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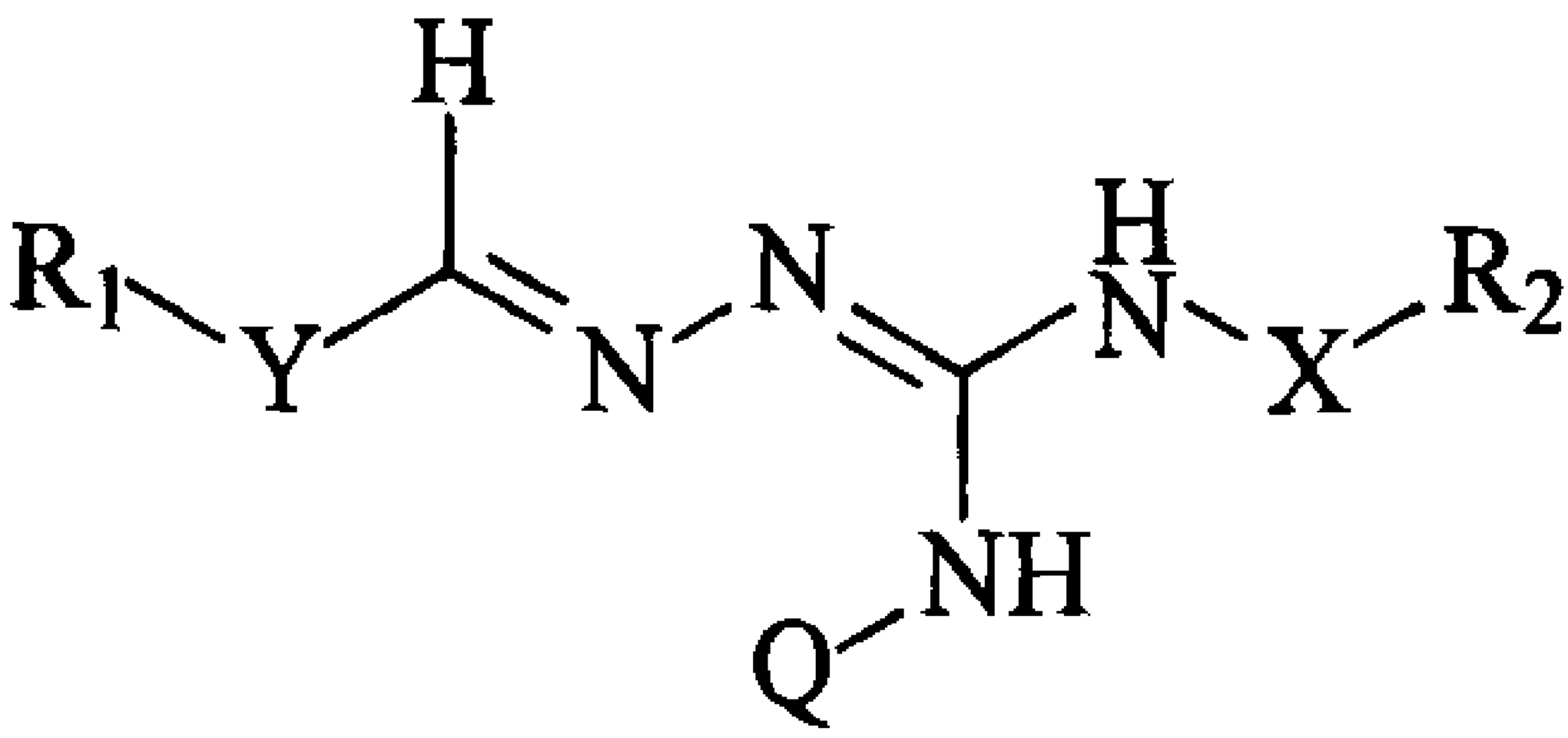
(72) Inventeurs/Inventors:
LUNDSTEDT, TORBJORN, SE;
SKOTTNER, ANNA, SE;
BOMAN, ARNE, SE;
...

(54) Titre : COMPOSANTS AGISSANT COMME LIGANDS DE RECEPTEUR DE LA MELANOCORTINE
(54) Title: COMPOUNDS ACTING AS MELANOCORTIN RECEPTOR LIGANDS



(I)

(57) Abrégé/Abstract:
The present invention provides novel compounds and use of compounds of general formula (I) as ligands to the melanocortin receptors and/or for treatment of disorders in the melanocortin system: Wherein X and Y are independently chosen from O, N, S

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(72) Inventeurs(suite)/Inventors(continued): ANDERSSON, PER, SE; ANDRIANOV, VICTOR, LV; KALVINS, IVARS, LV

(73) Propriétaires(suite)/Owners(continued):ANAMAR AB, SE

(74) Agent: FETHERSTONHAUGH & CO.

(57) Abrégé(suite)/Abstract(continued):
and $(CH_2)_n$, where n is 0, 1, 2, 3, 4 or 5, or a combination of these and may contain carbon-carbon multiple bonds and branched chains as well as alicyclic and heterocyclic groups; Q is H or OH; R_1 and R_2 can be either the same or different and are chosen from hydrogen or the residue of an aromatic group as listed in Scheme 1 and the pharmacologically active salts thereof.

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(71) Applicant *(for all designated States except US)*: **MELACURE THERAPEUTICS AB** [SE/SE]; Ulleråkersvägen 38, S-756 43 Uppsala (SE).

(71) Applicant *(for GB only)*: **PETT, Christopher, Phineas** [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LUNDSTEDT, Torbjörn** [SE/SE]; Granelidsvägen 7B, S-756 55 Uppsala (SE). **SKOTTNER, Anna** [SE/SE]; Lobovägen 3, S-178 32 Ekerö (SE). **BOMAN, Arne** [SE/SE]; Gustaf Kjellbergs Väg 4, S-756 43 Uppsala (SE). **ANDERSSON, Per** [SE/SE]; Spinnrocksvägen 5, S-756 48 Uppsala (SE). **ANDRIANOV, Victor** [Stateless/LV]; Zemes Street 11-4, LV-1083 Riga (LV). **KALVINS, Ivars** [LV/LV]; Libiesu 25, LV-5052 Ikskile (LV).

(74) Agents: **PETT, Christopher, Phineas** et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

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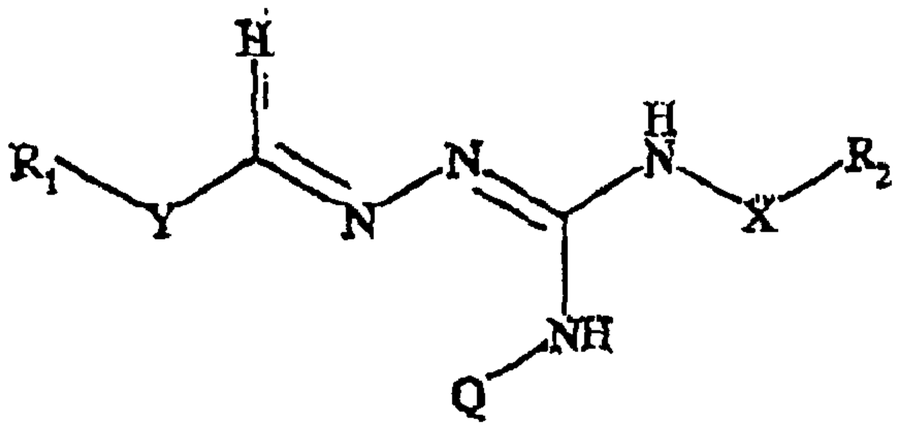
(54) Title: COMPOUNDS ACTING AS MELANOCORTIN RECEPTOR LIGANDS



(I)

in Scheme 1 and the pharmacologically active salts thereof.

(57) Abstract: The present invention provides novel compounds and use of compounds of general formula (I) as ligands to the melanocortin receptors and/or for treatment of disorders in the melanocortin system: Wherein X and Y are independently chosen from O, N, S and $(CH_2)_n$, where n is 0, 1, 2, 3, 4 or 5, or a combination of these and may contain carbon-carbon multiple bonds and branched chains as well as alicyclic and heterocyclic groups; Q is H or OH; R_1 and R_2 can be either the same or different and are chosen from hydrogen or the residue of an aromatic group as listed

COMPOUNDS ACTING AS MELANOCORTIN RECEPTOR LIGANDS

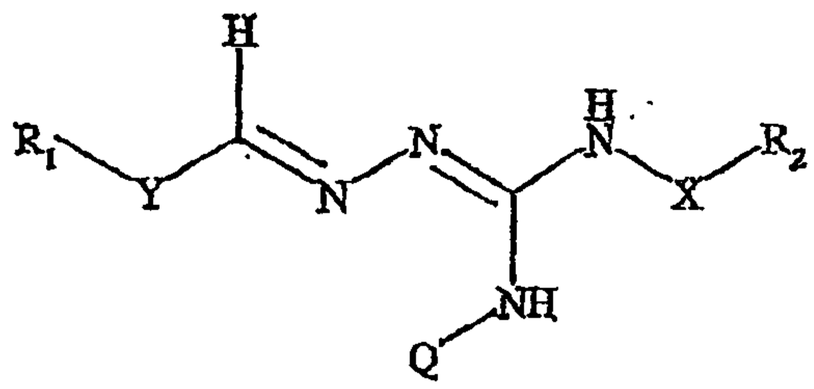
The present invention relates to novel guanidines and to the use of guanidines for the treatment of obesity, anorexia, inflammation, mental disorders and other diseases associated with the melanocortin receptors or related systems, e.g. the melanocyte stimulating hormones.

A number of large linear and cyclic peptides are known in the art which show high specific binding to melanocortin (MC) receptors. The agonistic and/or antagonistic properties of these peptides are also known. See for example "Melanocortin Receptor ligands and methods of using same" by Dooley, Girten and Houghten (WO 99/21571). There remains, however, a need to provide low molecular weight compounds showing agonistic or antagonistic properties to the melanocortin receptors.

A number of low molecular weight compounds are known, e.g. isoquinolines, spiropyridines and benzimidazoles, which show activity on the MC- receptors. See "Isoquinoline compound melanocortin receptor ligands and methods of using same" by Basu *et al*, Trega Biosciences Inc. (PCT/US99/09216), "Spiropiperidine derivatives as melanocortin receptor agonists" by **Nargund**, Ye, Palucki, Bakshi, Patchett and van der Ploeg (PCT/US99/13252) and "Melanocortin receptor-3 ligands to treat sexual dysfunction" by Dines *et al* (WO 01/05401). The compounds in the present invention are structurally different from the above mentioned compounds and, consequently, constitute a new class of compounds that show activity to the MC-receptors.

One aspect of the present invention is therefore to provide low molecular weight compounds showing activity on melanocortin receptors and which may be taken up after per oral administration and which may penetrate well through the blood brain barrier.

The present invention provides novel compounds within and the use of compounds of general formula (I) and their tautomeric forms:



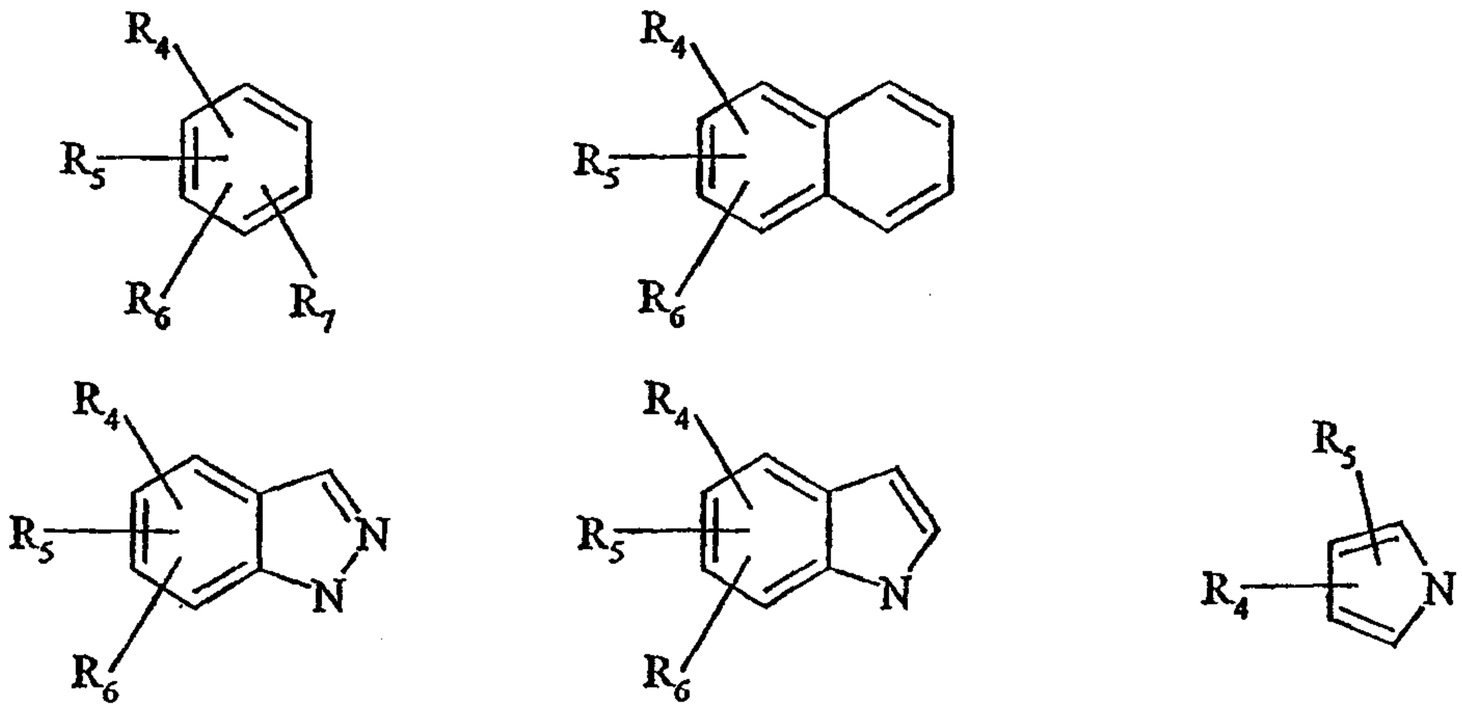
(I)

wherein X and Y are independently chosen from O, N, S and $(CH_2)_n$ where n is 0, 1, 2, 3, 4 or 5, or a combination of these and may contain carbon-carbon multiple bonds and branched chains as well as alicyclic and heterocyclic groups.

Q is H or OH;

R_1 and R_2 can be either the same or different and are chosen from hydrogen or the residue of an aromatic group as listed in Scheme 1:

Scheme 1



wherein R_4, R_5, R_6 and R_7 are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, electron donor groups such as alkoxy having 1 to 5 carbon atoms, which with another substituent group may form part of a ring, hydroxy or an amine (primary, secondary or tertiary) having 0, 1 or 2 carbon atoms, electron accepting groups such as cyano, nitro, trifluoroalkyl, amide or sulpho, or from;

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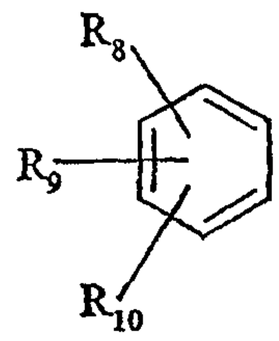


wherein R_8, R_9 and R_{10} are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, electron donor groups such as alkoxy having 1 to 5 carbon atoms, which with another substituent group may form part of a ring, hydroxy or an amine (primary, secondary or tertiary) having 0, 1 or 2 carbon atoms, electron accepting groups such as cyano, nitro, trifluoroalkyl, amide or sulpho;
with the proviso that where X is $(CH_2)_n$ and n is O, R_2 is not H;
and the pharmacologically active salts thereof.

In a further aspect, the present invention provides a commercial package comprising a compound as defined herein, or a pharmaceutically acceptable salt or prodrug thereof, together with a written matter describing instructions for the use thereof for treating a disease or disorder as defined herein.

When used in the foregoing definitions, the term alkyl is meant to include straight or branched chain hydrocarbon groups as well as alicyclic and fused alicyclic groups; and the term alkoxy is meant to include straight or branched chain alkoxy groups.

The term halogen includes fluoro, chloro, bromo and iodo.

Preferably, the "alkyl having 1 to 8 carbon atoms" is a lower alkyl such as methyl, ethyl, propyl or iso-propyl.

Preferably, the "alkoxy having 1 to 5 carbon atoms" is a lower alkoxy such as methoxy, ethoxy, propoxy or iso-propoxy.

Preferably, the trifluoroalkyl is trifluoromethyl, trifluoroethyl, trifluoropropyl or trifluoroiso-propyl.

X and Y may also be NH or N-alkyl, preferably N-methyl or N-ethyl.

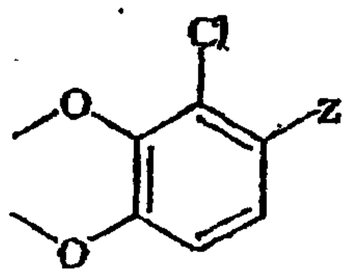
When X represents $(CH_2)_n$, *n* is preferably 1 or 2.
When Y represents $(CH_2)_n$, *n* is preferably 0, 1 or 2.

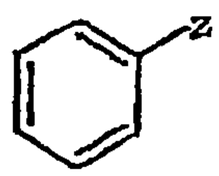
In cases where R_1 and/or R_2 are chosen from the compounds given in Scheme 1 and the compound is a bicyclic or tricyclic ring, it should be noted that the R_4-R_7 substituents may be present on any of the rings.

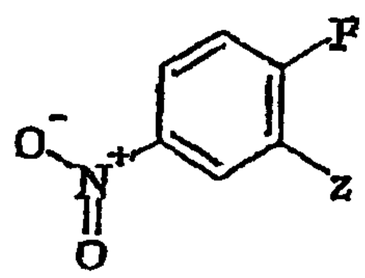
Furthermore, it should be noted that the Scheme 1 compounds may be attached to the carbon backbone of the compound of general Formula (I) at any suitable point within the compound of Scheme 1, preferably at the 1, 2 or 3 position.

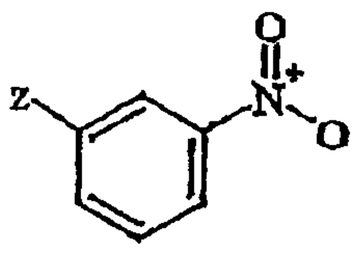
In one embodiment, one or more of R_5 to R_{10} can be alkyl having 1 to 8 carbon atoms, e.g. methyl or ethyl. In another embodiment, one or more of R_4 to R_{10} can be alkoxy, e.g. methoxy. In a further embodiment, one or more of R_4 to R_{10} can be halogen atoms.

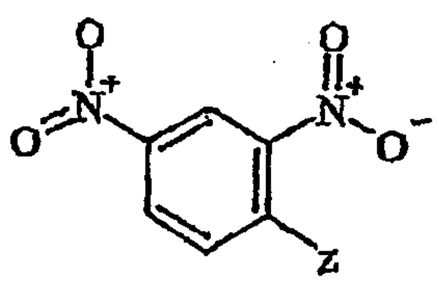
Examples of novel compounds which comprise a further feature of the present invention are those wherein R_1 and R_2 are selected from;

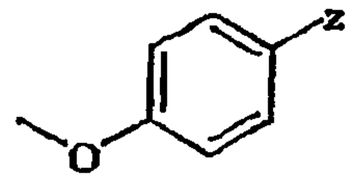


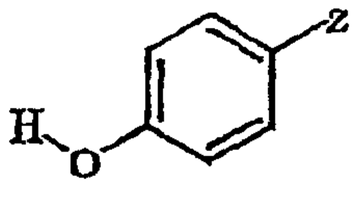


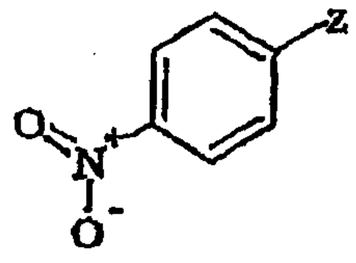


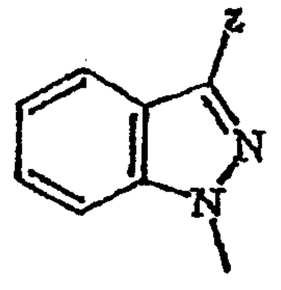




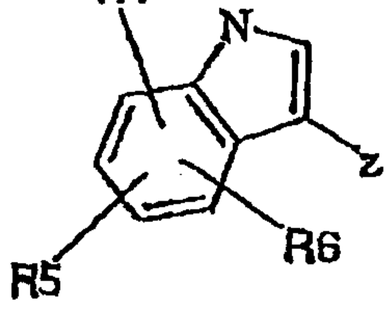


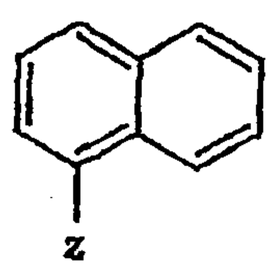


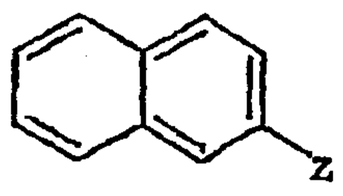


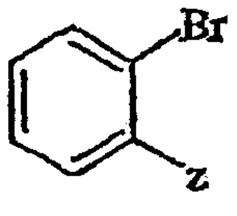


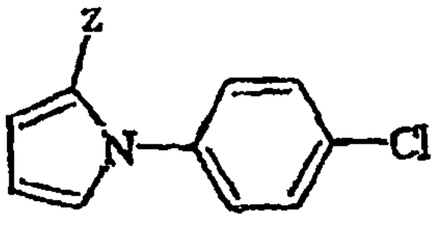
R4

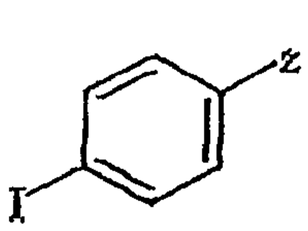


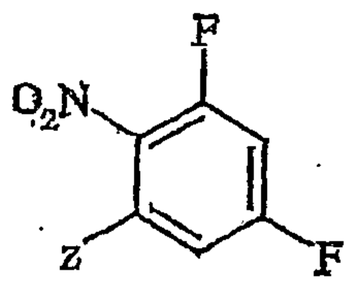


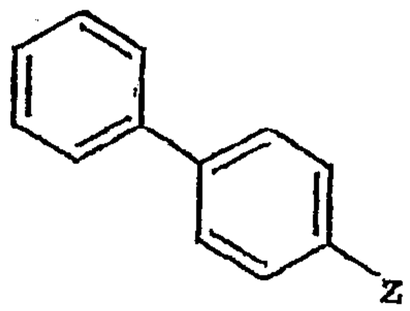


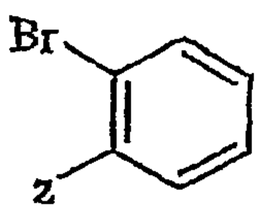


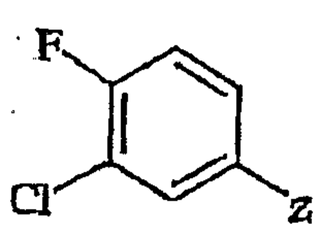


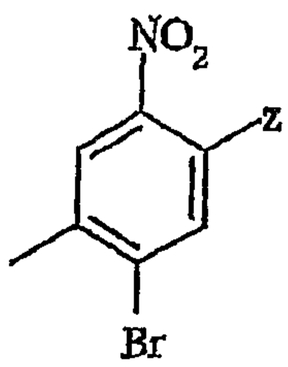


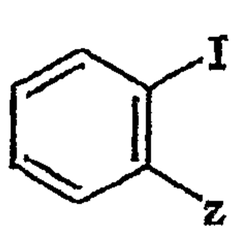


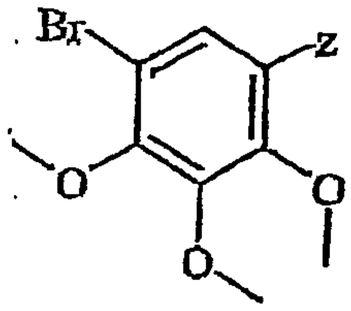


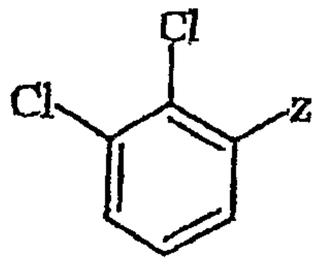


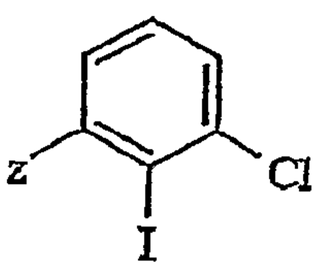


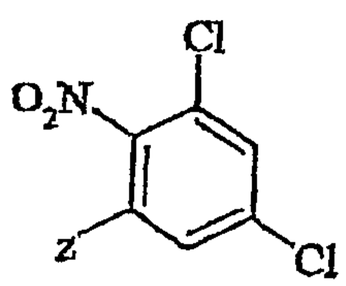


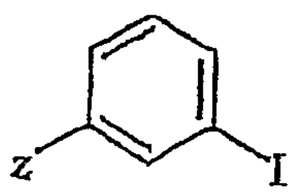


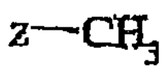


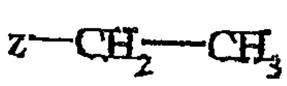












wherein *z* denotes the point of attachment;
with the proviso that:

when R_1 is phenyl, R_2 must be selected from a different substituent than phenyl;

when R_1 is 4-methoxyphenyl, R_2 must be selected from a different substituent than 4-methoxyphenyl or 1,3-dinitrophenyl;

when R_2 is 4-methoxyphenyl, R_1 must be selected from a different substituent than 4-methoxyphenyl ; and

when R_2 is methyl, R_1 must be selected from a substituent different than phenyl.

The compounds of Formula (I) have basic properties and, consequently, they may be converted to their therapeutically active acid addition salts by treatment with appropriate physiologically acceptable acids, e.g. inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulphuric, nitric and phosphoric acid, or organic acids such as acetic, propanoic, glycolic, lactic, malonic, succinic, fumaric, tartaric, citric, pamoic, oxalic and *para*-toluene-sulphonic acid.

Conversely, the salt form may be converted into the free base form by treatment with alkali.

The present invention relates to novel guanidines. Compounds of the present invention have been biologically tested in the melanocortin system and have surprisingly been shown to be capable of binding to melanocortin receptors as well as showing activity in functional assays.

Compounds of the present invention are either agonists or antagonists of a specific MC-receptor or of a number of MC-receptors, e.g. MC1, MC3, MC4 or/and MC5 receptors.

The MC-receptors belong to the class of G-protein coupled receptors which are all built from a single polypeptide forming 7 transmembrane domains. Five such receptors types, termed MC1, MC2, MC3, MC4 and MC5, have been described. The MC receptor's signaling is mainly mediated via cAMP but also other signal transduction pathways are known. They are distinctly distributed in the body.

MC-receptors are linked to a variety of physiological actions that are thought to be mediated by distinct subtypes of the MC-receptors. In many cases, however, it is not entirely clear which of the subtypes is responsible for the effect.

It has long been known that MSH-peptides may affect many different processes such as motivation, learning, memory, behaviour (including feeding and sexual), inflammation (including immunostimulatory and immunosuppressive), body temperature, pain perception, blood pressure, heart rate, vascular tone, brain blood flow, trophic effects in different organs, nerve growth, placental development, endocrine and exocrine functions, aldosterone synthesis and release, thyroxin release, spermatogenesis, ovarian weight, prolactin and FSH secretion, effects on other organs, uterine bleeding in women, sebum and pheromone secretion, blood glucose levels, intrauterine foetal growth, as well as other events surrounding parturition and natriuresis (Eberle, AN: The melanotropins: Chemistry, physiology and mechanisms of action. Basel: Karger, Switzerland. 1988, ISBN 3-8055-4678-5; Gruber, and Callahan, Am. J. Physiol. 1989, 257, R681-R694; De Wildt *et al.*, J. Cardiovascular Pharmacology. 1995, 25, 898-905), as well as inducing natriuresis (Lin *et al.*, Hypertension. 1987, 10, 619-627).

It is also well-known that the immunomodulatory action of α-MSH includes both immunostimulatory and immunosuppressive effects. Several studies have shown that α-MSH antagonizes the effects of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6 and TNFα, and induces the production of the anti-inflammatory cytokine, IL-10 (for review see Catania & Lipton, 1993).

Eating behaviour is regulated by a complex network of physiological regulatory pathways that involve both the central nervous system and peripheral sites. Factors such as leptin, insulin, NPY (neuropeptide Y), orexins, CRF (Corticotropin-Releasing Factor, release hormone) and melanocortic peptides (Schwartz; Nature Medicine 1998, 4, 385-386) are known to control the amount of food intake both during short and long term, which may affect body weight, body fat mass and growth rate. Recent studies have shown a role of MC-receptors, especially the MC4 receptor, for control of food intake, and there is evidence indicating that the melanocortins and the MC4 receptor are important factors downstream of leptin. Intracerebroventricular injections of the melanocortic peptides α-MSH and ACTH(1-24) have been shown to markedly inhibit feeding (Poggioli *et al.*, Peptides, 1986, 7, 843-848; Vergoni *et al.*, Neuropeptides, 1986, 7, 153-158).

The MC5-receptor has recently been attributed a role in control of exocrine gland function (van der Kraan, *et al.*, Endocrinol. 1998, 139, 2348-2355; Chen *et al.*, Cell. 1997, 91, 789-798).

In addition, the melanocortic peptides have distinct effects on sexual functions in that they cause erection in males (Donovan, Psychol. Med. 1978, 8, 305-316), presumably mediated by a central agonistic effect of the peptide on MC-receptors. It has also been shown that a MC-receptor blocker could inhibit the erectogenic effect of melanocortic peptides (Vergoni *et al.*, Eur. J. Pharmacol, 1998, 362; 95-101).

Some of the compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of mental disorders such as psychoses, depression, anxiety, senile dementia, Alzheimer's disease, drug abuse disorders and eating disorders such as anorexia and bulimia.

Compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of dysfunctions of the endocrine system and other hormonal systems such as excessive menstruations, endometriosis, events related to parturition, dysfunctions related to prolactin, dysfunctions related to growth hormone, dysfunctions related to testosterone, dysfunctions related to estrogen, dysfunctions related to glucocorticoids, dysfunctions related to luteinizing hormone and follicle stimulating hormone, inducing abortion, for prevention of abortion and/or for treatment of events related to parturition.

Compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of sexual functions / dysfunctions such as inducing erection in man, to induce erection in animal breeding, to stimulate intercourse in animals which are difficult to mate, in particular rare species or valuable strains, pets, cats, dogs, horses or to reduce sexual behaviour in animals, e.g. for pets, cats etc., to treat impotence and disorders related to sexual drive, including lack of sexual drive or abnormal sexual drive in both men and women.

Compounds of Formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of inflammation such as inflammations related to the production of nitric oxide, inflammation related to increased amounts (upregulated amounts) of inducible nitric oxide synthase, inflammation related to activation of transcriptional activators, inflammation related to nuclear factor kappa beta, inflammation related to macrophages, neutrophils, monocytes, keratinocytes, fibroblasts, melanocytes, pigment cells and endothelial cells, inflammation related to increased production and/or release of inflammatory cytokines, such as e.g. interleukins, in particular interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α).

In the present specification, "increased production" refers to increased formation, increased release, or increased amount of an endogenous compound locally, regionally or systemically in a patient compared to the amount of said endogenous compound in a healthy individual. In the present specification, "upregulated" refers to an increased activity or amount of the compound compared with that in a healthy individual.

In the present specification, "decreased production" refers to decreased formation, decreased release, or decreased amount of an endogenous compound in a patient compared to the amount of said endogenous compound in a healthy individual. In the present specification, "downregulated" refers to a decreased activity or amount of the compound compared with that in a healthy individual.

In particular, positive treatment effects or preventive effects may be seen in conditions where inflammation or an inflammatory-like condition is caused by or being associated with one or more of the following: allergy, hypersensitivity, bacterial infection, viral infection, inflammation caused by toxic agent, fever, autoimmune disease, radiation damage by any source including UV-radiation, X-ray radiation, γ -radiation, α- or β-particles, sun burns, elevated temperature or mechanical injury. Moreover, inflammation due to hypoxia, which is optionally followed by reoxygenation of the hypoxic area, is typically followed by severe inflammation, which condition may be positively affected by treatment with a compound of the invention.

In very specific embodiments of the invention, a compound of the invention may be administered for the prevention or therapeutic treatment of inflammatory diseases of the skin (including the dermis and epidermis) of any origin, including skin diseases having an inflammatory component. Specific examples of this embodiment of the invention include treatment of contact dermatitis of the skin, sunburns of the skin, burns of any cause, and inflammation of the skin caused by chemical agents, psoriasis, vasculitis, pyoderma gangrenosum, discoid lupus erythematosus, eczema, pustulosis palmo-plantaris, and phemphigus vulgaris.

Also comprised by the invention is the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of an inflammatory disease in the abdomen, including an abdominal disease having an inflammatory component. Specific examples of the treatment of such a disease with a compound of the invention are gastritis, including one of unknown origin, gastritis perniciosa (atrophic gastritis), ulcerous colitis (colitis ulcerosa), morbus Crohn, systemic sclerosis, ulcus duodeni, coeliac disease, oesophagitis and ulcus ventriculi.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of systemic or general and/or local immunological diseases, including those of an autoimmune nature, and other inflammatory diseases of a general nature. Specific examples include treatment of rheumatoid arthritis, psoriatic arthritis, systemic sclerosis, polymyalgia rheumatica, Wegener's granulomatosis, sarcoidosis, eosinophilic fasceitis, reactive arthritis, Bechterew's disease, systemic lupus erythematosus, arteritis temporalis, Behcet's disease, morbus Burger, Good Pastures' syndrome, eosinophilic granuloma, fibromyalgia, myositis, and mixed connective tissue disease. Included therein is also arthritis, including arthritis of unknown origin.

Further included in the invention is administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of a disease of the peripheral and/or central nervous system related to inflammation. Included in this aspect of the invention is the treatment of cerebral vasculitis, multiple sclerosis, autoimmune ophthalmitis and polyneuropathia. Comprised by the invention is also the administration of a compound of the invention for the treatment of an inflammation of the central nervous system to prevent apoptotic cell death. Moreover, as some of the compounds of the invention show a distinct ability to induce nerve regeneration, positive treatment effects are often seen in central nervous system diseases involving damage of cells in this region. This aspect of the invention also includes treatment of traumatic injuries to the central nervous system, brain edema, multiple sclerosis, Alzheimer's disease, bacterial and viral infections in the central nervous system, stroke, and haemorrhagia in the central nervous system.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the eye and tear glands related to inflammation. Specific examples of such diseases comprise anterior and posterior uveitis, retinal vasculitis, optic neuritis, optic neuromyelitis, Wegener's granulomatosis, Sjögren's syndrome, episcleritis, scleritis, sarcoidosis affecting the eye and polychondritis affecting the eye.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the ear related to inflammation, specific examples of which include polychondritis affecting the ear and external otitis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the nose related to inflammation, specific examples of which are sarcoidosis, polychondritis and mid-line granuloma of the nose.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the mouth, pharynx and salivary glands. Specific examples include Wegener's granulomatosis, mid-line granuloma, Sjögren's syndrome and polychondritis in these areas.

Included in the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation in the lung. Specific examples include treatment of idiopathic alveolitis, primary pulmonary hypertension, bronchitis, chronic bronchitis, sarcoidosis, alveolitis in inflammatory systemic disease, pulmonary hypertension in inflammatory systemic disease, Wegener's granulomatosis and Good Pastures' syndrome.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the heart. Specific examples include treatment of pericarditis, idiopathic pericarditis, myocarditis, Takayasus' arteritis, Kawasaki's disease, coronary artery vasculitis, pericarditis in inflammatory systemic disease, myocarditis in inflammatory systemic disease, endocarditis and endocarditis in inflammatory systemic disease.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the liver. Specific examples include treatment of hepatitis, chronic active hepatitis, biliary cirrhosis, hepatic damage by toxic agents, interferon induced hepatitis, hepatitis induced by viral infection, liver damage induced by anoxia and liver damage caused by mechanical trauma.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation

of the pancreas. Specific examples include treatment (and prevention) of diabetes mellitus, acute pancreatitis and chronic pancreatitis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the thyroidea. Specific examples of these embodiments of the invention include treatment of thyreoiditis, autoimmune thyreoiditis and Hashimoto's thyreoiditis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the kidney. Specific examples include treatment of glomerulonephritis, glomerulonephritis in systemic lupus erythematosus, periarteritis nodosa, Wegener's granulomatosis, Good-Pastures' syndrome, HLAb27 associated diseases, IgA nephritis (IgA = Immunoglobulin A), pyelonephritis, chronic pyelonephritis and interstitial nephritis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the joints. Specific examples include treatment of Bechterew's disease, psoriatic arthritis, rheumatoid arthritis, arthritis in colitis ulcerosa, arthritis in morbus Crohn, affection of joints in systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, reactive arthritis, Reiter's syndrome. Moreover, included in this embodiment of the invention is treatment of arthrosis of any joint, in particular arthrosis of finger joints, the knee and the hip.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of blood vessels. Specific examples include treatment of arteritis temporalis, periarteritis nodosa, arteriosclerosis, Takayasus' arteritis and Kawasaki's disease. Particularly advantageous is the capacity of some compounds of the invention to afford protection against and prevention of arteriosclerosis. This is in part due to the capacity of some compounds of Formula (I) or the pharmacologically acceptable salts thereof to prevent the induction of inducible nitric oxide synthesis (iNOS) caused by the action of oxidized Low Density Lipoprotein on endothelial cells and blood vessel walls.

Comprised by the invention is also the administration of a compound of the invention for the treatment of drug-induced disorders of the blood and lymphoid system, including the treatment of drug-induced hypersensitivity (including drug hypersensitivity) affecting blood cells and blood cell forming organs (e.g. bone marrow and lymphoid tissue). Specific embodiments of this aspect of the invention include the treatment of anemia, granulocytopenia, thrombocytopenia, leukopenia, aplastic anemia, autoimmune hemolytic anemia, autoimmune thrombocytopenia and autoimmune granulocytopenia.

The compounds of the invention may also be administered for the treatment of allergic disorders e.g. fast allergic disorders (Type I allergy). Included in this embodiment of the invention is the treatment of anaphylactic reactions, anaphylactoid reactions, asthma, asthma of allergic type, asthma of unknown origin, rhinitis, hay fever and pollen allergy.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of inflammation related to infections of any origin. Specific examples include treatment of inflammation secondary to infection caused by virus, bacteria, helminths and protozoae.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of inflammations related to trauma and/or tissue injury of any origin.

Compounds of formula (I) or pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of disorders of the cardiovascular system such as disorders related to blood pressure, heart rate, vascular tone, natriuresis, bleeding, shock, disorders related to ischemia, infarction, repercussion injuries, arrhythmias of the heart, in particular during ischemia, or for the treatment of arrhythmias associated with reoxygenation of a previously ischemic period of the heart.

Compounds of formula (I) or the pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of pain such as pain of central origin, pain seen after damage to the CNS, stroke, infarction, pain of peripheral origin, chronic pain, neuropathies and disorders where a treatment effect is achieved by stimulation of receptors in the periaqueductal grey area.

Because of the capacity of compounds of the invention to stimulate pigment formation in epidermal cells, compounds of the invention may be also useful for inducing skin tanning for cosmetic reasons, for treatment of vitiligo, or any other condition where darkening of skin color is desired. Moreover, because of the ability of some of the compounds of the invention to inhibit pigment formation in cells of the skin, they may also be useful for inducing lighter skin color for cosmetic reasons, or during any condition where a lighter color of skin is desired.

Compounds of formula (I) or the pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful to cause skin tanning, darkening the colour of the skin, to induce melanin synthesis in the skin, to reduce skin tanning, lightening the colour of the skin, to reduce or block melanin synthesis in the skin, to cause anti-inflammatory actions in the skin, to modulate epidermal growth, to improve wound healing, to treat acne, seborrhoea, acne roseacea, conditions related to malfunctions of the glands of the skin, e.g. sebacous glands and over or underproduction of sebum.

Compounds of the invention are useful for inhibiting or stimulating the *in vivo* formation of second messenger elements such as cAMP. Such inhibition/stimulation may be used in cells or crushed cell systems *in vitro*, e.g. for analytical or diagnostic purposes.

For analytical and diagnostic purposes the compounds of the invention may be used in radioactive form where they comprise one or more radioactive labels or gamma or positron emitting isotopes, to be used in radioligand binding for the quantification as well as tissue localisation of MC-receptors, for analysis of dissociation/association constants, and for imaging of *in vivo* binding by the use of scintigraphy, positron emission tomography (PET) or single photon emission computed tomography (SPECT), or for the diagnosis of disease and treatment of any malignancy where the malignant cells contain MC receptors.

Alternatively the compounds of the invention can be labelled with any other type of label that allows detection of the respective compound, e.g. fluorescence, biotin, NMR, MRI, or labels activated by gamma-irradiation, light photons or biochemical processes, or by light or UV-light (the latter in order to obtain a compound useful for covalent labelling of MC receptors by a photoaffinity technique).

Compounds of formula (I) or the pharmacologically acceptable salts thereof may also be tagged with a toxic agent (i.e. doxorubicin, ricin, diphtheria toxin or other) and used for targeted delivery to malignant cells bearing MC receptors, or tagged with a compound capable of activating the endogenous immune system for triggering the immune system (for example a compound, monoclonal antibody or other, capable of binding to a T-cell antigen, e.g. CD3 or other) for treatment of malignancies and other MC receptor expressing diseases. The thus formed hybrid compound will direct cytotoxic cells to the malignant melanoma cells or the MC1-receptor bearing malignant cells and inhibit the tumor growth.

Compounds of formula (I) or a pharmacologically acceptable salt thereof may be attached to the antibody chemically by covalent or non-covalent bond(s).

Compounds of the invention may be used for the treatment and diagnosis of diseases, disorders and/or pathological conditions in an animal, in particular in man.

In a further embodiment, compounds as defined herein can be used for the treatment of diabetes type 2, for treating anorexic conditions caused by cancer, cachexia, geriatric conditions, HIV, trauma or psychological conditions. In another embodiment, the compounds as defined herein can be used for inducing peripheral nerve regeneration. In still a further embodiment, the compounds as defined herein can be used for the treatment of skin disorders such as melanoma, or for the treatment and/or diagnosis of malignancies selected from melanoma and metastases.

The present invention also relates to a pro-drug which, upon administration to an animal or a human, is converted to a compound of the invention. Pro-drugs of the compounds of formula (I) and their pharmacologically acceptable salts may be used for the same purposes as described in this specification for the compounds of the invention, as well as is disclosed in the Examples given below.

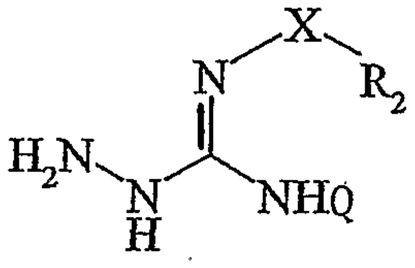
The compounds of the present invention may be bound covalently or non-covalently to one or several of other molecule(s) of any desired structure(s); the thus formed modified compound or complex may be used for the same purposes as described in this specification for the compounds of the invention, as well as is disclosed in the Examples given below. In a particularly important embodiment of the invention, a radioactively-labelled molecule is covalently bound to a compound of formula (I) or a pharmacologically acceptable salt thereof so as to make a compound of formula (I) or a pharmacologically acceptable salt thereof radioactively labelled.

The invention also relates to methods for the manufacture of and pharmaceutical preparations comprising one or more of the compounds of the invention, as well as to their uses for various medical and veterinary practices related to melanocyte stimulating hormone receptors.

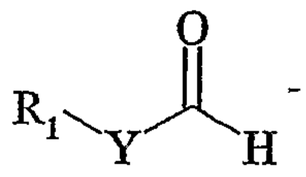
Compounds of the invention have an effect on xanthine oxidase in mammals, including man.

METHODS OF PREPARATION

Compounds of the invention may be prepared as follows:

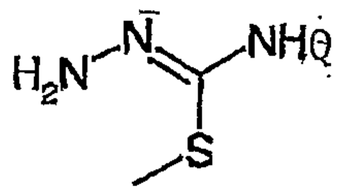


II

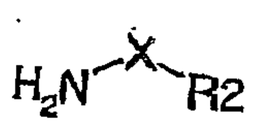


III

A guanidine derivative, II, is reacted with the appropriate aldehyde, III, resulting in the formation of a compound of the general Formula (I). X, Y, Q, R_1 and R_2 are as previously defined. Any of derivatisation, protection, deprotection and activation steps are used if necessary. If necessary, guanadine derivative II may be prepared by reacting a thiosemicarbazide (IV) with an amine (V):



IV



V

EXAMPLES

The following examples are intended to illustrate but not to limit the scope of the invention, although the compounds named are of particular interest for the intended purposes. The preparation of the compounds of general formula (I) is given schematically in Example 1 below. Specific synthetic procedures are given in methods 1 and 2. The compounds are numbered and are listed with their complete name below.

Method 1

Preparation of Compound 1, N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-benzylguanidine

536 mg (5 mmol) benzylamine and 1.17 g (5 mmol) S'-methylthiosemicarbazide hydroiodide was mixed in 10 ml of ethanol. The reaction mixture was refluxed for 5 minutes after which it was cooled down to room temperature and the residue filtered off. The crude product of N-amino-N'-benzylguanidine was reacted with 1.0 g (5 mmol) 2-chloro-3,4-dimethoxybenzaldehyde under reflux for 5h, after which the solvent was removed under vacuum to give a white solid. The product was obtained by recrystallisation from methanol. Yield of title compound 1 was 1.65 g (77%). M.p. 223-225°C.

Method 2

Preparation of Compound 2, N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-hydroxy-N''-phenylguanidine

0.22 g (1.1 mmol) 2-chloro-3,4-dimethoxybenzaldehyde and 0.34 g (1 mmol) N-hydroxy-N'-phenylaminoguanidine tosylate was mixed in 7 ml methanol. The reaction mixture was refluxed for 80 min after which it was cooled down to room temperature. The solvent was evaporated and 10 ml acetonitrile was added and the solution was stirred for 1 h. The precipitate formed was filtered, washed with ether and subseqently dried. The yield of title compound 2 was 0.40 g (77%) as a crystalline solid. M.p. 167-169°C.

Compounds 3 – 83 were prepared in an analogous manner:

Compounds 1-83

No.	Name	Melting point (°C)
1	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-benzylguanidine	215-217

10	N-(4-methoxybenzylideneamino)-N′-(2-phenylethyl)guanidine	126-128
11	N-(pyrid-4-yl-methylideneamino)-N′-(naphthalen-1-yl-methyl)guanidine	260-262
12	N-(1H-indol-3-ylmethylideneamino)-N′-(2-phenylethyl)guanidine	207-209
13	N-(1H-indol-3-yl-methylideneamino)-N-(naphthalen-1-ylmethyl) guanidine	213-215
14	N,N′-bis[1H-indol-3-yl-methylideneamino]guanidine	296-298

16	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N′-phenylguanidine	179-181
17	N-(2-fluoro-5-nitrobenzylideneamino)-N′-phenylguanidine	191-193
18	N-(4-hydroxybenzylideneamino)-N′-benzylguanidine	192-194
19	N-(2,4-dinitrobenzylideneamino)-N′-phenylguanidine	180-190
20	N-(4-nitrobenzylideneamino)-N′-(2-phenylethyl)guanidine	241-243
21	N-(naphthalen-2-yl-methylideneamino)-N′-(2-phenylethyl) guanidine	244-246
22	N-(naphthalenl-2-yl-methylideneamino)-N′-benzylguanidine	242-244
23	N-(naphthalen-2-yl-methylideneamino)-N′-naphthalen-2-ylguanidine	218-220
24	N-(4-Nitrobenzylideneamino)-N′-benzylguanidine	239-241

27	N-(2-Bromobenzylideneamino)-N′-phenethylguanidine	154-155
28	N-(2-Bromobenzylideneamino)-N′-phenylguanidine	149-152
29	N-[1-(4-Chlorophenyl) 1H-Pyrrol-2-ylmethyleneamino]-N′-benzylguanidine	190-192
30	N,N′-Di-(naphthalen-1-ylmethyleneamino)guanidine	253-255
31	N,N′-Di-(2-Bromobenzylideneamino)guanidine	268-270
32	N,N′-Di-(2-Chloro-3,4-Dimethoxybenzylideneamino)guanidine	228-230
33	(3-Phenyl-allylideneamino)-N′-2-phenylethyl)guanidine	175-177
34	N,N′-Di-(1-(4-Chlorophenyl)-1H-pyrrol-2-ylmethyleneamino)guanidine	221-223
35	N-(2-Fluoro-5-nitrobenzylideneamino)-N'-methylguanidine	217-219
36	N-(Indol-3-ylmethylenimino)-N'-(1-methylindazol-3-ylmethyl)guanidine	foam
37	N-(2-Chloro-3,4-dimethoxybenzylideneamino)-N'-methylguanidine	207-210

38	N-(indol-3-ylethylideneamino)-N′-(indol-3-ylethyl) guanidine	
39	N-(indol-3-ylmethylideneamino)-N′-indol-3-ylguanidine	
40	N-(2-methyl-5-methoxy-indol-3-yl-ethylideneamino)-N′-(N′′-methyl-2-azaindol-3-yl-methyl)guanidine	
41	N-(indol-3-yl-methylideneaminio)-N′-(N′′-methyl-2-azaindol-3-yl-methyl)guanidine	
42	N-(indol-3-yl-butylideneamino)-N′(N′′-methyl-2-azaindol-3-yl-methyl)guanidine	
43	N-(1-methyl-indol-3-yl-methylideneamino)-N′-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
44	N-(2-methyl-5-methoxy-indol-3-ylethylideneamino)-N′(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
45	N-(indol-3-ylmethylideneamino)-N′-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
46	N-(indol-3-ylbutylideneamino)-N′-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
47	N-(1-methyl-2-azaindol-3-ylmethylideneamino)-N′-(indol-3-ylmethyl) guanidine	
48	N-(2-methyl-5-methoxy-indol-3-yl-ethylideneamino)-N′-(indol-3-ylmethyl)guanidine	
49	N-(indol-3-ylmethylideneamino)-N′-(indol-3-ylmethyl) guanidine	
50	N-(indol-3-ylbutylideneamino)-N′-(indol-3-ylmethyl) guanidine	
51	N-(1-methyl-2-azaindol-3-ylmethylideneamino)-N′-(indol-3-ylbutyl) guanidine	
52	N-(2-methyl-5-methoxy-indol-3-ylethylideneamino)-N′-(indol-3-ylbutyl) guanidine	
53	N-(indol-3-ylmethylideneamino)-N′-(indol-3-ylbutyl) guanidine	
54	N-(indol-3-ylbutylideneamino)-N′-(indol-3-ylbutyl) guanidine	
55	N-(2-methyl-indol-3-ylethylideneamino)-N′-(2-methyl-indol-3-ylethyl)guanidine	
56	N-(pyrid-3-ylpropylideneamino)-N′-(pyrid-3-ylpropyl) guanidine	
62	N-(pyrid-3-ylmethylideneamino)-N′-(2-chloro-6-methyl-pyrid-3-ylmethyl)guanidine	
64	N-(2-chloro-6-methyl-pyrid-3-ylmethylideneamino)-N′-(2-chloro-6-methyl-pyrid-3-ylmethyl) guanidine	
65	N-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethylideneamino)-N′-(2-chloro-6-methyl-pyrid-3-ylmethyl) guanidine	
66	N-(pyrid-3-ylmethylideneamino)-N′-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethyl) guanidine	
68	N-(3-chloro-5-methyl-pyrid-2-ylmethylideneamino)-N'-(3-chloro-5-trifluoromethyl-pyrid-2-yl) guanidine	
69	N-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethylideneamino)-N'-(3-chloro-5-trifluoromethyl-pyrid-2-yl) guanidine	
70	N-(2-ethoxy-pyrid-3-ylmethylideneamino)-N'-(2-ethoxy-pyrid-3-ylmethyl)guandine	
71	N-(pyrrol-2-ylmethylideneamino)-N'-(pyrrol-2-ylmethyl) Guanidine	
72	N-(3-nitrobenzylideneamino)-N'-phenylguanidine	
73	N-(3-nitrobenzylideneamino)-N'-methylguanidine	
74	N-(2,4-dinitrobenzylideneamino)-N'-methylguanidine	

75	N-(3,5-Difluoro-2-nitrobenzylideneamino)-N'-(4-Iodobenzyl)guanidine	
76	N-2-Bromobenzylideneamino)-N'-[2-(4-Biphenyl)-Ethyl]guanidine	
77	N-(3-Chloro-4-Fluorobenzylideneamino)-N'-[2-(3-Chloro-4-Fluorophenyl)ethyl]guanidine	
78	N-(4-Phenylbenzylideneamino)-N'-(5-Bromo-4-Methyl-2-Nitrobenzyl)guanidine	
79	N-(4-Phenylbenzylideneamino)-N'-(2-[2-Iodophenyl)ethyl]guanidine	
80	N-(3-Chloro-4-fluorobenzylideneamino)-N'-(2,3,4-trimethoxy-5-bromobenzyl)guanidine	-
81	N-(3-Chloro-2-iodobenzylideneamino)-N'-(2,3-Dichlorobenzyl)guanidine	
82	N-(3,5-Dichloro-2-nitrobenzylideneamino)-N'-[2-(3,5-difluoro-2-nitrophenyl)ethyl]guanidine	
83	N-(3-Iodobenzylideneaamino)-N'-[2-(3-chloro-2-iodophenyl)ethyl]guanidine	

Example 2

This example illustrates the potency of some of the compounds of formula (I) and their therapeutically active acid addition salts for treatment of mental disorders.

Test 1. Affinity for the MC1-receptor

The binding assay was carried out essentially as described by Lunec *et al*, Melanoma Res 1992; 2; 5-12 using I^{125}-NDP-αMSH as ligand.

Test 2. Affinity for the MC3-receptors, the MC4-receptors and the MC5-receptors

The binding assays were carried out essentially as described by Szardenings *et al*, J Biol Chem 1997; 272; 27943-27948 and Schiöth *et al*, FEBS Lett 1997; 410; 223-228 using I125-NDP-αMSH as ligand.

Test 3. cAMP

The stimulation of cAMP was carried out essentially as described by Schiöth *et al*, Br J Pharmacol 1998; 124; 75-82, however, the response is given relative to α-MSH.

Table 1. Affinity for MC-receptors

Compound	K_i (μM)			
	MC1	MC3	MC4	MC5
27	1.24	7.96	1.35	5.80
29	3.12		0.61	1.32
33	1.32	5.36	3.59	8.23

Table 1b Influence on cAMP

Compound	cAMP agonist/plateau stim. α-MSH (%)		
	MC1	MC3	MC4
27	12	9	97
29	10	3	111
33	8	4	161

EXAMPLE 3

The following formulations are representative for all of the pharmacologically active compounds of the invention

Example of a preparation comprising a capsule

	Per capsule
Active ingredient, as salt	5 mg
Lactose	250 mg
Starch	120 mg
Magnesium stearate	5 mg
Total	380 mg

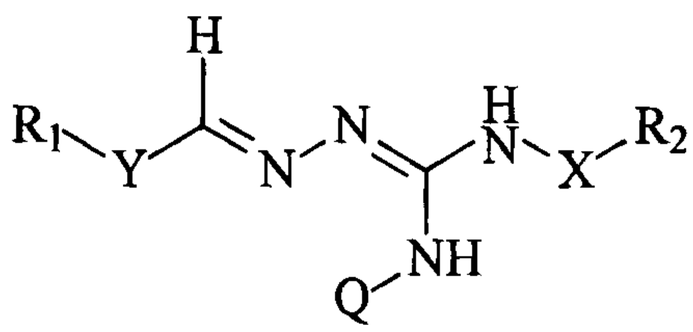
In case of higher amounts of active ingredient, the amount of lactose used may be reduced.

Example of a suitable tablet formulation.

	Per tablet
Active ingredient, as salt	5 mg
Potato starch	90 mg
Colloidal Silica	10 mg
Talc	20 mg
Magnesium stearate	2 mg
5 % aqueous solution of gelatine	25 mg
Total	152 mg

CLAIMS:

1. The use of a compound of general formula (I)



(I)

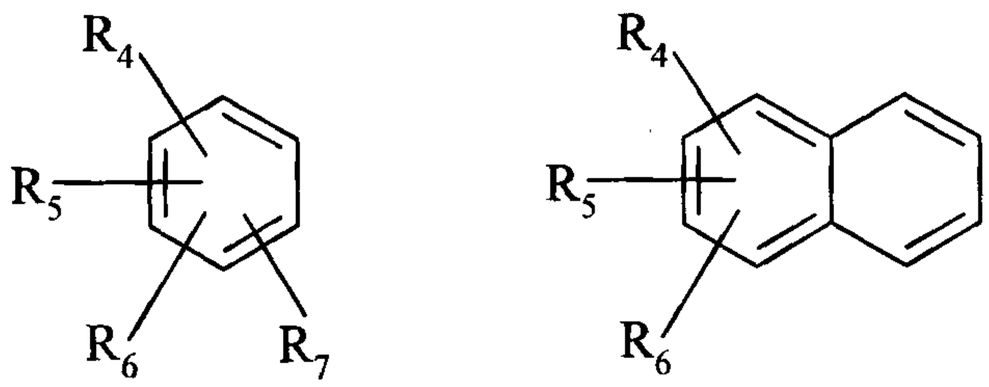
wherein

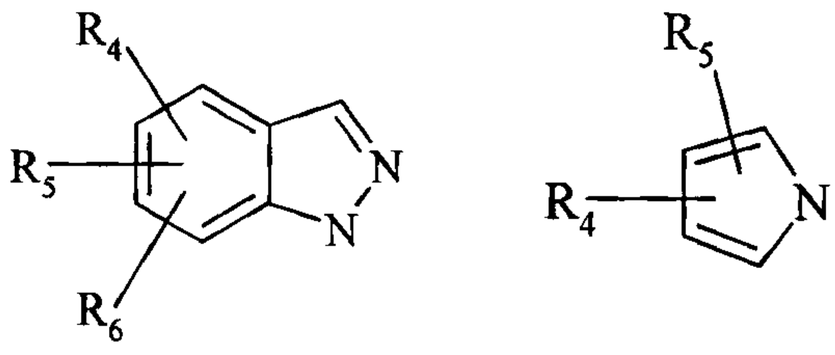
X and Y are independently chosen from O, N, S and $(CH_2)_n$ where *n* is 0, 1, 2, 3, 4 or 5 or a combination of O, N, S and $(CH_2)_n$ and may contain carbon-carbon multiple bonds and branched chains as well as alicyclic and heterocyclic groups;

Q is H;

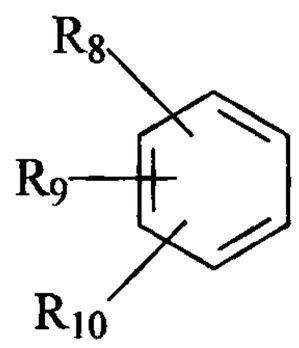
R_1 and R_2 can be either the same or different and are chosen from hydrogen, methyl, ethyl or the residue of an aromatic group as listed in Scheme 1:

Scheme 1





wherein R_4, R_5, R_6 and R_7 are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 5 carbon atoms, hydroxy, a primary, secondary or tertiary amine having 0, 1 or 2 carbon atoms, cyano, nitro, trifluoroalkyl, amide, sulpho, and a group:



wherein R_8, R_9 and R_{10} are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 5 carbon atoms, hydroxy, a primary, secondary or tertiary amine having 0, 1 or 2 carbon atoms, cyano, nitro, trifluoroalkyl, amide and sulpho;

wherein when any one of the substituents R_4 to R_7 is an alkoxy, it may form a ring, together with another substituent R_4 to R_7 and the carbon atoms to which they are respectively attached, and

wherein when any one of the substituents R_8 to R_{10} is an alkoxy, it may form a ring, together with another substituent R_8 to R_{10} and the carbon atoms to which they are respectively attached, and

wherein by "alkyl" is meant straight or branched chain hydrocarbon groups, alicyclic groups or fused alicyclic groups;

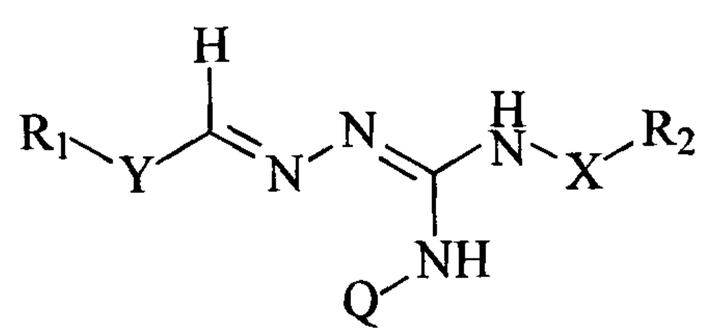
with the proviso that where X is $(CH_2)_n$ and n is 0, R_2 is not H; and when R_2 is methyl, R_1 must be selected from a substituent different than phenyl; or a pharmacologically active salt thereof,

or the use of a compound selected from N,N'-Di-(naphthalen-1-ylmethyleneamino)-guanidine; N,N'-Di-(2-bromobenzylideneamino)guanidine; N,N'-Di-(2-chloro-3,4-dimethoxybenzylideneamino)guanidine; and N,N'-Di-(1-(4-chlorophenyl)-1H-pyrrol-2-ylmethyleneamino)guanidine;

or a pharmacologically active salt thereof,

in the preparation of a medicament for the treatment of conditions associated with the melanocortin receptors selected from inflammation, immunological diseases, mental disorders, dysfunctions of the endocrine system, sexual dysfunctions, drug-induced disorders of the blood and/or lymphoid system, anemia, granulocytopenia, thrombocytopenia, leucopenia, aplastic anemia, autoimmune haemolytic anemia, autoimmune thrombocytopenia, autoimmune granulocytopenia, allergic disorders, disorders of the cardiovascular system, pain, diabetes type II, obesity, eating disorders, skin disorders, ischemia and/or ischemia/reperfusion; or for inducing peripheral nerve regeneration; or for inducing central nerve regeneration; for the treatment and/or diagnosis of malignancies; or to stimulate pigment formation in epidermal cells.

2. The use of a compound of general formula (I)



(I)

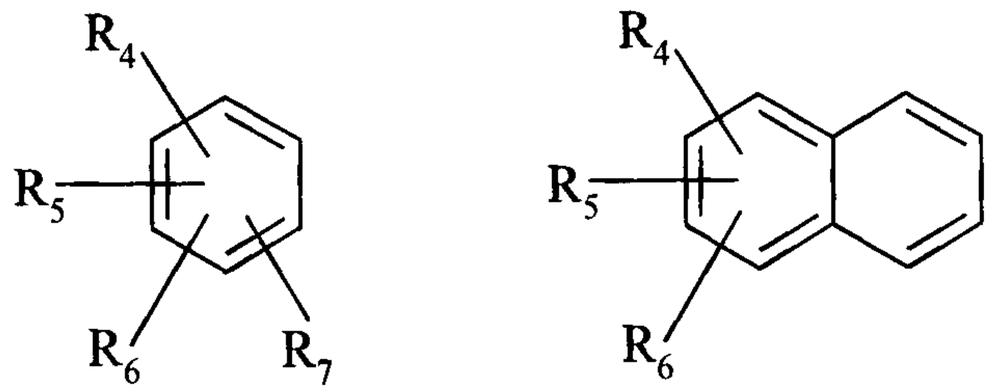
wherein

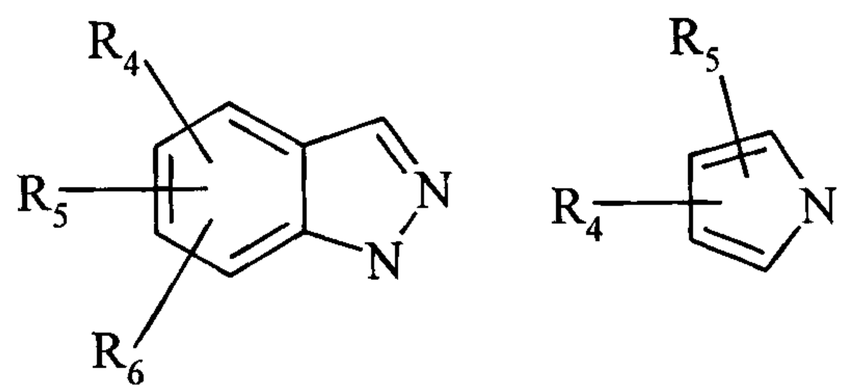
X and Y are independently chosen from O, N, S and $(CH_2)_n$ where *n* is 0, 1, 2, 3, 4 or 5 or a combination of O, N, S and $(CH_2)_n$ and may contain carbon-carbon multiple bonds and branched chains as well as alicyclic and heterocyclic groups;

Q is H;

R_1 and R_2 can be either the same or different and are chosen from hydrogen, methyl, ethyl or the residue of an aromatic group as listed in Scheme 1:

Scheme 1





wherein R_4, R_5, R_6 and R_7 are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 5 carbon atoms, hydroxy, a primary, secondary or tertiary amine having 0, 1 or 2 carbon atoms, cyano, nitro, trifluoroalkyl, amide, sulpho, and a group:

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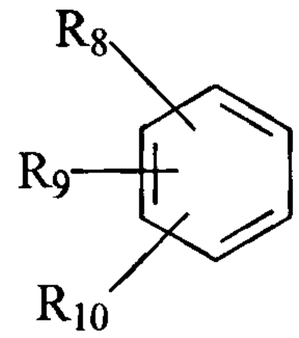


wherein R_8, R_9 and R_{10} are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 5 carbon atoms, hydroxy, a primary, secondary or tertiary amine having 0, 1 or 2 carbon atoms, cyano, nitro, trifluoroalkyl, amide and sulpho;

wherein when any one of the substituents R_4 to R_7 is an alkoxy, it may form a ring, together with another substituent R_4 to R_7 and the carbon atoms to which they are respectively attached, and

wherein when any one of the substituents R_8 to R_{10} is an alkoxy, it may form a ring, together with another substituent R_8 to R_{10} and the carbon atoms to which they are respectively attached, and

wherein by "alkyl" is meant straight or branched chain hydrocarbon groups, alicyclic groups or fused alicyclic groups;

with the proviso that where X is $(CH_2)_n$ and n is 0, R_2 is not H; and when R_2 is methyl, R_1 must be selected from a substituent different than phenyl; or a pharmacologically active salt thereof,

or use of a compound selected from N,N'-Di-(naphthalen-1-ylmethyleneamino)-guanidine; N,N'-Di-(2-bromobenzylideneamino)guanidine; N,N'-Di-(2-chloro-3,4-dimethoxybenzylideneamino)guanidine; and N,N'-Di-(1-(4-chlorophenyl)-1H-pyrrol-2-ylmethyleneamino)guanidine;

or a pharmacologically active salt thereof,

for the treatment of conditions associated with the melanocortin receptors selected from inflammation, immunological diseases, mental disorders, dysfunctions of the endocrine system, sexual dysfunctions, drug-induced disorders of the blood and/or lymphoid system, anemia, granulocytopenia, thrombocytopenia, leucopenia, aplastic anemia, autoimmune haemolytic anemia, autoimmune thrombocytopenia, autoimmune granulocytopenia, allergic disorders, disorders of the cardiovascular system, pain, diabetes type II, obesity, eating disorders, skin disorders, ischemia and/or ischemia/reperfusion; or for inducing peripheral nerve regeneration; or for inducing central nerve regeneration; for the treatment and/or diagnosis of malignancies; or to stimulate pigment formation in epidermal cells.

3. Use according to claim 1 or 2, wherein one or more of R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are alkyl having 1 to 8 carbon atoms.

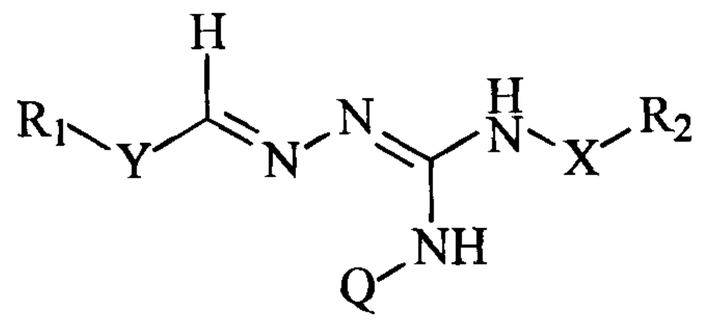
4. Use according to claim 3, wherein the alkyl is methyl or ethyl.

5. Use according to any one of claims 1 to 4, wherein one or more of R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are alkoxy.

6. Use according to claim 5, wherein the alkoxy is methoxy.

7. Use according to any one of claims 1 to 6, wherein one or more of R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are halogen atoms.

8. A compound of the general formula (I)



(I)

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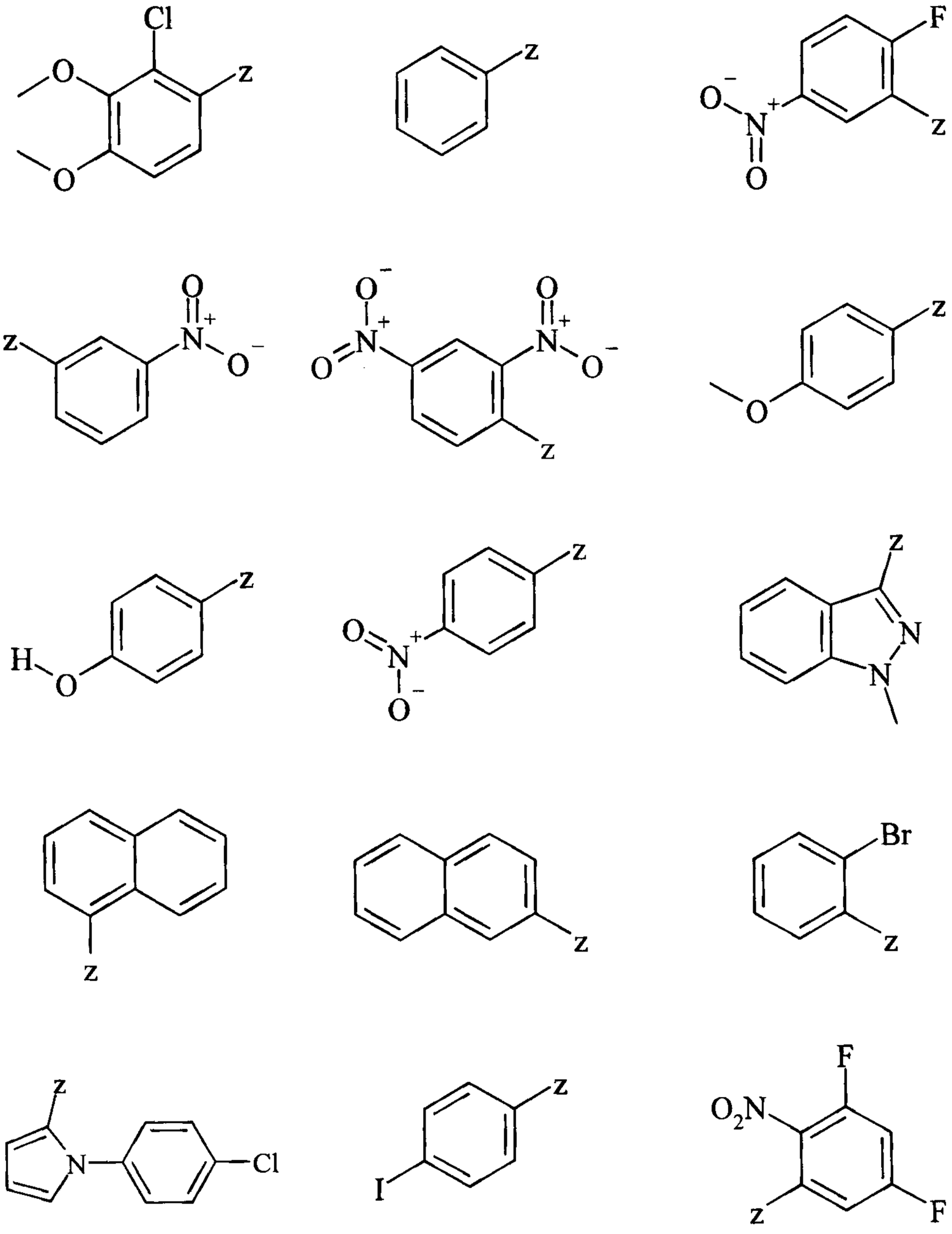
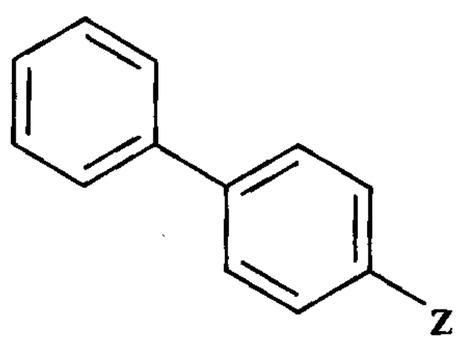
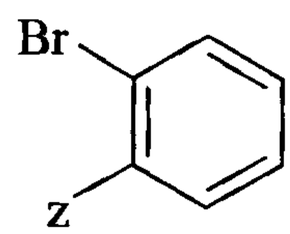
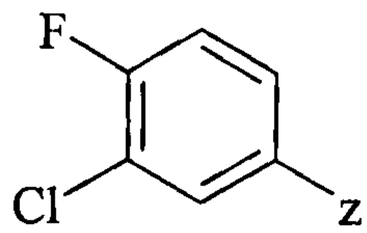
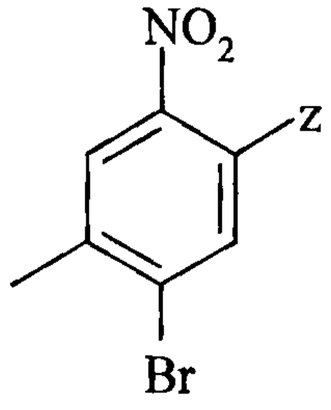
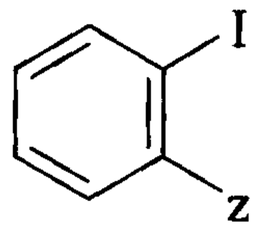
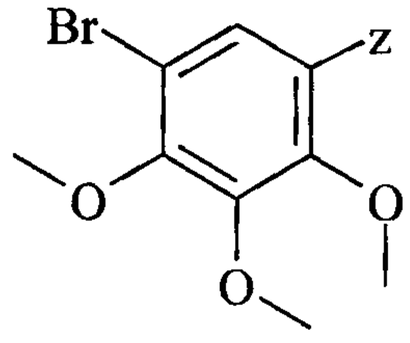
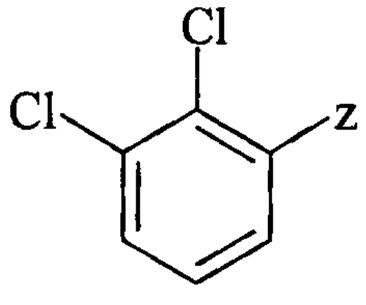
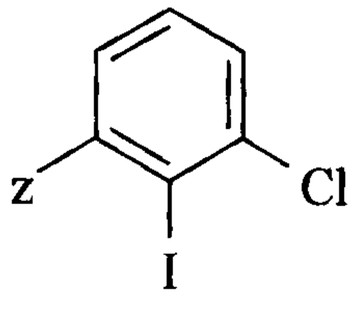
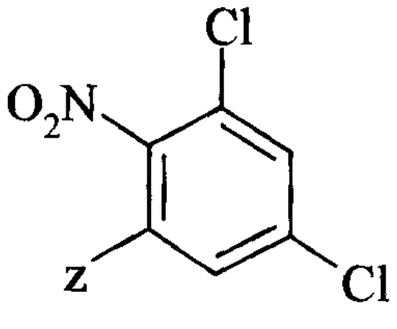
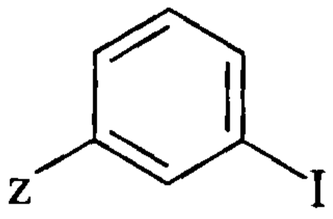
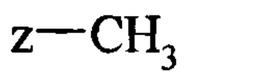
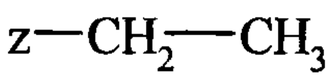
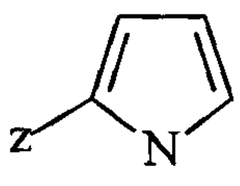
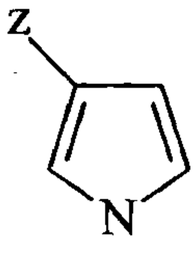
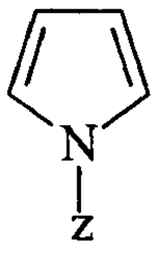
wherein X, Y and Q are as defined in claim 1, and wherein R_1 and R_2 are independently selected from



and

wherein *z* denotes the point of attachment;

or a pharmaceutically acceptable salt or prodrug thereof;

with the proviso that:

when R_1 is a phenyl, R_2 must be selected from a different substituent than phenyl;

when R_1 is 4-methoxyphenyl, R_2 must be selected from a different substituent than 4-methoxyphenyl and 1,3-dinitrophenyl;

when R_2 is 4-methoxyphenyl, R_1 must be selected from a different substituent than 4-methoxyphenyl; and

when R_2 is methyl, R_1 must be selected from a substituent different than phenyl.

9. A compound selected from

N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-benzylguanidine

N-(4-methoxybenzylideneamino)-N'-(2-phenylethyl)guanidine

N-(pyrid-4-yl-methylideneamino)-N'-(naphthalen-1-yl-methyl)guanidine

N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-phenylguanidine

N-(2-fluoro-5-nitrobenzylideneamino)-N'-phenylguanidine

N-(4-hydroxybenzylideneamino)-N'-benzylguanidine

N-(2,4-dinitrobenzylideneamino)-N'-phenylguanidine

N-(4-nitrobenzylideneamino)-N'-(2-phenylethyl)guanidine

N-(naphthalen-2-yl-methylideneamino)-N'-(2-phenylethyl)guanidine

N-(naphthalen-2-yl-methylideneamino)-N'-benzylguanidine

N-(naphthalen-2-yl-methylideneamino)-N'-naphthalen-2-ylguanidine

N-(4-nitrobenzylideneamino)-N'-benzylguanidine

N-(2-bromobenzylideneamino)-N'-phenethylguanidine

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N-(2-bromobenzylideneamino)-N'-phenylguanidine

N-[1-(4-chlorophenyl)-1H-pyrrol-2-ylmethyleneamino]-N'-benzylguanidine

N,N'-di-(naphtalen-1-ylmethyleneamino)guanidine

N,N'-di-(2-bromobenzylideneamino)guanidine

N,N'-di-(2-chloro-3,4-dimethoxybenzylideneamino)guanidine

(3-phenyl-allylideneamino)-N'-(2-phenylethyl)guanidine

N,N'-di-(1-(4-chlorophenyl)-1H-pyrrol-2-ylmethyleneamino)guanidine

N-(2-fluoro-5-nitrobenzylideneamino)-N'-methylguanidine

N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-methylguanidine

N-(pyrrol-2-ylmethylideneamino)-N'-(pyrrol-2-ylmethyl)guanidine

N-(3-nitrobenzylideneamino)-N'-phenylguanidine

N-(3-nitrobenzylideneamino)-N'-methylguanidine

N-(2,4-dinitrobenzylideneamino)-N'-methylguanidine

N-(3,5-difluoro-2-nitrobenzylideneamino)-N'-(4-iodobenzyl)guanidine

N-(2-bromobenzylideneamino)-N'-[2-(4-biphenyl)-ethyl]guanidine

N-(3-chloro-4-fluorobenzylideneamino)-N'-[2-(3-chloro-4-fluorophenyl)ethyl]guanidine

N-(4-phenylbenzylideneamino)-N'-(5-bromo-4-methyl-2-nitrobenzyl)guanidine

N-(4-phenylbenzylideneamino)-N'-(2-[2-iodophenyl]ethyl)guanidine

N-(3-chloro-4-fluorobenzylideneamino)-N'-(2,3,4-trimethoxy-5-bromobenzyl)guanidine

N-(3-chloro-2-iodobenzylideneamino)-N'-(2,3-dichlorobenzyl)guanidine

N-(3,5-dichloro-2-nitrobenzylideneamino)-N'-[2-(3,5-difluoro-2-nitrophenyl)ethyl]guanidine and

N-(3-iodobenzylideneamino)-N'-[2-(3-chloro-2-iodophenyl)ethyl]guanidine,

or a pharmacologically acceptable salt or prodrug thereof.

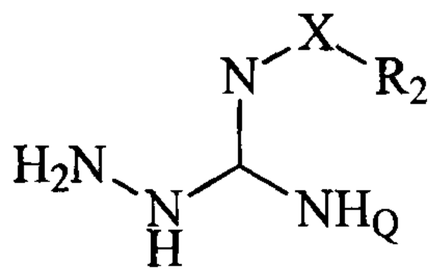
10. A compound as defined in claim 8 or 9 which additionally comprises a label or a toxic agent.

11. A compound as claimed in claim 10, wherein the label is a radioactive label.

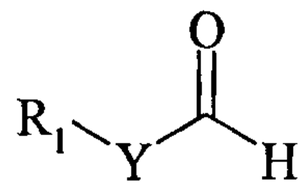
12. A pharmaceutical composition comprising a compound as defined in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, together with one or more adjuvants, carriers or excipients.

13. The pharmaceutical composition according to claim 12, which is for the treatment of conditions associated with the melanocortin receptors selected from inflammation, immunological diseases, mental disorders, dysfunctions of the endocrine system, sexual dysfunctions, drug-induced disorders of the blood and/or lymphoid system, anemia, granulocytopenia, thrombocytopenia, leucopenia, aplastic anemia, autoimmune haemolytic anemia, autoimmune thrombocytopenia, autoimmune granulocytopenia, allergic disorders, disorders of the cardiovascular system, pain, diabetes type II, obesity, eating disorders, skin disorders, ischemia and/or ischemia/reperfusion; or for inducing peripheral nerve regeneration; or for inducing central nerve regeneration; for the treatment and/or diagnosis of malignancies; or to stimulate pigment formation in epidermal cells.

14. A process for the production of a compound as defined in claim 1 which comprises reacting a guanidine derivative of formula (II) with an aldehyde of formula (III)



II



III

wherein X, Y, Q, R_1 and R_2 are as defined in claim 1.

15. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of inflammation.

16. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of mental disorders.

17. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of dysfunctions of the endocrine system.

18. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of dysfunctions of a hormonal system.

19. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of sexual dysfunctions.

20. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of disorders of the blood and/or lymphoid system.

21. The use of claim 20, wherein the disorders are drug-induced.

22. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of allergic disorders.

23. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of disorders of the cardiovascular system.

24. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of pain.

25. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament stimulating pigment formation in epidermis cells.

26. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of diabetes type II.

27. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of obesity.

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28. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of anorexic conditions caused by cancer, cachexia, geriatric conditions, HIV, trauma or psychological conditions.

29. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for inducing peripheral nerve regeneration.

30. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for inducing central nerve regeneration.

31. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of skin disorders.

32. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of melanoma.

33. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment and/or diagnosis of malignancies selected from melanoma and metastases.

34. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, in the production of a medicament for the treatment of ischemia and/or ischemia/reperfusion.

35. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of inflammation.

36. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of mental disorders.

37. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of dysfunctions of the endocrine system.

38. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of dysfunctions of a hormonal system.

39. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of sexual dysfunctions.

40. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of disorders of the blood and/or lymphoid system.

41. The use of claim 40, wherein the disorders are drug-induced.

42. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of allergic disorders.

43. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of disorders of the cardiovascular system.

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44. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of pain.

45. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, stimulating pigment formation in epidermis cells.

46. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of diabetes type II.

47. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of obesity.

48. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of anorexic conditions caused by cancer, cachexia, geriatric conditions, HIV, trauma or psychological conditions.

49. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for inducing peripheral nerve regeneration.

50. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for inducing central nerve regeneration.

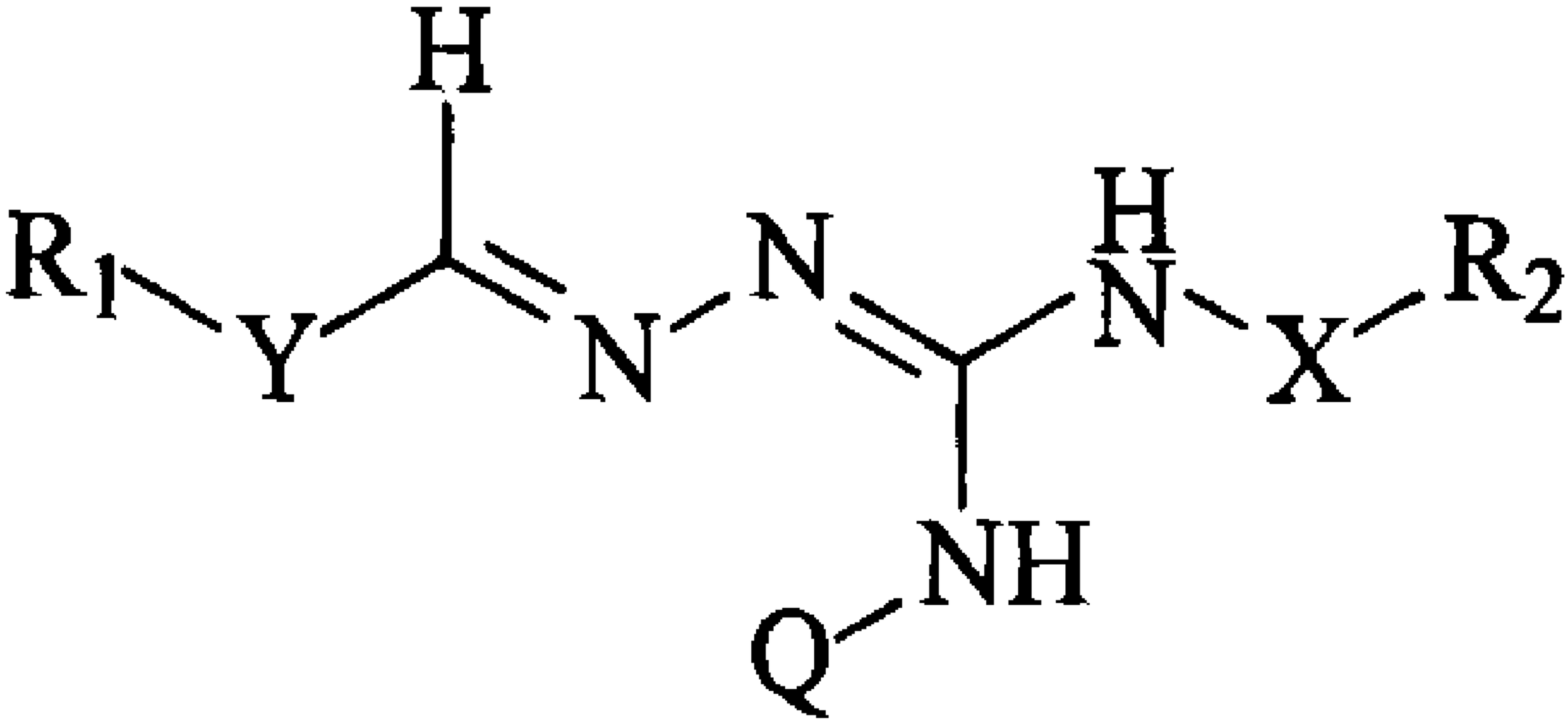
51. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of skin disorders.

52. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of melanoma.

53. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment and/or diagnosis of malignancies selected from melanoma and metastases.

54. Use of a compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for the treatment of ischemia and/or ischemia/reperfusion.

55. A commercial package comprising the compound as defined in any one of claims 1 to 7 or as claimed in any one of claims 8 to 11, or a pharmaceutically acceptable salt or prodrug thereof, together with a written matter describing instructions for the use thereof for the treatment of conditions associated with the melanocortin receptors selected from inflammation, immunological diseases, mental disorders, dysfunctions of the endocrine system, sexual dysfunctions, drug-induced disorders of the blood and/or lymphoid system, anemia, granulocytopenia, thrombocytopenia, leucopenia, aplastic anemia, autoimmune haemolytic anemia, autoimmune thrombocytopenia, autoimmune granulocytopenia, allergic disorders, disorders of the cardiovascular system, pain, diabetes type II, obesity, eating disorders, skin disorders, ischemia and/or ischemia/reperfusion; or for inducing peripheral nerve regeneration; or for inducing central nerve regeneration; for the treatment and/or diagnosis of malignancies; or to stimulate pigment formation in epidermal cells.



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