(19) DANMARK

(10) DK/EP 2348016 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 D 207/32 (2006.01)* *A 61 K 31/402 (2006.01)* *A 61 P 25/00 (2006.01)*
C 07 D 207/34 (2006.01) *C 07 D 207/36 (2006.01)* *C 07 D 207/38 (2006.01)*
C 07 D 207/40 (2006.01) *C 07 D 207/42 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2016-05-30**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-02-17**

(86) Europæisk ansøgning nr.: **11164583.4**

(86) Europæisk indleveringsdag: **2007-06-11**

(87) Den europæiske ansøgnings publiceringsdag: **2011-07-27**

(30) Prioritet: **2006-06-09 DK 200600780**

(62) Stamansøgningsnr: **07730054.9**

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR**

(73) Patenthaver: **SynAct Pharma ApS, Brendstrupgårdsvej 102, 8200 Århus N, Danmark**

(72) Opfinder: **Boman, Arne, Gustaf Kjellbergs väg 22, 756 43, Uppsala, Sverige**
Jonassen, Thomas Engelbrecht Norkild, Pile Allé 20, 2840 Holte, Danmark
Lundstedt, Torbjörn, Granelidsvägen 7B, 756 55, Uppsala, Sverige

(74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Rued Langgaards Vej 8, 2300 København S, Danmark**

(54) Benævnelse: **Phenylpyrrolaminoguanidinderivater**

(56) Fremdragne publikationer:
WO-A-03/013509

DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to phenyl pyrrole aminoguanidine derivatives. The present invention further relates to such phenyl pyrrole aminoguanidine derivatives for use in the treatment of diseases associated with the melanocortin receptors or related systems, e.g. the melanocyte stimulating hormones.

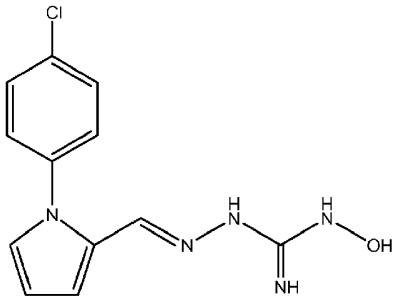
BACKGROUND OF THE INVENTION

[0002] 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.

[0003] 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 W0O 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.

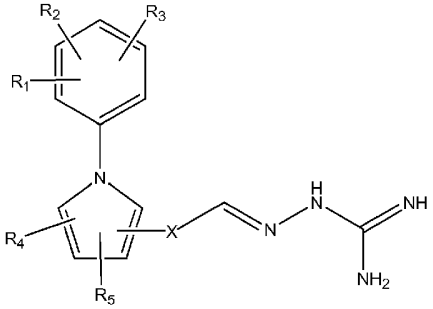
[0004] However, there is still a large need to provide low molecular weight compounds showing agonistic or antagonistic properties to the MC receptors. The compounds of the present invention are structurally different from the above-mentioned compounds and, consequently, constitute a new class of compounds that show activity to the MC receptors.

[0005] Prior art compounds, which have some structural relationship to the compounds of the present invention include the compounds described in WO 98/23267:



[0006] This hydroxyguanidine derivative has proven activity against xanthine oxidase/xanthine dehydrogenase enzymes.

[0007] Likewise, the compounds disclosed in WO 03/013509 exhibit antiinflammatory properties and significant affinity to the MC receptors. The general structure of the compounds disclosed in WO 03/013509 is as follows:

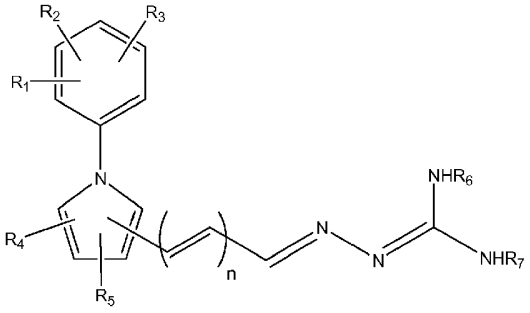


where X is $(CH_2)_n$, and n is 0, 1 or 2.

[0008] The compounds of the present invention differ from the compounds disclosed in WO 03/013509 in that the aminoguanidine substituent of 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.

SUMMARY OF THE INVENTION

[0009] Thus, in a first aspect the present invention relates to a compound of the general formula (I)



(I)

including tautomeric forms thereof,
wherein
n is 1, 2 or 3;
each R_1, R_2, R_3, R_4 and R_5 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}-alkenyloxy, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkylcarbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio and halogen,
where any nitrogen-bound C_{1-6}-alkyl is optionally substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino or guanidine;
each R_6 and R_7 is independently 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 aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl; or R_6 and R_7 may together form a five- or six-membered nitrogen-containing ring;
or a pharmaceutically acceptable salt thereof.

[0010] 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.

[0011] In a still further aspect the present invention relates to a dosage form comprising a pharmaceutical composition of the invention.

[0012] In yet another aspect the present invention relates to a compound of the invention for use a medicament.

[0013] In an even further aspect the present invention relates to the use of a compound of the invention for the manufacture of a medicament for the treatment of a disease selected from the group consisting of inflammatory conditions, e.g. acute or chronic inflammatory conditions, 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.

[0014] Analogously, the present invention also relates to a compound of the invention for use in a method of treating a mammal having a disease or disorder selected from the group consisting of inflammatory conditions, e.g. acute or chronic inflammatory conditions, 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.

[0015] Other aspects of the present invention will be apparent from the appended claims and the below description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016]

Fig. 1 shows specific phenyl pyrrole aminoguanidine derivatives.

Fig. 2 shows the synthetic route to compound 2 of the invention, [1-(2-Nitrophenyl)-1H-pyrrol-2-yl-allylideneamino] guanidinium actate (see figure 1, structure no.19).

Fig. 3 shows the synthetic route to compound 3 of the invention, [1-(2-Bromophenyl)-1H-pyrrol-2-yl-allylideneamino] guanidinium actate (see figure 1, structure no.53).

Fig. 4 shows the competition curve obtained for compound 3 of the invention, [1-(2-bromophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium acetate (see figure 1, structure no.53), in the MC1 receptor assay, cf. Example 3 herein. The X-axis shows log[Compound] and the Y-axis shows specific binding in %.

Fig. 5 shows Mean Concentration of compound 1 of the invention [1-(4-chlorophenyl)-1H-pyrrol-2-yl-allylideneamino] guanidinium actate (see figure 1, structure no.1) in plasma following a single intravenous administration to male rats. Target dose level: 10 mg/kg. Results are expressed as ng/mL.

Fig. 6 shows Mean Concentration of compound 3 of the invention, [1-(2-bromophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium acetate (see figure 1, structure no.53) in plasma following a single intravenous administration to male rats. Target dose level: 10 mg/kg. Results are expressed as ng/mL.

Fig. 7 shows Mean Concentration of compound 2 of the invention, [1-(2-Nitrophenyl)-1H-pyrrol-2-yl-allylideneamino] guanidinium actate (see figure 1, structure no.19) in plasma following a single intravenous administration to male rats. Target dose level: 10 mg/kg. Results are expressed as ng/mL.

Fig. 8 shows Mean Concentration of compound 1 of the invention, [1-(4-chlorophenyl)-1H-pyrrol-2-yl-allylideneamino] guanidinium actate (see figure 1, structure no.1) in plasma following a single oral administration to male rats. Target dose level: 10 mg/kg. Results are expressed as ng/mL.

Fig. 9 shows Mean Concentration of compound 3 of the invention, [1-(2-bromophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium acetate (see figure 1, structure no.53) in plasma following a single oral administration to male rats. Target dose level: 10 mg/kg. Results are expressed as ng/mL.

Fig. 10 shows Mean Concentration of compound 2 of the invention in plasma, [1-(2-Nitrophenyl)-1H-pyrrol-2-yl-allylideneamino] guanidinium actate (see figure 1, structure no.19) following a single oral administration to male rats. Target Dose Level: 10 mg/kg. Results are expressed as ng/mL.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0017] In the present context, the term "C_{1-6}-alkyl" is intended to mean a linear or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl, *sec*-butyl, tert-butyl, n-pentyl, *iso*-pentyl, neo-pentyl and n-hexyl, and the term "C_{1-4}-alkyl" is intended to cover a linear or branched hydrocarbon group having 1 to 4 carbon atoms, e.g. methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl, *sec*-butyl and tert-butyl.

[0018] Whenever the term "C_{1-6}-alkyl" is used herein, it should be understood that a particularly interesting embodiment thereof is "C_{1-4}-alkyl".

[0019] When used herein, the term "C_{3-6}-cycloalkyl" is intended to mean a cyclic hydrocarbon group having 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0020] Similarly, the terms "C_{2-6}-alkenyl" and "C_{4-6}-alkadienyl", are intended to cover linear or branched hydrocarbon groups having 2 to 6 and 4 to 6, carbon atoms, respectively, and comprising one and two unsaturated bonds, respectively. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl and hexenyl. Examples of alkadienyl groups include butadienyl, pentadienyl and hexadienyl. Preferred examples of alkenyl are vinyl, allyl and butenyl, especially allyl.

[0021] In the present context the term "C_{2-6}-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 6 carbon atoms and containing one or more triple bonds. Illustrative examples of C_{2-6}-alkynyl groups include acetylene, propynyl, butynyl, as well as branched forms of these. The position of unsaturation (the triple bond) may be at any position along the carbon chain. More than one bond may be unsaturated such that the "C_{2-6}-alkynyl" is a di-yne or enedi-yne as is known to the person skilled in the art.

[0022] When used herein the term "C_{1-6}-alkoxy" is intended to mean C_{1-6}-alkyl-oxy, such as methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, sec-butoxy, *tert*-butoxy, *n*-pentoxy, *iso*-pentoxy, *neo*-pentoxy and *n*-hexoxy, and the term "C_{1-4}-alkoxy" is intended to mean C_{1-4}-alkyl-oxy, e.g. methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, sec-butoxy and tert-butoxy.

[0023] Whenever the term "C_{1-6}-alkoxy" is used herein, it should be understood that a particularly interesting embodiment thereof is "C_{1-4}-alkoxy".

[0024] Likewise, the term "C_{2-6}-alkenyl-oxy" is intended to mean C_{2-6}-alkenyl-oxy.

[0025] Herein, the term "halogen" includes fluoro, chloro, bromo, and iodo. In particular, fluoro, chloro and bromo are preferred.

[0026] 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), C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroarylsulphonyl-amino, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, C_{1-6}-alkylthio and halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl", and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino or guanidine.

[0027] 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), C_{1-6}-alkoxy (i.e. C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkylaminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylthio and halogen, where any aryl and

heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl".

[0028] Especially preferred examples of such substituents are hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino and guanidine, in particular halogen. Thus, particularly preferred "optionally substituted C_{1-6}-alkyl" groups include halogen-substituted alkyl groups, such as trihalo-C_{1-6}-alkyl, such as tribromomethyl, trichloromethyl or trifluoromethyl.

[0029] The term "optionally substituted C_{1-6}-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), C_{1-6}-alkoxy (i.e. C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, cyano, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, C_{1-6}-alkylthio and halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl".

[0030] Especially preferred examples of such substituents are and those carrying one or two substituents selected from hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, carboxy, halogen or C_{1-6}-alkylthio.

[0031] In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example.

[0032] 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, thienyl, quinolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxozolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl and phenoxazonyl.

[0033] Particularly interesting heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thienyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl and indolyl, in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thienyl, quinolyl, tetrazolyl and isoquinolyl.

[0034] In the present context, the term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane and oxathiepane.

[0035] Preferred examples of heterocyclyl 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.

[0036] In the present context, i.e. in connection with the terms "aryl", "heteroaryl", and "heterocyclyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times, with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)-amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-

sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, sulphanyl, amino, amino-sulfonyl, mono- and di(C_{1-6}-alkyl)amino-sulfonyl, dihalogen-C_{1-4}-alkyl, trihalogen-C_{1-4}-alkyl and halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with C_{1-4}-alkyl, C_{1-4}-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine.

[0037] Preferably, the above-mentioned substituents are selected from hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkylcarbonyl, formyl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroarylsulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, sulphanyl, amino, amino-sulfonyl, mono- and di(C_{1-6}-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino or guanidine.

[0038] Especially preferred examples of such substituents are C_{1-6}-alkyl, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino or guanidine.

[0039] 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, (Z)-2-butenedioic, (E)-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic acid, cyclohexanesulfamic, 2-hydoxybenzoic, 4-amino-2-hydroxybenzoic, and other acids known to the skilled practitioner.

[0040] 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.

[0041] In the present description and claims, any reference to "a" component, e.g. in the context of a substituent, etc., is intended to refer to one or more of such components, unless stated otherwise or unless it is clear from the particular context that this is not the case. For example, the expression "a component selected from the group consisting of A, B and C" is intended to include all combinations of A, B and C, i.e. A; B; C; A+B; A+C; B+C or A+B+C.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] The term "subject" as used herein includes, but is not limited to, an organism; a mammal, including, e.g., a human being,

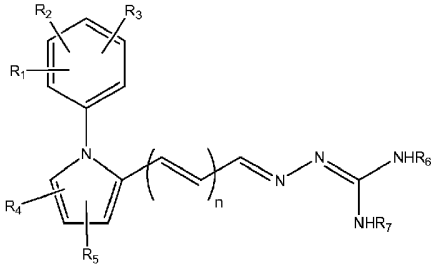
non-human primate (e.g., baboon, orangutan, monkey), mouse, pig, cow, goat, cat, rabbit, rat, guinea pig, hamster, horse, monkey, sheep, or other non-human mammal; a non-mammal, including, e.g., a non-mammalian vertebrate, such as a bird (e.g., a chicken or duck) or a fish, and a non-mammalian invertebrate. In a preferred embodiment of the invention the subject is a being.

[0046] In the present context the term "tautomeric forms thereof" or "tautomer" refers to one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Different tautomeric forms have the same molecular formula and are interchangeable forms involving the displacement of hydrogen atoms and electrons. Thus, it will be understood that when a compound of the invention is illustrated by its chemical structure, all possible tautomeric forms of the specifically depicted molecule are also within the scope of the present invention.

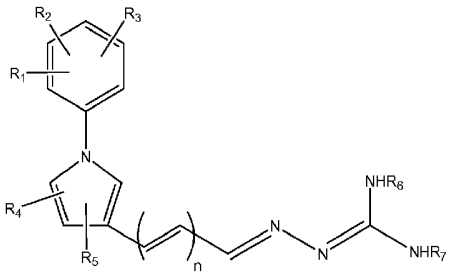
The compound of the invention

[0047] 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.

[0048] Accordingly, in another aspect the present invention relates to a compound of the general formula (Ia) or (Ib)



(Ia)



(Ib)

including tautomeric forms thereof,

wherein

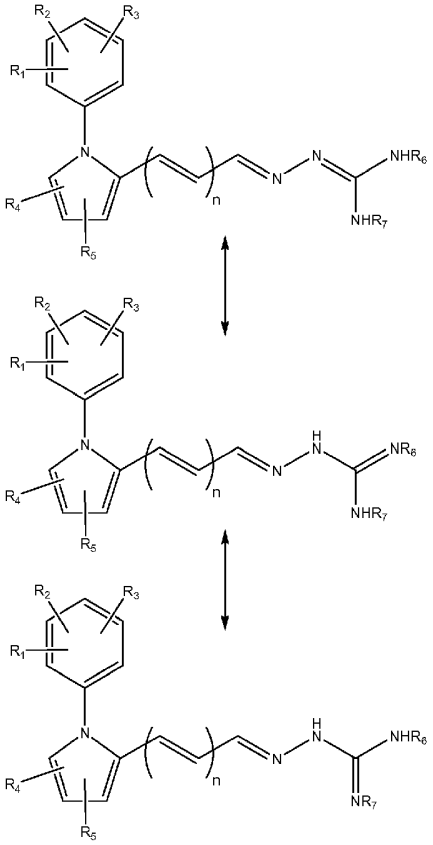
n is 1, 2 or 3;

each R_1, R_2, R_3, R_4 and R_5 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}-alkenyloxy, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkylcarbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio and halogen,

where any nitrogen-bound C_{1-6}-alkyl is optionally substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino or guanidine;
each R_6 and R_7 is independently 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 aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl; or R_6 and R_7 may together form a five- or six-membered nitrogen-containing ring;
or a pharmaceutically acceptable salt thereof.

[0049] As discussed above, in the compounds of the general formula (Ia) the aminoguanidine substituent is attached to the pyrrole ring at position 2, whereas in the compounds of the general formula (Ib) the aminoguanidine substituent is attached to the pyrrole ring at position 3. In the following description, only compounds where the aminoguanidine substituent is attached to the pyrrole ring at position 2 is described with respect to preferred substituents, method for manufacturing, etc. It should be understood, however, that all statements made below with respect to the compounds of the invention where the aminoguanidine substituent is attached to the pyrrole ring at position 2 also apply to the compounds of the invention where the aminoguanidine substituent is attached to the pyrrole ring at position 3. Furthermore, the compounds of the general formula (I) herein are all shown in their trans isomeric forms. It should be understood, however, that the compounds of the general formula (I) may also be in their cis isomeric form. Thus, the configuration around a double bond in the molecule may be either cis or trans, although the trans configuration is preferred.

[0050] As will be understood by the skilled person the compounds of the general formula (I) may exist in the various tautomeric forms illustrated below (illustrated for compound (Ia) only). Evidently, all possible tautomeric forms of the compounds of the invention are contemplated and hence included in the scope of the present invention.

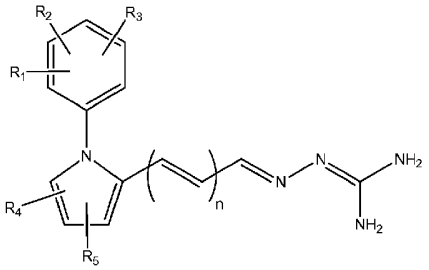


[0051] The compounds of the invention have basic properties and, consequently, they may be converted to their active acid addition salts by treatment with appropriate pharmaceutically acceptable acids. Examples of such acids include inorganic acids, such as hydrochloric acid, hydrobromic acid, hydrofluoric 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-hydroxybutanedioic acid, 2,3-dihydroxybutanedioic acid, 2-hydroxy-1,2,3-propanetricarboxylic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, cyclohexanesulfamic acid, 2-hydoxybenzoic acid, 4-amino-2-hydroxybenzoic acid, and other acids known to the person skilled in the art.

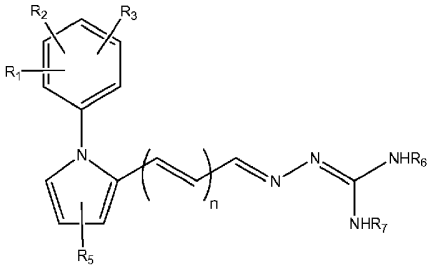
[0052] The substituents R_1, R_2, R_3, R_4 and R_5 may be individually selected from the group of substituents indicated above. However, in a preferred embodiment of the invention each R_1, R_2, R_3, R_4 and R_5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{2-6}-alkynyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{2-6}-alkenyloxy, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkylcarbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, cyano, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio and halogen.

[0053] In a more preferred embodiment of the invention each R_1, R_2, R_3, R_4 and R_5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, hydroxy, optionally substituted C_{1-6}-alkoxy, amino, cyano, nitro and halogen, such as bromo, chloro and fluoro. Specific examples of highly preferred (non-substituted) C_{1-6}-alkyl groups include C_{1-4}-alkyl, such as methyl or ethyl, in particular methyl. Specific examples of highly preferred substituted C_{1-6}-alkyl groups include substituted C_{1-4}-alkyl, such as halogen-substituted C_{1-4}-alkyl, e.g. trihalo-C_{1-4}-alkyl, in particular tribromomethyl, trichloromethyl and trifluoromethyl among which trichloromethyl and trifluoromethyl are particularly preferred. Specific examples of highly preferred (non-substituted) C_{2-6}-alkenyl groups include C_{2-4}-alkenyl, such as vinyl, allyl and butenyl, in particular allyl. Specific examples of highly preferred (non-substituted) C_{1-6}-alkoxy groups include C_{1-4}-alkoxy, such as methoxy or ethoxy, in particular methoxy. Concerning the substituents R_6 and R_7, these substituents may be each be independently 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 aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl; or R_6 and R_7 may together form a five- or six-membered nitrogen-containing ring. In a preferred embodiment of the invention, at least one of R_6 and R_7 is hydrogen. In a particular preferred embodiment of the invention R_6 and R_7 are both hydrogen, i.e. the compound of the invention has the structure shown in the general formula (II):



(II)

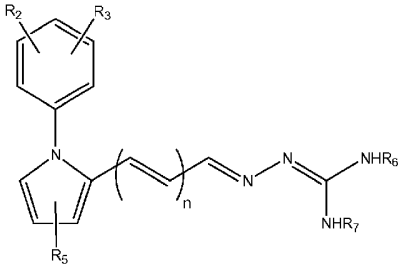
[0054] In an interesting embodiment of the invention, R_4 is hydrogen and R_1, R_2, R_3 and R_5 are as defined above. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (III):



(III)

wherein each of the substituents are as defined above. In particular, it is preferred that both of R_6 and R_7 are hydrogen.

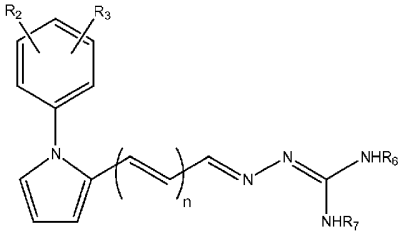
[0055] In a further interesting embodiment of the invention, R_1 and R_4 are hydrogen and R_2, R_3 and R_5 are as defined above. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (IV):



(IV)

wherein each of the substituents are as defined above. In particular, it is preferred that both of R_6 and R_7 are hydrogen.

[0056] In a preferred embodiment of the invention, R_1, R_4 and R_5 are hydrogen and R_2 and R_3 are as defined above. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (V):

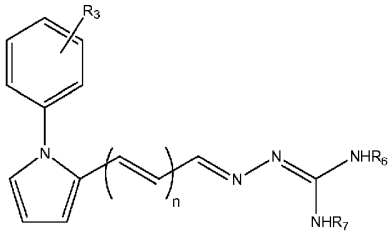


(V)

wherein each of the substituents are as defined above. In particular, it is preferred that both of R_6 and R_7 are hydrogen.

[0057] Concerning the compounds described above in connection with the general formulae (I), (II), (III), (IV) and (IV) it will be understood that the individual substituents may be attached to the ring systems at different positions. More particularly, and with reference to the general formula (V) above, the attachment of the R_2 and R_3 may be as follows: In one embodiment of the invention is R_2 located in the 2-position and R_3 is located in the 3-position. In another embodiment of the invention is R_2 located in the 2-position and R_3 is located in the 4-position. A yet another embodiment of the invention is R_2 located in the 2-position and R_3 is located in the 5-position. In a further embodiment of the invention is R_2 located in the 2-position and R_3 is located in the 6-position. In a still further embodiment of the invention is R_2 is located in the 3-position and R_3 is located in the 4-position. In an even further embodiment of the invention is R_2 located in the 3-position and R_3 is located in the 5-position. In yet another embodiment of the invention is R_2 located in the 3-position and R_3 is located in the 6-position.

[0058] In another preferred embodiment of the invention, R_1, R_2, R_4 and R_5 are hydrogen and R_3 is as defined above. Thus, according to this embodiment of the invention, the compound of the invention has the structure shown in the general formula (VI):



(VI)

wherein each of the substituents are as defined above. In particular, it is preferred that both of R_6 and R_7 are hydrogen.

[0059] In one embodiment of the invention is R_3 located in the 2-position. In another embodiment of the invention is R_3 located in the 3-position. In yet another embodiment of the invention is R_3 located in the 4-position.

[0060] In a still further interesting embodiment of the invention all of R_1, R_2, R_3, R_4 and R_5 are hydrogen.

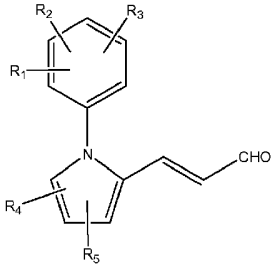
[0061] It should be understood that all of the above statements made in connection with the compounds of the invention apply equally well to compounds of the invention where the aminoguanidine substituent is attached to the pyrrole ring at position 2 or 3 (although usually only illustrated and discussed for compounds of the invention where the aminoguanidine substituent is attached to the pyrrole ring at position 2). Nevertheless, in a preferred embodiment of the invention it is preferred that the aminoguanidine substituent is attached to the pyrrole ring at position 2, i.e. in a preferred embodiment the compounds of the invention has the stereochemistry indicated in the general formula (Ia) and the formulae (II)-(VI) above.

[0062] As indicated above, n is an integer of 1, 2 or 3. In a preferred embodiment of the invention n is 1 or 2. In the most preferred embodiment of the invention n is 1.

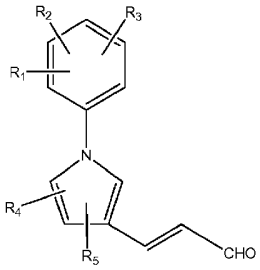
[0063] Compounds according to the invention which are currently believed to be of particular interest are shown in Fig. 1.

Methods of preparing the compounds of the invention

[0064] The compounds of the invention may be prepared by standard methods known to the skilled person. Thus, a compound of the general formula (Ia) or (Ib) above may be prepared essentially as described in WO 03/013509, i.e. a compound of the general formula (IIa) or (IIb)

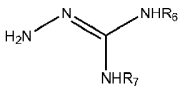


(IIa)



(IIb)

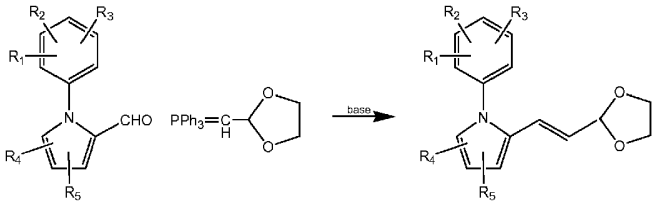
is reacted with an aminoguanidine derivative of the general formula (III) in a suitable organic solvent:



(III)

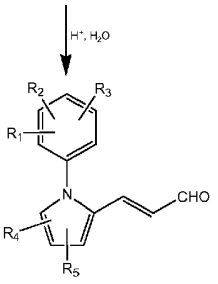
wherein the individual substitutents have the same meaning as described above. Preferably, a compound of the general formula (IIa) or (IIb) is reacted with an aminoguanidine derivative of the general formula (III) where the aminoguanidine derivative is in the form of an acid addition salt, such as the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

[0065] The compound (IIa) may easily be prepared from the starting compound (IVa) by the well-known Wittig reaction:



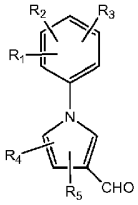
(IVa)

(Va)



(IIa)

[0066] Formation of the intermediate compound (Va) 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. The intermediate (Va) is subsequently converted to the desired (IIa) by acidic hydrolysis using standard methods. As will be understood, compound (IIb) may be achieved in an analogous way by using the starting compound (IVb) rather than the starting compound (IVa):



(IVb)

Pharmaceutical compositions

[0067] The compound of the invention is preferably administered in a composition including a pharmaceutically acceptable carrier or excipient. The term "pharmaceutically acceptable" means a carrier or excipient that does not cause any untoward effects in patients to whom it is administered. Such pharmaceutically acceptable carriers and excipients are well known in the art (Remington's Pharmaceutical Sciences, 18th edition, A. R. Gennaro, Ed., Mack Publishing Company [1990] ; Pharmaceutical Formulation Development of Peptides and Proteins, S. Frokjaer and L. Hovgaard, Eds., Taylor & Francis [2000]; and Handbook of Pharmaceutical Excipients, 3rd edition, A. Kibbe, Ed., Pharmaceutical Press [2000]).

[0068] 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.

[0069] 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.

[0070] The pharmaceutical composition may be administered orally, subcutaneously, intravenously, intracerebrally, intranasally, transdermally, intraperitoneally, 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.

[0071] 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

[0072] 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.

[0073] 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.

[0074] The compound of the invention may be admixed with adjuvants such as lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinyl-pyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compound of the invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, ethanol, oils (such as corn oil, peanut oil, cottonseed oil or sesame oil), tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

[0075] 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.

[0076] 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.

[0077] 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

[0078] 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. MCl, MC3, MC4 and/or MC5

receptors.

[0079] 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 MCl, 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.

[0080] 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 MC1 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.

[0081] 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).

[0082] 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 antiinflammatory cytokine, IL-10 (for review, see Catania & Lipton, Endocr Rev. 1993 Oct;14(5):564-76).

[0083] 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).

[0084] The MC5-receptor has recently been attributed a role in control of exocrine gland function 5 (van der Kraan, et al., Endocrinol. 1998, 139, 2348-2355; Chen et al., Cell. 1997, 91, 789-798).

[0085] 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).

[0086] The compounds of the present invention has valuable therapeutic properties, making them useful for the treatment of inflammatory conditions, e.g. acute or chronic inflammatory conditions, such as arthritis, including diseases associated with arthritis, osteoartritis, rheumatoid arthritis, spondylarthropathies (e.g. ankylosing spondilitis), reactive arthritis (including arthritis following rheumatic fever), Henoch-Schonlein purpura, and Reiter's disease, connective tissue disorders such as systemic lupus erythematosus, polymyositis/dermatomyositis, systemic sclerosis, mixed connetive tissue disease, sarcoidosis and primary Sjogrens syndrome including keratoconjunctivitis sicca, polymyalgia rheumatica, and other types of vasculitis, crystal deposition diseases (including gout), pyrophosphate arthropathy, acute calcific periarthritis; inflammatory bowel disease (including Chrons disease and ulcertive 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.

[0087] In the following the conditions and diseases of which the compounds of the present invention are useful for treating, are described in details.

Inflammatory conditions

[0088] 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).

[0089] 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.

[0090] In the present specification "decreased production" refers to decreased formation, decreased release, or decreased amount of an endogenous compound in a patient compared to the amount of said endogenous compound in a healthy individual. In the present specification "downregulated" refers to a decreased activity or amount of the compound compared with that in a healthy individual.

[0091] In particular, positive treatment effects or preventive effects may be seen in conditions where inflammation or an inflammatory-like condition is caused by or being associated with one or more of the following: allergy, hypersensitivity, bacterial infection, viral infection, inflammation caused by toxic agent, fever, autoimmune disease, radiation damage by any source including UV-radiation, X-ray radiation, γ-radiation, α- or β-particles, sun burns, elevated temperature or mechanical injury. Moreover, inflammation due to hypoxia, which is optionally followed by reoxygenation of the hypoxic area, is typically followed by severe inflammation, which condition may be positively affected by treatment with a compound of the invention.

[0092] 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.

[0093] Moreover inflammatory diseases include all kinds of soft-tissue rheumatism including rheumatoid arthritis, bursitis, tenosynovitis or peritendonitis, enthesitis, nerve compression, periarthritis or capsulitis, muscle tension and muscle dysfunction. Furthermore, inflammatory diseases include all kinds of arthtitis in children such as Juvenile Chronic arthritis including Still's disease, juvenile rheumatoid arthritis, juvenile ankylosing spondylitis.

[0094] Also comprised by the invention is a compound of formula (I) or a pharmacologically acceptable salt thereof for use in 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 herpitiformis, tropical sprue, Whipple's diease, radiation enteritis, systemic amyloidosis, eosinophilic gastroenteritis, intestinal lympangiectasia, inflammatory bowel disease, diverticular disease of the colon, and irritable bowel syndrome.

[0095] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of systemic or general and/or local immunological diseases, including those of an autoimmune nature, and other

inflammatory diseases of a general nature. Specific examples include treatment of rheumatoid arthritis, psoriatic arthritis, systemic sclerosis, polymyalgia rheumatica, Wegener's granulomatosis, sarcoidosis, eosinophilic fasceitis, reactive arthritis, Bechterew's disease, systemic lupus erythematosus, arteritis temporalis, Behcet's disease, morbus Burger, Good Pastures' syndrome, eosinophilic granuloma, fibromyalgia, myositis, and mixed connective tissue disease. Included therein is also arthritis, including arthritis of unknown origin.

[0096] Further included in the invention is a compound of formula (I) or a pharmacologically acceptable salt thereof for use in 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 a compound of the invention for use in 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 use in 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.

[0097] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases of the eye and tear glands related to inflammation. Specific examples of such diseases comprise anterior and posterior uveitis, retinal vasculitis, optic neuritis, optic neuromyelitis, Wegener's granulomatosis, Sjögren's syndrome, episcleritis, scleritis, sarcoidosis affecting the eye and polychondritis affecting the eye.

[0098] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases of the ear related to inflammation, specific examples of which include polychondritis affecting the ear and external otitis.

[0099] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases of the nose related to inflammation, specific examples of which are sarcoidosis, polychondritis and mid-line granuloma of the nose.

[0100] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases related to inflammation of the mouth, pharynx and salivary glands. Specific examples include Wegener's granulomatosis, mid-line granuloma, Sjögren's syndrome and polychondritis in these areas.

[0101] Included in the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in 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 use in 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.

[0102] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases related to the inflammation of the heart. Specific examples include use in 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.

[0103] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases related to inflammation of the liver. Specific examples include use in 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.

[0104] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases related to inflammation of the pancreas. Specific examples include use in treatment (and prevention) of acute pancreatitis, chronic pancreatitis.

[0105] Moreover, comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in 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.

[0106] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases related to the inflammation of the thyroidea. Specific examples of these embodiments of the invention include use in treatment of thyreoiditis, autoimmune thyreoiditis and Hashimoto's thyreoiditis.

[0107] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases related to inflammation of the kidney. Specific examples include use in treatment of glomerulonephritis, glomerulonephritis in systemic lupus erythematosus, periarteritis nodosa, Wegener's granulomatosis, Good-Pastures' syndrome, HLAb27 associated diseases, IgA nephritis (IgA = Immunoglobulin A), pyelonephritis, chronic pyelonephritis and interstitial nephritis.

[0108] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases related to the inflammation of the joints. Specific examples include use in 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 use in treatment of arthrosis of any joint, in particular arthrosis of finger joints, the knee and the hip.

[0109] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of diseases related to the inflammation of blood vessels. Specific examples include use in 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.

[0110] Inflammatory diseases also include all kind of inflammatory conditions causing backpain including infections, septic discitis, tuberculosis, malignancies (such as matastases, myeloma and others), spinal tumours, ancylosing spondylitis, acute disc prolapse, chronic disc diseaase/osteoarthritis, osteoporosis, and osteomalacia. It also includes Pagets disease, hyperparathyroidism, renal osteodystrophy, spondylolisthesis, spinal senosis congenital abnormalities and fibromyalgia.

[0111] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of inflammation related to infections of any origin. Specific examples include use in treatment of inflammation secondary to infection caused by virus, bacteria, helminths, protozoae and fungus and include conditions such as AIDS, bacterial septicemia, systemic fungal infections, Rickettsial diseases, toxic shock syndrome, infectious mononucleosis, chlamydia thrachomatis, chlamydia psittaci, cytomegalovirus infection, campylobacter, salmonella, influenza, poliomyelitis, toxoplasmosis, Lassa Fever, Yellow Fever, billharziose, colibacteria, enterococcus, preteus, klebsiella, pseudomonas, staphylococcus aureus, staphylococcus epidermidis, candida albicans, tuberculosis, mumps, infectious mononucleosis, hepatitis and Coxackie virus.

[0112] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in 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

[0113] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of inflammations related to insulin resistance, metabolic syndrome, diabetes mellitus, including Type II diabetes mellitus where low grade inflammation in fatty tissue and muscles, plays a significant role for the development of impairment in the signal transduction of insulin and thereby the development of insulin resistance and eventually diabetes mellitus. Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of insulin resistance, metabolic syndrome, diabetes mellitus, including Type II diabetes mellitus.

Eating disorders

[0114] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of inflammations related to eating disorders, such as e.g. anorexia and bulimia. Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of eating disorders, such as e.g. anorexia and bulimia.

Obesity

[0115] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of inflammations related to obesity where low grade inflammation in fatty tissue and muscles, plays a significant role for the development of the complications to obesity the includes the development of insulin resistance and eventually diabetes mellitus, e.g. diabetes mellitus type II, dyslipidemia, hypertension and aterosclerosis. Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of obesity and/or metabolic syndrome.

Congestive heart failure

[0116] Comprised by the invention is also a compound of formula (I) or a pharmacologically acceptable salt thereof for use in 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 a compound of formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of congestive heart failure

Sexual dysfunction

[0117] Compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of sexual functions / dysfunctions such as inducing erection in man, to induce erection in animal breeding, to stimulate intercourse in animals which are difficult to mate, in particular rare species or valuable strains, pets, cats, dogs, horses or to reduce sexual behaviour in animals, e.g. for pets, cats etc., to treat impotence and disorders related to sexual drive, including lack of sexual drive or abnormal sexual drive in both men and women.

Mental disorders

[0118] 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

[0119] 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

[0120] Comprised by the invention is also a compound of the invention for use in the treatment of drug-induced disorders of the

blood and lymphoid system, including use in 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 use in the treatment of anemia, granulocytopenia, thrombocytopenia, leukopenia, aplastic anemia, autoimmune hemolytic anemia, autoimmune thrombocytopenia and autoimmune granulocytopenia.

Allergy disorders

[0121] 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 use in 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

[0122] Compounds of formula (I) or pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of disorders of the cardiovascular system such as disorders related to blood pressure, heart rate, vascular tone, natriuresis, bleeding, shock, disorders related to ischemia, infarction, reperfusion injuries, arrhythmias of the heart, in particular during ischemia, or for the treatment of arrhythmias associated with reoxygenation of a previously ischemic period of the heart.

Pain

[0123] Compounds of formula (I) or the pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of pain such as pain of central origin, pain seen after damage to the CNS, stroke, infarction, pain of peripheral origin, chronic pain, neuropathies and disorders where a treatment effect is achieved by stimulation of receptors in the periaqueductal grey area.

Other uses

Skin tanning

[0124] 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.

[0125] 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. sebacous glands and over or underproduction of sebum.

In vivo formation of second messenger elements

[0126] 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

[0127] 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.

[0128] 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).

[0129] Compounds of formula (I) or the pharmacologically acceptable salts thereof may also be tagged with a toxic agent (i.e. doxorubicin, ricin, diphtheria toxin or other) and used for targeted delivery to malignant cells bearing MC receptors, or tagged with a compound capable of activating the endogenous immune system for triggering the immune system (for example a compound, monoclonal antibody or other, capable of binding to a T-cell antigen, e.g. CD3 or other) for treatment of malignancies and other MC receptor expressing diseases. The thus formed hybrid compound will direct cytotoxic cells to the malignant melanoma cells or the MC1-receptor bearing malignant cells and inhibit the tumor growth.

[0130] Compounds of formula (I) or a pharmacologically acceptable salt thereof may be attached to the antibody chemically by covalent or non-covalent bond(s).

[0131] 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.

[0132] 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.

[0133] Some of the compounds of the invention have an effect on xanthine oxidase in mammals, including humans.

[0134] The invention is further illustrated by the following non-limiting examples.

EXPERIMENTAL

Example 1 - Synthesis

[0135] [1-(2-Nitrophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium actate (see figure 1, structure no.19) was synthesised as described below and as illustrated in Fig. 2.

Synthesis of 1-(2-Nitro-phenyl)-1H-pyrrole (1a)

[0136] 1.37 g (9.9 mmol) 2-nitro-anilin and 1.3 ml (11 mmol) of 2,5-dimethoxy-tetrahydrofuran was refluxed for 1 hour in 20 ml acetic acid. The reaction mixture was evaporated and the residue was diluted in EtOAc and washed with water, $NaHCO_3$ (sat.), water, and then dried over Na_2SO_4. The solvent was evaporated and 1.8 g (96%) of **1a** was obtained as an oil.

Synthesis of 1-(2-Nitro-phenyl)-1H-pyrrole-2-carbaldehyde (2a)

[0137] $POCl_3$ was added to DMF at 0-10°C after which 50 ml of CCl_4 was added at room temperature. A solution of 4.5 g (24 mmol) **1a** in 50 ml of CCl_4 was added slowly to the reaction mixture at about 10° C during 1 hour. The reaction mixture was refluxed for 15 min. and a solution of 50 g of NaOAc,$3H_2O$ in 50 ml of H_2O was added and refluxing was continued for 15 min. The mixture was cooled, extracted with ether and dried over Na_2SO_4. 8.0 g (65%) of **2a** was isolated by column chromatography using EtOAc:petroleum ether as eluent.

Synthesis of 1-(2-Nitro-phenyl)-2-(2-[1,3]dioxolan-2-yl-vinyl)-1H-pyrrole (3a)

[0138] 2.98 g (13.8 mmol) **2a,** 1.2 eqv. of tributyl-[1,3]dioxolan-2-ylmethyl-λ^5-phosphane and 1.5 eqv. KOtBu in DMSO was stirred at 60°C for 24 hours. The reaction was monitored by TLC (EtOAc:petroleum ether 1:2). After cooling, the reaction mixture was poured into water and extracted with ether and the solvent was evaporated. The semi-solid residue was diluted with ether and filtrated to remove residual Bu_3PO and the product was purified by column chromatography (EtOAc: petroleum ether 1:2) to yield 2.6 g (66%) of **3a.**

Synthesis of 3-[1-(2-Nitro-phenyl)-1H-pyrrol-2-yl]-propenal (4a)

[0139] A solution of 2.6 g (9.1 mmol) **3a** in 50 ml diethyl ether was stirred with 10% aqueous HCl for 1 hour. The reaction mixture was washed with 5% $NaHCO_3$, dried over $NaHCO_3$. After evaporation of the solvent, 2 g (91%) of **4a** was obtained.

Synthesis of [1-(2-Nitrophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium actate (5a)

[0140] 2 g (8.3 mmol) **4a** and 1.1 eqv. of aminoguanidine bicarbonate was mixed in THF and refluxed for 30 min. The solvent was evaporated and the residue was diluted with acetonitrile and the product crystallised. Purification by recrystallisation from acetonitrile yielded 1.35 g (55%) of the final product **5a** (m.p. 192-194°C).

^{1}H NMR spectrum

[0141] (Varian 200 MHz) (DMSO-D_6) δ (ppm): 1.79 (s, 3H); 6.17-6.37 (m, 2H); 6.2-7-2 (br s, 5H); 6.45 (dd, J=9.1 Hz and 15.8 Hz, 1H); 6.62-6.71 (m, 1H); 6.94-7.01 (m, 1H); 7.60 (d, J=9.1 Hz, 1H); 7.63 (dd, J=1.3 Hz and 7.6 Hz, 1H); 7.77 (dt, J=1.3 Hz and 7.6 Hz, 1H); 7.89 (dt, J=1.3 Hz and 7.6 Hz, 1H); 8.13 (dd, J=1.3 Hz and 8.2 Hz, 1H)

Elemental analysis

[0142]

Found:	C 53.7, H 5.1, N 23.3
Calculated:	C 53.6, H 5.1, N 23.5

Example 2 - Synthesis

[0143] [1-(2-Bromophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium actate (see figure 1, structure no.53) was synthesised as described below and as illustrated in Fig. 3.

Synthesis of 1-(2-Bromo-phenyl)-2-(2-[1,3]dioxolan-2-yl-vinyl)-1H-pyrrole (3b)

[0144] 3.12 g (12.5 mmol) of 1-(2-Bromo-phenyl)-1H-pyrrole-2-carbaldehyde and 1.2 eqv. of tributyl-[1,3]dioxolan-2-ylmethyl-λ^5-

phosphane and 1.5 eqv. KOtBu in 20 ml DMSO was stirred for 2 hours. The reaction mixture was heated to 47°C and stirred over night. The reaction mixture was cooled down to room temperature and poured into 200 ml of water and extracted with diethyl ether, dried over Na_2SO_4 and the solvent was evaporated. An oily residue was obtained which crystallised over night. The precipitate was washed with diethyl ether, filtered and dried. A mixture of E and Z isomers was obtained. Purification by column chromatography yielded 2 g (50%) of the E isomer **3b.**

Synthesis of 3-[1-(2-Bromo-phenyl)-1H-pyrrol-2-yl]-propenal (4b)

[0145] 1.74 g (5.4 mmol) **3b** was dissolved in 20 ml of diethyl ether and stirred with 20 ml 10% aqueous HCl for 40 min. The reaction was monitored by TLC (EtOAc:petroleum ether 1:2). The reaction mixture was washed with 5% $NaHCO_3$, dried over $NaHCO_3$ and the solvent was evaporated. The product was isolated by column chromatography (EtOAc:petroleum ether 1:5) to yield 0.9 g (60%) of **4b.**

Synthesis of [1-(2-Bromophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium acetate (5b)

[0146] 0.9 g (3.26 mmol) **4b** and 1.2 eqv. of aminoguanidine bicarbonate was mixed in 10 ml of ethanol and 2 ml of acetic acid and refluxed for 30 min. The solvent was evaporated and the oily residue was dissolved in acetonitrile and a few drops of diethyl ether was added.

[0147] After three days in refrigerator a precipitate was formed that was filtered, washed with diethyl ether and dried. 340 mg (31%) of the final product **5b** was obtained as white crystals (m.p. 166-168°C).

^{1}H NMR spectrum

[0148] (Varian 200 MHz) (DMSO-D_6) δ (ppm): 1.75 (s, 3H); 6.21 (d, J= 16.0 Hz, 1H); 6.28-6.33 (m, 1H); 6.42 (dd, J=9.2Hz and 16.0 Hz, 1H); 6.5-8.0 (br s, 5H); 6,68 (dd, J= 1.4 Hz and 3.8 Hz, 1H); 6.93 (dd, J=1.6 Hz and 2.6 Hz, 1H); 7.41-7.59 (m, 3H); 7.63 (d, J=9.2 Hz, 1H); 7.79-7.90 (m, 1H)

Elemental analysis

[0149]

Found:	C 48.6, H 4.5, N 18.2
Calculated:	C 49.0, H 4.6, N 17.9

Example 3 - *In vitro* pharmacology and binding assays

Description of applied methods

[0150] Determination of binding affinities for MC receptors was performed by [^{125}I]-[Nle4,D-Phe7]α-MSH ([^{125}I]-NDP-MSH) radio-ligand binding. In short, murine B16-F1 melanoma cells expressing MC1, but not other MC receptors, were used for binding affinity studies against the murine MC1 receptor (Siegrist et al.; 1988, J. Recept. Res., 8(1-4):323-43). For human MC3, MC4 and MC5 receptor affinities human recombinant CHO cells were used (Schioth et al. 1997, Neuropeptides 31:565-71,1997). Cells were 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} were added. After incubation at 37°C (22°C for the MC1 receptor assay) separation of bound and free [^{125}I]-NDP-MSH was done by multiple washings with buffer.

[0151] The results were expressed as a percent of control specific binding obtained in the presence of the test compounds.

Mean values for each assay are presented in Table I below. The IC_{50} values (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficients (n_H) were determined by non-linear regression analysis of the competition curves using Hill equation curve fitting. The inhibition constants (K_i) were calculated from the Cheng Prusoff equation ($K_i = IC_{50}/(1+(L/K_D))$), where L = concentration of radio-ligand in the assay, and K_D = affinity of the radio-ligand for the receptor).

Table I

Assay	Ligand	Conc.	Non Specific	Incubation
MC_1	[^{125}I]NDP-MSH	0.05 nM	NDP-MSH (1 µM)	90 min/22°C
MC_3 *(h)*	[^{125}I]NDP-MSH	0.075 nM	NDP-MSH (1 µM)	60 min/37°C
MC_4 *(h)*	[^{125}I]NDP-MSH	0.05 nM	NDP-MSH (1 µM)	120 min/37°C
MC_5 *(h)*	[^{125}I]NDP-MSH	0.05 nM	NDP-MSH (1 µM)	60 min/37°C

[0152] Three reference compounds, all belonging to the class of compounds disclosed in WO 03/013509, as well as three compounds according to the present invention were tested. As can be seen, the assayed compounds of the invention differed from the corresponding reference compounds only in the structure of the aminoguanidine substituent of the pyrrole ring.

Reference-compound 1:

[0153] [1-[4-chlorophenyl)-1H-pyrrol-2-yl-methyleneamino]guanidinium acetate

Reference-compound 2:

[0154] [1-[2-nitrophenyl)-1H-pyrrol-2-yl-methyleneamino]guanidinium acetate

Reference-compound 3:

[0155] [1-[2-bromophenyl)-1H-pyrrol-2-yl-methyleneamino]guanidinium acetate

Compound 1 of the invention (see figure 1, structure no.1):

[0156] [1-(4-chlorophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium acetate

Compound 2 of the invention (see figure 1 structure no.19):

[0157] [1-(2-nitrophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium acetate

Compound 3 of the invention (see figure 1 structure no.53):

[0158] [1-(2-bromophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium acetate

Results

[0159] Surprisingly, Compound 1 of the invention showed marked increased binding affinity to both the murine MC1 and the

human MC4 receptor when compared to reference-compound 1 (see Table II below). This result shows that the present modification of the aminoguanidine substituent of the pyrrole ring results in a compound of marked increased binding affinity to the MC1 and MC4 receptor when compared to the compounds disclosed in WO 03/013509.

Table II

K_i (nM)	MC_1	MC_3 *(h)*	MC_4 *(h)*	MC_5 *(h)*
Reference-compound 1	>1,000	> 1,000	> 1,000	> 1,000
Compound 1	88	> 1,000	620	> 1,000

[0160] Compound 2 of the invention showed marked increased binding affinity to the murine MC1 receptor when compared to reference-compound 2 (see Table III below). This result confirms the surprising finding seen with Compound 1 of the invention that modification of the aminoguanidine substituent of the pyrrole ring results in increased binding affinity for the MC1 receptor. Surprisingly, the results further show that substituting the chlorine atom in the 4-position of the phenyl ring (Compound 1 of the invention) with a nitro group in the 2-position (Compound 2 of the invention) induced specific binding affinity to the MC1 receptor.

Table III

Ki (nM)	MC_1	MC_3 *(h)*	MC_4 *(h)*	MC_5 *(h)*
Reference-compound 2	> 1,000	> 1,000	> 1,000	> 1,000
Compound 2	360	> 1,000	> 1,000	> 1,000

[0161] Compound 3 of the invention showed marked increased binding affinity to the murine MC1, as well as the human MC3 and MC4 receptor when compared to reference-compound 3 (see Table IV below). This result confirms the surprising finding seen with Compounds 1 and 2 of the invention that modification of the aminoguanidine substituent of the pyrrole ring results in increased binding affinity for the MC1 receptor. Surprisingly, the results further show that substituting the chlorine atom in the 4-position of the phenyl ring (Compound 1 of the invention) or the nitro group in the 2-position of the phenyl ring (Compound 2 of the invention) with a bromine atom in the 2-position (Compound 3 of the invention) further increased binding affinity to the MC1, MC3 and MC4 receptor.

Table IV

Ki (nM)	MC_1	MC_3 *(h)*	MC_4 *(h)*	MC_5 *(h)*
Reference-compound 3	>1.000	>1.000	>1.000	>1.000
Compound 3	2.6	630	300	>1.000

[0162] The competition curve obtained for Compound 3 of the invention in the MC1 receptor assay is shown in Fig. 4.

[0163] In the following examples methods for testing the *in vitro* and *in vivo* effects of the compounds of the invention are described. The aim of the methods is to test the compounds of the invention for anti-inflammatory effects and ability to inhibit or prevent the cell/tissue/organ impairment or destruction occurring as a result of ischemia, inflammation or toxic effects of a drug.

[0164] An inflammatory response or an exacerbation in chronic inflammation is characterized by production of cell-derived mediators such as tumor necrosis factor α (TNF-α), interleukins (IL-1ß, IL-8, IL10), nitric oxide (NO), and free oxygen radicals, which eventually will induce widespread endothelial damage with loss of arteriolar tonus in systemic vessels, increased capillary permeability, sustained hypotension and organ dysfunction, which in the lung is associated with accumulation of leucocytes including neutrophils and eosinophils within the alveolar space. Lipopolysaccharide (LPS), released from infectious agents, plays a central role in the inflammatory response to infection by inducing a number of inflammatory mediators including TNF-α. Treatments with the ability to inhibit TNF-α production are therefore believed to have marked anti-inflammatory effects. The

inventor is using LPS stimulation to produce an inflammatory response in a number of experimental setups and the primary marker for an anti-inflammatory effect of the compounds according to the invention is the ability to inhibit TNF-α production.

Example 4 *In vivo* effect - Inhibition of LPS-induced TNF-α and IL10 production in rats

[0165] Experimental animals. Female Wistar rats (~250 g) were obtained from the Charles River, Sulzfeld, Germany, and housed in a temperature- (22-24°C) and moisture-controlled (40-70 %) room with a 12 h light-dark cycle (light on from 6:00 A.M. to 6:00 P.M.). The rats were maintained on a standard rodent diet with 140 mmol/kg of sodium, 275 mmol/kg potassium and 23% protein (Altromin International, Lage, Germany) and had free access to water.

[0166] Animal preparation. In isoflurane-nitrous oxide anesthesia, the animals were implanted with permanent medical grade Tygon catheters into the abdominal aorta and the inferior caval vein, respectively, via a femoral artery and vein. After instrumentation, the animals were housed individually for 7-10 days until the day of the experiment.

[0167] Experimental protocol. Prior to the experiments all rats were adapted to the restraining cage used for the experiments by training. On the day of the experiment, the animal were transferred to a restraining cage, and an intravenous infusion of vehicle solution containing 150 mM glucose was started. The infusion rate was 0.5 ml/h throughout the experiment. After a short adaptation period, infusion of lipopolysaccharide (LPS) was started. LPS (E *coli* serotype 0127 B8, L 3129, Sigma, St. Louis, USA) was given at a dose of 4 mg/kg body weight delivered as an i.v. infusion over 1 hour.

[0168] Arterial blood samples of 0.3 ml were taken 120 minutes after start of the LPS infusion.

Experimental groups:

[0169] In addition to LPS infusion all rats were treated with a bolus injection of:

Vehicle (0.5 mL 20% PEG200) or test compound in one of the following doses:

0.1; 1.0; 5.0 mg/kg given intravenously 5 min prior to initiation of the LPS infusion.

[0170] Test compounds: Compound 1 of the invention (figure 1, structure no.1), compound 2 of the invention (figure 1, structure no.19) and compound 3 of the invention (figure 1, structure no. 53).

[0171] Measurement of TNF-α and IL-10 in plasma: The blood samples were collected in a prechilled test tube with 0.5 mM EDTA, pH 7.4, and 20 x 10^6 IU/ml aprotinin. After centrifugation at 4°C, plasma samples were transferred to pre-chilled test tubes and stored at -20°C for later measurements of TNF-α and IL-10. TNF-α and Il-10 in plasma were determined by an ELISA (Biotrak, Amersham, UK).

[0172] Statistical analyses. Results are presented as means ± SE. A two-way ANOVA for repeated measures was used to test for differences between groups. In case of $P<0.05$, the differences between corresponding periods are evaluated by unpaired t-tests with Bonferroni 's correction of the level of significance.

Results

[0173] Compound no.1 and compound no.3 of the invention reduced LPS-induced TNF-α liberation as evaluated by the levels of serum TNF-α 120 min after initiation of the LPS infusion. At the 5.0 mg/kg dose level both compounds reduced the serum level of TNF-α by ~ 60 % when compared to vehicle treatment (13950±486 pg/ml) (see Table V). The maximal anti-inflammatory effect of compound no.2 was obtained at the 0.1 mg/kg dose level (see Table V).
Table V

Serum TNF-α measured 120 after initiation of LPS infusion. N=6 in all groups			
	0.1 mg/kg	1.0 mg/kg	5.0 mg/kg
Compound no.1	10830 ± 4031	6230 ± 1786	5800 ± 703
Compound no.2	5964 ± 957	6130 ± 601	8380 ± 2694
Compound no. 3	10310 ± 2728	5250 ± 1113	5020 ± 862

[0174] All three compounds reduced LPS-induced IL10 liberation as evaluated by the levels of serum TNF-α 120 min after initiation of the LPS infusion. For compound no.2 and compound no.1 the maximal effect were obtained at the 5.0 mg/kg dose level, where the compounds reduced the serum level of IL10 by ~ 46 and 25 % when compared to vehicle treatment (7402±1739 pg/ml) (see Table VI). The maximal anti-inflammatory effect of compound no.3 was obtained at the 1.0 mg/kg dose level where the compound reduced the IL10 response with ~ 55% compared to vehicle treatment (see Table VI).

Table VI

Serum IL10 measured 120 after initiation of LPS infusion. N=6 in all groups				
	0.1 mg/kg	1.0 mg/kg	5.0 mg/kg	
Compound no.1	8485 ± 960	5978 ± 890	5651 ± 325	
Compound no.2	7606 ± 1313	4770 ± 1387	4053 ± 894	
Compound no. 3	5658 ± 1119	3452 ± 1091	3856 ± 973	

Example 5

Inhibition of LPS-induced TNF-α production by human leucocytes *in vitro*

[0175] 20 mL human blood is collected in vacutainer tubes containing EDTA. PBMC is isolated using Ficoll-Paque Plus as in Amersham's Instruction 71-7167-00 AD, 2002-06. PBMC is counted using Tryphan Blue Solution (Sigma) and incubated in RPMI 1640, (Applichem), supplemented with 10 mM Hepes (Sigma), 2 mM L-glutamin (Sigma), 0,1 % BSA (Sigma) and 50U/50µg/mL Penicillin/Streptomycin (Sigma) in the concentration 5 x 10^5 cells/mL. The isolated PBMC is incubated in a humidified 5% CO_2, 95% air atmosphere, at 37°C, in 24 well flat-bottomed plates (Corning Incorporated) with medium, 10 ng LPS/mL (Sigma), and test compound. After 18 hours the samples are centrifuged, and TNF-α in the supernatants is measured using Tumour Necrosis Factor Alpha [(h)TNF-α] from Human Biotrak ELISA System (Amersham).

The samples are incubated as following per donor:

PBMC's in RPMI (Time Control)

PBMC's with 10 ng LPS/mL (Vehicle)

PBMC's, 10 ng LPS/mL, 10^{-17}M reference compound or test compound

PBMC's, 10 ng LPS/mL, 10^{-15}M reference compound or test compound

PBMC's, 10 ng LPS/mL, 10^{-13}M reference compound or test compound

PBMC's, 10 ng LPS/mL, 10^{-11}M reference compound or test compound

PBMC's, 10 ng LPS/mL, 10^{-9}M reference compound or test compound

PBMC's, 10 ng LPS/mL, 10^{-7}M reference compound or test compound

[0176] All samples are diluted from an initial stock solution between $1,4x10^{-4}$M and $1,8x10^{-3}$M. All solutions are handled in BSA coated vials in order to protect against binding of the compound to the surface of the vials.

[0177] Data is presented as mean t SE. The effect of test compounds on LPS induced TNF-α liberation is expressed as percentage of the TNF-α accumulation in the LPS-vehicle group. All comparisons are analysed with Student's unpaired t-test. Differences are considered significant at probability levels (p) of 0.05.

Example 6

Inhibition of neutrophil and eosinophil infiltration after LPS-inhalation in rats.

[0178] Male Sprague-Dawley rats (weight ~200 g) from M&B A/S, DK-8680 Ry, Denmark, are used. The rats are caged in standard cages type 3 and housed in a temperature- (22-24 °C) and moisture-controlled (40-70 %) room with a 12 h light-dark cycle (light on from 6:00 A.M. to 6:00 P.M.). The diet is autoclaved Altromin 1324 special formulation, Produced by Altromin Denmark, Chr. Pedersen A/S, 4100 Ringsted, Denmark. Diet and water are administered ad libitum.

[0179] After acclimatization the rats are randomly allocated to the experimental groups and dosed i.v. with test compound at start of LPS-induction and once again 8 hours after LPS-induction.

[0180] Rats in groups of 3 are anaesthetized with 0,1 ml hypnorm/dormicum pr. 100 g and dosed i.v with the test compound. Immediately after dosing they are placed in the inhalation chamber where they are subjected to a nebulized LPS solution. The concentration of LPS is 1 mg/ml. Dosing time is 15 minutes. The rats are euthanized 24 hours after dosing with the test substance. At termination the rats are eutanized with CO_2/O_2.

[0181] Then bronchoalveolar lavage is performed by installing and withdrawing 6 x 2,5 ml of PBS to the right lung. Lavage is done with the lungs remaining in the thorax after removing sternum and costae. The connection to the left lung is tied off during this procedure. Bronchoalveolar fluid (BALF) is centrifuged at 1000 rpm at 4°C for 10 minutes. After removing the supernatant the cell pellet is resuspended in 0.5 ml PBS and total cell count performed. Two smears of BALF stained with May-Grüwald Giemsa stain is made from each rat. BALF from each rat is subjected to total cell count and to differential count of leucocytes.

Experimental groups:

[0182] In addition to LPS infusion all rats are treated with bolus injections of either:

Vehicle (0.5 mL isotonic saline);

Reference compound: e.g. reference-compound no.1 (e.g. 0.1, 0.2, 1.0 or 5.0 mg/kg/bw) and/or reference-compound no.2 (e.g 0.1, 0.2, 1.0 or 5.0 mg/kg/bw) and/or reference-compound no.3 (0.1, 0,2, 1.0 or 5.0 mg/kg/bw) and/or α-MSH (e.g. 0.1, 0,2, 1.0 or 5.0 mg/kg/bw). Finally a time control group without LPS inhalation is treated with Vehicle.

Statistics

[0183] Data are presented as mean ± S.E.. Between group comparisons are performed by one way analysis of variance followed by Fishers Least Significant Difference test. Differences are considered significant at the 0.05 level.

Example 7

Inhibition of LPS-induced cytokine release and pulmonary hypertension in pigs *in vivo*.

[0184] Female Landrace pigs (~30 kg) are fasted overnight but allowed free access to water. Then the pigs are premedicated with intramuscular ketamine (10 mg/kg) and midazolam (0.25 mg/kg). Anesthesia is induced with intravenous ketamine (5 mg/kg). The pigs are orally intubated, and anesthesia is maintained with a continuous intravenous infusion of fentanyl (60 µg/kg/h and midazolam (6 mg/kg/h). The animals are ventilated with a volume-controlled ventilator (Servo 900 ventilator; Siemens Elema, Solna, Sweden) with a positive end-expiratory pressure of 5 cm H_2O. Tidal volume is kept at 10-15 ml/kg, and the respiratory rate adjusted (20-25 breaths/min) to maintain normocapnia (arterial carbon dioxide tension [$PaCO_2$] in the range of 34-45 mmHg). Ventilation is performed with oxygen in air aimed tot reach an arterial oxygen tension (PaO_2) higher than 105 mmHg. One arterial and 2 venous sheaths are placed in the carotid artery and corresponding veins for infusion, blood pressure measurements through fluid filled catheter, blood sampling and for introducing catheters.

[0185] A Swan-Ganz catheter (Edwards Lifescience Corp., Irvine, CA) is inserted in the pulmonary artery via the right cava superior vein. Localization of the balloon-tipped catheter is determined by observing the characteristic pressure trace on the monitor as it is advance through the right side of the heart into the pulmonary artery as well as by x-ray. Another catheter (5 French; St. Jude Medical Company, St. Paul, MN) is inserted into the left carotid artery for continuous blood pressure monitoring and blood sampling. A urine catheter is inserted for urine collection. A temporary pace catheter is inserted through the venous sheath to the right atrium (x-ray guided) to standardise heart rate, when assessing cardiac performance.

[0186] **Hemodynamic Monitoring.** Continuous observations is performed of arterial blood pressure, heart rate (from the electrocardiogram), and pulmonary artery pressure (PAP). **Lipopolysaccharide Infusion.** *Escherichia coli* lipopolysaccharide endotoxin, (*E. coli* 026:_6, Bacto Lipopolysaccharides; Difco Laboratories, Detroit, MI) is dissolved in saline 120 min before each experiment to dissolve any precipitate. After a stabilization period, lipopolysaccharide infusion is started at baseline at a rate of 2.5 µg/kg/h and increased stepwise to 15 µg/kg/min during 30 min. After this, the fusion was kept at a rate of 2.5 µg/h kg/h during 150 min and thereafter discontinued.

[0187] **Interventional groups:** The control group is given vehicle in equal volume to the intervention group immediately before LPS infusion is initiated. The interventional group is given a dose of reference compound (e.g. 0.1, 0.2, 1.0 or 5.0 mg/kg) or test compound (e.g 0.1, 0.2, 1.0 or 5.0 mg/kg), as a single intravenous bolus injection.

[0188] **Cytokines.** Fresh frozen plasma samples (-80°C) obtained from EDTA-stabilized blood is used for measurements of TNFα by use of commercial available enzyme-linked immunosorbent assays according to the manufacturer's instructions.

[0189] **Statistics.** Data are presented as mean ± S.E.. Between group comparisons are performed by one way analysis of variance followed by Fishers Least Significant Difference test. Differences are considered significant at the 0.05 level.

[0190] In the following two examples of models of temporarily ischemia are described. Ischemia induced by reduced/complete arrest in arterial blood supply induces multiple tissue reactions including neutrophil accumulation, other inflammatory responses and cell death. Identification of compounds that could inhibit or prevent (either completely or partially) many of the cell/tissue/organ impairments or destructions occurring as a result of ischemia/inflammation is of great benefit. The inventor is using two models of temporarily ischemia: 1) the myocardial ischemia reperfusion model in rats, which mimics the development of acute myocardial infarction followed by restoration of blood supply as it is achieved by either fibrinolytic therapy or coronary angioplasty (example 8); and 2) bilateral renal artery occlusion, which induces acute renal failure (ARF) comparable to AFR induced by temporarily reduction in the renal blood supply as seen in patients undergoing major surgical interventions (an example could be surgical intervention due to abdominal aorta aneurism) (example 9).

Example 8

Inhibition of myocardial infarction size, induced by 60 minutes occlusion of the left anterior descending coronary artery in rats.

[0191] Barrier-bred and specific pathogen-free female Wistar rats (250 g) are obtained from Charles River, Hannover, Germany. The animals are housed in a temperature (22-24°C) and moisture (40-70%) controlled room with a 12-hour light-dark cycle (light on from 6:00 A.M. to 6:00 P.M.). All animals are given free access to tap water and a pelleted rat diet containing approximately

140 mmol/kg of sodium, 275 mmol/kg potassium and 23% protein (Altromin catalogue no. 1310, Altromin International, Lage, Germany).

[0192] The rats are instrumented with permanent medical grade Tygon catheters in the inferior caval vein and the abdominal aorta via the femoral vein and artery. One week later the Rats are anaesthetized in an inhalation chamber with 4% isoflurane in O_2. After insertion of an endotracheal tube the animal is artificially ventilated with 1.0% isoflurane in O_2 using af Hugo Basile Rodent ventilator. Tidal volume is 8-10 ml/kg b.w. and respiratory rate 75 min^{-1}, which maintains arterial pH between 7.35 and 7.45. During surgery the animal is placed on a heated table that maintains rectal temperature at 37-38°C. Standard ECG (second lead) is measured using a Hugo Sachs ECG Coupler and collected on line at 4,000 Hz in PowerLab. After parasternal thoracotomy and opening of the pericardium the left anterior descending coronary artery (LAD) is localized visually. An atraumatic 6-0 silk suture with an occluder that allows reopening of the ligature is placed around the LAD between the pulmonary trunk and the lower right end of the left auricle. After 10 minutes the left anterior descending coronary artery (LAD) is occluded. Successful occluding is confirmed by alterations in ECG (ST-segment elevation and increase in R-wave amplitude) and by fall in MAP. Reperfusion is made after 60 minutes by opening the occluder. Control rats are sham-operated.

[0193] The rats are subjected to one of the following i.v treatments:

Vehicle: 0.5 ml 150 mM NaCl.

Reference compound: e.g reference-compound no.1, reference-compound no.2 or reference-compound no.3 (e.g. 0.1, 0.2, 1.0 or 5.0 mg/kg b.w.) or e.g. α-MSH (e.g. 0.1, 0.2, 1.0 or 5.0 mg α-melanocyte stimulating hormone/kg b.w.) in 0.5 ml 150 mM NaCl.

Test compound e.g. 0.1, 0.2, 1.0 or 5 mg test compound/kg b.w. in 0.5 ml 150 mM NaCl.

Treatment is given 5 minutes prior to reperfusion.

Determination af the size of the ischemic and necrotic myocardium

[0194] The rats are kept anaesthetized after the ischemia/reperfusion and re-occluding of the LAD is performed after three hours reperfusion. During this period ECG and MAP are measured continuously. Then Evans Blue dye (1 ml; 2% w/v) is administered i.v. to determine the size of the ischemic area. The heart is removed and cut into horizontal slices to determine the size of the ischemic area and to separate the ischemic myocardium from the non-ischemic myocardium. The ischemic area is isolated and incubated in a 0.5% triphenyltetrazolium chloride solution for 10 minutes at 37°C. The size of the necrotic tissue is then measured by used of a computerized image program. An additional setup of animals are treated with buprenorphine post-surgical and returned to there cages for measurement of left ventricular end diastolic pressure (LVEDP) two weeks later in order to evaluate the effect of the pharmacological treatment on the development of congestive heart failure. LVEDP is measured using a 2F microtip catheters inserted into the left ventricle via the right carotid artery. Isoflurane concentration is adjusted to stabilize mean arterial pressure (MAP) at 85-90 mmHg.

Statistics

[0195] Data are presented as mean ± S.E.. Within group comparisons are analysed with Student's paired *t* test. Between group comparisons are performed by one way analysis of variance followed by Fishers Least Significant Difference test. Differences are considered significant at the 0.05 level.

Example 9

Inhibition of renal failure induced by 40 minutes bilateral occlusion of the renal arteries in rats

[0196] Barrier-bred and specific pathogen-free female Wistar rats (250 g) are obtained from Charles River, Hannover, Germany. The animals are housed in a temperature (22-24°C) and moisture (40-70%) controlled room with a 12-hour light-dark cycle (light

on from 6:00 A.M. to 6:00 P.M.). All animals are given free access to tap water and a pelleted rat diet containing approximately 140 mmol/kg of sodium, 275 mmol/kg potassium and 23% protein (Altromin catalogue no. 1310, Altromin International, Lage, Germany).

[0197] The rats, which previously have been instrumented with a chronic venous catheter, are placed in metabolic cages and after a two days acclimation period to the metabolic cages, experimental ARF is induced by occlusion of both renal arteries for 60 min. During surgery, the rats are anesthetized with isoflurane-nitrous oxide and placed on a heated table to maintain rectal temperature at 37°C. Both kidneys are exposed through flank incisions, mobilized by being dissected free from the perirenal fat, then a small portion of the renal artery is gently dissected from the vein. The renal arteries are occluded with a smooth surfaced vascular clip (60 g pressure; World Precision Instruments, UK) for 40 min. Total ischemia is confirmed by observing blanching of the entire kidney surface. During the period of ischemia, the wounds are closed temporarily to maintain body temperature. After the clips are removed, the kidneys are observed for additional 2-5 min. to ensure color change, indicating blood reflow. Then the wound are closed with 3-0 silk ligatures. The rats returned to the metabolic cages, and daily 24 h urine output and water intake are measured for five days. As a control group, rats are subjected to sham operations identical to the ones used for ARF rats without occlusion of the renal arteries. Sham-operated rats are monitored in parallel with rats with ARF.

[0198] The rats are subjected to one of the following i.v treatments:

Vehicle: 0.5 ml 150 mM NaCl.

Reference compound: e.g reference-compound no.1, reference-compound no.2 or reference-compound no.3 (e.g. 0.1, 0.2, 1.0 or 5.0 mg/kg b.w.) or e.g. α-MSH (e.g. 0.1, 0.2, 1.0 or 5.0 mg α-melanocyte stimulating hormone/kg b.w.) in 0.5 ml 150 mM NaCl.

Test compound: e.g. 0.1, 0.2, 1.0 or 5 mg test compound/kg b.w. in 0.5 ml 150 mM NaCl. Treatment is given 5 minutes prior to reperfusion of the kidney and subsequently 6 and 24 hours later.

Statistics

[0199] Data are presented as mean ± S.E.. Within group comparisons are analysed with Student's paired t test. Between group comparisons are performed by one way analysis of variance followed by Fishers Least Significant Difference test. Differences are considered significant at the 0.05 level.

[0200] Furthermore, an example (example 10) is given on a model of cisplatin-induced renal failure. Nephrotoxicity is a well-known side effect to cisplatin treatment. Though not necessarily dose limiting renal toxicity still affects the majority of patients and a significant decrease in glomerular filtration rate is observed during treatment. The renal toxicity of cisplatin is seen as a direct cytotoxic damage on the nephrons in the outer medulla especially in the S3 segment of the proximal tubules and in the thick ascending limb of the loop of Henle. Hence cisplatin treatment often results in tubular reabsorption defects including an impaired ability to dilute the urine. Hypomagnesemia is observed in approximately 50% of patients treated with cisplatin and is probably due to a defect in renal magnesium (Mg) reabsorption. A recent study has suggested that Mg supplementation is a crucial factor in protection against the nephrotoxic actions of Cyclosporin A and a possible relation between Mg loss and cisplatin induced nephrotoxicity has recently been suggested. Treatment aimed to prevent hypomagnesemia would therefore have beneficial effects in order not only to reduce the need of Mg supplementation, but also in order to reduce the renal toxicity of cisplatin.

Example 10

Inhibition of Cisplatin induced renal failure

[0201] Rats, which previously have been instrumented with a chronic venous catheter, are placed in metabolic cages and after a period of acclimation to the metabolic cages the rats are treated with an interperitoneal cisplatin injection 5.0 mg/kg bw in 0.5 ml 150 mM NaCl or vehicle (0.5 ml 150 mM NaCl). Five days later the rats are then returned to metabolic cages, and daily 24 h urine output and water intake are measured and collected for the next five days. All rats are then anesthetized in halothan/N_2O and an arterial blood sample collected in prechilled EDTA coated vials. The blood samples are collected in a prechilled test tube with 0.5

mM EDTA, pH 7.4, and 20 x 10^6 IU/ml aprotinin. After centrifugation at 4°C, plasma samples are transferred to pre-chilled test tubes and stored at -20 °C for later measurements of creatinine and Magnesium (Mg). In addition to this creatinine is also measured in the urine collected in the last 24 hours period prior to the blood collection. Creatinine clearance (C_{cr}), used as an index of glomerular filtration rate (GFR), can then be calculated as the $C_{cr}= V_U \times U_{cr}/P_{cr}$, where V_U is 24 hours urine production; U_{cr} is the creatinine concentration on the urine and P_{cr} is the creatinine concentration in plasma. Measurement of creatinine in urine and plasma is performed by use of the clinical chemistry systems VITROS 950 (Ortho-Clinical Diagnostics Inc., Johnson & Johnson, NJ) and Roche Hitachi Modular (Roche Diagnostics, Mannheim, Germany).

[0202] The rats are subjected to one of the following i.v treatments:

Vehicle: 0.5 ml 150 mM NaCl

Reference compound: e.g reference-compound no.1, reference-compound no.2 or reference-compound no.3 (e.g. 0.1, 0.2, 1.0 or 5.0 mg/kg b.w.) or e.g. α-MSH (e.g. 0.1, 0.2, 1.0 or 5.0 mg α-melanocyte stimulating hormone/kg b.w.) in 0.5 ml 150 mM NaCl.

Test compound: e.g. 0.1, 0.2, 1.0 or 5 mg test compound/kg b.w. in 0.5 ml 150 mM NaCl. Treatment is given 5 minutes prior to reperfusion of the kidney and subsequently 6 and 24 hours later.

Statistics

[0203] Data are presented as mean ± S.E.. Within group comparisons are analysed with Student's paired t test. Between group comparisons are performed by one way analysis of variance followed by Fishers Least Significant Difference test. Differences are considered significant at the 0.05 level.

[0204] In the following a model for testing the compounds of the invention for a curative effect on arthritis is described.

Example 11

[0205] Lewis Rats are used ~150g (n=10 / group). On Day 0 sensitization by intradermal injection of collagen at base of tail (collagen type II / IFA) is performed. On Day 11, 14, 16, 18 and 21 evaluation of paws is performed.
END POINTS: - PAW OEDEMA
- CLINICAL JOINT SCORE
- BODY WEIGHT

[0206] Compound dosing once daily prophylactically (group b) or therapeutically (group c) by gastric lavage.

[0207] The groups for evaluation are:

a)	Vehicle	treatment from Day 0
b)	Prophylactically	treatment from Day 0
c)	Therapeutically	treatment from Day 0

[0208] 20% PEG200, 40% Cremophor RH40, 25 % Labrasol or 30 % Hydroxypropyl-β-cyclodextrin were used as vehicle, based on previous studies showing that the formulation was well tolerated and associated with significant plasma exposure in rats.

Collection of blood and preparation of plasma

Day 4, 24 h after the dosing on Day 3:	0.25 ml blood sample,
Day 21, 24 h after the dosing on Day 20:	0.25 ml blood sample,
Day 21, 5 h after dosing on Day 21:	0.25 ml blood sample,

[0209] Samples are stored in -80°C until measurement of cytokines.

Measurement of TNF-α in plasma:

[0210] By an ELISA (Biotrak, Amersham, UK).

Statistical analyses

[0211] Results are presented as means ± SE. A two-way ANOVA for repeated measures is used to test for differences between groups. In case of $P<0.05$, the differences between corresponding periods are evaluated by unpaired t-tests with Bonferroni's correction of the level of significance.

Example 12

Aims of the study

Objectives:

[0212]

- Determine the effects of up to 32 days treatment with compounds of the invention on food intake, water intake and body-weight in selectively bred male Sprague-Dawley rats displaying enhanced likelihood of developing diet-induced obesity (DIO) and/or in homozygote Zucker rats.
- Determine whether repeated treatment with compounds of the invention alter glucose handling and insulin resistance examined by standard oral glucose test
- Determine whether repeated treatment with compounds of the invention alters body composition in DIO and/or homozygote Zucker rats.
- Determine whether repeated treatment with compounds of the invention affects adipose tissue inflammation as assessed by mean number of infiltrating macrophages.

[0213] In addition to this, the objective of the study is to sample baseline and end of study blood sample for analysis of insulin, and other relevant biochemical markers.

Experimental protocol

Animals

[0214] DIO and/or homozygote Zucker rats are used in the experiments. In DIO rats the experiment start when the animals have reached an age of 22 weeks and has been set on a high fat diet from week 3 to week 22 (HF-diet: High fat diet (4.41 kcal/g - Energy %: Carbohydrate 51.4 kcal %, Fat 31.8 kcal %, Protein 16.8 kcal %; diet #12266B; Research Diets, New Jersey, USA).

[0215] In Homozygous Zucker rats experiments are started when the rats have reached an age of 8 weeks.

[0216] The rats are housed individually under a normal light cycle at controlled temperature conditions.

Randomization and Dosing

[0217] All animals are randomized according to body weight to participate in one of following drug treatment groups (n=10).

[0218] Vehicle group: Rats receiving once daily or twice daily dosing of Vehicle given either orally, intravenously or subcutaneously where the vehicle in most cases is one of the following: 20% PEG200, 40% Cremophor RH40, 25 % Labrasol or 30 % Hydroxypropyl-β-cyclodextrin

[0219] Treatment group: Rats receiving once daily or twice daily dosing of a compound of the invention given either orally, intravenously or subcutaneously at the dose levels up to 50 mg/kg per dose.
All compounds are administered 3 hours prior to lights out for up to 32 days.

[0220] For all groups, the experiment is immediately preceded by 3 day training period with mock gavage daily to accustom the animals to the procedure.

[0221] Animals will be randomized into 6 treatment groups at day -3 based on body weight.

Compounds and Dosing

[0222] Compounds of the invention (e.g compound no.1 and compound no.2) will be dissolved on a weekly basis in vehicle (20% PEG200, 40% Cremophor RH40, 25 % Labrasol or 30 % Hydroxypropyl-β-cyclodextrin) and administered via oral gavage, intravenous injection or subcutaneous injection (volume up to 5ml/kg) once or twice daily.
Vehicle (20% PEG200, 40% Cremophor RH40, 25 % Labrasol or 30 % Hydroxypropyl-β-cyclodextrin) will be prepared on a weekly basis and administered via oral gavage, intravenous injection or subcutaneous injection (volume up to 5ml/kg) once or twice daily.

Experimental Protocol

[0223] From day -3 of dosing to the end of the experiment body weight and 24-hour food- and water intake is recorded daily or bi-weekly.
Baseline and terminal blood samples are collected for measurement of glucose, cholesterol, insulin, triglycerides and free fatty acid.

[0224] Oral glucose tolerance test will be conducted either on a paired basis prior to treatment and after two weeks treatment or alternatively only after up to four weeks treatment. Body body composition at termination and subsequently histology/quantitative assessment of infiltrating macrophages will be conducted by the end of the study period (see procedure below).

Oral Glucose Tolerance Test (OGTT)

[0225] The rats are fasted to 50% of normal intake, ie that 50% of normal food supply is offered is offered at 12/noon the previous day in case the dark cycle begins at 5PM.

[0226] Animals are dosed PO with compound at the regular time point on day prior to the OGTT. The following morning at 8AM the animals receive the oral glucose load of 2 g/kg glucose (Glucose 500 mg/ml. Venous blood samples are taken in heparinised tubes at time points - 15, 0, 15, 30, 60, 120, 180 and 240 minutes after oral administration of glucose for measurement of glucose and insulin. The oral glucose load is given as gavage via a gastric tube connected to a syringe ensuring accurate dosing. After the OGTT, animals are re-fed and dosed their respective compounds.

Blood sampling and plasma measurements

[0227] Baseline and terminal blood samples (approximately 0.4ml of processed plasma) are collected at on day -3 prior to initiation of dosing and again at the termination of the study. Animals are fasted to 50% of normal intake prior to sampling. 50% food is offered at 12/noon the previous day. Blood is collected in sample tubes Heparinised Vacutainer for glucose, cholesterol, insulin, triglycerides, and EDTA vacutainers containing 1% NaF for free fatty acids.

[0228] Samples for analysis of plasma glucose, triglyceride and cholesterol collected during the OGTT and at baseline/termination are measured using standard enzyme assay kits. Plasma insulin is measured in duplicates for each data point using the sensitive ELISA based assay. Plasma for measuring FFA is analyzed using a Vako NEFA C kit.

Termination

[0229] After sacrifation at the termination of the study, body white adipose tissue compartments are removed and weighed. Fat depot analysis includes mesenterial, retroperitoneal, epididymal, subcutaneous inguinal white fat. Fat compartments are finally fixated in 4% formalin buffered paraformaldehyde (PFA) for subsequent analyses of tissue inflammation (infiltrating macrophages) buy use of stereology.

Data, reporting, and Statistical Evaluation

[0230] Statistical evaluation of the data is carried out using one-way analysis of variance (ANOVA) with appropriate post-hoc analysis between vehicle and treatment groups in cases where statistical significance is established ($p<0.05$; Fishers).

Example 13

Plasma kinetics in rat following intravenous and oral administration of the compounds of the invention

[0231] This study determined the intravenous pharmacokinetics and oral bioavailability of compound 1 of the invention (see figure 1, structure no.1), compound 2 of the invention (see figure 1, structure no.19) and compound 3 of the invention (see figure 1, structure no.53) following administration to Sprague Dawley rats at a dose level of 10 mg/kg.

[0232] Six groups of 3 male rats received either a single intravenous or single oral administration of compound 1, 2 or 3 of the invention at a dose level of 10 mg/kg. Blood samples were obtained at various times after dosing. Plasma samples were analysed for unchanged test item using a suitable LC-MS/MS method. Pharmacokinetic parameters were estimated from individual plasma concentrations.

[0233] No adverse effects were noted following either intravenous or oral administration of compound 1, 2 or 3 of the invention.

[0234] Following intravenous administration of compound 1 of the invention, mean plasma concentrations declined slowly with a mean apparent terminal half-life of 5.70 h. Systemic clearance of compound 1 of the invention was moderate and volume of distribution exceeded the total body water suggesting extensive distribution to the tissues.

[0235] Following oral administration of compound 1 of the invention, the maximum plasma concentration was observed at 8 h post dose. Thereafter mean plasma concentrations declined slowly with an apparent terminal half-life of 4.61 h. Mean absolute oral bioavailability of compound no.1 was 34.8 %.

[0236] Following intravenous administration of compound 3 of the invention, mean plasma concentrations declined quickly with a mean apparent terminal half-life of 3.14 h. Systemic clearance of compound 3 was high and volume of distribution exceeded the total body water suggesting extensive distribution to the tissues.

[0237] Following oral administration of compound 3 of the invention, the maximum plasma concentration was observed at 4 h post dose. Thereafter the mean plasma concentrations declined quickly with an apparent terminal half-life of 3.30 h. Mean absolute oral bioavailability of compound 3 of the invention was 20.6 %.

[0238] Following intravenous administration of compound 2 of the invention, mean plasma concentrations declined quickly with a mean apparent terminal half-life of 3.25 h. Systemic clearance of compound 2 of the invention was high and volume of distribution exceeded the total body water suggesting extensive distribution to the tissues.

[0239] Following oral administration of compound 2 of the invention, the maximum plasma concentration was observed at 2.5 h post dose. Thereafter mean plasma concentration declined quickly with an apparent terminal half-life of 2.25 h. Mean absolute oral bioavailability of compound 2 of the invention was 3.20 %.

Analytical method

[0240] Plasma samples were analysed for compound 1, 2 or 3 of the invention concentrations using a suitable LC-MS/MS.

Animals and husbandry

[0241] Eighteen male Sprague Dawley rats, age 8-9 weeks at dosing were obtained from Charles River (UK) Limited.

[0242] The animals were housed for at least 5 days in the experimental unit before use on the study.

[0243] During the pretrial holding period, the animals were multiply housed in suitable Home Office compliant polypropylene and stainless steel caging. During on-study periods, the animals were housed singly in polypropylene and stainless steel cages with raised wire-mesh floors.

[0244] Standard laboratory diet (SDS Rat and Mouse Maintenance Diet No. 1, Special Diet Services, Witham, UK) and tap water were available *ad libitum* to the animals and the room temperature and humidity were monitored on a daily basis.

[0245] The appearance and behaviour of the animals were monitored at least daily in order to assess any reaction to treatment.

Dose preparation and Administration

[0246] Phase 1 and 4: Compound 1 formulation for intravenous and oral administration Compound 1 (27.15 mg) was dissolved in an appropriate volume of polyethylene glycol 200 (2.7 mL). An appropriate volume of sterile water (10.8 mL) was then added to achieve a target concentration of 2 mg/mL (final weight of formulation: 13.4931 g).

[0247] Phase 2 and 5: Compound 3 formulation for intravenous and oral administration compound 3 (27.83 mg) was dissolved in an appropriate volume of polyethylene glycol 200 (2.8 mL). An appropriate volume of sterile water (11.2 mL) was then added to achieve a target concentration of 2 mg/mL (final weight of formulation: 13.81604 g).

[0248] Phase 3 and 6: Compound 2 formulation for intravenous and oral administration compound 2 (27.69 mg) was dissolved in an appropriate volume of polyethylene glycol 200 (2.8 mL). An appropriate volume of sterile water (11.2 mL) was then added to achieve a target concentration of 2 mg/mL (final weight of formulation: 13.72737 g).

[0249] Each dose formulation was filtered using a 0.22 µm filter unit (Millipore).

[0250] Eighteen male rats each received either a single intravenous or a single oral administration of either compound 1, 2 or 3 at a dose level of 10 mg/kg. The formulation was orally administered to each animal by gastric gavage and intravenously administered to each animal *via* a tail vein. The dose was administered at a dose volume of 5 mL/kg. The formulations were administered to each animal according to the details in the following table:

Phase	Animal Number	Test Item	Dose Route	Dose Level	Dose Volume	Dose Concentration
1	001M-003M	Compound 1	Intravenous	10 mg/kg	5 mL/kg	2 mg/mL
2	004M-006M	Compound 3				
3	007M-009M	Compound 2				
4	010M-012M	Compound 1	Oral			
5	013M-015M	Compound 3				
6	016M-018M	Compound 2				

[0251] The dose volume administered was calculated according to the bodyweight of each animal on the day of dose administration. The weight of the administered dose was recorded.

[0252] The actual dose received by each animal is presented in Appendix 2.

Surgical Procedure

[0253] Animals were surgically prepared with a single indwelling femoral cannula. The cannula was truncated subcutaneously and externalised through the ventral surface of the tail. The cannula was protected by a metal tail cuff, overlying the exit site, and a spring assembly. The animals were returned to singly to holding cages and the free end of each cannula attached to a swivel joint fixed about the cage.

[0254] The animals were treated with Carprofen (Zenecarp™, C-Vet VP, 50 mg/mL) at a dosage of 5 mg/kg by the subcutaneous route as a premedication prior to surgery and approximately 24 h after surgery.

[0255] Animals were approved for entry on to the study on the basis of satisfactory clinical examination and body weight gain profile, following a recovery period of at least 5 days.

Blood Sampling

[0256] Blood samples (*ca* 0.3 mL) were removed from the femoral vein of each animal into tubes containing lithium heparin as anticoagulant.

Intravenous administration

[0257] Blood samples were collected from 3 rats at the following times after dose administration:

3, 6, 15, 45 min and 1.5, 2.5, 4, 6, 8, 24 h post dose.

Oral administration

[0258] Blood samples were collected from 3 rats at the following times after dose administration:

5, 15, 45 min and 1.5, 2.5, 4, 6, 8, 24 h post dose.

Processing of blood samples

[0259] As soon as practically possible, blood samples were centrifuged at *ca* 1200 *g* at *ca* 4°C for 10 min. Plasma samples stored frozen at *ca* -20°C prior to analysis of test item concentration.

Analysis of Plasma Samples

Preparation of calibration standards

[0260] Compound 1, 2 and 3 were diluted in 5 mM ammonium acetate. Aliquots of these solutions when spiked into control

plasma gave a range of plasma concentrations *ca.* 1-5000 ng/mL.

Internal standards

[0261] [1-(4-chlorophenyl)-1H-pyrrol-2-yl-methyleneamino] guanidinium actate was used as the internal standard (IS) for compound 1, 2 and 3. Internal standard was diluted in 5 mM ammonium acetate and added at a plasma concentration of *ca* 100 ng/mL.

Sample preparation and analysis

[0262] For each batch, calibration and replicate quality control samples were prepared over the range 1-15000 ng/mL for compound 1, 2 and 3.

[0263] Dose solutions were diluted using 5 mM ammonium acetate to give a target plasma concentration of *ca.* 100 ng/mL. Once diluted, the dose solutions were prepared as quality control samples.

[0264] The standards, quality control and test samples were prepared, extracted and analysed in batches along with the freshly prepared blank sample.

[0265] Test samples resulting in a determined concentration below the lowest calibration standard were reported as <LLOQ.

Key analytical equipment

[0266] Mass spectrometer (API4000), Applied Biosystems.
Micro HPLC pump & Vacuum Degasser (Series 200), Perkin Elmer.
Autosampler (HTS Pal), CTC Analytics.
Data handling system (Analyst Version 1.4), Applied Biosystems.
Laboratory information management system, Watson 7.0, Thermo Electron.
Analytical column: Synergi Fusion, 20 x 2.0 mm I D. 2um. (Phenomenex).
Guard column: KrudKatcher, 0.5 µm, Phenomenex.
Key mass spectrometer parameters

Ionisation Mode:	TurbolonSpray
Q1 Resolution:	Unit
Q3 Resolution:	Unit
Ions Monitored:	

Compound	Q1 (M/Z)	Q3 (M/Z)	Polarity	Dwell Time (ms)
Compound 1	288.4	228.9	Positive	75
Compound 3	332.3	272.9	Positive	75
Compound 2	299.5	193.2	Positive	75
Internal standard	262.2	202.9	Positive	75

[0267] Key chromatographic parameters
Mobile Phase A: 100% Acetonitrile
Mobile Phase B: 10 mM ammonium acetate + 0.1% formic acid

Time (min)	% A
0.0	15
0.6	15
1.2	95

Time (min)	% A
1.9	95
2.0	15
2.5	15

Acceptance criteria

[0268] The acceptance criteria for the method establishment were: 75% of the bracketing calibration samples must back-calculate to within 30% of their actual concentration and the assay accuracy and precision of the QC samples should be within 100 ± 30% and ≤30%, respectively.

[0269] The acceptance criteria for the sample analysis were: 75% of the bracketing calibration samples must back-calculate to within 30% of their actual concentration and at least 66% of the QC samples must be within 30% of their actual concentration.

Pharmacokinetic Analysis

[0270] Pharmacokinetic parameters of compound 1, 2 and 3 were derived by non-compartmental analysis using WinNonLin Pro version 5.0.1 (Pharsight 2005). The following parameters were derived, where appropriate, from the individual plasma concentration versus time profiles:

C_0
: The theoretical concentration estimated by back-extrapolation of the initial 2 concentrations to time zero

Cmax
: The maximum observed concentration.

Tmax
: The time of occurrence of Cmax.

AUC_{0-t}
: The area under the concentration versus time curve from time zero (calculated by the linear trapezoidal rule) to the sampling time at the last measurable concentration.

$AUC_{0-\infty}$
: The area under the concentration versus time curve from time zero to infinite time, calculated from AUC0-t + Clast/λz.

λz
: The apparent terminal rate constant.

$t_{½}$
: The apparent terminal half-life, calculated from ln 2/λz.

CL
: The systemic clearance, calculated as Dose/AUC.

V_{ss}
: The apparent volume of distribution at steady state, calculated as (AUMC/AUC) x CL where AUMC is the area under the first moment curve

MRT
: The mean residence time calculated as $AUMC/AUC_{0-\infty}$

MAT
: The mean absorption time calculated as MRT(oral)-MRT(intravenous)

F%
: The absolute oral bioavailability calculated as [AUC_{0-t} (oral)*Dose (iv)/AUC_{0-t} (iv)*Dose (oral)]*100 based on mean values derived after oral and intravenous administration

[0271] Consideration was given to the estimation of λz and corresponding $t_{½}$ values. Three or more points are required within the terminal phase for λz and $t_{½}$ to be estimated. The following additional variables were tabulated to aid identification of

potentially unreliable estimates of $t_{½}$ and AUC:

#pts
The number of data points used in the calculation of λ
λz lower
The lower limit on time for values included in the calculation of λz
λz upper
The upper limit on time for values included in the calculation of λz
λz period
Estimated as (λz upper - λz lower)/t½. Values < 2 will indicate that λz and corresponding t½ estimates are potentially unreliable (Purves 1992)

%AUCextrap The percentage of $AUC_{0-\infty}$ that is due to extrapolation from Clast to infinity

[0272] Pharmacokinetic parameters were reported as geometric mean except Tmax which was reported as the median. Geometric coefficient of variation was calculated as:

$$\sqrt{\exp(SD_{ln}^{2})-1}*100,$$

where SD_{ln} is the standard deviation of the natural logarithmically transformed data)

[0273] Actual sampling times were used for all calculations of pharmacokinetic parameters. Blood sampling time deviation are summarised in Table 7. Plasma concentrations that were below the limit of quantification were taken as zero for the pharmacokinetic analysis.

[0274] Data values are displayed to three significant digits for numbers less than or equal to 1000 and to the nearest integer for numbers greater than 1000.

Results

Dose Administered

[0275] The dose administrations were performed without incident and there were no adverse affects noted for any animal. Animal body weights and dose administration information are given in Appendix 2.

Bioanalysis

[0276] The study plasma samples were extracted and analysed in batches along with the freshly prepared blank samples, calibration standards and quality control samples.

[0277] The calibration data and quality control samples for compound 1, 2 and 3 met the acceptance criteria and results are presented in Appendix 1.

[0278] The quality control establishment batch for compound 1 failed due to carryover, but this was addressed prior to the analysis of the samples. The overall accuracy and bias of the high quality controls were outside the acceptance criteria but each batch met their individual acceptance criteria.

[0279] Study samples resulting in a determined concentration below the lowest calibration standard were reported as <LLOQ.

Pharmacokinetics Following Intravenous Administration of compound 1 of the invention

[0280] The concentrations of compound 1 of the invention in plasma following a single intravenous administration at a dose level of 10 mg/kg are shown in Table VII and presented in Figure 5. The pharmacokinetic parameter estimates are presented in Table XIII.

[0281] Following intravenous administration, the highest mean concentration of compound 1 of the invention in plasma was seen at 3 min post dose with a mean value of 2247 ng/mL. Thereafter the mean plasma concentration of compound 1 of the invention declined with a mean apparent terminal half-life of 5.70 h.

[0282] On average, systemic plasma clearance (CL) of compound 1 of the invention in plasma of male rats was 2709 mL/h/kg, which is approximately 82 % of hepatic blood flow in rats (3312 mL/h/kg, Davies 1993). Mean apparent volume of distribution of compound 1 of the invention in male rats was 17521 mL/kg, which is markedly greater than that of the total body water in rats (668 mL/kg, Davies 2003). The large distribution volume suggests that compound 1 of the invention is widely distributed to tissues.

[0283] Between-animal variability in systemic exposure of male rats to compound 1 of the invention was low (coefficient of variation (CV) of AUC_{0-t} was less than 20%).

Pharmacokinetics Following Intravenous Administration of compound 3 of the invention

[0284] The concentrations of compound 3 of the invention in plasma following a single intravenous administration at a dose level of 10 mg/kg are shown in Table VIII and presented in Figure 6. The pharmacokinetic parameter estimates are presented in Table XIV.

[0285] Following intravenous administration, the highest mean concentration of compound 3 of the invention in plasma was seen at 3 min post dose with a mean value of 3170 ng/mL. Thereafter the mean plasma concentration of compound 3 of the invention declined with a mean apparent terminal half-life of 3.14 h.

[0286] On average, systemic plasma clearance (CL) of compound 3 of the invention in plasma of male rats was 4194 mL/h/kg, which is greater than hepatic blood flow in rats (3312 mL/h/kg, Davies 1993). Mean apparent volume of distribution of compound 3 of the invention in male rats was 13361 mL/kg, which is markedly greater than that of the total body water in rats (668 mL/kg, Davies 2003). The large distribution volume suggests that compound 3 of the invention is widely distributed to tissues.

[0287] Between-animal variability in systemic exposure of male rats to compound 3 of the invention was low (coefficient of variation (CV) of AUC_{0-t} was less than 30%).

Pharmacokinetics Following Intravenous Administration of compound 2 of the invention

[0288] The concentrations of compound 2 of the invention in plasma following a single intravenous administration at a dose level of 10 mg/kg are shown in Table IX and presented in Figure 7. The pharmacokinetic parameter estimates are presented in Table XV.

[0289] Following intravenous administration, the highest mean concentration of compound 2 of the invention in plasma was seen at 3 min post dose with a mean value of 2353 ng/mL. Thereafter the mean plasma concentration of compound 2 of the invention declined with a mean apparent terminal half-life of 3.25 h.

[0290] On average, systemic plasma clearance (CL) of compound 2 of the invention in plasma of male rats was 5075 mL/h/kg, which is greater than hepatic blood flow in rats (3312 mL/h/kg, Davies 1993). Mean apparent volume of distribution of compound 2 of the invention in male rats was 18504 mL/kg, which is markedly greater than that of the total body water in rats (668 mL/kg, Davies 2003). The large distribution volume suggests that compound 2 of the invention is widely distributed to tissues.

[0291] Between-animal variability in systemic exposure of male rats to compound 2 of the invention was low (coefficient of variation (CV) of AUC_{0-t} was less than 30%).

Pharmacokinetics Following Oral Administration of compound 1 of the invention

[0292] The concentrations of compound 1 of the invention in plasma following a single oral administration at a dose level of 10 mg/kg are shown in Table X and presented in Figure 8. The pharmacokinetic parameter estimates are presented in Table XVI.

[0293] Following oral administration of compound 1 of the invention at a target dose of 10 mg/kg, the maximum observed plasma concentration of compound 1 of the invention was achieved at 8 h (t_{max}) post dose with a mean value of 92.9 ng/mL. Thereafter the mean plasma concentrations of compound 1 of the invention declined with an apparent terminal half-life of 4.61 h. The mean absorption time (MAT) was 2.10 h, suggesting that absorption of compound 1 of the invention was largely complete by this time.

[0294] Mean absolute oral bioavailability of compound 1 of the invention in male rats was 34.8 %.

Pharmacokinetics Following Oral Administration of compound 3 of the invention

[0295] The concentrations of compound 3 of the invention in plasma following a single oral administration at a dose level of 10 mg/kg are shown in Table XI and presented in Figure 9. The pharmacokinetic parameter estimates are presented in Table XVII.

[0296] Following oral administration of compound 3 of the invention at a target dose of 10 mg/kg, maximum plasma concentrations of compound 3 of the invention were achieved at 4 h (t_{max}) post dose with a mean value of 92.5 ng/mL. Thereafter the mean plasma concentration of compound 3 of the invention declined with an apparent terminal half-life of 3.30 h. The mean absorption time (MAT) in male rats was 3.52 h, suggesting that absorption of compound 3 of the invention was largely complete by this time.

[0297] Mean absolute oral bioavailability of compound 3 of the invention in male rats was 20.6 %.

Pharmacokinetics Following Oral Administration of compound 2 of the invention

[0298] The concentrations of compound 2 of the invention in plasma following a single oral administration at a dose level of 10 mg/kg are shown in Table XII and presented in Figure 10. The pharmacokinetic parameter estimates are presented in Table XVIII.

[0299] Following oral administration of compound 2 of the invention at a target dose of 10 mg/kg, the maximum plasma concentrations of compound 2 of the invention was achieved at 2.5 h (t_{max}) post dose with a mean value of 17.1 ng/mL. Thereafter the mean plasma concentration of compound 2 of the invention declined with an apparent terminal half-life of 2.25 h.

[0300] Mean absolute oral bioavailability of compound 2 of the invention in rats was 3.20 %.

Conclusions

[0301] The aim of this study was to determine the intravenous pharmacokinetics and oral bioavailability of compound 1, 2 and 3 of the invention following administration to Sprague Dawley rats at a dose level of 10 mg/kg.

[0302] No adverse affects were noted following either intravenous or oral administration of compound 1, 2 and 3 of the invention.

[0303] Following intravenous administration at 10 mg/kg, mean plasma concentrations of compound 1 of the invention declined slowly with a mean apparent terminal half-life of 5.70 h. Systemic clearance of compound 1 of the invention was moderate and volume of distribution exceeded the total body water suggesting extensive distribution to the tissues.

[0304] Following oral administration at a target dose of 10 mg/kg, the maximum plasma concentration of compound 1 of the invention was observed at 8 h post dose. Thereafter mean plasma concentrations declined slowly with an apparent terminal half-life of 4.61 h. Mean absolute oral bioavailability of compound 1 of the invention was 34.8 %.

[0305] Following intravenous administration at 10 mg/kg, mean plasma concentrations of compound 3 of the invention declined quickly with a mean apparent terminal half-life of 3.14 h. Systemic clearance of compound 3 of the invention was high and volume

of distribution exceeded the total body water suggesting extensive distribution to the tissues.

[0306] Following oral administration at a target dose of 10 mg/kg, the maximum plasma concentration of compound 3 of the invention was observed at 4 h post dose. Thereafter the mean plasma concentrations declined quickly with an apparent terminal half-life of 3.30 h. Mean absolute oral bioavailability of compound 3 of the invention was 20.6 %.

[0307] Following intravenous administration at 10 mg/kg, mean plasma concentrations of compound 2 of the invention declined quickly with a mean apparent terminal half-life of 3.25 h. Systemic clearance of compound 2 of the invention was high and volume of distribution exceeded the total body water suggesting extensive distribution to the tissues.

[0308] Following oral administration at a target dose of 10 mg/kg, the maximum plasma concentration of compound 2 of the invention was observed at 2.5 h post dose. Thereafter mean plasma concentration declined quickly with an apparent terminal half-life of 2.25 h. Mean absolute oral bioavailability of compound 2 of the invention was 3.20 %.

Table VII

Plasma Concentrations of compound 1 of the invention Following a Single Intravenous Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
001M		1460		
002M	0.05	1650	2247	1202
003M		3630		
001M		941		
002M	0.1	1220	1120	156
003M		1200		
001M		589		
002M	0.25	830	705	121
003M		696		
001M		441		
002M	0.75	332	392	55.2
003M		402		
001M		347		
002M	1.5	236	308	62.2
003M		340		
001M		239		
002M	2.5	202	233	28.9
003M		259		
001M		317		
002M	4	208	254	56.3
003M		238		
001M		140		
002M	6	172	160	17.4
003M		168		
001M		151		
002M	8	135	97.0	80.1
003M		5.04		
001M		13.2		
002M	24	16.8	20.2	9.24

Plasma Concentrations of compound 1 of the invention Following a Single Intravenous Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
003M		30.7		

Table VIII

Plasma Concentrations of compound 3 of the invention Following a Single Intravenous Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
004M		4040		781
005M	0.05	2530	3170	
006M		2940		
004M		978		173
005M	0.1	1300	1103	
006M		1030		
004M		481		
005M	0.25	904	780	260
006M		954		
004M		404		72.5
005M	0.75	445	465	
006M		545		
004M		274		64.8
005M	1.5	327	335	
006M		403		
004M		240		
005M	2.5	274	251	19.6
006M		240		
004M		179		29.1
005M	4	225	192	
006M		171		
004M		103		
005M	6	129	119	13.8
006M		124		
004M		<LLOQ		
005M	8	62.3	81.2	26.7
006M		100		
004M		3.08		0.375
005M	24	<LLOQ	2.82	
006M		2.55		
<LLOQ=<LLOQ<2.50				

Table IX

Plasma Concentrations of compound 2 of the invention Following a Single Intravenous Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
007M		3150		
008M	0.05	1640	2353	758
009M		2270		
007M		1590		
008M	0.1	1020	1340	291
009M		1410		
007M		847		
008M	0.25	612	724	118
009M		712		
007M		264		
008M	0.75	237	278	50.1
009M		334		
007M		250		
008M	1.5	232	217	43.1
009M		168		
007M		195		
008M	2.5	183	191	6.66
009M		194		
007M		122		
008M	4	158	132	23.1
009M		115		
007M		83.9		
008M	6	116	86.0	29.0
009M		58.1		
007M		42.7		
008M	8	98.4	65.1	29.4
009M		54.1		
007M		<LLOQ		
008M	24	3.95	3.95	N/A
009M		<LLOQ		
<LLOQ=<LLOQ<2.50				

Table X

Plasma Concentrations of compound 1 of the invention Following a Single Oral Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
010M		**<LLOQ		
011M	0.08	*<LLOQ	2.66	N/A
012M		2.66		
010M		6.53		

Plasma Concentrations of compound 1 of the invention Following a Single Oral Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
011M	0.25	5.92	7.29	1.88
012M		9.43		
010M		11.8		
011M	0.75	15.9	17.3	6.26
012M		24.1		
010M		20.5		
011M	1.5	52.1	39.1	16.5
012M		44.6		
010M		65.9		
011M	2.5	57.1	60.1	5.05
012M		57.2		
010M		102		
011M	4	79.4	90.3	11.3
012M		89.4		
010M		72.3		
011M	6	98.4	86.5	13.2
012M		88.8		
010M		68.8		
011M	8	104	92.9	20.9
012M		106		
010M		5.35		
011M	24	7.50	7.68	2.43
012M		10.2		
*<LLOQ=<LLOQ<5.0 (sample diluted 2 fold) **<LLOQ=<LLOQ<25 (sample diluted 10 fold)				

Table XI

Plasma Concentrations of compound 3 of the invention Following a Single Oral Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
013M		<LLOQ		
014M	0.08	<LLOQ	2.53	N/A
015M		2.53		
013M		14.7		
014M	0.25	14.1	20.5	10.6
015M		32.8		
013M		29.1		
014M	0.75	26.6	30.8	5.20
015M		36.6		
013M		61.4		
014M	1.5	19.2	39.2	21.2

Plasma Concentrations of compound 3 of the invention Following a Single Oral Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
015M		37.0		
013M		82.5		
014M	2.5	37.2	62.7	23.2
015M		68.4		
013M		112		
014M	4	*33.4	92.5	52.1
015M		132		
013M		70.4		
014M	6	85.5	80.1	8.44
015M		84.5		
013M		50.1		
014M	8	76.1	60.8	13.6
015M		56.2		
013M		<LLOQ		
014M	24	<LLOQ	<LLOQ	N/A
015M		<LLOQ		
<LLOQ=<LLOQ<2.50 * = Incongrous result. Result confirmed by reassay				

Table XII

Plasma Concentrations of compound 2 of the invention Following a Single Oral Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
016M		<LLOQ		
017M	0.05	<LLOQ	4.68	N/A
018M		4.68		
016M		9.11		28.5
017M	0.25	9.01	25.5	
018M		58.4*		
016M		9.02		7.36
017M	0.75	10.4	13.9	
018M		22.4		
016M		9.56		4.45
017M	1.5	9.84	12.3	
018M		17.4		
016M		16.5		1.46
017M	2.5	18.8	17.1	
018M		16.1		
016M		12.6		4.13
017M	4	4.79	7.91	
018M		6.35		

Plasma Concentrations of compound 2 of the invention Following a Single Oral Administration to Male Rats				
Target Dose Level: 10 mg/kg				
Animal Number	Timepoint (h)	Sample Concentration (ng/mL)	Mean Concentration (ng/mL)	SD
016M		2.76		
017M	6	3.74	3.81	1.09
018M		4.94		
016M		<LLOQ		
017M	8	<LLOQ	<LLOQ	N/A
018M		<LLOQ		
016M		<LLOQ		
017M	24	<LLOQ	<LLOQ	N/A
018M		<LLOQ		
<LLOQ=<LLOQ<2.50 * = Sample reassayed due to incongrous result. Reassay was within 20% of original value, mean value reported.				

Table XIII

Pharmacokinetic Parameter Estimates from Plasma Concentrations of compound 1 of the invention Following Intravenous Administration							
Target Dose Level: 10 mg/kg							
Animal	C_0	AUC_{0-t}	$AUC_{0-\infty}$	$T_{1/2}$	CL	V_{ss}	MRT
Number	(ng/mL)	(ng.h/mL)	(ng.h/mL)	(h)	(mL/h/kg)	(mL/kg)	(h)
001M	4069	3662	3755	4.87	2709	15606	5.76
002M	2729	3262	3394	5.44	2991	19225	6.43
003M	5834	3867	4177	7.00	2454	17928	7.31
Geometric mean	4016	3588	3762	5.70	2709	17521	6.47
Geometric mean CV (%)	39.4	8.70	10.4	18.8	9.91	10.6	11.9
Arithmetic Mean	4210	3597	3775	5.77	2718	17586	6.50
Arithmetic Mean SD	1557	308	392	1.10	268	1834	0.774
CV (%)	37.0	8.55	10.4	19.1	9.87	10.4	11.9
Median	4069	3662	3755	5.44	2709	17928	6.43

[0309] An anomalous concentration of 5.04 ng/mL at 8 h post-dose for animal 003M was excluded from the analysis

Table XIV

Pharmacokinetic Parameter Estimates from Plasma Concentrations of compound 3 of the invention Following Intravenous Administration							
Target Dose Level: 10 mg/kg							
Animal	C_0	AUC_{0-t}	$AUC_{0-\infty}$	$t_{1/2}$	CL	V_{ss}	MRT
Number	(ng/mL)	(ng.h/mL)	(ng.h/mL)	(h)	(mL/h/kg)	(mL/kg)	(h)
004M	9463	1896	1911	3.46	5418	13694	2.53
005M	4924	2258	2504	2.74	4095	13225	3.23
006M	5516	3082	3094	3.26	3325	13169	3.96
Geometric mean	6358	2363	2456	3.14	4194	13361	3.19
Geometric mean CV (%)	36.0	25.0	24.5	12.0	24.9	2.14	22.8
Arithmetic Mean	6634	2412	2503	3.15	4279	13363	3.24

Pharmacokinetic Parameter Estimates from Plasma Concentrations of compound 3 of the invention Following Intravenous Administration							
Target Dose Level: 10 mg/kg							
Animal	C_0	AUC_{0-t}	$AUC_{0-\infty}$	$t_{1/2}$	CL	V_{ss}	MRT
Number	(ng/mL)	(ng.h/mL)	(ng.h/mL)	(h)	(mL/h/kg)	(mL/kg)	(h)
Arithmetic Mean SD	2467	608	592	0.368	1059	288	0.717
CV (%)	37.2	25.2	23.6	11.7	24.7	2.15	22.1
Median	5516	2258	2504	3.26	4095	13225	3.23

Table XV

Pharmacokinetic Parameter Estimates from Plasma Concentrations of compound 2 of the invention Following Intravenous Administration							
Target Dose Level: 10 mg/kg							
Animal	C_0	AUC_{0-t}	$AUC_{0-\infty}$	$t_{1/2}$	CL	V_{ss}	MRT
Number	(ng/mL)	(ng.h/mL)	(ng.h/mL)	(h)	(mL/h/kg)	(mL/kg)	(h)
007M	4747	1701	1868	2.718	5427	15408	2.84
005M	2637	2445	2468	3.8896	4133	20008	4.84
006M	3021	1497	1751	3.2509	5827	20551	3.53
Geometric mean	3356	1840	2006	3.25	5075	18504	3.65
Geometric mean CV (%)	31.5	25.9	18.4	18.1	18.3	16.0	27.3
Arithmetic Mean	3468	1881	2029	3.29	5129	18656	3.74
Arithmetic Mean SD	1124	499	385	0.59	886	2826	1.02
CV (%)	32.4	26.5	19.0	17.9	17.3	15.1	27.2
Median	3021	1701	1868	3.25	5427	20008	3.53

Table XVI

Pharmacokinetic Parameter Estimates from Plasma Concentrations of compound 1 of the invention Following Oral Administration							
Target Dose Level: 10 mg/kg							
Animal	Cmax	tmax	AUC_{0-t}	$AUC_{0-\infty}$	$t_{1/2}$	MRT	MAT
Number	(ng/mL)	(h)	(ng.h/mL)	(ng.h/mL)	(h)	(h)	(h)
010M	102	4.00	1094	1129	4.61	7.86	2.10
011M	104	7.98	1460	NC	NC	NC	NC
012M	106	7.97	1497	NC	NC	NC	NC
Geometric mean	104	6.34	1337	NC	NC	NC	NC
Geometric mean CV (%)	1.92	NC	17.6	NC	NC	NC	NC
Arithmetic Mean	104	6.65	1350	NC	NC	NC	NC
Arithmetic Mean SD	2.00	2.29	223	NC	NC	NC	NC
CV (%)	1.92	34.5	16.5	NC	NC	NC	NC
Median	104	7.97	1460	NC	NC	NC	NC
NC = not calculated; a terminal monoexponential phase could not be unambiguously identified							

Table XVII

Pharmacokinetic Parameter Estimates from Plasma Concentrations of compound 3 of the invention Following Oral Administration							
Target Dose Level: 10 mg/kg							
Animal	Cmax	tmax	AUC_{0-t}	$AUC_{0-\infty}$	$t_{1/2}$	MRT	MAT
Number	(ng/mL)	(h)	(ng.h/mL)	(ng.h/mL)	(h)	(h)	(h)
013M	112	4.00	565	812	3.42	6.84	4.32
014M	85.5	6.00	386	NC	NC	NC	NC
015M	132	4.02	605	863	3.19	6.82	2.86
Geometric mean	108	4.59	509	837	3.30	6.83	3.52
Geometric mean CV (%)	22.2	NC	24.6	4.31	4.91	0.195	29.6
Arithmetic Mean	110	4.67	518	838	3.30	6.83	3.59
Arithmetic Mean SD	23.3	1.15	117	36.1	0.162	0.0133	1.03
CV (%)	21.2	24.6	22.5	4.31	4.91	0.195	28.6
Median	112	4.02	565	838	3.30	6.83	3.59
NC = not calculated; a terminal monoexponential phase could not be unambiguously identified							

Table XVIII

Pharmacokinetic Parameter Estimates from Plasma Concentrations of compound 2 of the invention Following Oral Administration							
Target Dose Level: 10 mg/kg							
Animal	Cmax	tmax	AUC_{0-t}	$AUC_{0-\infty}$	$t_{1/2}$	MRT	MAT
Number	(ng/mL)	(h)	(ng.h/mL)	(ng.h/mL)	(h)	(h)	(h)
016M	16.5	2.50	62.6	NC	NC	NC	NC
017M	18.8	2.50	54.0	NC	NC	NC	NC
							-
018M	58.4	0.250	85.6	102	2.25	3.06	0.465
Geometric mean	26.3	1.16	66.1	NC	2.25	3.06	NC
Geometric mean CV (%)	78.8	NC	23.9	NC	NC	NC	NC
Arithmetic Mean	31.2	1.75	67.4	NC	NC	NC	NC
Arithmetic Mean SD	23.6	1.30	16.3	NC	NC	NC	NC
CV (%)	75.4	74.2	24.2	NC	NC	NC	NC
Median	18.8	2.50	62.6	NC	NC	NC	NC
NC = not calculated; a terminal monoexponential phase could not be unambiguously identified							

Appendix 1 Calibration and Quality Control Results for the Analytical Method for the Determination of compound 1, 2 and 3 of the invention Concentrations

Calibration Sample Results for compound 1 of the invention

[0310]

Batch	LOW	MID	HIGH
	2.5 ng/mL	100 ng/mL	4000 ng/mL
	*3.33	78.7	*2690
2	2.65	76.6	2900

Batch	LOW	MID	HIGH
	2.5 ng/mL	100 ng/mL	4000 ng/mL
	*1.71	72.4	2870
	*3.61	72.9	*2660
3	2.60	76.4	2800
	2.73	73.1	*2580
Mean	2.77	75.0	2750
S.D.	0.661	2.57	126
CV (%)	23.9	3.4	4.6
Accuracy (%)	110.8	75.0	68.8
Bias (%)	10.8	-25.0	-31.3
N	6	6	6
* = Outside acceptance criteria (100 ± 20%), Included in statistical calculations			

Appendix 1 Calibration and Quality Control Results for the Analytical Method for (continued) the Determination of compound 1, 2, and 3 of the invention Concentrations

Calibration Sample Results for compound 3 of the invention

[0311]

Batch	LOW	MID	HIGH
	2.5 ng/mL	100 ng/mL	4000 ng/mL
	2.62	99.4	4080
	2.39	109	3940
1	2.26	99.9	4020
	2.18	102	3800
	2.22	103	3860
	2.05	97.0	4030
	*3.95	120	4200
2	*3.57	111	4710
	2.68	98.9	4280
	2.85	111	4100
3	2.04	110	4510
	2.57	103	4560
Mean	2.62	105	4170
S.D.	0.598	6.82	288
CV (%)	22.8	6.5	6.9
Accuracy (%)	104.8	105.0	104.3
Bias (%)	4.8	5.0	4.3
N	12	12	12
* = Outside acceptance criteria (100 ± 20%), Included in statistical calculations			

Appendix 1 Calibration and Quality Control Results for the Analytical Method for (continued) the Determination of

compound 1, 2 and 3 of the invention Concentrations

Calibration Sample Results for compound 2 of the invention

[0312]

Batch	LOW	MID	HIGH
	2.5 ng/mL	100 ng/mL	4000 ng/mL
	2.30	98.6	3550
	2.09	99.0	3710
1	2.22	108	3580
	2.34	105	3670
	2.12	109	3440
	2.25	99.6	3560
	3.02	129	3490
2	*3.51	116	3840
	1.90	101	3600
	2.85	108	3350
3	2.62	114	3850
	2.11	110	3550
Mean	2.44	108	3600
S.D.	0.469	8.76	149
CV (%)	19.2	8.1	4.1
Accuracy (%)	97.6	108.0	90.0
Bias (%)	-2.4	8.0	-10.0
N	12	12	12
* = Outside acceptance criteria (100 ± 20%), Included in statistical calculations			

Appendix 1 Calibration and Quality Control Results for the Analytical Method for (continued) the Determination of compound 1, 2 and 3 of the invention Concentrations

Quality Control Results for compound 1 of the invention

[0313]

Replicate	Pre-Filtration 100 ng/mL	Post-Filtration 100 ng/mL	Post-Dose 100 ng/mL
1	98.2	88.2	88.2
2	85.9	96.1	86.2
2	95.8	94.9	89.9
Mean	93.3	93.1	88.1
S.D.	6.52	4.26	1.85
CV (%)	7.0	4.6	2.1
Bias (%)	-6.7	-6.9	-11.9
N	3	3	3

Quality Control Results for compound 3 of the invention

[0314]

Replicate	Pre-Filtration 100 ng/mL	Post-Filtration 100 ng/mL	Post-Dose 100 ng/mL
1	86.9	92.6	90.2
2	89.0	100	85.7
2	91.4	75.4	83.2
Mean	89.1	89.3	86.4
S.D.	2.25	12.6	3.55
CV (%)	2.5	14.1	4.1
Bias (%)	-10.9	-10.7	-13.6
N	3	3	3

Quality Control Results for compound 2 of the invention

[0315]

Replicate	Pre-Filtration 100 ng/mL	Post-Filtration 100 ng/mL	Post-Dose 100 ng/mL
1	83.7	77.1	81.9
2	89.9	68.3	82.8
2	133	72.4	84.4
Mean S.D.	102 26.9	72.6 4.40	83.0 1.27
CV (%)	26.3	6.1	1.5
Bias (%)	2.2	-27.4	-17.0
N	3	3	3

Appendix 2 Individual Animal Dosing Summary

Intravenous Administration of compound 1 of the invention Target Dose Level: 10 mg/kg

[0316]

Anima l No.	Animal Body Weight (g)	Weight of Administered Dose (g)	Dose Concentratio n (mg/g)	mg	mg/kg
001M	303	1.5317		3.082	10.171
002M	286	1.4428	2.012	2.903	10.150
003M	280	1.4266		2.870	10.251

Intravenous Administration of compound 3 of the invention Target Dose Level: 10 mg/kg

[0317]

Anima l No.	Animal Body Weight (g)	Weight of Administered Dose (g)	Dose Concentratio n (mg/g)	mg	mg/kg
004M	292	1.5012		3.023	10.354
005M	301	1.5325	2.014	3.086	10.254
006M	305	1.5580		3.138	10.288

Intravenous Administration of compound 2 of the invention Target Dose Level: 10 mg/kg

[0318]

Anima l No.	Animal Body Weight (g)	Weight of Administered Dose (g)	Dose Concentratio n (mg/g)	mg	mg/kg
007M	296	1.4882		3.002	10.141
008M	304	1.5372	2.017	3.101	10.199
009M	281	1.4211		2.866	10.201

Oral Administration of compound 1 of the invention Target Dose Level: 10 mg/kg

[0319]

Anima l No.	Animal Body Weight (g)	Weight of Administered Dose (g)	Dose Concentratio n (mg/g)	mg	mg/kg
010M	297	1.5314		3.081	10.374
011M	287	1.4933	2.012	3.004	10.469
012M	305	1.5801		3.179	10.423

Oral Administration of compound 3 of the invention Target Dose Level: 10 mg/kg

[0320]

Anima l No.	Animal Body Weight (g)	Weight of Administered Dose (g)	Dose Concentratio n (mg/g)	mg	mg/kg
013M	314	1.6165		3.256	10.368
014M	264	1.3735	2.014	2.766	10.478
015M	297	1.5181		3.057	10.294

Oral Administration of compound 2 of the invention Target Dose Level: 10 mg/kg

[0321]

Anima l No.	Animal Body Weight (g)	Weight of Administered Dose (g)	Dose Concentratio n (mg/g)	mg	mg/kg
016M	283	1.4694		2.964	10.473
017M	275	1.4368	2.017	2.898	10.538
018M	237	1.2320		2.485	10.485

Example 14

[0322] Male Sprague-Dawley rats (ManiFeedWin) of about 7 week of age (~180 g) will be kept under a 12/12 L/D cycle and in temperature and humidity controlled rooms. The animals are allowed one week of acclimation in individual cages mounted with feeders containing powdered chow and tap water. During the acclimation period, rats are handled daily to accustom them to the po gavage procedure.

[0323] The animals are randomized into weight-matched groups prior to dosing. Each animal can be doses up to 4 times with a 7 days drug wash-out period.

[0324] After each dosing, food-, water intake and locomotor activity will be monitored on a repeated base 1, 2, 4, 8, 12, 18 and 24 hours post dosing.

Compounds and Dosing

[0325] Compounds of the invention (e.g compound 1, compound 2 and compound 3) will be dissolved on a weekly basis in vehicle (20% PEG200, 40% Cremophor RH40, 25 % Labrasol or 30 % Hydroxypropyl-β-cyclodextrin) and administered via oral gavage, intravenous injection or subcutaneous injection (volume up to 5ml/kg) once or twice daily. Vehicle (20% PEG200, 40% Cremophor RH40, 25 % Labrasol or 30 % Hydroxypropyl-β-cyclodextrin) will be prepared on a weekly basis and administered via oral gavage, intravenous injection or subcutaneous injection (volume up to 5ml/kg) once or twice daily.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO9921571A [0002]
- WO9955679A [0003]
- WO9964002A [0003]
- WO0105401A [0003]
- WO0058361A [0003]
- WO0218327A [0003]
- WO0212166A [0003]
- WO0155106A [0003]
- WO0155107A [0003]
- WO0155109A [0003]
- WO0211715A [0003]
- WO0212178A [0003]
- WO9823267A [0005]
- WO03013509A [0007] [0007] [0008] [0064] [0152] [0159]

Non-patent literature cited in the description

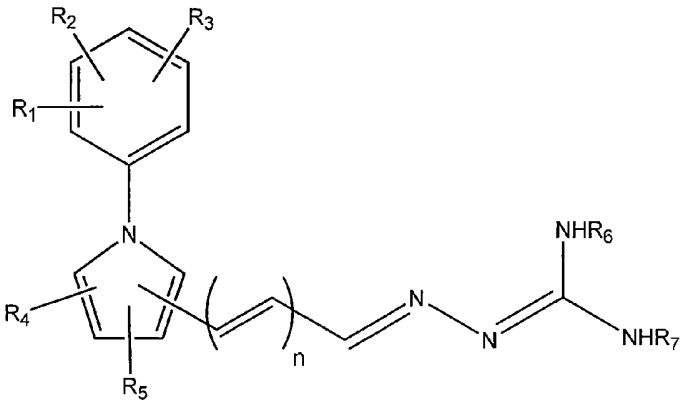
- Remington's Pharmaceutical SciencesMack Publishing Company19900000 [0067]

- Pharmaceutical Formulation Development of Peptides and ProteinsTaylor & Francis20000000 [0067]
- Handbook of Pharmaceutical ExcipientsPharmaceutical Press20000000 [0067]
- **EBERLE**The melanotropins: Chemistry, physiology and mechanisms of actionKarger19880000 [0081]
- **GRUBER et al.**Am. J. Physiol., 1989, vol. 257, R681-R694 [0081]
- **DE WILDT et al.**J. Cardiovascular Pharmacology, 1995, vol. 25, 898-905 [0081]
- **TIN et al.**Hypertension, 1987, vol. 10, 619-627 [0081]
- **CATANIALIPTON**Endocr Rev., 1993, vol. 14, 5564-76 [0082]
- **SCHWARTZ**Nature Medicine, 1998, vol. 4, 385-386 [0083]
- **POGGIOLI et al.**Peptides, 1986, vol. 7, 843-848 [0083]
- **VERGONI et al.**Neuropeptides, 1986, vol. 7, 153-158 [0083]
- **VAN DER KRAAN et al.**Endocrinol., 1998, vol. 139, 2348-2355 [0084]
- **CHEN et al.**Cell, 1997, vol. 91, 789-798 [0084]
- **DONOVAN**Psychol. Med., 1978, vol. 8, 305-316 [0085]
- **VERGONI et al.**Eur. J. Pharmacol., 1998, vol. 362, 95-101 [0085]

Phenylpyrrolaminoguanidinderivater

Patentkrav

1. Forbindelse med den almene formel (I)



(I)

inkluderende tautomere former deraf,

hvor

n er 1, 2 eller 3;

hver R_1, R_2, R_3, R_4 og R_5 er uafhængigt valgt fra gruppen bestående af hydrogen, eventuelt substitueret C_{1-6}-alkyl, eventuelt substitueret C_{3-6}-cycloalkyl, eventuelt substitueret C_{2-6}-alkenyl, eventuelt substitueret C_{4-6}-alkadienyl, eventuelt substitueret C_{2-6}-alkynyl, hydroxy, eventuelt substitueret C_{1-6}-alkoxy, eventuelt substitueret C_{2-6}-alkenyloxy, carboxy, eventuelt substitueret C_{1-6}-alkoxycarbonyl, eventuelt substitueret C_{1-6}-alkylcarbonyl, formyl, C_{1-6}-alkylsulfonylamino, eventuelt substitueret aryl, eventuelt substitueret aryloxycarbonyl, eventuelt substitueret aryloxy, eventuelt substitueret arylcarbonyl, eventuelt substitueret arylamino, arylsulfonylamino, eventuelt substitueret heteroaryl, eventuelt substitueret heteroaryloxycarbonyl, eventuelt substitueret heteroaryloxy, eventuelt substitueret heteroarylcarbonyl, eventuelt substitueret heteroarylamino, heteroarylsulfonylamino, eventuelt substitueret heterocyclyl, eventuelt substitueret heterocyclyloxycarbonyl, eventuelt substitueret heterocyclyloxy, eventuelt substitueret heterocyclylcarbonyl, eventuelt substitueret heterocyclylamino, heterocyclylsulfonylamino, amino, mono- og di(C_{1-6}-alkyl)amino, carbamoyl, mono- og di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- og di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-

alkylcarbonylamino, amino-C_{1-6}-alkylcarbonylamino, mono- og di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulfonyloxy, aminosulfonyl, mono- og di(C_{1-6}-alkyl)aminosulfonyl, nitro, eventuelt substitueret C_{1-6}-alkylthio og halogen,

hvor en hvilken som helst nitrogenbundet C_{1-6}-alkyl eventuelt er substitueret med hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- og di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulfonyl-amino eller guanidin;

hver R_6 og R_7 er uafhængigt valgt fra gruppen bestående af hydrogen, eventuelt substitueret C_{1-6}-alkyl, eventuelt substitueret C_{2-6}-alkenyl, eventuelt substitueret C_{4-6}-alkadienyl, eventuelt substitueret C_{2-6}-alkynyl, eventuelt substitueret C_{1-6}-alkoxycarbonyl, eventuelt substitueret C_{1-6}-alkylcarbonyl, eventuelt substitueret aryl, eventuelt substitueret aryloxycarbonyl, eventuelt substitueret arylcarbonyl, eventuelt substitueret heteroaryl, eventuelt substitueret heteroaryloxycarbonyl, eventuelt substitueret heteroarylcarbonyl, aminocarbonyl, mono- og di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl og mono- og di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl; eller R_6 og R_7 sammen kan danne en fem- eller seks-leddet nitrogen-indeholdende ring;

eller et farmaceutisk acceptabelt salt deraf.

2. Forbindelsen ifølge krav 1, hvor hver R_1, R_2, R_3, R_4 og R_5 er uafhængigt valgt fra gruppen bestående af hydrogen, eventuelt substitueret C_{1-6}-alkyl, eventuelt substitueret C_{2-6}-alkenyl, eventuelt substitueret C_{2-6}-alkynyl, hydroxy, eventuelt substitueret C_{1-6}-alkoxy, eventuelt substitueret C_{2-6}-alkenyloxy, carboxy, eventuelt substitueret C_{1-6}-alkoxycarbonyl, eventuelt substitueret C_{1-6}-alkylcarbonyl, formyl, amino, mono- og di(C_{1-6}-alkyl)amino, carbamoyl, mono- og di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkylaminocarbonyl, mono- og di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- og di(C_{1-6}-alkyl)amino-C_{1-6}-alkylcarbonylamino, cyano, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulfonyloxy, aminosulfonyl, mono- og di(C_{1-6}-alkyl)aminosulfonyl, nitro, eventuelt substitueret C_{1-6}-alkylthio og halogen.

3. Forbindelsen ifølge krav 2, hvor hver R_1, R_2, R_3, R_4 og R_5 er uafhængigt valgt fra gruppen bestående af hydrogen, eventuelt substitueret C_{1-6}-alkyl, eventuelt substitueret C_{2-6}-alkenyl, hydroxy, eventuelt substitueret C_{1-6}-alkoxy, amino, cyano, nitro og halogen.

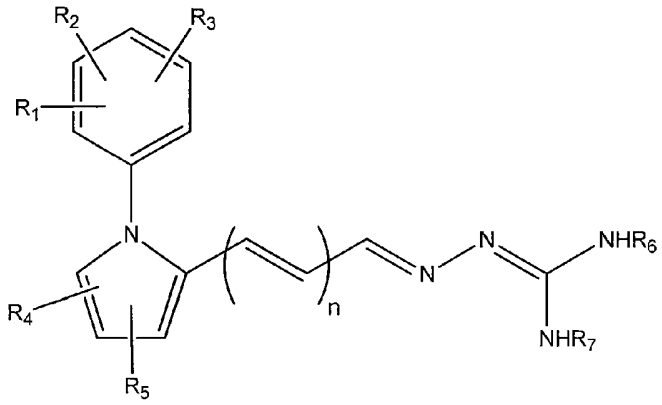
4. Forbindelsen ifølge et hvilket som helst af kravene 1-3, hvor R_6 og R_7 begge er hydrogen.

5. Forbindelsen ifølge et hvilket som helst af kravene 1-4, hvor R_1, R_2, R_4 og R_5 er hydrogen og R_3 er som defineret i et hvilket som helst af kravene 1-3.

6. Forbindelsen ifølge krav 5, hvor R_3 er er placeret i 2-positionen.

7. Forbindelsen ifølge krav 5, hvor R_3 er placeret i 4-positionen.

8. Forbindelsen ifølge et hvilket som helst af kravene 1-7, hvor forbindelsen har strukturen vist i den almene formel (Ia)



(Ia)

og hvor n, R_1, R_2, R_3, R_4, R_5, R_6 og R_7 er som defineret i et hvilket som helst af kravene 1-7.

9. Forbindelsen ifølge et hvilket som helst af kravene 1-8, hvor n er 1.

10. Farmaceutisk sammensætning omfattende en forbindelse som defineret i et hvilket som helst af kravene 1-9 og en farmaceutisk acceptabel bærer eller excipiens.

11. Forbindelse som defineret i et hvilket som helst af kravene 1-9 til anvendelse som medikament.

12. Forbindelse som defineret i et hvilket som helst af kravene 1-9 til anvendelse i behandlingen af fedme.

13. Forbindelse som defineret i et hvilket som helst af kravene 1-9 til anvendelse i behandlingen af insulin-resistens.

14. Forbindelse som defineret i et hvilket som helst af kravene 1-9 til fremstillingen af et medikament til behandlingen af diabetes mellitus.

15. Forbindelse som defineret i et hvilket som helst af kravene 1-9 til anvendelse i behandlingen af en inflammatorisk tilstand.

DRAWINGS

Examples of phenyl pyrrole aminoguanidine derivatives of the invention

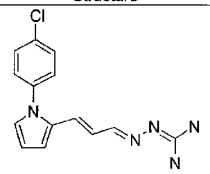
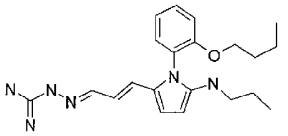
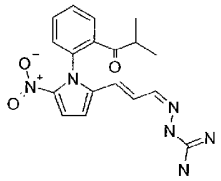
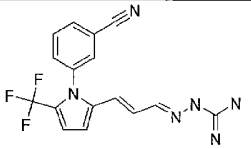
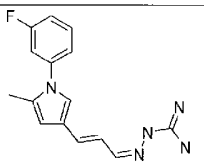
No.	Name	Structure
1	{3-[1-(4-Chloro-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
2	{3-[1-(2-butoxy-phenyl)-5-propylamino-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
3	1-(2-{2-[3-imino-N-(guanidino)-propenyl]-5-nitro-pyrrol-1-yl}-phenyl)-2-methyl-propan-1-one	
4	{3-[1-(3-cyano-phenyl)-5-trifluoromethyl-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
5	{3-[1-(3-fluoro-phenyl)-5-methyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	

Fig. 1

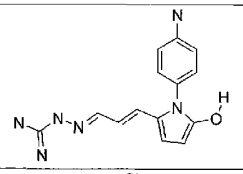
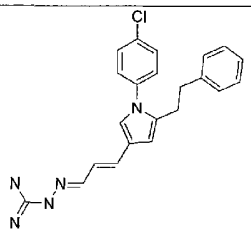
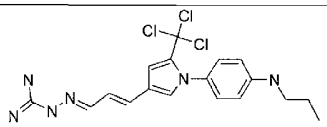
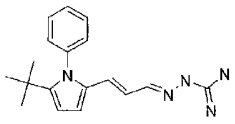
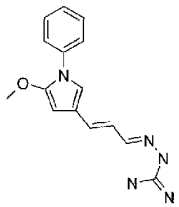
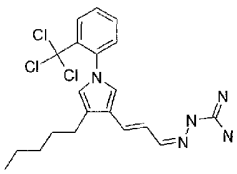
6	{3-[1-(4-amino-phenyl)-5-hydroxy-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
7	{3-[1-(4-chloro-phenyl)-5-phenethyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
8	{3-[1-(4-propylamino-phenyl)-5-trichloromethyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
9	{3-[1-(phenyl)-5-tert-butyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
10	{3-[1-(phenyl)-5-methoxy-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
11	{3-[1-(2-trichloromethyl-phenyl)-4-pentyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	

Fig. 1

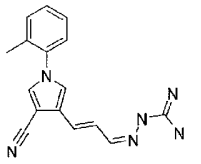
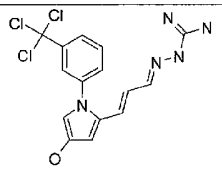
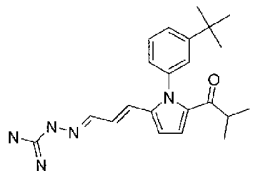
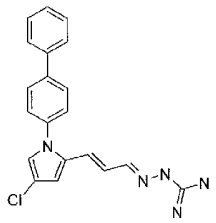
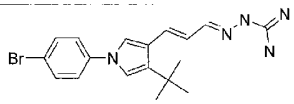
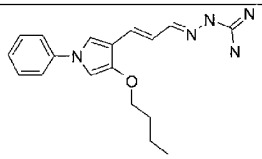
12	{3-[1-(2-methyl-phenyl)-4-cyano-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
13	{3-[1-(3-trichloromethyl-phenyl)-4-hydroxy-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
14	N-{3-[1-(3-tert-Butyl-phenyl)-5-isobutyryl-1H-pyrrol-2-yl]-allylideneamino}-guanidine	
15	{3-[1-(4-phenyl-phenyl)-4-chloro-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
16	{3-[1-(4-bromo-phenyl)-4-tert-butyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
17	{3-[1-(phenyl)-4-butoxy-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	

Fig. 1

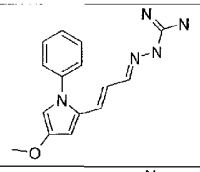
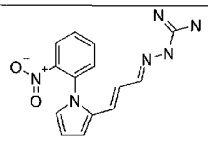
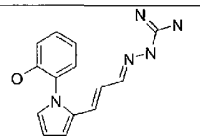
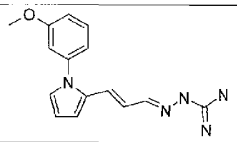
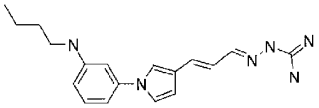
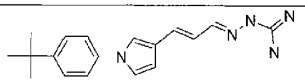
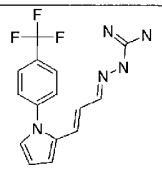
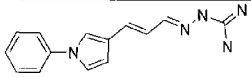
18	{3-[1-(phenyl)-4-methoxy-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
19	{3-[1-(2-nitro-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
20	{3-[1-(2-hydroxy-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
21	{3-[1-(3-methoxy-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
22	{3-[1-(3-butylamino-phenyl)-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
23	{3-[1-(4-tert-butyl-phenyl)-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
24	{3-[1-(4-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
25	{3-[1-(phenyl)-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	

Fig. 1

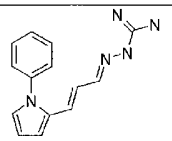
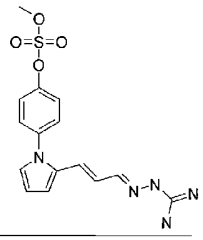
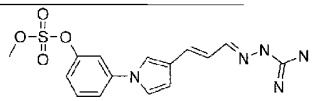
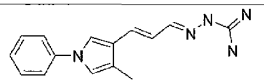
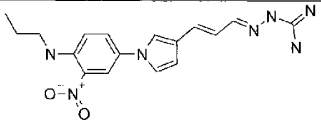
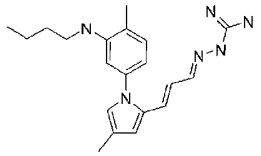
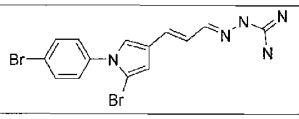
26	{3-[1-(phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
27	{3-[1-(4-bromo-phenyl)-4-tert-butyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
28	Sulfuric acid 3-{3-[3-imino-N-(guanidino)-propenyl]-pyrrol-1-yl}-phenyl ester methyl ester	
29	{3-[1-(phenyl)-4-methyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
30	{3-[1-(3-nitro-4-butylamino-phenyl)-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
31	{3-[1-(3-butylamino-4-methyl-phenyl)-4-methyl-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
32	{3-[1-(4-bromo-phenyl)-5-bromo-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	

Fig. 1

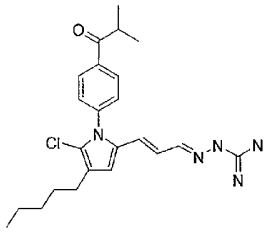
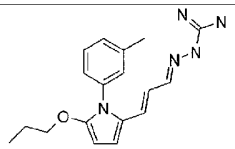
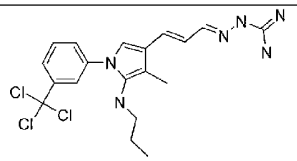
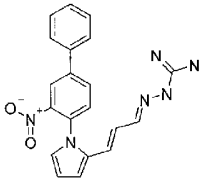
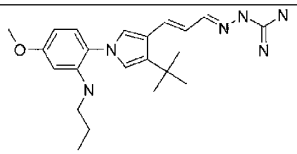
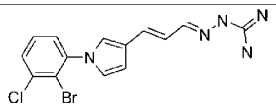
33	{3-[1-(4-isobutyryl-phenyl)-4-pentyl-5-chloro-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
34	{3-[1-(3-methyl-phenyl)-5-propoxy-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
35	{3-[1-(3-trichloromethyl-phenyl)-4-methyl-5-propylamino-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
36	{3-[1-(2-nitro-4-phenyl-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
37	{3-[1-(2-propylamino-4-methoxy-phenyl)-4-tert-butyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
38	{3-[1-(2-bromo-3-chloro-phenyl)-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	

Fig. 1

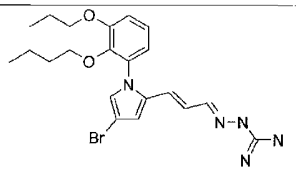
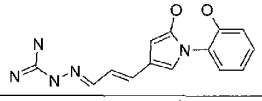
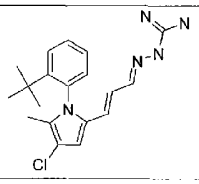
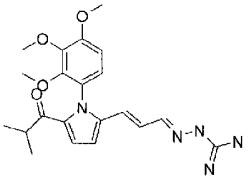
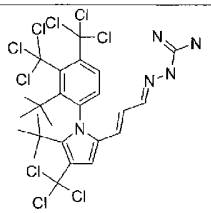
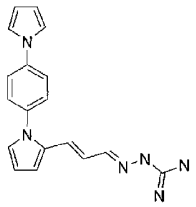
39	{3-[1-(2-butoxy-3-propoxy-phenyl)-4-bromo-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
40	{3-[1-(2-hydroxy-phenyl)-5-hydroxy-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
41	{3-[1-(2-tert-butyl-phenyl)-4-chloro-5-methyl-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
42	{3-[1-(2,3,4-trimethoxy-phenyl)-5-isobutyryl-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
43	{3-[1-(2-tert-butyl-3,4-bis-trichloromethyl-phenyl)-4-trichloromethyl-5-tert-butyl-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
44	{3-[1-(4-pyrrolyl-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	

Fig. 1

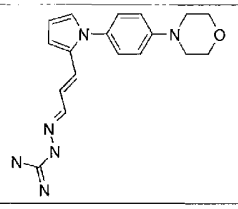
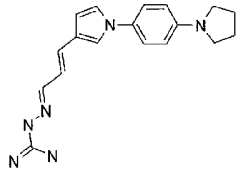
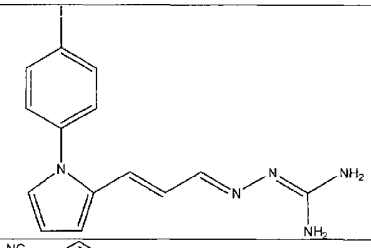
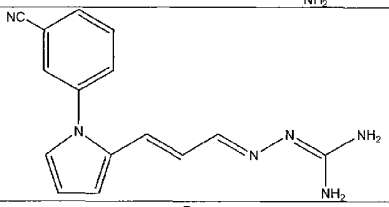
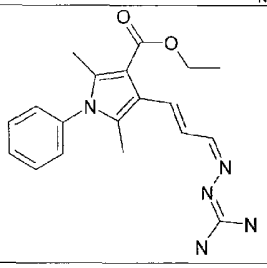
45	{3-[1-(4-morpholino-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
46	{3-[1-(4-pyrrolidino-phenyl)-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	
47	{3-[1(4-iodo-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
48	{3-[1(3-cyano-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
49	{3-[1-(phenyl)-2,5-dimethyl-4-ethoxycarbonyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	

Fig. 1

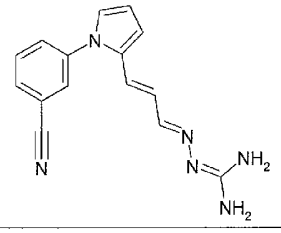
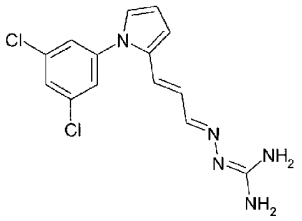
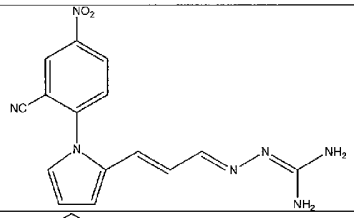
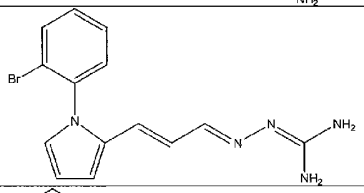
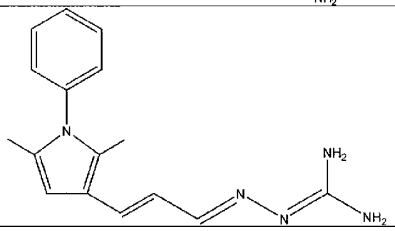
50	{3-[1-(3-cyano-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
51	{3-[1-(3,5-dichloro-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
52	{3-[1(2-cyano-4-nitro-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
53	{3-[1-(2-Bromophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
54	{3-[1-(phenyl)-2,5-dimethyl-1H-pyrrol-3-yl]-allylidene}-aminoguanidine	

Fig. 1

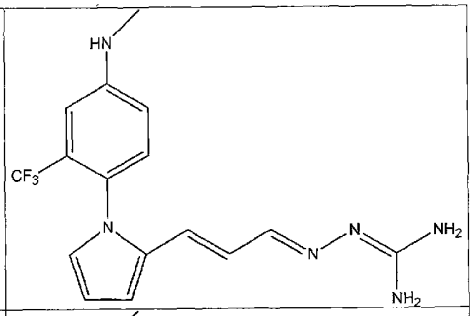
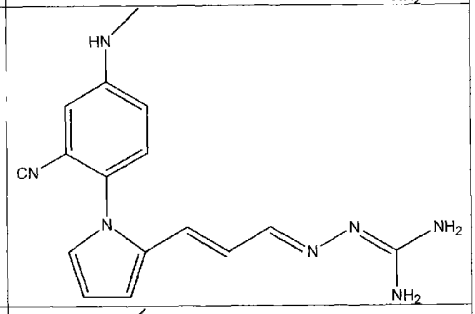
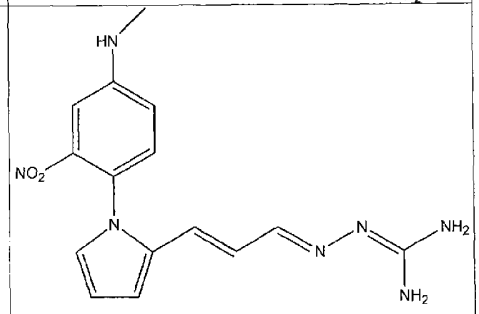
55	{3-[1(2-trifluoromethyl-4-methylamino-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
56	{3-[1(2-cyano-4-methylamino-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
57	{3-[1(2-nitro-4-methylamino-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	

Fig. 1

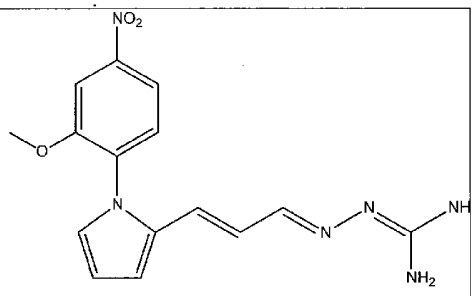
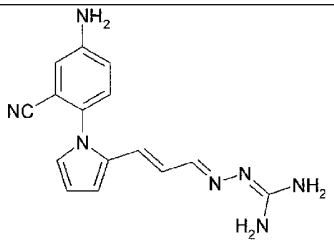
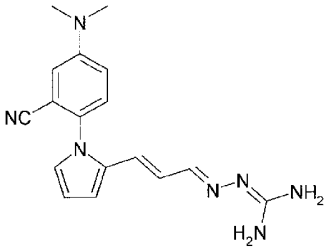
58	{3-[1(2-methoxy-4-nitro-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
59	{3-[1-(2-cyano-4-amino-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	
60	{3-[1-(2-cyano-4-dimethylamino-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	

Fig. 1

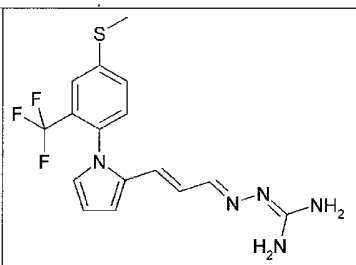
61	{3-[1-(2-trifluoromethyl-4-thiomethyl-phenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine	

Fig. 1

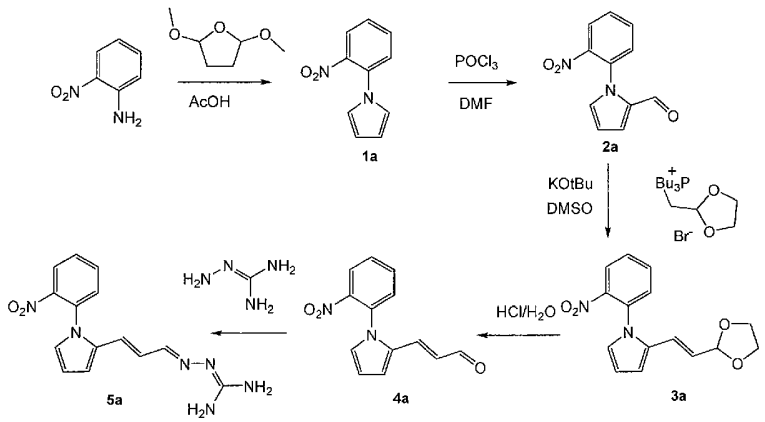


Fig. 2

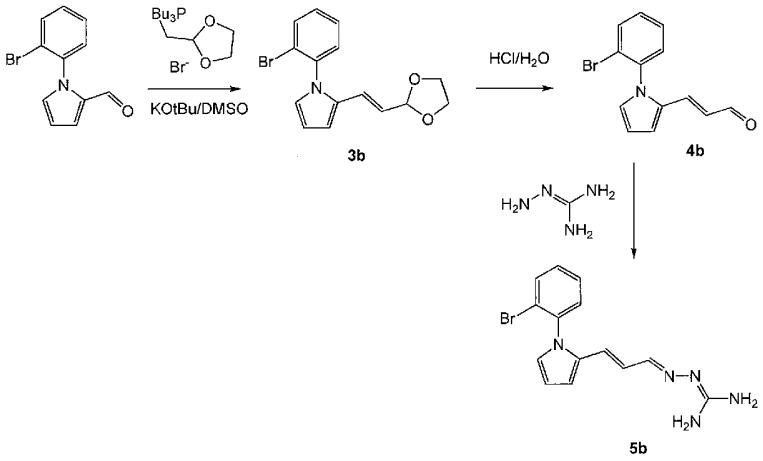


Fig. 3

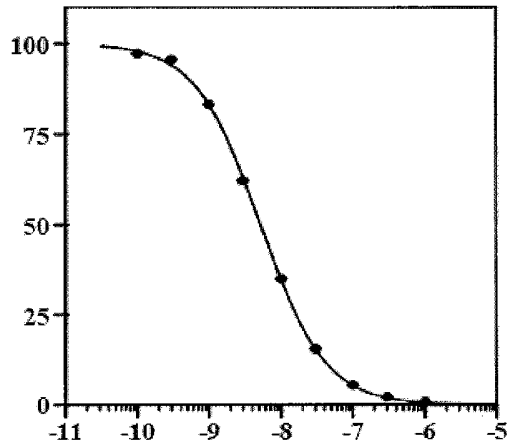


Fig. 4

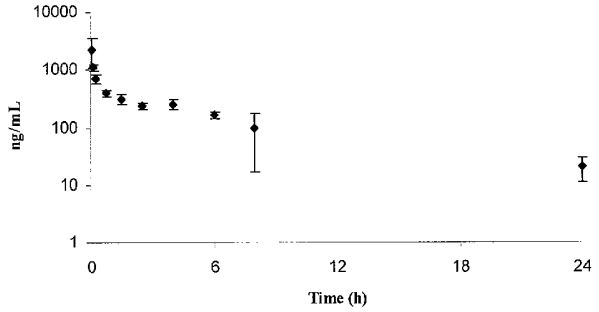


Fig. 5

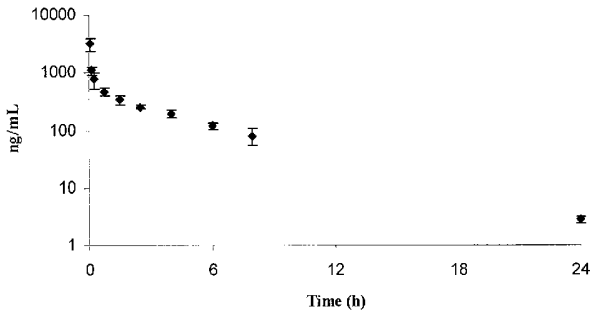


Fig. 6

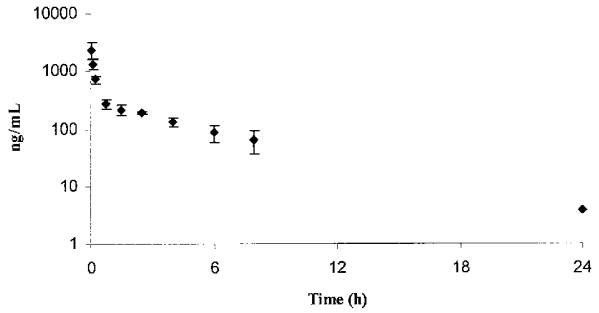


Fig. 7

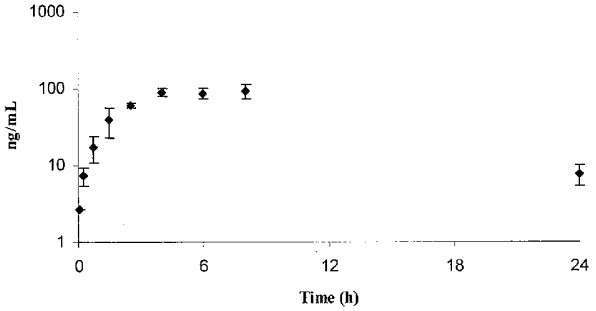


Fig. 8

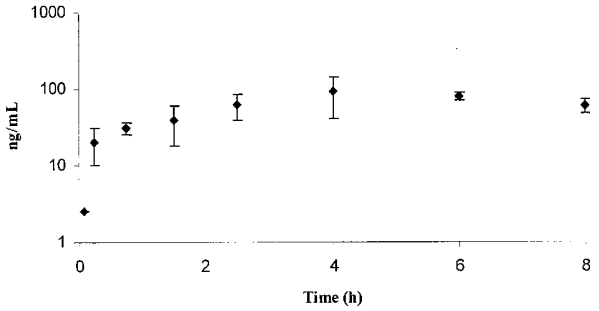


Fig. 9

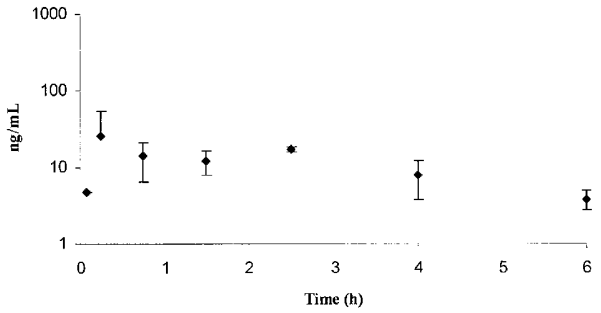


Fig. 10