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(54) Title: MELANOCORTIN RECEPTOR LIGANDS

(57) Abstract: The present invention is directed to compounds according to formula, (R^2R^3)-A^1-c(A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9)-A^{10}-R^1, and pharmaceutically-acceptable salts thereof that act as ligands for one or more of the melanocortin receptors, to methods of using such compounds to treat mammals and to pharmaceutical compositions comprising said compounds.

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.

,613,874; U.S. Patent No. 6,600,015; Fehm, H. L. et al., J. Clin. Endo. & Metab., 6:1144-1148 (2001); Hansen, M. J. et al., Brain Res., 1039:137-145 (2005); Ye, Z. et al., eptides, 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. harm., 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), affin-Sanson, M. L., Eu. J. Endo., 144:207-208 (2001), Hamilton, B. S. et al., Obesity es. 10:182-187 (2002)), feeding disorders (U.S. Patent No. 6,720,324; Fehm, H. L. et l., J. Clin. Endo. & Metab., 86:1144-1148 (2001); Pontillo, J. et al., Bioorganic & Med. hem. Ltrs., 15:2541-2546 (2005)) and Prader-Willi Syndrome (GE, Y. et al., Brain esearch, 957:42-45 (2002)); metabolic diseases and medical conditions accompanied y weight loss such as anorexia (U.S. Patent No. 6,613,874; Wisse, B. R. et al., Endo., 42:3292-3301 (2001)), bulimia (U.S. Patent No. 6,720,324), AIDS wasting (Marsilje, T. I. et al., Bioorg. Med. Chem. Lett., 14:3721-3725 (2004); Markison, S. et al., ndocrinology, 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. trs., 15:2541-2546 (2005)), cancer cachexia (U.S. Patent No. 6,639,123) and wasting in rail elderly (U.S. Patent No. 6,639,123); diabetes (U.S. Patent No. 6,713,487) and iabetalogical 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 s skin cancer (Sturm, R.A., Melanoma Res., 12:405-416 (2002); Bastiens, M. T. et al., m. J. Hum. Genet., 68:884-894 (2001)), and prostate cancer (Luscombe, C. J. et al., ritish J. Cancer, 85:1504-1509 (2001); reproductive or sexual medical conditions such s endometriosis (U.S. Patent No. 6,713,487) and uterine bleeding in women (U.S. atent No. 6,613,874), sexual dysfunction (U.S. Patent No. 6,720,324; Van der Ploeg, . H. T. et al., PNAS, 99:11381-11386 (2002), Molinoff, P. B. et al., Ann. N.Y. Acad. ci., 994:96-102 (2003), Hopps, C. V. et al., BJU International, 92:534-538 (2003)), rectile dysfunction ((U.S. Patent No. 6,613,874; Diamond, L. E. et al., Urology, 5:755-759 (2005), Wessells, H. et al., Int. J. Impotence Res., 12:S74-S79 (2000), ndersson, K-E. et al., Int. J. Impotence Res., 14:S82-S92 (2002), Bertolini, A. et. al., exual 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;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2;

Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

n-butanoyl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-ß-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2;

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2;

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;

Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2;

Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-OH;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-OH;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-OH;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-OH;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-OH;

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-OH;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH; or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; 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;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH; or

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH;

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;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2;

Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;

Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-3Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2;

Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2; or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

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;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2;

Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2; or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

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;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

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;

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;

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;

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;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;

Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2;

Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;

Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; or

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH_2;

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, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-

c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 or Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2. 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. 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. 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.

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, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, or Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2. 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. 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. 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.

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.

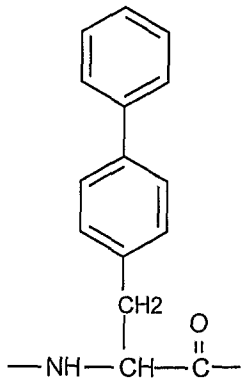
DETAILED DESCRIPTION OF THE INVENTION

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.

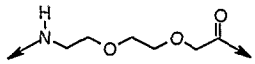
Nomenclature and Abbreviations

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

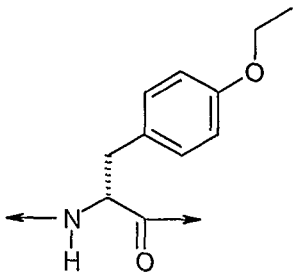


Bpa	4-benzoylphenylalanine
4-Br-Phe	4-bromo-phenylalanine
Cha	ß-cyclohexylalanine
hCha	homo-cyclohexylalanine
Chg	cyclohexylglycine
Cys or C	cysteine
hCys	homocysteine
Dab	2,4-diaminobutyric acid
Dap	2,3-diaminopropionic acid
Dip	ß,ß-diphenylalanine
Doc	8-amino-3,6-dioxaoctanoic acid with the structure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



2-Fua	β-(2-furyl)-alanine
Gaba	4-aminobutyric acid
Gln or Q	glutamine
Glu or E	glutamic acid
Gly or G	glycine
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

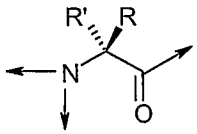
Certain other abbreviations used herein are defined as follows:

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

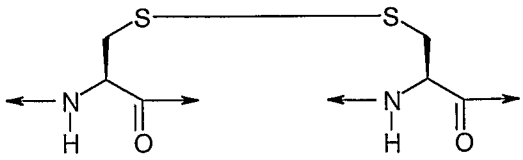
Unless otherwise indicated, with the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-C(R)(R')-CO-, wherein R and R' each is, independently, hydrogen or the side chain of an amino acid (e.g., R = CH_3 and R' = H for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

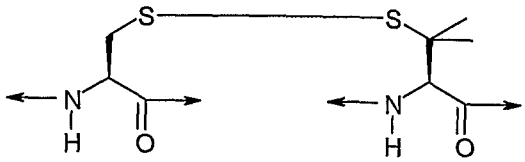


The designation "NH_2" in e.g., Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, indicates that the C-terminus of the peptide is amidated. Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys), or alternatively Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)- OH, indicates that the C-terminus is the free acid.

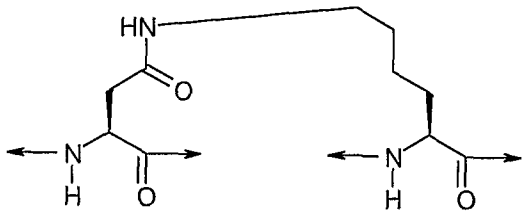
"-c(Cys-Cys)-" or "-cyclo(Cys-Cys)-" denotes the structure:



"-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 $-C_{1-20}$ alkyl, wherein said $-C_{1-20}$ 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 $-(CH_2)_{0-20}$-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 $-C_{1-20}$ alkyl, wherein said $-C_{1-20}$ 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 $-(CH_2)_{0-20}$-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

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

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;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2;

Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

n-butanoyl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2;

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2;

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2;

Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;

Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2;

Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;

Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;

Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2;

Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-OH;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-OH;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-OH;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-OH;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-OH;

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-OH;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2;

Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2;

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2; and

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH.

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
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2	1095.27	1095.2	96.4
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH_2	1149.36	1149.05	96
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2	1116.38	1115.8	98
D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH_2	1167.38	1167.3	99
D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2	1167.38	1167.5	93
D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2	1181.41	1181.9	99
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	1102.35	1103	99
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2	1123.32	1123.9	99
Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1121.31	1121.2	93
Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1193.37	1193.2	92.6
Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;	1149.36	1149.4	94.5
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1109.3	1109.2	91.5
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.6	98.3
Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.4	91

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity
Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1088.4	93
Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1088.4	80
Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2	1060.27	1060.4	90
Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.4	93
Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.4	81
Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1074.3	1074.4	92
Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1088.4	94
Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1088.4	91
Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2	1060.27	1060.4	96
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.4	66
Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.2	94
Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1088.32	1088.2	93
Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1088.32	1088.4	90
Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1060.27	1060.4	91
Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.4	65
Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.2	93
Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1074.3	1074.4	92
Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1088.32	1088.4	90
Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2	1088.32	1088	95
Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1147.35	1147.4	97.5
Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1135.33	1135.1	99

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity
Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1163.39	1163.4	99
Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1149.36	1149.2	99
Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1107.28	1107	98.9
Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1107.28	1107.4	99
Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1123.32	1123.2	99
Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1163.39	1163.6	94
Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1143.31	1143.3	96.9
Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1143.31	1143.3	96.5
Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1135.33	1135.4	99
n-Butyryl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1177.41	1177.5	88.6
Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1157.34	1157.2	70
Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1141.36	1141.2	89
Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1081.24	1080.9	92.5
Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1135.33	1135.2	85
Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1149.36	1149.1	87
Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1095.27	1095.4	98.6
Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1109.3	1109.2	93.8
Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2	1129.29	1129.2	81.9
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH_2	1095.27	1095.3	97
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH_2	1095.27	1095.3	82
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH_2	1109.3	1109.1	99

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH_2	1137.35	1137.4	98
Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH_2	1123.32	1123.3	97.3
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH_2	1102.35	1102	99
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH_2	1088.32	1087.8	97
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH_2	1116.38	1116.2	99
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2	1074.3	1073.8	99.9
Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH_2	1074.3	1073.8	99.9
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	1124.36	1123.6	96.1
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2	1135.38	1134.5	99.1
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2	1135.38	1134.6	94.8
nButanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2	1113.37	1112.6	95.7
nButanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1102.35	1101.5	99.9
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2	1085.32	1084.4	97.7
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH_2	1085.32	1084.5	96.6
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH_2	1091.35	1090.4	96.2
Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2	1132.33	1131.5	99.9
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH_2	1095.27	1094.6	99.9
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2	1141.41	1140.5	95.6
Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1102.35	1101.6	99.9
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	1102.35	1101.6	99.9
Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	1130.4	1129.6	99.9

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity
D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2	1181.41	1181.7	96.9
D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2	1211.43	1211.7	97.1
D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2	1204.44	1204.6	99
D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2	1225.46	1225.7	97
D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2	1218.47	1218.8	99
D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2	1262.52	1263	99
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH_2	1131.35	1131.2	96.8
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH_2	1145.37	1145.3	96.4
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2	1145.37	1145.2	98.2
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1159.4	1159.2	95.1
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	1173.43	1173.3	96.8
Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	1060.31	1060.3	98.5
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2	1095.27	1094.7	96.2
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2	1112.32	1111.7	96.5
Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	1090.25	1089.6	99.9
Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2	1101.27	1100.6	98.3
Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	1032.22	1031.5	95.2
Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2	1043.24	1042.5	95.6
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	1144.39	1144.6	95.3
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2	1145.37	1144.6	97.3
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1158.41	1158.6	96.5

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH	1103.33	1103	99.9
Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2	1088.32	1087.6	99.9
Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2	1102.35	1101.7	99.9
Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2	1116.38	1115.7	99.9
Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2	1116.38	1115.8	97.4
Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2	1116.38	1115.5	96.5
Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2	1156.44	1155.6	96.4
Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1116.38	1115.7	95
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1116.38	1115.5	99.9
Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1144.43	1144	99.9
Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1088.32	1088	96.7
Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1128.39	1128.4	95.8
Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1088.32	1088.4	95
Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1122.34	1122	95.2
Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1074.3	1074.6	95.4
Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1172.4	1172.2	95.2
Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1046.29	1046.4	97.6
Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1080.3	1080	95.8
Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	1099.35	1099.6	96.6
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH	1075.28	1075.2	99.9
Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2	1088.32	1088	95.8

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH_2	1183.4	1182.85	99.9
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2	1145.33	1145	99.99
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-βAla-Lys)-NH_2	1145.33	1145	99.99
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2	1138.38	1137.8	99.99
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2	1166.44	1166	99
Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	1207.4	1206.9	99
Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	1199.42	1198.8	100
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1117.3	1116.9	95.10
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	1117.33	1116.8	99.2
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	1145.38	1144.9	96.4
Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1159.41	1158.9	99.9
Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1159.41	1159.1	99
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	1145.38	1145.1	99
Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	1138.3	1138.0	98.0
Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	1138.3	1138.1	99.0

Table 1B

Compound	Calculated Molecular Weight	Experimental Molecular Weight	Purity
Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	1167.39	1167.40	99.9

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 hMC1-R	Ki hMC3-R	Ki hMC4-R	Ki hMC5-R	Ki hMC1-R/MC4-R
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	3.87	10.1	2.09	430	1.9
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	4.01	12.1	1.76	352	2.3
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	8.29	13.3	2.78	816	3.0
Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	3.93	172	11.0	538	0.36
Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	1.81	20.5	4.57	502	0.4
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	9.67	22.0	4.2	1900	2.3
Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	0.79	45.5	1.21	493	0.6
Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	0.68	20.7	1.01	783	0.7

Table 2B

Compound	Ki hMC1-R	Ki hMC3-R	Ki hMC4-R	Ki hMC5-R	Ki hMC1-R/MC4-R
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2	114	63.9	3.07	1657	37.1
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	11	26	7.6	1800	1.4
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
Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	0.07	4.1	0.85	8.8	0.1
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	0.12	10	0.43	0.42	0.3
Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.05	1.3	0.47	0.2	0.1
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2	0.0996	9318	0.617	10.9	0.16
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2	.0132	16.1	1.23	0.359	0.11
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

Compound	Ki hMC1-R	Ki hMC3-R	Ki hMC4-R	Ki hMC5-R	Ki hMC1-R/MC4-R
D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2	0.420	106	4.75	1260	0.09
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	0.0951	9.33	0.894	13.4	0.11
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2	0.999	300	11.1	431	0.09
Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.106	11.8	1.49	110	0.07
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.0506	9.89	1.04	16.3	0.05
Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.884	223	22.5	609	0.04
Ac-hCha-c(Asp-His-D-P-he-Arg-Trp-Gaba-Lys)-NH_2	0.721	93.5	56.0	747	0.01
Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.227	14.5	2.99	164	0.08
Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	0.277	25.2	3.37	203	0.08
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
Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	34.1	118	17.0	5560	2.01
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	29.1	22.8	3.84	2550	7.58
D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2	0.442	123	10.3	521	0.04
D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2	5.80	3370	583	1130	0.01
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
D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2	1.68	1260	172	1220	0.01
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
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH_2	0.352	149	3.01	339	0.12
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH_2	3.93	876	48.0	4940	0.08
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2	0.995	287	4.80	766	0.21

Compound	Ki hMC1-R	Ki hMC3-R	Ki hMC4-R	Ki hMC5-R	Ki hMC1-R/MC4-R
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.848	184	3.76	956	0.23
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	1.10	228	7.58	859	0.15
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2	0.659	98.9	2.55	4.19	0.26
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2	4.12	445	50.6	4300	0.08
Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	111	1710	47.7	694	2.33
Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2	262	2500	96.4	1460	2.72
Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	199	5990	96.7	> 10000	2.06
Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2	132	4560	40.7	8810	3.24
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2	9.12	1130	22.1	2860	0.41
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2	1.00	227	5.55	496	0.18
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.536	169	3.12	358	0.17
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH	32.1	330	17.4	165	1.84
Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2	10.6	41.1	7.69	54.9	1.38
Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2	13.0	104	10.1	40	1.29
Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2	4.28	38.5	9.0	12.5	0.48
Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2	1.60	6.82	4.13	5.57	0.39
Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2	12.0	85.8	11.2	40	1.07
Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2	0.353	2.08	1.41	0.857	0.25
Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.537	86.1	5.89	2.56	0.09
Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	0.744	178	3.51	2.69	0.21
Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.216	17.4	0.995	0.486	0.22

Compound	Ki hMC1-R	Ki hMC3-R	Ki hMC4-R	Ki hMC5-R	Ki hMC1-R/MC4-R
Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.107	9.11	0.884	0.354	0.12
Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.148	13.9	1.06	0.423	0.14
Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.254	18.5	2.13	0.714	0.12
Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.256	29.9	1.98	0.864	0.13
Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.560	39.2	2.94	2.73	0.19
Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.186	15.2	4.93	0.537	0.04
Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	21.1	151	10.4	92.6	2.03
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH	30.7	152	15.6	114	1.97
Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2	5.20	150	138	20.3	0.04
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH_2	4.89	290	21.3	11.1	0.23
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	25.5	3.82	7.61	102	3.35
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
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2	22.2	12.7	16.6	125	1.34
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2	1.17	1.56	0.277	3.24	4.22
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
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2	0.393	1.86	0.375	1.11	1.05
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2	0.333	2.91	0.998	0.366	0.33
Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	0.461	2.45	0.931	1.37	0.50
Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	0.576	3.98	2.82	3.91	0.20

Table 2C

Compound	Ki hMC1-R	Ki hMC3-R	Ki hMC4-R	Ki hMC5-R	Ki hMC1-R/MC4-R
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

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
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	5.79	5.25	0.313	1630	18.0
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	6.17	5.6	0.397	1020	16.0
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	26.5	10.5	0.493	2440	54.0
Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	8.43	32.4	0.959	2140	9.0
Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	4.23	8.09	0.719	23.2	6.0
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	48.3	13.3	0.79	10000	61.0
Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	1.48	5.76	0.078	297	19.0
Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2	1.39	2.89	0.055	467	25.0

ND = not determined

Table 3B

Compound	EC_{50} hMC1-R	EC_{50} hMC3-R	EC_{50} hMC4-R	EC_{50} hMC5-R	EC_{50} hMC1-R/MC4-R

Compound	EC_{50} hMC1-R	EC_{50} hMC3-R	EC_{50} hMC4-R	EC_{50} hMC5-R	EC_{50} hMC1-R/MC4-R
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	2.4	0.33	0.078	420	31
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
Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	0.31	0.27	0.018	3.1	17
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2	0.28	0.24	0.028	3.9	10
Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2	0.37	0.1	0.021	1.7	18
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2	0.834	0.145	0.128	2.79	6.52
Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2	0.76	0.199	0.0492	1.73	15.45
Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	3.26	0.189	0.0949	30.2	34.35
Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	1.37	0.628	0.131	3.48	10.46
Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2	2.27	3.32	7.24	415	0.31
Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2	ND	1.89	0.531	ND	ND
Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2	14.3	2.03	0.183	2240	78.14
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
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
Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2	0.931	3.22	1.65	>10000	0.56
Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2	3.24	0.465	0.0915	78.5	35.41

Compound	EC_{50} hMC1-R	EC_{50} hMC3-R	EC_{50} hMC4-R	EC_{50} hMC5-R	EC_{50} hMC1-R/MC4-R
Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2	0.819	0.541	0.453	45.3	1.81

ND = not determined

Table 3C

Compound	EC50 hMC1-R	Kb hMC3-R	Kb MC4-R	EC50 hMC5-R
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	17.6	12.4	38.8	11.8
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2	0.619	2.98	0.109	0.189
Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2	0.913	0.536	0.346	0.489
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2	0.231	18.4	0.782	0.153
Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2	0.581	10.8	0.967	0.126
Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2	0.413	9.32	0.824	0.307
Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH2	1.27	3.02	0.442	0.736
Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2	383	61.5	53.6	2842

Table 3D

Compound	EC50 hMC1-R	Kb hMC3-R	Kb MC4-R	EC50 hMC5-R
Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2	193	5.72	1.58	1111

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
Compound B	Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2
Compound C	Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2
Compound D	D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2
Compound E	Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2
Compound F	Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2
Compound G	Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2

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.

What is claimed is:

1. A compound according to 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 $-NH_2$;

R^2 and R^3 is, independently for each occurrence, 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 or substituted aryl(C_1-C_{30})acyl;

R^4 and R^5 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; and

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, (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.

2. A compound according to claim 1, wherein:

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; and

A^{10} is Thr or deleted;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2, wherein:

R^2 and R^3 is, independently for each occurrence, H, acyl, n-propanoyl or n-butanoyl;

or a pharmaceutically acceptable salt thereof.

4. A compound according claim 1, wherein:

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; and

A^{10} is Thr or deleted;

provided that either A^3 or A^8 is deleted, but not both;

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4, wherein said compound is:

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2;

Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

n-butanoyl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-ß-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2;

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2;

n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;

Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Bala-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2;

Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-OH;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-OH;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-OH;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-OH;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-OH;

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-OH;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH; or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 5, wherein said compound is:

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH; or

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH;

or a pharmaceutically acceptable salt thereof.

7. A compound according claim 1, wherein:

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; and

R^2 and R^3 is, independently for each occurrence, H or acyl;

or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 7, wherein said compound is:

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2;

Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2;

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;

Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;

Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2;

Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2;

Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2; or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1, wherein:

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

or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 9, wherein

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.

11. A compound according to claim 10, wherein:

R^2 and R^3 is, independently for each occurrence, H, acyl, n-propanoyl or n-butanoyl;

or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 11, wherein

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.

13. A compound according to claim 12, wherein:

R^2 and R^3 is, independently for each occurrence, H or acyl;

or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 13, wherein said compound is:

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2;

Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2; or

Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

or pharmaceutically acceptable salts thereof.

15. A compound according to claim 14, wherein said compound is:
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2; or
Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;
or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 15, wherein said compound is:
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;
or a pharmaceutically acceptable salt thereof.

17. A compound according to claim 15, wherein said compound is:
Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;
or a pharmaceutically acceptable salt thereof.

18. A compound according to claim 15, wherein said compound is:
Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;
or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

20. A pharmaceutical composition according to claim 19, wherein said compound is a selective melanocortin-4 receptor agonist or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition according to claim 20, wherein said compound 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.

22. A pharmaceutical composition according to claim 21, wherein the functional activity of the melanocortin-4 receptor agonist is characterized by an EC_{50} at least 17-fold more selective for the human melanocortin-4 receptor than for the human melanocortin-3 receptor.

23. A pharmaceutical composition according to claim 21, wherein the functional activity of the melanocortin-4 receptor agonist is characterized by an EC_{50} at least 90-fold more selective for the human melanocortin-4 receptor than for the human melanocortin-3 receptor.

24. A pharmaceutical composition according to claim 21, wherein the functional activity of the melanocortin-4 receptor agonist is characterized by an EC_{50} at least 200-fold more selective for the human melanocortin-4 receptor than for the human melanocortin-5 receptor.

25. A pharmaceutical composition according to claim 21, wherein the functional activity of the melanocortin-4 receptor agonist is characterized by an EC_{50} at least 3000-fold more selective for the human melanocortin-4 receptor than for the human melanocortin-5 receptor.

26. A pharmaceutical composition according to claim 19 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.

27. A pharmaceutical composition according to claim 19 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.

28. A pharmaceutical composition according to claim 19 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.

29. A pharmaceutical composition according to claim 28, wherein obesity is treated.

30. A pharmaceutical composition according to claim 28, wherein a feeding disorder is treated.

31. A pharmaceutical composition according to claim 19 useful for decreasing food intake.

32. A pharmaceutical composition according to claim 19 useful for decreasing body weight.

33. A pharmaceutical composition according to claim 19 useful for decreasing food intake and decreasing body weight.

34. A pharmaceutical composition according to claim 31 useful for decreasing food intake wherein said compound is selected from the group consisting of Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 and Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition according to claim 34 useful for decreasing food intake wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

36. A pharmaceutical composition according to claim 34 useful for decreasing food intake wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

37. A pharmaceutical composition according to claim 34 useful for decreasing food intake wherein said compound is Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, or a pharmaceutically acceptable salt thereof.

38. A pharmaceutical composition according to claim 32 useful for decreasing body weight wherein said compound is selected from the group consisting of Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 and Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

39. A pharmaceutical composition according to claim 38 useful for decreasing food intake wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

40. A pharmaceutical composition according to claim 38 useful for decreasing food intake wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

41. A pharmaceutical composition according to claim 38 useful for decreasing food intake wherein said compound is Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, or a pharmaceutically acceptable salt thereof.

42. A pharmaceutical composition according to claim 33 useful for decreasing food intake and decreasing body weight wherein said compound is selected from the group consisting of Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 and Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

43. A pharmaceutical composition according to claim 42 useful for decreasing food intake wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

44. A pharmaceutical composition according to claim 42 useful for decreasing food intake wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

45. A pharmaceutical composition according to claim 42 useful for decreasing food intake wherein said compound is Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, or a pharmaceutically acceptable salt thereof.

46. A pharmaceutical composition according to claim 19 useful for treating a metabolic disease or medical condition accompanied by weight loss wherein said disease or condition is selected from the group consisting of anorexia, bulimia, AIDS wasting, cachexia, cancer cachexia and wasting in frail elderly.

47. A pharmaceutical composition according to claim 46 useful for treating anorexia.

48. A pharmaceutical composition according to claim 46 useful for treating bulimia.

49. A pharmaceutical composition according to claim 46 useful for treating AIDS wasting or wasting in frail elderly.

50. A pharmaceutical composition according to claim 46 useful for treating cachexia or cancer cachexia.

51. A pharmaceutical composition according to claim 19 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.

52. A pharmaceutical composition according to claim 19 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.

53. A pharmaceutical composition according to claim 19 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.

54. A pharmaceutical composition according to claim 19 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.

55. A pharmaceutical composition according to claim 19 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.

56. A pharmaceutical composition according to claim 19 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.

57. A pharmaceutical composition according to claim 19 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.

58. A pharmaceutical composition according to claim 19 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.

59. A pharmaceutical composition according to claim 19 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.

60. A pharmaceutical composition according to claim 19 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.

61. A pharmaceutical composition according to claim 19 useful for modulating bone metabolism, bone formation and bone development.

62. A pharmaceutical composition according to claim 19 useful for inhibiting alcohol consumption, for reducing alcohol consumption, for treating alcoholism, or for treating alcohol abuse.

63. A pharmaceutical composition according to claim 62 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

64. A pharmaceutical composition according to claim 62 useful for reducing alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

65. A pharmaceutical composition according to claim 62 useful for treating alcoholism wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

66. A pharmaceutical composition according to claim 62 useful for treating alcohol abuse wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

67. A pharmaceutical composition according to claim 63 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist exhibiting 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.

68. A pharmaceutical composition according to claim 67 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist exhibiting a function 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.

69. A pharmaceutical composition according to claim 67 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist exhibiting a function activity characterized by an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

70. A pharmaceutical composition according to claim 67 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist exhibiting a function activity characterized by an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

71. A pharmaceutical composition according to claim 67 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist exhibiting a function activity characterized by an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

72. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to inhibit alcohol consumption in a subject in need of such treatment.

73. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist of according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to reduce alcohol consumption in a subject in need of such treatment.

74. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to treat alcoholism in a subject in need of such treatment.

75. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to treat alcohol abuse in a subject in need of such treatment.

76. A method of eliciting an agonist or antagonist effect from a melanocortin receptor in a subject in need thereof which comprises administering to said subject a therapeutically effective amount of a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof.

77. A method according to claim 76, wherein said compound is a selective melanocortin 4 receptor agonist.

78. A method according to claim 77, 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.

79. A method according to claim 78, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

80. A method according to claim 78, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

81. A method according to claim 78, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

82. A method according to claim 78, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

83. A method of treating an acute or chronic inflammatory disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of general inflammation, inflammatory bowel disease, brain inflammation, sepsis and septic shock.

84. A method of treating a disease or medical condition with an autoimmune component by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of rheumatoid arthritis, gouty arthritis and multiple sclerosis.

85. A method of treating a metabolic disease or medical condition accompanied by weight gain by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of obesity, feeding disorders and Prader-Willi Syndrome.

86. A method according to claim 85, wherein obesity is treated.

87. A method according to claim 85, wherein a feeding disorder is treated.

88. A method of decreasing food intake according to claim 76.

89. A method of decreasing body weight according to claim 76.

90. A method of decreasing food intake and decreasing body weight by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76.

91. A method of decreasing food intake by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 88 wherein said compound is Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 or Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

92. A method according to claim 91, wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

93. A method according to claim 91, wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

94. A method according to claim 91, wherein said compound is Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, or a pharmaceutically acceptable salt thereof.

95. A method of decreasing body weight by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 89 wherein said compound is Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 or Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

96. A method according to claim 95, wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

97. A method according to claim 95, wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

98. A method according to claim 95, wherein said compound is Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, or a pharmaceutically acceptable salt thereof.

99. A method of decreasing food intake and decreasing body weight by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 90 wherein said compound is Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2, Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, or Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

100. A method according to claim 99, wherein said compound is 22493 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

101. A method according to claim 99, wherein said compound is Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2, or a pharmaceutically acceptable salt thereof.

102. A method according to claim 99, wherein said compound is Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2, or a pharmaceutically acceptable salt thereof.

103. A method of treating a metabolic disease or medical condition accompanied by weight loss by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of anorexia, bulimia, AIDS wasting, cachexia, cancer cachexia and wasting in frail elderly.

104 A method according to claim 103, wherein anorexia is treated.

105. A method according to claim 103, wherein bulimia is treated.

106. A method according to claim 103, wherein AIDS wasting or wasting in frail elderly is treated.

107. A method according to claim 103, wherein cachexia or cancer cachexia is treated.

108. A method of treating a neoplastic disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of skin cancer and cancer cachexia.

109. A method of treating a reproductive or sexual medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, 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.

110. A method of treating a disease or medical condition resulting from treatment or insult to an organism by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, 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.

111. A method of treating a cardiovascular disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of hemorrhagic shock, cardiogenic shock, hypovolemic shock, cardiovascular disorders and cardiac cachexia.

112. A method of treating a pulmonary disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease and asthma.

113. A method of treating a disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of enhanced immune tolerance and allergies.

114. A method of treating a dermatological disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of psoriasis, skin pigmentation depletion, acne and keloid formation.

115. A method of treating a behavioral or central nervous system or neuronal disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of anxiety, depression, memory dysfunction and neuropathic pain.

116. A method of treating a renal disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76, wherein said disease or condition is selected from the group consisting of renal cachexia and natriuresis.

117. A method of 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 by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76.

118. A method of modulating bone metabolism, bone formation and bone development by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76.

119. A method of inhibiting alcohol consumption, reducing alcohol consumption, treating alcoholism, or treating alcohol abuse by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 76.

120. A method of inhibiting alcohol consumption according to claim 119, wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

121. A method of reducing alcohol consumption according to claim 119, wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

122. A method of treating alcoholism according to claim 119, wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

123. A method of treating alcohol abuse according to claim 119, wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

124. A method of inhibiting alcohol consumption according to claim 120, wherein said compound of said pharmaceutical composition 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.

125. A method according to claim 124, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

126. A method according to claim 124, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

127. A method according to claim 124, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

128. A method according to claim 124, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

129. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist or antagonist according to any one of claims 1-18, 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.

130. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist or antagonist according to any one of claims 1-18, 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.

131. A compound according to 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.

132. A compound according to claim 131, wherein said compound is:

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;

Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2;

Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;

Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH_2;

Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2; or

Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH_2; or

a pharmaceutically acceptable salt thereof.

133. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 131 or 132, or a

pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

134. A pharmaceutical composition according to claim 133, wherein said compound is a selective melanocortin 4 receptor agonist, or a pharmaceutically acceptable salt thereof.

135. A pharmaceutical composition according to claim 134, wherein said compound 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.

136. A pharmaceutical composition according to claim 135, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

137. A pharmaceutical composition according to claim 135, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

138. A pharmaceutical composition according to claim 135, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

139. A pharmaceutical composition according to claim 135, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50}

at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

140. A pharmaceutical composition according to claim 133 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.

141. A pharmaceutical composition according to claim 133 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.

142. A pharmaceutical composition according to claim 133 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.

143. A pharmaceutical composition according to claim 142, wherein obesity is treated.

144. A pharmaceutical composition according to claim 142, wherein a feeding disorder is treated.

145. A pharmaceutical composition according to claim 133 useful for decreasing food intake.

146. A pharmaceutical composition according to claim 133 useful for decreasing body weight.

147. A pharmaceutical composition according to claim 133 useful for decreasing food intake and decreasing body weight.

148. A pharmaceutical composition according to claim 133 useful for treating a metabolic disease or medical condition accompanied by weight loss wherein said disease or condition is selected from the group consisting of anorexia, bulimia, AIDS wasting, cachexia, cancer cachexia and wasting in frail elderly.

149. A pharmaceutical composition according to claim 148 useful for treating anorexia.

150. A pharmaceutical composition according to claim 148 useful for treating bulimia.

151. A pharmaceutical composition according to claim 148 useful for treating AIDS wasting or wasting in frail elderly.

152. A pharmaceutical composition according to claim 148 useful for treating cachexia or cancer cachexia.

153. A pharmaceutical composition according to claim 133 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.

154. A pharmaceutical composition according to claim 133 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.

155. A pharmaceutical composition according to claim 133 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.

156. A pharmaceutical composition according to claim 133 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.

157. A pharmaceutical composition according to claim 133 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.

158. A pharmaceutical composition according to claim 133 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.

159. A pharmaceutical composition according to claim 133 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.

160. A pharmaceutical composition according to claim 133 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.

161. A pharmaceutical composition according to claim 133 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.

162. A pharmaceutical composition according to claim 133 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.

163. A pharmaceutical composition according to claim 133 useful for modulating bone metabolism, bone formation and bone development.

164. A pharmaceutical composition according to claim 133 useful for inhibiting alcohol consumption, for reducing alcohol consumption, for treating alcoholism, or for treating alcohol abuse.

165. A pharmaceutical composition according to claim 164 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

166. A pharmaceutical composition according to claim 164 useful for reducing alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

167. A pharmaceutical composition according to claim 164 useful for treating alcoholism wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

168. A pharmaceutical composition according to claim 164 useful for treating alcohol abuse wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

169. A pharmaceutical composition according to claim 165 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist exhibiting 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.

170. A pharmaceutical composition according to claim 169 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist exhibiting a function 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.

171. A pharmaceutical composition according to claim 169 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist exhibiting a function activity characterized by an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

172. A pharmaceutical composition according to claim 169 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist exhibiting a function activity characterized by an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

173. A pharmaceutical composition according to claim 169 useful for inhibiting alcohol consumption wherein said compound of said pharmaceutical

composition is a selective melanocortin 4 receptor agonist exhibiting a function activity characterized by an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

174. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist according to any one of claims 131 or 132, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to inhibit alcohol consumption in a subject in need of such treatment.

175. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist of according to any one of claims 131 or 132, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to reduce alcohol consumption in a subject in need of such treatment.

176. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist according to any one of claims 131 or 132, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to treat alcoholism in a subject in need of such treatment.

177. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist according to c any one of claims 131 or 132, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful to treat alcohol abuse in a subject in need of such treatment.

178. A method of eliciting an agonist or antagonist effect from a melanocortin receptor in a subject in need thereof which comprises administering to said subject a therapeutically effective amount of a compound according to any one of claims 131 or 132, or a pharmaceutically acceptable salt thereof.

179. A method according to claim 178, wherein said compound is a selective melanocortin 4 receptor agonist.

180. A method according to claim 179, 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.

181. A method according to claim 180, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

182. A method according to claim 180, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

183. A method according to claim 180, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

184. A method according to claim 180, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

185. A method of treating an acute or chronic inflammatory disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is selected from

the group consisting of general inflammation, inflammatory bowel disease, brain inflammation, sepsis and septic shock.

186. A method of treating a disease or medical condition with an autoimmune component by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is selected from the group consisting of rheumatoid arthritis, gouty arthritis and multiple sclerosis.

187. A method of treating a metabolic disease or medical condition accompanied by weight gain by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is selected from the group consisting of obesity, feeding disorders and Prader-Willi Syndrome.

188. A method according to claim 187, wherein obesity is treated.

189. A method according to claim 187 wherein a feeding disorder is treated.

190. A method of decreasing food intake according to claim 178.

191. A method of decreasing body weight according to claim 178.

192. A method of decreasing food intake and decreasing body weight by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178.

193. A method of treating a metabolic disease or medical condition accompanied by weight loss by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is

selected from the group consisting of anorexia, bulimia, AIDS wasting, cachexia, cancer cachexia and wasting in frail elderly.

194. A method according to claim 193, wherein anorexia is treated.

195. A method according to claim 193, wherein bulimia is treated.

196. A method according to claim 193, wherein AIDS wasting or wasting in frail elderly is treated.

197. A method according to claim 193, wherein cachexia or cancer cachexia is treated.

198. A method of treating a neoplastic disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is selected from the group consisting of skin cancer and cancer cachexia.

199. A method of treating a reproductive or sexual medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, 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.

200. A method of treating a disease or medical condition resulting from treatment or insult to an organism by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, 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.

201. A method of treating a cardiovascular disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is selected from the group consisting of hemorrhagic shock, cardiogenic shock, hypovolemic shock, cardiovascular disorders and cardiac cachexia.

202. A method of treating a pulmonary disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is selected from the group consisting of acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease and asthma.

203. A method of treating a disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is selected from the group consisting of enhanced immune tolerance and allergies.

204. A method of treating a dermatological disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is selected from the group consisting of psoriasis, skin pigmentation depletion, acne and keloid formation.

205. A method of treating a behavioral or central nervous system or neuronal disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178, wherein said disease or condition is selected from the group consisting of anxiety, depression, memory dysfunction and neuropathic pain.

206. A method of treating a renal disease or medical condition by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178,

wherein said disease or condition is selected from the group consisting of renal cachexia and natriuresis.

207. A method of 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 by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178.

208. A method of modulating bone metabolism, bone formation and bone development by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178.

209. A method of inhibiting alcohol consumption, reducing alcohol consumption, treating alcoholism, or treating alcohol abuse by eliciting an agonist or antagonist effect from a melanocortin receptor according to claim 178.

210. A method of inhibiting alcohol consumption according to claim 209, wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

211. A method of reducing alcohol consumption according to claim 209, wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

212. A method of treating alcoholism according to claim 209, wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

213. A method of treating alcohol abuse according to claim 209, wherein said compound of said pharmaceutical composition is a selective melanocortin 4 receptor agonist.

214. A method of inhibiting alcohol consumption according to claim 210, wherein said compound of said pharmaceutical composition 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.

215. A method according to claim 214, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 17-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

216. A method according to claim 214, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 90-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 3 receptor.

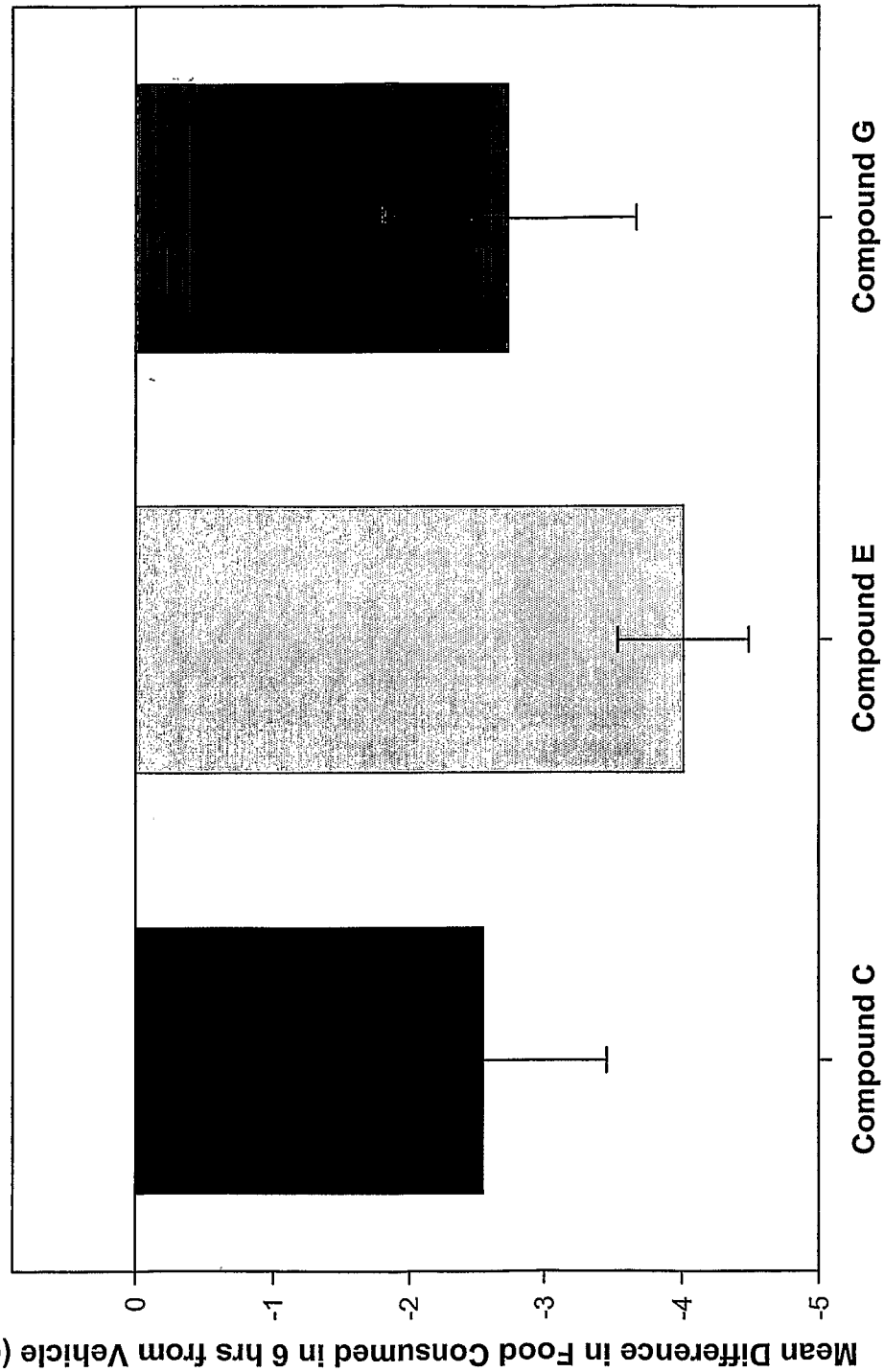
217. A method according to claim 214, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 200-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

218. A method according to claim 214, wherein the functional activity of the melanocortin 4 receptor agonist is characterized by an EC_{50} at least 3000-fold more selective for the human melanocortin 4 receptor than for the human melanocortin 5 receptor.

219. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist or antagonist according to any one of claims 131 or 132, 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.

220. The use of a therapeutically effective amount of a melanocortin 4 receptor agonist or antagonist according to any one of claims 131 or 132, 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.

Figure 1A


Mean Difference in Food Consumed in 6 hrs from Vehicle (g)
0
-1
-2
-3
-4
-5
Compound C
Compound E
Compound G

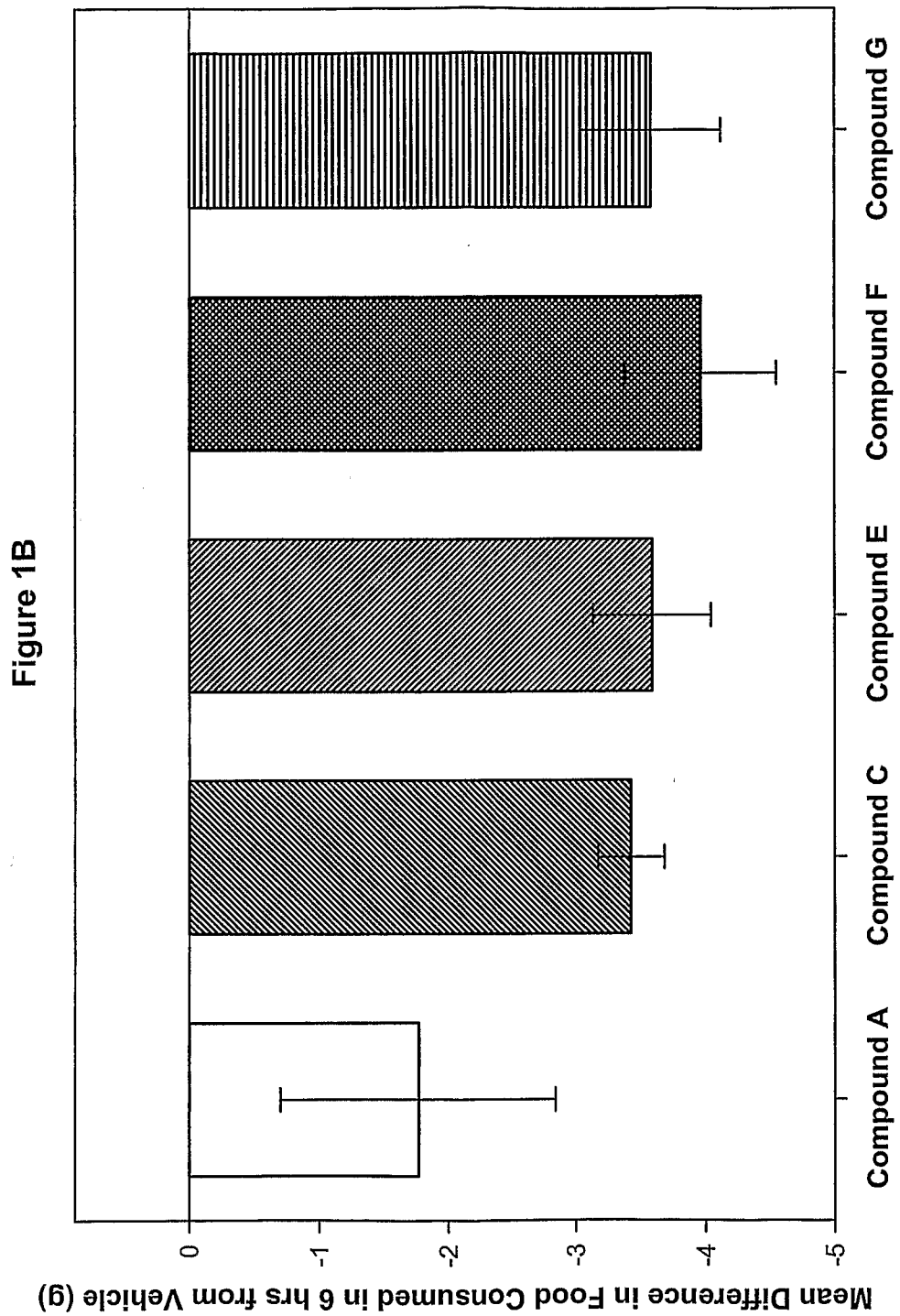
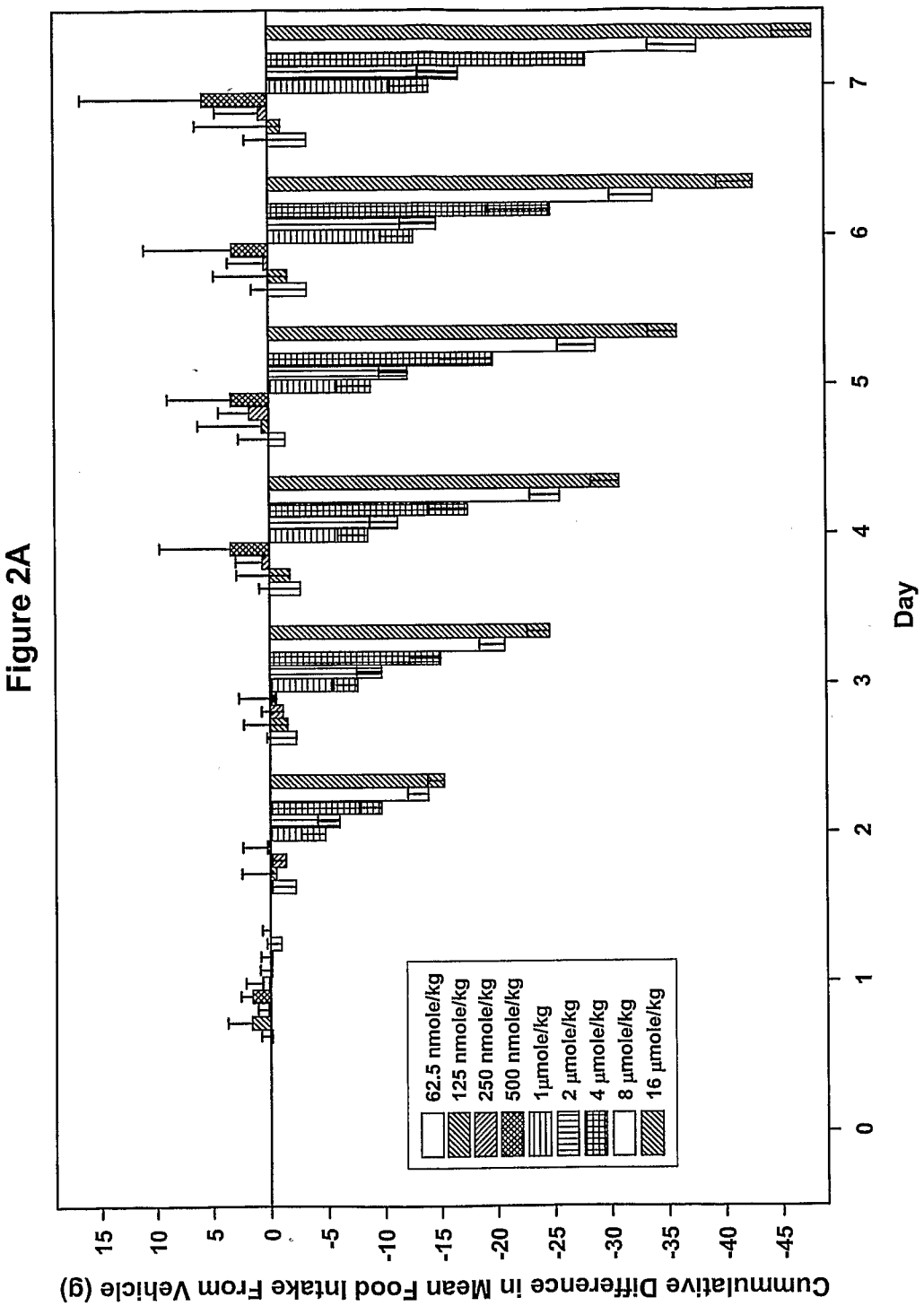

Mean Difference in Food Consumed in 6 hrs from Vehicle (g)
0
-1
-2
-3
-4
-5
Compound A
Compound C
Compound E
Compound F
Compound G

Figure 1B

Figure 2A


Cummulative Difference in Mean Food Intake From Vehicle (g)
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
0
1
2
3
4
5
6
7
Day
62.5 nmole/kg
125 nmole/kg
250 nmole/kg
500 nmole/kg
1 µmole/kg
2 µmole/kg
4 µmole/kg
8 µmole/kg
16 µmole/kg

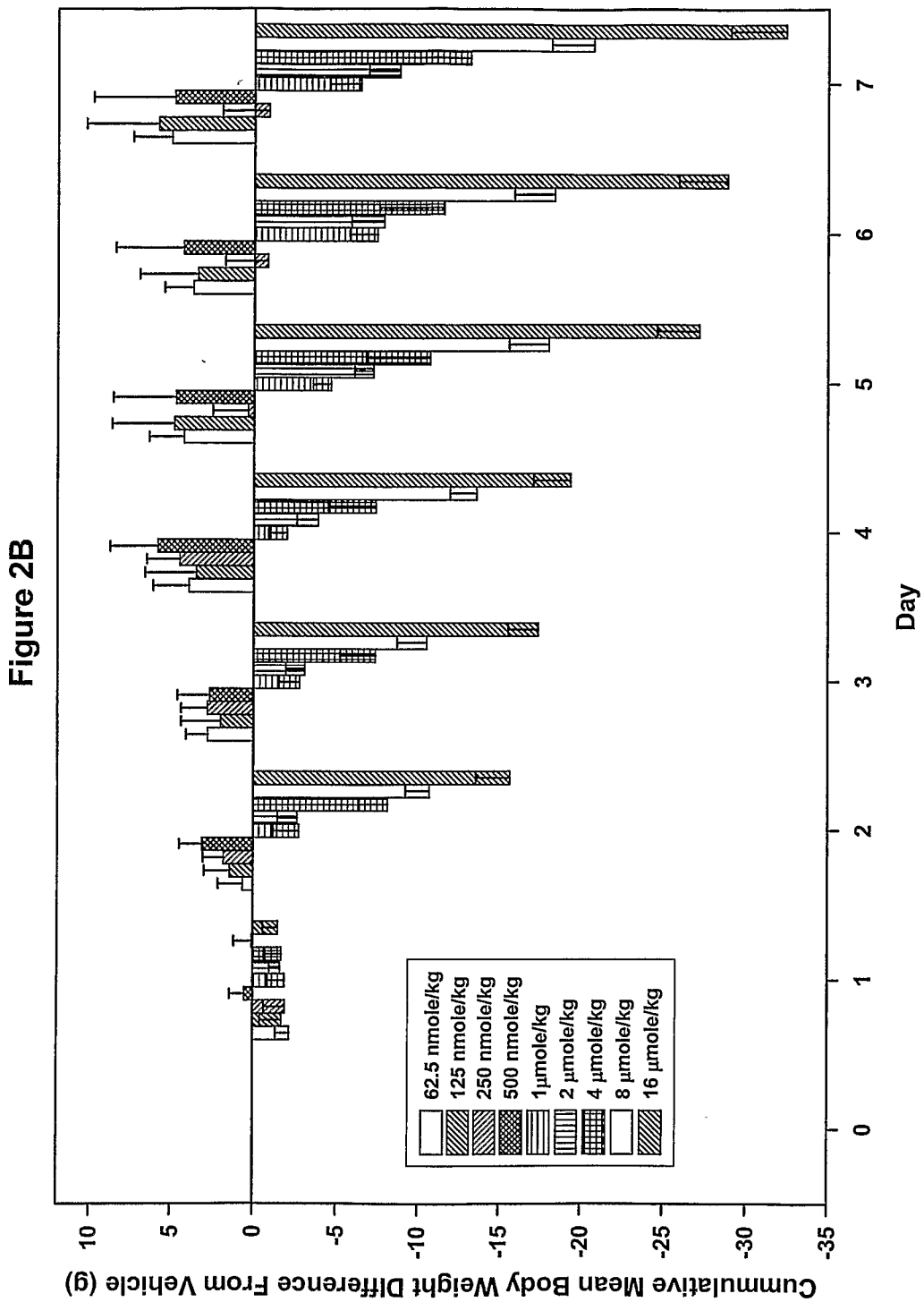

Cummulative Mean Body Weight Difference From Vehicle (g)
10
5
0
-5
-10
-15
-20
-25
-30
-35
0
1
2
3
4
5
6
7
Day
62.5 nmole/kg
125 nmole/kg
250 nmole/kg
500 nmole/kg
1 µmole/kg
2 µmole/kg
4 µmole/kg
8 µmole/kg
16 µmole/kg

Figure 2B

Figure 3A

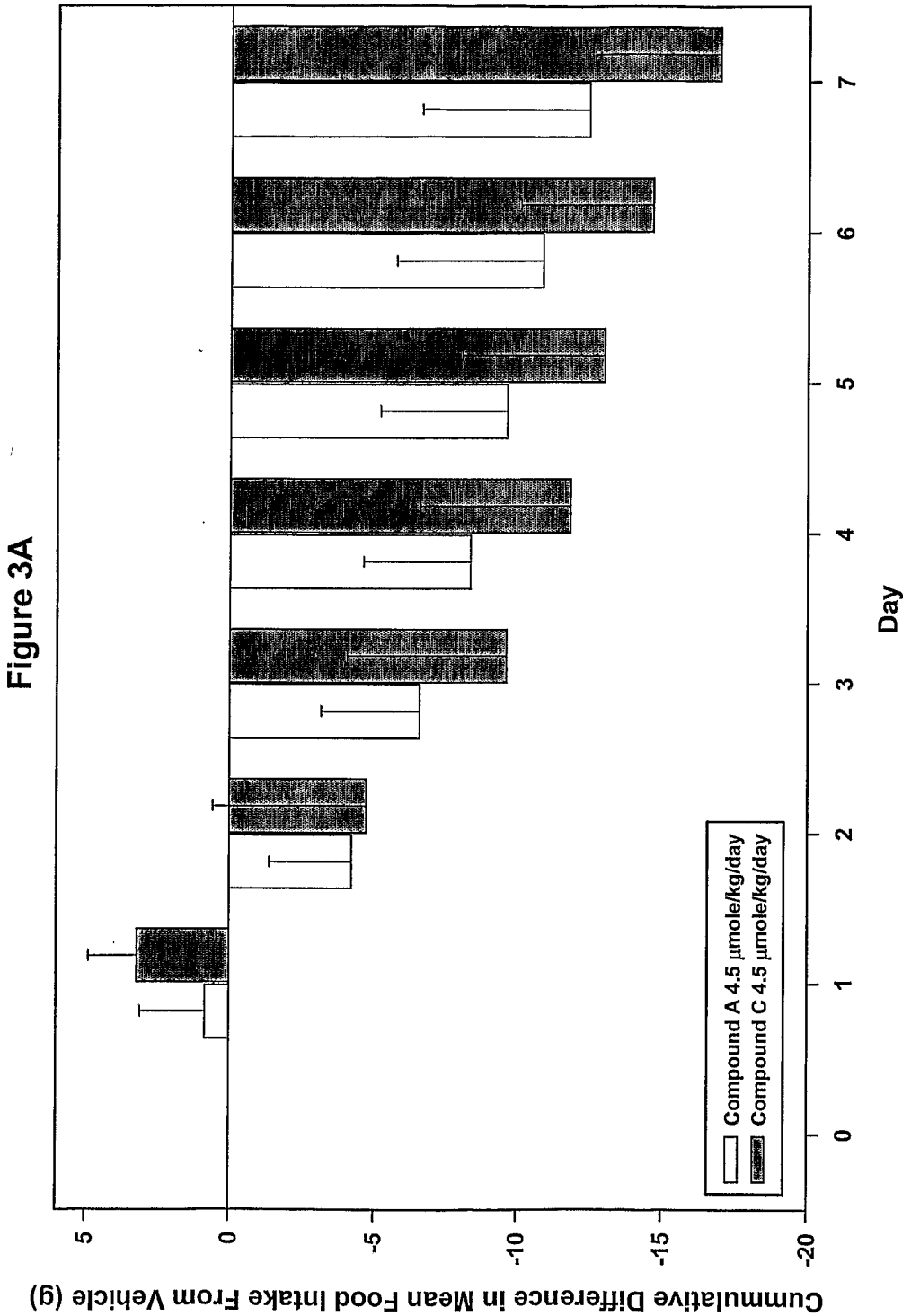

Cummulative Difference in Mean Food Intake From Vehicle (g)
5
0
-5
-10
-15
-20
0
1
2
3
4
5
6
7
Day
Compound A 4.5 µmole/kg/day
Compound C 4.5 µmole/kg/day

Figure 3B

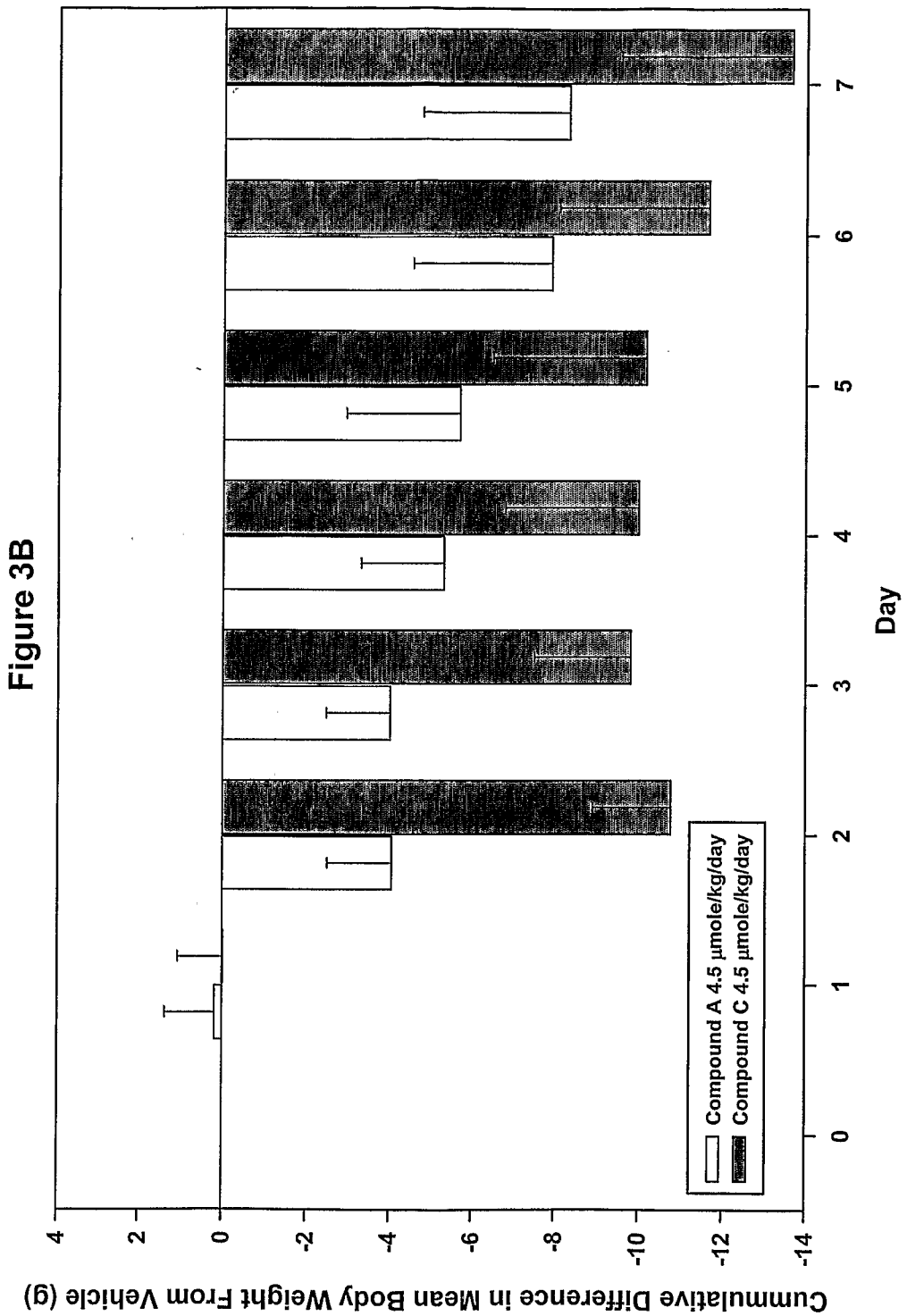

Cummulative Difference in Mean Body Weight From Vehicle (g)
4
2
0
-2
-4
-6
-8
-10
-12
-14
0
1
2
3
4
5
6
7
Day
Compound A 4.5 µmole/kg/day
Compound C 4.5 µmole/kg/day

Figure 4A

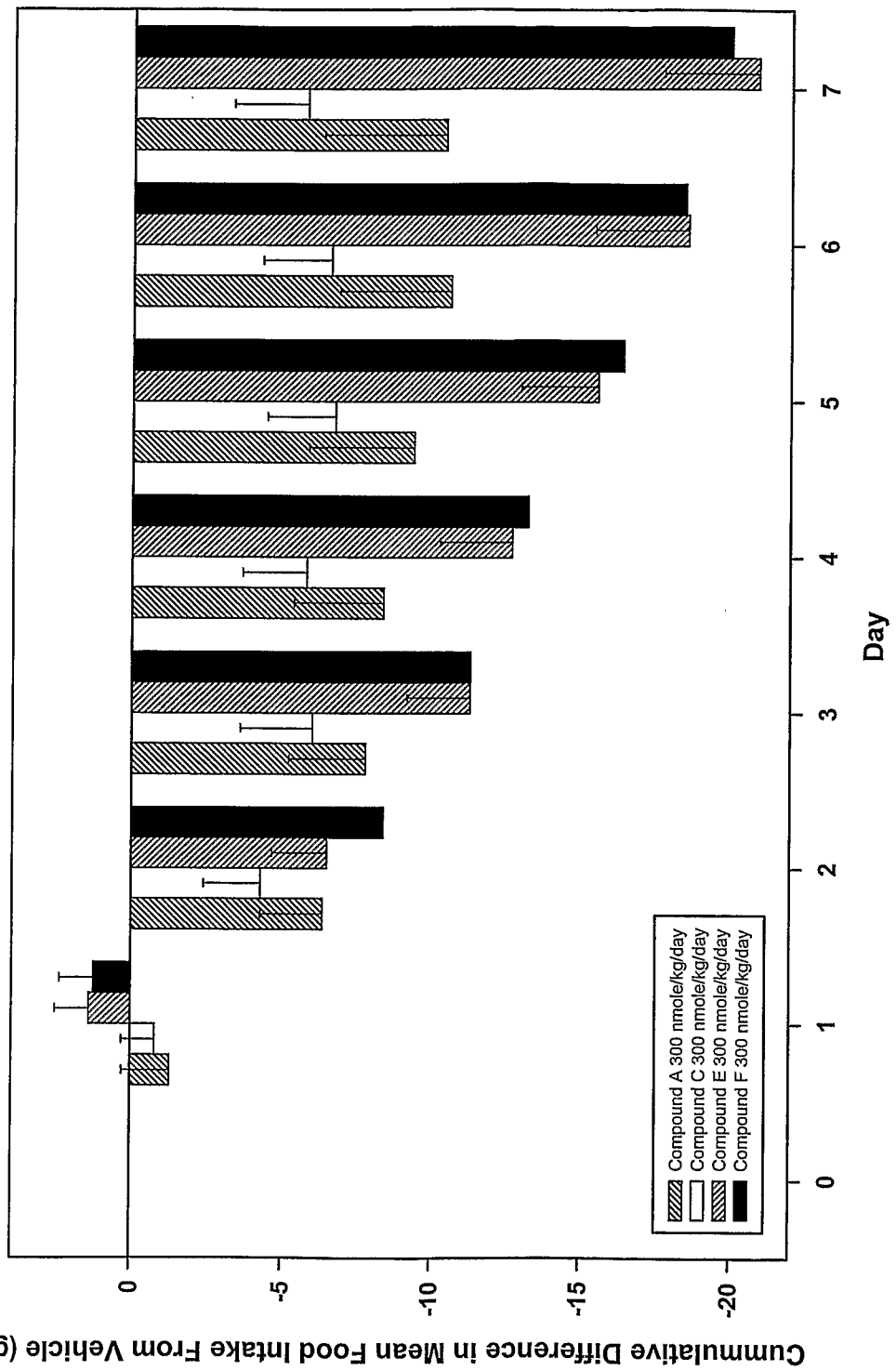
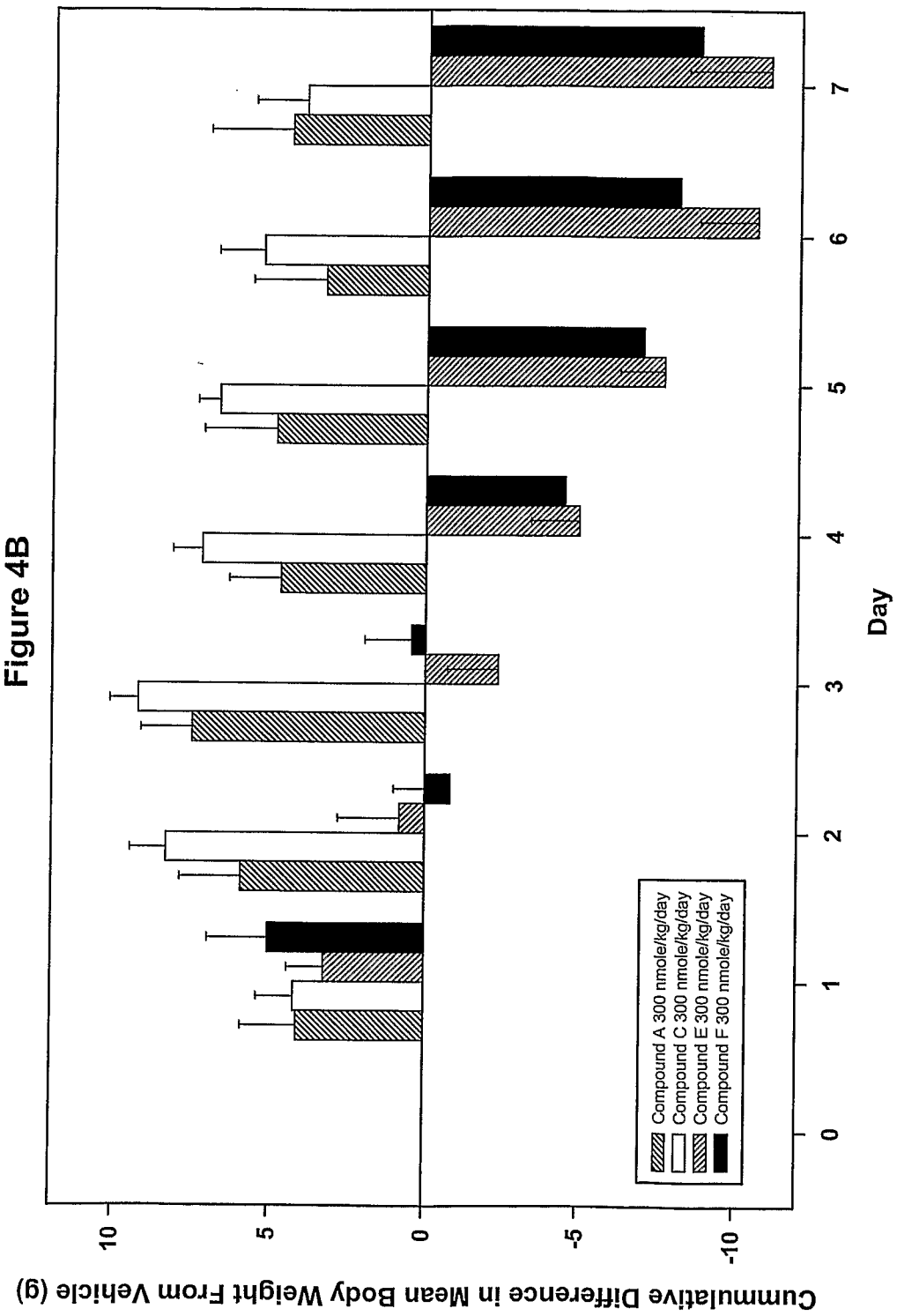

Cummulative Difference in Mean Food Intake From Vehicle (g)
0
-5
-10
-15
-20
0
1
2
3
4
5
6
7
Day
Compound A 300 nmole/kg/day
Compound C 300 nmole/kg/day
Compound E 300 nmole/kg/day
Compound F 300 nmole/kg/day

Figure 4B


Cummulative Difference in Mean Body Weight From Vehicle (g)
10
5
0
-5
-10
0
1
2
3
4
5
6
7
Day
Compound A 300 nmole/kg/day
Compound C 300 nmole/kg/day
Compound E 300 nmole/kg/day
Compound F 300 nmole/kg/day