MELANOCORTIN RECEPTOR LIGANDS

BACKGROUND OF THE INVENTION

The present invention is directed to peptides which are ligands of one or more of the melanocortin receptors (MC-R), the pharmaceutically-acceptable salts thereof, to methods of using such peptides to treat mammals and to useful pharmaceutical compositions comprising said peptides.

Melanocortins are a family of regulatory peptides which are formed by post-translational processing of pro-hormone pro-opiomelanocortin (POMC; 131 amino acids in length). POMC is processed into three classes of hormones; the melanocortins, adrenocorticotropin hormone, and various endorphins (e.g. lipotropin) (Cone, et al., Recent Prog. Horm. Res., 51:287-317, (1996); Cone et al., Ann. N.Y. Acad. Sci., 31:342-363, (1993)).

Melanocortins have been found in a wide variety of normal human tissues including the brain, adrenal, skin, testis, spleen, kidney, ovary, lung, thyroid, liver, colon, small intestine and pancreas (Tatro, J. B. et al., Endocrinol. 121:1900-1907 (1987); Mountjoy, K. G. et al., Science 257:1248-1251 (1992); Chhajlani, V. et al., FEBS Lett. 309:417-420 (1992); Gantz, I. et al. J. Biol. Chem. 268:8246-8250 (1993) and Gantz, I. et al., J. Biol. Chem. 268:15174-15179 (1993)).

Melanocortin peptides have been shown to exhibit a wide variety of physiological activities including the control of behavior and memory, affecting neurotrophic and antipyretic properties, as well as affecting the modulation of the immune system. Aside from their well known effects on adrenal cortical functions (adrenocorticotropic hormone, ACTH) and on melanocytes (melanocyte stimulating hormone, MSH), melanocortins have also been shown to control the cardiovascular system, analgesia, thermoregulation and the release of other neurohumoral agents including prolactin, luteinizing hormone and biogenic amines (De Wied, D. et al., Methods Achiev. Exp. Pathol. 15:167-199 (1991); De Wied, D. et al., Physiol. Rev. 62:977-1059 (1982); Guber, K.A. et al., Am. J. Physiol. 257:R681-R694 (1989); Walker J.M. et al., Science 210:1247-1249 (1980); Murphy, M. T. et al., Science 221:192-193

(1983); Ellerkmann, E. et al., Endocrinol. 130:133-138 (1992) and Versteeg, D. H. G. et al., Life Sci. 38:835-840 (1986)).

It has also been shown that binding sites for melanocortins are distributed in many different tissue types including lachrymal and submandibular glands, pancreas, adipose, bladder, duodenum, spleen, brain and gonadal tissues as well as malignant melanoma tumors. Five melanocortin receptors (MC-R) have been characterized to date. These include melanocyte-specific receptor (MC1-R), corticoadrenal-specific ACTH receptor (MC2-R), melacortin-3 (MC3-R), melanocortin-4 (MC4-R) and melanocortin-5 receptor (MC5-R). All of the melanocortin receptors respond to the peptide hormone class of melanocyte stimulating hormones (MSH) (Cone, R. D. et al., Ann. N.Y. Acad. Sci., 680:342-363 (1993); Cone, R. D. et al., Recent Prog. Horm. Res., 51:287-318 (1996)).

MC1-R, known in the art as Melanocyte Stimulating Hormone Receptor (MSH-R), Melanotropin Receptor or Melanocortin-1 Receptor, is a 315 amino acid transmembrane protein belonging to the family of G-Protein coupled receptors. MC1-R is a receptor for both MSH and ACTH. The activity of MC1-R is mediated by G-proteins which activate adenylate cyclase. MC1-R receptors are found in melanocytes and corticoadrenal tissue as well as various other tissues such as adrenal gland, leukocytes, lung, lymph node, ovary, testis, pituitary, placenta, spleen and uterus. MC2-R, also called Adrenocorticotropic hormone receptor (ACTH-R), is a 297 amino acid transmembrane protein found in melanocytes and the corticoadrenal tissue. MC2-R mediates the corticotrophic effect of ACTH. In humans, MC3-R is a 360 AA protein found in brain tissue; in mice and rats MC3-R is a 323 AA protein. MC4-R is a 332 amino acid transmembrane protein which is also expressed in brain as well as placental and gut tissues. MC5-R is a 325 amino acid transmembrane protein expressed in the adrenals, stomach, lung and spleen and very low levels in the brain. MC5-R is also expressed in the three layers of adrenal cortex, predominantly in the aldosterone-producing zona glomerulosa cells.

The five known melanocortin receptors differ, however, in their functions. For example, MC1-R is a G-protein coupled receptor that regulates pigmentation in response to α-MSH, a potent agonist of MC1-R. Agonism of the MC1-R receptor

results in stimulation of the melanocytes which causes eumelanin and increases the risk for cancer of the skin. Agonism of MC1-R can also have neurological effects. Stimulation of MC2-R activity can result in carcinoma of adrenal tissue. Recent pharmacological confirmation has established that central MC4-R receptors are the prime mediators of the anorexic and orexigenic effects reported for melanocortin agonists and antagonists, respectively. The effects of agonism of the MC3-R and MC5-R are not yet known.

There has been great interest in melanocortin (MC-R) receptors as targets for the design of novel therapeutics to treat disorders of body weight such as obesity and cachexia. Both genetic and pharmacological evidence points toward central MC4-R receptors as the principal target (Giraudo, S. Q. et al., Brain Res., 809:302-306 (1998); Farooqi, I. S. et al., NE J Med., 348:1085-1095 (2003); MacNeil, D. J. et al., Eu. J. Pharm., 44:141-157 (2002); MacNeil, D. J. et al., Eu. J. Pharm., 450:93-109 (2002); Kask, A. et al., NeuroReport, 10:707-711 (1999)). The current progress with receptor-selective agonists and antagonists evidences the therapeutic potential of melanocortin receptor activation, particularly MC4-R.

Agonist, antagonist or other ligand compounds activating one or more melanocortin receptor would be useful for treating a wide variety of indications in a subject in need thereof or at risk thereof including acute and chronic inflammatory diseases such as general inflammation (U.S. Patent No. 6,613,874; Catania, A. et al., Pharm. Rev., 56:1-29 (2004)), inflammatory bowel disease (U.S. Patent No. 6,713,487; Catania, A. et al., Pharm. Rev., 56:1-29 (2004)), brain inflammation (Catania, A. et al., Pharm. Rev., 56:1-29 (2004)), sepsis (U.S. Patent No. 6,613,874; U.S. Patent No. 6,713,487; Catania, A. et al., Pharm. Rev., 56:1-29 (2004)) and septic shock (U.S. Patent No. 6,613,874; Catania, A. et al., Pharm. Rev., 56:1-29 (2004)); diseases with an autoimmune component such as rheumatoid arthritis (U.S. Patent No. 6,713,487; Catania, A. et al., Pharm. Rev., 56:1-29 (2004)), gouty arthritis (Catania, A. et al., Pharm. Rev., 56:1-29 (2004), Getting, S. J. et al., Curr. Opin. Investig. Drugs, 2:1064-1069 (2001)), and multiple sclerosis ((U.S. Patent No. 6,713,487); metabolic diseases and medical conditions accompanied by weight gain such as obesity (U.S. Patent No. 6,613,874; U.S. Patent No. 6,600,015; Fehm, H. L. et al., J. Clin. Endo. & Metab.,

86:1144-1148 (2001); Hansen, M. J. et al., Brain Res., 1039:137-145 (2005); Ye, Z. et al., Peptides, 26:2017-2025 (2005); Farooqi, I. S. et al., NE J Med., 348:1085-1095 (2003); MacNeil, D. J. et al., Eu. J. Pharm., 44:141-157 (2002); MacNeil, D. J. et al., Eu. J. Pharm., 450:93-109 (2002); Kask, A. et al., NeuroReport, 10:707-711 (1999); Schwartz, M. W., J. Clin. Invest., 108:963-964 (2001), Gura, T., Science, 287:1738-1740 (2000), Raffin-Sanson, M. L., Eu. J. Endo., 144:207-208 (2001), Hamilton, B. S. et al., Obesity Res. 10:182-187 (2002)), feeding disorders (U.S. Patent No. 6,720,324; Fehm, H. L. et al., J. Clin. Endo. & Metab., 86:1144-1148 (2001); Pontillo, J. et al., Bioorganic & Med. Chem. Ltrs., 15:2541-2546 (2005)) and Prader-Willi Syndrome (GE, Y. et al., Brain Research, 957:42-45 (2002)); metabolic diseases and medical conditions accompanied by weight loss such as anorexia (U.S. Patent No. 6,613,874; Wisse, B. R. et al., Endo., 142:3292-3301 (2001)), bulimia (U.S. Patent No. 6,720,324), AIDS wasting (Marsilje, T. H. et al., Bioorg. Med. Chem. Lett., 14:3721-3725 (2004); Markison, S. et al., Endocrinology, 146:2766-2773 (2005)), cachexia (U.S. Patent No. 6,613,874; Lechan, R. M. et al., Endo., 142:3288-3291 (2001); Pontillo, J. et al., Bioorganic & Med. Chem. Ltrs., 15:2541-2546 (2005)), cancer cachexia (U.S. Patent No. 6,639,123) and wasting in frail elderly (U.S. Patent No. 6,639,123); diabetes (U.S. Patent No. 6,713,487) and diabetalogical related conditions and complications of diabetes such as retinopathy (U.S. Patent No. 6,525,019); neoplastic proliferation (U.S. Patent No. 6,713,487) such as skin cancer (Sturm, R.A., Melanoma Res., 12:405-416 (2002); Bastiens, M. T. et al., Am. J. Hum. Genet., 68:884-894 (2001)), and prostate cancer (Luscombe, C. J. et al., British J. Cancer, 85:1504-1509 (2001); reproductive or sexual medical conditions such as endometriosis (U.S. Patent No. 6,713,487) and uterine bleeding in women (U.S. Patent No. 6,613,874), sexual dysfunction (U.S. Patent No. 6,720,324; Van der Ploeg, L. H. T. et al., PNAS, 99:11381-11386 (2002), Molinoff, P. B. et al., Ann. N.Y. Acad. Sci., 994:96-102 (2003), Hopps, C. V. et al., BJU International, 92:534-538 (2003)), erectile dysfunction ((U.S. Patent No. 6,613,874; Diamond, L. E. et al., Urology, 65:755-759 (2005), Wessells, H. et al., Int. J. Impotence Res., 12:S74-S79 (2000), Andersson, K-E. et al., Int. J. Impotence Res., 14:S82-S92 (2002), Bertolini, A. et. al., Sexual Behavior: Pharmacology and Biochemistry, Raven Press, NY, p 247-257 (1975); Wessells, H. et al., Neuroscience, 118:755-762 (2003), Wessells, H. et al.,

Urology, 56:641-646 (2000), Shadiack, A. M. et al., Society for Neuroscience Abstract, (2003); Wessells, H. et al., J. Urology, 160:389-393 (1998), Rosen, R. C. et al., Int. J. Impotence Res., 16:135-142 (2004), Wessells, H. et al., Peptides, 26:1972-1977 (2005)) and decreased sexual response in females (U.S. Patent No. 6,713,487; Fourcroy, J. L., Drugs, 63:1445-1457 (2003)); diseases or conditions resulting from treatment or insult to the organism such as organ transplant rejection (U.S. Patent No. 6,713,487; Catania, A. et al., Pharm. Rev., 56:1-29 (2004)), ischemia and reperfusion injury (Mioni, C. et al., Eu. J. Pharm., 477:227-234 (2003); Catania, A. et al., Pharm. Rev., 56:1-29 (2004)), treatment of spinal cord injury and to accelerate wound healing (Sharma H. S. et al., Acta. Nerochir. Suppl., 86:399-405 (2003); Sharma H.S., Ann. N.Y. Acad. Sci. 1053: 407–421 (2005); U.S. Patent No. 6,525,019), as well as weight loss caused by chemotherapy, radiation therapy, temporary or permanent immobilization (Harris, R. B. et al., Physiol. Behav., 73:599-608 (2001)) or dialysis; cardiovascular diseases or conditions such as hemorrhagic shock (Catania, A. et al., Pharm. Rev., 56:1-29 (2004)), cardiogenic shock (U.S. Patent No. 6,613,874), hypovolemic shock (U.S. Patent No. 6,613,874), cardiovascular disorders (U.S. Patent No. 6,613,874) and cardiac cachexia (Markison, S. et al., Endocrinology, 146:2766-2773 (2005); pulmonary diseases or conditions such as acute respiratory distress syndrome (U.S. Patent No. 6,350,430; Catania, A. et al., Pharm. Rev., 56:1-29 (2004)), chronic obstructive pulmonary disease (U.S. Patent No. 6,713,487), asthma (U.S. Patent No. 6,713,487) and pulmonary fibrosis; to enhance immune tolerance (Luger, T. A. et al., Pathobiology, 67:318-321 (1999)) and to combat assaults to the immune system such as those associated with certain allergies (U.S. Patent No. 6,713,487) or organ transplant rejection (U.S. Patent No. 6,713,487; Catania, A. et al., Pharm. Rev., 56:1-29 (2004)); treatment of dermatological diseases and conditions such as psoriasis (U.S. Patent No. 6,713,487), skin pigmentation depletion (U.S. Patent No. 6,713,487; Ye, Z. et al., Peptides, 26:2017-2025 (2005)), acne (Hatta, N. et al., J. Invest. Dermatol., 116:564-570 (2001); Bohm, M. et al., J. Invest. Dermatol., 118:533-539 (2002)), keloid formation (U.S. Patent No. 6,525,019) and skin cancer (Sturm, R.A., Melanoma Res., 12:405-416 (2002); Bastiens, M. T. et al., Am. J. Hum. Genet., 68:884-894 (2001)); behavioral, central nervous system or neuronal conditions and disorders such as

anxiety (U.S. Patent No. 6,720,324; Pontillo, J. et al., Bioorganic & Med. Chem. Ltrs., 15:2541-2546 (2005)), depression (Chaki, S. et al., Peptides, 26:1952-1964 (2005), Bednarek, M. A. et al., Expert Opinion Ther. Patents, 14:327-336 (2004); U.S. Patent No. 6,720,324), memory and memory dysfunction (U.S. Patent No. 6,613,874; Voisey, J. et al., Curr. Drug Targets, 4:586-597 (2003)), modulating pain perception (U.S. Patent No. 6,613,874; Bertolini, A. et al., J. Endocrinol. Invest., 4:241-251 (1981); Vrinten, D. et al., J. Neuroscience, 20:8131-8137 (2000)) and treating neuropathic pain (Pontillo, J. et al., Bioorganic & Med. Chem. Ltrs., 15:2541-2546 (2005)); conditions and diseases associated with alcohol consumption, alcohol abuse and/or alcoholism (WO 05/060985; Navarro, M. et al., Alcohol Clin. Exp. Res., 29:949-957 (2005)); and renal conditions or diseases such as the treatment of renal cachexia (Markison, S. et al., Endocrinology, 146:2766-2773 (2005)) or natriuresis (U.S. Patent No. 6,613,874).

Ligand compounds activating one or more melanocortin receptor would be useful for modulating a wide variety of normalizing or homeostatic activities in a subject in need thereof including thyroxin release (U.S. Patent No. 6,613,874), aldosterone synthesis and release (U.S. Patent No. 6,613,874), body temperature (U.S. Patent No. 6,613,874), blood pressure (U.S. Patent No. 6,613,874), heart rate (U.S. Patent No. 6,613,874), vascular tone (U.S. Patent No. 6,613,874), brain blood flow (U.S. Patent No. 6,613,874), blood glucose levels (U.S. Patent No. 6,613,874), bone metabolism, bone formation or development (Dumont, L. M. et al., Peptides, 26:1929-1935 (2005), ovarian weight (U.S. Patent No. 6,613,874), placental development (U.S. Patent No. 6,613,874), prolactin and FSH secretion (U.S. Patent No. 6,613,874), intrauterine fetal growth (U.S. Patent No. 6,613,874), parturition (U.S. Patent No. 6,613,874), spermatogenesis (U.S. Patent No. 6,613,874), sebum and pheromone secretion (U.S. Patent No. 6,613,874), neuroprotection (U.S. Patent No. 6,639,123) and nerve growth (U.S. Patent No. 6,613,874) as well as modulating motivation (U.S. Patent No. 6,613,874), learning (U.S. Patent No. 6,613,874) and other behaviors (U.S. Patent No. 6,613,874).

It is, therefore, an objective of the present invention to provide ligands for the melanocortin receptors which exhibit greater stability and selectivity for melanocortin receptors than native melanocortin receptor ligands.

SUMMARY OF THE INVENTION

In one aspect, the present invention is directed to a compound according formula (I):

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1$$

wherein:

A^1 is Acc, HN-$(CH_2)_m$-C(O), L- or D-amino acid, or deleted;

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

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

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

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

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

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

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

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

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

R^1 is -OH, or -NH_2;

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

R^4 and R^5 each is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl,

aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

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

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

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

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

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

provided that

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

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

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

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

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

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

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

or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediate foregoing formula, is where A^1 is A6c, Gaba, Nle, Met, Phe, D-Phe, D-2-Nal, hPhe, Chg, D-Chg, Cha, hCha, hPro, hLeu, Nip, ß-hMet, or Oic;

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

A^3 is Gly, Ala, D-Ala, D-Glu, β-Ala, Gaba, Aib, or deleted;

A^4 is His;

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

A^6 is Arg, or hArg;

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

A^8 is A6c, Ala, β-Ala, Gaba, Apn, or Ahx;

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

A^{10} is Thr, or deleted

or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds is where R^2 and R^3 each is, independently, H, acyl, n-propanoyl, or n-butanoyl or a pharmaceutically acceptable salt thereof.

A more preferred compound of formula (I) is where said compound is of the formula:

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

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

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

A^4 is His or 3-Pal;

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

A^6 is Arg or hArg;

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

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

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

A^{10} is Thr or deleted;

wherein at least one of A^3 or A^8 is deleted, but not both,

or a pharmaceutically acceptable salt thereof.

More preferred compounds of the immediately foregoing group of compounds is where said compound is of the formula:

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2; SEQ ID NO:1

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH_2; SEQ ID NO:1

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2; SEQ ID NO:2

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:3

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:3

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2; SEQ ID NO:3

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2; SEQ ID NO:2

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2; SEQ ID NO:4

Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:5

Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:6

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:6

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:6

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:9

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:9

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:9

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:9

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:9

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

n-butanoyl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:12

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-*β*-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; SEQ ID NO:16

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2; SEQ ID NO:16

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2; SEQ ID NO:16

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2; SEQ ID NO:17

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:17

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2; SEQ ID NO:18

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH_2; SEQ ID NO:18

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH_2; SEQ ID NO:18

Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:61

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH_2;SEQ ID NO:19

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2; SEQ ID NO:20

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;SEQ ID NO:21

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;SEQ ID NO:22

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;SEQ ID NO:22

D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:23

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:24

D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:25

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:24

D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:26

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:26

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2; SEQ ID NO:27

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2;SEQ ID NO:28

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2; SEQ ID NO:28

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH; SEQ ID NO:29

Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:31

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:32

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:32

Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:34

Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:34

Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:35

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH; SEQ ID NO:36

Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2; SEQ ID NO:37

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2; SEQ ID NO:38

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2; SEQ ID NO:38

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:39

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2;SEQ ID NO:39

Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:40

Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:40

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-OH; SEQ ID NO:41

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-OH; SEQ ID NO:42

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-OH; SEQ ID NO:43

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-OH; SEQ ID NO:43

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-OH; SEQ ID NO:43

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-OH; SEQ ID NO:42

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-OH; SEQ ID NO:41

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH; SEQ ID NO:29

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;SEQ ID NO:44

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-OH; SEQ ID NO:45

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-OH; SEQ ID NO:45

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-OH; SEQ ID NO:45

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-OH; SEQ ID NO:45

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-OH; SEQ ID NO:46

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-OH; SEQ ID NO:46

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-OH; SEQ ID NO:46

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-OH; SEQ ID NO:46

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH; SEQ ID NO:47

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH; SEQ ID NO:29

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH; SEQ ID NO:48 or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; SEQ ID NO:49 or

or pharmaceutically acceptable salts thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;SEQ ID NO:7

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;SEQ ID NO:22

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:32

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH; SEQ ID NO:29

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH; SEQ ID NO:29 or

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH; SEQ ID NO:48

or pharmaceutically acceptable salts thereof.

A more preferred compound of formula (I) is where said compound is of the formula:

A^1 is Arg, D-Arg, Cha, hCha, Chg, D-Chg, Ile, Leu, 2-Nal, Nle, Phe, D-Phe, hPhe, Val or deleted;

A^2 is Cys, Pen or Asp;

A^3 is D-Ala, D-Abu, D-Cha, D-Ile, D-Leu, D-Tle, D-Val or deleted;

A^4 is His or 3-Pal;

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

A^6 is Arg or hArg;

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

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

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

A^{10} is Thr or deleted;

each of R^2 and R^3 is independently selected from the group consisting of H or acyl;

or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:50

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:50

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; SEQ ID NO:51

Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:52

Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:52

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; SEQ ID NO:51

Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2; SEQ ID NO:53

Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2; SEQ ID NO:53

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:24

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2; SEQ ID NO:27

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:32

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:34

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2; SEQ ID NO:1

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2; SEQ ID NO:2

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:3

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2; SEQ ID NO:3

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2; SEQ ID NO:2

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2; SEQ ID NO:4

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:6

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:6

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:21

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; SEQ ID NO:22

D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:23

D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:25

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:24

D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:26

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:26

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2; SEQ ID NO:28

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2; SEQ ID NO:28

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH; SEQ ID NO:29

Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:31

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:32

Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:34

Ac-Nle-c(Cys-3Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:35

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH; SEQ ID NO:36

Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2; SEQ ID NO:37

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; SEQ ID NO:16

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2; SEQ ID NO:16

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2; SEQ ID NO:20

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2; SEQ ID NO:38

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2; SEQ ID NO:38

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:39

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2; SEQ ID NO:39

Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:40

Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:40 or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; SEQ ID NO:49

or a pharmaceutically acceptable salt thereof.

A more preferred compound of formula (I) is where said compound is of the formula:

A^1 is Arg, D-Arg, hArg or D-hArg;

or a pharmaceutically acceptable salt thereof.

A more preferred compound of the immediately foregoing group of compounds is where said compound is of the formula:

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

A^3 is Gly, Ala, D-Ala, D-Glu, β-Ala, Gaba, Aib, or deleted;

A^4 is His;

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

A^6 is Arg, or hArg;

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

A^8 is A6c, Ala, β-Ala, Gaba, Apn, or Ahx;

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

A^{10} is Thr, or deleted;

or a pharmaceutically acceptable salt thereof.

A more preferred compound of the immediately foregoing group of compounds is where R^2 and R^3 each is, independently, H, acyl, n-propanoyl, or n-butanoyl or a pharmaceutically acceptable salt thereof.

A more preferred compound of the immediately foregoing group of compounds is where said compound is of the formula:

A^2 is Cys or Asp;

A^3 is D-Ala or deleted;

A^4 is His;

A^5 is D-Phe or D-2-Nal;

A^6 is Arg;

A^7 is Trp;

A^8 is Ala, Gaba or deleted;

A^9 is Cys, Pen or Lys;

A^{10} is deleted;

or a pharmaceutically acceptable salt thereof.

A more preferred compound of the immediately foregoing group of compounds is where R^2 and R^3 each is, independently, H or acyl; or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:50

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:50

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; SEQ ID NO:51

Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:52

Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:52

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; SEQ ID NO:51

Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2; SEQ ID NO:53

Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2; SEQ ID NO:53 or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; SEQ ID NO:49

or pharmaceutically acceptable salts thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:50

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; SEQ ID NO:51 or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; SEQ ID NO:49

or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:50

or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; SEQ ID NO:51

or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; SEQ ID NO:49

or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention is directed to a compound according formula (II):

(R^2R^3)-A^1-c(A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9)-NH_2

wherein:

A^1 is Nle or deleted;

A^2 is Cys or Asp;

A^3 is Glu or D-Ala;

A^4 is His;

A^5 is D-Phe;

A^6 is Arg;

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

A^8 is Gly, Ala, D-Ala, β-Ala, Gaba or Apn;

A^9 is Cys or Lys;

each of R^2 and R^3 is independently selected from the group consisting of H or (C_1-C_6)acyl;

provided that

(I). when R^2 is (C_1-C_6)acyl, then R^3 is H; and

(II). when A^2 is Cys, then A^9 is Cys,

or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH_2; SEQ ID NO:54

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH_2; SEQ ID NO:54

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2; SEQ ID NO:54

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:54

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2; SEQ ID NO:54

Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2; SEQ ID NO:55

Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2; SEQ ID NO:55

Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;SEQ ID NO:56

Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2; SEQ ID NO:56

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2; SEQ ID NO:57

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2; SEQ ID NO:57

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:57 or

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH_2; SEQ ID NO:58

or a pharmaceutically acceptable salt thereof.

Another more preferred compound of formula (I) or formula (II) is each of the compounds that are specifically enumerated herein below in the Examples section of the present disclosure, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein said compound is a selective melanocortin-4 receptor agonist.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein said compound is a selective melanocortin 4 receptor agonist with a functional activity characterized by an EC_{50} at least 15- fold more selective for the human melanocortin 4 receptor than for the human melanocortin 1 receptor, the human melanocortin 3 receptor and the human melanocortin 5 receptor.

In yet another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, wherein said compound is a selective melanocortin 4 receptor agonist with a functional activity characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor, an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor, an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor, or an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or

formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating an acute or chronic inflammatory disease or medical condition such as general inflammation, inflammatory bowel disease, brain inflammation, sepsis and septic shock. In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating a disease or medical condition with an autoimmune component such as rheumatoid arthritis, gouty arthritis and multiple sclerosis. In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating a metabolic disease or medical condition accompanied by weight gain such as obesity, feeding disorders and Prader-Willi Syndrome. In a further aspect, the disease or condition treated is obesity. In yet a further aspect, the disease or condition treated is a feeding disorder. In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for decreasing food intake, for decreasing body weight or a combination thereof. In a preferred embodiment, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, which is useful for diminishing food intake, decreasing body weight, or a combination thereof, wherein the active ingredient is one or more of the following compounds: Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2 SEQ ID NO:32, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:50, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:50, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 SEQ ID NO:51, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-

NH_2 SEQ ID NO:7, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2 SEQ ID NO:24, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 SEQ ID NO:22 or Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2 SEQ ID NO:49. In yet another preferred embodiment, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, which is useful for diminishing food intake, decreasing body weight, or a combination thereof, wherein the active ingredient is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:50. In yet another preferred embodiment, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, which is useful for diminishing food intake, decreasing body weight, or a combination thereof, wherein the active ingredient is Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 SEQ ID NO:51. In yet another preferred embodiment, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, which is useful for diminishing food intake, decreasing body weight, or a combination thereof, wherein the active ingredient is Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2 SEQ ID NO:49.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically-acceptable carrier or diluent, which is useful for decreasing appetite without compromising body weight. In yet another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically-acceptable carrier or diluent, useful for decreasing food consumption while

increasing body weight.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating a metabolic disease or medical condition accompanied by weight loss such as anorexia, bulimia, AIDS wasting, cachexia, cancer cachexia and wasting in frail elderly. In a further aspect, the disease or condition treated is anorexia. In a further aspect, the disease or condition treated is bulimia. In a further aspect, the disease or condition treated is AIDS wasting or wasting in frail elderly. In a further aspect, the disease or condition treated is cachexia or cancer cachexia.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating a neoplastic disease or medical condition such as skin cancer and cancer cachexia.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating a reproductive or sexual medical condition such as endometriosis, uterine bleeding, sexual dysfunction, erectile dysfunction and decreased sexual response in females.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating a disease or medical condition resulting from treatment or insult to an organism such as organ transplant rejection, ischemia and reperfusion injury, wounding and spinal cord injury, and weight loss due to a medical procedure selected from the group consisting of chemotherapy, radiation therapy, temporary or permanent immobilization and dialysis.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating a cardiovascular disease or medical condition such as hemorrhagic shock, cardiogenic shock, hypovolemic shock, cardiovascular disorders and cardiac cachexia.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating a pulmonary disease or medical condition such as acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease and asthma.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for enhancing immune tolerance and treating allergies.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent, useful for treating a dermatological disease or medical condition such as psoriasis, skin pigmentation depletion, acne and keloid formation.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically-acceptable carrier or diluent, useful for treating a behavioral or central nervous system or neuronal disease or medical condition such as anxiety, depression, memory dysfunction and neuropathic pain.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or

formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically-acceptable carrier or diluent, useful for treating a renal disease or medical condition such as renal cachexia and natriuresis.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically-acceptable carrier or diluent, useful for modulating ovarian weight, placental development, prolactin secretion, FSH secretion, intrauterine fetal growth, parturition, spermatogenesis, thyroxin release, aldosterone synthesis and release, body temperature, blood pressure, heart rate, vascular tone, brain blood flow, blood glucose levels, sebum secretion, pheromone secretion, motivation, learning and behavior, pain perception, neuroprotection and nerve growth.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically-acceptable carrier or diluent, useful for modulating bone metabolism, bone formation and bone development.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically-acceptable carrier or diluent, useful for inhibiting alcohol consumption, for reducing alcohol consumption, for treating alcoholism, or for treating alcohol abuse. In a further aspect, the compound of the composition useful for inhibiting alcohol consumption, for reducing alcohol consumption, for treating alcoholism, or for treating alcohol abuse is a selective melanocortin 4 receptor agonist. In yet a further aspect, the compound of the composition useful for inhibiting alcohol consumption is a selective melanocortin 4 receptor agonist, or a pharmaceutically acceptable salt thereof, with a functional activity characterized by an EC_{50} at least 15-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 1 receptor, the human melanocortin 3 receptor and the

human melanocortin 5 receptor. In yet another aspect, the compound of the composition useful for inhibiting alcohol consumption is a selective melanocortin 4 receptor agonist, or a pharmaceutically acceptable salt thereof, with a functional activity characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor, an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor, an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor, or an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

In another aspect, the present invention provides the use of a therapeutically effective amount of a melanocortin 4 receptor agonist compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful for inhibiting alcohol consumption, for reducing alcohol consumption, for treating alcoholism, or for treating alcohol abuse in a subject in need of such treatment.

In yet another aspect, the present invention provides a method of eliciting an agonist or an antagonist effect from a melanocortin receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of eliciting an agonist or an antagonist effect from a melanocortin receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, wherein said compound is a selective melanocortin 4 receptor agonist.

In another aspect, the present invention provides a method of eliciting an agonist or an antagonist effect from a melanocortin receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a

pharmaceutically acceptable salt thereof, wherein said compound is a selective melanocortin 4 receptor agonist with a functional activity characterized by an EC_{50} at least 15- fold more selective for the human melanocortin 4 receptor than for the human melanocortin 1 receptor, the human melanocortin 3 receptor and the human melanocortin 5 receptor.

In yet another aspect, the present invention provides a method of eliciting an agonist or an antagonist effect from a melanocortin receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, wherein said compound is a selective melanocortin 4 receptor agonist with a functional activity characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor, an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor, an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor, or an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

In another aspect, the present invention provides a method of treating an acute or chronic inflammatory disease or medical condition such as general inflammation, inflammatory bowel disease, brain inflammation, sepsis and septic shock by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of treating a disease or medical condition with an autoimmune component such as rheumatoid arthritis, gouty arthritis and multiple sclerosis by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of treating a metabolic disease or medical condition accompanied by weight gain such as obesity,

feeding disorders and Prader-Willi Syndrome by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof. In a further aspect of the foregoing method, the disease or condition treated is obesity. In yet a further aspect of the foregoing method, the disease or condition treated is a feeding disorder. In another aspect, the present invention provides a method of decreasing food intake, decreasing body weight or a combination thereof, by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the present invention provides a method of decreasing food intake, decreasing body weight or a combination thereof, by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein said compound is Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2 SEQ ID NO:32, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:50, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:50, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 SEQ ID NO:51, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:7, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2 SEQ ID NO:24, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 SEQ ID NO:22, or Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2 SEQ ID NO:49. In another preferred embodiment, the present invention provides a method of decreasing food intake, decreasing body weight or a combination thereof, by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:50. In another preferred embodiment, the present invention provides a method of decreasing food intake, decreasing body weight or a combination thereof, by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein said compound is

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 SEQ ID NO:51. In another preferred embodiment, the present invention provides a method of decreasing food intake, decreasing body weight or a combination thereof, by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2 SEQ ID NO:49. In another aspect, the present invention provides a method of decreasing appetite without compromising body weight by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof. In another aspect, the present invention provides a method of decreasing food consumption while increasing body weight by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof. In another aspect, the present invention provides a method of treating a metabolic disease or medical condition accompanied by weight loss such as anorexia, bulimia, AIDS wasting, cachexia, cancer cachexia and wasting in frail elderly by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof. In a further aspect, the foregoing method is used to treat anorexia. In a further aspect, the foregoing method is used to treat bulimia. In a further aspect, the foregoing method is used to treat AIDS wasting or wasting in frail elderly. In a further aspect, the foregoing method is used to treat cachexia or cancer cachexia. In another aspect, the present invention provides a method of treating a neoplastic disease or medical condition such as skin cancer and cancer cachexia by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.In another aspect, the present invention provides a method of treating a reproductive or sexual medical condition such as endometriosis, uterine bleeding, sexual dysfunction, erectile dysfunction and decreased sexual response in females by eliciting an agonist or antagonist effect from a melanocortin receptor by

administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of treating a disease or medical condition resulting from treatment or insult to an organism such as organ transplant rejection, ischemia and reperfusion injury, wounding and spinal cord injury, and weight loss due to a medical procedure selected from the group consisting of chemotherapy, radiation therapy, temporary or permanent immobilization and dialysis by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of treating a cardiovascular disease or medical condition such as hemorrhagic shock, cardiogenic shock, hypovolemic shock, cardiovascular disorders and cardiac cachexia by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of treating a pulmonary disease or medical condition such as acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease and asthma by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of enhancing immune tolerance or treating allergies by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of treating dermatological disease or medical condition such as psoriasis, skin pigmentation depletion, acne and keloid formation by eliciting an agonist or antagonist effect from

a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of treating a behavioral or central nervous system or neuronal disease or medical condition such as anxiety, depression, memory dysfunction and neuropathic pain by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of treating a renal disease or medical condition such as renal cachexia and natriuresis by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of modulating a normalizing or homeostatic activity such as ovarian weight, placental development, prolactin secretion, FSH secretion, intrauterine fetal growth, parturition, spermatogenesis, thyroxin release, aldosterone synthesis and release, body temperature, blood pressure, heart rate, vascular tone, brain blood flow, blood glucose levels, sebum secretion, pheromone secretion, motivation, learning and behavior, pain perception, neuroprotection and nerve growth by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of modulating a normalizing or homeostatic activity such as bone metabolism, bone formation and bone development by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a method of inhibiting alcohol consumption, for reducing alcohol consumption, for treating alcoholism, or

for treating alcohol abuse by eliciting an agonist or antagonist effect from a melanocortin receptor by administering an effective amount of a compound of formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof. In a further aspect of the foregoing method, the compound is a selective melanocortin 4 receptor agonist. In yet a further aspect of the immediately foregoing method, the compound of the composition useful for inhibiting alcohol consumption is a selective melanocortin 4 receptor agonist, or a pharmaceutically acceptable salt thereof, with a functional activity characterized by an EC_{50} at least 15- fold more selective for the human melanocortin 4 receptor than for the human melanocortin 1 receptor, the human melanocortin 3 receptor and the human melanocortin 5 receptor. In yet another aspect of the foregoing method, the compound of the composition useful for inhibiting alcohol consumption is a selective melanocortin 4 receptor agonist, or a pharmaceutically acceptable salt thereof, with a functional activity characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor, an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor, an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor, or an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

In a further aspect, the present invention provides the use of a therapeutically effective amount of a melanocortin 4 receptor agonist or antagonist compound according formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to treat a disease and/or medical condition selected from the group consisting of acute and chronic inflammatory diseases such as general inflammation, inflammatory bowel disease, brain inflammation, sepsis and septic shock; diseases with an autoimmune component such as rheumatoid arthritis, gouty arthritis and multiple sclerosis; metabolic diseases and medical disorders accompanied by weight gain such as obesity, feeding disorders and Prader-Willi Syndrome; metabolic diseases and medical disorders accompanied by weight loss such as anorexia, bulimia, AIDS

wasting, cachexia, cancer cachexia and wasting in frail elderly; diabetes, diabetalogical related conditions and complications of diabetes such as retinopathy; neoplastic proliferation such as skin cancer and prostate cancer; reproductive or sexual medical conditions such as endometriosis and uterine bleeding in women, sexual dysfunction, erectile dysfunction and decreased sexual response in females; diseases or conditions resulting from treatment or insult to the organism such as organ transplant rejection, ischemia and reperfusion injury, spinal cord injury and wounding, as well as weight loss caused chemotherapy, radiation therapy, temporary or permanent immobilization or dialysis; cardiovascular diseases or conditions such as hemorrhagic shock, cardiogenic shock, hypovolemic shock, cardiovascular disorders and cardiac cachexia; pulmonary diseases or conditions such as acute respiratory distress syndrome, chronic obstructive pulmonary disease, asthma and pulmonary fibrosis; to enhance immune tolerance and to combat assaults to the immune system such as those associated with certain allergies or organ transplant rejection; treatment of dermatological diseases and conditions such as psoriasis, skin pigmentation depletion, acne, keloid formation and skin cancer; behavioral, central nervous system and neuronal disorders such as anxiety, depression, memory dysfunction, and neuropathic pain; and renal conditions or diseases such as the treatment of renal cachexia and natriuresis.

In a further aspect, the present invention provides the use of a therapeutically effective amount of a melanocortin 4 receptor agonist or antagonist compound according formula (I) or formula (II) as defined hereinabove, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to modulate normalizing or homeostatic activities such as ovarian weight, placental development, prolactin secretion, FSH secretion, intrauterine fetal growth, parturition, spermatogenesis, thyroxin release, aldosterone synthesis and release, body temperature, blood pressure, heart rate, vascular tone, brain blood flow, blood glucose levels, sebum secretion, pheromone secretion, motivation, learning and behavior, pain perception, neuroprotection, nerve growth, bone metabolism, bone formation and bone development.

It will be appreciated that therapeutic interventions addressing both normal physiological and pathophysiological processes which utilize the melanocortin receptors are also contemplated.

Additional objects, advantages, and features of the present invention will become apparent from the following description and appended claims, taken in conjunction with the accompanying drawings.

The compounds of formulae (I) or (II) are ligands for at least one of the melanocortin receptors (MC1-R, MC2-R, MC3-R, MC4-R and MC5-R) and a selection thereof were tested for their ability to act as a ligand in the *in vitro* assay described below.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1A: Mean difference in food consumed from vehicle in fasted rats 6 hours after administration of 100 nmole/Kg of selected compounds.

Figure 1B. Mean difference in food consumed from vehicle in fasted rats 6 hours after administration of 500 nmole/Kg of selected compounds.

Figure 2A. Cumulative difference in mean food intake from vehicle in rats after administration of various concentrations of Compound A.

Figure 2B. Cumulative mean body weight difference from vehicle in rats after administration of various concentrations of Compound A.

Figure 3A. Cumulative difference in mean food intake from vehicle in rats after administration of selected compounds.

Figure 3B. Cumulative mean body weight difference from vehicle in rats after administration of selected compounds.

Figure 4A. Cumulative difference in mean food intake from vehicle in rats after administration of selected compounds.

Figure 4B. Cumulative mean body weight difference from vehicle in rats after administration of selected compounds.

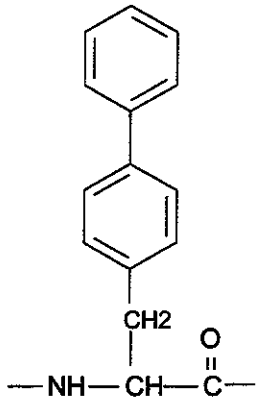
DETAILED DESCRIPTION OF THE INVENTION

The nomenclature used to define the peptides is that typically used in the art wherein the amino group at the N-terminus appears to the left and the carboxyl group at the C-terminus appears to the right. Where the amino acid has isomeric forms, it is the L form of the amino acid that is represented unless otherwise explicitly indicated. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference.

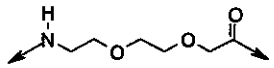
Nomenclature and Abbreviations

Symbol	Meaning
Abu	α-aminobutyric acid
Ac	acyl group
Acc	1-amino-1-cyclo(C_3-C_9)alkyl carboxylic acid
A3c	1-amino-1-cyclopropanecarboxylic acid
A4c	1-amino-1-cyclobutanecarboxylic acid
A5c	1-amino-1-cyclopentanecarboxylic acid
A6c	1-amino-1-cyclohexanecarboxylic acid
Aha	7-aminoheptanoic acid
Ahx	6-aminohexanoic acid
Aib	α-aminoisobutyric acid
Ala or A	alanine
β-Ala	β-alanine
Apn	5-aminopentanoic acid (HN-$(CH2)_4$-C(O)
Arg or R	arginine
hArg	homoarginine
Asn or N	asparagine
Asp or D	aspartic acid
Bal	3-benzothienylalanine

	Bip	4,4'-biphenylalanine, represented by the structure

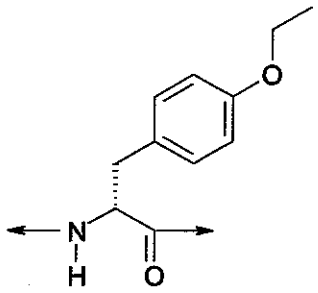


	Bpa	4-benzoylphenylalanine
	4-Br-Phe	4-bromo-phenylalanine
5	Cha	ß-cyclohexylalanine
	hCha	homo-cyclohexylalanine
	Chg	cyclohexylglycine
	Cys or C	cysteine
	hCys	homocysteine
10	Dab	2,4-diaminobutyric acid
	Dap	2,3-diaminopropionic acid
	Dip	ß,ß-diphenylalanine
	Doc	8-amino-3,6-dioxaoctanoic acid with the structure of:



15	2-Fua	β-(2-furyl)-alanine
	Gaba	4-aminobutyric acid
	Gln or Q	glutamine
	Glu or E	glutamic acid
	Gly or G	glycine
20	His or H	histidine
	3-Hyp	trans-3-hydroxy-L-proline, i.e., (2S, 3S)-3-hydroxypyrrolidine-2-carboxylic acid
	4-Hyp	4-hydroxyproline, i.e., (2S, 4R)-4-hydroxypyrrolidine-2-carboxylic acid
	Ile or I	isoleucine

Leu or L	leucine
hLeu	homoleucine
Lys or K	lysine
Met or M	methionine
ß-hMet	ß-homomethionine
1-Nal	ß-(1-naphthyl)alanine:
2-Nal	ß-(2-naphthyl)alanine
Nip	nipecotic acid
Nle	norleucine
Oic	octahydroindole-2-carboxylic acid
Orn	ornithine
2-Pal	ß-(2-pyridiyl)alanine
3-Pal	ß-(3-pyridiyl)alanine
4-Pal	ß-(4-pyridiyl)alanine
Pen	penicillamine
Phe or F	phenylalanine
hPhe	homophenylalanine
Pro or P	proline
hPro	homoproline
Ser or S	serine
Tle	tert-Leucine
Taz	ß-(4-thiazolyl)alanine
2-Thi	ß-(2-thienyl)alanine
3-Thi	ß-(3-thienyl)alanine
Thr or T	threonine
Trp or W	tryptophan
Tyr or Y	tyrosine
D-(Et)Tyr	has a structure of



Val or V valine

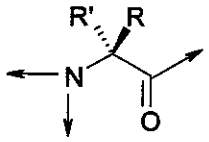
Certain other abbreviations used herein are defined as follows:

Boc:	*tert*-butyloxycarbonyl
Bzl:	benzyl
DCM:	dichloromethane
DIC:	N, N-diisopropylcarbodiimide
DIEA:	diisopropylethyl amine
Dmab:	4-{N-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl)-amino} benzyl
DMAP:	4-(dimethylamino)pyridine
DMF	dimethylformamide
DNP:	2,4-dinitrophenyl
Fm:	fluorenylmethyl
Fmoc:	fluorenylmethyloxycarbonyl
For:	formyl
HBTU:	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
cHex	cyclohexyl
HOAT:	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt:	1-hydroxy-benzotriazole
MBHA	4-methylbenzhydrylamine
Mmt:	4-methoxytrityl
NMP:	N-methylpyrrolidone
O-tBu	oxy-tert-butyl

Pbf:	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
tBu:	tert-butyl
TIS:	triisopropylsilane
TOS:	tosyl
Trt	trityl
TFA:	trifluoro acetic acid
TFFH:	tetramethylfluoroforamidinium hexafluorophosphate
Z:	benzyloxycarbonyl

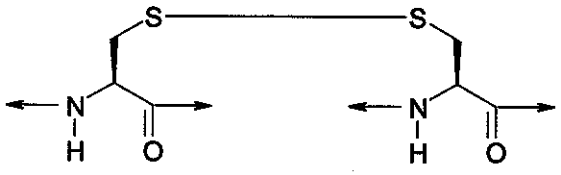
Unless otherwise indicated, with the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-C(R)(R')-CO-, wherein R and R' each is, independently, hydrogen or the side chain of an amino acid (e.g., R = CH_3 and R' = H for Ala), or R and R' may be joined to form a ring system.

For the N-terminal amino acid, the abbreviation stands for the structure of:

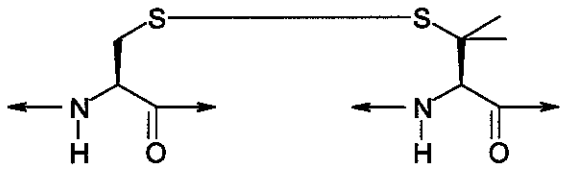


The designation "NH_2" in e.g., Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, indicates that the C-terminus of the peptide is amidated. Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys), or alternatively Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)- OH, indicates that the C-terminus is the free acid.

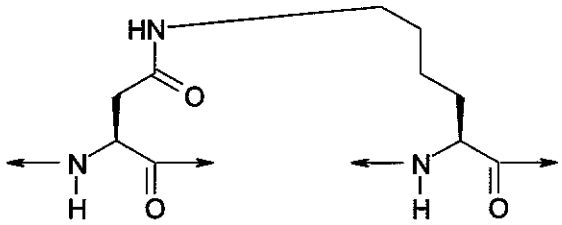
"-c(Cys-Cys)-" or "-cyclo(Cys-Cys)-" denotes the structure:



"-c(Cys-Pen)-" or "-cyclo(Cys-Pen)-" denotes the structure:



"-c(Asp-Lys)-" or "-cyclo(Asp-Lys)-" denotes the structure:



"Acyl" refers to R"-C(O)-, where R" is H, alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, alkenyl, substituted alkenyl, aryl, alkylaryl, or substituted alklyaryl, and is indicated in the general formula of a particular embodiment as "Ac".

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

"Hydroxyalkyl" refers to an alkyl group wherein one or more hydrogen atoms of the hydrocarbon group are substituted with one or more hydroxy radicals, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like.

"Substituted alkyl" refers to an alkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, $-NH_2$, $-NHCH_3$, $-NO_2$, and $-C_{1\text{-}20}$ alkyl, wherein said $-C_{1\text{-}20}$ alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens, $-CF_3$, $-OCH_3$, $-OCF_3$, and $-(CH_2)_{0\text{-}20}$-COOH. In different embodiments 1, 2, 3 or 4 substituents are present. The presence of $-(CH_2)_{0\text{-}20}$-COOH results in the production of an alkyl acid. Non-limiting examples of alkyl acids containing, or consisting of, $-(CH_2)_{0\text{-}20}$-COOH include

2-norbornane acetic acid, tert-butyric acid, 3-cyclopentyl propionic acid, and the like.

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

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

"Substituted heteroalkyl" refers to a heteroalkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, $-NH_2$, $-NHCH_3$, $-NO_2$, and $-C_{1\text{-}20}$ alkyl, wherein said $-C_{1\text{-}20}$ alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens, $-CF_3$, $-OCH_3$, $-OCF_3$, and $-(CH_2)_{0\text{-}20}$-COOH. In different embodiments 1, 2, 3 or 4 substituents are present.

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

"Substituted alkenyl" refers to an alkenyl wherein one or more hydrogens are replaced with one or more substituents selected from the group consisting of halogen (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, $-NH_2$, $-NHCH_3$, $-NO_2$, and $-C_{1\text{-}20}$ alkyl, wherein said $-C_{1\text{-}20}$ alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens, $-CF_3$, $-OCH_3$, $-OCF_3$, and $-(CH_2)_{0\text{-}20}$-COOH. In different embodiments 1, 2, 3 or 4 substituents are present.

"Aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to three conjugated or fused ring systems. Aryl includes carbocyclic aryl, heterocyclic aryl and biaryl groups. Preferably, the aryl is a 5- or 6-membered ring. Preferred atoms for a heterocyclic aryl are one or more sulfur, oxygen, and/or nitrogen. Non-limiting examples of aryl include phenyl, 1-naphthyl, 2-naphthyl, indole, quinoline, 2-imidazole, 9-anthracene, and the like. Aryl substituents are selected from the group

consisting of -C_{1-20} alkyl, -C_{1-20} alkoxy, halogen (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, -NH_2, -NO_2, -C_{1-20} alkyl substituted with halogens, -CF_3, -OCF_3, and -$(CH_2)_{0-20}$-COOH. In different embodiments the aryl contains 0, 1, 2, 3, or 4 substituents.

"Alkylaryl" refers to an "alkyl" joined to an "aryl".

The term "(C_1-C_{12})hydrocarbon moiety" encompasses alkyl, alkenyl and alkynyl and in the case of alkenyl and alkynyl there is C_2-C_{12}.

As used herein, the term "normalizing" functions or activities refers to those types of functions which may be considered to be involved in normal body function or homeostasis of an organism. Such functions include but are not limited to activities and functions affecting body temperature, blood pressure, heart rate, vascular tone, brain blood flow, blood glucose levels and the like.

As used herein, compounds which are considered to be "selective" for a particular melanocortin receptor are those compounds with a functional activity characterized by an EC_{50} at least about 2-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, at least about 17-fold, at least about 90-fold, at least about 200-fold, at least about 3000-fold or at least about 10,000-fold, or even greater, selectivity for any melanocortin receptor as compared to any other melanocortin receptor. For example, a selective melanocortin 4 receptor agonist of the invention exhibits a functional activity characterized by an EC_{50} at least about 15-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 1 receptor, the human melanocortin 3 receptor and the human melanocortin 5 receptor. Also for example, a selective melanocortin 4 receptor agonist of the invention exhibits a functional activity characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

Synthesis

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R^2 and R^3 of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C_1-C_{30})alkyl, may be attached

using reductive alkylation. Hydroxyalkyl groups, e.g., (C_1-C_{30})hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxyl group is protected with a t-butyl ester. Acyl groups, e.g., COE^1, may be attached by coupling the free acid, e.g., E^1COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxyl group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBt.

When R^1 is $-NH_2$, the synthesis of the peptide starts with an Fmoc-amino acid which is coupled to the Rink Amide MBHA resin. If R^1 is -OH, the synthesis of the peptide starts with a Fmoc-amino acid which is coupled to Wang resin.

In the synthesis of a peptide of this invention containing A6c and/or Aib, the coupling time is 2 hours for these residues and the residue immediately following them.

The following examples describe synthetic methods for making a peptide of this invention, which methods are well-known to those skilled in the art. Other methods are also known to those skilled in the art. The examples are provided for the purpose of illustration and are not meant to limit the scope of the present invention in any manner.

EXAMPLES

Example 1: Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:7

The title peptide was synthesized on an Advanced ChemTech model 396® multiple peptide synthesizer (Louisville, KY 40228) using Fluorenylmethyloxycarbonyl (Fmoc) chemistry. A Rink Amide 4-methylbenzylhydrylamine (MBHA) resin (Novabiochem®, San Diego, CA) with substitution of 0.58 mmol/g was used. The Fmoc amino acids (Novabiochem®, CA and Chem-Impex®, IL) used were Fmoc-Nle-OH, Fmoc-Cys(Trt)-OH, Fmoc-D-Ala-OH, Fmoc-His(Trt)-OH, Fmoc-D-Phe-OH, Fmoc-Arg(Pbf)-OH, and Fmoc-Trp(Boc)-OH. The synthesis was carried out on a 0.035 mmol scale. The Fmoc groups were

removed by treatment with 25% piperidine in *N,N*-dimethylformamide (DMF) for 30 minutes. In each coupling step, the Fmoc amino acid (10 eq, 0.35 mmol), N, N-diisopropylcarbodiimide (DIC) (10 eq, 0.35 mmol), and 1-hydroxy-benzotriazole (HOBt) (10 eq, 0.35 mmol) were used in DMF (1.4 mL). After washing with DMF, double-coupling was performed with the Fmoc-amino acid (10 eq, 0.35 mmol), 2-(1-H-benzotriazole-1-yl)-1,1,2,3-tetramethyluronium hexafluorophosphate (HBTU) (8 eq, 0.28 mmol), HOBT (10 eq, 0.35 mmol), and diisopropylethyl amine (DIEA) (20 eq, 0.7 mmol) in DMF (1.26 mL). The ACT 396® multiple peptide synthesizer was programmed to perform the following reaction cycle: (1) washing with DMF, (2) removing Fmoc protecting group with 25% piperidine in DMF for 30 minutes, (3) washing with DMF, (4) coupling with Fmoc amino acid in the presence of DIC and HOBT for 1 hour, (5) washing with DMF, (6) double-coupling with the same Fmoc amino acid in step 4 in the presence of HBTU, HOBt, and DIEA for 1 hour. The resin was coupled successively according to the sequence of the title peptide. After the peptide chain was assembled and the last Fmoc- protecting group was removed, the resin was washed completely by using DMF and dichloromethane (DCM).

To cleave the title peptide, the resin was treated with a solution (1.5 mL) of TFA, H_2O and triisopropylsilane (TIS) (v/v/v: 90/6.2/3.8) for 2 hours at room temperature. The resin was filtered off and the filtrate was poured into 30 mL of ether. The precipitate was collected by centrifugation. This crude product was dissolved in water (~7 mL) and the pH of the aqueous solution was adjusted to ~7.5 by adding 2N NH_4HCO_3. The solution was opened to the air for 72 hours at room temperature. The resulting crude product was purified on a reverse-phase preparative HPLC system with a column (4 x 43 cm) of C_{18} DYNAMAX-100® A^0 (Varian®, Walnut Creek, CA). The column was eluted over approximately 1 hour using a linear gradient of 85% A:15% B to 30% A:70% B, where A was 0.1% TFA in water and B was 0.1% TFA in acetonitrile. The fractions were checked by analytical HPLC and those containing pure product were pooled and lyophilized to dryness to give 10.3 mg (27% yield) of a white solid. Purity was assayed using HPLC and found to be approximately 88%. Electro-spray ionization mass spectrometry (ESI-MS) analysis gave the molecular weight at 1073.6 (in agreement with the calculated

molecular weight of 1074.3).

Example 2: Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2 SEQ ID NO:6

The title peptide was synthesized on an Applied Biosystems® (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnolzer, et al., Int. J. Peptide Protein Res., 40:180 (1992). 4-methylbenzhydrylamine (MBHA) resin (Peninsula®, Belmont, CA) with the substitution of 0.91 mmol/g was used. The Boc amino acids (Novabiochem®, San Diego, CA and Chem-Impex®, Wood Dale, IL) used were: Boc-Cha-OH, Boc-Asp(OFm)-OH, Boc-His(DNP)-OH, Boc-D-Phe-OH, Boc-Arg(Tos)-OH, Boc-Trp(For)-OH, Boc-Gaba-OH, and Boc-Lys(Fmoc)-OH. The synthesis was carried out on a 0.20 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 minute. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were 5 minutes.

At the end of the assembly of Boc-Asp(OFm)-His(DNP)-D-Phe-Arg(Tos)-Trp(For)-Gaba-Lys(Fmoc)-MBHA, the peptide-resin was transferred into a reaction vessel on a shaker. The resin was treated twice with 25% piperidine in DMF for 15 minutes per session, washed with DMF, and shaken with bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP) (6 eq, 0.3 mmol), DIEA (1 mL), and 4-(dimethylamino)pyridine (DMAP) (24 mg) in DMF (2 mL) for 12 hours. After washing with DMF, the resin was treated twice with 100% TFA for 2 minutes per treatment, washed with DMF and DCM, and then dried under reduced pressure. One fourth of the peptide-resin (0.05 mmol) was used for the next coupling with Boc-Cha-OH (10 eq, 0.5 mmol) in the presence of HBTU (9 eq, 0.45 mmol) and DIEA (0.25 mL) in DMF for 10 minutes. After the deprotection with 100% TFA in two sessions lasting approximately 2 minutes each, the peptide-resin was then washed with DMF. The final capping step was done by shaking the resin with acetic anhydride (40 eq, 2.0 mmol) and DIEA (20 eq, 1.0 mmol) in DMF for 1 hour. After washing with DMF, the resin was treated twice with a solution of 20% mercaptoethanol/10% DIEA in DMF, each treatment lasting approximately 30 minutes, to remove the DNP group on

the Histidine side chain. The formyl group on the side chain of Tryptophan was removed by shaking with a solution of 15% ethanolamine/ 15% water/ 70% DMF twice for 30 minutes per shaking. The peptide-resin was washed with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole and dithiothreitol (30 mg) at 0°C for 75 minutes. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase VYDAC® C_{18} column (Nest Group®, Southborough, MA). The column was eluted with a linear gradient (10% to 50% of solution B over 40 minutes) at a flow rate of 10 mL/minute (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 5.1 mg of a white solid was obtained. Yield was 8.9%. Purity was 94.5% based on analytical HPLC analysis. Electro-spray mass spectrometer (MS(ES))S analysis gave the molecular weight at 1148.5 (in agreement with the calculated molecular weight of 1148.3).

Other peptides of the invention can be prepared by a person of ordinary skill in the art using synthetic procedures analogous to those disclosed generally hereinabove and/or to those disclosed specifically in the foregoing examples, as were the compounds depicted in Tables 1A and 1B.

Other peptides of the invention can be prepared by a person of ordinary skill in the art using synthetic procedures analogous to those disclosed generally hereinabove and/or to those disclosed specifically in the foregoing examples, as were the compounds depicted in Tables 1A and 1B.

The following examples can be made according to the appropriate procedures described above:

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2; SEQ ID NO:1

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH_2; SEQ ID NO:1

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2; SEQ ID NO:2

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:3

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:3

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2; SEQ ID NO:3

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2; SEQ ID NO:2

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2; SEQ ID NO:4

Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:5

Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:6

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:6

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:7

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:8

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2;SEQ ID NO:8

Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2;SEQ ID NO:8

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:9

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:9

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:9

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2;SEQ ID NO:9

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH_2;SEQ ID NO:9

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2; SEQ ID NO:10

Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;SEQ ID NO:11

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

n-butanoyl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:12

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-*ß*-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:11

Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2; SEQ ID NO:13

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH_2; SEQ ID NO:14

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH_2; SEQ ID NO:15

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; SEQ ID NO:16

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2; SEQ ID NO:16

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2; SEQ ID NO:16

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2; SEQ ID NO:17

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:17

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2; SEQ ID NO:18

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH_2; SEQ ID NO:18

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH_2; SEQ ID NO:18

Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:61

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH_2;SEQ ID NO:19

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2; SEQ ID NO:20

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;SEQ ID NO:21

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;SEQ ID NO:22

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;SEQ ID NO:22

D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:23

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:24

D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:25

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:24

D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:26

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2; SEQ ID NO:26

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH_2; SEQ ID NO:54

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH_2; SEQ ID NO:54

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2; SEQ ID NO:54

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:54

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2; SEQ ID NO:54

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2; SEQ ID NO:27

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2;SEQ ID NO:28

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2; SEQ ID NO:28

Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2; SEQ ID NO:55

Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2; SEQ ID NO:55

Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;SEQ ID NO:56

Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2; SEQ ID NO:56

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2; SEQ ID NO:57

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2; SEQ ID NO:57

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:57

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH; SEQ ID NO:29

Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2;SEQ ID NO:30

Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:30

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:31

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:32

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:32

Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:33

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:34

Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:34

Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:35

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH; SEQ ID NO:36

Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2; SEQ ID NO:37

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH_2; SEQ ID NO:58

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2; SEQ ID NO:38

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2; SEQ ID NO:38

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2; SEQ ID NO:39

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2;SEQ ID NO:39

Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:40

Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2; SEQ ID NO:40

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-OH; SEQ ID NO:41

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-OH; SEQ ID NO:42

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-OH; SEQ ID NO:43

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-OH; SEQ ID NO:43

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-OH; SEQ ID NO:43

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-OH; SEQ ID NO:42

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-OH; SEQ ID NO:41

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH; SEQ ID NO:29

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH; SEQ ID NO:44

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-OH; SEQ ID NO:45

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-OH; SEQ ID NO:45

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-OH; SEQ ID NO:45

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-OH; SEQ ID NO:45

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-OH; SEQ ID NO:46

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-OH; SEQ ID NO:46

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-OH; SEQ ID NO:46

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-OH; SEQ ID NO:46

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH; SEQ ID NO:47

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH; SEQ ID NO:29

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:50

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2; SEQ ID NO:50

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; SEQ ID NO:51

Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:52

Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2; SEQ ID NO:52

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; SEQ ID NO:51

Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2; SEQ ID NO:53

Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2; SEQ ID NO:53

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; SEQ ID NO:49 and

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH SEQ ID NO:48.

Other peptides of the invention can be prepared by a person of ordinary skill in the art using synthetic procedures analogous to those disclosed generally hereinabove and/or to those disclosed specifically in the foregoing examples, as were the compounds depicted in Tables 1A and 1B.

TABLES 1A and 1B - Molecular Weight and Purity for Selected Embodiments

Table 1A

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity	SEQ ID NO:
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2	1095.27	1095.2	96.4	SEQ ID NO:1
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH_2	1149.36	1149.05	96	SEQ ID NO:1
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2	1116.38	1115.8	98	SEQ ID NO:2
D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH_2	1167.38	1167.3	99	SEQ ID NO:3
D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2	1167.38	1167.5	93	SEQ ID NO:3
D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2	1181.41	1181.9	99	SEQ ID NO:3
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	1102.35	1103	99	SEQ ID NO:2
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2	1123.32	1123.9	99	SEQ ID NO:4
Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1121.31	1121.2	93	SEQ ID NO:5
Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1193.37	1193.2	92.6	SEQ ID NO:6
Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1149.36	1149.4	94.5	SEQ ID NO:6
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1109.3	1109.2	91.5	SEQ ID NO:6
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.6	98.3	SEQ ID NO:7
Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.4	91	SEQ ID NO:7

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity	SEQ ID NO:
Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1088.4	93	SEQ ID NO:7
Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1088.4	80	SEQ ID NO:7
Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2	1060.27	1060.4	90	SEQ ID NO:7
Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.4	93	SEQ ID NO:8
Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.4	81	SEQ ID NO:8
Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.4	92	SEQ ID NO:8
Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1088.4	94	SEQ ID NO:8
Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1088.4	91	SEQ ID NO:8
Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2	1060.27	1060.4	96	SEQ ID NO:8
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.4	66	SEQ ID NO:9
Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.2	94	SEQ ID NO:9
Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1088.32	1088.2	93	SEQ ID NO:9
Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1088.32	1088.4	90	SEQ ID NO:9
Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1060.27	1060.4	91	SEQ ID NO:9
Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.4	65	SEQ ID NO:10
Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.2	93	SEQ ID NO:10
Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.4	92	SEQ ID NO:10
Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1088.32	1088.4	90	SEQ ID NO:10
Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1088.32	1088	95	SEQ ID NO:10
Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1147.35	1147.4	97.5	SEQ ID NO:11
Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1135.33	1135.1	99	SEQ ID NO:11

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity	SEQ ID NO:
Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1163.39	1163.4	99	SEQ ID NO:11
Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1149.36	1149.2	99	SEQ ID NO:11
Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1107.28	1107	98.9	SEQ ID NO:11
Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1107.28	1107.4	99	SEQ ID NO:11
Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1123.32	1123.2	99	SEQ ID NO:11
Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1163.39	1163.6	94	SEQ ID NO:59
Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1143.31	1143.3	96.9	SEQ ID NO:11
Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1143.31	1143.3	96.5	SEQ ID NO:11
Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1135.33	1135.4	99	SEQ ID NO:11
n-Butyryl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1177.41	1177.5	88.6	SEQ ID NO:60
Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1157.34	1157.2	70	SEQ ID NO:11
Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1141.36	1141.2	89	SEQ ID NO:11
Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1081.24	1080.9	92.5	SEQ ID NO:11
Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1135.33	1135.2	85	SEQ ID NO:13
Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1149.36	1149.1	87	SEQ ID NO:13
Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1095.27	1095.4	98.6	SEQ ID NO:13
Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1109.3	1109.2	93.8	SEQ ID NO:13
Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1129.29	1129.2	81.9	SEQ ID NO:13
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH_2	1095.27	1095.3	97	SEQ ID NO:14
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH_2	1095.27	1095.3	82	SEQ ID NO:14
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH_2	1109.3	1109.1	99	SEQ ID NO:14

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity	SEQ ID NO:
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH_2	1137.35	1137.4	98	SEQ ID NO:14
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH_2	1123.32	1123.3	97.3	SEQ ID NO:14
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH_2	1102.35	1102	99	SEQ ID NO:15
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH_2	1088.32	1087.8	97	SEQ ID NO:15
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH_2	1116.38	1116.2	99	SEQ ID NO:15
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2	1074.3	1073.8	99.9	SEQ ID NO:15
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH_2	1074.3	1073.8	99.9	SEQ ID NO:15
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	1124.36	1123.6	96.1	SEQ ID NO:16
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2	1135.38	1134.5	99.1	SEQ ID NO:16
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2	1135.38	1134.6	94.8	SEQ ID NO:16
nButanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2	1113.37	1112.6	95.7	SEQ ID NO:17
nButanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1102.35	1101.5	99.9	SEQ ID NO:17
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2	1085.32	1084.4	97.7	SEQ ID NO:18
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH_2	1085.32	1084.5	96.6	SEQ ID NO:18
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH_2	1091.35	1090.4	96.2	SEQ ID NO:18
Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2	1132.33	1131.5	99.9	SEQ ID NO:61
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH_2	1095.27	1094.6	99.9	SEQ ID NO:19
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2	1141.41	1140.5	95.6	SEQ ID NO:20
Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1102.35	1101.6	99.9	SEQ ID NO:21
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	1102.35	1101.6	99.9	SEQ ID NO:22
Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	1130.4	1129.6	99.9	SEQ ID NO:22

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity	SEQ ID NO:
D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2	1181.41	1181.7	96.9	SEQ ID NO:23
D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2	1211.43	1211.7	97.1	SEQ ID NO:24
D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2	1204.44	1204.6	99	SEQ ID NO:25
D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2	1225.46	1225.7	97	SEQ ID NO:24
D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2	1218.47	1218.8	99	SEQ ID NO:26
D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2	1262.52	1263	99	SEQ ID NO:26
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH_2	1131.35	1131.2	96.8	SEQ ID NO:54
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH_2	1145.37	1145.3	96.4	SEQ ID NO:54
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2	1145.37	1145.2	98.2	SEQ ID NO:54
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1159.4	1159.2	95.1	SEQ ID NO:54
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	1173.43	1173.3	96.8	SEQ ID NO:54
Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	1060.31	1060.3	98.5	SEQ ID NO:27
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2	1095.27	1094.7	96.2	SEQ ID NO:28
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2	1112.32	1111.7	96.5	SEQ ID NO:28
Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	1090.25	1089.6	99.9	SEQ ID NO:55
Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2	1101.27	1100.6	98.3	SEQ ID NO:55
Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	1032.22	1031.5	95.2	SEQ ID NO:56
Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2	1043.24	1042.5	95.6	SEQ ID NO:56
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	1144.39	1144.6	95.3	SEQ ID NO:57
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2	1145.37	1144.6	97.3	SEQ ID NO:57
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1158.41	1158.6	96.5	SEQ ID NO:57

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity	SEQ ID NO:
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH	1103.33	1103	99.9	SEQ ID NO:29
Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1087.6	99.9	SEQ ID NO:30
Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2	1102.35	1101.7	99.9	SEQ ID NO:30
Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2	1116.38	1115.7	99.9	SEQ ID NO:30
Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2	1116.38	1115.8	97.4	SEQ ID NO:30
Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2	1116.38	1115.5	96.5	SEQ ID NO:30
Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2	1156.44	1155.6	96.4	SEQ ID NO:30
Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1116.38	1115.7	95	SEQ ID NO:31
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1116.38	1115.5	99.9	SEQ ID NO:32
Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1144.43	1144	99.9	SEQ ID NO:32
Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1088.32	1088	96.7	SEQ ID NO:33
Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1128.39	1128.4	95.8	SEQ ID NO:33
Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1088.32	1088.4	95	SEQ ID NO:33
Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1122.34	1122	95.2	SEQ ID NO:33
Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1074.3	1074.6	95.4	SEQ ID NO:33
Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1172.4	1172.2	95.2	SEQ ID NO:33
Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1046.29	1046.4	97.6	SEQ ID NO:34
Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1080.3	1080	95.8	SEQ ID NO:34
Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1099.35	1099.6	96.6	SEQ ID NO:35
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH	1075.28	1075.2	99.9	SEQ ID NO:36
Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2	1088.32	1088	95.8	SEQ ID NO:37

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity	SEQ ID NO:
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH_2	1183.4	1182.85	99.9	SEQ ID NO:58
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2	1145.33	1145	99.99	SEQ ID NO:38
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-βAla-Lys)-NH_2	1145.33	1145	99.99	SEQ ID NO:38
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2	1138.38	1137.8	99.99	SEQ ID NO:39
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2	1166.44	1166	99	SEQ ID NO:39
Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	1207.4	1206.9	99	SEQ ID NO:40
Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	1199.42	1198.8	100	SEQ ID NO:40
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1117.3	1116.9	95.10	SEQ ID NO:50
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1117.33	1116.8	99.2	SEQ ID NO:50
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	1145.38	1144.9	96.4	SEQ ID NO:51
Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1159.41	1158.9	99.9	SEQ ID NO:52
Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1159.41	1159.1	99	SEQ ID NO:52
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	1145.38	1145.1	99	SEQ ID NO:51
Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	1138.3	1138.0	98.0	SEQ ID NO:53
Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	1138.3	1138.1	99.0	SEQ ID NO:53

Table 1B

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity	SEQ ID NO:
Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	1167.39	1167.40	99.9	SEQ ID NO:49

Example 3: *In vitro* studies

Compounds of the present invention can be and were tested for activity as ligands of one or more of the melanocortin receptors according to the following

procedures. One skilled in the art would know that procedures similar to those described herein may be used to assay the binding activities of the compounds of the invention to melanocortin receptor molecules.

Radioligand Binding Assays

Cellular membranes used for the *in vitro* receptor binding assays were obtained from transgenic CHO-K1 cells stably expressing hMC-R receptor subtypes 1, 3, 4 or 5. The CHO-K1 cells expressing the desired hMC-R receptor type were sonicated (Branson® setting 7, approximately 30 sec) in ice-cold 50 mM Tris-HCl at pH 7.4 and then centrifuged at 39,000 g for 10 minutes at approximately 4°C. The pellets were resuspended in the same buffer and centrifuged at 50,000 g for 10 minutes at approximately 4°C. The washed pellets containing the cellular membranes were stored at approximately - 80°C.

Competitive inhibition of [^{125}I](Tyr^2)-(Nle^4-D-Phe^7)α-MSH ([^{125}I]-NDP-α-MSH, Amersham Biosciences®) binding was carried out in polypropylene 96 well plates. Cell membranes (1-10 μg protein/well) prepared as described above were incubated in 50 mM Tris-HCl at pH 7.4 containing 0.2% bovine serum albumin (BSA), 5 mM $MgCl_2$, 1 mM $CaCl_2$ and 0.1 mg/mL bacitracin, with increasing concentrations of the test compound and 0.1-0.3 nM [^{125}I]-NDP-α-MSH for approximately 90-120 minutes at approximately 37°C. Bound [^{125}I]-NDP-α-MSH ligand was separated from free [^{125}I]-NDP-α-MSH by filtration through GF/C glass fiber filter plates (Unifilter®; Packard) presoaked with 0.1 % (w/v) polyethylenimine (PEI), using a Packard Filtermate® harvester. Filters were washed three times with 50 mM Tris-HCl at pH 7.4 at a temperature of approximately 0-4°C and then assayed for radioactivity using a Packard Topcount® scintillation counter. Binding data were analyzed by computer-assisted non-linear regression analysis (XL fit; IDBS).

A selection of the preferred embodiments was tested using the above-discussed assay and the binding constants (Ki in nM) are reported in Tables 2A, 2B and 2C.

TABLES 2A, 2B and 2C - Radioligand Binding Assay Data for Selected Compounds

Table 2A

Compound	Ki hMC 1-R	Ki hMC 3-R	Ki hMC4-R	Ki hMC5-R	Ki hMC1-R/ MC4-R	SEQ ID NO:
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	3.87	10.1	2.09	430	1.9	SEQ ID NO:50
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	4.01	12.1	1.76	352	2.3	SEQ ID NO:50
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	8.29	13.3	2.78	816	3.0	SEQ ID NO:51
Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	3.93	172	11.0	538	0.36	SEQ ID NO:52
Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1.81	20.5	4.57	502	0.4	SEQ ID NO:52
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	9.67	22.0	4.2	1900	2.3	SEQ ID NO:51
Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	0.79	45.5	1.21	493	0.6	SEQ ID NO:53
Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	0.68	20.7	1.01	783	0.7	SEQ ID NO:53

Table 2B

Compound	Ki hMC1-R	Ki hMC 3-R	Ki hMC4-R	Ki hMC 5-R	Ki hMC1-R /MC4-R	SEQ ID NO:
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2	114	63.9	3.07	1657	37.1	SEQ ID NO:16
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	11	26	7.6	1800	1.4	SEQ ID NO:7
D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2	0.05	9.3	1.1	2.9	0.0	SEQ ID NO:24
Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	0.07	4.1	0.85	8.8	0.1	SEQ ID NO:27
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	0.12	10	0.43	0.42	0.3	SEQ ID NO:32
Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.05	1.3	0.47	0.2	0.1	SEQ ID NO:34
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2	0.0996	9318	0.617	10.9	0.16	SEQ ID NO:1
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2	.0132	16.1	1.23	0.359	0.11	SEQ ID NO:2
D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2	0.207	43.2	2.58	344	0.08	SEQ ID NO:3

Compound	Ki hMC1-R	Ki hMC 3-R	Ki hMC4-R	Ki hMC 5-R	Ki hMC1-R /MC4-R	SEQ ID NO:
D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2	0.420	106	4.75	1260	0.09	SEQ ID NO:3
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	0.0951	9.33	0.894	13.4	0.11	SEQ ID NO:2
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2	0.999	300	11.1	431	0.09	SEQ ID NO:4
Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.106	11.8	1.49	110	0.07	SEQ ID NO:6
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.0506	9.89	1.04	16.3	0.05	SEQ ID NO:6
Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.884	223	22.5	609	0.04	SEQ ID NO:11
Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.721	93.5	56.0	747	0.01	SEQ ID NO:11
Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.227	14.5	2.99	164	0.08	SEQ ID NO:11
Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.277	25.2	3.37	203	0.08	SEQ ID NO:11
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2	0.323	14.1	1.96	24.0	0.16	SEQ ID NO:15
Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	34.1	118	17.0	5560	2.01	SEQ ID NO:21
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	29.1	22.8	3.84	2550	7.58	SEQ ID NO:22
D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2	0.442	123	10.3	521	0.04	SEQ ID NO:23
D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2	5.80	3370	583	1130	0.01	SEQ ID NO:25
D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2	0.0567	31.4	14.7	9.27	0	SEQ ID NO:24
D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2	1.68	1260	172	1220	0.01	SEQ ID NO:26
D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2	0.128	85.6	36.9	38.0	0	SEQ ID NO:26
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH_2	0.352	149	3.01	339	0.12	SEQ ID NO:54
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH_2	3.93	876	48.0	4940	0.08	SEQ ID NO:54
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2	0.995	287	4.80	766	0.21	SEQ ID NO:54

Compound	Ki hMC1-R	Ki hMC 3-R	Ki hMC4-R	Ki hMC 5-R	Ki hMC1-R /MC4-R	SEQ ID NO:
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.848	184	3.76	956	0.23	SEQ ID NO:54
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	1.10	228	7.58	859	0.15	SEQ ID NO:54
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2	0.659	98.9	2.55	4.19	0.26	SEQ ID NO:28
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2	4.12	445	50.6	4300	0.08	SEQ ID NO:28
Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	111	1710	47.7	694	2.33	SEQ ID NO:55
Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2	262	2500	96.4	1460	2.72	SEQ ID NO:55
Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	199	5990	96.7	> 10000	2.06	SEQ ID NO:56
Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2	132	4560	40.7	8810	3.24	SEQ ID NO:56
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	9.12	1130	22.1	2860	0.41	SEQ ID NO:57
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2	1.00	227	5.55	496	0.18	SEQ ID NO:57
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.536	169	3.12	358	0.17	SEQ ID NO:57
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH	32.1	330	17.4	165	1.84	SEQ ID NO:29
Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2	10.6	41.1	7.69	54.9	1.38	SEQ ID NO:30
Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2	13.0	104	10.1	40	1.29	SEQ ID NO:30
Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2	4.28	38.5	9.0	12.5	0.48	SEQ ID NO:30
Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2	1.60	6.82	4.13	5.57	0.39	SEQ ID NO:30
Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2	12.0	85.8	11.2	40	1.07	SEQ ID NO:30
Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2	0.353	2.08	1.41	0.857	0.25	SEQ ID NO:30
Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.537	86.1	5.89	2.56	0.09	SEQ ID NO:31
Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	0.744	178	3.51	2.69	0.21	SEQ ID NO:32
Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.216	17.4	0.995	0.486	0.22	SEQ ID NO:33

Compound	Ki hMC1-R	Ki hMC 3-R	Ki hMC4-R	Ki hMC 5-R	Ki hMC1-R /MC4-R	SEQ ID NO:
Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.107	9.11	0.884	0.354	0.12	SEQ ID NO:33
Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.148	13.9	1.06	0.423	0.14	SEQ ID NO:33
Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.254	18.5	2.13	0.714	0.12	SEQ ID NO:33
Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.256	29.9	1.98	0.864	0.13	SEQ ID NO:33
Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.560	39.2	2.94	2.73	0.19	SEQ ID NO:33
Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.186	15.2	4.93	0.537	0.04	SEQ ID NO:34
Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	21.1	151	10.4	92.6	2.03	SEQ ID NO:35
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH	30.7	152	15.6	114	1.97	SEQ ID NO:36
Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2	5.20	150	138	20.3	0.04	SEQ ID NO:37
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH_2	4.89	290	21.3	11.1	0.23	SEQ ID NO:58
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	25.5	3.82	7.61	102	3.35	SEQ ID NO:16
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2	32.5	5.85	2.53	94.6	12.85	SEQ ID NO:16
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2	22.2	12.7	16.6	125	1.34	SEQ ID NO:20
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2	1.17	1.56	0.277	3.24	4.22	SEQ ID NO:38
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2	0.648	2.78	0.329	1.4	1.97	SEQ ID NO:38
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2	0.393	1.86	0.375	1.11	1.05	SEQ ID NO:39
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2	0.333	2.91	0.998	0.366	0.33	SEQ ID NO:39
Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	0.461	2.45	0.931	1.37	0.50	SEQ ID NO:40
Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	0.576	3.98	2.82	3.91	0.20	SEQ ID NO:40

Table 2C

Compound	Ki hMC1-R	Ki hMC 3-R	Ki hMC4-R	Ki hMC 5-R	Ki hMC1-R /MC4-R	SEQ ID NO:
Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	17.9	1.68	0.256	23.4	69.9	SEQ ID NO:49

cyclic AMP Bioassay

Intracellular cyclic AMP (cAMP) levels were determined by an electrochemiluminescence (ECL) assay (Meso Scale Discovery ®, Gaithersburg, MD; referred to hereinafter as MSD). CHO-K1 cells stably expressing the hMC receptor subtypes were suspended in RMPI 1640® assay buffer (RMPI 1640 buffer contains 0.5 mM isobutylmethylxanthine (IBMX), and 0.2% protein cocktail (MSD blocker A)). Transgenic CHO-K1 cells stably expressing hMC receptor subtypes 1, 3, 4 or 5 were dispensed at a density of approximately 7,000 cells/well in 384-well Multi-Array® plates (MSD) containing integrated carbon electrodes and coated with anti-cAMP antibody. Increasing concentrations of the test compounds were added and the cells were incubated for approximately 40 minutes at approximately 37°C. Following this incubation, lysis buffer (HEPES-buffered saline solution with $MgCl_2$ and Triton X-100® at ph 7.3) containing 0.2% protein cocktail and 2.5 nM TAG™ ruthenium-labeled cAMP (MSD) was added and the cells were incubated for approximately 90 minutes at room temperature. At the end of the second incubation period read buffer (Tris-buffered solution containing an ECL co-reactant and Triton X-100 at ph 7.8) was added and the cAMP levels in the cell lysates were immediately determined by ECL detection with a Sector Imager 6000 reader® (MSD). Data were analyzed using a computer-assisted non-linear regression analysis (XL fit; IDBS) and reported as either an EC_{50} value or a Kb value.

EC_{50} represents the concentration of an agonist compound needed to obtain 50% of the maximum reaction response, *e.g.*, 50% of the maximum level of cAMP as determined using the assay described above. The Kb value reflects the potency of an antagonist and is determined by Schild analysis. In brief, concentration-response curves of an agonist are carried out in the presence of increasing concentrations of an antagonist. The Kb value is the concentration of antagonist which would produce a

2-fold shift in the concentration-response curve for an agonist. It is calculated by extrapolating the line on a Schild plot to zero on the y-axis.

A selection of compounds was tested using the above-discussed assays and the results are reported in Tables 3A, 3B, 3C, and 3D.

TABLES 3A, 3B, 3C, and 3D - cAMP Bioassay Data for Selected Compounds

Table 3A

Compound	EC_{50} hMC1-R	EC_{50} hMC3-R	EC_{50} hMC4-R	EC_{50} hMC5-R	EC_{50} hMC1-R /MC4-R	SEQ ID NO:
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	5.79	5.25	0.313	1630	18.0	SEQ ID NO:50
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	6.17	5.6	0.397	1020	16.0	SEQ ID NO:50
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	26.5	10.5	0.493	2440	54.0	SEQ ID NO:51
Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	8.43	32.4	0.959	2140	9.0	SEQ ID NO:52
Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	4.23	8.09	0.719	23.2	6.0	SEQ ID NO:52
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	48.3	13.3	0.79	10000	61.0	SEQ ID NO:51
Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	1.48	5.76	0.078	297	19.0	SEQ ID NO:53
Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	1.39	2.89	0.055	467	25.0	SEQ ID NO:53

ND = not determined

Table 3B

Compound	EC_{50} hMC 1-R	EC_{50} hMC 3-R	EC_{50} hMC4-R	EC_{50} hMC5-R	EC_{50} hMC1-R /MC4-R	SEQ ID NO:

Compound	EC_{50} hMC 1-R	EC_{50} hMC 3-R	EC_{50} hMC4-R	EC_{50} hMC5-R	EC_{50} hMC1-R /MC4-R	SEQ ID NO:
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	2.4	0.33	0.078	420	31	SEQ ID NO:7
D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2	0.35	1.1	0.11	0.37	3	SEQ ID NO:24
Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	0.31	0.27	0.018	3.1	17	SEQ ID NO:27
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	0.28	0.24	0.028	3.9	10	SEQ ID NO:32
Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.37	0.1	0.021	1.7	18	SEQ ID NO:34
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2	0.834	0.145	0.128	2.79	6.52	SEQ ID NO:1
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	0.76	0.199	0.0492	1.73	15.45	SEQ ID NO:2
Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	3.26	0.189	0.0949	30.2	34.35	SEQ ID NO:6
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1.37	0.628	0.131	3.48	10.46	SEQ ID NO:6
Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	2.27	3.32	7.24	415	0.31	SEQ ID NO:11
Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	ND	1.89	0.531	ND	ND	SEQ ID NO:21
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	14.3	2.03	0.183	2240	78.14	SEQ ID NO:22
D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2	0.345	2.71	5376	2.38	0.06	SEQ ID NO:24
D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2	0.685	81.8	86.9	31.8	0.01	SEQ ID NO:26
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2	0.931	3.22	1.65	>10000	0.56	SEQ ID NO:28
Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2	3.24	0.465	0.0915	78.5	35.41	SEQ ID NO:30

Compound	EC_{50} hMC 1-R	EC_{50} hMC 3-R	EC_{50} hMC4-R	EC_{50} hMC5-R	EC_{50} hMC1-R /MC4-R	SEQ ID NO:
Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2	0.819	0.541	0.453	45.3	1.81	SEQ ID NO:30

ND = not determined

Table 3C

Compound	EC50 hMC1-R	Kb hMC3-R	Kb MC4-R	EC50 hMC5-R	SEQ ID NO:
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	17.6	12.4	38.8	11.8	SEQ ID NO:16
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2	0.619	2.98	0.109	0.189	SEQ ID NO:38
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2	0.913	0.536	0.346	0.489	SEQ ID NO:38
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2	0.231	18.4	0.782	0.153	SEQ ID NO:39
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2	0.581	10.8	0.967	0.126	SEQ ID NO:39
Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	0.413	9.32	0.824	0.307	SEQ ID NO:40
Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH2	1.27	3.02	0.442	0.736	SEQ ID NO:40
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2	**383**	**61.5**	**53.6**	**2842**	**SEQ ID NO:16**

Table 3D

Compound	EC50 hMC1 -R	Kb hMC3 -R	Kb MC4-R	EC50 hMC5 -R	SEQ ID NO:
Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	**193**	**5.72**	**1.58**	**1111**	**SEQ ID NO:49**

Example 4: *In vivo* studies

Compounds of the present invention can be and were tested for an effect upon food intake and/or body weight according to the following procedures. One skilled in the art would know that procedures similar to those described herein may be used to assay the effect of the compounds of the invention upon food intake and/or body weight.

Ligand compounds activating melanocortin receptors tested in the *in vivo* studies were as follows (Table 4):

Table 4

Ligand Code	Structure
Compound A	Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:7
Compound B	Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 SEQ ID NO:22
Compound C	Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2 SEQ ID NO:32
Compound D	D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2 SEQ ID NO:24
Compound E	Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:50
Compound F	Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 SEQ ID NO:50
Compound G	Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 SEQ ID NO:51

Acute feeding experiments (fasting)

Male Sprague Dawley rats (250g) were housed in individual cages and maintained under 12:12 hour light:dark conditions. The rats were fasted for 18 hours prior to the start of the experiment with water available *ad libitum*. At time 0, the rats were injected subcutaneously (sc) with selected compounds at doses of either 500 or 100 nmole/kg, or with vehicle, and were provided with food. Individual food consumption was measured at about 1, 2, 3, 4, 5 and 6 hours after injection. Data for selected compounds of the invention are reported in Figures 1A and 1B.

Acute feeding experiments (non fasting)

Male Sprague Dawley rats (250g) are housed in individual cages and maintained under 12:12 hour light:dark conditions. Food and water is available *ad libitum* throughout the experiment. At time 0, the rats are injected sc with compound at doses of either 500 or 100 nmole/kg, or with vehicle. Individual food consumption is measured at about 1, 2, 3, 4, 5 and 6 hours after injection.

Chronic feeding experiments

Male Sprague Dawley rats (250g) were housed in individual cages and maintained under 12:12 hour light:dark conditions with both food and water available *ad libitum*. The rats were injected sc 3x/day (approximately 0800 hour, 1200 hour, and 1600 hour) with compound at various doses or with vehicle for 7 days. Individual body weight and food consumption were measured daily. Data for selected compounds of the invention are reported in Figures 2A and 2B, Figures 3A and 3B, and Figures 4A and 4B.

Administration and Use

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids). A typical method of making a salt of a peptide of the present invention is well known in the art and can be accomplished by standard methods of salt exchange. Accordingly, the TFA salt of a peptide of the present invention (the TFA salt results from the purification of the peptide by using preparative HPLC, eluting with TFA containing buffer solutions) can be converted into another salt, such as an acetate salt, by dissolving the peptide in a small amount of 0.25 N acetic acid aqueous solution. The resulting solution is applied to a semi-prep HPLC column (Zorbax®, 300 SB, C-8). The column is eluted with: (1) 0.1N ammonium acetate aqueous solution for 0.5 hours; (2) 0.25N acetic acid aqueous

solution for 0.5 hours; and (3) a linear gradient (20% to 100% of solution B over 30 minutes) at a flow rate of 4 ml/min (solution A is 0.25N acetic acid aqueous solution; solution B is 0.25N acetic acid in acetonitrile/water, 80:20). The fractions containing the peptide are collected and lyophilized to dryness.

As is well known to those skilled in the art, the known and potential uses of peptides with melanocortin receptor (MC-R) agonist or antagonist activity is varied and multitudinous, thus the administration of the compounds of this invention for purposes of eliciting an agonist effect can have the same effects and uses as melanocortin itself.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula (I) in association with a pharmaceutically acceptable carrier.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. In general, an effective dosage for the activities of this invention is in the range of $1x10^{-7}$ to 200 mg/kg/day, preferably $1x10^{-4}$ to 100 mg/kg/day which can be administered as a single dose or divided into multiple doses.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also

comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Preparations may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. Preparations can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents and patent applications. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Patent No. 5,821,221 teaches polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Patent No. 5,916,883 teaches sustained release

compositions comprising a bioactive agent and cyclodextrin. The teachings of the foregoing patents and applications are incorporated herein by reference.

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<150> US 60/748850
<151> 2005-12-09

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<151> 2005-07-08

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<222> (8)..(8)
<223> Xaa = penicillamine (Pen)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 22
Xaa Xaa Xaa His Xaa Arg Trp Xaa
1 5

<210> 23
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = D-Phe

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = homo-Arg (hArg)

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = beta-Ala

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa = D-Cys

<220>
<221> MOD_RES
<222> (9)..(9)
<223> AMIDATION

<400> 23
Xaa Cys His Xaa Xaa Trp Xaa Xaa Thr
1 5

<210> 24
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = D-Phe

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-(Et)Tyr

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = Arg or homo-Arg (hArg)

<220>
<221> MISC_FEATURE

<222> (7)..(7)
<223> Xaa = beta-Ala

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa = D-Cys

<220>
<221> MOD_RES
<222> (9)..(9)
<223> AMIDATION

<400> 24
Xaa Cys His Xaa Xaa Trp Xaa Xaa Thr
1 5

<210> 25
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = D-Phe

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa = 4,4'-biphenylAla (Bip)

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = beta-Ala

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa = D-Cys

<220>
<221> MOD_RES
<222> (9)..(9)
<223> AMIDATION

<400> 25
Xaa Cys His Xaa Arg Xaa Xaa Xaa Thr
1 5

<210> 26
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = D-Phe

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe or D-(Et)Tyr

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = homo-Arg (hArg)

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa = 4,4'-biphenylAla (Bip)

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = beta-Ala

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa = D-Cys

<220>
<221> MOD_RES
<222> (9)..(9)
<223> AMIDATION

<400> 26
Xaa Cys His Xaa Xaa Xaa Xaa Xaa Thr
1 5

<210> 27

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

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 5-aminopentanoic acid (Apn)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 27
Xaa Cys His Xaa Arg Trp Xaa Cys
1 5

<210> 28
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa = D-Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = Trp or 3-benzothienylAla (Bal)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 28
Xaa Asp Xaa His Xaa Arg Xaa Lys
1 5

<210> 29
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa = D-Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa = penicillamine (Pen) or Cys

<220>
<221> MOD_RES
<222> (8)..(8)
<223> C-terminus is the free acid

<400> 29
Xaa Cys Xaa His Xaa Arg Trp Xaa

1 5

<210> 30
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa = D-alpha-aminobutyric acid (D-Abu), D-Val, D-Ile, D-Leu, D-tert-Leu (D-Tle) or D-beta-cyclohexylAla (D-Cha)

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 30
Xaa Cys Xaa His Xaa Arg Trp Cys
1 5

<210> 31
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa = penicillamine (Pen)

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 31
Xaa Xaa His Xaa Arg Trp Xaa Cys
1 5

<210> 32
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa = Cys or penicillamine (Pen)

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MISC_FEATURE

<222> (8)..(8)
<223> Xaa = penicillamine (Pen)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 32
Xaa Xaa His Xaa Arg Trp Xaa Xaa
1 5

<210> 33
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Leu, beta-cyclohexylAla (Cha), Ile, Phe, Val or
beta-(2-naphthyl)Ala (2-Nal), all modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 33
Xaa Cys His Xaa Arg Trp Xaa Cys
1 5

<210> 34
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle or Phe

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 34
Xaa Cys His Xaa Arg Trp Xaa Cys
1 5

<210> 35
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa = beta-(3-pyridiyl)Ala (3-Pal)

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE

<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 35
Xaa Cys Xaa Xaa Arg Trp Xaa Cys
1 5

<210> 36
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa = D-Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> C-terminus is the free acid

<400> 36
Xaa Cys Xaa His Xaa Arg Trp Cys
1 5

<210> 37
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>

<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa = D-Trp

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 37
Xaa Cys His Phe Arg Xaa Xaa Cys
1 5

<210> 38
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-beta-(2-naphthyl)Ala (D-2-Nal)

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = Ala or beta-Ala

<220>
<221> MOD_RES
<222> (8)..(8)

<223> AMIDATION

<400> 38
Xaa Asp His Xaa Arg Trp Xaa Lys
1 5

<210> 39
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-beta-(2-naphthyl)Ala (D-2-Nal)

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba) or 6-aminohexanoic acid (Ahx)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 39
Xaa Cys His Xaa Arg Trp Xaa Cys
1 5

<210> 40
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = homo-Phe (hPhe) or beta-cyclohexylAla (Cha), both modified with acyl (Ac)

<220>

<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-beta-(2-naphthyl)Ala (D-2-Nal)

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 40
Xaa Asp His Xaa Arg Trp Xaa Lys
1 5

<210> 41
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = beta-Ala or 5-aminopentanoic acid (Apn)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> C-terminus is the free acid

<400> 41
Xaa Asp His Xaa Arg Trp Xaa Lys
1 5

<210> 42
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 6-aminohexanoic acid (Ahx) or 5-aminopentanoic acid (Apn)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> C-terminus is the free acid

<400> 42
Xaa Cys His Xaa Arg Trp Xaa Cys
1 5

<210> 43
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = D-Phe

<220>
<221> DOMAIN
<222> (2)..(9)
<223> Cyclic

<220>
<221> MISC_FEATURE

<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = Ala, beta-Ala or 4-aminobutyric acid (Gaba)

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa = D-Cys

<220>
<221> MOD_RES
<222> (9)..(9)
<223> C-terminus is the free acid

<400> 43
Xaa Cys His Xaa Arg Trp Xaa Xaa Thr
1 5

<210> 44
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = beta-cyclohexylAla (Cha), Nle, cyclohexylGly (Chg), D-beta-cyclohexylAla (D-Cha), homo-cyclohexylAla (hCha), D-cyclohexylGly(D-Chg) or homo-Phe (hPhe), all modified with acyl(Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> C-terminus is the free acid

<400> 44
Xaa Asp His Xaa Arg Trp Xaa Lys
1 5

<210> 45
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa = D-Trp

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba), 6-aminohexanoic acid (Ahx),
beta-Ala or D-Ala

<220>
<221> MOD_RES
<222> (8)..(8)
<223> C-terminus is the free acid

<400> 45
Xaa Cys His Xaa Arg Xaa Xaa Cys
1 5

<210> 46
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)

<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa = D-Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = D-beta-(2-naphthyl)Ala (D-2-Nal)

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = Trp, beta-(2-naphthyl)Ala (2-Nal), beta-(1-naphthyl)Ala (1-Nal) or 3-benzothienylalanine (Bal)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> C-terminus is the free acid

<400> 46
Xaa Cys Xaa His Xaa Arg Xaa Cys
1 5

<210> 47
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa = penicillamine (Pen)

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa = D-Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> C-terminus is the free acid

<400> 47
Xaa Xaa Xaa His Xaa Arg Trp Cys
1 5

<210> 48
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa = penicillamine (Pen)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> C-terminus is the free acid

<400> 48
Xaa Cys His Xaa Arg Trp Xaa Xaa
1 5

<210> 49
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MOD_RES
<222> (1)..(1)
<223> modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(8)
<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa = D-Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = D-beta-(2-naphthyl)Ala (D-2-Nal)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 49
Arg Cys Xaa His Xaa Arg Trp Cys
1 5

<210> 50
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa = Arg or D-Arg, both modified with acyl (Ac)

<220>
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<222> (2)..(8)
<223> Cyclic

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<223> Xaa = D-Ala

<220>
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<223> Xaa = D-Phe

<220>
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<223> AMIDATION

<400> 50
Xaa Cys Xaa His Xaa Arg Trp Cys
1 5

<210> 51
<211> 8
<212> PRT
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<220>
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<223> Xaa = D-Phe

<220>
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<223> Xaa = penicillamine (Pen)

<220>
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<223> AMIDATION

<400> 51
Xaa Cys Xaa His Xaa Arg Trp Xaa
1 5

<210> 52
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Xaa = D-Phe

<220>
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<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
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<223> Xaa = penicillamine (Pen)

<220>
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<222> (8)..(8)
<223> AMIDATION

<400> 52
Xaa Cys His Xaa Arg Trp Xaa Xaa
1 5

<210> 53
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Xaa = D-Arg or Arg, both modified with acyl (Ac)

<220>
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<223> Cyclic

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<222> (4)..(4)
<223> Xaa = D-Phe

<220>
<221> MOD_RES
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<223> AMIDATION

<400> 53
Xaa Asp His Xaa Arg Trp Ala Lys
1 5

<210> 54
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> Xaa = Nle modified with acyl (Ac)

<220>
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<223> Cyclic

<220>
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<223> Xaa = D-Ala

<220>
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<223> Xaa = D-Phe

<220>
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<223> Xaa = Gly, D-Ala, beta-Ala, 4-aminobutyric acid (Gaba) or
5-aminopentanoic acid (Apn)

<220>
<221> MOD_RES
<222> (9)..(9)
<223> AMIDATION

<400> 54
Xaa Cys Xaa His Xaa Arg Trp Xaa Cys
1 5

<210> 55
<211> 8
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<220>
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<223> Xaa = Trp or beta-(2-naphthyl)alanine (2-Nal)

<220>
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<400> 55
Cys Glu His Xaa Arg Xaa Ala Cys
1 5

<210> 56
<211> 8
<212> PRT
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<220>
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<223> modified with acyl (Ac)

<220>
<221> DOMAIN
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<223> Cyclic

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<223> Xaa = D-Phe

<220>
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<222> (6)..(6)
<223> Xaa = Trp or beta-(2-naphthyl)Ala (2-Nal)

<220>
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<400> 56
Cys Xaa His Xaa Arg Xaa Ala Cys
1 5

<210> 57
<211> 9
<212> PRT
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<220>
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<220>
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<223> Xaa = Nle modified with acyl (Ac)

<220>
<221> DOMAIN
<222> (2)..(9)
<223> Cyclic

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<223> Xaa = D-Ala

<220>
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<222> (5)..(5)
<223> Xaa = D-Phe

<220>
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<223> Xaa = Ala, beta-Ala or 4-aminobutyric acid (Gaba)

<220>

<221> MOD_RES
<222> (9)..(9)
<223> AMIDATION

<400> 57
Xaa Cys Xaa His Xaa Arg Trp Xaa Cys
1 5

<210> 58
<211> 9
<212> PRT
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<220>
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<220>
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<223> Xaa = Nle modified with acyl (Ac)

<220>
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<223> Cyclic

<220>
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<223> Xaa = D-Ala

<220>
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<222> (5)..(5)
<223> Xaa = D-Phe

<220>
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<222> (7)..(7)
<223> Xaa = 3-benzothienylAla (Bal)

<220>
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<222> (9)..(9)
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<400> 58
Xaa Asp Xaa His Xaa Arg Xaa Ala Lys
1 5

<210> 59
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
<221> MISC_FEATURE
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<223> Xaa = D-homo-cyclohexylAla (D-hCha) modified with acyl (Ac)

<220>
<221> DOMAIN
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<223> Cyclic

<220>
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<222> (4)..(4)
<223> Xaa = D-Phe

<220>
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<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 59
Xaa Asp His Xaa Arg Trp Xaa Lys
1 5

<210> 60
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
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<222> (1)..(1)
<223> Xaa = beta-cyclohexylAla (Cha) modified with n-butyryl

<220>
<221> DOMAIN
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<220>
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<222> (4)..(4)
<223> Xaa = D-Phe

<220>
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<222> (7)..(7)
<223> Xaa = 4-aminobutyric acid (Gaba)

<220>
<221> MOD_RES

<222> (8)..(8)
<223> AMIDATION

<400> 60
Xaa Asp His Xaa Arg Trp Xaa Lys
1 5

<210> 61
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Melanocortin receptor ligand

<220>
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<222> (1)..(1)
<223> Xaa = Nle modified with acyl (Ac)

<220>
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<223> Cyclic

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa = D-Glu

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa = D-Phe

<220>
<221> MOD_RES
<222> (8)..(8)
<223> AMIDATION

<400> 61
Xaa Cys Xaa His Xaa Arg Trp Cys
1 5

What is claimed is:

1. A melanocortin-4 selective receptor agonist compound according to the formula:

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO:50) or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a therapeutically effective amount of a melanocortin-4 selective receptor agonist compound according to the formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO:50), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

3. A pharmaceutical composition according to claim 2 useful for treating an acute or chronic inflammatory disease or medical condition wherein said disease or condition is selected from the group consisting of general inflammation, inflammatory bowel disease, brain inflammation, sepsis and septic shock.

4. A pharmaceutical composition according to claim 2 useful for treating a disease or medical condition with an autoimmune component wherein said disease or condition is selected from the group consisting of rheumatoid arthritis, gouty arthritis and multiple sclerosis.

5. A pharmaceutical composition according to claim 2 useful for treating a metabolic disease or medical condition accompanied by weight gain wherein said disease or condition is selected from the group consisting of obesity, feeding disorders and Prader-Willi Syndrome.

6. A pharmaceutical composition according to claim 5, wherein obesity or a feeding disorder is treated.

7. A pharmaceutical composition according to claim 2 useful for decreasing food intake, or useful for decreasing body weight, or useful for decreasing food intake and decreasing body weight.

8. A pharmaceutical composition according to claim 2 useful for treating a neoplastic disease or medical condition wherein said disease or condition is selected from the group consisting of skin cancer and cancer cachexia, or useful for treating a reproductive or sexual medical condition wherein said disease or condition is selected from the group consisting of endometriosis, uterine bleeding, sexual dysfunction, erectile dysfunction and decreased sexual response in females, or useful for treating a disease or medical condition resulting from treatment or insult to an organism wherein said disease or condition is selected from the group consisting of organ transplant rejection, ischemia and reperfusion injury, wounding and spinal cord injury, and weight loss due to a medical procedure selected from the group consisting of chemotherapy, radiation therapy, temporary or permanent immobilization and dialysis, or useful for treating a cardiovascular disease or medical condition wherein said disease or condition is selected from the group consisting of hemorrhagic shock, cardiogenic shock, hypovolemic shock, cardiovascular disorders and cardiac cachexia, or useful for treating a pulmonary disease or medical condition wherein said disease or condition is selected from the group consisting of acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease and asthma, or useful for treating a disease or medical condition wherein said disease or condition is selected from the group consisting of enhanced immune tolerance and allergies, or useful for treating a dermatological disease or medical condition wherein said disease or condition is selected from the group consisting of psoriasis, skin pigmentation depletion, acne and keloid formation, or useful for treating a behavioral or central nervous system or neuronal disease or medical condition wherein said disease or condition is selected from the group consisting of anxiety, depression, memory dysfunction and neuropathic pain, or useful for treating a renal disease or medical condition wherein said disease or condition is selected from the group consisting of renal cachexia and

natriuresis, or useful for modulating ovarian weight, placental development, prolactin secretion, FSH secretion, intrauterine fetal growth, parturition, spermatogenesis, thyroxin release, aldosterone synthesis and release, body temperature, blood pressure, heart rate, vascular tone, brain blood flow, blood glucose levels, sebum secretion, pheromone secretion, motivation, learning and behavior, pain perception, neuroprotection and nerve growth, or useful for modulating bone metabolism, bone formation and bone development.

9. A pharmaceutical composition according to claim 2 useful for inhibiting alcohol consumption, for reducing alcohol consumption, for treating alcoholism, or for treating alcohol abuse.

10. The use of a therapeutically effective amount of a melanocortin-4 receptor selective agonist compound according to the formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO:50), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to inhibit alcohol consumption, to reduce alcohol consumption, to treat alcoholism , or to treat alcohol abuse, in a subject in need of such treatment.

11. A melanocortin-4 selective receptor agonist compound according to the formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO:50), or a pharmaceutically acceptable salt thereof, for eliciting an agonist effect from a melanocortin receptor in a subject in need thereof.

12. A compound according to claim 11 for treating an acute or chronic inflammatory disease or medical condition, wherein said disease or condition is selected from the group consisting of general inflammation, inflammatory bowel disease, brain inflammation, sepsis and septic shock.

13. A compound according to claim 11 for treating a disease or medical condition with an autoimmune component, wherein said disease or condition is

selected from the group consisting of rheumatoid arthritis, gouty arthritis and multiple sclerosis.

14. A compound according to claim 11 for treating a metabolic disease or medical condition accompanied by weight gain, wherein said disease or condition is selected from the group consisting of obesity, feeding disorders and Prader-Willi Syndrome.

15. A compound according to claim 14, wherein obesity or a feeding disorder is treated.

16. A compound according to claim 11 for decreasing food intake, or for decreasing body weight, or for decreasing food intake and decreasing body weight.

17. A compound according to claim 11 for treating a neoplastic disease or medical condition, wherein said disease or condition is selected from the group consisting of skin cancer and cancer cachexia, or for treating a reproductive or sexual medical condition, wherein said disease or condition is selected from the group consisting of endometriosis, uterine bleeding, sexual dysfunction, erectile dysfunction and decreased sexual response in females, or for treating a disease or medical condition resulting from treatment or insult to an organism, wherein said disease or condition is selected from the group consisting of organ transplant rejection, ischemia and reperfusion injury, wounding and spinal cord injury, and weight loss due to a medical procedure selected from the group consisting of chemotherapy, radiation therapy, temporary or permanent immobilization and dialysis, or for treating a cardiovascular disease or medical condition, wherein said disease or condition is selected from the group consisting of hemorrhagic shock, cardiogenic shock, hypovolemic shock, cardiovascular disorders and cardiac cachexia, or for treating a pulmonary disease or medical condition, wherein said disease or condition is selected from the group consisting of acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease and

asthma, or for treating a disease or medical condition, wherein said disease or condition is selected from the group consisting of enhanced immune tolerance and allergies, or for treating a dermatological disease or medical condition, wherein said disease or condition is selected from the group consisting of psoriasis, skin pigmentation depletion, acne and keloid formation, or for treating a behavioral or central nervous system or neuronal disease or medical condition, wherein said disease or condition is selected from the group consisting of anxiety, depression, memory dysfunction and neuropathic pain, or for treating a renal disease or medical condition, wherein said disease or condition is selected from the group consisting of renal cachexia and natriuresis, or for modulating ovarian weight, placental development, prolactin secretion, FSH secretion, intrauterine fetal growth, parturition, spermatogenesis, thyroxin release, aldosterone synthesis and release, body temperature, blood pressure, heart rate, vascular tone, brain blood flow, blood glucose levels, sebum secretion, pheromone secretion, motivation, learning and behavior, pain perception, neuroprotection and nerve growth, or for modulating bone metabolism, bone formation and bone development.

18. A compound according to claim 11 for inhibiting alcohol consumption, reducing alcohol consumption, treating alcoholism, or treating alcohol abuse.

19. The use of a therapeutically effective amount of a melanocortin-4 receptor selective agonist compound according to the formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO:50), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to treat a disease or condition selected from the group consisting of general inflammation, inflammatory bowel disease, brain inflammation, sepsis, septic shock, rheumatoid arthritis, gouty arthritis, multiple sclerosis, a metabolic disease or medical condition accompanied by weight gain, obesity, feeding disorders, Prader-Willi Syndrome, a metabolic disease or medical condition accompanied by weight loss, anorexia, bulimia, AIDS wasting, cachexia, cancer cachexia, wasting in frail elderly, skin cancer, endometriosis, uterine

bleeding, sexual dysfunction, erectile dysfunction, decreased sexual response in females, organ transplant rejection, ischemia and reperfusion injury, wounding and spinal cord injury, weight loss due to a medical procedure selected from the group consisting of chemotherapy, radiation therapy, temporary or permanent immobilization and dialysis, hemorrhagic shock, cardiogenic shock, hypovolemic shock, cardiovascular disorders, cardiac cachexia, acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease, asthma, enhanced immune tolerance, allergies, psoriasis, skin pigmentation depletion, acne, keloid formation, anxiety, depression, memory dysfunction, neuropathic pain, renal cachexia and natriuresis.

20. The use of a therapeutically effective amount of a melanocortin-4 receptor selective agonist compound according to the formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO:50), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to modulate ovarian weight, placental development, prolactin secretion, FSH secretion, intrauterine fetal growth, parturition, spermatogenesis, thyroxin release, aldosterone synthesis and release, body temperature, blood pressure, heart rate, vascular tone, brain blood flow, blood glucose levels, sebum secretion, pheromone secretion, motivation, learning and behavior, pain perception, neuroprotection, nerve growth, bone metabolism, bone formation and bone development.