The invention relates to phenyl pyrrole aminoguanidines modified at the guanidine group of the general formula (I), including tautomeric and isomeric forms thereof, wherein, X is (II) and i is 0,lor 2, Y is (III) and j is 0 or 1; wherein Q is nitrogen (N) or carbon (C), and U represents, together with Q and the carbon atom covalently linked to Q, an optionally substituted five- or six-membered heterocyclyl or cycloalkyl group; and Z is (IV) and k is 0,1,2 or 3. The invention further relates to the use of such modified phenyl pyrrole aminoguanidines for the treatment of diseases associated with the melanocortin receptors or related systems, e.g. the melanocyte stimulating hormones. Such diseases include inflammatory diseases, metabolic syndrome, insulin-resistance, diabetes mellitus, and obesity.
FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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FULLY-MODIFIED PHENYL PYRROLE AMINO GUANIDINES

FIELD OF THE INVENTION
The present invention relates to phenyl pyrrole aminoguanidines modified at the guanidine group. The present invention further relates to the use of such modified phenyl pyrrole aminoguanidines 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:

![Chemical Structure](image-url)
This hydroxyguanidine derivative has proven activity against xanthine oxidase/xanthine dehydrogenase enzymes.

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

\[
\begin{align*}
&\text{R}_1 \text{ } \text{R}_2 \text{ } \text{R}_3 \\
&\text{R}_4 \text{ } \text{X} \text{ } \text{R}_5 \\
&\text{N} \text{ } \text{N} \text{ } \text{H} \text{ } \text{NH} \text{ } \text{NH}_2
\end{align*}
\]

where \( X = (\text{CH}_2)_n \) and \( n = 0, 1 \) 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, \( \alpha \)-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 \( \alpha \)-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 \textit{inter alia} in that the aminoguanidine group has been modified and/or in that the aminoguanidine substituent at the pyrrole ring has been modified into a more rigid structure allowing only minimal rotational freedom around the carbon atoms present in the aminoguanidine substituent.

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-I, 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 adenylyl cyclase and production of cAMP via activation of one or more of the MC-I, 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 adenylyl cyclase and production of cAMP via activation of one or more of the MC-I, 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 and i is 0, 1 or 2;

Y is and j is 0 or 1;

wherein Q is nitrogen (N) or carbon (C), and u represents, together with Q and the carbon atom covalently linked to Q, an optionally substituted five- or six-membered heterocyclyl or cycloalkyl group;

Z is and k is 0, 1, 2 or 3;

each R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ is independently selected from the group consisting of hydrogen, optionally substituted C₁₋₅-alkyl, optionally substituted C₅₋₆-cycloalkyl, optionally substituted C₂₋₆-alkenyl, optionally substituted C₄₋₆-alkadienyl, optionally substituted C₂₋₆-alkynyl, hydroxy, optionally substituted C₁₋₅-alkoxy, optionally substituted C₂₋₆-alkenyl, carboxy, optionally substituted C₁₋₆-alkoxycarbonyl, optionally substituted C₁₋₆-alkylcarbonyl, formyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted...
heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally
substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(Ci-alkyl)amino, carbamoyl, mono- and di(Ci-alkyl)aminocarbonyl, amino-Ci-alkyl-aminocarbonyl, mono- and di(Ci-alkyl)amino-Ci-alkyl-aminocarbonyl, Ci-alkylcarbonylamino, amino-Ci-alkylcarbonylamino, mono- and di(Ci-alkyl)aminocarbonyl, mono- and di(Ci-alkyl)amino-Ci-alkyl-carbonylamino, mono- and di(Ci-alkyl)amino-Ci-alkyl-carbonylamino, cyano, guanidino, carbamido, Ci-alkanoyloxy, Ci-alkylsulphonylamino, Ci-alkylsulphonylamino, Ci-alkylsulphonylamino, aminosulfonyl, mono- and di(Ci-alkyl)aminosulfonyl, nitro, optionally substituted Ci-alkylthio and halogen,
where any nitrogen-bound Ci-alkyl is optionally substituted with hydroxy, Ci-alkoxy, Calkenoyloxy, amino, mono- and di(Ci-alkyl)amino, carboxy, Ci-alkylcarbonylamino, halogen, Ci-alkylthio, Ci-alkyl-sulphonylamino or guanidine;

each R, R, R and R is independently selected from the group consisting of hydrogen, optionally substituted Ci-alkyl, optionally substituted Calkenyl, optionally substituted Calkadienyl, optionally substituted Calkynyl, optionally substituted Ci-alkoxycarbonyl, optionally substituted Ci-alkylcarbonyl, optionally substituted aryl, optionally substituted arylcarbonyl, optionally substituted carbamoyl, optionally substituted heteroaryl, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(Ci-alkyl)aminocarbonyl, amino-Ci-alkylaminocarbonyl and mono- and di(Ci-alkyl)amino-Ci-alkylaminocarbonyl; or R and R may together form a five- or six-membered nitrogen-containing ring and/or R and R may together form a five- or six-membered nitrogen-containing ring; or R and R may together form a five- or six-membered nitrogen-containing ring;

or a pharmaceutically acceptable salt thereof;

with the proviso that at least three of R, R, R and R are not hydrogen, or if R and R are both hydrogen then R and R are not hydrogen, or if R and R are both hydrogen then R and R are not hydrogen.

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 the synthetic route of a compound of the general formula (IV), wherein Q is nitrogen.

Fig. 2 shows the synthetic route of a compound of the general formula (IV), wherein Q is carbon.

Fig. 3 shows specific examples of preferred compounds of the invention.

Figs. 4-10 show the synthetic route for selected preferred compounds of the invention.
DETAILED DESCRIPTION OF THE INVENTION

Definitions

In the present context, the term "Ci₆-alkyl" is intended to mean a linear or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, π-propyl, iso-propyl, π-butyl, /so-butyl, sec-butyl, ferf-butyl, π-pentyl, /so-pentyl, πeo-pentyl and π-hexyl, and the term "Ci₄-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-butoxy, sec-butoxy and ferf-butoxy.

Whenever the term "Ci₆-alkyl" is used herein, it should be understood that an interesting embodiment thereof is "Ci₄-alkyl". Most preferably, "Ci₆-alkyl" (and "Ci₄-alkyl") is methyl or ethyl, in particular methyl.

When used herein, the term "Cs₄-cycloalkyl" is intended to mean a cyclic hydrocarbon group having 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, the term "five- or six-membered cycloalkyl group" refers to cyclopentyl and cyclohexyl.

Similarly, the terms "C₂₆-alkenyl" and "C₄₆-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 "C₂₆-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 C₂₆-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 "C₂₆-alkynyl" is a di-yne or enedi-yne as is known to the person skilled in the art.

When used herein the term "Ci₆-alkoxy" is intended to mean Ci₆-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 "Ci₄-alkoxy" is intended to mean Ci₄-alkyl-oxy, e.g. methoxy, ethoxy, π-propoxy, /so-propoxy, π-butoxy, /so-butoxy, sec-butoxy and ferf-butoxy.
Whenever the term "Ci₆-alkoxy" is used herein, it should be understood that a particularly interesting embodiment thereof is "Ci₄-alkoxy". Most preferably, "Ci₆-alkoxy" (and "Ci₄-alkoxy") is methoxy or ethoxy, in particular methoxy.

Likewise, the term "C₂₆-alkenyl-oxy" is intended to mean C₂₆-alkenyl-oxy.

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

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), Ci₆-alkoxy, C₂₆-alkenylxy, carboxy, oxo (forming a keto or aldehyde functionality), Ci₆-alkoxycarbonyl, Ci₆-alkylcarbonyl, formyl, aryl, aryloxy-carbonyl, aryloxy, aminocarbonyl, heteroaryl, heteroarylamino, heteroaryloxy-carbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(Ci₆-alkyl)amino, carbamoyl, mono- and di(Ci₆-alkyl)aminocarbonyl, amino-Ci₆-alkyl-aminocarbonyl, mono- and di(Ci₆-alkyl)amino-Ci₆-alkyl-aminocarbonyl, Ci₆-alkylcarbonylaminocarbonyl, cyano, guanidino, carbamido, Ci₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, Ci₆-alkanoyloxy, Ci₆-alkyl-sulphonyl, Ci₆-alkyl-sulphinyl, Ci₆-alkyl-sulphonyloxy, nitro, Ci₆-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, Ci₆-alkoxy, C₂₆-alkenylxy, amino, mono- and di(Ci₆-alkyl)amino, carboxy, Ci₆-alkylcarbonylaminocarbonyl, halogen, Ci₆-alkylthio, Ci₆-alkyl-sulphonyl-amino 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), Ci₆-alkoxy (i.e. Ci₆-alkyl-oxo), C₂₆-alkenylxy, carboxy, oxo (forming a keto or aldehyde functionality), Ci₆-alkylcarbonyl, formyl, aryl, aryloxy, aminocarbonyl, heteroaryl, heteroarylamino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and (Ji(Ci₆-alkyl)amino; carbamoyl, mono- and di(Ci₆-alkyl)aminocarbonyl, amino-Ci₆-alkylaminocarbonyl, mono- and di(Ci₆-alkyl)amino-Ci₆-alkylaminocarbonyl, Ci₆-alkylaminocarbonyl, guanidino, carbamido, Ci₆-alkyl-sulphonyl-amino, Ci₆-alkyl-aminocarbonyl, Ci₆-alkyl-sulphinyl, Ci₆-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_6-alkoxy, C_2-alkenylhydroxy, amino, mono- and di(Ci-alkyl)amino, carboxyl, Ci-alkylcarboxyamino, halogen, Ci-alkylthio, Ci-alkyl-sulphonyl-amino and guanidine, in particular halogen. Thus, particularly preferred "optionally substituted Ci-alkyl" groups include halogen-substituted alkyl groups, such as trihalo-Ci-alkyl, such as tribromomethyl, trichloromethyl or trifluoromethyl. In a particular interesting embodiment trihalo-Ci-alkyl is trifluoromethyl.

The term "optionally substituted Ci-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-alkoxy (i.e. Ci-alkyl-oxy), C_2-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), Ci-alkoxycarbonyl, Ci-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, carbamoyl, mono- and di(Ci-alkyl)aminocarbonyl, amino-Ci-alkyl-aminocarbonyl, mono- and di(Ci-alkyl)aminocarbonyl, cyan group(s), guanidino, carbamido, Ci-alkyl-sulphonylamino, aryloxysulphonylamino, heteroaryl-sulphonylamino, Ci-alkanoyloxy, Ci-alkyl-sulphonyl, Ci-alkyl-sulphinyl, Ci-alkylsulphonyloxy, nitro, Cl-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-alkyl, Ci-alkoxy, C_2-alkenylhydroxy, carboxy, halogen or Ci-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, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl, xanthenyl, 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, thiencarbonylamino, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxazolyl, phthalazinyl, phthalanyl,
triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl, phenyl pyrrolyl and N-phenyl pyrrolyl.

Particularly interesting heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thiényl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl, phenyl pyrrolyl and N-phenyl pyrrolyl, in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thiényl, 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 "heterocycyl" 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 heterocycyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydrazepine, tetrahydrazepine, hexahydropyridazine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofurran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane and oxathiepane.

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

In connection with the terms "aryl", "heteroaryl", "cycloalkyl" and "heterocycyl", 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), Ci-6-alkyl, Ci-6-alkoxy, C2-6-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, Ci-6-alkoxycarbonyl, Ci-6-alkylcarbonyl, formyl, aryl, aryloxy, aroylamino, aryloxycarbonyl, aroylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(Ci-6-alkyl)amino; carbamoyl, mono- and di(Ci-6-alkyl)aminocarbonyl, amino-Ci-6-alkyl-aminocarbonyl, mono- and di(Ci-6-alkyl)amino-Ci-6-alkyl-aminocarbonyl, Ci-6-alkylaminocarbonylmino, cyano, guanidino, carbamido, Ci-6-alkanoyloxy, Ci-6-alkyl-sulphonyl-amino, aroyl-sulphonyl-amino, heteroaryl-sulphonyl-amino, Ci-6-
alkyl-suphonyl, \( \text{Ci-}_6\)-alkyl-sulphinyl, \( \text{Ci-}_6\)-alkyl-sulphonyloxy, nitro, sulphanyl, amino, aminosulfonyl, mono- and di(\( \text{Ci-}_6\)-alkyl)amino-sulfonyl, dihalogen-\( \text{Ci-}_4\)-alkyl, trihalogen-\( \text{Ci-}_4\)-alkyl and halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with \( \text{Ci-}_4\)-alkyl, \( \text{Ci-}_4\)-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, \( \text{Ci-}_6\)-alkoxy, \( \text{C}_2\text{e-}\)alkenyloxy, amino, mono- and di(\( \text{Ci-}_6\)-alkyl)amino, carboxy, \( \text{Ci-}_6\)-alkylcarbonylamino, halogen, \( \text{Ci-}_6\)-alkylthio, \( \text{Ci-}_6\)-alkyl-sulphonyl-amino, or guanidine.

Preferably, the above-mentioned substituents are selected from hydroxy, \( \text{Ci-}_6\)-alkyl, \( \text{Ci-}_6\)-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, \( \text{Ci-}_6\)-alkylcarbonyl, formyl, amino, mono- and di(\( \text{Ci-}_6\)-alkyl)amino; carbamoyl, mono- and di(\( \text{Ci-}_6\)-alkyl)aminocarbonyl, amino-\( \text{Ci-}_6\)-alkyl-aminocarbonyl, \( \text{Ci-}_6\)-alkylsulphonyl-amino, guanidine, carbamido, \( \text{Ci-}_6\)-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, \( \text{Ci-}_6\)-alkyl-sulphonyl, \( \text{Ci-}_6\)-alkylsulphonyloxy, \( \text{Ci-}_6\)-alkylcarbonylamino, halogen, \( \text{Ci-}_6\)-alkylthio, \( \text{Ci-}_6\)-alkyl-sulphonyl-amino or guanidine.

Especially preferred examples of such substituents are \( \text{Ci-}_6\)-alkyl, \( \text{Ci-}_6\)-alkoxy, amino, mono- and di(\( \text{Ci-}_6\)-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, \( \text{Ci-}_6\)-alkoxy, \( \text{C}_2\text{e-}\)alkenyloxy, amino, mono- and di(\( \text{Ci-}_6\)-alkyl)amino, carboxy, \( \text{Ci-}_6\)-alkylcarbonylamino, halogen, \( \text{Ci-}_6\)-alkylthio, \( \text{Ci-}_6\)-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 acids; typically hydrochloric, 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 and
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.

5 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)

![Chemical structure](image)

(Ia)

(Ib)
including tautomeric and isomeric forms thereof, wherein

\[ X \text{ is } \begin{pmatrix} \text{i} \end{pmatrix} \text{ and } i \text{ is } 0, 1 \text{ or } 2; \]

\[ Y \text{ is } \begin{pmatrix} \text{j} \end{pmatrix} \text{ and } j \text{ is } 0 \text{ or } 1; \]

wherein Q is nitrogen (N) or carbon (C), and u represents, together with Q and the carbon atom covalently linked to Q, an optionally substituted five- or six-membered heterocycl or cycloalkyl group;

\[ Z \text{ is } \begin{pmatrix} \text{k} \end{pmatrix} \text{ and } k \text{ is } 0, 1, 2 \text{ or } 3; \]

each Ri, R2, R3, R4, R5, R6, and R8 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 C2-6-alkenyloxy, carboxy, optionally substituted C1-6-alkoxy carbonyl, optionally substituted C1-6-alkylcarbonyl, optionally substituted C1-6-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted arylsulphonylamino, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxy carbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, optionally substituted heterocarbonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonylamino, optionally substituted heterocyclylsulphonylamino, amino, mono- and di(C1-6-alkyl)amino, carbamoyl, mono- and di(C1-6-alkyl)aminocarbonyl, amino-C1-6-alkylaminocarbonyl, mono- and di(C1-6-alkyl)amino-C1-6-alkylaminocarbonyl, C1-6-alkylcarbonylamino, amino-C1-6-alkylcarbonylamino, mono- and di(C1-6-alkyl)amino-C1-6-alkyl-carbonylamino, amino-C1-6-alkylcarbonylamino, carbamido, C1-6-alkanoyloxy, C1-6-alkysulphonyl, C1-6-alkylsulphynil, C1-6-alkylsulphonyl-.
oxy, aminosulfonyl, mono- and di(Ci-6-alkyl)aminosulfonyl, nitro, optionally substituted Ci-6-alkylthio and halogen,

where any nitrogen-bound Ci-6-alkyl is optionally substituted with hydroxy, Ci-6-alkoxy, C2-6-alkenyloxy, amino, mono- and di(Ci-6-alkyl)amino, carboxy, Ci-6-alkylcarbonylamino, halogen, Ci-6-alkylthio, Ci-6-alkyl-sulphonyl-amino or guanidine;

each Rb, Ri0, Rn and Rs2 is independently selected from the group consisting of hydrogen, 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 aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, 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 R0

and Ri0 may together form a five- or six-membered nitrogen-containing ring and/or Rn and Ri2 may together form a five- or six-membered nitrogen-containing ring; or Rb and Rn may together form a five- or six-membered nitrogen-containing ring;

or a pharmaceutically acceptable salt thereof;

with the proviso that at least three of Rb, Ri0, Rn and Rs2 are not hydrogen, or if Rb and Ri0 are both hydrogen then Rn and Rs2 are not hydrogen, or if Rn and Rs2 are both hydrogen then Rb and Ri0 are not hydrogen.

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. Although attachment of the aminoguanidine substituent to the pyrrole ring at position 2 is currently preferred, 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 described herein are typically shown in their trans isomeric forms. It should be understood, however, that the compounds described herein may also be in their cis isomeric form. Thus, the configuration around a double bond in a molecule described herein 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, provided that at least one of \( R_9, R_10, R_n \) and \( R_{12} \) is hydrogen, exist in various tautomeric forms. 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.

Moreover, when \( j = 1 \) further isomers will be possible. With respect to \( Q \), which forms part of the ring system present in the aminoguanidine substituent, this atom may be a carbon atom or a nitrogen atom, i.e. \( u \) represents, together with \( Q \) and the carbon atom covalently linked to \( Q \), an optionally substituted five- or six-membered heterocyclyl or cycloalkyl group. As will be understood, the molecule contains, in case \( Q \) is nitrogen, a single asymmetric carbon atom. Thus, in this embodiment of the invention the molecule of invention may be either in its enantiomeric S-form, its enantiomeric R-form, or the molecule of the invention may be a racemic mixture. Likewise, the molecule contains, in case \( Q \) is carbon, two asymmetric carbon atoms. Thus, in this embodiment of the invention the molecule of invention may be either in its SS-form, its RR-form, its SR-form, its RS-form, or any mixture thereof.

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, ethandioic acid, propanedioic acid, butanedioic acid, (Z)-2-butenedioic acid, (E)-butenedioic acid, 2-hydroxybutenedioic acid, 2,3-dihydroxybutenedioic acid, 2-hydroxy-1,2,3-propanetricarboxylic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, cyclohexanesulfamic acid, 2-hydroxybenzoic acid, 4-aminoo-2-hydroxybenzoic acid, and other acids known to the person skilled in the art.

The substituents \( R_1, R_2, R_3, R_4, R_5, R_6, R_7 \) and \( R_8 \)
The substituents on the phenyl-pyrrole ring system will be discussed in the following. It should be understood that all statements made in the following concerning preferred
substituents is independent of the presence or absence of A, B and C (cf. formula (I)) and the actual values of i, j and k.

The substituents \( R_1, R_2, R_3, R_4, R_5, R_6, R_7 \) and \( R_8 \) may be individually selected from the group of substituents indicated above, cf. formula (I). However, in a preferred embodiment of the invention each \( R_1, R_2, R_3, R_4, R_5, R_6, R_7 \) and \( R_8 \) is independently selected from the group consisting of hydrogen, optionally substituted \( \text{Ci}-6\text{-alkyl} \), optionally substituted \( \text{C}2\text{-alkenyl} \), optionally substituted \( \text{C}2\text{-alkynyl} \), hydroxy, optionally substituted \( \text{Ci}-6\text{-alkoxy} \), optionally substituted \( \text{C}2\text{-alkenyl} \), carboxy, optionally substituted \( \text{Ci}-6\text{-alkoxycarbonyl} \), optionally substituted \( \text{Ci}-6\text{-alkylcarbonyl} \), formyl, amino, mono- and di(\( \text{Ci}-6\text{-alkyl} \))amino, carbamoyl, mono- and di(\( \text{Ci}-6\text{-alkyl} \))aminocarbonyl, "amino-\( \text{Ci}-6\text{-alkyl} \)aminocarbonyl", mono- and di(\( \text{Ci}-6\text{-alkyl} \))amino-\( \text{Ci}-6\text{-alkyl} \)-aminocarbonyl, \( \text{Ci}-6\text{-alkylcarbonylamino} \), amino-\( \text{Ci}-6\text{-alkyl} \)-carbonylamino, mono- and di(\( \text{Ci}-6\text{-alkyl} \))amino-\( \text{Ci}-6\text{-alkyl} \)-carbonylamino, cyano, carbamido, \( \text{Ci}-6\text{-alkanoyloxy} \), \( \text{Ci}-6\text{-alkylsulphonyl} \), \( \text{Ci}-6\text{-alkylsulphonyl} \), \( \text{ox} \), aminosulfonyl, mono- and di(\( \text{Ci}-6\text{-alkyl} \))aminosulfonyl, nitro, optionally substituted \( \text{Ci}-6\text{-alkythio} \) and halogen.

In a more preferred embodiment of the invention each \( R_1, R_2, R_3, R_4, R_5, R_6, R_7 \) and \( R_8 \) is independently selected from the group consisting of hydrogen, optionally substituted \( \text{C}1\text{-6} \)-alkyl, optionally substituted \( \text{C}2\text{-alkenyl} \), hydroxy, optionally substituted \( \text{C}6\text{-alkoxy} \), amino, cyano, nitro and halogen, such as bromo, chloro and fluoro. Specific examples of highly preferred (non-substituted) \( \text{C}6\text{-alkyl} \) groups include \( \text{C}1\text{-4} \)-alkyl, such as methyl or ethyl, in particular methyl. Specific examples of highly preferred substituted \( \text{C}6\text{-alkyl} \) groups include substituted \( \text{C}1\text{-4} \)-alkyl, such as halogen-substituted \( \text{C}1\text{-4} \)-alkyl, e.g. trihalo-\( \text{C}1\text{-4} \)-alkyl, in particular tribromomethyl, trichloromethyl and trifluoromethyl among which trichloromethyl and trifluoromethyl are particularly preferred. Specific examples of highly preferred (non-substituted) \( \text{C}2\text{-4} \)-alkenyl groups include \( \text{C}2\text{-4} \)-alkenyl, such as vinyl, allyl and butenyl, in particular allyl. Specific examples of highly preferred (non-substituted) \( \text{C}6\text{-alkoxy} \) groups include \( \text{Ci}-6\text{-alkoxy} \), such as methoxy or ethoxy, in particular methoxy.

In an interesting embodiment of the invention, the invention relates to compounds of the general formula (I), wherein \( R_8 \) is hydrogen. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (Ic):
It should be understood that all statements made herein concerning preferred embodiments of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $X$, $Y$ and $Z$ also apply to the compounds of the general formula (Ic).

In a further interesting embodiment of the invention, the invention relates to compounds of the general formula (I), wherein $R_5$ and $R_8$ are hydrogen. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (Id):

It should be understood that all statements made herein concerning preferred embodiments of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $X$, $Y$ and $Z$ also apply to the compounds of the general formula (Id).

In a yet further embodiment of the invention, the invention relates to compounds of the general formula (I), wherein $R_4$, $R_5$ and $R_8$ are hydrogen. Thus, according to this
embodiment of the invention, the compound of the invention has the structure shown in the general formula (le):

\[
\begin{array}{c}
\text{\(R_1\)} \\
\text{\(R_2\)}
\end{array}
\begin{array}{c}
\text{\(R_3\)} \\
\text{\(N\)}
\end{array}
\begin{array}{c}
\text{\(X\)} \\
\text{\(Y\)} \\
\text{\(Z\)}
\end{array}
\begin{array}{c}
\text{\(N\)} \\
\text{\(N\)} \\
\text{\(R_{11}R_{12}\)}
\end{array}
\begin{array}{c}
\text{\(NR_{10}R_{10}\)}
\end{array}
\]

(\text{\textit{le}})

It should be understood that all statements made herein concerning preferred embodiments of \(R_i, R_2, R_3, R_e, R_7, R_9, R_{10}, R_{12}, X, Y\) and \(Z\) also apply to the compounds of the general formula (\textit{le}).

In another embodiment of the invention, the invention relates to compounds of the general formula (\textit{f}), wherein \(R_4, R_5, R_7\) and \(R_9\) are hydrogen. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (\textit{ff}):

\[
\begin{array}{c}
\text{\(R_1\)} \\
\text{\(R_2\)}
\end{array}
\begin{array}{c}
\text{\(R_3\)} \\
\text{\(N\)}
\end{array}
\begin{array}{c}
\text{\(X\)} \\
\text{\(Y\)} \\
\text{\(Z\)}
\end{array}
\begin{array}{c}
\text{\(N\)} \\
\text{\(N\)} \\
\text{\(NR_{10}R_{10}\)}
\end{array}
\begin{array}{c}
\text{\(NR_{11}R_{12}\)}
\end{array}
\]

(\text{\textit{ff}})

It should be understood that all statements made herein concerning preferred embodiments of \(R_i, R_2, R_3, R_e, R_7, R_9, R_{10}, R_{12}, X, Y\) and \(Z\) also apply to the compounds of the general formula (\textit{ff}).
In still another embodiment of the invention, the invention relates to compounds of the general formula (I), wherein \( R_3, R_4, R_5, R_7 \) and \( R_8 \) are hydrogen. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (Ig):

\[
\begin{align*}
& \text{NR}_{10}R_{10} \\
& \text{NR}_{11}R_{12}
\end{align*}
\]

(Ig)

It should be understood that all statements made herein concerning preferred embodiments of \( R_i, R_2, R_e, R_9, R_0, R_n, R_{12}, X, Y \) and \( Z \) also apply to the compounds of the general formula (Ig).

In yet another embodiment of the invention, the invention relates to compounds of the general formula (I), wherein \( R_3, R_4, R_5, R_6, R_7 \) and \( R_8 \) are hydrogen. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (Ih):

\[
\begin{align*}
& \text{NR}_{10}R_{10} \\
& \text{NR}_{11}R_{12}
\end{align*}
\]

(Ih)
It should be understood that all statements made herein concerning preferred embodiments of $R_i$, $R_2$, $R_g$, $R_{i0}$, $R_n$, $R_{i2}$, $X$, $Y$, and $Z$ also apply to the compounds of the general formula (Ih).

Concerning the compounds described above in connection with the general formulae (Ia)-(Ih) 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 (Ih) above, the attachment of the $R_i$ and $R_2$ may be as follows: In one embodiment of the invention is $R_i$ located in the 2-position and $R_2$ is located in the 3-position. In another embodiment of the invention is $R_i$ located in the 2-position and $R_2$ is located in the 4-position. In yet another embodiment of the invention is $R_i$ located in the 2-position and $R_2$ is located in the 5-position. In a further embodiment of the invention is $R_i$ located in the 2-position and $R_2$ is located in the 6-position. In a still further embodiment of the invention is $R_i$ is located in the 3-position and $R_2$ is located in the 4-position. In an even further embodiment of the invention is $R_i$ located in the 3-position and $R_2$ is located in the 5-position. In yet another embodiment of the invention is $R_i$ located in the 3-position and $R_2$ is located in the 6-position.

In an even further embodiment of the invention, the invention relates to compounds of the general formula (I), wherein $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$ and $R_8$ are hydrogen. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (II):

$$\begin{align*}
\begin{array}{c}
\text{NR}_9\text{R}_{10} \\
\text{NR}_{11}\text{R}_{12}
\end{array}
\end{align*}$$

(ii)

It should be understood that all statements made herein concerning preferred embodiments of $R_i$, $R_g$, $R_{i0}$, $R_n$, $R_{i2}$, $X$, $Y$, and $Z$ also apply to the compounds of the general formula (II). In one embodiment of the invention is $R_i$ located in the 2-position. In another embodiment of the invention is $R_i$ located in the 3-position. In a third embodiment
of the invention is $R_4$ located in the 4-position. In a preferred embodiment, the invention relates to compounds of formula (ii), wherein $R_l$ is a halogen selected from the group of chloro and bromo. In another preferred embodiment, the invention relates to compounds of formula (ii), wherein $R_l$ is chloro. In yet a preferred embodiment, the invention relates to compounds of formula (ii), wherein $R_l$ is chloro located in the 4-position. In still another embodiment, the invention relates to compounds of formula (ii), wherein $R_l$ is bromo. In still another embodiment, the invention relates to compounds of formula (ii), wherein $R_l$ is bromo located in the 2-position. In yet another embodiment, the invention relates to compounds of formula (ii), wherein $R_l$ is trihalo-C$_l$-alkyl, such as trifluoromethyl. In a further embodiment, the invention relates to compounds of formula (ii), wherein $R_l$ is trihalo-C$_l$-alkyl, such as trifluoromethyl, located in the 4-position.

In an even further interesting embodiment of the invention all of $R_l,$ $R_2,$ $R_3,$ $R_4,$ $R_5,$ $R_6,$ $R_7$ and $R_8$ are hydrogen, i.e. in an even further embodiment of the invention, the invention relates to compounds of the general formula (i), wherein $R_{11},$ $R_{12},$ $R_4,$ $R_5,$ $R_6,$ $R_7,$ $R_8,$ $R_9$ and $R_{10}$ are all hydrogen. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (i):

\[\text{(i)}\]

It should be understood that all statements made herein concerning preferred embodiments of $R_{11},$ $R_{12},$ $R_9$, $R_{10},$ $R_n,$ $R_{11}$, $X,$ $Y$ and $Z$ also apply to the compounds of the general formula (i).

25 **The substituents $R_9,$ $R_{10},$ $R_n$ and $R_{12}$**

The substituents on the amino groups of the aminoguanidine substituent will be discussed in the following. It should be understood that all statements made in the following concerning preferred substituents is independent of the presence or absence of $X,$ $Y$ and $Z$ (cf. formula (i)) and the actual values of $i,$ $j$ and $k.$
As discussed previously, the substituents $R_b$, $R_i^0$, $R_n$ and $R_{12}$ may be individually selected from the group consisting of hydrogen, optionally substituted C$_{1-6}$-alkyl, optionally substituted C$_{2-6}$-alkenyl, optionally substituted C$_{4-6}$-alkadienyl, optionally substituted C$_{2-6}$-alkynyl, optionally substituted C$_{1-6}$-alkoxycarbonyl, optionally substituted C$_{1-6}$-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy carbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy carbonyl, optionally substituted heteroarylc arboxyl, aminocarbonyl, mono- and di(C$_{1-6}$-alkyl)aminocarbonyl, amino-C$_{1-6}$-alkyl-aminocarbonyl and mono- and di(C$_{1-6}$-alkyl)aminocarbonyl; or $R_b$ and $R_i^0$ may together form a five- or six-membered nitrogen-containing ring and/or $R_n$ and $R_{12}$ may together form a five- or six-membered nitrogen-containing ring; or $R_b$ and $R_n$ may together form a five- or six-membered nitrogen-containing ring;

with the proviso that at least three of $R_b$, $R_i^0$, $R_n$ and $R_{12}$ are not hydrogen, or if $R_b$ and $R_i^0$ are both hydrogen then $R_n$ and $R_{12}$ are not hydrogen, or if $R_n$ and $R_{12}$ are both hydrogen then $R_b$ and $R_i^0$ are not hydrogen.

Preferably, each $R_b$, $R_i^0$, $R_n$ and $R_{12}$ is independently selected from the group consisting of hydrogen, optionally substituted C$_{1-6}$-alkyl, optionally substituted C$_{2-6}$-alkenyl, optionally substituted C$_{2-6}$-alkynyl, optionally substituted aryl and optionally substituted heteroaryl; with the proviso that at least three of $R_b$, $R_i^0$, $R_n$ and $R_{12}$ are not hydrogen, or if $R_b$ and $R_i^0$ are both hydrogen then $R_n$ and $R_{12}$ are not hydrogen, or if $R_n$ and $R_{12}$ are both hydrogen then $R_b$ and $R_i^0$ are not hydrogen. More preferably, each $R_b$, $R_i^0$, $R_n$ and $R_{12}$ is independently hydrogen or optionally substituted C$_{1-6}$-alkyl, preferably optionally substituted C$_{1-6}$-alkyl; with the proviso that at least three of $R_b$, $R_i^0$, $R_n$ and $R_{12}$ are not hydrogen, or if $R_b$ and $R_i^0$ are both hydrogen then $R_n$ and $R_{12}$ are not hydrogen, or if $R_n$ and $R_{12}$ are both hydrogen then $R_b$ and $R_i^0$ are not hydrogen.

In one embodiment of the invention all of $R_b$, $R_i^0$, $R_n$ and $R_{12}$ are different from hydrogen, i.e. in one embodiment of the invention, the invention relates to compounds of the general formula (I), wherein each $R_b$, $R_i^0$, $R_n$ and $R_{12}$ is optionally substituted C$_{1-6}$-alkyl.

Preferably, each $R_b$, $R_i^0$, $R_n$ and $R_{12}$ is independently methyl or ethyl. More preferably, $R_b$, $R_i^0$, $R_n$ and $R_{12}$ are methyl or ethyl, in particular methyl. Thus, according to this embodiment of the invention, the compound of the invention may have the structures shown in the general formulae (I(k)-(l)):
It should be understood that all statements made herein concerning preferred embodiments of $R_i$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $X$, $Y$ and $Z$ also apply to the compounds of the general formulae (I)-(I0).

In another, and preferred, embodiment of the invention, $R_9$ is hydrogen and each $R_{i0}$, $R_n$ and $R_{i2}$ is independently hydrogen or optionally substituted $C_i$-$alkyl$, preferably optionally substituted $C_i$-$alkyl$; with the proviso that $R_{i0}$, $R_n$ and $R_{i2}$ are not hydrogen, or if $R_{i0}$ is hydrogen then $R_n$ and $R_{i2}$ are not hydrogen.

In one embodiment of this particular aspect $R_9$ is hydrogen and each $R_{i0}$, $R_n$ and $R_{i2}$ are different from hydrogen, i.e. in one embodiment of the invention, the invention relates to compounds of the general formula (I), wherein $R_9$ is hydrogen and $R_{i0}$, $R_n$ and $R_{i2}$ are optionally substituted $C_i$-$alkyl$. Preferably, each $R_{i0}$, $R_n$ and $R_{i2}$ is independently methyl or ethyl. More preferably, $R_{i0}$, $R_n$ and $R_{i2}$ are methyl or ethyl, in particular methyl. Thus, according to this embodiment of the invention, the compound of the invention may have the structures shown in the general formulae (Ip) and (Ir):
It should be understood that all statements made herein concerning preferred embodiments of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, ..., of the invention, the compound of the invention may have the structures shown in the general formulae (Ip) and (Ir).

In another embodiment of this particular aspect $R_9$ and $R_{10}$ are hydrogen and $R_n$ and $R_{12}$ are different from hydrogen, such as optionally substituted $C_{6}$-alkyl, preferably optionally substituted $C_{4}$-alkyl. Therefore, in one embodiment of the invention, the invention relates to compounds of the general formula (I), wherein $R_9$ and $R_{10}$ are hydrogen and $R_n$ and $R_{12}$ are optionally substituted $C_{4}$-alkyl. Preferably, each $R_n$ and $R_{12}$ is independently methyl or ethyl. More preferably, $R_n$ and $R_{12}$ are methyl or ethyl, in particular methyl. Thus, according to this embodiment of the invention, the compound of the invention may have the structures shown in the general formulae (Is) and (It):
It should be understood that all statements made herein concerning preferred embodiments of $R_i$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $X$, $Y$ and $Z$ also apply to the compounds of the general formulae (Is) and (It).

In a similar, and also preferred, embodiment of the invention, $R_n$ is hydrogen and each $R_9$, $R_{10}$ and $R_{12}$ is independently hydrogen or optionally substituted $C_1$-$C_6$-alkyl, preferably optionally substituted $C_1$-$C_4$-alkyl; with the proviso that $R_9$, $R_{10}$ and $R_{12}$ are not hydrogen, or if $R_{12}$ is hydrogen then $R_9$ and $R_{10}$ are not hydrogen.

In one embodiment of this particular aspect $R_n$ is hydrogen and each $R_9$, $R_{10}$ and $R_{12}$ are different from hydrogen, i.e. in one embodiment of the invention, the invention relates to compounds of the general formula (I), wherein $R_n$ is hydrogen and $R_9$, $R_{10}$ and $R_{12}$ are optionally substituted $C_1$-$C_4$-alkyl. Preferably, each $R_9$, $R_{10}$ and $R_{12}$ is independently methyl or ethyl. More preferably, $R_9$, $R_{10}$ and $R_{12}$ are methyl or ethyl, in particular methyl. Thus,
according to this embodiment of the invention, the compound of the invention may have the structures shown in the general formulae (Iu) and (Iv):

![Diagram of chemical structure](image)

It should be understood that all statements made herein concerning preferred embodiments of $R_i$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $X$, $Y$ and $Z$ also apply to the compounds of the general formulae (Iu) and (Iv).

In another embodiment of this particular aspect, $R_n$ and $R_{12}$ are hydrogen and $R_9$ and $R_{10}$ are different from hydrogen, such as optionally substituted $C_{1-6}$-alkyl, preferably optionally substituted $C_{1-4}$-alkyl. Therefore, in one embodiment of the invention, the invention relates to compounds of the general formula (I), wherein $R_n$ and $R_{12}$ are hydrogen and $R_9$ and $R_{10}$ are optionally substituted $C_{1-4}$-alkyl. Preferably, each $R_9$ and $R_{10}$ is independently methyl or ethyl. More preferably, $R_9$ and $R_{10}$ are methyl or ethyl, in particular methyl. Thus,
according to this embodiment of the invention, the compound of the invention may have the structures shown in the general formulae (Iw) and (Ix):

![Diagram of compound (Iw)](image1)

It should be understood that all statements made herein concerning preferred embodiments of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $X$, $Y$, and $Z$ also apply to the compounds of the general formulae (Iw) and (Ix).

The $X$, $Y$, and $Z$ moieties

The $X$, $Y$, and $Z$ moieties will be discussed in the following. It should be understood that all previous statements made herein concerning preferred embodiments of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, and $R_{16}$ also apply to the following section.

As discussed previously, the moieties $X$, $Y$, and $Z$ may be as follows:
X is \( (\text{atom}) \) and \( i \) is 0, 1 or 2;

\[
Y \text{ is } (\text{atom}) \quad \text{and } j \text{ is 0 or 1;}
\]

wherein \( Q \) is nitrogen (N) or carbon (C), and \( u \) represents, together with \( Q \) and the carbon atom covalently linked to \( Q \), an optionally substituted five- or six-membered heterocyclyl or cycloalkyl group;

\[
Z \text{ is } (\text{atom}) \quad \text{and } k \text{ is 0, 1, 2 or 3.}
\]

10 The embodiment where \( Y \) and \( Z \) are absent (\( j=0 \) and \( k=0 \))

In one interesting embodiment of the invention, \( Y \) and \( Z \) are absent, i.e. \( j=0 \) and \( k=0 \).

Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (II):

\[
\text{(II)}
\]

wherein \( i \) is 0, 1 or 2, and \( R_i \), \( R_2 \), \( R_3 \), \( R_4 \), \( R_5 \), \( R_6 \), \( R_7 \), \( R_8 \), \( R_9 \), \( R_{10} \), \( R_{11} \), \( R_{12} \) are as discussed above. It should be understood that all statements made herein concerning preferred embodiments of \( R_i \), \( R_2 \), \( R_3 \), \( R_4 \), \( R_5 \), \( R_6 \), \( R_7 \), \( R_8 \), \( R_9 \), \( R_{10} \), \( R_{11} \), \( R_{12} \) also apply to the compounds of the general formula (II).
The aminoguanidine substituent may be attached to the pyrrole ring at its position 2 or 3, i.e. the compounds of the general formula (Ha) and (lib), cf. below, merely differ from each other by the site of attachment to the pyrrole ring.

Accordingly, the present invention relates to a compound of the general formula (Ha) or (lib)

![Diagram](image1)

wherein i is 0, 1 or 2, and R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 are as discussed above. It should be understood that all statements made herein concerning preferred embodiments of R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12 also apply to the compounds of the general formulae (Ha) and (lib).
In a preferred embodiment of the invention, X is absent, i.e. \( i=0 \). Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (lie):

\[
\begin{align*}
R_1 &\quad R_2 &\quad R_3 &\quad R_4 \\
&\quad R_5 &\quad R_6 &\quad R_7 &\quad R_8 &\quad R_9 &\quad R_{10} \\
N &\quad N &\quad \text{NR}_{11} &\quad \text{R}_{12}
\end{align*}
\]

wherein \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) are as discussed above. It should be understood that all statements made herein concerning preferred embodiments of \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) also apply to the compounds of the general formula (lie), i.e. in preferred embodiments of the invention, the compound of the general formula (He) has the structure shown in the general formulae (Hd)-(Ilp):

\[
\begin{align*}
R_1 &\quad R_2 &\quad R_3 &\quad R_4 \\
&\quad R_5 &\quad R_6 &\quad R_7 &\quad R_8 &\quad R_{11} &\quad \text{N(CH}_3)_2 \\
N &\quad N &\quad \text{N(CH}_3)_2
\end{align*}
\]
It should be understood that all statements made herein concerning preferred embodiments of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ also apply to the compounds of the general formulae (Hd)-(IIp).

The embodiment where $X$ and $Y$ are absent ($i=0$ and $j=0$)

In another interesting embodiment of the invention, $X$ and $Y$ are absent, i.e. $i=0$ and $j=0$. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (III):
wherein \( k \) is 1, 2 or 3, and \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_10, R_n \) and \( R_{12} \) are as discussed above. It should be understood that all statements made herein concerning preferred embodiments of \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_n \), \( R_{12} \) also apply to the compounds of the general formula (III).

The aminoguanidine substituent may be attached to the pyrrole ring at its position 2 or 3, i.e. the compounds of the general formula (IIia) and (HIb), cf. below, merely differ from each other by the site of attachment to the pyrrole ring.

Accordingly, the present invention relates to a compound of the general formula (IIia) or (HIb)

and

(IIIa)
wherein \( k \) is 1, 2 or 3, and \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) are as discussed above. It should be understood that all statements made herein concerning preferred embodiments of \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) also apply to the compounds of the general formulae (IIia) and (IIib).

In a preferred embodiment of the invention \( k=1 \). Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (IIIc):

wherein \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_{10}, R_{11}, R_{12} \) are as discussed above. It should be understood that all statements made herein concerning preferred embodiments of \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_{10}, R_{11}, R_{12} \) also apply to the compounds of the general
formula (IIIc), i.e. in preferred embodiments of the invention, the compound of the general formula (IIIc) has the structure shown in the general formulae (HId)-(IIIp):

(MId)

(IIIe)
It should be understood that all statements made herein concerning preferred embodiments of Ri, R2, R3, R4, R5, Re, R7, and R8 also apply to the compounds of the general formulae (HId)-(IIIp).

The embodiment where Y is present (j=1)
In still another interesting embodiment of the invention, Y is present, i.e. j = 1. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (IV):

wherein k, i, Q, u, Ri, R2, R3, R4, R5, Re, R7, R9, R10, R11, R12 are as discussed above.

It should be understood that all statements made herein concerning preferred embodiments of Ri, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, Rn and R12 also apply to the compounds of the general formula (IV).
The aminoguanidine substituent may be attached to the pyrrole ring at its position 2 or 3, i.e. the compounds of the general formula (IVa) and (IVb), cf. below, merely differ from each other by the site of attachment to the pyrrole ring.

Accordingly, the present invention relates to a compound of the general formula (IVa) or (IVb)

\[
\text{(IVa)}
\]

and

\[
\text{(IVb)}
\]

wherein \(k, i, Q, u, R_i, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_n\) and \(R_{12}\) are as discussed above.

It should be understood that all statements made herein concerning preferred embodiments of \(R_i, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}\) also apply to the compounds of the general formulae (IVa) and (IVb).
As indicated above, \( i = 0, 1 \) or \( 2 \). In a preferred embodiment, \( i=0 \), i.e. according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (IVc):

![Diagram of structure (IVc)]

wherein \( k, Q, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) are as discussed above. It should be understood that all statements made herein concerning preferred embodiments of \( k, Q, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) also apply to the compounds of the general formula (IVc).

As also indicated previously, \( k = 0, 1, 2 \) or \( 3 \). In a preferred embodiment, \( k=0 \), i.e. according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (IVd):

![Diagram of structure (IVd)]

wherein \( i, Q, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) are as discussed above. It should be understood that all statements made herein concerning preferred embodiments
of \( i, Q, R_i, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) also apply to the compounds of the general formula (IVd).

Based on the above discussion of compounds having the general formulae (IVc) and (IVd), it will be understood, that compounds which are particularly preferred according to this embodiment of the invention has the general formula (IVe):

\[
\text{(IVe)}
\]

wherein \( Q, R_i, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) are as discussed above. It should be understood that all statements made herein concerning preferred embodiments of \( Q, R_i, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) also apply to the compounds of the general formula (IVe).

Concerning \( Q \), which forms part of the ring system present in the aminoguanidine substituent, this atom may be a carbon atom or a nitrogen atom, i.e. \( u \) represents, together with \( Q \) and the carbon atom covalently linked to \( Q \), an optionally substituted five- or six-membered heterocyclyl or cycloalkyl group. As will be understood, the molecule contains, in case \( Q \) is nitrogen, a single asymmetric carbon atom. Thus, in this embodiment of the invention the molecule of invention may be in either its enantiomeric S-form, its enantiomeric R-form, or the molecule of the invention may be a racemic mixture. Likewise, the molecule contains, in case \( Q \) is carbon, two asymmetric carbon atoms. Thus, in this embodiment of the invention the molecule of invention may be in either its SS-form, its RR-form, its SR-form, its RS-form, or any mixture thereof.

In an interesting embodiment, \( Q \) is carbon (C). Accordingly, in an interesting embodiment of the invention the compounds disclosed and discussed herein (where \( Y \) is present, i.e. where \( j = 1 \)) contains a ring system wherein \( u \) together with \( Q \) and the carbon atom
covalently linked to Q represents an optionally substituted five- or six-membered cycloalkyl group.

In one embodiment, the optionally substituted six-membered cycloalkyl group has the following chemical structure:

![Chemical structure diagram](image)

wherein each of $R_{i3}$, $R_{i4}$, $R_{i5}$, and $R_{i6}$ is independently selected from the group consisting of hydrogen, optionally substituted $C_{6}$-alkyl, optionally substituted $C_{3-6}$-cycloalkyl, optionally substituted $C_{2-6}$-alkenyl, optionally substituted $C_{2-6}$-alkadienyl, optionally substituted $C_{2-6}$-alkynyl, hydroxy, optionally substituted $C_{6}$-alkoxy, carboxy, optionally substituted $C_{6}$-alkoxycarbonyl, optionally substituted $C_{6}$-alkylcarbonyl, optionally substituted $C_{6}$-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, or guanidine.

Preferably, each of $R_{i3}$, $R_{i4}$, $R_{i5}$, and $R_{i6}$ is independently selected from the group consisting of hydrogen, optionally substituted $C_{6}$-alkyl, optionally substituted $C_{2-6}$-alkenyl,
optionally substituted C$_2$-$6$-alkynyl, hydroxy, optionally substituted C$_1$-$6$-alkoxy, optionally substituted C$_2$-$6$-alkenyl, carboxy, optionally substituted C$_1$-$6$-alkoxycarbonyl, optionally substituted C$_1$-$6$-alkylcarbonyl, formyl, amino, mono- and di(Ci-$6$-alkyl)amino, carbamoyl, mono- and di(Ci-$6$-alkyl)aminocarbonyl, amino-Ci-$6$-alkyl-aminocarbonyl, mono- and di(Ci-$6$-alkyl)amino-Ci-$6$-alkyl-aminocarbonyl, C$_2$-$6$-alkylcarbonylamino, amino-Ci-$6$-alkyl-carbonylamino, mono- and di(Ci-$6$-alkyl)amino-Ci-$6$-alkyl-carbonylamino, cyano, carbamido, C$_2$-$6$-alkanoyloxy, C$_2$-$6$-alkylsulphonyl, C$_3$-$6$-alkylsulphinyl, C$_2$-$6$-alkylsulphonyleoxy, aminosulfonyl, mono- and di(Ci-$6$-alkyl)aminosulfonyl, nitro, optionally substituted Ci-$6$-alkylthio and halogen.

More preferably, each of R$_3$, R$_4$, R$_5$, and R$_6$ is independently selected from the group consisting of hydrogen, optionally substituted Ci-$6$-alkyl, optionally substituted C$_2$-$6$-alkenyl, hydroxy, optionally substituted Ci-$6$-alkoxy, amino, cyano, nitro and halogen. In a particular interesting embodiment of the invention all of R$_3$, R$_4$, R$_5$, and R$_6$ are hydrogen.

In another embodiment of the invention u represents, together with Q and the carbon atom covalently linked to Y, an optionally substituted five-membered cycloalkyl group as illustrated below:

![Diagram](image)

wherein each of R$_{13}$, R$_{14}$ and R$_{15}$ is as defined above. Again, in a particular interesting embodiment of the invention all of R$_{13}$, R$_{14}$ and R$_{15}$ are hydrogen.

In a preferred embodiment of the invention Q is nitrogen (N), i.e. u represents, together with Q and the carbon atom covalently linked to Q, an optionally substituted five- or six-membered heterocyclyl group. Any of the heterocyclyl groups mentioned in connection with the definition of this term may be used for this purpose. However, in one embodiment of the invention u represents, together with Q and the carbon atom covalently linked to Q, an optionally substituted six-membered heterocyclyl group as illustrated below:
wherein each of $R_{i3}$, $R_{i4}$, $R_{i5}$, and $R_{i6}$ is as defined above. Also in this embodiment of the invention is it preferred that all of $R_{i3}$, $R_{i4}$, $R_{i5}$ and $R_{i6}$ are hydrogen.

In an even more preferred embodiment of the invention, $u$ represents, together with $Q$ and the carbon atom covalently linked to $Q$, an optionally substituted five-membered heterocyclic group as illustrated below:

wherein each of $R_{i3}$, $R_{i4}$ and $R_{i5}$ are as defined above. In the most preferred embodiment of the invention, all of $R_{i3}$, $R_{i4}$ and $R_{i5}$ are hydrogen.

Based on the above disclosure, it will be understood that in preferred embodiments of this aspect of the invention, the compound of the general formula (IV) has the structure shown in the general formulae (IVf)-(IVr):

(IVf)
It should be understood that all statements made herein concerning preferred embodiments of \( i, k, R_1, R_2, R_3, R_4, R_5, R_6, R_7, \) and \( R_8 \) also apply to the compounds of the general formulae (IVf)-(IVr). In a highly preferred embodiment, \( i=k=0 \) in all of the above formulae (IVf)-(IVr). It is furthermore preferred that \( Q \) is nitrogen (N). In particular, it is preferred that \( u \) represents, together with \( Q \) and the carbon atom covalently linked to \( Q \), an optionally substituted five- or six-membered heterocyclyl group, preferably an optionally substituted five-membered heterocyclyl group.

Methods of preparing the compounds of the invention
The compounds of the invention may be prepared by standard methods known to the skilled organic chemist. In general, a compound of the general formula (I) above may be prepared essentially as described in WO 03/013509.
More particularly, a compound of the general formula (II).

![Chemical Structure](image)

wherein \( i \) is 0, 1 or 2, and \( R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10}, R_{11}, \) and \( R_{12} \) are as discussed above, may be prepared by reacting an aldehyde of the general formula A.

![Chemical Structure](image)

wherein \( i \) is 0, 1 or 2, and \( R_1, R_2, R_3, R_4, R_5, R_7, R_8 \) are as discussed above, with an aminoguanidine derivative of the general formula B.

![Chemical Structure](image)
wherein $R_9$, $R_{10}$, $R_n$ and $R_2$ are as discussed above, in a suitable organic solvent.

Preferably, a compound of the general formula A 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 A is reacted with a thiosemicarbazide of the general formula C

\[
\begin{align*}
\text{C} & : \quad \text{H}_2\text{N} \quad \text{N} \quad \text{NR}_9\text{R}_{10} \\
\end{align*}
\]

wherein $R_9$ and $R_{10}$ are as discussed above. The reaction is preferably performed in a polar aprotic solvent, such as ethanol.

The resulting intermediate product of the general formula D

\[
\begin{align*}
\text{D} & : \quad \text{R}_2 \quad \text{R}_3 \\
\quad \quad \text{R}_4 \\
\quad \quad \text{R}_5 \\
\quad \quad \text{R}_6 \\
\quad \quad \text{R}_7 \\
\quad \quad \text{R}_8 \\
\end{align*}
\]

is subsequently reacted with an amine of the general formula E

\[
\begin{align*}
\text{E} & : \quad (\text{R}_{11})(\text{R}_{12})-\text{NH} \\
\end{align*}
\]
in a suitable solvent, e.g. a non-polar aprotic solvent, such as toluene, to obtain a
compound of the general formula (II). The individual substituents have the same meaning
as described above.

Similarly, a compound of the general formula (III)

![Compound (III)](image)

wherein \(k\) is 1, 2 or 3, and \(R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}\) are as
discussed above, may be prepared by reacting an aldehyde of the general formula \(F\)

![Compound F](image)

with an aminoguanidine derivative of the general formula \(B\) (shown above) in a similar
way as described above in connection with the preparation of compounds of the general
formula (II). Evidently, the compounds of the general formula (III) may also be prepared
by reacting the aldehyde \(F\) with thiosemicarbazide of the general formula \(C\), followed by
reaction with the amine \(E\), as described above. The aldehyde \(F\) is easily prepared from the
starting aldehyde \(G\).
by the well-known Wittig reaction.

The compounds of the general formula (IV)

wherein k, i, Q, u, Ri, R2, R3, R4, R5, Re, R7, R9, R10, Rn and R12 are as discussed above, may be prepared as shown in Figs. 1 and 2.

More particularly, in case Q=N the compound of the general formula (IV) may be prepared as illustrated in Fig. 1.

Referring to Fig. 1, an aldehyde of the general formula A is reacted with the amino acid ester H, where H may be in its S-form, R-form or a racemic mixture, in a suitable solvent (Step 1). The amino acid ester H is typically an amino acid Ci-6-alkyl ester, i.e. R17 is Ci-6-alkyl, preferably methyl or ethyl. Step 1 is carried out in the presence of a suitable
reducing agent, such as sodium cyanoborohydride, sodium triacetoxy borohydride, sodium borohydride, or hydrogen in the presence of a suitable catalyst such as palladium or carbon, in a suitable organic solvent to yield an ester of the general formula J.

In Step 2, the obtained ester J may be reduced to its corresponding aldehyde K using a suitable reducing agent, such as lithium aluminium hydride in a suitable organic solvent, such as diethyl ether or THF.

The aldehyde K is then converted to the chain-elongated aldehyde M, via the intermediate L, by the well-known Wittig reaction (Steps 3 and 4).

Formation of the intermediate compound L is carried out in a suitable organic solvent, typically a protic solvent, such as dimethylsulfoxide, dimethylformamide, hexamethylphosphorotriamide, in the presence of a strong base, such as an alkoxide, e.g. sodium or potassium tert-butoxide (Step 3). The intermediate L is subsequently converted to the desired aldehyde M by acidic hydrolysis using standard methods (Step 4). As will be understood, Steps 3 and 4 may be repeated until the desired chain length (k) has been obtained. Thus, after repeated cycles of Steps 3 and 4, the aldehyde N is obtained.

The aldehyde N is then converted to the desired end-product (IV, Q=N) by reacting the aldehyde N with an aminoguanidine derivative of the below general formula B as described previously. Evidently, the compounds of the general formula (IV) may also be prepared by reacting the aldehyde N with thiosemicarbazide of the general formula C, followed by reaction with the amine E, as described above.

More particularly, in case Q=C the compound of the general formula (IV) may be prepared as illustrated in Fig. 2.

Referring to Fig. 2, a halide, such as the bromide, of the general formula O is transformed into a Wittig reagent of the general formula P by standard methods by reaction with triphenyl phosphine in a suitable solvent (Step 1). In the well-known Wittig reaction, the Wittig reagent P is reacted with a cyclic ketoester of the general formula Q, cf. Step 2 of Fig. 2, to yield the ester R. The cyclic ketoester Q is typically a Cl-alkyl ester, i.e. Ri is Cl-alkyl, preferably methyl or ethyl.

The thus obtained ester R is transformed to its corresponding aldehyde T, via the alcohol intermediate S, using standard methods known to the person skilled in the art (Steps 3 and 4). Step 3 is conveniently carried out using a suitable reducing agent, such as lithium aluminium hydride in a suitable organic solvent, such as diethyl ether or THF. The alcohol
intermediate S is subsequently oxidised to its corresponding aldehyde T by means of a suitable oxidising agent, such as sulfur trioxide pyridine complex or oxalylchloride, dimethyl sulfoxide and triethyl amine (Swern oxidation) (Step 4).

The obtained aldehyde T corresponds to the aldehyde K described above in the case where Q is nitrogen. Accordingly, Steps 5, 6 and 7 shown in Fig. 2 (where Q=C) may be conducted in a similar way as Steps 3, 4 and 5 (where Q=N) 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*, intraperitoneal*, 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 alkanoid acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinyl-pyrollidone, 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 glyceryl monostearate or glyceryl 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 have been tested in the melanocortin system and have surprisingly been shown to be capable of binding to MC receptors as well as showing activity in functional assays. 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. MCI, MC3, MC4 and/or MC5 receptors.

The MC-receptors belong to the class of G-protein coupled receptors which are all built from a single polypeptide forming 7 transmembrane domains. Five such receptors types, termed MCI, MC2, MC3, MC4 and MC5, 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 MCI 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 MC3 and/or MC5 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 MC3 and MC4 receptor stimulation or only stimulation of one of the receptors are needed.

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-1α, IL-1β, IL-6 and TNFα, and induces the production of the anti-inflammatory 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).

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

In addition, the melanocortic peptides have distinct effects on sexual functions in that they cause erection in males (Donovan, Psychol. Med., 1978, 8, 305-316), presumably mediated by a central agonistic effect of the peptide on MC-receptors. It has also been shown that 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 have 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 connective 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.

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

25 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).

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

In the present specification "decreased production" refers to decreased formation, decreased release, or decreased amount of an endogenous compound in a patient compared to the amount of said endogenous compound in a healthy individual. In the present specification "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, \( \gamma \)-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 phemphigus vulgaris.

Moreover inflammatory diseases include all kinds of soft-tissue rheumatism including rheumatoid arthritis, bursitis, tenosynovitis or peritendonitis, enthesitis, nerve compression, periartthritis 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, helicobacteer pylori infection, coeliac disease, gluten sensitive enteropathy, dermatitis herpimiformis, tropical sprue, Whipple's disease, radiation enteritis, systemic amyloidosis, eosinophilic gastroenteritis, intestinal lymangiectasia, 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 fascitis, reactive arthritis, Bechterew's disease, systemic lupus erythematous, arteritis temporalis, Behcet's disease, morbus Burger, Good Pastures' syndrome, eosinophilic granuloma, fibromyalgia, myositis, and mixed connective tissue disease. Included therein is also arthritis, including arthritis of unknown origin.

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

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the eye and tear glands related to inflammation. Specific examples of such diseases comprise anterior and posterior uveitis, retinal vasculitis, optic neuritis, optic neuromyelitis, Wegener's granulomatosis, 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 thyroid. Specific examples of these embodiments of the invention include treatment of thyreoiditis, autoimmune thyreoiditis and Hashimoto's thyreoiditis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the kidney. Specific examples include treatment of glomerulonephritis, glomerulonephritis in systemic lupus erythematosus, periarteritis nodosa, Wegener's granulomatosis, Good-Pastures' syndrome, HLA27 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 arthroposis of any joint, in particular arthroposis 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 Paget's 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, protozoa and fungus and include conditions such as AIDS, bacterial septicemia, systemic fungal infections, Rickettsial diseases, toxic shock syndrome, infectious mononucleosis, chlamydia thrachomatis, 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 diabetes mellitus Type I, diabetes mellitus Type II, obesity-induced diabetes mellitus, obesity-induced diabetes mellitus Type I and diabetes mellitus Type II. Diabetes mellitus Type II includes 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 diabetes mellitus Type I, diabetes mellitus Type II, obesity-induced diabetes mellitus, obesity-induced diabetes mellitus Type II.

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 and metabolic syndrome. Obesity includes obesity where low grade inflammation in fatty tissue and muscles, plays a significant role for the development of the complications to obesity this 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 falling 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.

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**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.

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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

15 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 MCI-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-(l-[4-trifluoromethyl-phenyl]pyrrole-2-yl methylideneamino)-N',N',N"-trimethyl guanidine.

l-(4-trifluoromethyl-phenyl)-pyrrole-2-carbaldehyde (239 mg, 1 mmol) and 4,4,S-trimethyl-isothiosemicarbazide hydroiodide (247 mg, 1 mmol) are 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 dimethylamine (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. The synthesis is illustrated in Fig. 4.


Dimethylthiocarbamoyl chloride (161 mg, 1.3 mmol) and hydrazine monohydrate (65 mg, 1.3 mmol) are mixed in ethanol (3 ml). The mixture is stirred at room temperature until the acid chloride is consumed. Methyl iodide is added (185 mg, 1.3 mmol) and the reaction mixture is stirred at room temperature. The solvent is removed in vacuo to give crude 4,4,S-trimethyl-isothiosemicarbazide hydroiodide, which is mixed with l-(4-chlorophenyl)-pyrrole-2-carbaldehyde (206 mg, 1 mmol) 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 dimethylamine (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. The synthesis is illustrated in Fig. 5.

Example 3 - Synthesis of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N',N'-diethyl-N",N"-dimethyl guanidine.

In analogy to Example 2, l-(4-chlorophenyl)-pyrrole-2-carbaldehyde (206 mg, 1 mmol) and crude 4,4,S-trimethyl-isothiosemicarbazide hydroiodide are 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 diethylamine (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. The synthesis is illustrated in Fig. 6.
Example 4 - Synthesis of N-(l-[4-chlorophenyl]pyrrol-2-yl methylideneamino)-N',N'-dimethyl guanidine.

1-(4-chlorophenyl)pyrrole-2-carbaldehyde (206 mg, 1 mmol) and S-methylthiosemicarbazide hydroiodide (233 mg, 1 mmol) are 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 diethylamine (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. The synthesis is illustrated in Fig. 7.

Example 5 - Synthesis of N-[3-(l-[4-chlorophenyl]pyrrol-2-yl)allylidene]amino-N',N'-diethyl guanidine.

3-[l-(4-chlorophenyl)pyrrol-2-yl]-propenal (232 mg, 1 mmol) and S-methylthiosemicarbazide hydroiodide (233 mg, 1 mmol) are 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 diethylamine (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. The synthesis is illustrated in Fig. 8.

Example 6 - Synthesis of N-[l-[l-(4-chlorophenyl)pyrrol-2-ylmethyl]-pyrrolidin-2-ylmethylene amino]-N',N',N'-triethyl guanidine.

1-(4-chlorophenyl)pyrrole-2-carboxaldehyde (411 mg, 2 mmol) and pyrrolidin-2-ylmethanol (404 mg, 4 mmol) are dissolved in 2% AcOH in MeOH and NaCNBH₃ (378 mg, 6 mmol) is added. The solution is stirred at room temperature for 18 hr. evaporated and purified by flash chromatography to give l-[l-[4-Chloro-phenyl]-pyrrol-2-ylmethyl]-pyrrolidin-2-ylmethanol. The alcohol (1 eqv.) is dissolved in DMSO:DCM (3:1). Triethylamine (5 eq) and subsequently SO₃-pyridine complex (5 eq) are added and the reaction mixture is stirred at room temperature for 1 h. The mixture is diluted with H₂O and extracted with EtOAc. The combined layers are washed with 1 N HCl and brine, dried (Na₂SO₄), filtered and evaporated in vacuo to give crude l-[l-(4-chlorophenyl)pyrrol-2-ylmethyl]-pyrrolidin-2-carbaldehyde.

Diethylthiocarbamoyl chloride (198 mg, 1.3 mmol) and hydrazine monohydrate (65 mg, 1.3 mmol) are mixed in ethanol (3 ml). The mixture is stirred at room temperature until the acid chloride is consumed. Methyl iodide is added (185 mg, 1.3 mmol) and the reaction
mixture is stirred at room temperature. The solvent is removed \textit{in vacuo} to give crude 4,4-diethyl-S-methyl-isothiosemicarbazide hydroiodide, which is mixed with crude l-[l-(4-Chloro-phenyl)-pyrrol-2-ylmethyl]-pyrrolidine-2-carbaldehyde prepared as described above (289 mg, 1 mmol) 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 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. The synthesis is illustrated in Fig. 9.

10 \textbf{Example 7 - Synthesis of N-\{3-\{l-[4-trifluoromethylphenyl]pyrrol-2-yl\}allyliden\}amino-N',N',N",N"-tetraethyl guanidine}

Diethylthiocarbamoyl chloride (198 mg, 1.3 mmol) and hydrazine monohydrate (65 mg, 1.3 mmol) are mixed in ethanol (3 ml). The mixture is stirred at room temperature until the acid chloride is consumed. Methyl iodide is added (185 mg, 1.3 mmol) and the reaction mixture is stirred at room temperature. The solvent is removed \textit{in vacuo} to give crude 4,4-diethyl-S-methyl-isothiosemicarbazide hydroiodide, which is mixed with 3-[l-(4-trifluoromethylphenyl)-pyrrol-2-yl]-propenal (239 mg, 1 mmol) 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 diethylamine (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. The synthesis is illustrated in Fig. 10.

25 \textbf{Example 8 - \textit{In vitro} pharmacology and binding assays}

\textit{Description of applied methods}

Determination of binding affinities for MC receptors is performed by \textsuperscript{125}I-[Nle4,D-Phe7] \textalpha-MSH (\textsuperscript{125}I-NDP-MSH) radio-ligand binding. In short, murine B16-F1 melanoma cells expressing MCl, but not other MC receptors, are used for binding affinity studies against the murine MCl receptor (Siegrist et al.; 1988, J. Recept. Res., 8(l-4):323-43). For human MC3, MC4 and MC5 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 \textsuperscript{125}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\textsubscript{50} values (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficients (n\textsubscript{H}) are determined by non-linear regression analysis of the competition curves using Hill equation curve fitting. The inhibition constants (K\text{O}) are calculated from the Cheng Prusoff equation (K\text{O} = IC\textsubscript{50}/(1+(L/K\text{D}))), where L = concentration of radio-ligand in the assay, and K\text{D} = affinity of the radio-ligand for the receptor).

<table>
<thead>
<tr>
<th>Assay</th>
<th>Ligand</th>
<th>Cone.</th>
<th>Non Specific</th>
<th>Incubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC\textsubscript{1}</td>
<td>[\textsuperscript{125}I]NDP-MSH ° -0.5 nM</td>
<td>NDP-MSH (1 µM)</td>
<td>90 min/22°C</td>
<td></td>
</tr>
<tr>
<td>MC\textsubscript{3} (h)</td>
<td>[\textsuperscript{125}I]NDP-MSH 0.075 nM</td>
<td>NDP-MSH (1 µM)</td>
<td>60 min/37°C</td>
<td></td>
</tr>
<tr>
<td>MC\textsubscript{4} (h)</td>
<td>[\textsuperscript{125}I]NDP-MSH ° -0.5 nM</td>
<td>NDP-MSH (1 µM)</td>
<td>120 min/37°C</td>
<td></td>
</tr>
<tr>
<td>MC\textsubscript{5} (h)</td>
<td>[\textsuperscript{125}I]NDP-MSH ° -0.5 nM</td>
<td>NDP-MSH (1 µM)</td>
<td>60 min/37°C</td>
<td></td>
</tr>
</tbody>
</table>
CLAIMS

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

\[
\begin{align*}
&X = \begin{array}{c} \text{ring} \\ \text{i} \end{array}, \quad \text{and } i \text{ is 0, 1 or 2;} \\
&Y = \begin{array}{c} \text{ring} \\ \text{j} \end{array}, \quad \text{and } j \text{ is 0 or 1;} \\
&Z = \begin{array}{c} \text{double bond} \\ \text{k} \end{array}, \quad \text{and } k \text{ is 0, 1, 2 or 3;} \\
&Q_i \text{ is nitrogen (N) or carbon (C), and } u \text{ represents, together with } Q \text{ and the carbon atom covalently linked to } Q, \text{ an optionally substituted five- or six-membered heterocyclyl or cycloalkyl group;}
\end{align*}
\]

including tautomeric and isomeric forms thereof, wherein each R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ is independently selected from the group consisting of hydrogen, optionally substituted C₁-₆-alkyl, optionally substituted C₅₋₆-cycloalkyl, optionally substituted C₂₋₆-alkenyl, optionally substituted C₄₋₆-alkadienyl, optionally substituted C₂₋₆-alkynyl, hydroxy, optionally substituted C₁-₆-alkoxy, optionally substituted C₂₋₆-alkenyloxy, carboxy, optionally substituted C₁₋₆-alkoxycarbonyl, optionally substituted C₁₋₆-
alkylcarbonyl, formyl, \( \text{Ci-6-alkylsulphonylamino} \), optionally substituted aryl, optionally substituted arylxoycarbonyl, optionally substituted arylxoy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxy, heteroarylcarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylamino, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylsaphonylamino, optionally substituted heteroarylcarbonyle, optionally substituted heteroaryloxy, any arylamino, arylxoy, optionally substituted arylxoycarbonyl, optionally substituted arylxoy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylxoy, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylsaphonylamino, optionally substituted heteroarylcarbonyle, optionally substituted heteroaryloxy, optionally substituted heteroarylamino, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylsaphonylamino, amino, mono- and di(Ci-6-alkyl)amino, carbamoyl, mono- and di(Ci-6-alkyl)aminocarbonyl, amino-Ci-6-alkyl-aminocarbonyl, mono- and di(Ci-6-alkyl)amino-Ci-6-alkyl-aminocarbonyl, Ci-6-alkylcarbonylamino, amino-Ci-6-alkylcarbonylaminocarbonyl, amino-Ci-6-alkylcarbonylaminocarbonyl, mono- and di(Ci-6-alkyl)amino-Ci-6-alkyl-carbonylamino, mono- and di(Ci-6-alkyl)amino-Ci-6-alkyl-carbonylamino, cyan, guanidino, carbamido, Ci-6-alkanoyloxy, Ci-6-alkylsulphonyl, Ci-6-alkylsulphonylox, aminosulfonyl, mono- and di(Ci-6-alkyl)aminosulfonyl, nitro, optionally substituted halogen, and halogen, where any nitrogen-bound Ci-6-alkyl is optionally substituted with hydroxy, Ci-6-alkoxy, Ci-6-alkenylxy, amino, mono- and di(Ci-6-alkyl)amino, carboxy, Ci-6-alkylcarbonylamino, Ci-6-alkylthio, Ci-6-alkyl-sulphonyl-amino or guanidine;

each \( R_n, R_i, R_0, R_n \) and \( R_{12} \) is independently selected from the group consisting of hydrogen, optionally substituted Ci-6-alkyl, optionally substituted Ci-6-alkyl, optionally substituted Ci-6-alkylenyl, optionally substituted Ci-6-alkynyl, optionally substituted Ci-6-alkyloxycarbonyl, optionally substituted Ci-6-alkyloxycarbonyl, optionally substituted Ci-6-alkyloxycarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylamino, mono- and di(Ci-6-alkyl)aminocarbonyl, amino-Ci-6-alkylaminocarbonyl and mono- and di(Ci-6-alkyl)aminocarbonyl, or \( R_n \) and \( R_{12} \) may together form a five- or six-membered nitrogen-containing ring and/or \( R_n \) and \( R_{12} \) may together form a five- or six-membered nitrogen-containing ring; or \( R_n \) and \( R_{12} \) may together form a five- or six-membered nitrogen-containing ring; or a pharmaceutically acceptable salt thereof;

with the proviso that at least three of \( R_n, R_i, R_0, R_n \) and \( R_{12} \) are not hydrogen, or if \( R_n \) and \( R_{12} \) are both hydrogen then \( R_n \) and \( R_{12} \) are not hydrogen, or if \( R_n \) and \( R_{12} \) are both hydrogen then \( R_n \) and \( R_{12} \) are not hydrogen.

2. The compound according to claim 1, wherein each \( R_1, R_2, R_3, R_4, R_5, R_6, R_7 \) and \( R_8 \) is independently selected from the group consisting of hydrogen, optionally substituted Ci-6-
alkyl, optionally substituted C₂₋₆-alkenyl, optionally substituted C₂₋₆-alkynyl, hydroxy, optionally substituted Ci₋₆-alkoxy, optionally substituted C₂₋₆-alkenyloxy, carboxy, optionally substituted Ci₋₆-alkoxycarbonyl, optionally substituted Ci₋₆-alkylcarbonyl, formyl, amino, mono- and di(Ci₋₆-alkyl)amino, carboxamyl, mono- and di(Ci₋₆-alkyl)aminocarbonyl, amino-Ci₋₆-alkyl-aminocarbonyl, mono- and di(Ci₋₆-alkyl)amino-Ci₋₆-alkyl-aminocarbonyl, Ci₋₆-alkylcarbonylamino, amino-Ci₋₆-alkyl-carbonylamino, mono- and di(Ci₋₆-alkyl)aminocarbonyl, Ci₋₆-alkyl-carbonylamino, amino-Ci₋₆-alkyl-carbonylamino, mono- and di(Ci₋₆-alkyl)amino-Ci₋₆-alkyl-carbonylamino, 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₋₆-alkylthio and halogen.

3. The compound according to claim 2, wherein R₉, R₁₀, Rₙ and R₁₂ is independently selected from the group consisting of hydrogen, optionally substituted Ci₋₆-alkyl, optionally substituted C₂₋₆-alkenyl, hydroxy, optionally substituted Ci₋₆-alkoxy, amino, cyano, nitro and halogen.

4. The compound according to any of the preceding claims, wherein each R₉, R₁₀, Rₙ and R₁₂ is independently selected from the group consisting of hydrogen, optionally substituted Ci₋₆-alkyl, optionally substituted C₂₋₆-alkenyl, optionally substituted C₂₋₆-alkynyl, optionally substituted aryl and optionally substituted heteroaryl; with the proviso that at least three of R₉, R₁₀, R₁₁ and R₁₂ are not hydrogen, or if R₉ and R₁₀ are both hydrogen then Rₙ and R₁₂ are not hydrogen, or if Rₙ and R₁₂ are both hydrogen then R₉ and R₁₀ are not hydrogen.

5. The compound according to claim 4, wherein each R₉, R₁₀, Rₙ and R₁₂ is independently hydrogen or optionally substituted Ci₋₆-alkyl, preferably optionally substituted Ci₋₄-alkyl; with the proviso that at least three of R₉, R₁₀, Rₙ and R₁₂ are not hydrogen, or if R₉ and R₁₀ are both hydrogen then Rₙ and R₁₂ are not hydrogen, or if Rₙ and R₁₂ are both hydrogen then R₉ and R₁₀ are not hydrogen.

6. The compound according to claim 5, wherein R₉, R₁₀, Rₙ and R₁₂ are optionally substituted Ci₋₄-alkyl.

7. The compound according to claim 6, wherein each R₉, R₁₀, Rₙ and R₁₂ is independently methyl or ethyl.

8. The compound according to claim 7, wherein R₉, R₁₀, Rₙ and R₁₂ are methyl.

9. The compound according to claim 8, wherein R₉, R₁₀, Rₙ and R₁₂ are ethyl.
10. The compound according to claim 5, wherein $R_9$ is hydrogen and each $R_i\_0$, $R_n$ and $R_{i2}$ is independently hydrogen or optionally substituted $C_{i-6}$-alkyl, preferably optionally substituted $C_{i-4}$-alkyl; with the proviso that $R_i\_0$, $R_n$ and $R_{i2}$ are not hydrogen, or if $R_i\_0$ is hydrogen then $R_n$ and $R_{i2}$ are not hydrogen.

11. The compound according to claim 10, wherein $R_i\_0$, $R_n$ and $R_{i2}$ are optionally substituted $C_{i-4}$-alkyl.

12. The compound according to claim 11, wherein each $R_i\_0$, $R_n$ and $R_{i2}$ is independently methyl or ethyl.

13. The compound according to claim 12, wherein $R_i\_0$, $R_n$ and $R_{i2}$ are methyl.

14. The compound according to claim 13, wherein $R_i\_0$, $R_n$ and $R_{i2}$ are ethyl.

15. The compound according to claim 10, wherein $R_9$ and $R_i\_0$ are hydrogen and $R_n$ and $R_{i2}$ are optionally substituted $C_{i-6}$-alkyl, preferably optionally substituted $C_{i-4}$-alkyl.

16. The compound according to claim 15, wherein $R_n$ and $R_{i2}$ are optionally substituted $C_{i-4}$-alkyl.

17. The compound according to claim 16 wherein each $R_n$ and $R_{i2}$ is independently methyl or ethyl.

18. The compound according to claim 17, wherein $R_n$ and $R_{i2}$ are methyl.

19. The compound according to claim 18, wherein $R_n$ and $R_{i2}$ are ethyl.

20. The compound according to claim 5, wherein $R_n$ is hydrogen and each $R_9$, $R_i\_0$ and $R_{i2}$ is independently hydrogen or optionally substituted $C_{i-6}$-alkyl, preferably optionally substituted $C_{i-4}$-alkyl; with the proviso that $R_9$, $R_i\_0$ and $R_{i2}$ are not hydrogen, or if $R_{i2}$ is hydrogen then $R_9$ and $R_i\_0$ are not hydrogen.

21. The compound according to claim 20, wherein $R_9$, $R_i\_0$ and $R_{i2}$ are optionally substituted $C_{i-4}$-alkyl.

22. The compound according to claim 21, wherein each $R_9$, $R_i\_0$ and $R_{i2}$ is independently methyl or ethyl.
23. The compound according to claim 22, wherein \( R_9, R_i, \) and \( R_{12} \) are methyl.

24. The compound according to claim 23, wherein \( R_9, R_i, \) and \( R_{12} \) are ethyl.

25. The compound according to claim 20, wherein \( R_n \) and \( R_{12} \) are hydrogen and \( R_9 \) and \( R_{i0} \) are optionally substituted \( \text{Ci}_6 \)-alkyl, preferably optionally substituted \( \text{Ci}_4 \)-alkyl.

26. The compound according to claim 25, wherein \( R_9 \) and \( R_{i0} \) are optionally substituted \( \text{Ci}_4 \)-alkyl.

27. The compound according to claim 26 wherein each \( R_9 \) and \( R_{i0} \) is independently methyl or ethyl.

28. The compound according to claim 27, wherein \( R_9 \) and \( R_{i0} \) are methyl.

29. The compound according to claim 28, wherein \( R_9 \) and \( R_{i0} \) are ethyl.

30. The compound according to any of the preceding claims, wherein \( R_9 \) is hydrogen and \( R_{i}, R_{i}, R_i, R_9, \) \( R_{1}, R_6 \) and \( R_{7} \) are as defined in any of claims 1-3.

31. The compound according to claim 30, wherein \( R_{5} \) and \( R_8 \) are hydrogen and \( R_{i}, R_{i}, R_i, R_9, \) \( R_{1}, R_6 \) and \( R_{7} \) are as defined in any of claims 1-3.

32. The compound according to claim 31, wherein \( R_{4}, R_5 \) and \( R_8 \) are hydrogen and \( R_{i}, R_2, R_6, R_8, R_6 \) and \( R_{7} \) are as defined in any of claims 1-3.

33. The compound according to claim 32, wherein \( R_{4}, R_5, R_7 \) and \( R_8 \) are hydrogen and \( R_{i}, R_2, R_3 \) and \( R_6 \) are as defined in any of claims 1-3.

34. The compound according to claim 33, wherein \( R_{3}, R_4, R_5, R_7 \) and \( R_8 \) are hydrogen and \( R_{i}, R_2, \) and \( R_6 \) are as defined in any of claims 1-3.

35. The compound according to claim 34, wherein \( R_{3}, R_4, R_5, R_6, R_7 \) and \( R_6 \) are hydrogen and \( R_{i} \) and \( R_2 \) are as defined in any of claims 1-3.

36. The compound according to claim 34 or 35, wherein \( R_{7} \) is located in the 2-position and \( R_{2} \) is located in the 3-position.
37. The compound according to claim 34 or 35, wherein $R_1$ is located in the 2-position and $R_2$ is located in the 4-position.

38. The compound according to claim 34 or 35, wherein $R_i$ is located in the 2-position and $R_2$ is located in the 5-position.

39. The compound according to claim 34 or 35, wherein $R_i$ is located in the 2-position and $R_2$ is located in the 6-position.

40. The compound according to claim 34 or 35, wherein $R_i$ is located in the 3-position and $R_2$ is located in the 4-position.

41. The compound according to claim 34 or 35, wherein $R_i$ is located in the 3-position and $R_2$ is located in the 5-position.

42. The compound according to claim 34 or 35, wherein $R_i$ is located in the 3-position and $R_2$ is located in the 6-position.

43. The compound according to claim 35, wherein $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$ and $R_8$ are hydrogen and $R_i$ is as defined in any of claims 1-3.

44. The compound according to claim 43, wherein $R_i$ is located in the 2-position.

45. The compound according to claim 43, wherein $R_i$ is located in the 3-position.

46. The compound according to claim 43, wherein $R_i$ is located in the 4-position.

47. The compound according to claim 43, wherein all of $R_i$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$ and $R_8$ are hydrogen.

48. The compound according to any of the preceding claims, wherein $j=0$ and $k=0$.

49. The compound according to claim 48 of the general formula (II):


wherein \( i, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) are as defined in any of claims 1-47.

50. The compound according to claim 49 of the general formula (Ha):

wherein \( i, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} \) are as defined in any of claims 1-47.

51. The compound according to claim 49 of the general formula (lib):
wherein $i, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{n}$ and $R_{12}$ are as defined in any of claims 1-47.

52. The compound according to any of claims 48-51, wherein $i=0$.

53. The compound according to claim 52 of the general formula (II):

wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}$ and $R_{12}$ are as defined in any of claims 1-47.

54. The compound according to any of claims 1-47, wherein $i=0$ and $j=0$.

55. The compound according to claim 54 of the general formula (III):
wherein \( k \) is 1, 2 or 3, and \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} \) and \( R_{12} \) are as defined in any of claims 1-47.

56. The compound according to claim 55 of the general formula (IIa):

wherein \( k \) is 1, 2 or 3, and \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} \) and \( R_{12} \) are as defined in any of claims 1-47.

57. The compound according to claim 55 of the general formula (IIb):

wherein \( k \) is 1, 2 or 3, and \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} \) and \( R_{12} \) are as defined in any of claims 1-47.
wherein \( k \) is 1, 2 or 3, and \( R_i, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} \) and \( R_{12} \) are as defined in any of claims 1-47.

58. The compound according to any of claims 44-57, wherein \( k = 1 \).

59. The compound according to claim 58 of the general formula (IIIc):

wherein \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} \) and \( R_{12} \) are as defined in any of claims 1-47.

60. The compound according to any of claims 1-47, wherein \( j = 1 \).

61. The compound according to claim 60 of the general formula (IV):
wherein \( k, i, Q, u, Ri, R_2, R_3, R_4, R_6, R_7, R_9, R_{10}, R_n \) and \( R_{12} \) are as defined in any of claims 1-47.

62. The compound according to claim 60 or 61, wherein \( Q \) is carbon (C).

63. The compound according to claim 62, wherein \( u, \) together with \( Q \) and the carbon atom covalently linked to \( Q \), represents an optionally substituted five- or six-membered cycloalkyl group.

64. The compound according to claim 63, wherein \( u, \) together with \( Q \) and the carbon atom covalently linked to \( Q \), has the following chemical structure

wherein each of \( R_1, R_4, R_5, \) and \( R_6 \) is independently selected from the group consisting of hydrogen, optionally substituted \( C_1-6 \)-alkyl, optionally substituted \( C_3-6 \)-cycloalkyl, optionally substituted \( C_2-6 \)-alkenyl, optionally substituted \( C_4-6 \)-alkadienyl, optionally substituted \( C_2-6 \)-alkynyl, hydroxy, optionally substituted \( C_1-6 \)-alkoxy, optionally substituted \( C_2-6 \)-alkenylhydroxy, carboxy, optionally substituted \( C_1-6 \)-alkoxyformyl, optionally substituted \( C_1-6 \)-alkylcarbonyl, optionally substituted \( C_1-6 \)-alkylsulphonylamino, optionally substituted aryl, optionally substituted...
substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylicarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroaryl sulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, 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)

alkyQamino-C(6)-alkyl-aminocarbonyl, C(6)-alkylcarbonylamino, amino-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)-alkylsulphonyloxy, aminosulfonyl, mono- and di(C(6)-alkyl)aminosulfonyl, nitro, optionally substituted C(6)-alkythio and halogen,

where any nitrogen-bound C(6)-alkyl is optionally substituted with hydroxy, C(6)-alkoxy, C(2,6)-alkenyloxy, amino, mono- and di(C(6)-alkyl)amino, carboxy, C(6)-alkylcarbonylamino, amino-C(6)-alkyl-sulphonylamino, C(6)-alkyl-thio, C(6)-alkyl-sulphonylamino or guanidine.

65. The compound according to claim 64, wherein each of R(3), R(4), R(5), and R(6) is

independently selected from the group consisting of hydrogen, optionally substituted C(6)-alkyl, optionally substituted C(2,6)-alkenyl, optionally substituted C(2,6)-alkynyl, hydroxy, optionally substituted C(6)-alkoxy, optionally substituted C(2,6)-alkenyloxy, carboxy, optionally substituted C(6)-alkoxy carbonyl, optionally substituted C(6)-alkyl carbonyl, 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)-alkyl carbonylamino, amino-C(6)-alkyl-carbonylamino, mono- and di(C(6)-alkyl)amino-C(6)-alkyl-carbonylamino, cyano, carbamido, C(6)-alkanoyloxy, C(6)-alkylsulphonyl, C(6)-alkylsulphonyl, C(6)-alkylsulphonyloxy, aminosulfonyl, mono- and di(C(6)-alkyl)aminosulfonyl, nitro, optionally substituted C(6)-alkythio and halogen.

66. The compound according to claim 65, wherein each of R(3), R(4), R(5), and R(6) is

independently selected from the group consisting of hydrogen, optionally substituted C(6)-alkyl, optionally substituted C(2,6)-alkenyl, hydroxy, optionally substituted C(6)-alkoxy, amino, cyano, nitro and halogen.

67. The compound according to claim 66, wherein all of R(3), R(4), R(5), and R(6) are hydrogen.
68. The compound according to claim 63, wherein \( u \), together with \( Q \) and the carbon atom covalently linked to \( Q \), has the following chemical structure

![Chemical structure](image)

wherein each of \( R_{i3}, R_{i4} \), and \( R_{i5} \) is as defined in any of claims 64-66.

69. The compound according to claim 68, wherein all of \( R_{i3}, R_{i4} \), and \( R_{i5} \) are hydrogen.

70. The compound according to claim 60 or 61, wherein \( Q \) is nitrogen (N).

71. The compound according to claim 70, wherein \( u \), together with \( Q \) and the carbon atom covalently linked to \( Y \), represents an optionally substituted five- or six-membered heterocyclyl group.

72. The compound according to claim 71, wherein \( u \), together with \( Q \) and the carbon atom covalently linked to \( Q \), has the following chemical structure

![Chemical structure](image)

wherein each of \( R_{i3}, R_{i4}, R_{i5} \), and \( R_{i6} \) is as defined in any of claims 64-66.

73. The compound according to claim 72, wherein all of \( R_{i3}, R_{i4}, R_{i5} \), and \( R_{i6} \) are hydrogen.

74. The compound according to claim 71, wherein \( u \), together with \( Q \) and the carbon atom covalently linked to \( Q \), has the following chemical structure
wherein each of \( R_i \), \( R_4 \) and \( R_5 \) is as defined in any of claims 64-66.

5. The compound according to claim 74, wherein all of \( R_i \), \( R_4 \) and \( R_5 \) are hydrogen.

76. The compound according to any of claims 60-75, wherein \( i \) is 0 or 1.

77. The compound according to claim 76, wherein \( i=0 \).

78. The compound according to any of claims 60-77, wherein \( k \) is 0 or 1.

79. The compound according to claim 78, wherein \( k=0 \).

80. The compound according to any of claims 60-79 of the general formula (IVa):

![Diagram of compound (IVa)]

wherein \( k \), \( i \), \( Q \), \( u \), \( R_i \), \( R_2 \), \( R_3 \), \( R_4 \), \( R_5 \), \( R_6 \), \( R_7 \), \( R_8 \), \( R_9 \), \( R_{10} \), \( R_{11} \), \( R_{12} \) and \( R_{13} \) are as defined in any of claims 1-47.

81. The compound according to any of claims 60-79 of the general formula (IVb):
wherein $k$, $i$, $Q$, $u$, $R_i$, $R^2$, $R^3$, $R^4$, $R^5$, $R_{e}$, $R_{7}$, $R_{s}$, $R_{9}$, $R_{io}$, $R_{n}$ and $R_{2}$ are as defined in any of claims 1-47.

82. A pharmaceutical composition comprising a compound as defined in any of claims 1-81 and a pharmaceutically acceptable carrier or excipient.

83. A dosage form comprising the pharmaceutical composition as defined in claim 82.

84. The dosage form according to claim 83, wherein said dosage form is a solid dosage form.

85. The solid dosage form according to claim 84, wherein said solid dosage form is in the form of a tablet or capsule.

86. A compound as defined in any of claims 1-81 for use as a medicament.

87. A compound as defined in any of claims 1-81 for the treatment or prevention of a disease or condition associated with the melanocortin receptor system.

88. A compound as defined in any of claims 1-81 for the treatment or prevention of an inflammatory disease.

89. A compound as defined in any of claims 1-81 for the treatment or prevention of metabolic syndrome.
90. A compound as defined in any of claims 1-81 for the treatment or prevention of insulin-resistance.

91. A compound as defined in any of claims 1-81 for the treatment or prevention of diabetes mellitus.

92. The compound according to claim 91, 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.

93. A compound as defined in any of claims 1-81 for the treatment or prevention of obesity.
FIG. 1

A \xrightarrow{\text{Reducing agent}} J

\xrightarrow{\text{Reducing agent}}

\xrightarrow{\text{Base}} K

\xrightarrow{H^+} L

Repeating steps 3 and 4 k-1 times

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FIG. 1
FIG. 2

O → P

Step 1

P → Q

Step 2

S → R

Reducing agent

Step 3

R → T

Oxidizing agent

Step 4

T

Step 5 = step 3 of Fig. 1

Step 6 = step 4 of Fig. 1

Step 7 = step 8 of Fig. 1

(IV), Q=C
Examples of phenyl pyrrole aminoguanidine derivatives of the invention

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| \(52\) | \[
\begin{array}{c}
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\text{Ph} \\
\text{N} \\
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\text{N} \\
\text{CH}_2 \text{CH}_2 \\
\end{array}
\] |
| \(53\) | \[
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\text{N} \\
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\end{array}
\] |
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FIG. 3

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FIG. 3

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N-(1-[4-trifluoromethyl]phenyl]pyrrol-2-yl methylideneamino)-N',N',N'''-trimethyl guanidine
FIG. 5

N-(1-[4-chlorophenyl]pyrrol-2-yl methyldeneamino)-N',N',N'',N''-tetramethyl guanidine

Chemical reaction and structures shown in the diagram.
FIG. 6

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

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2\text{NNNH}_2 \quad \text{EtOH} \quad \text{N-NH}_2 \\
\text{Cl} & \quad \text{EtOH} \quad \text{Mel} \\
\text{Cl} & \quad \text{H}_2\text{NNNH}_2 \quad \text{EtOH} \\
\text{Cl} & \quad \text{EtOH} \quad \text{Toluene}
\end{align*}
\]
FIG. 7

N-(1-[4-chlorophenyl]pyrrol-2-yl methyldeneamino)-N',N'-dimethyl guanidine
N-(3-(1-[4-chlorophenyl]pyrrolyl-2-yl)allylidene)amino-N',N'-diethyl guanidine
FIG. 9

N-[1-[1-(4-Chloro-phenyl)-pyrrol-2-ylmethyl]-pyrrolidin-2-ylmethylene amino]-N',N',N'-triethyl guanidine

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FIG. 10

N-(3-(1-[4-trifluoromethylphenyl]pyrrol-2-y1)allylidene)amino-N',N',N'',N''-tetraethyl guanidine

\[
\begin{align*}
\text{NCl} & \xrightarrow{\text{H}_2\text{NNH}_2, \text{EtOH}} \text{N-NH}_2 \\
\text{EtOH} & \xrightarrow{\text{Mel}} \\
\text{CF}_3 & \xrightarrow{\text{H}_2\text{NNH}_2, \text{EtOH}} \\
\text{Toluene} & \xrightarrow{\text{NH}}
\end{align*}
\]
This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

- It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      - [x] the international application in the language in which it was filed
      - [ ] a translation of the international application into [language], which is the language
          of a translation furnished for the purposes of international search (Rules 12.5(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.8b(s)(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] Certain claims were found unsearchable (See Box No. II)

3. [ ] Unity of invention is lacking (see Box No. III)

4. With regard to the **title**,
   - [x] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**, 
   - [x] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**, 
   a. the figure of the drawings to be published with the abstract is Figure No. ________
      - [x] as suggested by the applicant
      - [ ] as selected by this Authority, because the applicant failed to suggest a figure
      - [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [x] none of the figures is to be published with the abstract
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D207/335  C07D403/06  A61K31/402  A61P3/00  A61P29/00

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D  A61K  A61P

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C. See patent family annex.

"A" document containing the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search: 6 May 2009

Date of mailing of the international search report: 13/05/2009

Name and mailing address of the ISA/Authorized officer

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016

Rufet, Jacques
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Form PCT/ISA/210 (patent family annex) (April 2005)