Abstract: The invention relates to novel phenyl pyrrole aminoguanidine derivatives modified at the guanidine group. The invention further relates to the use of such phenyl pyrrole aminoguanidine derivatives for the treatment of diseases associated with the melanocortin receptors or related systems, e.g. inflammation and inflammatory conditions. The novel phenyl pyrrole aminoguanidine derivatives of the invention have the general formula (I) and includes tautomeric and isomeric forms thereof, wherein X is (CH₂)n and n is 0, 1 or 2.
N-MODIFIED AMINOGUANIDINE DERIVATIVES

FIELD OF THE INVENTION
The present invention relates to phenyl pyrrole aminoguanidine derivatives modified at the guanidine group. The present invention further relates to the use of such phenyl pyrrole aminoguanidine derivatives for the treatment of diseases associated with the melanocortin receptors or related systems, e.g. the melanocyte stimulating hormones.

BACKGROUND OF THE INVENTION
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, WO 99/21571.

Moreover, a number of low molecular weight compounds are known, e.g., isoquinolines, spiropyridines and benzimidazoles, which show activity on the MC receptors. See, for example WO 99/55679, WO 99/64002 and WO 01/05401. For further literature disclosing other compounds also acting on the MC receptors, reference is made to WO 00/74679, WO 00/58361, WO 02/18327, WO 02/12166, WO 01/55106, WO 01/55107, WO 01/55109, WO 02/11715 and WO 02/12178.

However, there is still a large need to provide low molecular weight compounds showing agonistic or antagonistic properties to the MC receptors. The compounds of 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.

Prior art compounds, which have some structural relationship to the compounds of the present invention include the compounds described in WO 98/23267:
This hydroxyguanidine derivative has proven activity against xanthine oxidase/xanthine dehydrogenase enzymes.

Likewise, the compounds disclosed in WO 03/013509 exhibit antiinflammatory properties and binding affinity to the MC receptors. The general structure of the compounds disclosed in WO 03/013509 is as follows:

![Chemical structure](image)

where X is \((CH_2)_n\) and n is 0, 1 or 2.

Though these compounds are able to stimulate MC receptors, they do not possess a high binding affinity to the MC-receptors compared to the native agonist, α-MSH. The binding affinity of the compounds of WO 03/013509 for the MC-receptors lies within the sub-micromolar to micromolar range compared to α-MSH, which possesses a binding affinity for the MC-receptors lying in the nanomolar range. Furthermore, the compounds of WO 03/013509 are light-sensitive, i.e. light can induce a conversion from the trans isomeric form of the compounds to the cis isomeric form of the compounds. Trans-Cis conversion is well-known to be induced by light. The compounds of the present invention differ from the compounds disclosed in WO 03/013509 in that the aminoguanidine group has been modified.

In one embodiment, the compounds of the invention possess a higher binding affinity for the MC-receptors compared to the compounds disclosed in WO 03/013509. Accordingly, one object of the present invention is to provide compounds which exhibit an increased binding affinity for one or more of the MC-1, MC-2, MC-3, MC-4 and M-5 receptor(s) compared to the compounds described in WO 03/013509.
In another embodiment, the compounds of the invention possess a higher efficacy with regard to stimulation of the adenyl cyclase and production of cAMP via activation of one or more of the MC-1, MC-2, MC-3, MC-4 and M-5 receptor(s) compared to the compounds described in WO 03/013509. Accordingly, a second object of the present invention is to provide compounds which possess a higher efficacy with regard to stimulation of the adenyl cyclase and production of cAMP via activation of one or more of the MC-1, MC-2, MC-3, MC-4 and M-5 receptor(s) compared to the compounds described in WO 03/013509.

In yet another embodiment, the compounds of the invention are more stable, such as e.g. more stable when exposed to light, compared to the compounds disclosed in WO 03/013509. Thus, a third object of the present invention is to provide compounds which, compared to the compounds disclosed in WO 03/013509, are less light-sensitive (i.e. which are more stable).

In still another embodiment, the compounds of the invention possess a higher anti-inflammatory activity compared to the compounds disclosed in WO 03/013509. Accordingly, another object of the present invention is to provide compounds which exhibit an increased anti-inflammatory activity compared to the compounds described in WO 03/013509.

In a further embodiment, the compounds of the invention possess a more significant effect regarding inhibition of food intake compared to the compounds disclosed in WO 03/013509. Accordingly, a further object of the present invention is to provide compounds which exhibit a more significant effect with regard to inhibition of food intake compared to the compounds described in WO 03/013509.

In still a further embodiment, the compounds of the invention possess a more significant anti-diabetic effect compared to the compounds disclosed in WO 03/013509. Accordingly, a further object of the present invention is to provide compounds which exhibit an increased anti-diabetic effect compared to the compounds described in WO 03/013509.

**SUMMARY OF THE INVENTION**

Thus, in a first aspect the present invention relates to a compound of the general formula (I)
including tautomeric and isomeric forms thereof,

wherein X is (CH₂)ₙ, and n is 0, 1 or 2;

each R₁, R₂, R₃, R₄ and R₅ is independently selected from the group consisting of hydrogen, optionally substituted C₁-₆-alkyl, optionally substituted C₃-₆-cycloalkyl, optionally substituted C₂-₆-alkynyl, optionally substituted C₄-₆-alkadienyl, optionally substituted C₄-₆-alkenyl, hydroxy, optionally substituted C₁-₆-alkoxy, optionally substituted C₂-₆-alkenylhydroxy, carboxy, optionally substituted C₁-₆-alkoxycarbonyl, optionally substituted C₁-₆-alkylcarbonyl, optionally substituted aryl, optionally substituted arlyloxycarbonyl, optionally substituted aryl, optionally substituted arlyloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, optionally substituted arylsulphonylamino, optionally substituted arylothio and halogen,

where any nitrogen-bound C₁-₆-alkyl is optionally substituted with hydroxy, C₁-₆-alkoxy,
C_{2-6}-alkenyloxy, amino, mono- and di(C_i-6-alkyl)amino, carboxy, C_i-6-alkylcarbonylamino, halogen, C_i-6-alkylthio, C_i-6-alkyl-sulphonylamino or guanidine;

each R_b and R_f is independently selected from the group consisting of hydrogen, optionally substituted C_i-6-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{4-6}-alkadienyl, optionally substituted C_{2-6}-alkynyl, optionally substituted C_i-6-alkoxycarbonyl, optionally substituted C_i-6-alkylcarbonyl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_i-6-alkyl)aminocarbonyl, amino-C_i-6-alkyl-aminocarbonyl and mono- and di(C_i-6-alkyl)amino-C_i-6-alkyl-aminocarbonyl; or R_b and R_f may together form a five- or six-membered nitrogen-containing ring;

with the proviso that R_b and R_f are not both hydrogen;

or a pharmaceutically acceptable salt thereof.

In a further aspect the present invention relates to a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or excipient.

In a still further aspect the present invention relates to a dosage form comprising a pharmaceutical composition of the invention.

In yet another aspect the present invention relates to a compound of the invention for use as a medicament.

In an even further aspect the present invention relates to a compound of the invention for the treatment or prevention of a disease selected from the group consisting of inflammatory conditions, e.g. acute or chronic inflammatory conditions, diabetes mellitus, diabetes mellitus type I, diabetes mellitus type II, obesity-induced diabetes mellitus, insulin-resistance, sexual dysfunction including dysfunction of male erection, eating disorders including anorexia, obesity, mental disorders, dysfunction of the endocrine system, drug-induced disorders of the blood and lymphoid system, allergy disorders, disorders of the cardiovascular system and pain.

Analogously, the present invention also relates to a method of treating a mammal having a disease or disorder, or preventing a mammal from getting a disease or disorder, selected from the group consisting of inflammatory conditions, e.g. acute or chronic inflammatory
conditions, diabetes mellitus, diabetes mellitus type I, diabetes mellitus type II, obesity-induced diabetes mellitus, insulin-resistance, sexual dysfunction including dysfunction of male erection, eating disorders including anorexia, obesity, mental disorders, dysfunction of the endocrine system, drug-induced disorders of the blood and lymphoid system, allergy disorders, disorders of the cardiovascular system and pain, said method comprising administering to said mammal a therapeutically effective amount of a compound of the invention.

Other aspects of the present invention will be apparent from the appended claims and the description below.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Fig. 1 shows specific phenyl pyrrole aminoguanidine derivatives of the invention.

Fig. 2 shows the synthetic route of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-methyl guanidine (structure no. 1 in figure 1).

Fig. 3 shows the synthetic route of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-ethyl guanidine (structure no. 2 in figure 1).

Fig. 4 shows the synthetic route of N-(l-[2-nitrophenyl]pyrrol-2-yl methylideneamino)-N'-methyl guanidine (structure no. 13 in figure 1).

Fig. 5 shows the synthetic route of N-(l-[4-trifluoromethylphenyl]pyrrol-2-yl methylideneamino)-N'-methyl guanidine (structure no. 19 in figure 1).

Fig. 6 shows the synthetic route of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-phenyl guanidine (structure no. 25 in figure 1).

Fig. 7 shows the synthetic route of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-pyrrol-l-yl guanidine (structure no. 28 in figure 1).

Fig. 8 shows the synthetic route of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-methyl,N''-methyl guanidine (structure no. 30 in figure 1).

Fig. 9 shows the synthetic route of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-ethyl-N''-methyl guanidine (structure no. 31 in figure 1).
Fig. 10 shows the synthetic route of N-[1-(4-chlorophenyl)-1H-pyrrol-2-yl-methylene]-N'-(4,5-dihydro-1H-imidazol-2-yl)-hydrazine (structure no. 32 in figure 1).

**DETAILED DESCRIPTION OF THE INVENTION**

5 Definitions

In the present context, the term "Ci-6-alkyl" is intended to mean a linear or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, π-propyl, isopropyl, π-butyl, /so-butyl, sec-butyl, ferf-butyl, π-pentyl, /so-pentyl, πeo-pentyl and π-hexyl, and the term "Ci-4-alkyl" is intended to cover a linear or branched hydrocarbon group having 1 to 4 carbon atoms, e.g. methyl, ethyl, π-propyl, /so-propyl, π-butyl, /so-butyl, sec-butyl and ferf-butyl.

Whenever the term "Ci-6-alkyl" is used herein, it should be understood that an interesting embodiment thereof is "Ci-4-alkyl". Most preferably, "Ci-6-alkyl" (and "Ci-4-alkyl") is methyl or ethyl, in particular methyl.

When used herein, the term "Ci-6-cycloalkyl" is intended to mean a cyclic hydrocarbon group having 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Similarly, the terms "C2-6-alkenyl" and "C4-6-alkadienyl", are intended to cover linear or branched hydrocarbon groups having 2 to 6 and 4 to 6, carbon atoms, respectively, and comprising one and two unsaturated bonds, respectively. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl and hexenyl. Examples of alkadienyl groups include butadienyl, pentadienyl and hexadienyl. Preferred examples of alkenyl are vinyl, allyl and butenyl, especially allyl.

In the present context the term "C2-6-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 6 carbon atoms and containing one or more triple bonds. Illustrative examples of C2-6-alkynyl groups include acetylene, propynyl, butynyl, as well as branched forms of these. The position of unsaturation (the triple bond) may be at any position along the carbon chain. More than one bond may be unsaturated such that the "C2-6-alkynyl" is a di-yne or enedi-yne as is known to the person skilled in the art.

When used herein the term "Ci-6-alkoxy" is intended to mean Ci-6-alkyl-oxy, such as methoxy, ethoxy, π-propoxy, /so-propoxy, π-butoxy, /so-butoxy, sec-butoxy, ferf-butoxy, π-pentoxy, /so-pentoxy, πeo-pentoxy and π-hexoxy, and the term "Ci-4-alkoxy" is intended to mean Ci-4-alkyl-oxy, e.g. methoxy, ethoxy, π-propoxy, /so-propoxy, π-butoxy, /so-butoxy, sec-butoxy and ferf-butoxy.
Whenever the term "Cl\textsubscript{6}-alkoxy" is used herein, it should be understood that a particularly interesting embodiment thereof is "Cl\textsubscript{4}-alkoxy". Most preferably, "Cl\textsubscript{6}-alkoxy" (and "Cl\textsubscript{4}-alkoxy") is methoxy or ethoxy, in particular methoxy.

Likewise, the term "C\textsubscript{2}e-alkenyl-oxy" is intended to mean C\textsubscript{2}e-alkenyl-oxy.

Herein, the term "halogen" includes fluoro, chloro, bromo, and iodo. In particular, fluoro, chloro and bromo are preferred. Chloro and fluoro are the most preferred halogens.

In the present context, i.e. in connection with the terms "alkyl", "alkenyl", "alkadienyl" and "alkynyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), Cl\textsubscript{6}-alkoxy, C\textsubscript{2}e-alkenyl-oxy, carboxy, oxo (forming a keto or aldehyde functionality), Cl\textsubscript{6}-alkoxycarbonyl, Cl\textsubscript{6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, aminocarbonyl, heteroaryl, heteroarylcarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(Cl\textsubscript{6}-alkyl)amino, carbamoyl, mono- and di(Cl\textsubscript{6}-alkyl)aminocarbonyl, amino-Cl\textsubscript{6}-alkylaminocarbonyl, mono- and di(Cl\textsubscript{6}-alkyl)amino-Cl\textsubscript{6}-alkylaminocarbonyl, Cl\textsubscript{6}-alkylcarbonylamino, cyano, guanidino, carbamido, Cl\textsubscript{6}-alkyl-sulphonylamino, aryI-sulphonylamino, heteroaryl-sulphonylamino, Cl\textsubscript{6}-alkanoyloxy, Cl\textsubscript{6}-alkyl-sulphonyl, Cl\textsubscript{6}-alkyl-sulphinyl, Cl\textsubscript{6}-alkyl-sulphonyleoxy, nitro, Cl\textsubscript{6}-alkylthio and halogen, where any aryl and heteroaryl may be substituted as specifically described below for "optionally substituted aryl and heteroaryl", and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, Cl\textsubscript{6}-alkoxy, C\textsubscript{2}e-alkenyloxy, amino, mono- and di(Cl\textsubscript{6}-alkyl)amino, carboxy, Cl\textsubscript{6}-alkylcarbonylamino, halogen, Cl\textsubscript{6}-alkylthio, Cl\textsubscript{6}-alkyl-sulphonylamino or guanidine.

Preferably, the above-mentioned substituents are selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), Cl\textsubscript{6}-alkoxy (i.e. Cl\textsubscript{6}-alkyl-oxy), C\textsubscript{2}e-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), Cl\textsubscript{6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aminocarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaryloxy, heteroarylcarbonylamino, amino, mono- and di(Cl\textsubscript{6}-alkyl)amino; carbamoyl, mono- and di(Cl\textsubscript{6}-alkyl)aminocarbonyl, amino-Cl\textsubscript{6}-alkylaminocarbonyl, mono- and di(Cl\textsubscript{6}-alkyl)amino-Cl\textsubscript{6}-alkylaminocarbonyl, Cl\textsubscript{6}-alkylcarbonylamino, guanidino, carbamido, Cl\textsubscript{6}-alkyl-sulphonylamino, Cl\textsubscript{6}-alkyl-sulphinyl, Cl\textsubscript{6}-alkylthio and halogen, where any aryl and heteroaryl may be substituted as specifically described below for "optionally substituted aryl and heteroaryl".
Especially preferred examples of such substituents are hydroxy, C\textsubscript{6}-alkoxy, C\textsubscript{2}\textsubscript{-alkenyloxy}, amino, mono- and di(Ci\textsubscript{-alkyl}amino, carboxy, Ci\textsubscript{-alkylcarbonylamino, halogen, Ci\textsubscript{-alkylthio, Ci\textsubscript{-alkyl-sulphonyl-amino and guanidine, in particular halogen. Thus, particularly preferred "optionally substituted Ci\textsubscript{-alkyl" groups include halogen-substituted alkyl groups, such as trihalo-Ci\textsubscript{-alkyl, such as tribromomethyl, trichloromethyl or trifluoromethyl. In a particular interesting embodiment trihalo-Ci\textsubscript{-alkyl is trifluoromethyl.

The term "optionally substituted Ci\textsubscript{-alkoxy" is intended to mean that the alkoxy groups may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), Ci\textsubscript{-alkoxy (i.e. Ci\textsubscript{-alkyl-oxy), C\textsubscript{2}\textsubscript{-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), Ci\textsubscript{-alkoxycarbonyl, Ci\textsubscript{-alkylcarbonyl, formyl, aryl, aryloxy carbonyl, aryloxy, arylicarbonyl, heteroaryl, heteroaryloxy carbonyl, heteroaryloxy, heteroarylcarbonyl, carbamoyl, mono- and di(Ci\textsubscript{-alkyl)aminocarbonyl, amino-Ci\textsubscript{-alkyl-aminocarbonyl, mono- and di(Ci\textsubscript{-alkyl)amino-Ci\textsubscript{-alkyl-aminocarbonyl, cyanoguanidino, carbamido, Ci\textsubscript{-alkyl-sulphonyl-amino, ary1-sulphonylamino, heteroaryl-sulphonylamino, Ci\textsubscript{-alkanoyloxy, Ci\textsubscript{-alkyl-sulphonyl, Ci\textsubscript{-alkyl-sulphinyl, Ci\textsubscript{-alkylsulphonyloxy, nitro, Ci\textsubscript{6}-alkythio and halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl".

Especially preferred examples of such substituents are those carrying one or two substituents selected from hydroxy, Ci\textsubscript{-alkyl, Ci\textsubscript{-alkoxy, C\textsubscript{2}\textsubscript{-alkenyloxy, carboxy, halogen or Ci\textsubscript{-alkylthio.

In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, biphenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracly, pyrenyl, benzopyrenyl, fluorenyl, xantheny1, among which phenyl, biphenyl and naphthyl are preferred examples. In a particular preferred embodiment of the invention, the term "aryl" refers to phenyl.

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furyl, thiencyl, quinolyl, benzoazolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxazolyl, phthalazinyl, phthalany1,
triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl, phenyl pyrrolyl and N-phenyl pyrrolyl.

Particularly interesting heteroaryl groups are oxazolyl, isoaxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thiienyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl, phenyl pyrrolyl and N-phenyl pyrrolyl, in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thiienyl, quinolyl, tetrazolyl, isoquinolyl, phenyl pyrrolyl and N-phenyl pyrrolyl. The most preferred heteroaryl groups are pyrrolyl, indolyl, phenyl pyrrolyl and N-phenyl pyrrolyl.

In the present context, the term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydroazepidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofururan, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxeapane, oxathiane and oxathiepane.

Preferred examples of heterocyclyl groups are imidazolidine, piperazine, hexahydroazepidine, hexahydroazepidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyrididine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine) and thiazinane.

In the present context, i.e. in connection with the terms "aryl", "heteroaryl", and "heterocyclyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times, with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C_{i-6}-alkyl, C_{i-6}-alkoxy, C_{2-6}-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{i-6}-alkoxycarbonyl, C_{i-6}-alkylcarbonyl, formyl, aryl, arloxy, alylamino, alyloxy carbonyl, alycarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(C_{i-6}-alkyl)amino; carbamoyl, mono- and di(C_{i-6}-alkyl)aminocarbonyl, amino-C_{i-6}-alkyl-aminocarbonyl, mono- and di(C_{i-6}-alkyl)-amino-C_{i-6}-alkyl-aminocarbonyl, C_{i-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{i-6}-alkanoyloxy,
amino, \( \text{Ci-6-alkyl-suphonyl}, \) \( \text{Ci-6-alkyl-sulphinyl}, \) \( \text{Ci-6-alkylsulphonyloxy}, \) nitro, sulphonyl, amino, amino-sulfonyl, mono- and di(Ci-6-alkyl)amino-sulfonyl, dihalogen-Ci-4-alkyl, trihalogen-Ci-4-alkyl and halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with Ci-4-alkyl, Ci-4-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, Ci-6-alkoxy, \( \text{C}_2\text{-alkenyloxy}, \) amino, mono- and di(Ci-6-alkyl)amino, carboxy, Ci-6-alkyl-carbonylamino, halogen, Ci-6-alkylthio, Ci-6-alkyl-sulphonyl-amino, or guanidine.

Preferably, the above-mentioned substituents are selected from hydroxy, Ci-6-alkyl, Ci-6-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, Ci-6-alky/alkylcarbonyl, formyl, amino, mono- and di(Ci-6-alkyl)amino; carbamoyl, mono- and di(Ci-6-alkyl)aminocarbonyl, amino-Ci-6-alkyl-aminocarbonyl, Ci-β-alkylcarbonylamino, guanidino, carbamido, Ci-6-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonylamino, Ci-6-alkyl-sulphonyl, Ci-6-alkyl-sulphinyloxy, sulphanyl, amino, amino-sulfonyl, mono- and di(Ci-6-alkyl)sulfonylamino or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, Ci-6-alkoxy, \( \text{C}_2\text{-alkenyloxy}, \) amino, mono- and di(Ci-6-alkyl)amino, carboxy, Ci-6-alkyl-carbonylamino, halogen, Ci-6-alkylthio, Ci-6-alkyl-sulphonyl-amino or guanidine.

Especially preferred examples of such substituents are Ci-6-alkyl, Ci-6-alkoxy, amino, mono- and di(Ci-6-alkyl)amino, sulphonyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, Ci-6-alkoxy, \( \text{C}_2\text{-alkenyloxy}, \) amino, mono- and di(Ci-6-alkyl)amino, carboxy, Ci-β-alkylcarbonylamino, halogen, Ci-6-alkylthio, Ci-6-alkyl-sulphonyl-amino or guanidine.

The term "salt thereof" is intended to mean a pharmaceutically acceptable acid addition salt obtainable by treating the base form of a functional group, such as an amine, with appropriate acids such as inorganic acids, for example hydrohalic, hydrobromic, hydrofluoric or hydroiodic acid; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example acetic, propionic, hydroacetic, 2-hydroxypropanoic acid, 2-oxopropanoic acid, ethandioic, propanedioic, butanedioic, \( \text{Z} \)-2-butenedioic, \( \text{E} \)-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-l,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic acid, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic, and other acids known to the skilled practitioner.

The term "pharmaceutically acceptable" when used in connection with the term "salt thereof" means that the salt does not cause any untoward effects in the patients to whom it is administered. Likewise, the term "pharmaceutically acceptable" when used in
connection with the terms "carrier" and/or "excipient" means that the carrier and/or the excipient, at the dosages and with the concentrations employed, does not cause any untoward effects in the patients to whom it is administered.

In the present description and claims, any reference to "a" component, e.g. in the context of a substituent, etc., is intended to refer to one or more of such components, unless stated otherwise or unless it is clear from the particular context that this is not the case. For example, the expression "a component selected from the group consisting of A, B and C" is intended to include all combinations of A, B and C, i.e. A; B; C; A+B; A+C; B+C or A+B+C.

The term "therapeutically effective amount" means a dosage or amount sufficient to produce a desired result. The desired result may comprise an objective or subjective improvement in the recipient of the dosage or amount.

A "prophylactic treatment" is a treatment administered to a subject who does not display signs or symptoms of a disease, pathology, or medical disorder, or displays only early signs or symptoms of a disease, pathology, or disorder, such that treatment is administered for the purpose of diminishing, preventing, or decreasing the risk of developing the disease, pathology, or medical disorder. A prophylactic treatment functions as a preventative treatment against a disease or disorder. A "prophylactic activity" is an activity of an agent, such as a compound disclosed herein, or a composition thereof, that, when administered to a subject who does not display signs or symptoms of pathology, disease or disorder, or who displays only early signs or symptoms of pathology, disease, or disorder, diminishes, prevents, or decreases the risk of the subject developing a pathology, disease, or disorder.

In the present context the term "therapeutic treatment", or simply "treatment", means a treatment administered to a subject who displays symptoms or signs of pathology, disease, or disorder, in which treatment is administered to the subject for the purpose of diminishing or eliminating those signs or symptoms of pathology, disease, or disorder. A "therapeutic activity" is an activity of an agent, such as a compound disclosed herein, or composition thereof, that eliminates or diminishes signs or symptoms of pathology, disease or disorder, when administered to a subject suffering from such signs or symptoms.

The term "subject" as used herein includes, but is not limited to, an organism; a mammal, including, e.g., a human being, non-human primate (e.g., baboon, orangutan, monkey), mouse, pig, cow, goat, cat, rabbit, rat, guinea pig, hamster, horse, monkey, sheep, or
other non-human mammal; a non-mammal, including, e.g., a non-mammalian vertebrate, such as a bird (e.g., a chicken or duck) or a fish, and a non-mammalian invertebrate. In a preferred embodiment of the invention the subject is a human being.

In the present context the term "tautomeric forms thereof" or "tautomer" refers to one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Different tautomeric forms have the same molecular formula and are interchangeable forms involving the displacement of hydrogen atoms and electrons. Thus, it will be understood that when a compound of the invention is illustrated by its chemical structure, all possible tautomeric forms of the specifically depicted molecule are also within the scope of the present invention.

The compound of the invention
As indicated above, the present invention relates to a compound of the general formula (I) shown above. As can be seen from formula (I), the aminoguanidine substituent may be attached to the pyrrole ring at its position 2 or 3, i.e. the compounds of the general formula (Ia) and (Ib) merely differ from each other by the site of attachment to the pyrrole ring.

Accordingly, in another aspect the present invention relates to a compound of the general formula (Ia) or (Ib)
including tautomeric and isomeric forms thereof,

5 wherein X is (CH₂)ᵢ, and n is 0, 1 or 2;

each R₁, R₂, R₃, R₄ and R₅ is independently selected from the group consisting of hydrogen, optionally substituted C₁-₆-alkyl, optionally substituted C₃-₆-cycloalkyl, optionally substituted C₂₋₆-alkenyl, optionally substituted C₄₋₆-alkadienyl, optionally substituted C₂₋₆-alkynyl, hydroxy, optionally substituted C₁₋₆-alkoxy, optionally substituted C₁₋₆-alkenyl, optionally substituted C₁₋₆-alkyloxycarbonyl, optionally substituted C₁₋₆-alkylcarbonyl, optionally substituted aryloxycarbonyl, optionally substituted aryl, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, mono- and di(C₁₋₆-alkyloxy, C₂₋₆-alkenyloxycarbonyl, optionally substituted C₁₋₆-alkylcarbonyl, optionally substituted C₁₋₆-alkylsulphonylamino, optionally substituted C₁₋₆-alkylsulphonyl, amino, mono- and di(C₁₋₆-alkyl)aminosulfonyl, nitro, optionally substituted C₁₋₆-alkylthio and halogen,

where any nitrogen-bound C₁₋₆-alkyl is optionally substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxycarbonyl, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonylamino or guanidine;
each \( R_6 \) and \( R_7 \) is independently selected from the group consisting of hydrogen, optionally substituted \( \text{C}_1-6\text{-alkyl}, \) optionally substituted \( \text{C}_2-6\text{-alkenyl}, \) optionally substituted \( \text{C}_4-6\text{-alkadienyl}, \) optionally substituted \( \text{C}_2-6\text{-alkynyl}, \) optionally substituted \( \text{C}_1-6\text{-alkoxycarbonyl}, \) optionally substituted \( \text{C}_1-6\text{-alkylcarbonyl}, \) optionally substituted aryl, optionally substituted aryloxy carbonyl, optionally substituted aryl carbonyl, optionally substituted heteroaryl, optionally substituted heteroaryl carbonyl, aminocarbonyl, mono- and di(\( \text{C}_1-6\text{-alkyl} \))aminocarbonyl, amino-\( \text{C}_1-6\text{-alkyl} \)-aminocarbonyl and mono- and di(\( \text{C}_1-6\text{-alkyl} \))amino-\( \text{C}_1-6\text{-alkyl} \)-aminocarbonyl; or \( R_6 \) and \( R_7 \) may together form a five- or six-membered nitrogen-containing ring;

with the proviso that \( R_6 \) and \( R_7 \) are not both hydrogen;

or a pharmaceutically acceptable salt thereof.

As discussed above, in the compounds of the general formula (Ia) the aminoguanidine substituent is attached to the pyrrole ring at position 2, whereas in the compounds of the general formula (Ib) the aminoguanidine substituent is attached to the pyrrole ring at position 3. In the following description, only compounds where the aminoguanidine substituent is attached to the pyrrole ring at position 2 is described with respect to preferred substituents, method for manufacturing, etc. It should be understood, however, that all statements made below with respect to the compounds of the invention where the aminoguanidine substituent is attached to the pyrrole ring at position 2 also apply to the compounds of the invention where the aminoguanidine substituent is attached to the pyrrole ring at position 3. Furthermore, the compounds of the general formula (I) herein are all shown in their trans isomeric forms. It should be understood, however, that the compounds of the general formula (I) may also be in their cis isomeric form. Thus, the configuration around a double bond in the molecule may be either cis or trans, although the trans configuration is preferred.

As will be understood by the skilled person the compounds of the general formula (I) may exist in the various tautomeric forms illustrated below (illustrated for compound (Ia) only). Evidently, all possible tautomeric forms of the compounds of the invention are contemplated and hence included in the scope of the present invention.
The compounds of the invention have basic properties and, consequently, they may be converted to their active acid addition salts by treatment with appropriate pharmaceutically acceptable acids. Examples of such acids include inorganic acids, such as hydrochloric acid, hydrobromic acid, hydrofluoric acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or organic acids, such as acetic acid, propionic acid, hydroacetic acid, 2-hydroxypropanoic acid, 2-oxopropanoic acid, ethanoidic acid, propanedioic acid, butanedioic acid, (Z)-2-butenedioic acid, (E)-butenedioic acid, 2-hydroxybutanedioic acid, 2,3-dihydroxybutanedioic acid, 2-hydroxy-l,2,3-propanetricarboxylic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, cyclohexanesulfamic acid, 2-hydroxybenzoic acid, 4-amino-2-hydroxybenzoic acid, and other acids known to the person skilled in the art.

As indicated above, \( n \) is an integer of 0, 1 or 2. In a preferred embodiment of the invention \( n \) is 0 or 1. In the most preferred embodiment of the invention \( n \) is 0.

The substituents \( R_i, R_2, R_3, R_4 \) and \( R_5 \) may be individually selected from the group of substituents indicated above. However, in a preferred embodiment of the invention each \( R_i, R_2, R_3, R_4 \) and \( R_5 \) is independently selected from the group consisting of hydrogen, optionally substituted \( C_{2-6} \)-alkyl, optionally substituted \( C_{2-6} \)-alkenyl, optionally substituted \( C_{2-6} \)-alkynyl, hydroxy, optionally substituted \( C_{2-6} \)-alkoxy, optionally substituted \( C_{2-6} \)-alkenylhydroxy, carboxy, optionally substituted \( C_{2-6} \)-alkoxycarbonyl, optionally substituted \( O_{6-7} \)-alkylcarbonyl, formyl, amino, mono- and di(\( C_{2-6} \)-alkyl)amino, carbamoyl, mono- and di(\( C_{2-6} \)-alkyl)aminocarbonyl, \( C_{2-6} \)-alkylaminocarbonyl, mono- and di(\( C_{2-6} \)-alkyl)aminocarbonyl, amino-\( C_{2-6} \)-alkylaminocarbonyl, \( C_{2-6} \)-alkylamino-carbonylamino, amino-\( C_{2-6} \)-alkylamino-carbonylamino, cyano, carbamido, \( C_{2-6} \)-alkanoyloxy, \( C_{2-6} \)-alkylsulphonyl, \( C_{2-6} \)-alkylsulphinyl, \( C_{2-6} \)-alkylsulphonyloxy, aminosulfonyl, mono- and di(\( C_{2-6} \)-alkyl)aminosulfonyl, nitro, optionally substituted \( C_{2-6} \)-alkylthio and halogen.

In a more preferred embodiment of the invention each \( R_i, R_2, R_3, R_4 \) and \( R_5 \) is independently selected from the group consisting of hydrogen, optionally substituted \( O_{6-7} \)-alkyl, optionally substituted \( C_{2-6} \)-alkenyl, hydroxy, optionally substituted \( O_{6-7} \)-alkoxy, amino, cyano, nitro and halogen, such as bromo, chloro and fluoro. Specific examples of highly preferred (non-substituted) \( C_{2-6} \)-alkyl groups include \( O_{4-7} \)-alkyl, such as methyl or ethyl, in particular methyl. Specific examples of highly preferred substituted \( O_{6-7} \)-alkyl groups include substituted \( O_{4-7} \)-alkyl, such as halogen-substituted \( O_{4-7} \)-alkyl, e.g. trihalo-Ci-4-alkyl, in particular tribromomethyl, trichloromethyl and trifluoromethyl among which trichloromethyl and trifluoromethyl are particularly preferred. Specific examples of highly preferred (non-substituted) \( C_{2-6} \)-alkenyl groups include \( C_{2-4} \)-alkenyl, such as vinyl, allyl and...
butenyl, in particular allyl. Specific examples of highly preferred (non-substituted) Cl₆-alkoxy groups include Cl₄-alkoxy, such as methoxy or ethoxy, in particular methoxy.

Concerning the substituents R₆ and R₇, these substituents may each be independently selected from the group consisting of hydrogen, optionally substituted Cl₆-alkyl, optionally substituted C₂₆-alkenyl, optionally substituted C₄₆-alkadienyl, optionally substituted C₂₆-alkynyl, optionally substituted Cl₆-alkoxycarbonyl, optionally substituted Cl₆-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(Cl₆-alkyl)aminocarbonyl, amino-Cl₆-alkyl-aminocarbonyl and mono- and di(Cl₆-alkyl)amino-Cl₆-alkyl-aminocarbonyl; or R₆ and R₇ may together form a five- or six-membered nitrogen-containing ring; with the proviso that R₆ and R₇ are not both hydrogen.

In a preferred embodiment of the invention, R₆ is hydrogen and R₇ is selected from the group consisting of optionally substituted Cl₆-alkyl, optionally substituted C₂₆-alkenyl, optionally substituted C₄₆-alkadienyl, optionally substituted C₂₆-alkynyl, optionally substituted Cl₆-alkoxycarbonyl, optionally substituted Cl₆-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(Cl₆-alkyl)aminocarbonyl, amino-Cl₆-alkyl-aminocarbonyl and mono- and di(Cl₆-alkyl)amino-Cl₆-alkyl-aminocarbonyl, i.e. the compound of the invention has the structure shown in the general formula (II):

![Diagram](image)

In another interesting embodiment of the invention, neither R₆ nor R₇ are hydrogen, and each R₆ and R₇ is independently selected from the group consisting of optionally
substituted CI-6-alkyl, optionally substituted C2-6-alkenyl, optionally substituted C4-6-alkadienyl, optionally substituted CI-6-alkynyl, optionally substituted CI-6-alkoxycarbonyl, optionally substituted CI-6-alkylcarbonyl, optionally substituted aryl, optionally substituted arylcarbonyl, optionally substituted aminocarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(CI-6-alkyl)aminocarbonyl, amino-CI-6-alkyl-aminocarbonyl and mono- and di(CI-6-alkyl)amino-CI-6-alkyl-aminocarbonyl; or R6 and R7 may together form a five- or six-membered nitrogen-containing ring, i.e. the compound of the invention has the structure shown in the general formula (Ia).

In a particular preferred embodiment, the invention relates to compounds of formula II, wherein Rγ is selected from the group consisting of optionally substituted CI-6-alkyl, optionally substituted C2-6-alkenyl, optionally substituted C2-6-alkynyl, optionally substituted aryl and optionally substituted heteroaryl.

In another preferred embodiment, the invention relates to compounds of formula Ia, wherein each R6 and R7 is independently selected from the group consisting of optionally substituted CI-6-alkyl, optionally substituted C2-6-alkenyl, optionally substituted C2-6-alkynyl, optionally substituted aryl and optionally substituted heteroaryl. Preferably R6 and R7 are identical.

In a more preferred embodiment, each R6 and R7 is independently hydrogen or optionally substituted CI-6-alkyl, preferably optionally substituted CI-4-alkyl; with the proviso that R6 and R7 are not both hydrogen. In one specific embodiment, R6 is hydrogen and R7 is optionally substituted CI-6-alkyl, preferably optionally substituted CI-4-alkyl. In another specific embodiment, R6 and R7 are both optionally substituted CI-6-alkyl, preferably optionally substituted CI-4-alkyl. In its most preferred embodiment each R6 and R7 is independently selected from the group consisting of hydrogen, methyl and ethyl; with the proviso that R6 and R7 are not both hydrogen. A specific, and preferred, example includes the compound of formula II where R6 is hydrogen and R7 is methyl or ethyl, in particular methyl. Another specific, and also preferred, example includes the compound of formula Ia where R6 and R7 are both methyl or ethyl, in particular methyl.

In another embodiment, the optionally substituted aryl is selected from the group consisting of phenyl, substituted phenyl, biphenyl, substituted biphenyl, naphthalene and substituted naphthalene. In a preferred embodiment, the optionally substituted aryl is selected from the group consisting of phenyl and substituted phenyl.
Accordingly, in one embodiment of the invention, each $R_6$ and $R_7$ is independently hydrogen or optionally substituted aryl, preferably optionally substituted phenyl; with the proviso that $R_6$ and $R_7$ are not both hydrogen. A specific example includes the compound of formula II where $R_6$ is hydrogen and $R_7$ is optionally substituted aryl, preferably optionally substituted phenyl. Another specific example includes the compound of formula Ia where $R_6$ and $R_7$ are both optionally substituted aryl, preferably optionally substituted phenyl.

In yet another embodiment, the optionally substituted heteroaryl is selected from the group consisting of optionally substituted pyrrolyl, optionally substituted indolyl, optionally substituted phenyl pyrrolyl, and optionally substituted N-phenyl pyrrolyl.

Accordingly, in one embodiment of the invention, each $R_6$ and $R_7$ is independently hydrogen or optionally substituted heteroaryl, preferably optionally substituted pyrrolyl; with the proviso that $R_6$ and $R_7$ are not both hydrogen. A specific example includes the compound of formula II where $R_6$ is hydrogen and $R_7$ is optionally substituted heteroaryl, preferably optionally substituted pyrrolyl. Another specific example includes the compound of formula Ia where $R_6$ and $R_7$ are both optionally substituted heteroaryl, preferably optionally substituted pyrrolyl.

In an interesting embodiment of the invention, the invention relates to compounds of formula (I), wherein $R_4$ is hydrogen and $R_1$, $R_2$, $R_3$, $R_5$, $R_6$, and $R_7$ are as defined above. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (III):

![Formula III](image)

It should be understood that all statements made above in connection with preferred embodiments of $R_1$, $R_2$, $R_3$, $R_5$, $R_6$, $R_7$, $X$, and $n$ also apply to compounds of the general formula (III).
In a further interesting embodiment, the invention relates to compounds of formula \( I \), wherein \( R_i \) and \( R_4 \) are hydrogen and \( R_2, R_3, R_5, R_6 \) and \( R_7 \) are as defined above. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (IV):

\[
\text{(IV)}
\]

It should be understood that all statements made above in connection with preferred embodiments of \( R_2, R_3, R_5, R_6, X \) and \( n \) also apply to compounds of the general formula (III).

In yet a further embodiment of the invention, \( R_i, R_4 \) and \( R_5 \) are hydrogen and \( R_2, R_3, R_6 \) and \( R_7 \) are as defined above. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (V):

\[
\text{(V)}
\]

It should be understood that all statements made above in connection with preferred embodiments of \( R_2, R_3, R_5, R_7, X \) and \( n \) also apply to compounds of the general formula (V).

Concerning the compounds described above in connection with the general formulae (I), (II), (III), (IV) and (V) it will be understood that the individual substituents may be
attached to the ring systems at different positions. More particularly, and with reference to the general formula (V) above, the attachment of the R₂ and R₃ may be as follows: In one embodiment of the invention is R₂ located in the 2-position and R₃ is located in the 3-position. In another embodiment of the invention is R₂ located in the 2-position and R₃ is located in the 4-position. A yet another embodiment of the invention is R₂ located in the 2-position and R₃ is located in the 5-position. In a still further embodiment of the invention is R₂ located in the 3-position and R₃ is located in the 4-position. In an even further embodiment of the invention is R₂ located in the 3-position and R₃ is located in the 5-position. In yet another embodiment of the invention is R₂ located in the 3-position and R₃ is located in the 6-position.

In another preferred embodiment of the invention, R₁, R₂, R₄, and R₅ are hydrogen and R₆, R₇, and R₈ are as defined above. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (VI):

![Formula VI](image)

It should be understood that all statements made above in connection with preferred embodiments of R₃, R₄, R₇, X and n also apply to compounds of the general formula (VI). Accordingly, n is an integer of 0, 1 or 2. In a preferred embodiment of the invention n is 0 or 1. In the most preferred embodiment of the invention n is 0.

Likewise, the R₃ substituent may, in a preferred embodiment, be selected from the group of hydrogen, optionally substituted C₁₋₆-alkyl, optionally substituted C₂₋₆-alkenyl, optionally substituted C₂₋₆-alkynyl, hydroxy, optionally substituted C₁₋₆-alkoxy, optionally substituted C₂₋₆-alkenyl, carboxy, optionally substituted C₁₋₆-alkoxy, optionally substituted C₁₋₆-alkylcarbonyl, formyl, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkylaminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, cyano,
carbamido, Ci-6-alkanoyloxy, Ci-6-alkylsulphonyl, Ci-6-alkylsulphinyl, Ci-6-alkylsulphonyloxy, aminosulfonyl, mono- and di(Ci-6-alkyl)aminosulfonyl, nitro, optionally substituted Ci-s-alkylthio and halogen.

In a more preferred embodiment of the invention R₃ is selected from the group consisting of hydrogen, optionally substituted Ci₆-alkyl, optionally substituted C₂₂₆-alkenyl, hydroxy, optionally substituted Ci₆-alkoxy, amino, cyano, nitro and halogen, such as bromo, chloro and fluoro. In yet an interesting embodiment, R₃ is chloro. Specific examples of highly preferred (non-substituted) Ci₆-alkyl groups include d₄-alkyl, such as methyl or ethyl, in particular methyl. Specific examples of highly preferred substituted Ci₆-alkyl groups include substituted Ci₄-alkyl, such as halogen-substituted Ci₄-alkyl, e.g. trihalo-Ci₄-alkyl, in particular tribromomethyl, trichloromethyl and trifluoromethyl among which trichloromethyl and trifluoromethyl are particularly preferred. Specific examples of highly preferred (non-substituted) C₂₂₆-alkenyl groups include C₂₄-alkenyl, such as vinyl, allyl and butenyl, in particular allyl. Specific examples of highly preferred (non-substituted) Ci₆-alkoxy groups include Ci₄-alkoxy, such as methoxy or ethoxy, in particular methoxy.

As described previously, the substituents R₆ and R₇ may each be independently selected from the group consisting of hydrogen, optionally substituted d₆-alkyl, optionally substituted C₂₂₆-alkenyl, optionally substituted C₄₆-alkadienyl, optionally substituted C₂₂₆-alkynyl, optionally substituted Ci₆-alkoxy, optionally substituted Ci₆-alkoxycarbonyl, optionally substituted Ci₆-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aroyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(Ci₆-alkyl)aminocarbonyl, amino-Ci₆-alkyl-aminocarbonyl and mono- and di(Ci₆-alkyl)amino-Ci₆-alkyl-aminocarbonyl; or R₆ and R₇ may together form a five- or six-membered nitrogen-containing ring; with the proviso that R₆ and R₇ are not both hydrogen.

In a preferred embodiment of the invention, R₆ is hydrogen and R₇ is selected from the group consisting of optionally substituted Ci₆-alkyl, optionally substituted C₂₂₆-alkenyl, optionally substituted C₄₆-alkadienyl, optionally substituted C₂₂₆-alkynyl, optionally substituted Ci₆-alkoxycarbonyl, optionally substituted Ci₆-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aroyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(Ci₆-alkyl)aminocarbonyl, amino-Ci₆-alkyl-aminocarbonyl and mono- and di(Ci₆-alkyl)amino-Ci₆-alkyl-aminocarbonyl. In a particular preferred embodiment, R₇ is selected from the group consisting of optionally substituted Ci₆-alkyl, optionally substituted C₂₂₆-alkenyl, optionally substituted C₄₆-alkadienyl, optionally substituted C₂₂₆-alkynyl, optionally substituted Ci₆-alkoxycarbonyl, optionally substituted Ci₆-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aroyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(Ci₆-alkyl)aminocarbonyl, amino-Ci₆-alkyl-aminocarbonyl, amino-Ci₆-alkyl-aminocarbonyl and mono- and di(Ci₆-alkyl)amino-Ci₆-alkyl-aminocarbonyl.
substituted C₂⁻₆-alkynyl, optionally substituted aryl and optionally substituted heteroaryl.
More preferably, R₇ is optionally substituted Ci⁻₄-alkyl, such as methyl or ethyl, in
particular methyl. In another interesting embodiment, R₇ is optionally substituted aryl,
preferably optionally substituted phenyl. In yet another interesting embodiment, R₇ is
optionally substituted heteroaryl, such as optionally substituted pyrrol, optionally
substituted indol, optionally substituted phenyl pyrrol, and optionally substituted N-
phenyl pyrrol, in particular optionally substituted pyrrol.

In another interesting embodiment of the invention, neither R₆ nor R₇ are hydrogen, and
each R₆ and R₇ is independently selected from the group consisting of optionally
substituted Ci⁻₆-alkyl, optionally substituted C₂⁻₆-alkenyl, optionally substituted C₄⁻₆-
alkadienyl, optionally substituted C₂⁻₆-alkynyl, optionally substituted Ci⁻₆-alkoxycarbonyl,
optionally substituted Ci⁻₆-alkylcarbonyl, optionally substituted aryl, optionally substituted
arylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl,
optionally substituted heteroarylcarbonyl, optionally substituted heteroarylcarbonyl,
aminocarbonyl, mono- and di(Ci⁻₆-alkyl)aminocarbonyl, amino-Ci⁻₆-alkyl-aminocarbonyl
and mono- and di(Ci⁻₆-alkyl)amino-Ci⁻₆-alkyl-aminocarbonyl; or R₆ and R₇ may together
form a five- or six-membered nitrogen-containing ring. In a particular preferred
embodiment, each R₆ and R₇ is independently selected from the group consisting of
optionally substituted Ci⁻₆-alkyl, optionally substituted C₂⁻₆-alkenyl, optionally substituted
C₂⁻₆-alkynyl, optionally substituted aryl and optionally substituted heteroaryl. Preferably R₆
and R₇ are identical. More preferably, R₆ and R₇ are optionally substituted d⁻₄-alkyl, such
as methyl or ethyl, in particular methyl. In another interesting embodiment, R₆ and R₇ are
optionally substituted aryl, preferably optionally substituted phenyl. In yet another
interesting embodiment, R₆ and R₇ are optionally substituted heteroaryl, such as optionally
substituted pyrrol, optionally substituted indol, optionally substituted phenyl pyrrol,
and optionally substituted N-phenyl pyrrol, in particular optionally substituted pyrrol. R₆
and R₇ may be selected individually from the above lists, but preferably R₆ and R₇ are
identical.

In one embodiment of the invention is R₃ located in the 2-position. In another embodiment
of the invention is R₃ located in the 3-position. In a third embodiment of the invention is R₃
located in the 4-position.

In a still further interesting embodiment of the invention all of Ri, R₂, R₃, R₄ and R₅ are
hydrogen.

It should be understood that all of the above statements made in connection with the
compounds of the invention apply equally well to compounds of the invention where the
aminoguanidine substituent is attached to the pyrrole ring at position 2 or 3 (although usually only illustrated and discussed for compounds of the invention where the aminoguanidine substituent is attached to the pyrrole ring at position 2). Nevertheless, in one embodiment of the invention it is preferred that the aminoguanidine substituent is attached to the pyrrole ring at position 2, i.e. in a preferred embodiment the compounds of the invention has the stereochemistry indicated in the general formula (Ia) and the formulae (II)-(VI) above.

Compounds according to the invention which are currently believed to be of particular interest are shown in Figs. 1-10.

Methods of preparing the compounds of the invention
The compounds of the invention may be prepared by standard methods known to the skilled person. Thus, a compound of the general formula (Ia) or (lb) above may be prepared essentially as described in WO 03/013509, i.e. a compound of the general formula (Aa) or (Ab)
is reacted with an aminoguanidine derivative of the general formula (B) in a suitable organic solvent:

wherein the individual substituents have the same meaning as described above. Preferably, a compound of the general formula (Aa) or (Ab) is reacted with an aminoguanidine derivative of the general formula (B) where the aminoguanidine derivative is in the form of an acid addition salt, such as the bicarbonate salt.

Alternatively, the compound of the general formula (Aa) or (Ab) is reacted with a thiosemicarbazide of the general formula (C)

wherein the individual substituents have the same meaning as described above. The reaction is preferably performed in a polar aprotic solvent, such as ethanol.

The resulting intermediate product of the general formula (D)
is subsequently reacted with an amine of the general formula (E)

\[ R_7 - \text{NH}_2 \]

in a suitable solvent, e.g. a non-polar aprotic solvent, such as toluene, to obtain the compound of the invention. The individual substituents have the same meaning as described above.

**Pharmaceutical compositions**


The exact dose to be administered depends on the circumstances. Normally, the dose should be capable of preventing or lessening the severity or spread of the condition or indication being treated. It will be apparent to those of skill in the art that an effective amount of the compound of the invention depends, *inter alia*, upon the disease, the dose, the administration schedule, whether the compound of the invention is administered alone or in conjunction with other therapeutic agents, the general health of the patient, and the like. Generally, and in particular if administered via the oral route, the compound of the
invention should be administered in a dose of 0.1 to 100 mg body weight per kilo throughout the treatment period.

The pharmaceutical composition may be formulated in a variety of forms, including liquid, gel, lyophilised, powder, compressed solid, or any other suitable form. The preferred form will depend upon the particular indication being treated and will be apparent to one of skill in the art.

The pharmaceutical composition may be administered orally, subcutaneously, intravenously, intracerebral, intranasally, transdermal, intramuscularly, intrapulmonary, vaginally, rectally, intraocularly, or in any other acceptable manner, e.g. using PowderJect or ProLease technology. The composition can be administered continuously by infusion, although bolus injection is acceptable, using techniques well known in the art, such as pumps or implantation. In some instances the composition may be directly applied as a solution or spray. The preferred mode of administration will depend upon the particular indication being treated and will be apparent to one of skill in the art. However, the currently preferred mode of administration is via the oral route.

The pharmaceutical composition of the invention may be administered in conjunction with other therapeutic agents. These agents may be incorporated as part of the same pharmaceutical composition or may be administered separately from the composition of the invention, either concurrently or in accordance with any other acceptable treatment schedule.

Oral administration

For oral administration, the pharmaceutical composition may be in solid or liquid form, e.g. in the form of a capsule, tablet, suspension, emulsion or solution. The pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but can be determined by persons skilled in the art using routine methods.

Solid dosage forms for oral administration may include capsules, tablets, suppositories, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances, 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.

The compound of the invention may be admixed with adjuvants such as lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinyl-pyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compound of the invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, ethanol, oils (such as corn oil, peanut oil, cottonseed oil or sesame oil), tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glycercyl monostearate or glycercyl distearate alone or with a wax, or other materials well known in the art.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilisation and/or may contain conventional adjuvants such as preservatives, stabilisers, wetting agents, emulsifiers, buffers, fillers, etc.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, sweeteners, flavoring agents and perfuming agents.

The invention also relates to processes 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.

**Therapeutic use**

The compounds of the present invention are either agonists or antagonists of a specific MC-receptor or of a number of MC-receptors, e.g. MC-1, MC-2, MC3, MC4 and/or MC5 receptors.

In one embodiment, the compounds of the invention have been shown to be capable of binding with high affinity to MC receptors compared to the compounds disclosed in WO 03/013509.

In another embodiment, the compounds of the invention have been shown to exhibit higher efficacy in functional assays studying melanocortin receptor stimulation (MC-1, MC-
2, MC-3, MC-4 or MC-5), e.g. cAMP assay compared to the compounds disclosed in WO 03/013509.

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 MC-I, MC-2, MC-3, MC-4 and MC-5, have been described. The MC receptor’s signalling is mainly mediated via cAMP, but other signal transduction pathways are also 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 as exemplified by the finding that selective MC-I receptor agonists has marked anti-inflammatory action, but seems to lack the organ protective effect described for unspecific MC receptor agonists as α-MSH, where it has been suggested that additional MC-3 and/or MC-5 receptor stimulation are needed to get the organ protective effect. Another example is the central effects of melanocortin receptor stimulation where it is unclear whether both MC-3 and MC-4 receptor stimulation or only stimulation of one of the receptors are needed.

In accordance with the above described physiological actions, in one embodiment, the compounds of the invention have shown anti-inflammatory activity.

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 or other hormones, uterine bleeding in women, sebum and pheromone secretion, blood glucose levels, natriuresis, intrauterine foetal growth, as well as other events surrounding parturition, (see, for example, Eberle: The melanotropins: Chemistry, physiology and mechanisms of action. Basel: Karger, Switzerland. 1988, ISBN 3-8055-4678-5; Gruber et al., Am. J. Physiol. 1989, 257, R681-R694; De Wildt et al., J. Cardiovascular Pharmacology. 1995, 25, 898-905) as well as inducing natriuresis (Tin et al., Hypertension. 1987, 10, 619-627).

Moreover, 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 antagonises the effects of pro-inflammatory cytokines such as IL-1 α, IL-1 β, IL-6 and
TNFα, and induces the production of the antiinflammatory cytokine, IL-10 (for review, see Catania & Upton, Endocr Rev. 1993 Oct; 14(5): 564-76).

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, 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).

In accordance with the above, in one embodiment, the compounds of the invention have shown a significant effect regarding inhibition of food intake.

The MC-5 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 an MC-receptor blocker could inhibit the erectogenic effect of melanocortic peptides (Vergoni et al., Eur. J. Pharmacol., 1998, 362; 95-101).

The compounds of the present invention has valuable therapeutic properties, making them useful for the treatment of inflammatory conditions, e.g. acute or chronic inflammatory conditions, such as arthritis, including diseases associated with arthritis, osteoarthritis, rheumatoid arthritis, spondylarthropathies (e.g. ankylosing spondilitis), reactive arthritis (including arthritis following rheumatic fever), Henoch-Schonlein purpura, and Reiter's disease, connective tissue disorders such as systemic lupus erythematosus, polymyositis/dermatomyositis, systemic sclerosis, mixed connetive tissue disease, sarcoidosis and primary Sjogrens syndrome including keratoconjunctivitis sicca, polymyalgia rheumatica, and other types of vasculitis, crystal deposition diseases (including gout), pyrophosphate arthropathy, acute calcific periarthritis; inflammatory bowel disease (including Chrons disease and ulcerative colitis), diverticular disease of the
colon, and irritable bowel syndrome, pancreatitis, inflammatory upper and lower airway
diseases such as chronic obstructive pulmonary diseases (COPD), allergic and non-allergic
asthma, allergic rhinitis, allergic and non-allergic conjunctivitis, allergic and non-allergic
dermatitis, trauma and post operative stress syndromes, diabetes mellitus, insulin-
resistance, metabolic syndrome, sexual dysfunction including dysfunction of male erection,
eating disorders including anorexia, obesity, mental disorders, dysfunction of the endocrine
system, drug-induced disorders of the blood and lymphoid system, allergy disorders,
disorders of the cardiovascular system and pain.

10 In the following the conditions and diseases of which the compounds of the present
invention are useful for treating, are described in details.

**Inflammatory conditions**

Compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable
pharmacological properties, making them useful for the treatment of inflammation, an
inflammatory condition or an inflammatory disease such as inflammation 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 a (TNF-α).

25 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.

30 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 "down regulated" 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, \( \alpha \)- or \( \beta \)-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 pemphigus vulgaris.

Moreover inflammatory diseases include all kinds of soft-tissue rheumatism including rheumatoid arthritis, bursitis, tenosynovitis or peritendinitis, enthesitis, nerve compression, periartitis or capsulitis, muscle tension and muscle dysfunction.

Furthermore, inflammatory diseases include all kinds of arthritis in children such as Juvenile Chronic arthritis including Still 's disease, juvenile rheumatoid arthritis, juvenile ankylosing spondylitis.

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 (Chrons disease), systemic sclerosis, ulcus duodeni, coeliac disease, oesophagitis, ulcus ventriculi, acute and chronic gastritis, helicobacter pylori infection, coeliac disease, gluten sensitive enteropathy, dermatitis herpiformis, tropical sprue, Whipple 's disease, radiation enteritis, systemic amyloidosis, eosinophilic gastroenteritis, intestinal lymphangiectasia, inflammatory bowel disease, diverticular disease of the colon, and irritable bowel 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 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 fasciitis, 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 neuritis, Wegener's granulomatosis, Sjogren'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, Sjogren'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 and/or airways, such as e.g. acute or chronic or subchronic inflammation in the lung and/or airway. 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, Good Pastures' syndrome, upper and lower airway diseases such as chronic obstructive pulmonary disease (COPD), exacerbations in COPD, allergic and non-allergic asthma, allergic rhinitis, allergic and non-allergic conjunctivitis, acute respiratory diseases and/or chronic and/or subchronic airway and lung diseases.

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 acute pancreatitis, chronic pancreatitis.

Moreover, 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
conditions with increased fasting levels of LDL-Cholesterol, conditions with combined increased fasting levels of LDL-Cholesterol and triglyceride, conditions with increased fasting levels of triglyceride and conditions with increased fasting levels of HDL-Cholesterol.

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 thyroitis, autoimmune thyroitis and Hashimoto's thyroitis.

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.

Inflammatory diseases also include all kind of inflammatory conditions causing backpain including infections, septic discitis, tuberculosis, malignancies (such as metastases, myeloma and others), spinal tumours, ankylosing spondylitis, acute disc prolapse, chronic
disc disease/osteoarthritis, osteoporosis, and osteomalacia. It also includes Pagets
disease, hyperparathyroidism, renal osteodystrophy, spondylolisthesis, spinal senosis
congenital abnormalities and fibromyalgia.

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, protozoae and fungus and include conditions
such as AIDS, bacterial septicemia, systemic fungal infections, Rickettsial diseases, toxic
shock syndrome, infectious mononucleosis, chlamydia trachomatis, chlamydia psittaci,
cytomegalovirus infection, Campylobacter, salmonella, influenza, poliomyelitis, toxoplasmosis, Lassa Fever, Yellow Fever, bilharziose, colibacteria, enterococcus, preteus,
klebsiella, pseudomonas, staphylococcus aureus, staphylococcus epidermidis, Candida
albicans, tuberculosis, mumps, infectious mononucleosis, hepatitis and Coxackie virus.

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, such as e.g. a chemical trauma involving one or
more toxic substances and/or drugs. Such drugs include tricyclic antidepressants, lithium
salts, prenylamine, phenothizine derivatives, chemopreventive drugs including Adriamycin.
Also physical traumas including electromagnetic radiation may cause damages.

Insulin resistance and Diabetes mellitus
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
insulin resistance, metabolic syndrome, diabetes mellitus, including Type II diabetes
mellitus where low grade inflammation in fatty tissue and muscles, plays a significant role
for the development of impairment in the signal transduction of insulin and thereby the
development of insulin resistance and eventually diabetes mellitus. Comprised by the
invention is also the administration of a compound of formula (I) or a pharmacologically
acceptable salt thereof for the treatment of insulin resistance, metabolic syndrome,
diabetes mellitus, including Type II diabetes mellitus and obesity-induced Type II diabetes.

Eating disorders
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
eating disorders, such as e.g. anorexia and bulimia. Comprised by the invention is also the
administration of a compound of formula (I) or a pharmacologically acceptable salt thereof
for the treatment of eating disorders, such as e.g. anorexia and bulimia.
Obesity
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 obesity where low grade inflammation in fatty tissue and muscles, plays a significant role for the development of the complications to obesity the includes the development of insulin resistance and eventually diabetes mellitus, e.g. diabetes mellitus type II, dyslipidemia, hypertension and atherosclerosis. Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of obesity and/or metabolic syndrome.

Congestive heart failure
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 congestive heart failure where low grade inflammation including TNF-α production within the heart plays a significant role for the development of fibrosis and myocardial remodelling in the failing heart. Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of congestive heart failure

Sexual dysfunction
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.

Mental disorders
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.

Dysfunction of the endocrine system
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.

Drug-induced disorders of the blood and lymphoid system
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.

Allergy disorders
The compounds of the invention may also be administered for the treatment of 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.

Disorders of the cardiovascular system
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, reperfusion 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.

Pain
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.

Other uses
Skin tanning

Because of the capacity of compounds of the invention to stimulate pigment formation in epidermal cells, some of the 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, atopic dermatitis, psoriasis and conditions related to malfunctions of the glands of the skin, e.g. sebaceous glands and over or underproduction of sebum.

In vivo formation of second messenger elements

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.

Labels and tags

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 MCl-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.

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.

Some of the compounds of the invention have an effect on xanthine oxidase in mammals, including humans.

The invention is further illustrated by the following non-limiting examples.
EXPERIMENTAL

Example 1 - Synthesis of N-(1-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-methyl guanidine (structure no. 1 in figure 1), cf. figure 2.

1-(4-chloro-phenyl)-1H-pyrrole-2-carbaldehyde (206 mg, 1 mmol) and S-methylthiosemicarbazide hydroiodide (233 mg, 1 mmol) is mixed in ethanol (5 ml) and heated at reflux. When the aldehyde is consumed the solvent is removed. The residue is suspended in dry toluene (5 ml) and a solution of methylamine (3 mmol) in dry toluene (1 ml) is added. The mixture is heated at reflux in a sealed vial until completion of the reaction. The solvent is removed and the solid residue is recrystallized to give the title product.

Example 2 - Synthesis of N-(1-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-ethyl guanidine (structure no. 2 in figure 1), cf. figure 3.

Crude 1-(1-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-S-methylisothiourea hydroiodide (1 mmol) prepared as in Example 1 is suspended in dry toluene (5 ml) and a solution of ethylamine (3 mmol) in dry toluene (1 ml) is added. The mixture is heated at reflux in a sealed vial until completion of the reaction. The solvent is removed and the solid residue is recrystallized to give the title product.

Example 3 - Synthesis of N-(1-[2-nitrophenyl]pyrrol-2-yl methylideneamino)-N'-methyl guanidine (structure no. 13 in figure 1), cf. figure 4.

The title product is prepared from 1-(2-nitro-phenyl)-1H-pyrrole-2-carbaldehyde, S-methylthiosemicarbazide hydroiodide, and methylamine analogously to Example 1.

Example 4 - Synthesis of N-(1-[4-trifluoromethylphenyl]pyrrol-2-yl methylideneamino)-N'-methyl guanidine (structure no. 19 in figure 1), cf. figure 5.

The title product is prepared from 1-(4-trifluoromethylphenyl)-1H-pyrrole-2-carbaldehyde, S-methylthiosemicarbazide hydroiodide, and methylamine analogously to Example 1.

Example 5 - Synthesis of N-(1-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-phenyl guanidine (structure no. 25 in figure 1), cf. figure 6.

Crude 1-(1-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-S-methylisothiourea hydroiodide (1 mmol) prepared as in Example 1 is suspended in dry toluene (5 ml) and a
solution of aniline (1.2 mmol) in dry toluene (1 ml) is added. The mixture is heated at reflux until completion of the reaction. The solvent is removed and the solid residue is recrystallized to give the title product.

5 Example 6 - Synthesis of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-pyrrol-1-yl guanidine (structure no. 28 in figure 1), cf. figure 7.

The title product is prepared from crude l-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-S-methylisothiourea hydroiodide and 1-aminopyrrole analogously to Example 5.

10 Example 7 - Synthesis of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-methyl,N"-methyl guanidine (structure no. 30 in figure 1), cf. figure 8.

15 I-(4-chlorophenyl)-lH-pyrrole-2-carbaldehyde (206 mg, 1 mmol) and 4,S-dimethylisothiosemicarbazide hydroiodide (247 mg, 1 mmol) is mixed in ethanol (5 ml) and heated at reflux. When the aldehyde is consumed the solvent is removed. The residue is suspended in dry toluene (5 ml) and a solution of methylamine (3 mmol) in dry toluene (1 ml) is added. The mixture is heated at reflux in a sealed vial until completion of the reaction. The solvent is removed and the solid residue is recrystallized to give the title product.

Example 8 - Synthesis of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-ethyl-N"-methyl guanidine (structure no. 31 in figure 1), cf. figure 9.

20 Crude l-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-3,S-dimethylisothiourea hydroiodide (1 mmol) prepared as in Example 7 is suspended in dry toluene (5 ml) and a solution of ethylamine (3 mmol) in dry toluene (1 ml) is added. The mixture is heated at reflux in a sealed vial until completion of the reaction. The solvent is removed and the solid residue is recrystallized to give the title product.

Example 9 - N-[l-(4-chlorophenyl)-lH-pyrrol-2-ylmethylene]-N'-(4,5-dihydro-lH-imidazol-2-yl)-hydrazine (structure no. 32 in figure 1), cf. figure 10.

30 Crude l-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-S-methylisothiourea hydroiodide (1 mmol) prepared as in Example 1 is suspended in dry toluene (5 ml) and a solution of ethylenediamine (1.2 mmol) in dry toluene (1 ml) is added. The mixture is heated at reflux until completion of the reaction. The solvent is removed and the solid residue is recrystallized to give the title product.
Example 10 - *In vitro* pharmacology and binding assays

*Description of applied methods*

Determination of binding affinities for MC receptors is performed by $[^{125}\text{I}]$-[Nle4,D-Phe7] $\alpha$-MSH ([$^{125}\text{I}$]-NDP-MSH) radio-ligand binding. In short, murine B16-F1 melanoma cells expressing MC-1, but not other MC receptors, are used for binding affinity studies against the murine MC-1 receptor (Siegrist et al.; 1988, J. Recept. Res., 8(I-4):323-43). For human MC-3, MC-4 and MC-5 receptor affinities human recombinant CHO cells are used (Schioth et al. 1997, Neuropeptides 31:565-71,1997). Cells are suspended in HEPES buffer and by use of microwell plates radio-ligands, as well as test compound, in the concentration range of $10^{-10}$ to $10^{-6}$ are added. After incubation at 37°C (22°C for the MCI receptor assay) separation of bound and free $[^{125}\text{I}]$-NDP-MSH is performed by multiple washings with buffer.

The results are expressed as a percent of control specific binding obtained in the presence of the test compounds. Mean values for each assay are presented in Table I below. The $IC_{50}$ values (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficients ($\pi_H$) are determined by non-linear regression analysis of the competition curves using Hill equation curve fitting. The inhibition constants ($K_i$) are calculated from the Cheng Prusoff equation ($K_i = IC_{50}/(L+(L/K_D))$, where $L$ = concentration of radio-ligand in the assay, and $K_D$ = affinity of the radio-ligand for the receptor).

### Table I

<table>
<thead>
<tr>
<th>Assay</th>
<th>Ligand</th>
<th>Concentration</th>
<th>Incubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>$[^{125}\text{I}]$NDP-MSH</td>
<td>0.05 nM</td>
<td>NDP-MSH (1 µM)</td>
</tr>
<tr>
<td>MC3 (h)</td>
<td>$[^{125}\text{I}]$NDP-MSH</td>
<td>0.075 nM</td>
<td>NDP-MSH (1 µM)</td>
</tr>
<tr>
<td>MC4 (h)</td>
<td>$[^{125}\text{I}]$NDP-MSH</td>
<td>0.05 nM</td>
<td>NDP-MSH (1 µM)</td>
</tr>
<tr>
<td>MC5 (h)</td>
<td>$[^{125}\text{I}]$NDP-MSH</td>
<td>0.05 nM</td>
<td>NDP-MSH (1 µM)</td>
</tr>
</tbody>
</table>
CLAIMS

1. A compound of the general formula (I):

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_4 \\
\text{N} & \quad \text{X} \\
\text{R}_5 & \quad \text{NHR}_6 \\
\text{NHR}_7 & 
\end{align*}
\]

including tautomeric and isomeric forms thereof,

wherein \( X \) is \((\text{CH}_2)\_n\) and \( n \) is 0, 1 or 2;

each \( \text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4 \) and \( \text{R}_5 \) is independently selected from the group consisting of hydrogen, optionally substituted \( \text{C}_1\_\text{C}_6 \)-alkyl, optionally substituted \( \text{C}_3\_\text{C}_6 \)-cycloalkyl, optionally substituted \( \text{C}_2\_\text{C}_6 \)-alkenyl, optionally substituted \( \text{C}_4\_\text{C}_6 \)-alkadienyl, optionally substituted \( \text{C}_2\_\text{C}_6 \)-alkynyl, hydroxy, optionally substituted \( \text{C}_1\_\text{C}_6 \)-alkoxy, optionally substituted \( \text{C}_2\_\text{C}_6 \)-alkenyloxy, carboxy, optionally substituted \( \text{C}_1\_\text{C}_6 \)-alkoxycarbonyl, optionally substituted \( \text{C}_1\_\text{C}_6 \)-alkylcarbonyl, optionally substituted \( \text{C}_1\_\text{C}_6 \)-formyl, \( \text{C}_1\_\text{C}_6 \)-alkylsulphonylamino, optionally substituted aryl, optionally substituted arloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, optionally substituted arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, optionally substituted heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, optionally substituted heterocyclylsulphonylamino, amino, mono- and di(\( \text{C}_1\_\text{C}_6 \)-alkyl)amino, carbamoyl, mono- and di(\( \text{C}_1\_\text{C}_6 \)-alkyl)aminocarbonyl, amino-\( \text{C}_1\_\text{C}_6 \)-alkyl-aminocarbonyl, mono- and di(\( \text{C}_1\_\text{C}_6 \)-alkyl)amino-\( \text{C}_1\_\text{C}_6 \)-alkyl-aminocarbonyl, \( \text{C}_1\_\text{C}_6 \)-alkylcarbonylamino, amino-\( \text{C}_1\_\text{C}_6 \)-alkyl-
carbonylamino, mono- and di(C-6-alkyl)amino-C-6-alkyl-carbonylamino, cyano, guanidino,
carbamido, C-6-alkanoyloxy, C-6-alkylsulphonyl, C-6-alkylsulphinyl, C-6-alkylsulphonyloxy,
aminosulfonyl, mono- and di(C-6-alkyl)aminosulfonyl, nitro, optionally substituted
C-6-alkylthio and halogen,

5 where any nitrogen-bound C-6-alkyl is optionally substituted with hydroxy, C-6-alkoxy,
C-2-alkenyloxy, amino, mono- and di(C-6-alkyl)amino, carboxy, C-6-alkycarbamidylamino,
halogen, C-6-alkylthio, C-6-alkyl-sulphonyl-amino or guanidine;

each R-6 and R-7 is independently selected from the group consisting of hydrogen, optionally
substituted C-6-alkyl, optionally substituted C-2-alkenyl, optionally substituted C-4-6-
alkadienyl, optionally substituted C-2-alkynyl, optionally substituted C-6-alkoxycarbonyl,
only optionally substituted C-6-alkylcarbonyl, optionally substituted aryl, optionally substituted
arylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl,
only optionally substituted heteroarylcarbonyl, optionally substituted heteroarylcarbonyl,
aminocarbonyl, mono- and di(C-6-alkyl)aminocarbonyl, amino-C-6-alkyl-aminocarbonyl
and mono- and di(C-6-alkyl)amino-C-6-alkyl-aminocarbonyl; or R-6 and R-7 may together
form a five- or six-membered nitrogen-containing ring;

with the proviso that R-6 and R-7 are not both hydrogen;

20 or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein each R-1, R-2, R-3, R-4 and R-5 is independently
selected from the group consisting of hydrogen, optionally substituted C-6-alkyl, optionally
25 substituted C-2-alkenyl, optionally substituted C-2-alkynyl, hydroxy, optionally substituted
C-6-alkoxy, optionally substituted C-2-alkenyoxy, carboxy, optionally substituted C-1-6-
aloxycarbonyl, optionally substituted C-6-alkylcarbonyl, formyl, amino, mono- and
di(C-6-alkyl)amino, carbamoyl, mono- and di((C-6-alkyl)aminocarbonyl, amino-C-6-alkyl-
aminocarbonyl, mono- and di(C-6-alkyl)amino-C-6-alkyl-aminocarbonyl, C-6-alkycarbo-

30 lamo, amino-C-6-alkyl-carbonylaminoc, mono- and di(C-6-alkyl)amino-C-6-alkyl-
carbonylamino, cyano, carbamido, C-6-alkanoyloxy, C-6-alkylsulphonyl, C-6-alkylsulphinyl,
C-6-alkylsulphonyloxy, aminosulfonyl, mono- and di(C-6-alkyl)aminosulfonyl, nitro,
only optionally substituted C-6-alkylthio and halogen.

35 3. The compound according to claim 2, wherein each R-1, R-2, R-3, R-4 and R-5 is independently
selected from the group consisting of hydrogen, optionally substituted C-6-alkyl, optionally
substituted C-2-alkenyl, hydroxy, optionally substituted C-6-alkoxy, amino, cyano, nitro
and halogen.
4. The compound according to any of the preceding claims, wherein each \( R_6 \) and \( R_7 \) is independently selected from the group consisting of hydrogen, optionally substituted \( \text{C}_6^1 \)-alkyl, optionally substituted \( \text{C}_2^5 \)-alkenyl, optionally substituted \( \text{C}_2^5 \)-alkynyl, optionally substituted aryl and optionally substituted heteroaryl; with the proviso that \( R_6 \) and \( R_7 \) are not both hydrogen.

5. The compound according to claim 4, wherein each \( R_6 \) and \( R_7 \) is independently hydrogen or optionally substituted \( \text{C}_6^1 \)-alkyl, preferably optionally substituted \( \text{C}_4^1 \)-alkyl; with the proviso that \( R_6 \) and \( R_7 \) are not both hydrogen.

6. The compound according to claim 5, wherein \( R_6 \) is hydrogen and \( R_7 \) is optionally substituted \( \text{C}_6^1 \)-alkyl, preferably optionally substituted \( \text{C}_4^1 \)-alkyl.

7. The compound according to claim 5, wherein \( R_6 \) and \( R_7 \) are both optionally substituted \( \text{Cl}_6 \)-alkyl, preferably optionally substituted \( \text{Cl}_4 \)-alkyl.

8. The compound according to claim 4, wherein each \( R_6 \) and \( R_7 \) is independently selected from the group consisting of hydrogen, methyl and ethyl; with the proviso that \( R_6 \) and \( R_7 \) are not both hydrogen.

9. The compound according to claim 8, wherein \( R_6 \) is hydrogen and \( R_7 \) is methyl or ethyl.

10. The compound according to claim 9, wherein \( R_6 \) is hydrogen and \( R_7 \) is methyl.

11. The compound according to claim 9, wherein \( R_6 \) is hydrogen and \( R_7 \) is ethyl.

12. The compound according to claim 8, wherein \( R_6 \) and \( R_7 \) are both methyl.

13. The compound according to claim 8, wherein \( R_6 \) and \( R_7 \) are both ethyl.

14. The compound according to claim 4, wherein each \( R_6 \) and \( R_7 \) is independently hydrogen or optionally substituted aryl, preferably optionally substituted phenyl; with the proviso that \( R_6 \) and \( R_7 \) are not both hydrogen.

15. The compound according to claim 14, wherein \( R_6 \) is hydrogen and \( R_7 \) is optionally substituted aryl, preferably optionally substituted phenyl.

16. The compound according to claim 14, wherein \( R_6 \) and \( R_7 \) are both optionally substituted aryl, preferably optionally substituted phenyl.
17. The compound according to claim 4, wherein each R₆ and R₇ is independently hydrogen or optionally substituted heteroaryl, preferably optionally substituted pyrrolyl; with the proviso that R₆ and R₇ are not both hydrogen.

18. The compound according to claim 17, wherein R₆ is hydrogen and R₇ is optionally substituted heteroaryl, preferably optionally substituted pyrrolyl.

19. The compound according to claim 17, wherein R₆ and R₇ are both optionally substituted heteroaryl, preferably optionally substituted pyrrolyl.

20. The compound according to any of claims 1-4, wherein R₆ is hydrogen.

21. The compound according to any of the preceding claims, wherein R₆ is hydrogen and R₁, R₂, R₃ and R₅ are as defined in any of claims 1-3.

22. The compound according to claim 21, wherein R₁ and R₆ are hydrogen and R₂, R₃ and R₅ are as defined in any of claims 1-3.

23. The compound according to claim 22, wherein R₁, R₆ and R₅ are hydrogen and R₂ and R₃ are as defined in any of claims 1-3.

24. The compound according to claim 22 or 23, wherein R₂ is located in the 2-position and R₅ is located in the 3-position.

25. The compound according to claim 22 or 23, wherein R₂ is located in the 2-position and R₅ is located in the 4-position.

26. The compound according to claim 22 or 23, wherein R₂ is located in the 2-position and R₅ is located in the 5-position.

27. The compound according to claim 22 or 23, wherein R₂ is located in the 2-position and R₅ is located in the 6-position.

28. The compound according to claim 22 or 23, wherein R₂ is located in the 3-position and R₅ is located in the 4-position.

29. The compound according to claim 22 or 23, wherein R₂ is located in the 3-position and R₅ is located in the 5-position.
30. The compound according to claim 22 or 23, wherein R₂ is located in the 3-position and R₃ is located in the 6-position.

31. The compound according to claim 23, wherein R₁, R₂, R₄ and R₅ are hydrogen and R₃ is as defined in any of claims 1-3.

32. The compound according to claim 31, wherein R₂ is located in the 2-position.

33. The compound according to claim 31, wherein R₂ is located in the 3-position.

34. The compound according to claim 31, wherein R₂ is located in the 4-position.

35. The compound according to claim 31, wherein all of R₁, R₂, R₃, R₄ and R₅ are hydrogen.

36. The compound according to any of claims 1-35, wherein said compound has the structure shown in the general formula (Ia):

```
R₃
R₂
R₁
R₄
R₅
R₆
N
X
NHNHR₆
N
N
```

and wherein X, R₁, R₂, R₃, R₄, R₅, R₆ and R₇ are as defined in any of claims 1-35.

37. The compound according to any of claims 1-35, wherein said compound has the structure shown in the general formula (Ib)
and wherein $X$, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ and $R_7$ are as defined in any of claims 1-35.

38. The compound according to any of claims 1-37, wherein $n$ is 0.

39. A pharmaceutical composition comprising a compound as defined in any of claims 1-38 and a pharmaceutically acceptable carrier or excipient.

40. A dosage form comprising the pharmaceutical composition as defined in claim 39.

41. The dosage form according to claim 40, wherein said dosage form is a solid dosage form.

42. The solid dosage form according to claim 41, wherein said solid dosage form is in the form of a tablet or capsule.

43. A compound as defined in any of claims 1-38 for use as a medicament.

44. A compound as defined in any of claims 1-38 for the treatment or prevention of a disease or condition associated with the melanocortin receptor system.

45. A compound as defined in any of claims 1-38 for the treatment or prevention of an inflammatory disease.

46. A compound as defined in any of claims 1-38 for the treatment or prevention of metabolic syndrome.

47. A compound as defined in any of claims 1-38 for the treatment or prevention of insulin-resistance.
48. A compound as defined in any of claims 1-38 for the treatment or prevention of diabetes mellitus.

49. The compound according to claim 48, wherein the diabetes mellitus is selected from the group consisting of diabetes mellitus type I, diabetes mellitus type II and obesity-induced diabetes mellitus type II.

50. A compound as defined in any of claims 1-38 for the treatment or prevention of obesity.
Examples of phenyl pyrrole aminoguanidine derivatives of the invention

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure 2" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Structure 3" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Structure 4" /></td>
</tr>
</tbody>
</table>

Fig. 1
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td><img src="image" alt="Chemical Structure 10" /></td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Chemical Structure 11" /></td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Chemical Structure 12" /></td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="Chemical Structure 13" /></td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Chemical Structure 14" /></td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Chemical Structure 15" /></td>
</tr>
</tbody>
</table>

Fig. 1
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td><img src="image16.png" alt="Molecule 16" /></td>
</tr>
<tr>
<td>17</td>
<td><img src="image17.png" alt="Molecule 17" /></td>
</tr>
<tr>
<td>18</td>
<td><img src="image18.png" alt="Molecule 18" /></td>
</tr>
<tr>
<td>19</td>
<td><img src="image19.png" alt="Molecule 19" /></td>
</tr>
<tr>
<td>20</td>
<td><img src="image20.png" alt="Molecule 20" /></td>
</tr>
</tbody>
</table>

Fig. 1
Fig. 1
<table>
<thead>
<tr>
<th></th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>27</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>28</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>29</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>30</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

Fig. 1
<table>
<thead>
<tr>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure 31" /></td>
</tr>
<tr>
<td>32</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure 32" /></td>
</tr>
<tr>
<td>33</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure 33" /></td>
</tr>
<tr>
<td>34</td>
</tr>
<tr>
<td><img src="image4" alt="Chemical Structure 34" /></td>
</tr>
<tr>
<td>35</td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure 35" /></td>
</tr>
</tbody>
</table>

**Fig. 1**
Fig. 1
Fig. 1
Fig. 2

N-(1-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-methyl guanidine

Substituted Sheet (Rule 26)
**Fig. 3**

N-(1-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-ethyl guanidine

![Chemical structure diagram](image-url)
Fig. 4

N-(1-[2-nitrophenyl]pyrrole-2-yl methylideneamino)-N'-methyl guanidine

\[
\begin{align*}
\text{N-(1-[2-nitrophenyl]pyrrole-2-yl methylideneamino)-N'-methyl guanidine} \\
\text{[Diagram showing the chemical reaction process]} \\
\end{align*}
\]
Fig. 5

N-(1-[4-trifluorophenyl]pyrrol-2-yl methyldieneamino)-N'-methyl guanidine
Fig. 6

N-(1-[4-chlorophenyl]pyrro1-2-yl methylideneamino)-N'-phenyl guanidine

CONVERSION OF 

CONVERSION TO 

PhNH₂
Toluene
Fig. 7

N-(1-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N'-pyrrol-1-yl guanidine

[Chemical structure diagram]
Fig. 8

N-(1-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N',N''-dimethyl guanidine

\[
\begin{align*}
\text{EtOH} & \quad \text{MeNH}_2 \\
\end{align*}
\]
Fig. 9

N-(1-[4-chlorophenyl]pyrrol-2-yl methyldeneamino)-N'-ethyl-N"'-methyl guanidine

\[
\begin{align*}
\text{EtOH} & \quad \text{Toluene} \\
\end{align*}
\]
Fig. 10

\[ N-[1-(4-Chloro-phenyl)-1H-pyrrol-2-ylmethylene]-N'-(4,5-dihydro-1H-imidazol-2-yl)-hydrazine \]
A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D207/325 C07D207/335 A61K31/402

According to International Patent Classification (IPC) or to both national classification and IPC:

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 02/12178 A (MELACURE THERAPEUTICS AB [SE]; PETT CHRISTOPHER PHINEAS [GB]; LUNDSTED) 14 February 2002 (2002-02-14) &amp; compound with RN: 398459-63-7 ((hydrazinecarboximidamide,2-((1-((4-chloro phenyl)-lH-pyrrol-2-yl)methylene)-N-(phenylmethyl))methylen)-N-(phenylmethyl))claims 1,14-24</td>
<td>1-50</td>
</tr>
<tr>
<td>X</td>
<td>WO 03/013509 A (MELACURE THERAPEUTICS AB [SE]; LUNDSTEDT TORBJOERN [SE]; SKOTTNER ANNA) 20 February 2003 (2003-02-20) claims 1,24-27,29,36,37</td>
<td>1-50</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C

See patent family annex

Date of actual completion of the international search 9 March 2009

Date of mailing of the international search report 18/03/2009

Name and mailing address of the ISA:
European Patent Office, P B 5818 Patentlaan 2 NL- 2280 HV Rijswijk
Tel (+31-70) 340-2040, Fax (+31-70) 340-3016

Authorized officer: Voyi azoglou, D
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>wo 03/073999 A (PINTEX PHARMACEUTICALS INC [US]) 12 September 2003 (2003-09-12) &amp; compound with RN: 419540-77-5 (IH-pyrrol-2-carboxaldehyde, l-(4-nitrophe nyl)-2-(5-phenyl-1,2,4-triazin-3-yl)hydrazine) claims 1,122</td>
<td>1-43</td>
</tr>
<tr>
<td>X</td>
<td>MAMOLO M G ET AL: &quot;SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF AMINOQUANIDINE AND AMIDRAZONE DERIVATIVES&quot; EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 21, no. 6, 1 January 1986 (1986-01-01), pages 467-474, XP009063339 ISSN: 0223-5234 example 1f</td>
<td>1-43</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CHEMCATS 16 April 2004 (2004-04-16), XP002518243 Database accessi on no. RN: 675826-52-5 &amp; &quot;TimTec product list&quot;</td>
<td>1</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>P, X</td>
<td>WO 2007/141343 A (ACTION PHARMA AS [DK]; BOMAN ARNE [SE]; JONASSEN THOMAS ENGELBRECHT NO) 13 December 2007 (2007-12-13) &amp; compounds with RN: 959850-82-9 and 959850-78-3 claims 1,23-30; examples 1,53</td>
<td>1-50</td>
</tr>
<tr>
<td>A</td>
<td>WO 98/23267 A (WAPHARM AB [SE]; WIKBERG JARL [SE]; PRUSIS PETERIS [SE]; DAMBROVA MAIJ) 4 June 1998 (1998-06-04) &amp; compound with RN: 208582-96-1 page 45, last paragraph; claims 1,16</td>
<td>1-43</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>wo 0212178</td>
<td>A 14-02-2002</td>
<td>AT 413382 T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 7653901 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0113064 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2417904 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1309544 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2004505947 T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX PA03001073 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004019094 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200300883 A</td>
</tr>
<tr>
<td>wo 03013509</td>
<td>A 20-02-2003</td>
<td>BR 0210445 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2448356 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60217503 T2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 1414440 T3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1414440 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2280555 T3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2005504039 T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX PA04001037 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 529666 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2009018183 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2006148798 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004254093 Al</td>
</tr>
<tr>
<td>wo 03073999</td>
<td>A 12-09-2003</td>
<td>AU 2003217870 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004180889 Al</td>
</tr>
<tr>
<td>wo 2007141343</td>
<td>A 13-12-2007</td>
<td>AU 2007255366 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 5143098 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2272932 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1007025 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2001505209 T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 336378 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6599943 BI</td>
</tr>
</tbody>
</table>