the onset of symptoms.

Endothelial dysfunction plays a fundamental role in the development of atherosclerosis and restenosis. In a rabbit model with features similar to those of the early stage of atherosclerosis or restenosis, chronic peri-arterial administration of ANP or CNP prevented endothelial dysfunction and development of neointima (Gaspari et al. 2000, Clin Exp Pharmacol Physiol. 27:653-655, Barber et al. 2005, J Vasc Res. 42:101-110).

Prevention of thrombotic events is critical to the management of cardiovascular diseases. The anti-thrombotic effect of CNP is well known (Ahluwalia et al. 2004, Basic Res Cardiol. 99:83-89). Thrombus formation was significantly suppressed in the presence of CNP in antilogous rabbit jugular vein grafts (Ohno et al. 2002, Circulation. 105:1623-1626). In a

model of balloon-injured rabbit carotid arteries CNP was shown to exert anti-thrombotic activity, probably via an increase in the NO production by enhancing the expression of inducible NO synthase (Qian *et al.* 2002, *Circ Res* 91:1063-1069).

7. Stimulation of arteriogenesis

Arteriogenesis refers to the growth of collateral arterioles into functional collateral arteries, and is linked to elevated blood pressure, and elevated flow, causing shear stress against the wall of the arterioles. The stimulation of this event presents a strategy to treat arterial occlusive diseases (van Royen *et al.* 2001, *Cardiovasc Res.* 49:543-553). A beneficial effect of ANP on coronary collateral blood flow has been shown earlier (Kyriakides *et al.* 1998, *Clin Cardiol.* 21:737-742).

8. Inflammation, especially reduction of inflammatory mediators, e.g. TNF-alpha, other cytokines or any kind of inflammatory mediator

Several publications suggest a role of CNP in the modulation of inflammatory responses: in a model of balloon-injured rabbit carotid arteries, *in vivo* expression of CNP lowered the expression of the inflammatory marker ICAM-1, and reduced the infiltration of macrophages, supposedly via enhancement of NO generation (Qian *et al.* 2002, *Circ Res* 91:1063-1069). In another study, in rat aortic smooth muscle cells *in vitro*, CNP augmented the transcriptional activation of iNOS induced by inflammatory cytokines (interleukin-1 and tumour necrosis factor-α) and hence the production of NO (Marumo *et al.* 1995, *Endocrinology.* 136:2135-2142). CNP infusion in rats with an acute experimental myocarditis led to a reduction of CD68-positive inflammatory cell infiltration, and lowered myocardial and serum levels of monocyte chemoattractant protein-1 (Obata *et al.* 2007, *Biochem Biophys Res Commun.* 356:60-66). By selectively attenuating the expression of P-selectin, CNP suppressed leukocyte rolling induced by IL-1β or histamine in a rapid, reversible, and concentration-dependent manner in mice (Scotland *et al.* 2005, *Proc Natl Acad Sci U S A.* 102:14452-14457). In a model of bleomycin-induced pulmonary fibrosis in mice, infusion of CNP markedly reduced bronchoalveolar lavage fluid IL-1β levels (Murakami *et al.* 2004, *Am J Physiol Lung Cell Mol Physiol.* 287:L1172-1177).

9. Pathological leukocyte adhesion to endothelium and diapedesis into tissue

In mouse mesenteric postcapillary venules *in vivo* in animals with high basal leukocyte activation (endothelial nitric oxide synthase knockout mice) or under acute inflammatory conditions (induced by IL-1β or histamine), CNP suppressed basal leukocyte rolling in a rapid, reversible, and concentration-dependent manner. CNP was also able to inhibit platelet-leukocyte interactions (Scotland *et al.* 2005, *Proc Natl Acad Sci U S A.* 102:14452-14457). In a model of bleomycin-induced pulmonary fibrosis in mice, infusion of CNP for 14 days significantly inhibited infiltration of macrophages into the alveolar and interstitial regions (Murakami *et al.* 2004, *Am J Physiol Lung Cell Mol Physiol.* 287:L1172-1177). CNP is also known to lower the expression of cell adhesion molecules such as ICAM-1 (Qian *et al.* 2002, *Circ Res* 91:1063-1069), and P-Selectin (Scotland *et al.* 2005, *Proc Natl Acad Sci U S A.* 102:14452-14457), further strengthening its role in adhesion molecule modulation.

10. Kidney disease, especially renal insufficiency, renal failure due to reduced renal perfusion, glomerulonephritis and kidney fibrosis

Local CNP production and CNP receptor expression have previously been demonstrated in glomeruli (Terada et al. 1994, Am J Physiol. 267:F215-222, Lohe et al. 1995, J Am Soc Nephrol. 6:1552-1558, Mattingly et al. 1994, Kidney Int. 46:744-747, Dean et al. 1994, Am J Physiol. 266:F491-496), in kidney cells (Zhao et al. 1994, Kidney Int. 46:717-725) and in mesangial cells (Suga et al. 1992, Hypertension. 19:762-765), suggesting a role in kidney physiology. In several conditions CNP levels in plasma or urine are altered. CNP in plasma and urine was increased in nephrotic syndrome (Cataliotti et al. 2002, Am J Physiol Renal Physiol 283:F464-472), CNP was increased in urine in cirrhosis with renal impairment (Gulberg et al. 2000, Gut. 47:852-857), renal and urine levels of CNP were increased in experimental diabetes (Shin et al. 1998, J Endocrinol. 158:35-42), and NP levels were elevated in chronic kidney disease, but decreased after hemodialysis or transplantation (Horl 2005, J Investig Med 53:366-370).

The benefit from using CNP in indications such as renal insufficiency, and renal failure, comes from its ability to relax smooth muscles in conduit arteries (Drewett et al. 1995, J Biol Chem. 270:4668-4674, Madhani et al. 2003, Br J Pharmacol. 139:1289-1296), venodilation (Chen and Burnett 1998, J Cardiovasc Pharmacol. 32 Suppl 3:S22-28, Wei et al.

1993, J Clin Invest. 92:2048-2052), and dilation of both, afferent and efferent arterioles in glomeruli, as shown in the hydronephrotic rat kidney (Endlich and Steinhausen 1997, Kidney Int. 52:202-207).

Glomerulopathies like glomerulonephritis are typically associated with mesangial cell proliferation, and leukocyte infiltration (Buschhausen et al. 2001, Cardiovasc Res. 51:463-469). The inhibitory effect of CNP on leukocyte infiltration via downregulation of ICAM-1 has been shown before (Qian et al. 2002, Circ Res 91:1063-1069, Buschhausen et al. 2001, Cardiovasc Res. 51:463-469). In addition, all NPs show anti-proliferative effects on mesangial cells in vitro on rat cells (Suganami et al. 2001, J Am Soc Nephrol 12:2652-2663). In vivo, CNP infusion improved immune mediated glomerulonephritis in a rat mesangioproliferative anti-Thy 1.1 model (Canaan-Kuhl et al. 1998, Kidney Int 53:1143-1151). In yet another study CNP inhibited glomerular mesangial cell proliferation, MCP-1 secretion, and reduced collagen IV production from mesangial cells (Osawa et al. 2000, Nephron. 86:467-472).

The inhibitory effect of CNP on the proliferation of glomerular mesangial cells (Suganami *et al.* 2001, *J Am Soc Nephrol* 12:2652-2663, Canaan-Kuhl *et al.* 1998, *Kidney Int* 53:1143-1151, Osawa *et al.* 2000, *Nephron.* 86:467-472) suggests its use in the treatment of kidney fibrosis.

11. Liver diseases, especially portal vein hypertension, liver cirrhosis, liver ascites, liver fibrosis and hepatorenal syndrome

Evidence for a local natriuretic peptide system in the human liver comes from mRNA analysis; specific transcripts for all three NPRs, namely NPR-A, NPR-B, and NPR-C, could be detected, along with mRNA for ANP and CNP, but not BNP (Vollmar et al. 1997, Gut. 40:145-150). During chronic liver diseases, hepatic stellate cells, believed to play a role in the pathogenesis of liver fibrosis and portal hypertension (Friedman 1993, N Engl J Med. 328:1828-1835), acquire a myofibroblastic phenotype, proliferate, and synthetize components associated with fibrosis. Activation of NPR-B by CNP in myofibroblastic hepatic stellate cells was shown to inhibit both growth and contraction (Tao et al. 1999, J Biol Chem. 274:23761-23769), suggesting that during chronic liver diseases, CNP may counteract both liver fibrogenesis and associated portal hypertension.

Liver cirrhosis is the result of a chronic liver disease characterized by replacement of liver tissue by fibrous scar tissue. The presence of CNP in the human kidney and urine (Mattingly et al. 1994, Kidney Int. 46:744-747) suggests a role for CNP in fluid and electrolyte homeostasis, and thus possibly a role in renal function disturbances in patients with cirrhosis of the liver. CNP in the urine of cirrhotic patients with impaired renal function was increased, while plasma levels were normal (Gulberg et al. 2000, Gut. 47:852-857). In cirrhotic patients, ANP infusion reduced the portal pressure and increased the hepatic blood flow, indicative of a lowering of intra-hepatic resistance to portal flow (Brenard et al. 1992, J Hepatol. 14:347-356). Administration of pharmacological doses of CNP to cirrhotic rats significantly decreased portal pressure and peripheral vascular resistance, and increased cardiac output (Komeichi et al. 1995, J Hepatol. 22:319-325).

Many disorders can cause ascites, but cirrhosis is the most common. Hence, treatment of disorders such as liver cirrhosis will eventually help in the avoidance of ascites.

According to the vasodilation theory, the hepatorenal syndrome is the result of the effect of vasoconstrictor systems acting on the renal circulation. Due to this increased activity of the vasoconstrictor systems, renal perfusion and glomerular filtration rate are markedly reduced, while tubular function is preserved. Any substance that increases renal perfusion and/or glomerular filtration rate is thus suited to be used against the hepatorenal syndrome.

12. Lung diseases, especially pulmonary hypertension, asthma and pulmonary fibrosis

CNP was shown to be locally synthesized in pulmonary tissues and therefore might have action on airway patency (Suga et al. 1992, Circ Res. 71:34-39). In vitro CNP was one order of magnitude more potent than ANP in cGMP production in cultured aortic smooth muscle cells.

Pulmonary hypertension is a progressive disease, characterized by an elevated pressure in the pulmonary arterial system. Common treatment is the use of vasodilatory substances. The ability to relax arteries, probably via direct interaction with the VSMCs, has been shown before in isolated pig coronary arteries (Marton et al. 2005, Vascul Pharmacol. 43:207-212). More specifically, CNP was able to ameliorate monocrotaline-induced pulmonary hypertension in rats and to improve survival (Itoh et al. 2004, Am J Respir Crit

Care Med. 170:1204-1211), even if treatment with CNP started 3 weeks after the onset of symptoms.

In an ovalbumin-induced asthmatic guinea pig model CNP was able to significantly inhibit the bronchoconstriction and microvascular leakage in a dose-dependent manner (Ohbayashi et al. 1998, Eur J Pharmacol. 346:55-64). In vivo in asthmatics Fluge et al. could demonstrate dose-dependent bronchodilating properties of intravenous natriuretic peptide (Fluge et al. 1995, Regul Pept. 59:357-370).

In a model of bleomycin-induced pulmonary fibrosis in mice, infusion of CNP markedly attenuated the fibrosis, as indicated by significant decreases in Ashcroft score and lung hydroxyproline content (Murakami *et al.* 2004, *Am J Physiol Lung Cell Mol Physiol.* 287:L1172-1177). Immunohistochemistry on lung sections revealed a significantly reduced infiltration of macrophages into the alveolar and interstitial regions. The markedly decreased number of Ki-67-positive cells in fibrotic lesions of the lung further supports the notion of CNP's anti-proliferative effects on pulmonary fibrosis.

13. Male and female fertility problems, especially erectile dysfunction, stimulation of male fertility and stimulation of female fertility

Penile erection depends on relaxation of the smooth muscle of the corpus cavernosum, one of the sponge-like regions of erectile tissue. The presence of NPR-B in rat and rabbit cavernosal membrane was shown by Kim et al. (Kim et al. 1998, J Urol. 159:1741-1746). They also showed that CNP could trigger the production of cGMP in this tissue, and that CNP was much more potent than BNP and ANP in doing so. NPR-B was also shown to be located in the human corpus cavernosum penis; in organ bath studies with corpus cavernosum muscle strips CNP at concentrations of 0.1 nM to 1 μM led to smooth muscle relaxation from 5% to 40% (Kuthe et al. 2003, J Urol. 169:1918-1922); further support for a role of CNP in erectile dysfunction comes from a recent study, showing that CNP levels are associated with the presence, severity, and duration of erectile dysfunction (Vlachopoulos et al. 2008, Eur Urol. in press).

The rationale for using CNP to stimulate male fertility is based on its potential function in testicular blood supply, the modulation of germ cell development and spermatozoan motility, and its role in penile erection (as described above). CNP has been found in seminal plasma of several species (Hosang and Scheit 1994, DNA Cell Biol. 13:409-

417, Chrisman et al. 1993, J Biol Chem. 268:3698-3703); human Leydig cells, located adjacent to the seminiferous tubules in the testicle, contain both, CNP and the NPR-B receptor (Middendorff et al. 1996, J Clin Endocrinol Metab. 81:4324-4328). CNP was able to increase testosterone levels in vitro in purified mouse Leydig cells (Khurana and Pandey 1993, Endocrinology. 133:2141-2149), as well as in vivo in the spermatic vein in men (Foresta et al. 1991, J Clin Endocrinol Metab. 72:392-395). Because testosterone activates the initiation, processing and maintenance of spermatogenesis, CNP has thus an immediate influence on spermatogenesis. Local injection of natriuretic peptides in vivo in rats caused a dose-related increase in testicular blood flow (Collin et al. 1997, Int J Androl. 20:55-60).

A function of CNP in fertilization, pregnancy and embryonic development was first proposed after the detection of CNP in porcine seminal plasma (Chrisman et al. 1993, J Biol Chem. 268:3698-3703). Further studies showed expression of NPR-A and -B receptors in human placenta (Itoh et al. 1994, Biochem Biophys Res Commun. 203:602-607), and their modulation in rat ovary and uterus by the estrous cycle (Huang et al. 1996, Am J Physiol. 271:H1565-1575, Dos Reis et al. 1995, Endocrinology. 136:4247-4253, Noubani et al. 2000, Endocrinology. 141:551-559). In mice, uterine CNP mRNA concentrations increased during pregnancy, whereas in the ovaries these levels decreased compared to non-pregnant controls (Stepan et al. 2001, Regul Pept. 102:9-13). In human placenta and myometrium CNP is expressed with no dependency on gestational age in the third trimester. Pregnancies with intra-uterine growth retardation showed an opposite regulation of CNP in placenta and myometrium, indicating an organ-specific function of the peptide in human reproductive tissue (Stepan *et al.* 2002, *Fetal Diagn Ther.* 17:37-41). This could be substantiated by studying NPR-B knock-out mice; female mice were infertile due to the failure of the female reproductive tract to develop (Tamura *et al.* 2004, *Proc Natl Acad Sci U S A.* 101:17300-17305).

14. Pre-eclampsia and/or preterm labor

Pre-eclampsia, a hypertensive disorder of pregnancy, is usually associated with raised blood pressure, and affects about 2-8% of pregnancies. Inadequate blood supply to the placenta leads to endothelial dysfunction, eventually resulting in damage to the maternal endothelium and kidney and liver. In severe pre-eclampsia BNP levels are elevated, which might reflect ventricular stress and/or subclinical cardiac dysfunction associated with the condition (Resnik *et al.* 2005, *Am J Obstet Gynecol.* 193:450-454). Pregnancies with intra-

uterine growth retardation or pre-eclampsia showed an opposite regulation of CNP, with a decrease in the placenta and an increase in the myometrium compared with normal pregnancies (Stepan *et al.* 2002, *Fetal Diagn Ther.* 17:37-41), while maternal CNP plasma levels remained constant; this could indicate a compensatory or causative organ-specific function of the peptide in human reproductive tissue under these pathophysiological conditions, suggesting that application of CNP may have benefits.

15. Skeletal growth disturbances, especially decreased body height (dwarfism)

Dwarfism can be caused by over 200 separate medical conditions. C-type natriuretic peptide, acting through its receptor, NPR-B, plays a critical role in longitudinal bone growth (Olney 2006, *Growth Horm IGF Res.* 16 Suppl A:S6-14), as it stimulates endochondrial ossification (Tamura *et al.* 2004, *Proc Natl Acad Sci U S A.* 101:17300-17305, Miyazawa *et al.* 2002, *Endocrinology.* 143:3604-3610). A spontaneous autosomal recessive point mutation in the CNP gene, called long bone abnormality (lbab), causes severe dwarfism in mice (Yoder *et al.* 2008, *Peptides.* 29:1575-1581, Tsuji *et al.* 2008, *Biochem Biophys Res Commun.* 376:186-190). Complete absence of CNP in mice resulted in dwarfism and early death (Chusho *et al.* 2001, *Proc Natl Acad Sci U S A.* 98:4016-4021).

16. Defects of FGF-R (fibroblast derived growth factor receptor) signalling, especially overactivity of FGF-R, or deficiency of CNP or osteocrin, or reduced level of CNP or osteocrin in the growth plates of long bones

In vitro and *ex vivo* studies showed that CNP acts within the growth plate. CNP, most likely synthetised by proliferating chondrocytes (Chusho *et al.* 2001, *Proc Natl Acad Sci U S A.* 98:4016-4021), acts locally to stimulate further proliferation. As opposing element, the FGF/FGFR-3 pathway is known to negatively regulate endochondral ossification via activation of the Erk MAP kinase pathway, thus inhibiting chondrocyte proliferation and cartilage matrix production (Krejci et al. 2005, J Cell Sci. 118:5089-5100). The targeted overexpression of CNP in chondrocytes offset dwarfism in a mouse model of achondroplasia with activated fibroblast growth factor receptor 3 in the cartilage, suggesting a direct interaction of their signaling pathways (Yasoda et al. 2004, Nat Med. 10:80-86). Moreover, Ozasa et al. found that CNP was able to antagonize the activation of the MAPK cascade by FGFs, making the CNP/NPR-B pathway attractive as a novel therapeutic target in the

treatment of achondroplasia (Ozasa et al. 2005, Bone. 36:1056-1064). CNP also partially antagonized the FGF2-induced expression, release and activation of several matrix-remodeling molecules including several matrix metalloproteinases. Independent of FGF signaling, CNP stimulated the upregulation of matrix production (Krejci et al. 2005, J Cell Sci. 118:5089-5100).

Osteocrin is a specific ligand of the natriuretic peptide clearance receptor NPR-C that modulates bone growth (Thomas et al. 2003, J Biol Chem. 278:50563-50571). By blocking the clearance function of NPR-C, it causes the local elevation of CNP levels, resulting in the proliferation of chondrocytes (Moffatt et al. 2007, J Biol Chem. 282:36454-36462).

In summary, there is a strong rationale to use CNP in order to compensate for overactive FGF receptors, and for deficiencies or reduced levels of CNP or osteocrin.

17. Arthritis, especially degenerative diseases of cartilage tissue, osteoarthritis and cartilage degeneration and arthritis in response to traumatic cartilage injury

The rationale for the use of natriuretic peptides for the treatment and/or prevention of arthritic diseases comes from the observation that CNP is involved in the skeletal growth, especially in the generation of cartilage extracellular matrix (Chusho et al. 2001, Proc Natl Acad Sci U S A. 98:4016-4021, Yasoda et al. 2004, Nat Med. 10:80-86), which is able to stabilize damaged cartilage.

CNP depletion was shown to result in impaired bone growth, like that observed in achondroplastic bones, with a similar histological picture of decreased width in both the proliferative and hypertrophic chondrocyte layers of the growth plate (Chusho et al. 2001, Proc Natl Acad Sci U S A. 98:4016-4021). The targeted overexpression of CNP in chondrocytes counteracted dwarfism in a mouse model of achondroplasia with activated fibroblast growth factor receptor 3 in the cartilage. CNP corrected the decreased extracellular matrix synthesis in the growth plate through inhibition of the MAPK pathway of FGF signaling, resulting in the stimulation of glucosaminoglycans and cartilage collagen (type II) synthesis (Yasoda et al. 2004, Nat Med. 10:80-86).

In rat chondrosarcoma chondrocytes, after FGF2-mediated growth arrest, CNP mediated the inhibition of MMP induction, and stimulated extracellular matrix synthesis (Krejci *et al.* 2005, *J Cell Sci.* 118:5089-5100, Ozasa *et al.* 2005, *Bone.* 36:1056-1064), both effects resulting in a net increase in cartilage extracellular matrix (Krejci *et al.* 2005, *J Cell Sci.* 118:5089-5100).

18. Tissue engineering and cartilage regeneration, especially for the ex vivo expansion of cartilage cells to a cell number sufficient to transplant cells back into a patient

CNP has stimulatory activity on glucosaminoglycan and cartilage collagen (type II) synthesis in chondrocytes (Krejci *et al.* 2005, *J Cell Sci.* 118:5089-5100, Yasoda *et al.* 2004, *Nat Med.* 10:80-86), a feature that is beneficial for *in vivo* regeneration of cartilage. To produce *ex vivo* tissue from the limited number of cells that can be extracted from an individual for therapeutic purposes, it is also necessary to have a stimulation of cell proliferation. In a key publication, Waldman *et al.* reported, that in high-density 3D cultures low doses of CNP (10 to 100 pM) elicited chondrocyte proliferation of up to 43% increase in cellularity at the highest dose. Higher doses of CNP (10 nM) predominantly stimulated matrix deposition without affecting tissue cellularity (Waldman *et al.* 2008, *Tissue Eng Part A.* 14:441-448). CNP is thus suitable as a modulator of both chondrocyte proliferation and ECM deposition during *in vitro* cartilage growth.

19. Tissue engineering and bone regeneration, especially for the acceleration of bone healing or for the improvement of regenerating bone tissue

The role of the NPR-B/CNP system as an important regulator of bone growth has been established by several publications: NPR-B knock-out mice displayed reduced bone growth (Tamura *et al.* 2004, *Proc Natl Acad Sci U S A.* 101:17300-17305, Pfeifer *et al.* 1996, *Science.* 274:2082-2086); mice with a deletion of the CNP gene also showed reduced bone growth, and this phenotype could be rescued by the overexpression of CNP in chondrocytes (Chusho et al. 2001, Proc Natl Acad Sci U S A. 98:4016-4021); overexpression of BNP in mice resulted in skeletal overgrowth (Suda et al. 1998, Proc Natl Acad Sci U S A. 95:2337-2342). More specifically, CNP was able to promote chondrocyte proliferation and matrix formation (Krejci et al. 2005, J Cell Sci. 118:5089-5100, Ozasa et al. 2005, Bone. 36:1056-

1064). Using an organ culture of fetal mouse tibias, an in vitro model of endochondral ossification, longitudinal bone growth was stimulated by CNP (Yasoda et al. 1998, J Biol Chem. 273:11695-11700).

In summary, the experimental evidence strongly supports the use of CNP in bone regenerating applications.

20. Modulation of neuronal activity, especially for replacement of CNP in its "central nervous function"

The extensive distribution of the NPR-C receptor in the brainstem suggests an involvement of NPR-C in the neuromodulatory effect of natriuretic peptides (Abdelalim *et al.* 2008, *Neuroscience.* 155:192-202), which were shown to evoke a variety of peripheral effects when applied to the brain (Puurunen and Ruskoaho 1987, *Eur J Pharmacol.* 141:493-495, Bianciotti *et al.* 2001, *Regul Pept.* 102:127-133). Intra-cerebroventricular administration of atrial natriuretic peptide in anaesthetized rats, for example, resulted in the stimulation of gastric acid secretion, that was totally abolished by vagotomy, suggesting vagus nerve involvement (Puurunen and Ruskoaho 1987, *Eur J Pharmacol.* 141:493-495). In two studies by Sabbatini *et al.*, the cerebroventricular administration of CNP in rats dose-dependently enhanced the exocrine pancreatic fluid output through the activation of the NPR-C receptor and the vago-vagal reflex (Sabbatini *et al.* 2005, *Eur J Pharmacol.* 524:67-74, Sabbatini *et al.* 2007, *Eur J Pharmacol.* 577:192-202), thus mimicking the effect of endogenous CNP.

21. Cancer, through inhibition of proliferation of tumor cells, especially glioma cells, neuroblastoma cells, adenocarcinoma cells, adenocarcinoma cells in breast pancreas and prostate, melanoma cells and renal carcinoma cells

Several publications have shown the presence of natriuretic peptide receptors on tumor cells, suggesting a potential to affect the proliferation of those cells via application of CNP, as has been shown in a range of other cell types.

Early in vitro data from cultered rat glioma cells demonstrated the presence of receptors on those cells, that showed strongest activation by CNP, i.e. cGMP production (Eguchi et al. 1992, Eur J Pharmacol. 225:79-82). In another cell line, a AtT-20 pituitary tumor cell line, the only natriuretic receptor present on the cell surface was the NPR-B receptor. cGMP production in these AtT-20 cells was stimulated up to 200-fold by CNP (Gilkes et al. 1994, Biochem J. 299 (Pt 2):481-487).

Western immunoblotting identified NPR-A and NPR-C receptors in human colon adenocarcinoma cells. Application of 1 mM ANP to these cells resulted in a decrease of up to 97% in cell number within 24 h, suggesting an anti-proliferative activity (Gower et al. 2005, Int J Gastrointest Cancer. 36:77-87).

CNP caused a 39% decrease in the number of small-cell lung cancer cells at 100 μM. The mechanism of growth inhibition supposedly is based on the inhibition of DNA synthesis, mediated in part by cGMP (Vesely et al. 2005, Eur J Clin Invest. 35:388-398).

In yet another cell type, in human renal carcinoma cells, CNP also decreased the cell number, at a concentration of 100 μM by 10%. This effect was sustained without any proliferation of the cells occurring for three days after treatment with CNP. All three types of natriuretic peptide receptors, NPR-A, NPR-B, and NPR–C, were identified on renal cancer cells (Vesely *et al.* 2006, *Eur J Clin Invest.* 36:810-819).

22. Fibrosis, especially pulmonary fibrosis, renal fibrosis, cardiac fibrosis, hepatic fibrosis or systemic fibrosis/sclerosis

Several studies, investigating fibrotic events in different organ systems, have shown that the application of natriuretic peptides, in particular of CNP, has a beneficial effect on disease progression. A more general effect of CNP-mediated cGMP generation in fibroblasts is the block of the activation of the mitogen-activated protein kinase cascade (Chrisman and Garbers 1999, J Biol Chem. 274:4293-4299), which could be exploited to treat any kind of fibrosis, in particular the multiorgan systemic fibrosis/sclerosis; treatment of single organ fibrosis with CNP is supported by the following data:

In a model of bleomycin-induced pulmonary fibrosis in mice, infusion of CNP markedly reduced bronchoalveolar lavage fluid levels of inflammatory IL-1β, inhibited infiltration of macrophages into the alveolar and interstitial regions, and markedly attenuated the fibrosis, as indicated by significant decreases in Ashcroft score and lung hydroxyproline content (Murakami et al. 2004, Am J Physiol Lung Cell Mol Physiol. 287:L1172-1177).

With regard to kidney fibrosis, it was described that CNP had an inhibitory effect on the proliferation of glomerular mesangial cells (Suganami et al. 2001, J Am Soc Nephrol 12:2652-2663, Canaan-Kuhl et al. 1998, Kidney Int 53:1143-1151, Osawa et al. 2000, Nephron. 86:467-472). In particular, CNP inhibited also MCP-1 secretion, and reduced

collagen IV production from glomerular mesangial cells (Osawa et al. 2000, Nephron. 86:467-472).

Cardiac fibrosis, characterized by the proliferation of interstitial fibroblasts and the biosynthesis of extracellular matrix components in the ventricles of the heart, is a consequence of remodeling processes. Soeki et al. showed that the application of CNP improved cardiac function and protected against cardiac remodeling after myocardial infarct in rats (Soeki et al. 2005, J Am Coll Cardiol 45:608-616). In vitro, in cardiac fibroblasts, CNP had a suppressive effect on fibroblast proliferation and extracellular matrix production, the effect being stronger than by ANP or BNP (Horio et al. 2003, Endocrinology. 144:2279-2284).

During chronic liver diseases, hepatic stellate cells, believed to play a role in the pathogenesis of liver fibrosis and portal hypertension (Friedman 1993, N Engl J Med. 328:1828-1835), acquired a myofibroblastic phenotype, proliferated, and synthesized components associated with fibrosis. The activation of NPR-B by CNP in myofibroblastic hepatic stellate cells was shown to inhibit both growth and contraction (Tao *et al.* 1999, *J Biol Chem.* 274:23761-23769), suggesting that during chronic liver diseases, CNP may counteract fibrogenesis.

C. Pharmaceutical Preparations

Other embodiments of the present invention are directed to pharmaceutical compositions, comprising at least one novel NPR-B agonist described herein, directed to the treatment or prevention of a disease in a subject that is associated with elevated IOP, glaucoma, ocular hypertension, and/or retinal ganglion cell loss.

1. Effective Amount

As used herein, the term "effective amount," or "therapeutically effective amount," refers to an amount of the agent that will activate the function and/or activity of a type B natriuretic peptide receptor. The novel NPR-B agonists described herein lower intraocular pressure or treat ocular hypertension in a patient having elevated IOP or ocular hypertension. Thus, an effective amount is an amount sufficient to detectably and repeatedly ameliorate, reduce, minimize or limit the extent of any disease associated with elevated intraocular pressure or ocular hypertension, such as any of those diseases discussed above.

Treatment and/or prevention methods will involve treating an individual with an effective amount of a composition containing a therapeutically effective amount of at least one NPR-B agonist of the invention. A therapeutically effective amount is described, generally, as that amount that is known to be or suspected to be of benefit in the reduction of the signs or symptoms of a disease. In some embodiments of the present invention, an effective amount is generally an amount that is known or suspected to be of benefit in reducing the signs or symptoms of glaucoma and associated optic nerve or retinal damage in a subject. It is envisioned that the treatment with the NPR-B agonists hereof will stabilize or improve visual function (as measured by visual acuity, visual field, or other method known to those of ordinary skill in the art).

In some embodiments, an effective amount of a NPR-B agonist that may be administered to a subject includes a dose from about 1 microgram/kg/body weight to about 500 microgram/kg/body weight or more per administration, and any range derivable therein.

2. Formulations

Regarding the methods set forth herein, a NPR-B agonist can be formulated in any manner known to those of ordinary skill in the art. In the compositions set forth herein, the concentration of a NPR-B agonist can be any concentration known or suspected by those of ordinary skill in the art to be of benefit in the treatment and/or prevention of ophthalmic disease associated with elevated intraocular pressure or ocular hypertension.

The actual dosage amount of a composition of the present invention administered to a subject can be determined by physical and physiological factors such as body weight, severity of condition, the type of disease being treated, previous or concurrent therapeutic interventions, idiopathy of the patient and on the route of administration. The practitioner responsible for administration will, in any event, determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject.

In certain non-limiting embodiments, the ophthalmic pharmaceutical compositions may comprise, for example, at least about 0.03%, by weight or volume, of an active ingredient. In other embodiments, the active ingredient may comprise between about 0.001% to about 75% of the weight or volume of the unit, or between about 0.01% to about 60%, and any range derivable therein. In more particular embodiments, the pharmaceutical composition may comprise between about 0.03% to about 2.0% by weight or volume, of an

active ingredient. In more particular embodiments, the composition comprises between about 0.05% to about 1.5% by weight or volume of an active ingredient. In further embodiments, the composition comprises between about 0.05% to about 1.2% by weight or volume of an active ingredient.

A dose may be any amount of pharmaceutical composition that is known or suspected to be of therapeutic benefit. For example, a dose may be about 1 microgram/kg/body weight to about 500 microgram/kg/body weight or more per administration, and any range derivable therein. A dose may be repeated as necessary as determined by one of ordinary skill in the art to achieve a desired therapeutic effect. For example, a dose may be repeated once, twice, three times, and so forth. In some embodiments, a dose is administered twice a day, three times a day, four times a day, or more often. In further embodiments, a dose is administered every other day, twice a week, once a month, or at a longer interval.

In certain embodiments of the present invention, the compositions set forth herein can include more than one NPR-B agonist. One of ordinary skill in the art would be familiar with preparing and administering pharmaceutical compositions that include more than one therapeutic agent. In some embodiments, the composition includes one or more additional therapeutic agents that are not NPR-B agonists.

In addition to the NPR-B agonists, the compositions of the present invention optionally comprise one or more excipients. Excipients commonly used in pharmaceutical compositions include, but are not limited to, carriers, tonicity agents, preservatives, chelating agents, buffering agents, surfactants and antioxidants.

A person of ordinary skill will recognize that the compositions of the present invention can include any number of combinations of ingredients (e.g., active agent, polymers, excipients, etc.). It is also contemplated that that the concentrations of these ingredients can vary. In non-limiting aspects, the percentage of each ingredient in the composition can be calculated by weight or volume of the total composition. A person of ordinary skill in the art would understand that the concentrations can vary depending on the addition, substitution, and/or subtraction of ingredients in a given composition.

In some embodiments of the invention, a specific amount of a NPR-B agonist is administered via the compositions described herein.

The phrase "pharmaceutically acceptable carrier" is art-recognized, and refers to, for example, pharmaceutically acceptable materials, compositions or vehicles, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any supplement or composition, or component thereof, from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the supplement and not injurious to the patient.

Any of a variety of carriers may be used in the formulations of the present invention including water, mixtures of water and water-miscible solvents, such as C1-7-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% non-toxic water-soluble polymers, natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid, mixtures of those polymers. The concentration of the carrier is, typically, from 1 to 100000 times the concentration of the active ingredient.

Suitable tonicity-adjusting agents include mannitol, sodium chloride, glycerin, sorbitol and the like. Suitable preservatives include p-hydroxybenzoic acid ester, benzalkonium chloride, benzododecinium bromide, polyquaternium-1 and the like. Suitable chelating agents include sodium edetate and the like. Suitable buffering agents include phosphates, borates, citrates, acetates and the like. Suitable surfactants include ionic and nonionic surfactants, though nonionic surfactants are preferred, such as polysorbates, polyethoxylated castor oil derivatives and oxyethylated tertiary octylphenol formaldehyde polymer (tyloxapol). Suitable antioxidants include sulfites, ascorbates, BHA and BHT. The compositions of the present invention optionally comprise an additional active agent.

In particular embodiments, the compositions are suitable for application to mammalian eyes. For example, for ophthalmic administration, the formulation may be a solution, a suspension, a gel, or an ointment.

In preferred aspects, the compositions that include NPR-B agonists will be formulated for topical application to the eye in aqueous solution in the form of drops. The term "aqueous" typically denotes an aqueous composition wherein the carrier is to an extent of

>50%, more preferably >75% and in particular >90% by weight water. These drops may be delivered from a single dose ampoule which may preferably be sterile and thus rendering bacteriostatic or bacteriocidal components of the formulation unnecessary. Alternatively, the drops may be delivered from a multi-dose bottle which may preferably comprise a device which extracts preservative from the formulation as it is delivered, such devices being known in the art.

In other aspects, components of the invention may be delivered to the eye as a concentrated gel or similar vehicle which forms dissolvable inserts that are placed beneath the eyelids.

The compositions of the present invention may also be formulated as solutions that undergo a phase transition to a gel upon administration to the eye.

In addition to the one or more NPR-B agonists, the compositions of the present invention may contain other ingredients as excipients. For example, the compositions may include one or more pharmaceutically acceptable buffering agents, preservatives (including preservative adjuncts), non-ionic tonicity-adjusting agents, surfactants, solubilizing agents, stabilizing agents, comfort-enhancing agents, polymers, emollients, pH-adjusting agents and/or lubricants.

For topical formulations to the eye, the formulations are preferably isotonic, or slightly hypotonic in order to combat any hypertonicity of tears caused by evaporation and/or disease. The compositions of the present invention generally have an osmolality in the range of 220-320 mOsm/kg, and preferably have an osmolality in the range of 235-260 mOsm/kg. The compositions of the invention have a pH in the range of 5-9, preferably 6.5-7.5, and most preferably 6.9-7.4.

The formulations set forth herein may comprise one or more preservatives. Examples of preservatives include quaternary ammonium compounds, such as benzalkonium chloride or benzoxonium chloride. Other examples of preservatives include alkyl-mercury salts of thiosalicylic acid, such as, for example, thiomersal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate, sodium perborate, sodium chlorite, parabens, such as, for example, methylparaben or propylparaben, alcohols, such as, for example, chlorobutanol,

benzyl alcohol or phenyl ethanol, guanidine derivatives, such as, for example, chlorohexidine or polyhexamethylene biguanide, sodium perborate, or sorbic acid.

In certain embodiments, the NPR-B agonists are formulated in a composition that comprises one or more tear substitutes. A variety of tear substitutes are known in the art and include, but are not limited to: monomeric polyols, such as, glycerol, propylene glycol, and ethylene glycol; polymeric polyols such as polyethylene glycol; cellulose esters such hydroxypropylmethyl cellulose, carboxy methylcellulose sodium and hydroxy propylcellulose; dextrans such as dextran 70; water soluble proteins such as gelatin; vinyl polymers, such as polyvinyl alcohol, polyvinylpyrrolidone, and povidone; and carbomers, such as carbomer 934P, carbomer 941, carbomer 940 and carbomer 974P. The formulation of the present invention may be used with contact lenses or other ophthalmic products.

In some embodiments, the compositions set forth herein have a viscosity of 0.5-10 cps, preferably 0.5-5 cps, and most preferably 1-2 cps. This relatively low viscosity insures that the product is comfortable, does not cause blurring, and is easily processed during manufacturing, transfer and filling operations.

3. Route of Administration

Administration of the compositions of the invention can be by any method known to those of ordinary skill in the art, however, local administration is preferred. It is contemplated that all local routes to the eye may be used including topical, subconjunctival, periocular, retrobulbar, subtenon, intracameral, intravitreal, intraocular, subretinal, juxtascleral and suprachoroidal administration. Systemic or parenteral administration may be feasible including but not limited to intravenous, subcutaneous, intramuscular and oral delivery. The most preferred method of administration will be intravitreal or subtenon injection of solutions or suspensions, or intravitreal or subtenon placement of bioerodible or non-bioerodible devices, or by topical ocular administration of solutions or suspensions, or posterior juxtascleral administration of a gel formulation.

Those of skill in the art, in light of the present disclosure, will appreciate that obvious modifications of the embodiments disclosed herein can be made without departing from the spirit and scope of the invention. All of the embodiments disclosed herein can be made and executed without undue experimentation in light of the present disclosure. The full scope of the invention is set out in the disclosure and equivalent embodiments thereof. The

specification should not be construed to unduly narrow the full scope of protection to which the present invention is entitled.

While a particular embodiment of the invention has been shown and described, numerous variations and alternate embodiments will occur to those skilled in the art. Accordingly, the invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes to the claims that come within the meaning and range of equivalency of the claims are to be embraced within their scope. Further, all published documents, patents, and applications mentioned herein are hereby incorporated by reference, as if presented in their entirety.

D. Secondary Forms of Therapy

In certain embodiments of the present invention, the subject is receiving one or more secondary forms of therapy directed to treatment or prevention of a particular eye disease.

A NPR-B agonist-containing ophthalmic composition of the present invention may be administered along with another agent or therapeutic method. For example, administration of the NPR-B agonist-containing composition of the present invention to a human subject may precede, follow, or be concurrent with other therapies for glaucoma, elevated intraocular pressure or ocular hypertension. In some embodiments, the NPR-B agonist is formulated in the same composition as the secondary form of therapy. In other embodiments, the NPR-B agonist is formulated separately from the secondary form of therapy. One of ordinary skill in the art would be familiar with protocols for administering more than one form of pharmacological therapy to a subject with a disease, and would be familiar with methods of formulating more than one pharmacological agent in the same composition.

Examples of secondary therapeutic agents include, but are not limited to: anti-glaucoma agents, such as beta-blockers including timolol, betaxolol, levobetaxolol, carteolol, miotics including pilocarpine, carbonic anhydrase inhibitors, prostaglandins, seretonergics, muscarinics, dopaminergic agonists, adrenergic agonists including apraclonidine and brimonidine; anti-angiogenesis agents; anti-infective agents including quinolones such as ciprofloxacin, and aminoglycosides such as tobramycin and gentamicin; non-steroidal and steroidal anti-inflammatory agents, such as suprofen, diclofenac, ketorolac, rimexolone and

tetrahydrocortisol; growth factors, such as nerve growth factor (NGF), basic fibroblast growth factor (bFGF), brain-derived neurotrophic factor (BDNF), ciliary neutrophic factor (CNTF); immunosuppressant agents; and anti-allergic agents including olopatadine. Information pertaining to olopatadine formulations can be found in U.S. Patent 6,995,186, U.S. Patent App. Pub. No. 2005/0158387, and U.S. Patent App. Pub. No. 2003/0055102, each of which is hereby specifically incorporated by reference. The ophthalmic drug may be present in the form of a pharmaceutically acceptable salt, such as timolol maleate, brimonidine tartrate or sodium diclofenac.

Other examples of a secondary therapeutic agent include a receptor tyrosine kinase (RTK) inhibitor. Exemplary RTK inhibitors are described in U.S. Patent App. Pub. No. 2006/0189608, and U.S. Patent No. 7,297,709, both of which are hereby specifically incorporated by reference. In preferred embodiments, the receptor tyrosine kinase inhibitor is N-[4-[3-amino-1H-indazol-4-yl]phenyl]-N'-(2-fluoro-5-methylphenyl)urea.

In other particular embodiments, the secondary therapeutic agent is a prostaglandin or a prostaglandin analog. For example, the prostaglandin analog may be latanoprost, bimatoprost, unoprostone or travoprost.

In particular embodiments, the secondary therapeutic agent is a steroid. For example, the steroid may be a glucocorticoid, a progestin, a mineralocorticoid, or a corticosteroid. Exemplary corticosteroids include cortisone, hydrocortisone, prednisone, prednisolone, methylprednisone, triamcinolone, fluoromethalone, dexamethasone, medrysone, betamethasone, loteprednol, fluocinolone, flumethasone, or mometasone. Other examples of steroids include androgens, such as testosterone, methyltestosterone, or danazol. The secondary therapeutic agent may also be a glucocorticoid that is devoid of typical glucocorticoid side-effects, such as a cortisene. Preferred cortisenes for use in the methods of the invention include anecortave acetate and anecortave desacetate. Often steroids are administered as ester, acetal, or ketal prodrugs, many of which are water-insoluble. The secondary therapeutic agents may be directed to treatment or prevention of a single disease, or can be directed to treatment or prevention of two or more diseases.

In addition to pharmacological agents, surgical procedures can be performed in combination with the administration of the NPR-B agonists. One such surgical procedure can include laser trabeculoplasty or trabeculectomy. In laser trabeculoplasty, energy from a laser

is applied to a number of noncontiguous spots in the trabecular meshwork. It is believed that the laser energy stimulates the metabolism of the trabecular cells, and changes the extracellular material in the trabecular meshwork.

Another surgical procedure may include filtering surgery. With filtering surgery, a hole is made in the sclera near the angle. This hole allows the aqueous fluid to leave the eye through an alternate route. The most commonly performed filtering procedure is a trabeculectomy. In a trabeculectomy, a conjunctiva incision is made, the conjunctiva being the transparent tissue that covers the sclera. The conjunctiva is moved aside, exposing the sclera at the limbus. A partial thickness scleral flap is made and dissected half-thickness into the cornea. The anterior chamber is entered beneath the scleral flap and a section of deep sclera and/or trabecular meshwork is excised. The scleral flap is loosely sewn back into place. The conjunctival incision is tightly closed. Post-operatively, the aqueous fluid passes through the hole, beneath the scleral flap which offers some resistance and collects in an elevated space beneath the conjunctiva called a bleb. The fluid then is either absorbed through blood vessels in the conjunctiva or traverses across the conjunctiva into the tear film.

E. Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Material and methods

The materials and methods as well as general methods are further illustrated by the following examples:

Solvents:

Solvents were used in the specified quality without further purification.

Acetonitrile (Gradient grade, J.T. Baker); dichloromethane (for synthesis, VWR); diethylether (for synthesis, VWR); *N*,*N*-dimethylformamide (LAB, VWR); dioxane (for synthesis, Aldrich); methanol (for synthesis, VWR).

Water: Milli-Q Plus, Millipore, demineralized.

Reagents:

The used reagents were purchased from Advanced ChemTech (Bamberg, Germany), Sigma-Aldrich-Fluka (Deisenhofen, Germany), Bachem (Heidelberg, Germany), J.T. Baker (Phillipsburg, USA), Iris Biotech (Marktredwitz, Germany), Lancaster (Griesheim, Germany), VWR (Darmstadt, Germany), NeoMPS (Strasbourg, France), Novabiochem (Bad Soden, Germany, from 2003 on Merck Biosciences, Darmstadt, Germany) und Acros (Geel, Belgium, distributor Fisher Scientific GmbH, Schwerte, Germany), Peptech (Cambridge, MA, USA), Synthetech (Albany, OR, USA), Pharmacore (High Point, NC, USA), Anaspec (San Jose, CA, USA) and used in the specified quality without further purification.

Non-commercially available non-conventional amino acids were prepared according to standard protocols either as building blocks for solid phase synthesis or by derivatization of commercially available amino acids during solid phase synthesis.

If not stated differently, concentrations are given as percent by volume.

Analysis of peptides according to the present invention:

The analyses of peptides were performed with analytical HPLC methods followed by either ESI-MS or MALDI-MS detection. For analytic chromatography a Hewlett Packard 1100-system together with an ESI-MS (Finnigan LCQ ion trap mass spectrometer) was used. Helium was used as impact gas in the ion trap. For chromatographic separation a RP-18-column (Vydac (Merck) at 30°C was used. A binary gradient was applied for all chromatograms (5-95% B, linear, A: 0.1% TFA in water and B: 0.1% TFA in CH3CN). UV detection was at λ = 220 nm.

Analyses by means of HPLC/MS was performed using a linear gradient from 95:5 to 5:95 (A: 0.1% TFA in water and B: 0.1% TFA in acetonitrile), RP columns were from the companies Phenomenex or Waters (Typ Luna C-18, 3 µm, 2.00 x 50 mm, Symmetry C18 Column MV Kit, 5 µm, 4.6 x 250 mm, respectively); For ESI-MS measurements a mass spectrometer ThermoFinnigan Advantage and/or LCQ Classic (both iontrap) was used. For ESI ionization helium served as impact gas in the ion trap. In case of MALDI-MS analyses an Applied Biosystems Voyager RP MALDI mass spectrometer was used with α-Cyano-4-hydroxycinnamic acid as internal calibration matrix.

Purification of peptides with preparative HPLC:

Preparative HPLC separations were performed using Varian PLRP-S (10 µm, 100 Å) columns (150 x 25 mm or 150 x 50 mm) with the following gradient solvents: A: 0.05% TFA in H_2O and B: 0.05% TFA in CH_3CN

Table 4: Abbreviations:

AAV	general procedure
Ac	Acetyl
Acm	Acetamidomethyl
DCM	Dichloromethane
DIC	Diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	Dimethylsulfoxide
eq.	Equivalent(s)
ESI	Electrospray ionisation
Fig.	Figure
Fmoc	9-fluorenylmethyloxycarbonyl
H	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium-hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-hexafluorophosphate
HOBt	1-hydroxybenzotriazole
HPLC	high-pressure liquid chromatography
MALDI	Matrix Assisted Laser Desorption/Ionization
Me	Methyl
min	minute(s)
ml	Milliliter

MS	Mass spectrometry
MW	Molecular weight
NMP	*N*-methylpyrrolidone
Ph	Phenyl
RP	Reversed phase
^{t}Bu	tert-butyl
THF	Tetrahydrofuran
TIPS	Triisopropyl silane
TFA	trifluoroacetic acid
UV	Ultraviolet

EXAMPLE 2

Synthesis of Peptides

Linear peptides were synthesized using the Fmoc-tBu-strategy. The synthesis was done either manually in polypropylene syringes or via an automatic synthesizer (Syro from Multisyntech, Witten or Sophas from Zinsser-Analytic, Frankfurt).

For the preparation of peptides carrying a C-terminal carboxylic acid, the C-terminal amino acid was either attached to a tritylchloride resin (approx. 100 mg resin; loading of reactive groups approx. 1.5 mmol/g; coupling with 0.8 eq. Fmoc-amino acid and 3.0 eq. DIPEA in DCM for 2 h; loading of the first amino acid approx. 0.2-0.4 mmol/g) or to Wang resin (100-200 mg resin; loading of reactive groups approx. 0.6 mmol/g; coupling with 4 eq. Fmoc-amino acid, 4 eq. DIC and 3 eq. NMI in DMF for 3 h; loading of the first amino acid approx. 0.2-0.6 mmol/g).

For the preparation of peptides carrying a C-terminal carboxylic amide, the first amino acid was attached to the resin via Fmoc deprotection of the Fmoc-Rink amide resin (ca. 100 mg resin, ca. 0.5 mmol/g loading; Fmoc deprotection with 20% piperidine in DMF for 20 min) and subsequent coupling of the Fmoc amino acid (reaction with 5 eq. Fmoc

amino acid; 5 eq. HBTU or 5 eq. HATU and 10 eq. DIPEA in NMP for 30-60 min and this step was optionally repeated).

After the coupling of the first amino acid, the synthesis of the peptide was done via a repeated sequence of steps, as necessary, consisting of Fmoc deprotection and coupling of the corresponding Fmoc amino acid or carboxylic acid. For the Fmoc deprotection the resin was treated with 20% piperidine in DMF for 20 min. The coupling of the amino acids was carried out via reaction with 5 eq. of the amino acid, 5 eq. HBTU or 5 eq. HATU and 10 eq. DIPEA in DMF for 30-60 min. Each coupling step was optionally repeated.

For the introduction of the N-terminal acetyl group, the N-terminal free peptide, bound to the resin, was incubated with a solution of 10% acetic acid anhydride and 20% DIPEA in DMF for 20 min. For the introduction of the N-terminal sulfonyl group, the N-terminal free peptide, bound to the resin, was incubated with a solution of 2 eq. of the corresponding sulfonyl chloride and 4 eq. DIPEA in DMF or DCM for 30 min and this treatment was repeated once.

For the cleavage of the peptide from the resin and its side chain protecting groups, a mixture of 95% TFA, 2.5% H2O, 2.5% TIPS or a similar solution was added. Finally the crude peptide was isolated either by evaporation of TFA using a rotary evaporator or by precipitation with the aid of methyl-^{t}butyl-ether at 0°C.

EXAMPLE 3

NPR-A induced production of cyclic GMP in stably transfected cell

To assess the specificity of compounds for NPR activation, human 293-T cells transfected with NPR-A (Potter and Garbers 1992, J Biol Chem. 267:14531-14534) are used in stimulation experiments.

In this homogenous assay, the cells are stimulated in suspension with the test compound and the production of cyclic GMP (cGMP) is determined, from which EC50 values are calculated. ANP, the naturally occurring ligand of NPR-A is used as an internal control and to determine the maximal cGMP production of the cells, which allows the calculation of activation values of the tested compounds relative to ANP.

Preparation of cells: NPR-A transfected 293-T cells are washed once with phosphate buffered saline (PBS) and detached from a 75 cm^2 tissue culture flask by addition of 3 ml of non enzymatic cell dissociation solution (Sigma-Aldrich) and incubation for 10 min. at room temperature. Detached cells are harvested in 20 ml PBS and centrifuged for 10 min at 200xg at room temperature. The cells are resuspended in DMEM/Ham's F12 mix supplemented with 1 mM IBMX (Medium) and adjusted to a density of $1.25x10^5$ cells/ml and incubated for 15 min. at room temperature.

Stimulation of cells: 20 µl of cells ($2.5x10^3$ cells) are added to each well of a 96 well white optical bottom tissue culture plate (Nunc, Germany). 10 µl of compound dilution is added and the cells are stimulated for 25 min. at room temperature. The stimulation is stopped by addition of 20 µl of Lysis buffer (reagent included in cGMP Assay Kit).

Determination of cGMP: The amount of produced cGMP in the cells is determined using HitHunterTM cGMP Assay kit (DiscoveRX) according to manufacturer's instructions.

Dilution of compounds: For EC50 determinations, duplicate wells are stimulated with a serial dilution of a 10 mM DMSO compound stock solution. Dilutions are prepared in Medium supplemented with IBMX (1 mM). The final compound concentration in the assay is in the range from 45 µM to 20 nM. The internal standard compound ANP is used at concentrations ranging from 5 µM to 310 pM.

EXAMPLE 4

NPR-B induced production of cyclic GMP in human glaucoma trabecular meshwork cells (GTM-3)

The potency of compounds to activate NPR-B was evaluated in a functional assay using endogenously NPR-B expressing GTM-3 cells (Pang, Shade et al. 1994). In this assay the dose dependent production of cyclic GMP (cGMP) is determined and EC_{50} values are calculated. The natural occurring ligand for NPR-B, i.e. CNP is used as an internal control and to determine the maximal cGMP production of the cells, which allows the calculation of activation values of the tested compounds relative to CNP.

Preparation of cells: In a 96 well white optical bottom tissue culture plate (Nunc, Germany) $1.5x10^5$ cells/well are seeded in Dulbecco's MEM (DMEM, Biochrom) supplemented with Gentamycin (0.056 mg/ml) and incubated for 18 h with 10 % CO_2 in a humidified atmosphere.

Stimulation of cells: The cell culture medium is aspirated and each well is washed with 200 µl DMEM/Ham's F12 = Medium (Gibco). Then, 200 µl Medium supplemented with 1.5 mM IBMX (3-Isobutyl-1-methyl-Xanthin, Sigma) is added to each well and incubated for 15 min. at room temperature. 25 µl of compound dilution is added and the cells are stimulated for 15 min. at room temperature. The stimulation is stopped by aspiration of the medium and addition of 20 µl of Lysis buffer (reagent included in cGMP Assay Kit).

Determination of cGMP: The amount of produced cGMP in the cells is determined using HitHunter™ cGMP Assay kit (DiscoveRX) according to manufacturer's instructions.

Dilution of compounds: For EC_{50} determinations, duplicate wells are stimulated with a serial dilution of a 10 mM DMSO compound stock solution. Dilutions are prepared in Medium supplemented with IBMX (1.5 mM). Final compound concentrations are in the range from 45 µM to 20 nM. Highly active compounds, e.g. CNP are used for stimulation at concentrations ranging from 5 µM to 6 nM.

EXAMPLE 5

Efficacy in the Rabbit

A single 30 µL drop of a test item formulation was administered to rabbit eyes (n = 8 to 10). Intraocular pressure (IOP) was assessed in each eye at 0 hr, just prior to dosing, and again hourly for up to 4 hr post dose. The efficacy of a given formulation was determined based on the difference between the pretreatment IOP readings at 0 hr and the post treatment readings. A maximum percent reduction in IOP greater than 15% was noted by the "+" symbol. A maximum IOP reduction of less than 15% was assigned the "-" symbol.

Results obtained with novel compounds of the invention in the above-described assays are provided in Table 5, below:

Table 5: In vivo results with novel compounds of the invention according to the methods described in Example 5.

SEQ ID NO:	JAL	STRUCTURE	RIOP dose 300 ug - IOP reduction < 15% + IOP reduction > 15%
3	CNP	CNP	-
81	781^{+}	Occ-ala-ala-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Lle-NH_2;	-
127	955^{++}	Occ-pro-Phe-Gly-Leu-Pro-Nml-Asp-Arg-Ile-NH_2;	-
130	958^{++}	Occ-Sni-Nmf-Gly-Leu-Pro-Nml-Asp-Arg-Ile-NH_2;	-
135	967^{+}	Occ-Sni-Nmf-Gly-Leu-Pro-Leu-Asp-Arg-Ile-NH_2;	-
182	1041^{+}	Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	+
203	1085^{+}	Occ-ala-Nmf-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	+
187	1047^{++}	Occ-ala-Phe-arg-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2;	+
204	1086^{++}	Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	+
183	1042^{+}	Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	-
195	1060^{++}	Occ-ala-Phe-lys-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	+
267	1287	Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	+
274	1295^{+}	Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile-NH_2;	+
355	1400^{+}	Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Val-Arg-Ile- NH_2;	+
292	1325^{+}	Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	+
332	1369^{+}	Oct-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2;	+
372	1429^{++}	Oct-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2;	+
414	1496+	Occ-Sni-Eaa-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	-
421	1512++	Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-Che;	+
425	1555++	Occ-Sni-Phe-Apc-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2;	+
481	1654+	Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Pro-Che;	-
506	1729+	Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Arg-Che;	+
507	1730+	Occ-Sni-Phe-leu-Leu-Hyp-Nml-Val-Arg-Che;	+
269	1289+	Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-	+

SEQ ID NO:	JAL	STRUCTURE	RIOP dose 300 ug - IOP reduction < 15% + IOP reduction > 15%
		Arg-Ile- NH_2	

HCl salt except *TFA; Dose is 300 μg topical ocular unless (##); DB rabbits unless NZA, scores 1-4 (4 = IOP could not be taken); "" indicates hypertensive phase; (n=#R) means # of responders out of 10-12 animals tested; 1% is +susp ++ sol

* * * * *

All of the methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the methods described herein without departing from the concept, spirit, and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope, and concept of the invention as defined by the appended claims.

All references cited herein, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

WHAT IS CLAIMED IS:

1. A compound comprising the amino acid sequence of Formula I:

$$B\text{-}Xaa_1\text{-}Xaa_2\text{-}Xaa_3\text{-}Xaa_4\text{-}Xaa_5\text{-}Xaa_6\text{-}Xaa_7\text{-}Xaa_8\text{-}Xaa_9\text{-}\ Xaa_{10}\text{-}Z \qquad (I)$$

wherein

B is selected from the group consisting of H, R^{b1}-, R^{b2}-C(O)-, R^{b2}-$S(O_2)$-, R^{b3}-Baa-;

Baa is a conventional α-amino acid, a non-conventional α-amino acid or a β-amino acid;

R^{b1} is selected from C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkenyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkyl aryl optionally substituted by $NR^{b4}R^{b5}$, OH, or OR^{b6}; C_1-C_{12} alkynyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; aryl C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkyl C_3-C_8 cyclic alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, aryl, heteroaryl, or heterocyclyl; C_3-C_6 cyclic alkyl C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylthio C_2-C_{10} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylsulfonyl C_1-C_4 alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylsulfoxyl C_1-C_{10} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; CH_3-$(CH_2)_{qb}$ -O-[-CH_2-$(CH_2)_{nb}O]_{mb}$-CH_2-$(CH_2)_{pb}$-, 2-thiazolo optionally substituted by $C_{1\text{-}8}$ alkyl;

qb = 0-3

nb = 1-3

mb = 1-3

pb = 1-3

R^{b2} is selected from C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkenyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6} C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; aryl C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or

heterocyclyl; C_1-C_{12} alkynyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6} C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_{12} alkyl aryl optionally substituted by $NR^{b4}R^{b5}$, OH, or OR^{b6}; C_1-C_{12} alkyl C_3-C_8 cyclic alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_3-C_6 cyclic alkyl C_1-C_{12} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6} C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylthio C_1-C_{10} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylsulfonyl C_1-C_{10} alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl; C_1-C_9 alkylsulfoxyl C_1-C_4 alkyl optionally substituted by $NR^{b4}R^{b5}$, OH, OR^{b6}, C_3-C_8 cyclic alkyl, aryl, heteroaryl, or heterocyclyl, CH_3-$(CH_2)_{qb}$-O-[-CH_2-$(CH_2)_{nb}$O]$_{mb}$-CH_2-$(CH_2)_{pb}$-;

qb = 0-3

nb = 1-3

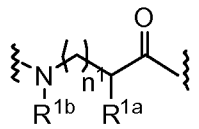
mb = 1-3

pb = 0-3

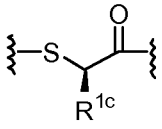
R^{b3} is selected from H, R^{b1}-, R^{b2}-C(O)-, or R^{b2}-S(O_2)-;

R^{b4}, R^{b5} and R^{b6} are, independently, selected from a group consisting of H, or C_1-C_4 alkyl, and

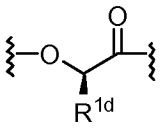
Xaa_1 is selected from the group consisting of a direct bond, a conventional α-amino acid; a non-conventional α-amino acid; a β-amino acid; a γ-amino acid; or a residue of Formula IIa-y:



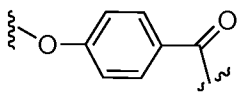
(IIa)



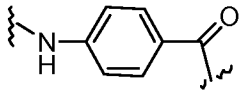
(IIb)



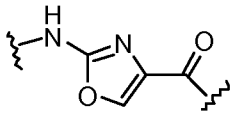
(IIc)



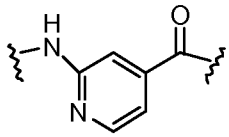
(IId)



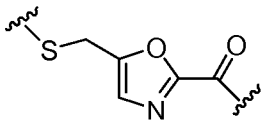
(IIe)



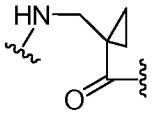
(IIf)



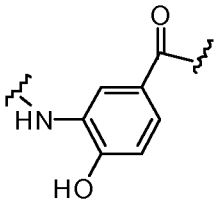
(IIg)



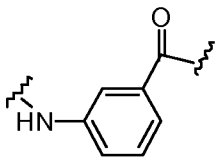
(IIh)



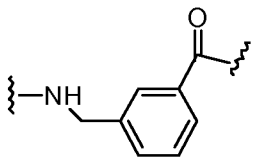
(IIi)



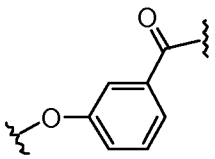
(IIj)



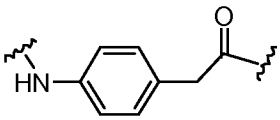
(IIk)



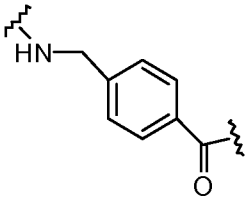
(IIl)



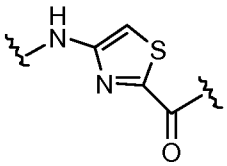
(IIm)



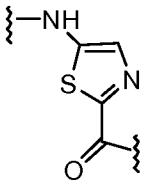
(IIn)



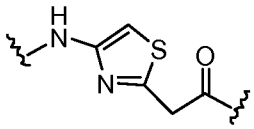
(IIo)



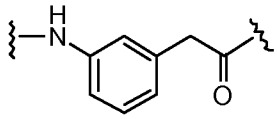
(IIp)



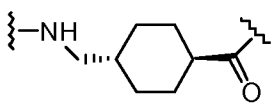
(IIq)



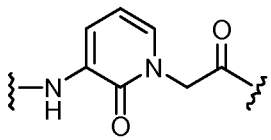
(IIr)



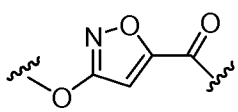
(IIs)



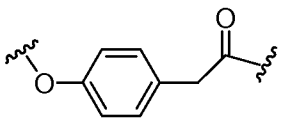
(IIt)



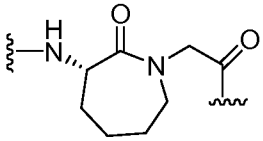
(IIu)



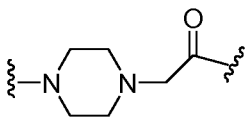
(IIv)



(IIw)



(IIx)



(IIy)

R^{1a} is selected from H, C_1-C_6 alkyl;

R^{1b} is selected from H, C_1-C_6 alkyl optionally substituted by OH, hydroxyC_1-C_6 alkyl optionally substitiuted by OH;

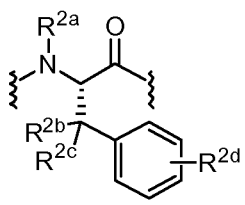
R^{1c} is selected from H, C_1-C_6 alkyl;

R^{1d} is selected from H, C_1-C_6 alkyl;

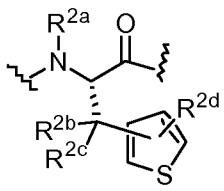
R^{1a} and R^{1b} together may form a heterocyclic ring;

n^1 is 0 to 3;

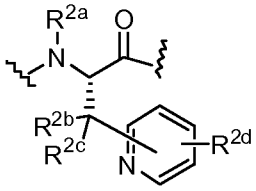
Xaa_2 is an amino acid residue of Formula IIIa-g:



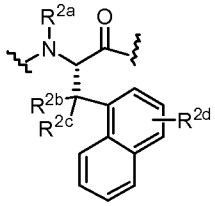
(IIIa)



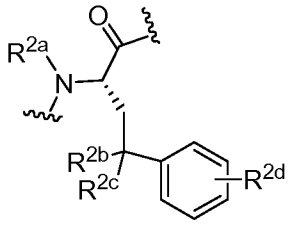
(IIIb)



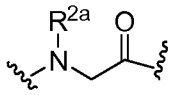
(IIIc)



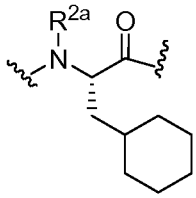
(IIId)



(IIIe)



(IIIf)



(IIIg)

wherein

R^{2a} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, C_1-C_2 alkyl C_3-C_7 cycloalkyl and aryl C_1-C_2 alkyl;

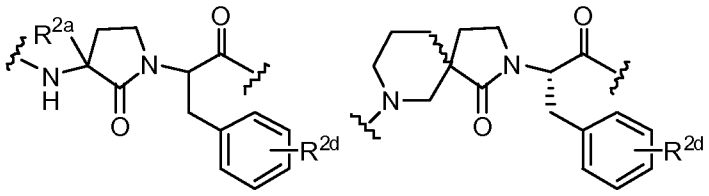
R^{2b} and R^{2c} are, independently, selected from the group consisting of H, methyl, ethyl, propyl; and isopropyl, with the proviso that at least one of R^{2b} and R^{2c} is H;

R^{2d} represents from 0 to 3 substituents, each such substituent being, independently, selected from the group consisting of H, Cl, F, Br, NO_2, NH_2, CN, CF_3, OH, OR^{2e} and C_1-C_4 alkyl;

R^{2a} and R^{2b} or R^{2a} and R^{2c} together may form a heterocyclic ring;

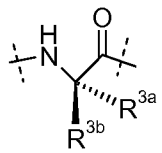
R^{2e} is selected from the group consisting of methyl, ethyl, propyl, and isopropyl; or

Xaa_1 and Xaa_2 together may be selected from an amino acid residue of Formula IVa-b



(IVa) (IVb)

Xaa_3 is selected from the group consisting of Gly, Ala, a conventional D-α-amino acid, a non-conventional D-α-amino acid, and an amino acid residue of Formula Va:



(Va)

wherein R^{3a} is selected from the group consisting of H or C_1-C_4 alkyl;

R^{3b} is selected from the group consisting of H, $-(CH_2)_{n3a}-X^{3a}$;

n3a is 1 to 5;

X^{3a} is selected from the group consisting of H, $NR^{3c}R^{3d}$;

R^{3c} and R^{3d} are independently selected from a group consisting of H, C_1-C_8 alkyl, $-(C=N)-NH_2$ and $-(CH_2)_{n3b}X^{3b}$;

n3b is 1 to 4;

X^{3b} is selected from the group consisting of $NR^{3e}R^{3f}$, C_5-C_6 heteroaryl, C_4-C_7 heterocyclyl, $-NHC(=N)NH_2$;

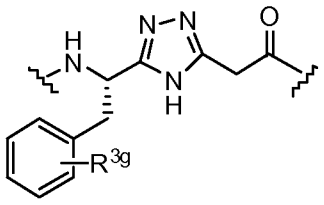
R^{3e} and R^{3f} are independently selected from a group consisting of H, C_1-C_8 alkyl, wherein R^{3e} and R^{3f} can form a cyclic structure;

R^{3a} and R^{3b} can be linked to form a cyclic structure;

or R^{3a} and R^{3b} can be linked with a heteroatom selected from the group consisting of N, O, and S, to form a heterocyclic structure;

or

Xaa_2 and Xaa_3 together may be selected from an amino acid residue of Formula Vb:

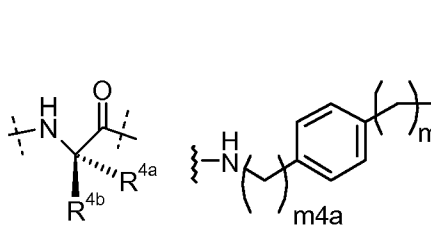


(Vb)

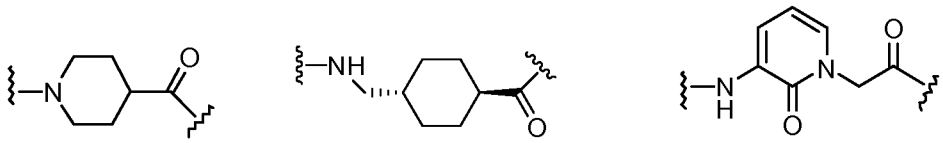
wherein R^{3g} represents from 0 to 3 substituents, each such substituent being, independently, selected from the group consisting of H, Cl, F, Br, NO_2, NH_2, CN; CF_3, OH, OR^{3h} and C_1-C_4 alkyl;

R^{3h} is selected from the group consisting of C_1-C_4 alkyl

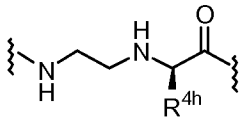
Xaa_4 is an amino acid residue of Formula VIa-h:



(VIa) (VIb) (VIc) (VId)



(VIe) (VIf) (VIg)



(VIh)

wherein R^{4a} is selected from the group consisting of H, C_1-C_8 alkyl which may be substituted with a moiety selected from the group consisting of OH, CO_2R^{4c}, $C(=O)$-NH_2, a 5-6 membered heteroaryl, C_1-C_{10} alkyl, C_5-C_8 cycloalkyl C_1-C_{10} alkyl, and C_5-C_8 cycloalkyl, -$(CH_2)_{n4a}$-X^{4a};

n4a is 1 or 2;

R^{4b} is selected from the group consisting of H and methyl;

R^{4c} is selected from the group consisting of H, and C_1-C_3 alkyl; and

X^{4a} is OH, CO_2R^{4d}, $NR^{4e}R^{4f}$, SR^{4g}, 4-imidazoyl, 4-hydroxyphenyl;

R^{4d}, R^{4e} and R^{4f} independently are selected from the group consisting of H, and C_1-C_3 alkyl;

R^{4g} is selected from the group consisting of C_1-C_3 alkyl;

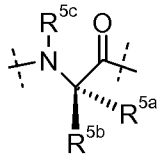
m4a, and m4b are independently selected from 0 or 1;

R^{4h} is C_2-C_6 alkyl;

or

Xaa_3 and Xaa_4 together may be selected from an amino acid residue of Formula VIb-h;

Xaa_5 is an amino acid residue of Formula VII:



(VII)

wherein R^{5a} is $(CH_2)_{n5a}$-X^{5a};

n5a is 1 to 6;

X^{5a} is selected from the group consisting of H, NH_2, and a C_{4-7} amine-containing aliphatic heterocyclic ring;

R^{5b} is selected from the group consisting of H and methyl;

R^{5c} is selected from the group consisting of H and methyl;

and wherein R^{5c} and R^{5a} can combine to form a four to six membered heterocyclic ring or can be linked with a heteroatom selected from the group consisting of N, O, and S to form a monocyclic or bicyclic heterocyclic structure; wherein said heterocyclic ring may have from 0 to 3 substituents, each such substituent being, independently, selected from from the group consisting of OH, OR^{5d}, F, C_1-C_4 alkyl, -NHC(=NH)NH_2, aryl and $NR^{5e}R^{5f}$;

R^{5d} is selected from C_1-C_4 alkyl, C_1-C_4 alkylaryl;

R^{5e} is selected from the group consisting of H, C_1-C_4 alkyl, -$C(=O)(CH_2)_{n5b}$-X^{5b}, -$CH_2(CH_2)_{n5c}$-X^{5b};

R^{5f} is selected from the group consisting of H, C_1-C_4 alkyl, -$CH_2(CH_2)_{n5d}$-X^{5c};

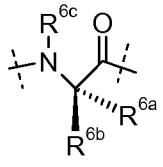
n5b is selected from the group consisting of 1, 2, 3, and 4;

n5c and n5d are independently selected from the group consisting of 2, 3, and 4;

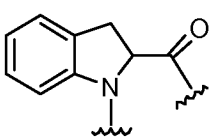
X^{5b} and X^{5c} are independently selected from the group consisting of H, $NR^{5g}R^{5h}$;

R^{5g} and R^{5h} are independently selected from a group consisting of H, C_1-C_4 alkyl;

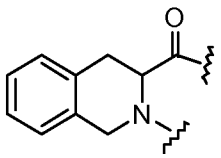
Xaa_6 is an amino acid residue of Formula VIIIa-d:



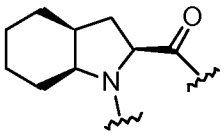
(VIIIa)



(VIIIb)



(VIIIc)



(VIIId)

wherein R^{6a} is selected from the group consisting of C_1-C_8 alkyl, aryl C_1-C_4 alkyl, C_4-C_7 cycloalkyl C_1-C_4 alkyl, C_1-C_4 alkyl S(C_1-C_4alkyl), and C_4-C_7 cycloalkyl, wherein said C_1-C_8 alkyl and C_4-C_7 cycloalkyl may be substituted with a moiety selected from the group consisting of OH, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), and $NR^{6d}R^{6e}$;

R^{6b} is H;

R^{6c} is selected from the group consisting of H, and C_1-C_4alkyl;

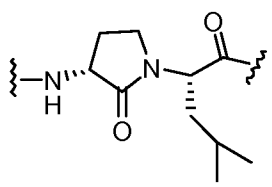
R^{6d}, and R^{6e} are, independently, selected from the group consisting of H, and C_1-C_4 alkyl;

wherein R^{6a} and R^{6c} can form a cyclic structure, which may be substituted with a moiety selected from the group consisting of OH, C_1-C_4 alkyl, NH_2 and F;

or R^{6a} and R^{6c} can be linked with a heteroatom selected from the group consisting of N, O, and S, to form a heterocyclic structure;

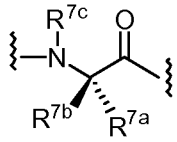
or

Xaa_5 and Xaa_6 together may be an amino acid residue of Formula VIIIe:

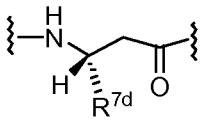


(VIIIe);

Xaa_7 is an amino acid residue of Formula IXa-b:



(IXa)



(IXb)

wherein R^{7a} is selected from the group consisting of C_1-C_4 alkyl, C_3-C_7 cycloalkyl, 2-thienyl, $(CH_2)_{n7a}$-X^{7a}, and C_1-C_4 alkyl substituted with OH;

R^{7b} is H, and 2-thienyl;

R^{7c} is selected from a group consisting of H, and methyl;

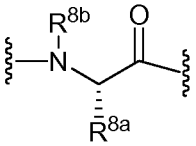
R^{7d} is C_{1-4}alkyl;

n^{7a} is selected from the group consisting of 1 and 2;

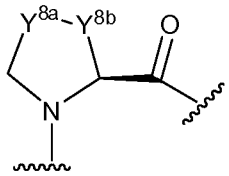
X^{7a} is selected from the group consisting of 2-thienyl, $C(=O)OR^{7e}$, $C(=O)NH_2$, $S(=O)_2OH$, $OS(=O)_2OH$, $B(OH)_2$, $P(=O)(OH)_2$, and $OP(=O)(OH)_2$;

wherein R^{7e} is selected from the group consisting of H, and C_{1-4}alkyl;

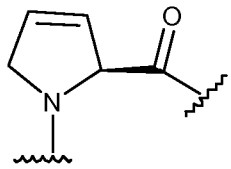
Xaa_8 is an amino acid residue of Formula Xa-g:



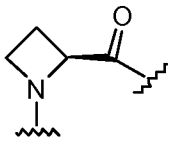
(Xa)



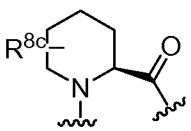
(Xb)



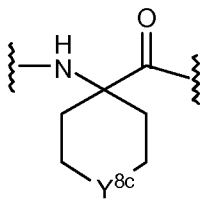
(Xc)



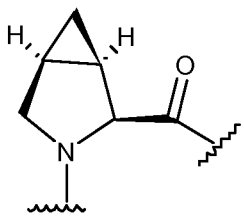
(Xd)



(Xe)



(Xf)



(Xg)

wherein R^{8a} is selected from the group consisting of $(CH_2)_{m8a}$-X^{8a}, and a C_4-C_7 nitrogen-containing aliphatic heterocyclic ring;

m^{8a} = 1-5;

X^{8a} is selected from the group consisting of H, NH_2, and -NHC(=NH)NH_2;

R^{8b} is selected from the group consisting of H and methyl;

R^{8c} is selected from the group consisting of H, NH_2, and OH;

Y^{8a} is selected from the group consisting of $CH(R^{8d})$, and S;

R^{8d} is selected from the group consisting H, aryl, and OH;

Y^{8b} is selected from the group consisting of $CH(R^{8e})$, and NH;

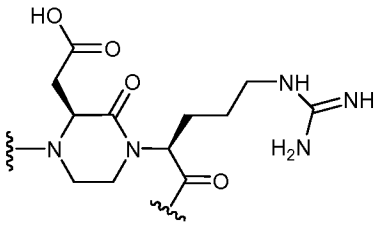
R^{8e} is selected from the group consisting H, NH_2 and OH;

Y^{8c} is selected from the group CH_2 , and NR^{8f};

R^{8f} is selected from the group H, -C(=NH)NH_2, and -C(=O)CH_2NH_2;

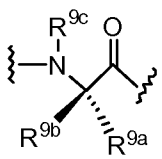
or

Xaa_7 and Xaa_8 together may be an amino acid residue of Formula Xh:

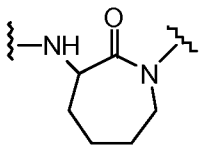


(Xh);

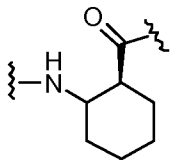
Xaa_9 is selected from the group consisting of a direct bond, and an amino acid residue of Formula XIa-c,



(XIa)



(XIb)



(XIc)

wherein R^{9a} is selected from the group consisting of C_1-C_5 alkyl, and C_4-C_7 cycloalkyl;

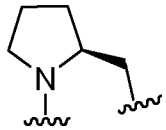
R^{9b} is selected from the group consisting of H, C_1-C_5 alkyl;

and wherein R^{9a} and R^{9b} can form a 5-7 membered cycloalkyl ring;

R^{9c} is selected from the group consisting of H, methyl;

or

Xaa_8 and Xaa_9 together may be a residue of Formula XId:

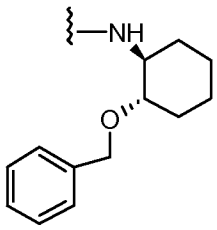


(XId);

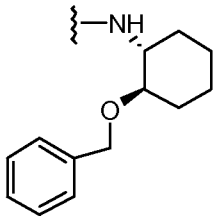
and

Z is selected from the group consisting of H, OR^{11a}, NHR^{11b} a conventional α-amino acid, a non-conventional α-amino acid, a β-amino acid; and a peptide consisting of from 2 to 30 amino acids selected from the group consisting of conventional α-amino acids, non-conventional α-amino acids, and β-amino acids;

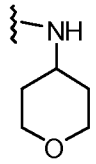
wherein R^{11a} and R^{11b} are independently selected from the group consisting of H, C_1-C_8 alkyl, C_4-C_8 cycloalkyl, C_7-C_{12} bicycloalkyl, C_7-C_{12} cycloalkylaryl, C_1-C_4 alkyl C_4-C_8 cycloalkyl, or a residue of formula XIIa-c:



(XIIa)



(XIIb)



(XIIc).

2. The compound of claim 1, wherein

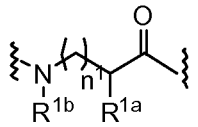
B is selected from the group consisting of R^{b1}-, and R^{b2}-C(O)-;

R^{b1} is selected from the group consisting of C_1-C_{12} alkyl, and C_1-C_{12} alkyl substituted by $NR^{b4}R^{b5}$;

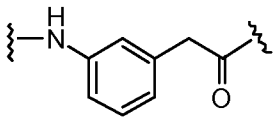
R^{b2} is selected from the group consisting of C_1-C_{12} alkyl, and C_1-C_{12} alkyl substituted by $NR^{b4}R^{b5}$;

R^{b4}, and R^{b5} are, independently, selected from the group consisting of H, and C_1-C_4 alkyl, and

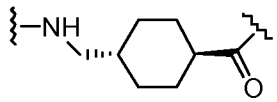
Xaa_1 is selected from the group consisting of a direct bond, a conventional α-amino acid; a non-conventional α-amino acid; a β-amino acid; or a residue selected from the group consisting of Formula IIa, IIs, IIt, IIu, and IIv:



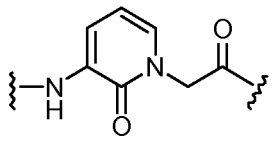
(IIa)



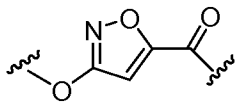
(IIs)



(IIt)



(IIu)



(IIv)

R^{1a} is selected from the group consisting of H, and C_1-C_6 alkyl;

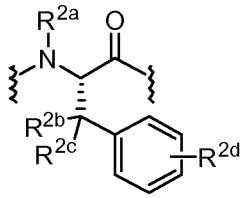
R^{1b} is selected from the group consisting of H, C_1-C_6 alkyl optionally substituted by OH, hydroxyC_1-C_6 alkyl optionally substitiuted by OH;

R^{1c} is selected from the group consisting of H, and C_1-C_6 alkyl;

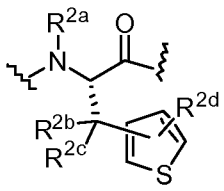
R^{1a} and R^{1b} together may form a heterocyclic ring;

n^1 is 0 to 3; and

Xaa_2 is an amino acid residue selected from the group consisting of Formula IIIa and Formula IIIb:



(IIIa)



(IIIb)

wherein

R^{2a} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, C_1-C_2 alkyl C_3-C_7 cycloalkyl and aryl C_1-C_2 alkyl;

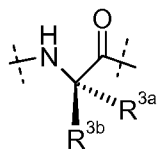
R^{2b} and R^{2c} are, independently, selected from the group consisting of H, methyl, ethyl, propyl, and isopropyl, with the proviso that at least one of R^{2b} and R^{2c} is H;

R^{2d} represents from 0 to 3 substituents, each such substituent being independently selected from the group consisting of H, Cl, F, Br, NO_2, NH_2, CN, CF_3, OH, OR^{2e} and C_1-C_4 alkyl;

R^{2a} and R^{2b} or R^{2a} and R^{2c} together may form a heterocyclic ring;

R^{2e} is selected from the group consisting of methyl, ethyl, propyl, and isopropyl; and

Xaa_3 is an amino acid residue of Formula Va:



(Va)

wherein R^{3a} is selected from the group consisting of H and C_1-C_4 alkyl;

R^{3b} is selected from the group consisting of H, and $-(CH_2)_{n3a}-X^{3a}$;

n3a is 1 to 5;

X^{3a} is selected from the group consisting of H, and $NR^{3c}R^{3d}$;

R^{3c} and R^{3d} are independently selected from the group consisting of H, C_1-C_8 alkyl, $-(C=N)-NH_2$ and $-(CH_2)_{n3b}X^{3b}$;

n3b is 1 to 4;

X^{3b} is selected from the group consisting of $NR^{3e}R^{3f}$, C_5-C_6 heteroaryl, C_4-C_7 heterocyclyl, and -NHC(=N)NH_2;

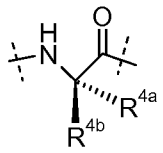
R^{3e} and R^{3f} are independently selected from a group consisting of H, and C_1-C_8 alkyl, wherein R^{3e} and R^{3f} can form a cyclic structure;

R^{3a} and R^{3b} can be linked to form a cyclic structure;

or R^{3a} and R^{3b} can be linked with a heteroatom selected from the group consisting of N, O, and S, to form a heterocyclic structure;

and

Xaa_4 is an amino acid residue of Formula VIa:



(VIa)

wherein R^{4a} is selected from the group consisting of H, and C_1-C_8 alkyl, and C_1-C_8 alkyl substituted with a moiety selected from the group consisting of OH, CO_2R^{4c}, C(=O)-NH_2, a 5-6 membered heteroaryl, C_1-C_{10} alkyl, C_5-C_8 cycloalkyl C_1-C_{10} alkyl, and C_5-C_8 cycloalkyl;

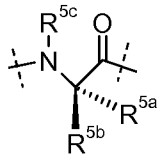
n4a is 1 or 2;

R^{4b} is selected from the group consisting of H and methyl;

R^{4c} is selected from the group consisting of H, and C_1-C_3alkyl; and

and

Xaa_5 is an amino acid residue of Formula VII:



(VII)

wherein R^{5a} is $(CH_2)_{n5a}$-X^{5a};

n5a is 1 to 6;

X^{5a} is selected from the group consisting of H, NH_2, and a C_4-C_7 amine-containing aliphatic heterocyclic ring;

R^{5b} is selected from the group consisting of H and methyl;

R^{5c} is selected from the group consisting of H and methyl;

and wherein R^{5c} and R^{5a} can combine to form a four to six membered heterocyclic ring, wherein said heterocyclic ring may have from 0 to 2 substituents, each such substituent being, independently, selected from from the group consisting of OH, OR^{5d}, F, C_1-C_4 alkyl, -NHC(=NH)NH_2, aryl and $NR^{5e}R^{5f}$;

R^{5d} is selected from the group consisting of C_1-C_4 alkyl, and C_1-C_4 alkylaryl;

R^{5e} is selected from the group consisting of H, C_1-C_4 alkyl, -C(=O)$(CH_2)_{n5b}$-X^{5b}, and -$CH_2(CH_2)_{n5c}$-X^{5b};

R^{5f} is selected from the group consisting of H, C_1-C_4 alkyl, and -$CH_2(CH_2)_{n5d}$-X^{5c};

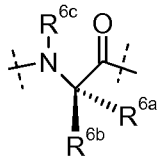
n5b is selected from the group consisting of 1, 2, 3, and 4;

n5c and n5d are independently selected from the group consisting of 2, 3, and 4;

X^{5b} and X^{5c} are independently selected from the group consisting of H, and $NR^{5g}R^{5h}$;

R^{5g} and R^{5h} are independently selected from a group consisting of H, and C_1-C_4 alkyl; and

Xaa_6 is an amino acid residue of Formula VIIIa:



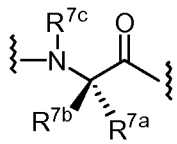
(VIIIa)

wherein R^{6a} is selected from the group consisting of C_1-C_8 alkyl, aryl C_1-C_4 alkyl , C_4-C_7 cycloalkyl C_1-C_4 alkyl, C_1-C_4 alkyl S(C_1-C_4alkyl), C_4-C_7 cycloalkyl, C_1-C_8 alkyl substituted with a moiety selected from the group consisting of OH, O(C_1-C_4 alkyl), and S(C_1-C_4 alkyl); and C_4-C_7 cycloalkyl substituted with a moiety selected from the group consisting of OH, O(C_1-C_4 alkyl), and S(C_1-C_4 alkyl);

R^{6b} is H;

R^{6c} is selected from the group consisting of H, and C_1-C_4alkyl; and

Xaa_7 is an amino acid residue of Formula IXa:



(IXa)

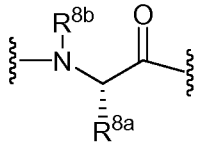
wherein R^{7a} is selected from the group consisting of C_1-C_4 alkyl, C_3-C_7 cycloalkyl, 2-thienyl, and C_1-C_4 alkyl substituted with OH;

R^{7b} is H, and 2-thienyl;

R^{7c} is selected from a group consisting of H, and methyl;

and

Xaa_8 is an amino acid residue of Formula Xa:



(Xa)

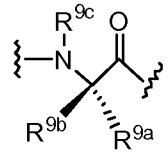
wherein R^{8a} is $(CH_2)_{m8a}$-X^{8a};

m^{8a} = 1-5;

X^{8a} is selected from the group consisting of H, NH_2, and -NHC(=NH)NH_2;

R^{8b} is selected from the group consisting of H and methyl; and

Xaa_9 is selected from the group consisting of a direct bond, and an amino acid residue of Formula XIa,



(XIa)

wherein R^{9a} is selected from the group consisting of C_1-C_5 alkyl, and C_4-C_7 cycloalkyl;

R^{9b} is selected from the group consisting of H, and C_1-C_5 alkyl;

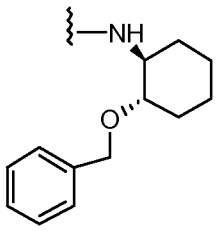
or R^{9a} and R^{9b} can form a 5-7 membered cycloalkyl ring;

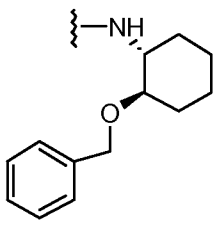
R^{9c} is selected from the group consisting of H, and methyl;

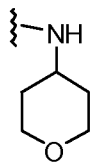
and

Z is NHR^{11b} ;

wherein R^{11b} is selected from the group consisting of H, C_1-C_8 alkyl, C_4-C_8 cycloalkyl, C_7-C_{12} bicycloalkyl, C_7-C_{12} cycloalkylaryl, C_1-C_4 alkyl C_4-C_8 cycloalkyl, a residue of formula XIIa, a residue of formula XIIb, and a residue of formula XIIc


(XIIa)


(XIIb)


(XIIc).

3. The compound of claim 1, wherein

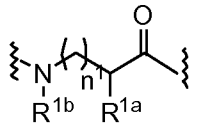
B is selected from the group consisting of R^{b1}-, and R^{b2}-C(O)-;

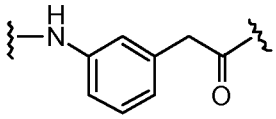
R^{b1} is selected from the group consisting of C_6-C_{10} alkyl and C_6-C_{10} alkyl substituted by $NR^{b4}R^{b5}$;

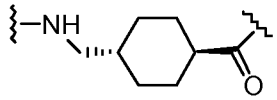
R^{b2} is selected from the group consisting of C_6-C_{10} alkyl and C_6-C_{10} alkyl substituted by $NR^{b4}R^{b5}$;

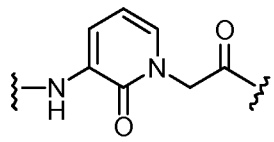
R^{b4}, and R^{b5} are, independently, selected from a group consisting of H, and C_1-C_4 alkyl, and

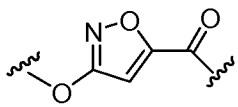
Xaa_1 is selected from the group consisting of a direct bond, a conventional α-amino acid; a non-conventional α-amino acid; a β-amino acid; a residue of Formula IIa, a residue of Formula IIs, a residue of Formula IIt, a residue of Formula IIu, and a residue of Formula IIv


(IIa)


(IIs)


(IIt)


(IIu)


(IIv)

wherein R^{1a} is selected from H, and C_1-C_4 alkyl;

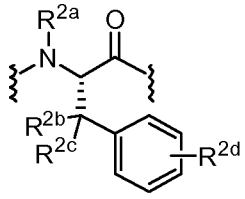
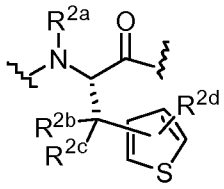
R^{1b} is selected from H, C_1-C_4 alkyl optionally substituted by OH, and hydroxy C_1-C_4 alkyl optionally substitiuted by OH;

R^{1c} is selected from H, C_1-C_6 alkyl;

R^{1a} and R^{1b} together may form a heterocyclic ring;

n^1 is 0 , 1; and

Xaa_2 is an amino acid residue of Formula III:

(IIIa) (IIIb)

wherein

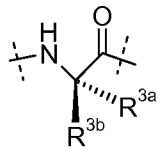
R^{2a} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, C_1-C_2 alkyl C_3-C_7 cycloalkyl and aryl C_1-C_2 alkyl;

R^{2b} and R^{2c} are, independently, selected from the group consisting of H, methyl, ethyl, propyl; and isopropyl, with the proviso that at least one of R^{2b} and R^{2c} is H;

R^{2d} represents from 0 to 3 substituents, each such substituent being, independently, selected from the group consisting of H, Cl, F, Br, CN, CF_3, OH, OR^{2e} and C_1-C_4 alkyl;

R^{2e} is selected from the group consisting of methyl, ethyl, propyl, and isopropyl; and

Xaa_3 is an amino acid residue of Formula Va:



(Va)

wherein R^{3a} is selected from the group consisting of H and C_1-C_4 alkyl;

R^{3b} is selected from the group consisting of H, and $-(CH_2)_{n3a}-X^{3a}$;

n3a is 1 to 5;

X^{3a} is selected from the group consisting of H, and $NR^{3c}R^{3d}$;

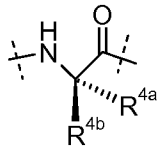
R^{3c} and R^{3d} are independently selected from a group consisting of H, C_1-C_8 alkyl, and $-(C=N)-NH_2$;

R^{3a} and R^{3b} can be linked to form a cyclic structure;

or R^{3a} and R^{3b} can be linked with a heteroatom selected from the group consisting of N, O, and S, to form a heterocyclic structure;

and

Xaa_4 is an amino acid residue of Formula VIa:



(VIa)

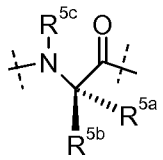
wherein R^{4a} is selected from the group consisting of H, C_1-C_8 alkyl which may be substituted with a moiety selected from the group consisting of OH, and CO_2R^{4c};

R^{4b} is selected from the group consisting of H and methyl;

R^{4c} is selected from the group consisting of H, and C_1-C_3alkyl; and

and

Xaa_5 is an amino acid residue of Formula VII:



(VII)

wherein R^{5a} is $(CH_2)_{n5a}$-X^{5a};

n5a is 1 to 6;

X^{5a} is selected from the group consisting of H, NH_2, and a C_4-C_7 amine-containing aliphatic heterocyclic ring;

R^{5b} is selected from the group consisting of H and methyl;

R^{5c} is selected from the group consisting of H and methyl;

and wherein R^{5c} and R^{5a} can combine to form a four to six membered heterocyclic ring wherein said heterocyclic ring may have from 0 to 2 substituents, each such substituent being independently selected from from the group consisting of OH, F, C_1-C_4 alkyl, -NHC(=NH)NH_2, aryl and $NR^{5e}R^{5f}$;

R^{5e} is selected from the group consisting of H, C_1-C_4 alkyl, -C(=O)$(CH_2)_{n5b}$-X^{5b}, and -$CH_2(CH_2)_{n5c}$-X^{5b};

R^{5f} is selected from the group consisting of H, C_1-C_4 alkyl, and -$CH_2(CH_2)_{n5d}$-X^{5c};

n5b is selected from the group consisting of 1, 2, 3, and 4;

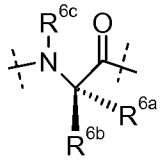
n5c and n5d are independently selected from the group consisting of 2, 3, and 4;

X^{5b} and X^{5c} are independently selected from the group consisting of H, and $NR^{5g}R^{5h}$;

R^{5g} and R^{5h} are independently selected from a group consisting of H, and C_1-C_4 alkyl

and

Xaa_6 is an amino acid residue of Formula VIIIa:



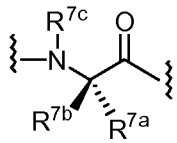
(VIIIa)

wherein R^{6a} is selected from the group consisting of C_1-C_8 alkyl, aryl C_1-C_4 alkyl , C_4-C_7 cycloalkyl C_1-C_4 alkyl, and C_4-C_7 cycloalkyl, wherein said C_1-C_8 alkyl and C_4-C_7 cycloalkyl may be substituted with a moiety selected from the group consisting of OH, and O(C_1-C_4 alkyl);

R^{6b} is H;

R^{6c} is selected from the group consisting of H, and C_1-C_4alkyl; and

Xaa_7 is an amino acid residue of Formula IX:



(IXa)

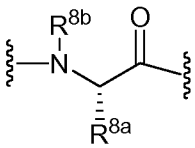
wherein R^{7a} is selected from the group consisting of C_1-C_4 alkyl, C_3-C_7 cycloalkyl, 2-thienyl, and C_1-C_4 alkyl substituted with OH;

R^{7b} is H, and 2-thienyl;

R^{7c} is selected from a group consisting of H, and methyl;

and

Xaa_8 is an amino acid residue of Formula Xa:



(Xa)

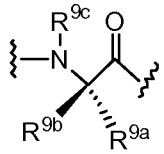
wherein R^{8a} is $(CH_2)_{m8a}$-X^{8a};

m^{8a} = 1-5;

X^{8a} is selected from the group consisting of H, NH_2, and -NHC(=NH)NH_2;

R^{8b} is selected from the group consisting of H and methyl; and

Xaa_9 is selected from the group consisting of a direct bond, and an amino acid residue of Formula XIa,



(XIa)

wherein R^{9a} is selected from the group consisting of C_1-C_5 alkyl, and C_4-C_7 cycloalkyl;

R^{9b} is selected from the group consisting of H, and C_1-C_5 alkyl;

and wherein R^{9a} and R^{9b} can form a 5-7 membered cycloalkyl ring;

R^{9c} is selected from the group consisting of H, and methyl;

and

Z is NHR^{11b};

wherein R^{11b} is selected from the group consisting of H, C_1-C_8 alkyl, C_4-C_8 cycloalkyl, C_7-C_{12} bicycloalkyl, C_7-C_{12} cycloalkylaryl, and C_1-C_4 alkyl C_4-C_8 cycloalkyl.

4. The compound of Claim 1, selected from the group consisting of

Occ-Sni-Phe-nle-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:166);
Occ-ala-Phe-leu-Leu-Pro-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:180);
Occ-Sni-Phe-leu-Leu-Pro-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:181);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:182);
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:183);
Occ-ala-Pcf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:184);
Occ-ala-Phe-nle-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:185);
Occ-ala-Phe-arg-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:187);
Occ-ala-Pcf-leu-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:190);
Occ-ala-Nmf-leu-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:192);
Occ-pro-Phe-leu-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:193);
Occ-pip-Phe-leu-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:194);
Occ-ala-Phe-lys-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:195);
Occ-ala-Phe-orn-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:196);
Occ-pip-Nmf-arg-Leu-Pro-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:201);
Occ-pip-Phe-arg-Leu-Pro-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:202);
Occ-ala-Nmf-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:203);
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:204);
Occ-pip-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:205);
Occ-ala-Pbf-arg-Leu-Hyp-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:208);
Occ-ala-Phe-arg-Leu-Hyp-Npg-Asp-Arg-Ile-NH_2 (SEQ ID NO:217);
Occ-ala-Phe-Gly-Leu-Tap-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:237);
Occ-ala-Phe-arg-Leu-Tap-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:238);
Occ-ala-Phe-leu-Leu-Tap-Asp-Arg-Ile-NH_2 (SEQ ID NO:239);
Occ-ala-Phe-ser-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:240);
Occ-Sni-Phe-lys-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:242);

Occ-Sni-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:243);
Occ-Sni-Phe-orn-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:252);
Occ-ala-Nmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:254);
Occ-ala-Phe-leu-Leu-Hyp-(SH-158)-Asp-Arg-Ile-NH_2 (SEQ ID NO:265);
Occ-ala-Phe-arg-Leu-Hyp-(SH-158)-Asp-Arg-Ile-NH_2 (SEQ ID NO:266);
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:267);
Occ-ala-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:268);
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:269);
(AR-201-49)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:273);
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:274);
Occ-ala-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:275);
Oct-Sni-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:276);
Oct-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:278);
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Tbg-NH_2 (SEQ ID NO:279);
Occ-Sni-Phe-arg-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:284);
Occ-Sni-Phe-orn-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:285);
Occ-Sni-Phe-Gly-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:287);
Occ-Sni-Phe-leu-Leu-Tap(G)-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:289);
Occ-Sni-Phe-leu-Leu-Tap(Bal)-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:290);
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:292);
Oct-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:293);
Occ-ala-Phe-leu-Leu-Hyp-Nml-Val-Arg-Ile-NH_2 (SEQ ID NO:299);
Occ-ala-Phe-Fhy-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:304);
Occ-ala-Phe-Apc-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:306);
Occ-Sni-Phe-leu-Leu-Tap(Et)-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:317);
Occ-ala-Phe-Apc-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:318);
Occ-Sni-Phe-Apc-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:319);
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Tbg-NH_2 (SEQ ID NO:320);
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Egz-NH_2 (SEQ ID NO:321);
Occ-ala-Phe-leu-Leu-Hyp-Dap(Me2)-Asp-Arg-Ile-NH_2 (SEQ ID NO:330);
Oct-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:332);
Occ-Sni-Phe-leu-Leu-Tap(Ae)-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:334);
Occ-Sni-Phe-leu-Leu-Tap(Ap)-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:335);
(AR-201-68)-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:343);
Sbt-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:345);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Val-Arg-Ile-NH_2 (SEQ ID NO:353);
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Arg-Ile-NH_2 (SEQ ID NO:356);
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Val-Arg-Ile-NH_2 (SEQ ID NO:358);

Oct-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Val-Arg-Ile-NH_2 (SEQ ID NO:360);
Occ-ala-Phe-Apc(Me)-Met-glu--Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:361);
Occ-ala-Phe-Apc(Et)-Glu-thr--Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:362);
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Aml-NH_2 (SEQ ID NO:365);
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Deg-NH_2 (SEQ ID NO:366);
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Nmr-Ile-NH_2 (SEQ ID NO:367);
Oct-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:372);
Miy-Hgl-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:373);
Occ-ala-Phe-Apc-Leu-Tap-Nml-Asp-Pro-Ile-NH_2 (SEQ ID NO:386);
Occ-ala-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Pro-Ile-NH_2 (SEQ ID NO:387);
Occ-ala-Phe-Egz-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:388);
Occ-ala-Phe-dap(1464)-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:396);
Occ-Sni-Pff-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:406);
Occ-Sni-Pcf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:412);
Occ-Sni-Pmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:413);
Occ-Sni-Eaa-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:414);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-1860 (SEQ ID NO:419);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-Che (SEQ ID NO:421);
Occ-Sni-Phe-Apc-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:425);
Occ-ala-Phe-leu-Leu-Hyp-Nml-(BB725)-Arg-Ile-NH_2 (SEQ ID NO:426);
Occ-ala-Phe-leu-Leu-Hyp-Nml-(BB727)-Arg-Ile-NH_2 (SEQ ID NO:428);
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Pro-Ile-NH_2 (SEQ ID NO:429);
Occ-Sni-Phe-Apc-Leu-Tap-Nml-Asp-Pro-Ile-NH_2 (SEQ ID NO:431);
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Pro-Che (SEQ ID NO:432);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Nmi-NH_2 (SEQ ID NO:433);
Occ-Sni-Nmf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:436);
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Nmr-Ile-NH_2 (SEQ ID NO:439);
Occ-Sni-Nmf-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:442);
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Pro-Ile-NH_2 (SEQ ID NO:443);
Occ-Sni-Phe-leu-Leu-Hyp-Npg-Asp-Pro-Che (SEQ ID NO:445);
Occ-Sni-Nmf-leu-Leu-Hyp-Nml-Asp-Pro-Che (SEQ ID NO:447);
Occ-Sni-Eaa-leu-Leu-Hyp-Nml-Asp-Pro-Che (SEQ ID NO:449);
Occ-Sni-Phe-Apc-Leu-Tap-Nml-Asp-Pro-Che (SEQ ID NO:452);
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Pro-Che (SEQ ID NO:453);
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Pro-Che (SEQ ID NO:454);
1319-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:455);
1320-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:456);
Occ-Sni-Mcf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:463);
Occ-Sni-Pbf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:464);

Occ-Sni-Thk-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:465);
Occ-Sni-Mtf-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:466);
Occ-Sni-Phe-ctb-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:468);
Occ-Sni-Phe-leu-Nle-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:469);
Occ-Sni-Phe-leu-Leu-Hyp-Ile-Asp-Arg-Ile-NH_2 (SEQ ID NO:470);
Occ-Sni-Phe-leu-Leu-Hyp-Cpg-Asp-Arg-Ile-NH_2 (SEQ ID NO:471);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Eaz-Che (SEQ ID NO:477);
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Pro-Che (SEQ ID NO:481);
Occ-Sni-Phe-leu-Nle-Hyp-Nml-Asp-Pro-Che (SEQ ID NO:482);
5587-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:488);
Occ-(AFL)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:491);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pca-Che (SEQ ID NO:495);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Che (SEQ ID NO:496);
Occ-Sni-Phe-leu-Leu-Tap(Ae)-Nml-Asp-Arg-Che (SEQ ID NO:497);
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Che (SEQ ID NO:498);
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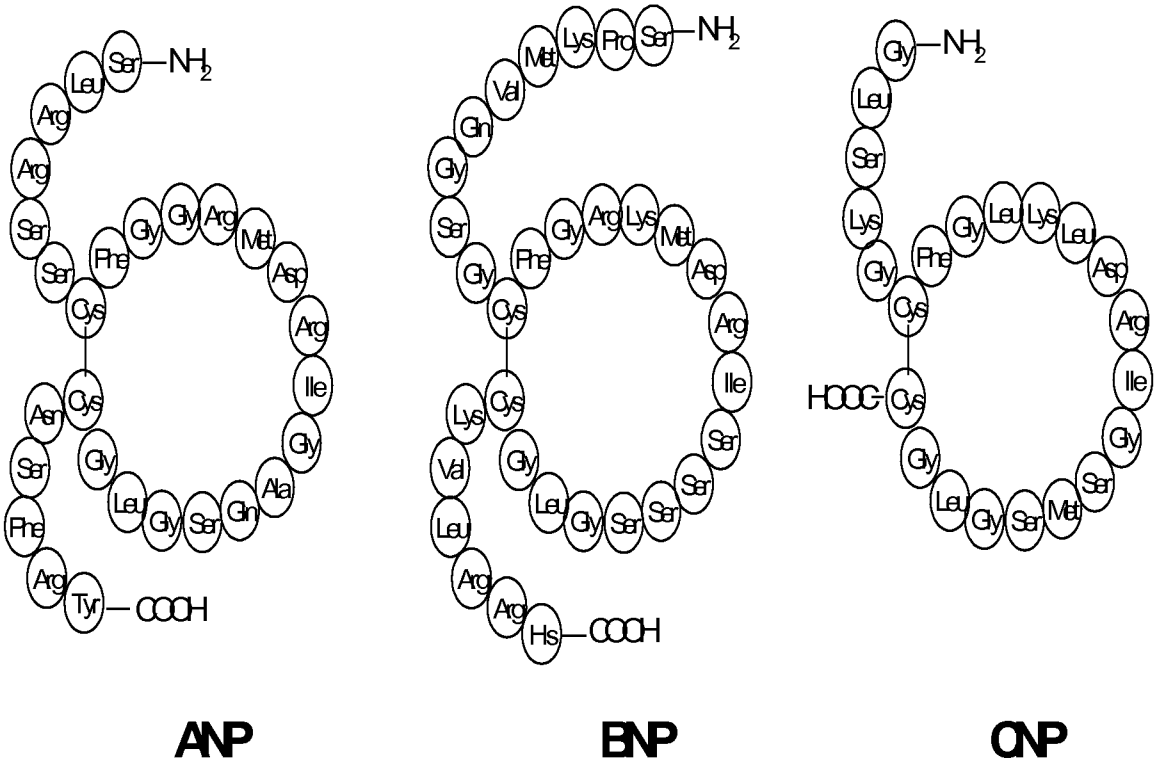
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Thr-Arg-Che (SEQ ID NO:511);
(AR-314-87)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:516);
(AR-314-102)-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:517);
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Che (SEQ ID NO:518);
Occ-Sni-Phe-lys(Me2)-Leu-Hyp-Nml-Asp-Arg-Che (SEQ ID NO:519);
Occ-Sni-Phe-lys(Me2)-Leu-Hyp-Nml-Val-Arg-Che (SEQ ID NO:521);
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Val-Arg-Ile-NH_2 (SEQ ID NO:523);
Occ-Sni-Phe-dab(Me2)-Leu-Hyp-Nml-Val-Arg-Che (SEQ ID NO:525);
Occ-Sni-Phe-dab(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:526);
H-Adx-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:538);
Oct-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Che (SEQ ID NO:541);
Occ-Sni-Phe-orn(Me2)-Leu-Tap-Nml-Val-Arg-Che (SEQ ID NO:548);
Occ-Sni-Phe-(AR-385-12)-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:559);
Occ-Sni-Phe-Egg-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:572);
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Thr-Arg-Che (SEQ ID NO:576);
H-Lys-Pro-Hgl-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:581);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Thr-Arg-Ile-NH_2 (SEQ ID NO:601);
Occ-Sni-Phe-orn(Me2)-Leu-Tap-Nml-Asp-Arg-Ile-NH_2 (SEQ ID NO:603).

5. The compound of Claim 1, selected from the group consisting of

Occ-ala-ala-Phe-Gly-Leu-Pro-Leu-Asp-Arg-Ile-NH_2 (SEQ ID NO:81);
Occ-pro-Phe-Gly-Leu-Pro-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:127);
Occ-Sni-Nmf-Gly-Leu-Pro-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:130);
Occ-Sni-Nmf-Gly-Leu-Pro-Leu-Asp-Arg-Ile- NH_2 (SEQ ID NO:135);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:182);
Occ-ala-Nmf-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:203);
Occ-ala-Phe-arg-Leu-Hyp-Leu-Asp-Arg-Ile- NH_2 (SEQ ID NO:187);
Occ-ala-Phe-arg-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:204);
Occ-ala-Phe-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:183);
Occ-ala-Phe-lys-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:195);
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:267);
Occ-Sni-Phe-leu-Leu-Tap-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:274);
Occ-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Val-Arg-Ile- NH_2 (SEQ ID NO:355);
Occ-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:292);
Oct-Sni-Phe-dap(Me2)-Leu-Tap-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:332);
Oct-Sni-Phe-dap(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:372);
Occ-Sni-Eaa-leu-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:414);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Asp-Pro-Che (SEQ ID NO:421);
Occ-Sni-Phe-Apc-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:425);
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Pro-Che (SEQ ID NO:481);
Occ-Sni-Phe-leu-Leu-Tap-Nml-Val-Arg-Che (SEQ ID NO:506);
Occ-Sni-Phe-leu-Leu-Hyp-Nml-Val-Arg-Che (SEQ ID NO:507);
Occ-Sni-Phe-orn(Me2)-Leu-Hyp-Nml-Asp-Arg-Ile- NH_2 (SEQ ID NO:269).


Ser—NH2
Leu
Arg
Arg
Ser
Ser
Cys
Phe
Gly
Gly
Arg
Met
Asp
Arg
Ile
Gly
Ala
Gln
Ser
Gly
Leu
Gly
Ser
Asn
Cys
Ser
Phe
Arg
Tyr—COOH
ANP
Lys
Pro
Ser—NH2
Met
Val
Gln
Gly
Ser
Gly
Cys
Phe
Gly
Arg
Lys
Met
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Arg
Ile
Ser
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Gly
Leu
Gly
Ser
Lys
Cys
Val
Leu
Arg
Arg
Hs—COOH
BNP
Gly—NH2
Leu
Ser
Lys
Gly
Cys
Phe
Gly
Leu
Lys
Leu
Asp
Arg
Ile
Gly
Ser
Met
Gly
Ser
Leu
HOOC-Cys
CNP

FIG. 1

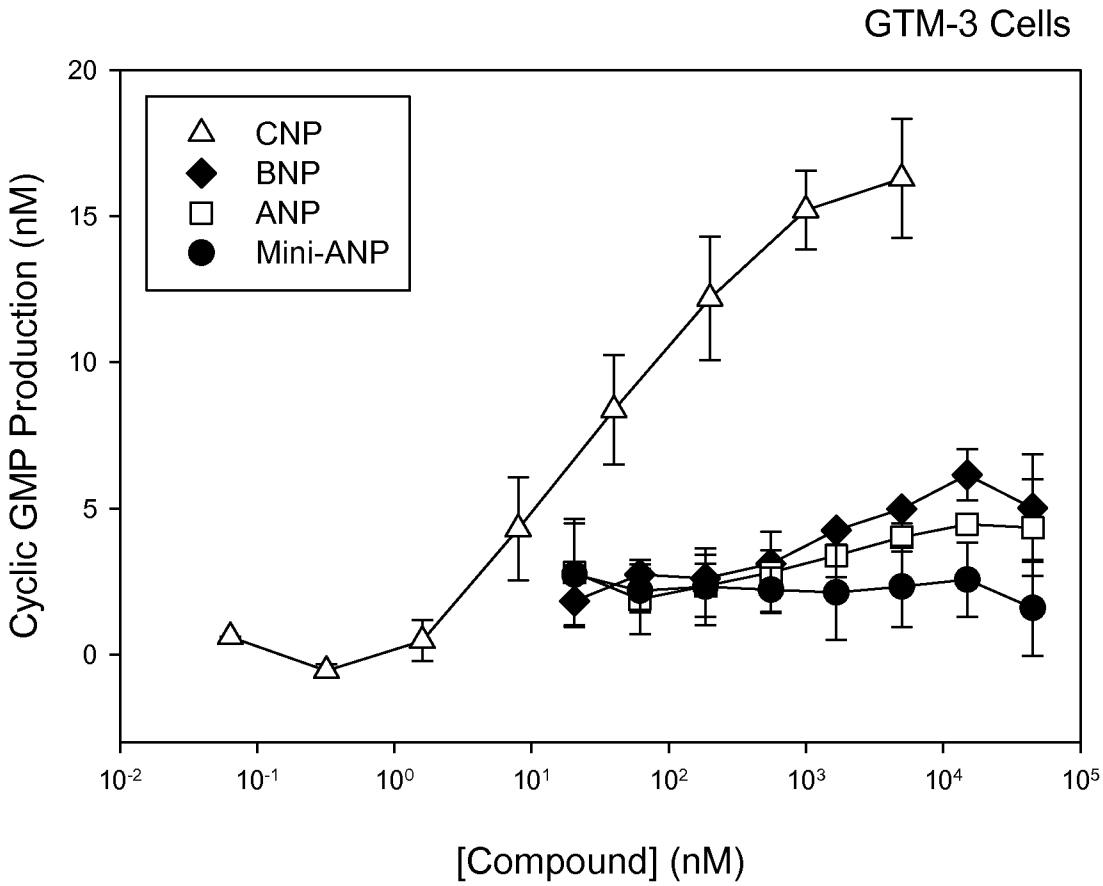
GTM-3 Cells
CNP
BNP
ANP
Mini-ANP
Cyclic GMP Production (nM)
[Compound] (nM)
20
15
10
5
0
10-2
10-1
100
101
102
103
104
105

FIG. 2

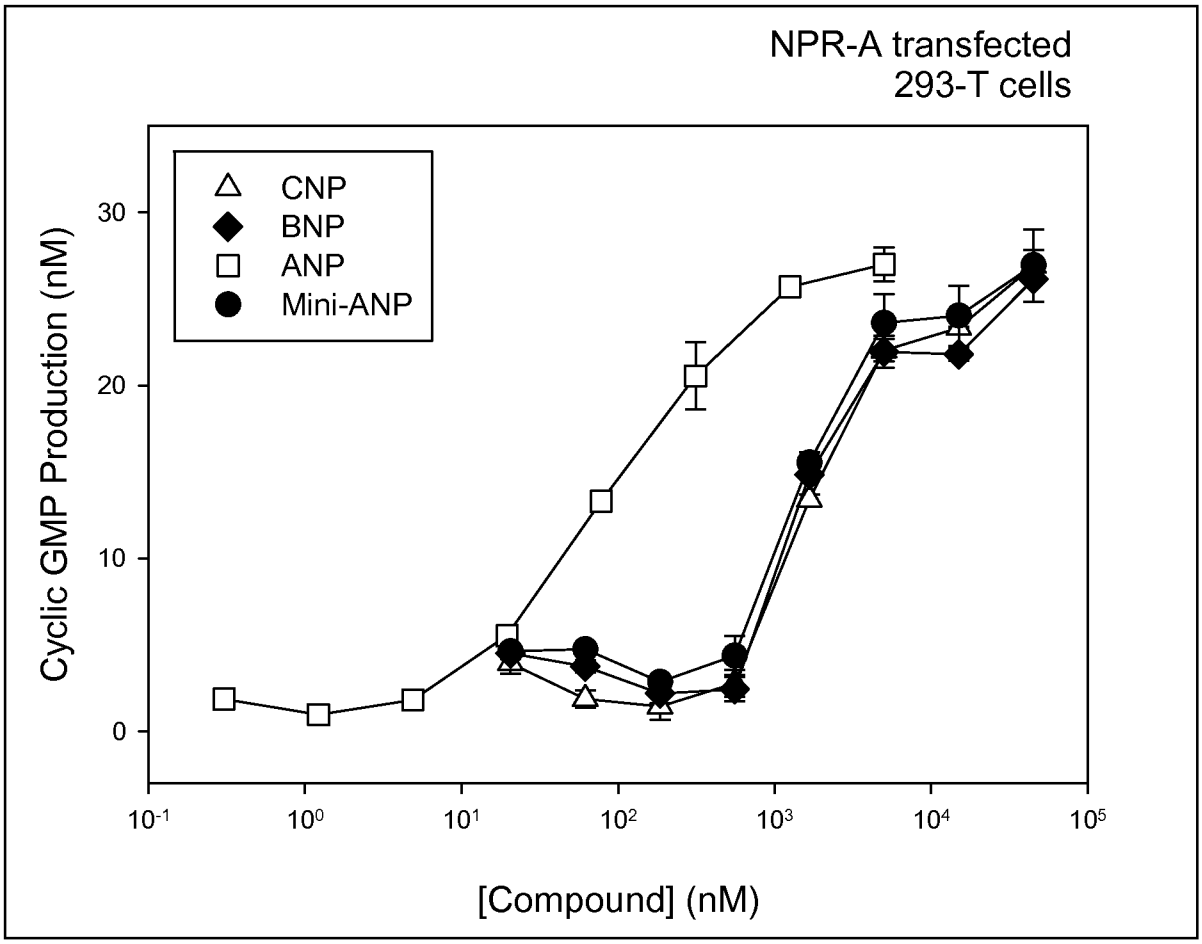
NPR-A transfected
293-T cells
CNP
BNP
ANP
Mini-ANP
Cyclic GMP Production (nM)
0
10
20
30
10-1
100
101
102
103
104
105
[Compound] (nM)

FIG. 3