Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2430280 A1 2002/06/06

(21) 2 430 280

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2001/11/28
(87) Date publication PCT/PCT Publication Date: 2002/06/06
(85) Entrée phase nationale/National Entry: 2003/05/28
(86) N° demande PCT/PCT Application No.: EP 2001/013910
(87) N° publication PCT/PCT Publication No.: 2002/044171
(30) Priorité/Priority: 2000/11/30 (100 59 864.1) DE

(51) Cl.Int.^{7}/Int.Cl.^{7} C07D 409/12, A61K 31/4436, A61P 29/02, A61K 31/443, A61K 31/44, A61K 31/4155, A61K 31/341, C07D 333/28, C07D 333/24, C07D 407/12, C07D 307/42, C07D 405/12, C07D 307/54, C07D 307/68, C07D 307/56

(71) Demandeur/Applicant:
GRUNENTHAL GMBH, DE

(72) Inventeurs/Inventors:
SUNDERMANN, CORINNA, DE;
ENGLBERGER, WERNER, DE;
PRZEWOSNY, MICHAEL, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : DERIVES D'ACIDE AMINO-FURANNE-2-YL-ACETIQUE ET D'ACIDE AMINO-THIEN-2-YL-ACETIQUE SUBSTITUES ET LEUR UTILISATION POUR LE TRAITEMENT DE LA MIGRAINE ET DE LA DOULEUR

(54) Title: SUBSTITUTED AMINO-FURAN-2-YL-ACETIC ACID AND AMINO-THIEN-2-YL-ACETIC ACID DERIVATIVES AND THEIR USE IN THE TREATMENT OF MIGRAINE AND PAIN

(57) Abrégé/Abstract:
The invention relates to substituted aminofuran-2-yl-acetic acid derivatives and substituted aminothien-2-yl-acetic acid derivatives of general formulae (I-A) and (I-B). The invention also relates to a method for the production thereof, medicaments containing the same, the use of said compounds for producing medicaments for treating, inter alia, pain and migraines, and pharmaceutical compositions containing the same.

ABSTRACT

The invention relates to substituted aminofuran-2-yl-acetic acid derivatives and substituted aminothien-2-yl-acetic acid derivatives of general formulae (I-A) and (I-B). The invention also relates to a method for the production thereof, medicaments containing the same, the use of said compounds for producing medicaments for treating, inter alia, pain and migraines, and pharmaceutical compositions containing the same.

SUBSTITUTED AMINO-FURAN-2-YL-ACETIC ACID AND AMINO-THIEN-2-YL-ACETIC ACID DERIVATIVES AND THEIR USE IN THE TREATMENT OF MIGRAINE AND PAIN

The invention relates to substituted amino-furan-2-yl-acetic acid derivatives and substituted amino-thien-2-yl-acetic acid derivatives, to processes for their preparation, to medicaments containing them, to the use of those compounds in the preparation of medicaments for the treatment of, *inter alia*, pain and migraine, and to pharmaceutical compositions containing them.

The treatment of chronic and non-chronic pain is of great importance in medicine. There is a worldwide need for highly effective therapies for the targeted treatment of chronic and non-chronic pain in a manner that is fair to the patient, which is understood to mean the successful and satisfactory treatment of pain for the patient.

Conventional opioids such as morphine are highly effective in the therapy of severe to severest pain. However, their use is limited by the known side-effects, such as, for example, respiratory depression, vomiting, sedation, constipation and tolerance. In addition, they are less effective in neuropathic or incidental pain, from which tumour patients in particular suffer.

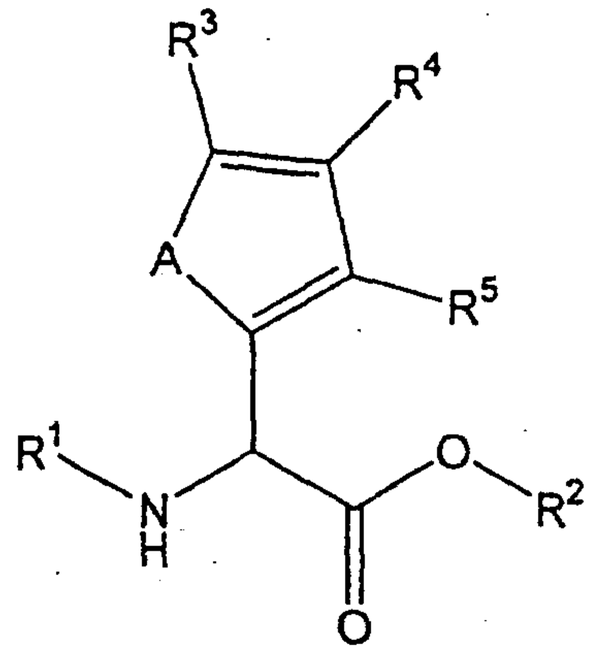
Opioids develop their analgesic action by binding to receptors in the cell membrane which belong to the family of the so-called G-protein-coupled receptors. In addition to these, there are further receptors and also ion channels which are substantially involved in the system

of pain formation and pain transmission, for example the N-methyl-D-aspartate ion channel (NMDA ion channel), *via* which a substantial part of the communication of synapses proceeds and through which the calcium ion exchange between a neuronal cell and its surroundings is controlled (see, for example, P.D. Leeson, L.L. Iversen, *J. Med. Chem.* 37 (1994) 4053-4067).

Important findings regarding the physiological importance of ion-channel-selective substances have been made possible by the development of the "patch-clamp" technique, by means of which the action of NMDA antagonists (i.e. antagonists of the NMDA ion channel) on the metabolism of calcium inside the cell can be demonstrated.

The object underlying the present invention is to provide novel compounds suitable for the therapy of pain. In addition, it is desirable that these substances should cause the side-effects that usually occur with the use of opioids such as morphine, such as, for example, nausea, vomiting, dependence, respiratory depression or constipation, either not at all, if possible, or to only a small degree.

That object is achieved by compounds having the general structure (I) and by their pharmaceutically acceptable salts



I

wherein

A represents oxygen or sulfur,

R^1 represents aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl,

R^2 represents H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl,

R^3, R^4 and R^5 each independently of the others represents H, OH, SH, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl, $-SiR^6R^7R^8$, $-(CH_2)_n-O-(CH_2)_m-R^9$ wherein n = 1, 2, 3 or 4 and m = 0, 1, 2, 3 or 4, $-(CH_2)_o-S_p-(CH_2)_q-R^{10}$ wherein o = 1, 2, 3 or 4, p = 1 or 2 and q = 0, 1, 2, 3 or 4, $-(CH_2)_r-CO_2R^{11}$ wherein r = 0, 1, 2, 3 or 4, $-(CH_2)_s-OCOR^{12}$ wherein s = 0, 1, 2, 3 or 4, or $-COR^{13}$,

R^6, R^7 and R^8 each independently of the others represents C_{1-6}-alkyl or phenyl,

R^9 and R^{10} each independently of the other represents H, CH_3, aryl, heterocyclyl or $-C(=O)-C_{1-6}$-alkyl, $-C(=O)-(C_{1-6}$-alkyl)-aryl or $-C(=O)$-aryl,

R^{11} represents H, C_{1-6}-alkyl or CH_2-phenyl,

R^{12} represents C_{1-6}-alkyl or aryl,

R^{13} represents H, C_{1-6}-alkyl, aryl, heterocyclyl or $NR^{14}R^{15}$,

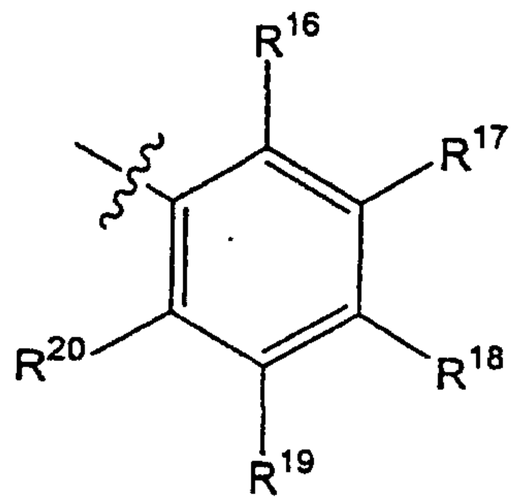
R^{14} and R^{15} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{14} and R^{15} together form $-(CH_2)_k-$ wherein k = 4, 5 or 6,

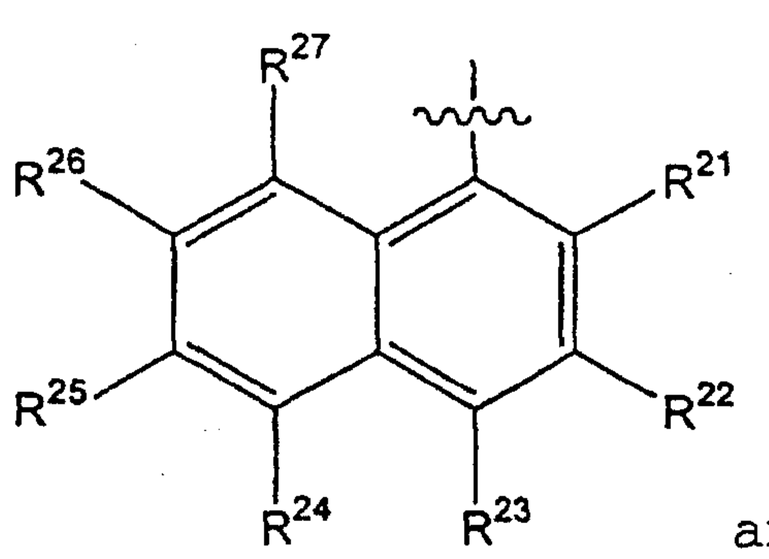
wherein

alkyl represents a non-cyclic hydrocarbon radical which is straight-chain or branched and is saturated or unsaturated and is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents,

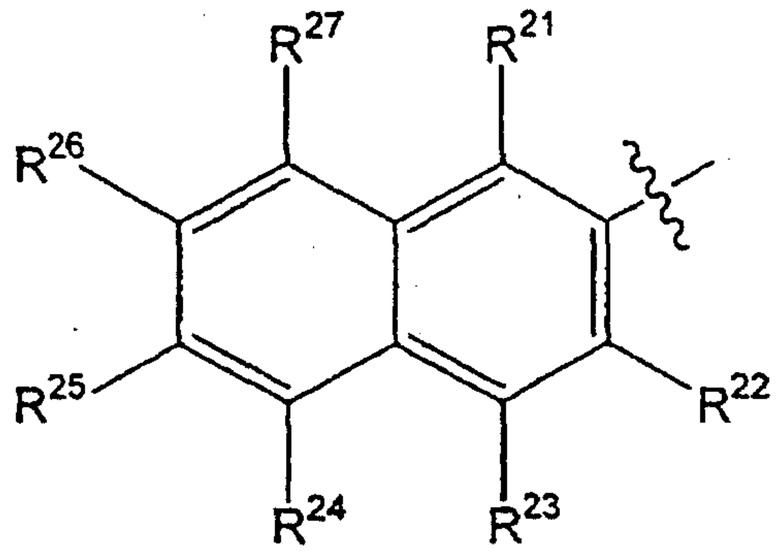
cycloalkyl represents an alicyclic hydrocarbon radical which is saturated or unsaturated and is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents,

aryl is a radical selected from the group comprising





and



heterocyclyl represents a monocyclic or polycyclic organic radical in which at least one ring contains one hetero atom or 2, 3, 4 or 5 identical or different hetero atoms selected from the group containing N, O and S, the radical being saturated or unsaturated and being unsubstituted or monosubstituted or polysubstituted by identical or different substituents,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} and R^{27} each independently of the others represents H, OR^{28}, $S(O)_tR^{29}$ wherein t = 0, 1 or 2, SO_2OR^{30}, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl or (C_{1-6}-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl, $-CO_2R^{31}$ or $-NR^{32}R^{33}$,

R^{28}, R^{29}, R^{30} and R^{31} each independently of the others represents H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl or (C_{1-6}-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl or $-NR^{34}R^{35}$,

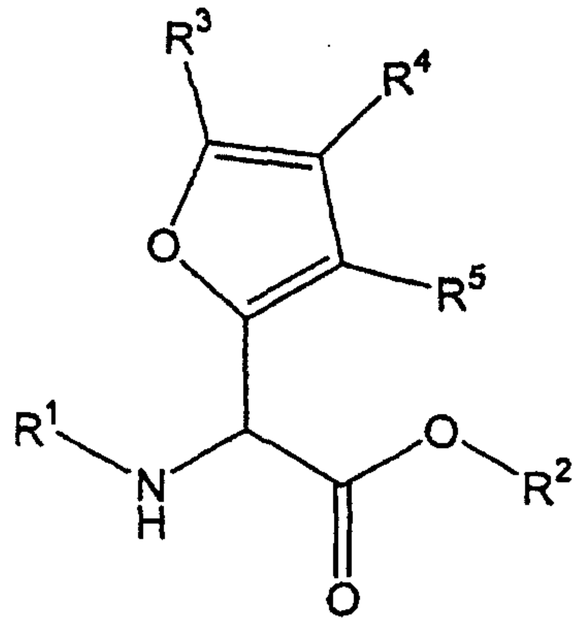
and

R^{32} and R^{33} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl, (C_{1-6}-alkyl)-phenyl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{32} and R^{33} together form $-(CH_2)_h-$ wherein h = 4, 5 or 6,

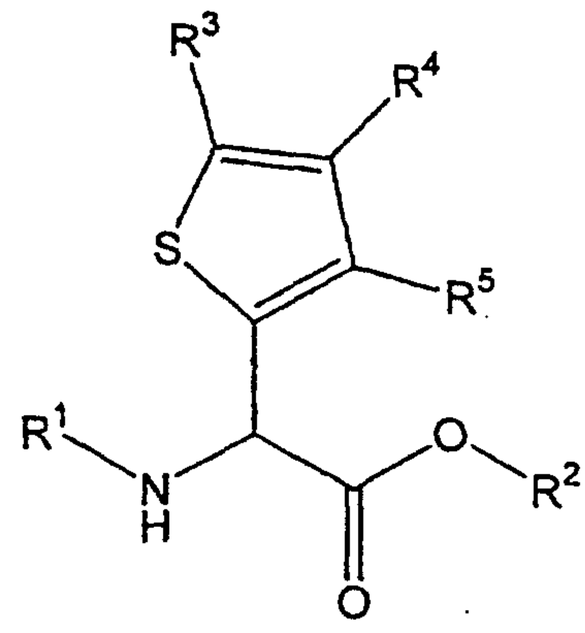
and

R^{34} and R^{35} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl, (C_{1-6}-alkyl)-phenyl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{34} and R^{35} together form $-(CH_2)_g-$ wherein g = 4, 5 or 6.

Accordingly, the compounds according to the invention having the general structure (I) are either amino-furan-2-yl-acetic acid derivatives having the general structure (I-A) or amino-thien-2-yl-acetic acid derivatives having the general structure (I-B):



I-A



I-B

It has been found that these compounds having the general structure (I-A) or (I-B) bind selectively to the glycine binding site of the NMDA ion channel and accordingly are suitable for the treatment of pain. The same is also true of (4-methoxy-phenylamino)-thien-2-yl-acetic acid, which

is known as such from the prior art (N.A. Petasis *et al.*, *Tetrahedron* (1997), 16463-16470) but for which no medicinal indication is disclosed in the prior art. The present invention therefore relates also to that compound, in so far as its use in a medicament, for the preparation of a medicament, especially for the treatment of pain, and a pharmaceutical composition containing it are concerned.

Within the scope of this invention, the term "aryl" means phenyls and naphthyls. Each aryl radical may be unsubstituted or mono- or poly-substituted, it being possible for the aryl substituents to be identical or different and to be at any desired and possible position of the aryl. Aryl is advantageously an unsubstituted or substituted phenyl. Particularly preferred aryl radicals for the purposes of the invention are mono- or di-substituted phenyl.

Within the scope of this invention, the terms "C_{1-12}-alkyl" and "C_{1-6}-alkyl" include acyclic saturated or unsaturated hydrocarbon radicals which may be branched- or straight-chain and may be unsubstituted or mono- or poly-substituted, having from 1 to 12 (i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12) and from 1 to 6 (i.e. 1, 2, 3, 4, 5 or 6) carbon atoms, respectively, that is to say C_{1-12}-alkanyls and C_{1-6}-alkanyls, C_{2-12}-alkenyls and C_{2-6}-alkenyls and C_{2-12}-alkynyls and C_{2-6}-alkynyls. "Alkenyls" have at least one C-C double bond and "alkynyls" have at least one C-C triple bond. Alkyl is advantageously selected from the group comprising methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-

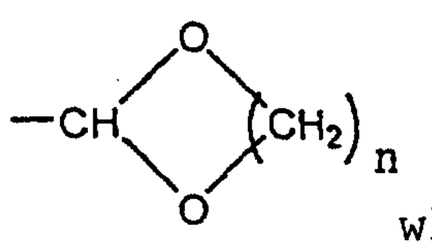
pentyl, isopentyl, neopentyl, n-hexyl, 2-hexyl, n-octyl, n-nonyl, n-decyl, n-dodecyl; ethenyl (vinyl), ethynyl, propenyl ($-CH_2CH=CH_2$, $-CH=CH-CH_3$, $-C(=CH_2)-CH_3$), propynyl ($-CH_2-C\equiv CH$, $-C\equiv C-CH_3$), butenyl, butynyl, pentenyl, pentynyl, hexenyl, hexynyl, octenyl and octynyl.

For the purposes of this invention, the term "C_{3-8}-cycloalkyl" means cyclic hydrocarbon radicals having 3, 4, 5, 6, 7 or 8 carbon atoms, it being possible for the radicals to be saturated or unsaturated, unsubstituted or monosubstituted or polysubstituted by identical or different substituents. C_{3-8}-Cycloalkyl is advantageously selected from the group containing cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

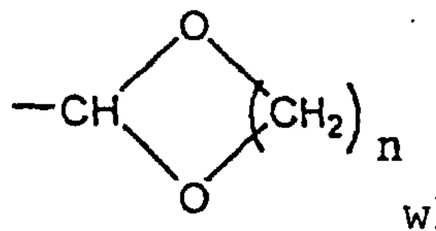
The term "heterocyclyl" denotes a 3-, 4-, 5-, 6- or 7-membered cyclic organic radical which contains at least one hetero atom, optionally 2, 3, 4 or 5 hetero atoms, wherein the hetero atoms are identical or different and are selected from the group containing oxygen, nitrogen and sulfur, and the cyclic radical is saturated or unsaturated and may be unsubstituted or mono- or polysubstituted. The heterocycle may also be part of a bicyclic or polycyclic system; for example, a benzene ring may be fused to the heterocycle. Examples of preferred heterocyclyl radicals are furanyl, thienyl (thiophene), indolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl and their benzo-fused derivatives. The bond to the compound having the general structure (I) (or (II), (III) and (IV)) can

be made *via* any desired and chemically possible ring member of the heterocyclyl radical.

For the purposes of the present invention, the expressions "(C_{1-6}-alkyl)-C_{3-8}-cycloalkyl", "(C_{1-6}-alkyl)-heterocyclyl" and "(C_{1-6}-alkyl)-aryl" mean that the cycloalkyl, heterocyclyl or aryl radical is bonded to the compound having the general structure (I) (or (II), (III) or (IV)) *via* a C_{1-6}-alkyl group.

In connection with "alkyl", "alkanyl", "alkenyl" and "alkynyl", the term "substituted" within the scope of this invention is understood to mean the substitution of a hydrogen atom by, for example, F, Cl, Br, I, -CN, NH_2, NH-alkyl, NH-aryl, NH-alkyl-aryl, NH-heterocyclyl, NH-alkyl-OH, $N(alkyl)_2$, $N(alkyl\text{-}aryl)_2$, $N(heterocyclyl)_2$, $N(alkyl\text{-}OH)_2$, NO, NO_2, SH, S-alkyl, S-aryl, S-alkyl-aryl, S-heterocyclyl, S-alkyl-OH, S-alkyl-SH, OH, O-alkyl, O-aryl, O-alkyl-aryl, O-heterocyclyl, O-alkyl-OH, CHO, $C(=O)C_{1-6}$-alkyl, $C(=S)C_{1-6}$-alkyl, C(=O)aryl, C(=S)aryl, $C(=O)C_{1-6}$-alkyl-aryl,  wherein n = 1, 2 or 3, $C(=S)C_{1-6}$-alkyl-aryl, C(=O)-heterocyclyl, C(=S)-heterocyclyl, CO_2H, CO_2-alkyl, CO_2-alkyl-aryl, $C(=O)NH_2$, C(=O)NH-alkyl, C(=O)NHaryl, C(=O)NH-heterocyclyl, $C(=O)N(alkyl)_2$, $C(=O)N(alkyl\text{-}aryl)_2$, $C(=O)N(heterocyclyl)_2$, SO-alkyl, SO_2-alkyl, SO_2-alkyl-aryl, SO_2NH_2, SO_3H, SO_3-alkyl, cycloalkyl, aryl or by heterocyclyl, polysubstituted radicals being understood to be radicals that are polysubstituted, for example di- or tri-substituted, either at different atoms or at the same atom, for example trisubstituted at the

same carbon atom, as in the case of CF_3 or $-CH_2CF_3$, or at different positions, as in the case of $-CH(OH)-CH=CCl-CH_2Cl$. Polysubstitution can be carried out with the same or with different substituents. For the purposes of the present invention, "alkyl" in this connection particularly preferably means methyl, ethyl, n-propyl, 2-propyl, n-butyl, 2-butyl, tert-butyl, CH_2-OH or CF_3.

With regard to "aryl", "phenyl", "heterocyclyl" and "cycloalkyl", "monosubstituted" or "polysubstituted" is understood to mean within the scope of this invention the mono- or poly-substitution, for example di-, tri- or tetra-substitution, of one or more hydrogen atoms of the ring system by a suitable substituent. If the meaning of such suitable substituents in connection with "aryl", "phenyl", "heterocyclyl" or "cycloalkyl" is not defined elsewhere in the description or in the claims, suitable substituents are F, Cl, Br, I, CN, NH_2, NH-alkyl, NH-aryl, NH-alkyl-aryl, NH-heterocyclyl, NH-alkyl-OH, $N(alkyl)_2$, $N(alkyl\text{-}aryl)_2$, $N(heterocyclyl)_2$, $N(alkyl\text{-}OH)_2$, NO, NO_2, SH, S-alkyl, S-cycloalkyl, S-aryl, S-alkyl-aryl, S-heterocyclyl, S-alkyl-OH, S-alkyl-SH, OH, O-alkyl, O-cycloalkyl, O-aryl, O-alkyl-aryl, O-heterocyclyl, O-alkyl-OH, CHO, $C(=O)C_{1-6}$-alkyl, $C(=S)C_{1-6}$-alkyl, C(=O)aryl, C(=S)aryl, $C(=O)C_{1-6}$-alkyl-aryl,  wherein n = 1, 2 or 3, $C(=S)C_{1-6}$-alkyl-aryl, C(=O)-heterocyclyl, C(=S)-heterocyclyl, CO_2H, CO_2-alkyl, CO_2-alkyl-aryl, $C(=O)NH_2$, C(=O)NH-alkyl, C(=O)NHaryl, C(=O)NH-heterocyclyl, $C(=O)N(alkyl)_2$, $C(=O)N(alkyl\text{-}aryl)_2$, $C(=O)N(heterocyclyl)_2$, S(O)-alkyl, S(O)-aryl, SO_2-alkyl,

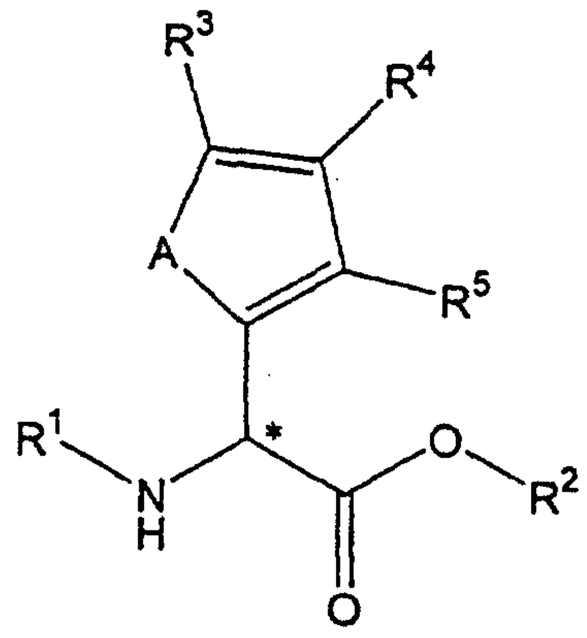
SO_2-aryl, SO_2NH_2, SO_3H, CF_3, =O, =S; alkyl, cycloalkyl, aryl and/or heterocyclyl; at one atom or optionally at different atoms (it being possible for a substituent itself to be substituted). Polysubstitution is carried out with the same or with different substituents. When "aryl" represents phenyl, the phenyl ring is optionally substituted by one or more substituents R^{16}, R^{17}, R^{18}, R^{19} and R^{20} as defined above for the general structure (I).

Pharmaceutically acceptable salts within the scope of this invention are those salts of the compounds according to the invention having the general structure (I) which are physiologically tolerable when used pharmaceutically - especially when used in mammals and/or humans. Such pharmaceutically acceptable salts can be formed, for example, with inorganic or organic acids or, where the compounds according to the invention are acids, especially carboxylic acids, with bases.

The pharmaceutically acceptable salts of the compounds according to the invention having the general structure (I) are preferably formed with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, carbonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid or aspartic acid. If the compounds according to the invention are acids, especially carboxylic acids, the pharmaceutically acceptable salts can also be formed by reaction with bases, such as, for example, sodium hydrogen carbonate or sodium carbonate. The salts formed are, *inter alia*,

hydrochlorides, hydrobromides, phosphates, carbonates, hydrogen carbonates, formates, acetates, oxalates, succinates, tartrates, fumarates, citrates and glutamates, or sodium salts. Also preferred are solvates and, especially, the hydrates of the compounds according to the invention, which can be obtained, for example, by crystallisation from aqueous solution.

The compounds according to the invention having the general structure (I) always have at least one centre of asymmetry, which is denoted by * in the formula below:



I*

The compounds according to the invention of the general formula (I) can therefore be in the form of their racemates, in the form of the pure enantiomers and/or - provided a further centre of asymmetry is present - in the form of the pure diastereoisomers, or in the form of mixtures of those enantiomers and diastereoisomers, both in substance and in the form of pharmaceutically acceptable salts of those compounds. The mixtures may be present in any desired mixing ratio of the stereoisomers.

Preference is given to those compounds having the general structure (I) which are characterised in that

R^1 represents aryl or heterocyclyl^1,

R^2 represents H, C_{1-12}-alkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl or (C_{1-6}-alkyl)-aryl,

R^3, R^4 and R^5 each independently of the others represents H, OH, SH, Cl, Br, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl^1, (C_{1-6}-alkyl)-heterocyclyl^1, $-SiR^6R^7R^8$, $-(CH_2)_n-O-(CH_2)_m-R^9$ wherein n = 1, 2, 3 or 4 and m = 0, 1 or 2, $-(CH_2)_o-S_p-(CH_2)_q-R^{10}$ wherein o = 1, 2, 3 or 4, p = 1 or 2 and q = 0, 1 or 2, $-(CH_2)_r-CO_2R^{11}$ wherein r = 0, 1, 2 or 3, $-(CH_2)_s-OCOR^{12}$ wherein s = 0, 1 or 2, or $-COR^{13}$,

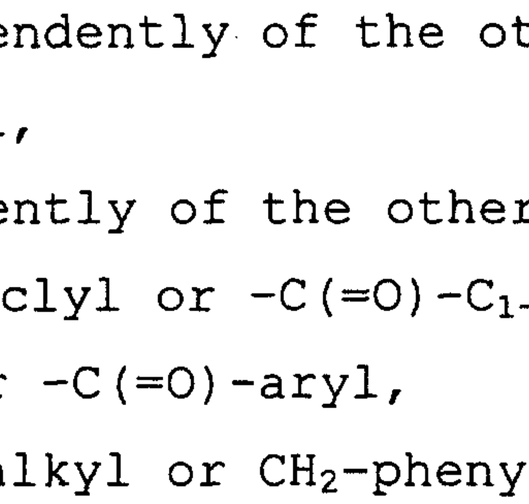
R^6, R^7 and R^8 each independently of the others represents C_{1-6}-alkyl or phenyl,

R^9 and R^{10} each independently of the other represents H, CH_3, aryl, heterocyclyl or $-C(=O)-C_{1-6}$-alkyl, $-C(=O)-(C_{1-6}$-alkyl)-aryl or $-C(=O)$-aryl,

R^{11} represents H, C_{1-6}-alkyl or CH_2-phenyl,

R^{12} represents C_{1-6}-alkyl or aryl,

R^{13} represents C_{1-6}-alkyl or aryl,

wherein aryl represents 

,

heterocyclyl represents a monocyclic or polycyclic organic radical in which at least one ring contains one hetero atom or 2, 3, 4 or 5 identical or

different hetero atoms selected from the group containing N, O and S, the radical being saturated or unsaturated and being unsubstituted or monosubstituted or polysubstituted by identical or different substituents,

heterocyclyl[1] represents a monocyclic or bicyclic organic radical in which at least one ring is 5- or 6-membered and contains one hetero atom or 2 identical or different hetero atoms selected from the group containing N, O and S, the radical being saturated or unsaturated and being unsubstituted or monosubstituted or polysubstituted by identical or different substituents,

R^{16}, R^{17}, R^{18}, R^{19} and R^{20} each independently of the others represents H, OR^{28}, $S(O)_tR^{29}$ wherein t = 0 or 2, SO_2OR^{30}, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl or (C_{1-6}-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl[1], (C_{1-6}-alkyl)-heterocyclyl[1], $-CO_2R^{31}$ or $-NR^{32}R^{33}$,

R^{28}, R^{29}, R^{30} and R^{31} each independently of the others represents H, C_{1-6}-alkyl or phenyl, and

R^{32} and R^{33} each independently of the other represents H, C_{1-6}-alkyl, (C_{1-6}-alkyl)-phenyl, or R^{32} and R^{33} together form $-(CH_2)_h-$ wherein h = 4, 5 or 6.

Of those compounds, particular preference is given to those in which

R^1 represents aryl or heterocyclyl[2],

R^2 represents H, methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl, n-hexyl,

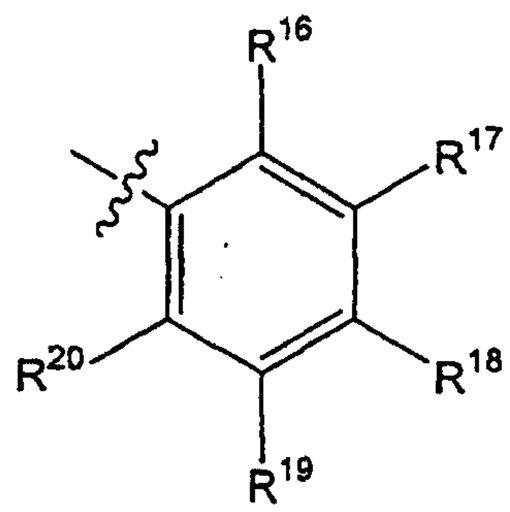
R^3, R^4 and R^5 each independently of the others represents H, OH, SH, Br, Cl, C_{1-6}-alkyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, $-SiR^6R^7R^8$, $-CH_2OH$, $-CH_2-O-(C=O)-CH_3$, $-(CH_2)-S_p-(CH_2)_q-R^{10}$ wherein p = 1 or 2 and q = 0 or 1, $-(CH_2)_r-CO_2R^{11}$ wherein r = 0 or 1, or $-COR^{13}$,

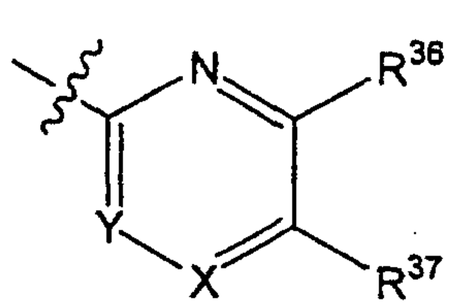
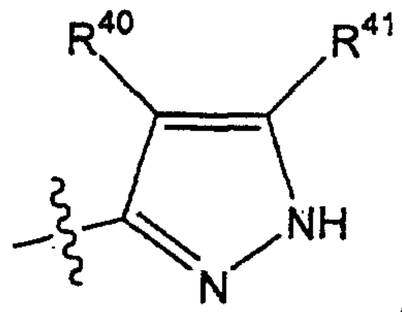
R^6, R^7 and R^8 each independently of the others represents methyl, tert-butyl or phenyl,

R^{10} represents H, methyl, ethyl, 2-furyl, 2-thienyl or $-C(=O)-CH_3$,

R^{11} represents H, methyl, ethyl or tert-butyl,

R^{13} represents methyl,

wherein aryl represents  ,

heterocyclyl[2] represents  or  ,

R^{16}, R^{17}, R^{18}, R^{19} and R^{20} each independently of the others represents H, OR^{28}, $S(O)_tR^{29}$ wherein t = 0, F, Cl, Br, I, -CN, $-NO_2$, methyl, ethyl, n-propyl, 2-propyl, n-butyl, 2-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl, CF_3 or $-CO_2R^{31}$,

R^{28}, R^{29} and R^{31} each independently of the others represents H, methyl, ethyl, $-CF_3$ or phenyl,

X-Y represents $CR^{38}-CR^{39}$, $CR^{38}-N$ or $N-CR^{39}$,

R^{36}, R^{37}, R^{38} and R^{39} each independently of the others represents H, F, Cl, Br, I, -CN, $-NO_2$, -OH, -SH, C_{1-6}-alkyl or $-CF_3$, and

R^{40} and R^{41} each independently of the other represents H, F, Cl, Br, I, -CN, -OH, $-O-C_{1-6}$-alkyl, -SH, $-S-C_{1-6}$-alkyl, C_{1-8}-alkyl, CO_2-C_{1-6}-alkyl or -N=N-aryl.

Very particularly preferred compounds having the general structure (I) are those which are characterised in that

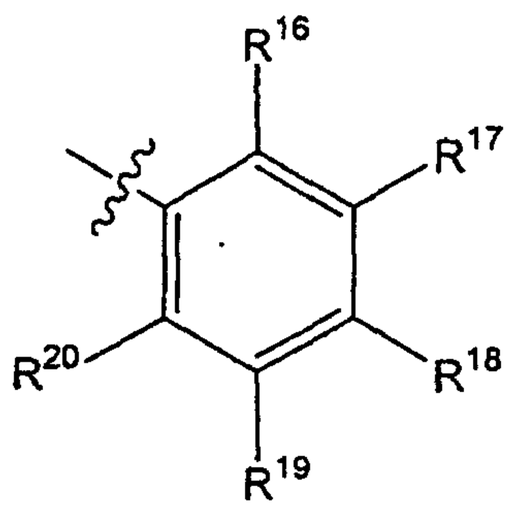
R^1 represents aryl or heterocyclyl^2,

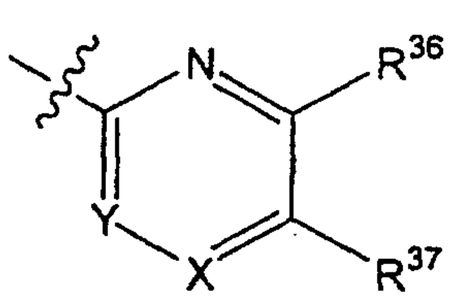
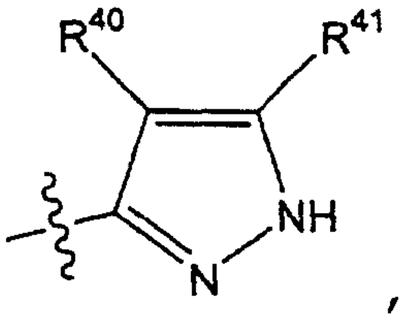
R^2 represents H, methyl, ethyl or tert-butyl,

R^3 represents H, Cl, methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl, $-CH_2OH$, $-CH_2SH$, $-CH_2-S-CH_3$, $-CH_2-S-CH_2$-furan-2-yl, $-CH_2-O-(C=O)-CH_3$, $-CH_2-S-(C=O)-CH_3$, $-CH_2-S-S-CH_3$, $-CH_2-S-S-CH_2$-furan-2-yl, $-CH_2-CO_2$methyl or $-CH_2-CO_2$ethyl,

R^4 represents H, Br, methyl, ethyl, $-CH_2OH$, $-CO_2$methyl, $-CO_2$ethyl or -COmethyl,

R^5 represents H, methyl or ethyl,



wherein aryl represents , heterocyclyl^2 represents  or  ,

R^{16} represents H, -O-phenyl, F, Cl, Br, methyl, ethyl, n-propyl, 2-propyl or tert-butyl,

R^{17} represents H, Cl, methyl, ethyl or CF_3,

R^{18} represents H, F, Cl, Br, I, -CN, $-O-CH_3$, $-O-CF_3$, -O-phenyl, methyl, ethyl, n-propyl, 2-propyl, n-butyl, 2-butyl or tert-butyl,

R^{19} represents H, Cl, Br, methyl or ethyl,

R^{20} represents H or methyl,

X-Y represents $CR^{38}-CR^{39}$, $CR^{38}-N$ or $N-CR^{39}$,

R^{36} represents H, methyl or ethyl,

R^{37} represents H, NO_2, Cl, Br, methyl or CF_3,

R^{38} represents H,

R^{39} represents H, Cl or Br,

R^{40} represents H, -N=N-phenyl, -CN, CO_2H, CO_2-methyl or CO_2-ethyl, and

R^{41} represents H, OH, SH, S-methyl, methyl, ethyl, n-propyl, 2-propyl, n-butyl or tert-butyl.

Of those very particularly preferred compounds, special preference is given to those in which

R^1 represents 4-trifluoromethoxy-phenyl, 2-phenoxy-phenyl, 4-phenoxy-phenyl, 2-chloro-phenyl, 4-chloro-phenyl, 4-iodo-phenyl, 4-cyano-phenyl, 2-methyl-phenyl, 2-ethyl-phenyl, 4-ethyl-phenyl, 2-(2-propyl)-phenyl, 4-(2-butyl)-phenyl, 4-tert-butyl-phenyl, 2,4-dichlorophenyl, 2,3-dichlorophenyl, 3,5-dichlorophenyl, 2,4-dibromo-phenyl, 4-chloro-2-fluoro-phenyl, 2-chloro-4-fluoro-phenyl, 4-bromo-2-chloro-phenyl, 2-chloro-4-iodo-phenyl, 3-chloro-2-methyl-phenyl, 4-chloro-2-methyl-phenyl, 5-chloro-2-methyl-phenyl, 2-chloro-4-methyl-phenyl, 4-chloro-3-trifluoromethyl-phenyl, 2,4-dibromo-5-methyl-phenyl, 5-nitro-pyridin-2-yl, 3,5-dibromo-pyridin-2-yl, 3,5-dichloro-pyridin-2-yl, 3-chloro-5-trifluoromethyl-

pyridin-2-yl, 3,5-dibromo-6-methyl-pyridin-2-yl, pyrazin-2-yl, 5-bromo-pyrimidin-2-yl, 4-carboxy-ethyl-pyrazol-3-yl, 4-cyano-pyrazol-3-yl, 5-tert-butyl-pyrazol-3-yl, 5-hydroxy-4-(4-phenylazo)-pyrazol-3-yl or 4-cyano-5-thiomethyl-pyrazol-3-yl,

R^2 represents H or ethyl,

R^3 represents H, Cl, methyl, ethyl, n-propyl, tert-butyl, $-CH_2OH$, $-CH_2SH$, $-CH_2S-CH_3$, $-CH_2-S-CH_2$-furan-2-yl, $-CH_2-O-(C=O)-CH_3$, $-CH_2-S-(C=O)-CH_3-$, $-CH_2-S-S-CH_3$, $-CH_2-S-S-CH_2$-furan-2-yl or $-CH_2-CO_2$ethyl,

R^4 represents H, Br, methyl, $-CH_2OH$, $-CO_2$methyl, $-CO_2$ethyl or $-C(=O)CH_3$, and

R^5 represents H or methyl.

Extremely preferred compounds according to the invention are those in which R^1 represents 3,5-dichlorophenyl and R^2 represents H.

Examples of advantageous compounds of the present invention are selected from the group containing

- (5-methylsulfanylmethyl-furan-2-yl)-(5-nitro-pyridin-2-ylamino)-acetic acid
- (5-bromopyrimidin-2-ylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- 5-[carboxy-(3,5-dichloropyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(3,5-dibromopyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(3,5-dibromo-6-methyl-pyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester

- (3,5-dibromo-6-methyl-pyridin-2-ylamino)-(4-hydroxy-methyl-furan-2-yl)-acetic acid
- (3,5-dichloro-pyridin-2-ylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (2,4-dibromo-5-methyl-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (4-methyl-thiophen-2-yl)-(5-nitro-pyridin-2-ylamino)-acetic acid
- (3,5-dichloro-pyridin-2-ylamino)-furan-2-yl-acetic acid
- (3,5-dibromopyridin-2-ylamino)-furan-2-yl-acetic acid
- (3,5-dibromo-6-methyl-pyridin-2-ylamino)-furan-2-yl-acetic acid
- (3-chloro-5-trifluoromethyl-pyridin-2-ylamino)-furan-2-yl-acetic acid
- (5-bromopyrimidin-2-ylamino)-furan-2-yl-acetic acid
- 5-[(3,5-dichloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- (5-hydroxy-4-phenylazo-1H-pyrazol-3-ylamino)-(5-methyl-sulfanylmethyl-furan-2-yl)-acetic acid ethyl ester
- 3-{[ethoxycarbonyl-(4-ethoxycarbonyl-5-methyl-furan-2-yl)-methyl]-amino}-1H-pyrazole-4-carboxylic acid ethyl ester
- 5-[(4-cyano-5-methylsulfanyl-1H-pyrazol-3-ylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-cyano-1H-pyrazol-3-ylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-bromo-2-chloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester

- 5-[(4-cyano-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- (4-hydroxymethyl-furan-2-yl)-(5-hydroxy-4-phenylazo-1H-pyrazol-3-ylamino)-acetic acid ethyl ester
- (4-cyano-5-methylsulfanyl-1H-pyrazol-3-ylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (4-bromo-2-chloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (3,5-dichloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (5-chloro-2-methyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid ethyl ester
- (2,4-dibromo-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (5-chloro-2-methyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (2-ethyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (4-sec-butyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (5-methylsulfanylmethyl-furan-2-yl)-(4-trifluoro-methoxy-phenylamino)-acetic acid
- (2-isopropyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (2,4-dibromo-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (4-tert-butyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (5-chloro-2-methyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid

- (2-ethyl-phenylamino)-[5-(furan-2-ylmethylsulfanyl-methyl)-furan-2-yl]-acetic acid
- (4-sec-butyl-phenylamino)-[5-(furan-2-ylmethylsulfanyl-methyl)-furan-2-yl]-acetic acid
- [5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-(2-isopropyl-phenylamino)-acetic acid
- (4-tert-butyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid
- 5-[ethoxycarbonyl-(4-iodo-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[(4-chloro-2-methyl-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[ethoxycarbonyl-(4-phenoxy-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[ethoxycarbonyl-(4-iodo-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(2-chloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-chloro-2-methyl-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(2-chloro-4-fluoro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[ethoxycarbonyl-(4-phenoxy-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(2,3-dichloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- (4-hydroxymethyl-furan-2-yl)-(4-iodo-phenylamino)-acetic acid ethyl ester
- (2,4-dichloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester

- (4-chloro-2-methyl-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (4-hydroxymethyl-furan-2-yl)-(4-phenoxy-phenylamino)-acetic acid ethyl ester
- (2,3-dichloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (2,3-dichloro-phenylamino)-furan-2-yl-acetic acid ethyl ester
- 5-[carboxy-(3,5-dibromo-6-methyl-pyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- (5-methylsulfanylmethyl-furan-2-yl)-(pyrazin-2-ylamino)-acetic acid
- (3,5-dibromo-pyridin-2-ylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (3,5-dibromo-6-methyl-pyridin-2-ylamino)-(5-methyl-sulfanylmethyl-furan-2-yl)-acetic acid
- 5-[(4-bromo-2-chloro-phenylamino)-carboxy-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[carboxy-(4-cyano-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[carboxy-(3,5-dichloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[carboxy-(2-phenoxy-phenylamino)-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-bromo-2-chloro-phenylamino)-carboxy-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(4-cyano-phenylamino)-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(3,5-dichloro-phenylamino)-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester

- 5-[(4-bromo-2-chloro-phenylamino)-carboxy-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(4-cyano-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(3,5-dichloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- (5-tert-butyl-1H-pyrazol-3-ylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid
- (4-bromo-2-chloro-phenylamino)-(3-methyl-thiophen-2-yl)-acetic acid
- (4-cyano-phenylamino)-(3-methyl-thiophen-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-(3-methyl-thiophen-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-furan-2-yl-acetic acid
- [5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-(4-phenoxy-phenylamino)-acetic acid ethyl ester
- (5-ethoxycarbonylmethyl-thiophen-2-yl)-(5-hydroxy-4-phenylazo-1H-pyrazol-3-ylamino)-acetic acid ethyl ester
- {5-[1-(4-cyano-1H-pyrazol-3-ylamino)-3-methoxy-2-oxo-propyl]-thiophen-2-yl}-acetic acid ethyl ester
- (4-ethyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (3-chloro-2-methyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (4-chloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (5-methylsulfanylmethyl-furan-2-yl)-o-tolylamino-acetic acid

- 5-[carboxy-(4-chloro-3-trifluoromethyl-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(2-chloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(2-chloro-4-fluoro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(4-chloro-2-fluoro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(2,3-dichloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- (2,4-dichloro-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (2,4-dichloro-phenylamino)-furan-2-yl-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-furan-2-yl-acetic acid
- (4-iodo-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (2,4-dichloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-(5-methyl-sulfanylmethyl-furan-2-yl)-acetic acid
- (2-chloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (4-chloro-2-methyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (2-chloro-4-fluoro-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid

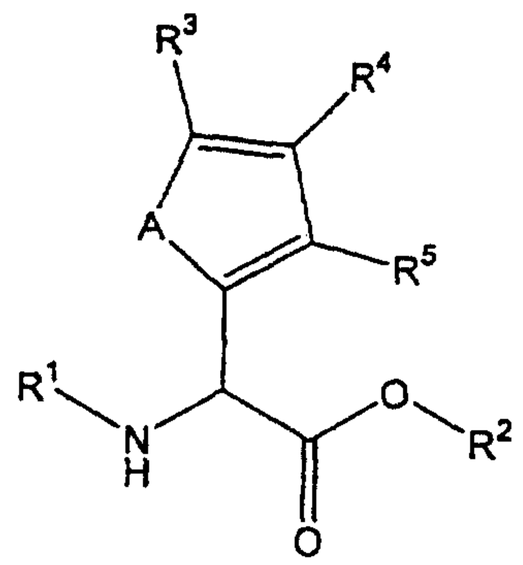
- (2-chloro-4-methyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (2,3-dichloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- [5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-(4-iodo-phenylamino)-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid
- (4-chloro-2-methyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid
- (2-chloro-4-methyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-(5-ethoxy-carbonylmethyl-thiophen-2-yl)-acetic acid
- (4-acetyl-3,5-dimethyl-furan-2-yl)-(2-chloro-4-methyl-phenylamino)-acetic acid
- (4-acetyl-3,5-dimethyl-furan-2-yl)-(2,3-dichloro-phenylamino)-acetic acid
- (3,5-dichloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- [2,2']bithiophenyl-5-yl-(3,5-dichloro-phenylamino-acetic acid
- (3,5-dichloro-phenylamino)-(5-methyldisulfanylmethyl-furan-2-yl)-acetic acid
- (3-chloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid
- (3,4-dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid

- (3,5-dichloro-phenylamino)-(5-methyl-thiophen-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-(5-hydroxymethyl-thiophen-2-yl)-acetic acid
- (5-acetylsulfanylmethyl-furan-2-yl)-(3,5-dichloro-phenylamino)-acetic acid
- (3,5-dichloro-phenylamino)-(5-ethyl-thiophen-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-(5-n-propyl-thiophen-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid
- (3-chloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid
- (3,4-dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid
- (3,5-dichlorophenylamino)-(thiophen-2-yl)-acetic acid ethyl ester
- (4-bromofuran-2-yl)-(3,5-dichloro-phenylamino)-acetic acid ethyl ester
- (3,5-dichloro-phenylamino)-(5-propylthiophen-2-yl)-acetic acid ethyl ester
- (3,5-dichloro-phenylamino)-(3-methylthiophen-2-yl)-acetic acid ethyl ester
- (5-tert-butylfuran-2-yl)-(3,5-dichloro-phenylamino)-acetic acid
- (3,5-dichlorophenylamino)-[5-(furan-2-ylmethyl-disulfanylmethyl)-furan-2-yl]-acetic acid
- (3,5-dichlorophenylamino)-(5-methyldisulfanylmethyl-furan-2-yl)-acetic acid

- (3,5-dichlorophenylamino)-[5-(furan-2-ylmethylsulfanyl-methyl)-furan-2-yl]-acetic acid
- 5-acetoxymethylfuran-2-yl-(3,5-dichlorophenylamino)-acetic acid
- (3,5-dichlorophenylamino)-thiophen-3-yl-acetic acid
- (3,5-dichlorophenylamino)-(5-methylthiophen-2-yl)-acetic acid
- (3,5-dichlorophenylamino)-(4-methylthiophen-2-yl)-acetic acid
- (5-chlorothiophen-2-yl)-(3,5-dichlorophenylamino)-acetic acid

and their pharmaceutically acceptable salts.

The compounds according to the invention having the general structure (I)



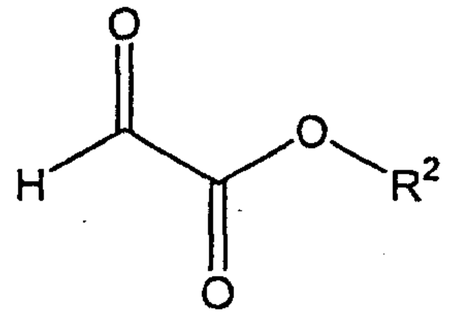
I

wherein A, R^1, R^2, R^3, R^4 and R^5 are as defined above, are obtainable according to a process which is also provided by the present invention and is characterised in that an amine having the general structure (II)

R^1-NH_2

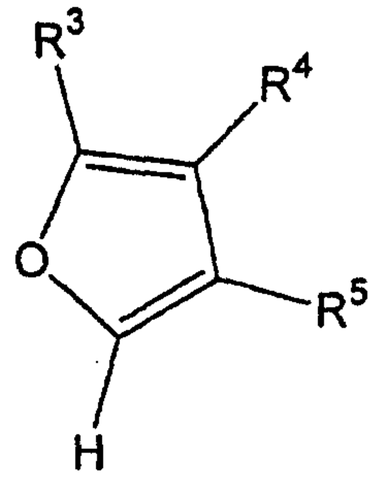
II ,

wherein R^1 is as defined above for the general structure (I),
is reacted, under the action of an acid, with a glyoxalic acid derivative having the general structure (III)

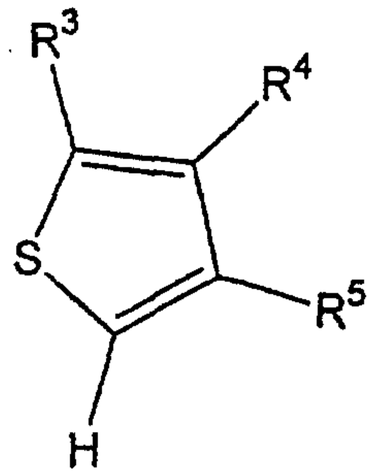


III

wherein R^2 is as defined above for the general structure (I),
and with a furan having the general structure (IV-A) or a thiophene having the general structure (IV-B)



IV-A



IV-B

wherein R^3, R^4 and R^5 are as defined above for the general structure (I). If the furan derivative (IV-A) is used, the corresponding amino-furan-2-yl-acetic acid derivative having the general structure (I-A) is obtained as the product, whereas the use of the thiophene derivative (IV-B) yields as the product of the 3-component reaction according to the invention the corresponding amino-thien-2-yl-acetic acid derivative having the general structure (I-B).

For the preparation of the furanylacetic acids (IV-A) and thienylacetic acids (IV-B), that is to say the compounds having the general structure (IV) wherein R^2 represents H, the glyoxalic acid reaction component (III) is preferably used in the form of its hydrate.

The process according to the invention can be carried out in the presence of small amounts of an inorganic or, especially, organic acid, for example trifluoroacetic acid, preferably in catalytic amounts of approximately from 1 to 10 mol% (based on the starting material (II)). If there is used as the glyoxalic acid derivative having the general structure (III) glyoxalic acid itself (i.e. the compound (III) wherein R^2 = H) or its hydrate in a slight excess of approximately from 1.01 to 1.5, preferably from 1.05 to 1.25, molar equivalents (based on the compound (II)), the reaction can be carried out without the addition of an acid or of a further reagent by simply mixing the starting compounds (II), (III) and (IV-A) or (IV-B), preferably in an organic solvent, for example acetonitrile, and then stirring at temperatures of from 0°C to 100°C - optionally also as a one-pot process. It is also advantageous to use the furan derivative (IV-A) or thiophene derivative (IV-B) in an excess of, for example, from 1.5 to 4.5 molar equivalents, especially from 2.5 to 3.5 molar equivalents (based on starting material (II)).

In order to achieve maximum conversion of the starting materials to the compounds according to the invention having the general structure (I), a reaction time of from 8 hours to approximately 18 hours, especially 14 hours,

is advantageous for the 3-component reaction according to the invention.

Alternatively, it is also possible to carry out the 3-component reaction according to the invention under the action of microwave radiation, whereby the reaction time for largely complete conversion is shortened to a few minutes, for example to from 0.5 minute to 5 minutes. In the case of this procedure, the chosen reaction temperature is preferably from 15°C to 60°C, especially approximately 50°C. A laboratory microwave from MLS-GmbH (D-88299 Leutkirch, Auenweg 37, Germany), model MLS ETHOS 600 having a power of about 800 W is suitable for the microwave irradiation. The reaction is advantageously carried out, for example, in a pressure-stable Teflon vessel.

The process according to the invention can also be carried out in semi- or fully automated form as the parallel synthesis of a group of compounds according to the invention having the general structure (I). By means of that technique, and by reaction of the compounds (II), (III) and (IV-A) or (IV-B), it is also possible to construct a substance library in the form of an array of compounds. Such a substance library contains the library members, which are the reaction products of the reaction of the compounds (II), (III) and (IV-A) or (IV-B), in the form of individual pure compounds. With the aid of such a substance library, it is possible, for example, to carry out medicinal screening in one or more *in vitro* screening processes in automated form.

The amines having the general structure (II), the glyoxalic acid derivatives having the general structure (III), the furan derivatives having the general structure (IV-A) and the thiophene derivatives having the general structure (IV-B) used in the process according to the invention are commercially available (from Acros, Geel; Avocado, Port of Heysham; Aldrich, Deisenhofen; Fluka, Seelze; Lancaster, Mülheim; Maybridge, Tintagel; Merck, Darmstadt; Sigma, Deisenhofen; TCI, Japan) or can be prepared by processes generally known in the art.

The compounds according to the invention having the general structure (I) can be isolated both in substance and in the form of a salt. The compound according to the invention having the general structure (I) is usually obtained after the reaction according to the above-described process according to the invention has taken place and after subsequent conventional working up. The compound having the general structure (I) so obtained or formed *in situ* without isolation can then be converted into the corresponding salt, for example by reaction with an inorganic or organic acid, preferably with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, carbonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid or aspartic acid. If the compounds according to the invention of the general formula (I) are acids, especially carboxylic acids, the salt formation can be effected by addition of a physiologically tolerable base, for example $NaHCO_3$ or sodium carbonate; the formation of

the sodium salt in particular is preferred for the carboxylic acids. The salts that are formed are, *inter alia*, hydrochlorides, hydrobromides, phosphates, carbonates, hydrogen carbonates, formates, acetates, oxalates, succinates, tartrates, fumarates, citrates and glutamates. Formation of the hydrochloride, which is particularly preferred, can also be effected by addition of trimethylsilyl chloride (TMSCl) to the base dissolved in a suitable organic solvent, such as, for example, butan-2-one (methyl ethyl ketone), advantageously in the presence of water.

If the compounds having the general structure (I) are obtained in the preparation process according to the invention in the form of racemates or in the form of mixtures of their different enantiomers and/or diastereoisomers, such mixtures can be separated by processes which are well known in the art. Suitable methods are, *inter alia*, chromatographic separation processes, especially liquid chromatography processes under normal or elevated pressure, preferably MPLC and HPLC processes, and also fractional crystallisation processes. By means of such processes it is possible especially to separate from one another, for example by means of HPLC on chiral phase or by means of crystallisation, individual enantiomers of diastereoisomeric salts formed with chiral acids, for example (+)-tartaric acid, (-)-tartaric acid or (+)-10-camphorsulfonic acid, or - where acids are concerned - with chiral bases, for example brucine or (-)-ephedrine.

The present invention also provides a medicament containing at least one compound having the general structure (I) as defined above or a pharmaceutical salt thereof, especially the hydrochloride salt. The medicament according to the invention preferably contains at least one of the compounds mentioned by way of example above in substance or in the form of a pharmaceutically acceptable salt, and optionally further active ingredients and excipients.

Such medicaments according to the invention are preferably used in the therapy of pain, such as, for example, acute pain, chronic pain or neuropathic pain. It has also been found that the medicaments according to the invention can also successfully be used in the treatment of migraine, inflammatory and/or allergic reactions, depression, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory diseases, coughs, mental diseases, neurodegenerative diseases, epilepsy, schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, cerebral ischaemia, cerebral infarct, psychoses caused by increased amino acid levels, strokes, cerebral oedemas, deficiencies of the central nervous system, hypoxia, anoxia, AIDS dementia, encephalomyelitis, Tourette syndrome, perinatal asphyxia, or for anxiolysis.

The present Application relates also to the use of at least one substituted amino-furan-2-yl-acetic acid derivative of formula (I-A) or substituted amino-thien-2-yl-acetic acid derivative of formula (I-B) in the preparation of a medicament for the treatment of pain,

migraine, inflammatory and/or allergic reactions, depression, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory diseases, coughs, mental diseases, neurodegenerative diseases, epilepsy, schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, cerebral ischaemia, cerebral infarct, psychoses caused by increased amino acid levels, strokes, cerebral oedemas, deficiencies of the central nervous system, hypoxia, anoxia, AIDS dementia, encephalomyelitis, Tourette syndrome, perinatal asphyxia, or for anxiolysis.

The present invention also provides pharmaceutical compositions that contain at least one compound having the general structure (I) as defined above in substance, or a pharmaceutically acceptable salt thereof, as well as one or more pharmaceutical excipients.

The medicaments and pharmaceutical compositions according to the invention can be in liquid, semi-solid or solid pharmaceutical dosage forms and can be administered in the form of, for example, injectable solutions, drops, juices, syrups, sprays, suspensions, granules, tablets, pellets, transdermal therapeutic systems, capsules, plasters, suppositories, ointments, creams, lotions, gels, emulsions or aerosols, and, in addition to at least one compound according to the invention having the general structure (I), they contain, according to the particular galenical form and depending on the route of administration, pharmaceutical excipients, such as, for example, carriers, fillers, solvents, diluents, surface-active substances, colourings, preservatives,

disintegrators, glidants, lubricants, flavourings and/or binders. Such excipients may be, for example: water, ethanol, 2-propanol, glycerol, ethylene glycol, propylene glycol, polyethylene glycol, polypropylene glycol, glucose, fructose, lactose, saccharose, dextrose, molasses, starch, modified starch, gelatin, sorbitol, inositol, mannitol, microcrystalline cellulose, methyl cellulose, carboxymethyl cellulose, cellulose acetate, shellac, cetyl alcohol, polyvinylpyrrolidone, paraffins, waxes, natural and synthetic gums, acacia gum, alginates, dextran, saturated and unsaturated fatty acids, stearic acid, magnesium stearate, zinc stearate, glyceryl stearate, sodium lauryl sulfate, edible oils, sesame oil, coconut oil, groundnut oil, soybean oil, lecithin, sodium lactate, polyoxyethylene and polyoxypropylene fatty acid esters, sorbitan fatty acid esters, sorbic acid, benzoic acid, citric acid, ascorbic acid, tannic acid, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, magnesium oxide, zinc oxide, silicon dioxide, titanium oxide, titanium dioxide, magnesium sulfate, zinc sulfate, calcium sulfate, potassium carbonate, calcium phosphate, dicalcium phosphate, potassium bromide, potassium iodide, talcum, kaolin, pectin, crospovidone, agar and bentonite.

The choice of excipients and the amounts thereof to be used depend on whether the medicament is to be administered by the oral, subcutaneous, parenteral, intravenous, vaginal, pulmonary, intraperitoneal, transdermal, intramuscular, nasal, buccal or rectal route, or locally, for example to infections of the skin, the mucosa and of the eyes. For oral administration there

are suitable, *inter alia*, preparations in the form of tablets, dragées, capsules, granules, drops, juices and syrups, and for parenteral and topical administration and for administration by inhalation there are suitable solutions, suspensions, readily reconstitutable powders for inhalation, and also sprays. Compounds according to the invention having the general structure I in a depot formulation in dissolved form or in a plaster, optionally with the addition of agents promoting penetration of the skin, are suitable preparations for percutaneous administration. Forms of preparation for rectal, transmucosal, parenteral, oral or percutaneous administration may release the compounds according to the invention having the general structure (I) in a delayed manner.

The medicaments and pharmaceutical compositions according to the invention are prepared by means, devices, methods and processes which are well known in the art of pharmaceutical formulation, as are described, for example, in "Remington's Pharmaceutical Sciences", ed. A.R. Gennaro, 17th ed., Mack Publishing Company, Easton, Pa. (1985), especially in Part 8, Chapter 76 to 93.

Accordingly, for a solid formulation, for example, such as a tablet, the active ingredient of the medicament, i.e. a compound having the general structure (I) or a pharmaceutically acceptable salt thereof, can be granulated with a pharmaceutical carrier, for example conventional tablet constituents such as maize starch, lactose, saccharose, sorbitol, talcum, magnesium stearate, dicalcium phosphate or pharmaceutically

acceptable gums, and pharmaceutical diluents, such as, for example, water, in order to form a solid composition which contains a compound according to the invention or a pharmaceutically acceptable salt thereof in homogeneous distribution. Homogeneous distribution is here understood to mean that the active ingredient is distributed evenly throughout the entire composition, so that the latter can readily be divided into unit dose forms, such as tablets, pills or capsules, which each have the same effectiveness. The solid composition is then divided into unit dose forms. It is also possible for the tablets or pills of the medicament according to the invention or of the compositions according to the invention to be coated or otherwise compounded, in order to prepare a delayed-release dosage form. Suitable coating agents are, *inter alia*, polymeric acids and mixtures of polymeric acids with materials such as, for example, shellac, cetyl alcohol and/or cellulose acetate.

The amount of active ingredient to be administered to a patient varies and is dependent on the weight, the age and the history of past disease in the patient, and also on the mode of administration, the indication and the severity of the disease. Normally, from 0.1 to 5000 mg/kg, especially from 1 to 500 mg/kg, preferably from 2 to 250 mg/kg body weight of at least one compound according to the invention having the general structure (I) are administered.

The present invention is explained further hereinbelow by means of Examples, without limiting it thereto.

Examples

Preliminary remarks

The chemicals and solvents used were purchased from Acros, Geel; Avocado, Port of Heysham; Aldrich, Deisenhofen; Fluke, Seelze; Lancaster, Mülheim; Maybridge, Tintagel; Merck, Darmstadt; Sigma, Deisenhofen and TCI, Japan or were synthesised by conventional processes known in the art.

Thin-layer chromatographic investigations were carried out using HPTLC precoated plates, silica gel 60 F 254, from E. Merck, Darmstadt.

ESI mass spectra were recorded using a LCQ Classic mass spectrometer from Finnigan, and ^{1}H-NMR spectra were recorded with a 300 MHz Avance DPX 300 NMR device or a 600 MHz Avance DRX 600 NMR device from Bruker.

General working procedure 1 (GWP 1)

A round-bottomed glass test tube (diameter 16 mm, length 125 mm) with a thread was provided with a magnetic stirring core and closed in an automated manner with a screw lid having a septum. By means of a robot, the test tube was placed in a stirring block adjusted to a temperature of 20°C. The following reagents were pipetted in in succession by a robot:

- 1 ml of a solution containing trifluoroacetic acid and the amine component (II) - in each case 0.1M - in acetonitrile

- 1 ml of a 0.11 M glyoxalic acid derivative (III) solution in acetonitrile
- 1 ml of a 0.3 M furan (IV-A) or thiophene (IV-B) solution in acetonitrile.

The reaction mixture was stirred for 600 minutes at 40°C in a stirring block. The reaction solution was then filtered off. The test tube was rinsed twice with 1.5 ml of a 7.5 % $NaHCO_3$ solution.

The rack with the samples was then placed manually onto a working-up unit. 2 ml of ethyl acetate were added to the reaction mixture in a vortexer, and shaking was carried out. To form the phase boundary, centrifugation was carried out for a short time in a centrifuge. The phase boundary was detected visually and the organic phase was removed by means of a pipette. In the next step, a further 2 ml of ethyl acetate was added to the aqueous phase, followed by shaking, centrifugation and removal of the organic phase by means of a pipette. The combined organic phases are dried over 2.4 g of $MgSO_4$ (granulated). The solvent was removed in a vacuum centrifuge. Each sample was analysed by ESI-MS and/or NMR.

The automatic synthesis ensured that all samples were treated equally and that the reaction procedure was highly constant.

The synthesised and isolated compounds are shown in Table 1.

Table 1

Example No.	Compound	Molar mass calculated	Molar mass found
1	(5-Methylsulfanylmethyl-furan-2-yl)-(5-nitro-pyridin-2-ylamino)-acetic acid	323.32	323.9; 278.1 (M-CO_2)
2	(5-Bromopyrimidin-2-ylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid	358.21	356.9/359.0
3	5-[Carboxy-(3,5-dichloropyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	373.19	372.9/374.9
4	5-[Carboxy-(3,5-dibromopyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	462.1	460.7/462.8/ 464.8
5	5-[Carboxy-(3,5-dibromo-6-methyl-pyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	476.13	474.9/476.9/ 478.8
6	(3,5-Dibromo-6-methyl-pyridin-2-ylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid	420.06	420.9/422.9
7	(3,5-Dichloro-pyridin-2-ylamino)-(4-methyl-thiophen-2-yl)-acetic acid	317.19	316.9/318.9
8	(2,4-Dibromo-5-methyl-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid	419.14	420.8/422.8
9	(4-Methyl-thiophen-2-yl)-(5-nitro-pyridin-2-ylamino)-acetic acid	293.3	293.9; 248.2 (M-CO_2)
10	(3,5-Dichloro-pyridin-2-ylamino)-furan-2-yl-acetic acid	287.1	286.9/289.0
11	(3,5-Dibromopyridin-2-ylamino)-furan-2-yl-acetic acid	376.01	376.9/378.9
12	(3,5-Dibromo-6-methyl-pyridin-2-ylamino)-furan-2-yl-acetic acid	390.04	390.9/392.9
13	(3-Chloro-5-trifluoromethyl-pyridin-2-ylamino)-furan-2-yl-acetic acid	320.65	320.9/322.9
14	(5-Bromopyrimidin-2-ylamino)-furan-2-yl-acetic acid	298.1	297.0/299.0
15	5-[(3,5-Dichloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid methyl ester	386.23	385.9/387.9
16	(5-Hydroxy-4-phenylazo-1H-pyrazol-3-ylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid ethyl ester	415.47	416.0
17	3-{[Ethoxycarbonyl-(4-ethoxycarbonyl-5-methyl-furan-2-yl)-methyl]-amino}-1H-pyrazole-4-carboxylic acid ethyl ester	393.39	393.9
18	5-[(4-Cyano-5-methylsulfanyl-1H-pyrazol-3-ylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	392.43	392.9
19	5-[(4-Cyano-1H-pyrazol-3-ylamino)-ethoxy-carbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	346.34	346.9

Example No.	Compound	Molar mass calculated	Molar mass found
20	5-[(4-Bromo-2-chloro-phenylamino)-ethoxy-carbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	444.71	443.9/445.9
21	5-[(4-Cyano-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	356.37	357.0
22	(4-Hydroxymethyl-furan-2-yl)-(5-hydroxy-4-phenylazo-1H-pyrazol-3-ylamino)-acetic acid ethyl ester	385.37	386.0
23	(4-Cyano-5-methylsulfanyl-1H-pyrazol-3-ylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester	336.36	336.9
24	(4-Bromo-2-chloro-phenylamino)-(4-hydroxy-methyl-furan-2-yl)-acetic acid ethyl ester	388.64	387.9/389.9
25	(3,5-Dichloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester	344.19	344.0/346.0
26	(5-Chloro-2-methyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid ethyl ester	419.92	420.0
27	(2,4-Dibromo-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid	405.11	(M-CO_2) 358.2/360.2/ 362.2
28	(5-Chloro-2-methyl-phenylamino)-(5-methyl-sulfanylmethyl-furan-2-yl)-acetic acid	325.81	326.0
29	(2-Ethyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid	305.39	306.0
30	(4-sec-Butyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid	333.44	334.1
31	(5-Methylsulfanylmethyl-furan-2-yl)-(4-trifluoro-methoxy-phenylamino)-acetic acid	361.33	362.0/ 316.2 (M-CO_2)
32	(2-Isopropyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid	319.42	320.1
33	(2,4-Dibromo-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid	435.14	(M-CO_2) 390.0/392.0
34	(4-tert-Butyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid	333.44	334.0
35	(5-Chloro-2-methyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid	391.87	392.0/394.0
36	(2-Ethyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid	371.45	372.1
37	(4-sec-Butyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid	399.5	400.1
38	[5-(Furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-(2-isopropyl-phenylamino)-acetic acid	385.48	386.2
39	(4-tert-Butyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid	399.5	400.1
40	5-[Ethoxycarbonyl-(4-iodo-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester	443.23	442.1/444.0/ 445.0
41	5-[(4-Chloro-2-methyl-phenylamino)-ethoxy-carbonyl-methyl]-2-methyl-furan-3-carboxylic acid methyl ester	365.81	366.1/368.1

Example No.	Compound	Molar mass calculated	Molar mass found
42	5-[Ethoxycarbonyl-(4-phenoxy-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester	409.43	408.3/410.2
43	5-[Ethoxycarbonyl-(4-iodo-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	457.26	456.2/458.0/459.1
44	5-[(2-Chloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	365.81	366.1/367.0/368.1
45	5-[(4-Chloro-2-methyl-phenylamino)-ethoxy-carbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	379.83	380.1/382.1
46	5-[(2-Chloro-4-fluoro-phenylamino)-ethoxy-carbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	383.8	384.1/385.0
47	5-[Ethoxycarbonyl-(4-phenoxy-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	423.46	422.4/424.2
48	5-[(2,3-Dichloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	400.25	400.0/402.0
49	(4-Hydroxymethyl-furan-2-yl)-(4-iodo-phenyl-amino)-acetic acid ethyl ester	401.19	402.2
50	(2,4-Dichloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester	344.19	344.2/346.2
51	(4-Chloro-2-methyl-phenylamino)-(4-hydroxy-methyl-furan-2-yl)-acetic acid ethyl ester	323.77	324.3
52	(4-Hydroxymethyl-furan-2-yl)-(4-phenoxy-phenyl-amino)-acetic acid ethyl ester	367.4	368.3
53	(2,3-Dichloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester	344.19	344.1/346.1
54	(2,3-Dichloro-phenylamino)-furan-2-yl-acetic acid ethyl ester	314.16	314.4/316.3
55	5-[Carboxy-(3,5-dibromo-6-methyl-pyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester	462.1	460.9/462.9/464.9
56	(5-Methylsulfanylmethyl-furan-2-yl)-(pyrazin-2-ylamino)-acetic acid	279.31	280.0
57	(3,5-Dibromo-pyridin-2-ylamino)-(5-methyl-sulfanylmethyl-furan-2-yl)-acetic acid	436.13	436.8/438.8
58	(3,5-Dibromo-6-methyl-pyridin-2-ylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid	450.15	448.9/450.8/452.8
59	5-[(4-Bromo-2-chloro-phenylamino)-carboxy-methyl]-2-methyl-furan-3-carboxylic acid methyl ester	402.63	(M-CO_2) 356.4/358.4/360.3
60	5-[Carboxy-(4-cyano-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester	314.29	(M-CO_2) 269.4
61	5-[Carboxy-(3,5-dichloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester	358.17	358.0/360.0 (M-CO_2) 312.4
62	5-[Carboxy-(2-phenoxy-phenylamino)-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester	409.43	410.1 (M-CO_2) 364.4

Example No.	Compound	Molar mass calculated	Molar mass found
63	5-[(4-Bromo-2-chloro-phenylamino)-carboxy-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester	430.68	(M-CO_2) 384.3/386.2/ 388.2
64	5-[Carboxy-(4-cyano-phenylamino)-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester	342.35	(M-CO_2) 297.4
65	5-[Carboxy-(3,5-dichloro-phenylamino)-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester	386.23	(M-CO_2) 340.3/342.3
66	5-[(4-Bromo-2-chloro-phenylamino)-carboxy-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	416.65	418.0, (M-CO_2) 370.4/372.3
67	5-[Carboxy-(4-cyano-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	328.32	(M-CO_2) 283.4
68	5-[Carboxy-(3,5-dichloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	372.2	372.0/374.0 (M-CO_2) 326.3
69	(5-tert-Butyl-1H-pyrazol-3-ylamino)-(4-hydroxy-methyl-furan-2-yl)-acetic acid	293.32	294.5
70	(4-Bromo-2-chloro-phenylamino)-(3-methyl-thiophen-2-yl)-acetic acid	360.66	(M-CO_2) 314.4/316.3/ 318.3
71	(4-Cyano-phenylamino)-(3-methyl-thiophen-2-yl)-acetic acid	272.32	(M-CO_2) 227.4
72	(3,5-Dichloro-phenylamino)-(3-methyl-thiophen-2-yl)-acetic acid	316.2	(M-CO_2) 270.4/272.4
73	(3,5-Dichloro-phenylamino)-furan-2-yl-acetic acid	286.11	286.3/288.3 (M-CO_2) 240.6/242.5
74	[5-(Furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-(4-phenoxy-phenylamino)-acetic acid ethyl ester	463.55	464.0
75	(5-Ethoxycarbonylmethyl-thiophen-2-yl)-(5-hydroxy-4-phenylazo-1H-pyrazol-3-ylamino)-acetic acid ethyl ester	457.5	458.0
76	{5-[1-(4-Cyano-1H-pyrazol-3-ylamino)-3-methoxy-2-oxo-propyl]-thiophen-2-yl}-acetic acid ethyl ester	362.4	363.0
77	(4-Ethyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid	305.39	306.1, (M-CO_2) 260.2
78	(3-Chloro-2-methyl-phenylamino)-(5-methyl-sulfanylmethyl-furan-2-yl)-acetic acid	325.81	326.0/328.0, (M-CO_2) 280.2
79	(4-Chloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid	311.78	311.9/314.0, (M-CO_2) 266.1
80	(5-Methylsulfanylmethyl-furan-2-yl)-o-tolylamino-acetic acid	291.36	292.1, (M-CO_2) 246.2
81	5-[Carboxy-(4-chloro-3-trifluoromethyl-phenyl-amino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	405.75	(M-CO_2) 360.2/362.1
82	5-[Carboxy-(2-chloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	337.75	338.0, (M-CO_2) 292.2
83	5-[Carboxy-(2-chloro-4-fluoro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	355.74	356.8/358.9, (M-CO_2) 310.2/312.2

Example No.	Compound	Molar mass calculated	Molar mass found
84	5-[Carboxy-(4-chloro-2-fluoro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	355.74	(M-CO_2) 310.2/312.2
85	5-[Carboxy-(2,3-dichloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester	372.2	(M-CO_2) 310.2/312.2
86	(2,4-Dichloro-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid	316.2	(M-CO_2) 270.3/272.3
87	(4-Chloro-3-trifluoromethyl-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid	349.75	(M-CO_2) 304.4/306.3
88	(2,4-Dichloro-phenylamino)-furan-2-yl-acetic acid	286.11	286.3/288.1, (M-CO_2) 240.4/242.4
89	(4-Chloro-3-trifluoromethyl-phenylamino)-furan-2-yl-acetic acid	319.66	(M-CO_2) 274.5/276.5
90	(4-Iodo-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid	403.23	403.9, (M-CO_2) 358.1
91	(2,4-Dichloro-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid	346.23	(M-CO_2) 300.2/302.1
92	(4-Chloro-3-trifluoromethyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid	379.78	(M-CO_2) 334.1/336.1
93	(2-Chloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid	311.78	312.0/314.0, (M-CO_2) 366.2/368.2
94	(4-Chloro-2-methyl-phenylamino)-(5-methyl-sulfanylmethyl-furan-2-yl)-acetic acid	325.81	326.0/328.0, (M-CO_2) 280.2/282.2
95	(2-Chloro-4-fluoro-phenylamino)-(5-methyl-sulfanylmethyl-furan-2-yl)-acetic acid	329.77	330.0, (M-CO_2) 284.2/286.2
96	(2-Chloro-4-methyl-phenylamino)-(5-methyl-sulfanylmethyl-furan-2-yl)-acetic acid	325.81	326.0/328.0, (M-CO_2) 280.2
97	(2,3-Dichloro-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid	346.23	(M-CO_2) 300.2/302.1
98	[5-(Furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-(4-iodo-phenylamino)-acetic acid	469.29	470.1/471.7
99	(4-Chloro-3-trifluoromethyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid	445.84	446.7/447.6 (M-CO_2) 400.6/401.5
100	(4-Chloro-2-methyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid	391.87	392.5/393.4
101	(2-Chloro-4-methyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid	391.87	392.2/394.8
102	(4-Chloro-3-trifluoromethyl-phenylamino)-(5-ethoxycarbonylmethyl-thiophen-2-yl)-acetic acid	421.82	(M-CO_2) 376.4/378.4
103	(4-Acetyl-3,5-dimethyl-furan-2-yl)-(2-chloro-4-methyl-phenylamino)-acetic acid	335.78	(M-CO_2) 290.3/292.2
104	(4-Acetyl-3,5-dimethyl-furan-2-yl)-(2,3-dichloro-phenylamino)-acetic acid	356.2	(M-CO_2) 310.3/312.2
106	(3,5-Dichloro-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid	346.23	345.9/347.9 300.0/302.0 (M-CO_2)

Example No.	Compound	Molar mass calculated	Molar mass found
113	(3-Chloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid	297.8	297.9 (MH)
114	(3,4-Dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid	332.2	332.0 (MH)

General working procedure 2 (GWP 2)

3,5-Dichloroaniline (10 mmol), glyoxalic acid hydrate (11 mmol) and the furan derivative (IV-A) or thiophene derivative (IV-B) (30 mmol) were dissolved in 10 ml of acetonitrile and stirred for 14 hours at 40°C. The reaction mixture was concentrated and purified by means of RP4 silica gel MPLC (Polygoprep 60-130 C4, Macherey-Nagel, P.O. Box 101352, D-52313 Düren, Germany) using methanol/water mixtures of various compositions and with the addition of 0.1 % glacial acetic acid. After concentration of the product fractions using a rotary evaporator, the product was isolated in the form of an oil.

General working procedure 3 (GWP 3) - microwave irradiation

The reactions with microwave irradiation were carried out in a laboratory microwave of type MLS ETHOS 600 from MLS-GmbH (D-88299 Leutkirch, Auenweg 37, Germany).

For the synthesis, the reaction components (II), (III) and (IV-A) or (IV-B) and the solvent were placed in a pressure-stable Teflon vessel which was closed with a Teflon lid and clamped into a safety holder for letting off excess pressure. Control of the reaction temperature took place in a second Teflon vessel which contained the same solvent as used in the synthesis. Temperature control was carried out by way of an internal glass fibre optics, which was guided in a quartz tube and was controlled from the outside by a control computer.

3,5-Dichloroaniline (10 mmol), glyoxalic acid hydrate (11 mmol) and furan derivative (IV-A) or thiophene derivative (IV-B) (30 mmol) were dissolved in 10 ml of acetonitrile, heated to 50°C in the course of one minute in the microwave and left at that temperature for five minutes. The microwave radiation was radiated with a power of 800 Watts, which was controlled and regulated by a control computer. After cooling, the vessel was placed in ice-water and opened carefully, and the solvent was removed using a rotary evaporator.

Purification was carried out by means of RP4 silica gel MPLC (Polygoprep 60-130 C4, Macherey-Nagel, P.O. Box 101352, D-52313 Düren, Germany) using methanol/water mixtures of various compositions and with the addition of 0.1 % glacial acetic acid. After concentration of the product fractions using a rotary evaporator, the product was isolated in the form of an oil.

In order to prepare the hydrochloride salt, the crude product was dissolved in butan-2-one, and an equimolar amount of water and then an equimolar amount of TMSCl were added thereto, while cooling with ice and with stirring. After standing overnight, the precipitated HCl salt was filtered off with suction and dried, or precipitation was brought about by removal of the solvent *in vacuo*.

The ^{1}H-NMR data of some of the compounds prepared according to GWP 2 and 3 are shown hereinbelow; the NMR data were obtained at 600 MHz, with d_6-DMSO being used as solvent:

(3,5-Dichloro-phenylamino)-(thiophen-2-yl)-acetic acid ethyl ester (**115**)

δ = 1.20 ppm (t, 3H, CH_3); 4.16 ppm (q, 2H, OCH_2); 5.65 ppm (d, 1H, α-CH); 6.65 ppm (s, 1H, aryl-4-H); 6.80 ppm (s, 2H, aryl-2-H and aryl-6-H); 7.10 ppm (m, 1H, thiophene-H); 7.20 ppm (d, 1H, thiophene-H); 7.50 ppm (d, 1H, thiophene-H).

(4-Bromofuran-2-yl)-(3,5-dichlorophenylamino)-acetic acid ethyl ester (**116**)

δ = 1.15 ppm (t, 3H, CH_3); 4.15 ppm (q, 2H, OCH_2); 5.50 ppm (d, 1H, α-CH); 6.60 ppm (s, 1H, furan-H); 6.70 ppm (s, 1H, furan-H); 6.75 ppm (s, 1H, aryl-4-H); 6.80 ppm (s, 2H, aryl-2-H and aryl-6H); 7.80 ppm (d, 1H, α-NH).

(3,5-Dichlorophenylamino)-(5-propylthiophen-2-yl)-acetic acid ethyl ester hydrochloride (**117-HCl**)

δ = 0.95 ppm (t, 3H, CH_3); 1.20 ppm (t, 3H, CH_3); 1.60 ppm (q, 2H, CH_2); 2.70 ppm (t, 2H, CH_2); 4.15 ppm (q, 2H, OCH_2); 4.80 ppm (s, 2H, α-NH_2^+ and 1H, α-CH); 5.50 ppm (d, 1H, thiophene-H); 6.40 ppm (d, 1H, thiophene-H); 6.40 ppm (s, 1H, aryl-4-H); 6.72 ppm (s, 2H, aryl-2-H and aryl-6-H).

(3,5-Dichlorophenylamino)-(3-methylthiophen-2-yl)-acetic acid ethyl ester (**118**)

δ = 1.15 ppm (t, 3H, CH_3); 2.20 ppm (s, 3H, 2-CH_3-thiophene); 4.10 ppm (q, 2H, OCH_2); 5.50 ppm (d, 1H, α-

CH); 6.65 ppm (s, 2H, aryl-2-H and aryl-6H); 6.80 ppm (d, 1H, thiophene-H); 7.28 ppm (d, 1H, thiophene-H).

(5-tert-Butylfuran-2-yl)-(3,5-dichlorophenylamino)-acetic acid (**119**)

δ = 1.22 ppm (s, 9H, tert-Bu); 5.24 ppm (d, 1H, α-CH); 5.99 ppm (d, 1H, furan-H); 6.26 ppm (d, 1H, furan-H); 6.54 ppm (s, 1H, aryl-4-CH); 6.73 ppm (s, 2H, aryl-2H and aryl-6H); 8.27 ppm (d, 1H, α-NH); 13.80 ppm (s (broad), 1H, CO_2H).

(5-tert-Butyl-furan-2-yl)-(3,5-dichlorophenylamino)-acetic acid hydrochloride (**119-HCl**)

δ = 1.25 ppm (s, 9H, tert-butyl); 5.30 ppm (m, 1H, α-CH); 6.00 ppm (d, 1H, furyl-H); 6.30 ppm (d, 1H, furyl-H); 6.65 ppm (m, 1H, α-NH); 6.70 ppm (s, 1H, aryl-H); 6.75 ppm (s, 2H, aryl-H).

(3,5-Dichlorophenylamino)-[5-(methylsulfanyl)methyl-furan-2-yl]-acetic acid (**106**)

δ = 2.02 ppm (s, 3H, SCH_3); 3.69 ppm (s, 2H, CH_2S); 5.30 ppm (d, 1H, α-CH); 6.22 ppm (s, 1H, furan-H); 6.37 ppm (s, 1H, furan-H); 6.63 ppm (s, 1H, aryl-4-H); 6.73 ppm (s, 2H, aryl-2-H and aryl-4H); 6.79 ppm (d, 1H, α-NH); 13.17 ppm (s (broad), 1H, CO_2H).

(3,5-Dichlorophenylamino)-[5-(methylsulfanyl)methyl-furan-2-yl]-acetic acid hydrochloride (**106-HCl**)

δ = 2.08 ppm (s, 3H, SCH_3); 2.50 ppm (2, 2H, CH_2S); 3.70 ppm (s, 2H, α-NH_2^+); 5.37 ppm (m, 1H, α-CH); 6.25 ppm

(d, 1H, furan-H); 6.40 ppm (d, 1H, furan-H); 6.80 ppm (s, 1H, aryl-4-H); 6.78 ppm (s, 2H, aryl-2-H and aryl-6-H).

(3,5-Dichlorophenylamino)-(5-methylsulfanylmethylfuran-2-yl)-acetic acid sodium salt (**106-Na**)

δ = 2.99 ppm (s, 3H, SCH_3); 3.65 ppm (s, 2H, CH_2S); 4.45 ppm (m, 1H, α-CH); 6.10 ppm (m, 3H, aryl-H); 6.45 ppm (m, 1H, α-NH); 6.50 ppm (d, 1H, thiophene-H); 6.55 ppm (d, 2H, thiophene-H).

(3,5-Dichlorophenylamino)-[5-(furan-2-ylmethylsulfanyl-methyl)-furan-2-yl]-acetic acid (**122**)

δ = 3.68 ppm (s, 2H, CH_2S); 3.73 (s, 2H, CH_2S); 5.33 (d, 1H, α-CH); 5.72 ppm (m, 1H, furan-H); 6.26 ppm (d, 1H, furan-H); 6.27 ppm (d, 1H, furan-H); 6.36 ppm (d, 1H, furan-H); 6.39 ppm (d, 1H, furan-H); 6.64 ppm (s, 1H, aryl-4-H); 6.74 ppm (s, 2H, aryl-2-H and aryl-6-H); 7.55 ppm (d, 1H, α-NH); 13.23 ppm (s (broad), 1H, CO_2H).

(3,5-Dichlorophenylamino)-[5-(furan-2-ylmethyldisulfanyl-methyl)-furan-2-yl]-acetic acid (**120**)

δ = 3.73 ppm (s, 2H, CH_2S); 3.80 ppm (s, 2H, CH_2S); 5.35 ppm (d, 1H, α-CH); 6.24 ppm (m, 1H, furan-H); 6.24 (d, 1H, furan-H); 6.30 ppm (d, 1H, furan-H); 6.38 ppm (s, 1H, furan-H); 6.43 ppm (d, 1H, furan-H); 6.43 ppm (s, 1H, aryl-4-H); 6.74 ppm (s, 2H, aryl-2-H and aryl-6-H); 7.58 ppm (d, 1H, α-NH); 13.20 ppm (s (broad), 1H, CO_2H).

(3,5-Dichlorophenylamino)-(5-methyldisulfanylmethylfuran-2-yl)-acetic acid (**121**)

δ = 2.08 ppm (s, 3H, SCH_3); 3.96 ppm (s, 2H, CH_2S); 5.30 (d, 1H, α-CH); 6.32 ppm (d, 1H, furan-H); 6.41 ppm (d, 1H, furan-H); 6.61 ppm (s, 1H, aryl-4-H); 6.73 ppm (s, 2H, aryl-2-H and aryl-6-H); 8.25 ppm (d, 1H, α-NH); 13.19 ppm (s (broad), 1H, CO_2H).

(5-Acetylsulfanylmethyl-furan-2-yl)-(3,5-dichlorophenyl-amino)-acetic acid (**110**)

δ = 2.35 ppm (s, 3H, $COCH_3$); 4.13 ppm (s, 2H, CH_2S); 5.28 ppm (d, 1H, α-CH); 6.24 ppm (s, 1H, furan-H); 6.35 (d, 1H, furan-H); 6.63 ppm (s, 1H, aryl-4-H); 6.71 ppm (s, 2H, aryl-2-H and aryl-6-H); 8.29 ppm (d, 1H, α-NH); 13.13 ppm (s (broad), 1H, CO_2H).

(5-Acetoxymethyl-furan-2-yl)-(3,5-dichlorophenylamino)-acetic acid (**123**)

Molar mass (calc.): 358.18 g/mol; found 356.0

δ = 2.05 ppm (s, 3H, $COCH_3$); 5.00 ppm (s, 2H, CH_2O); 5.20 ppm (m, 1H, α-CH); 6.40-6.50 ppm (m, 2H, furyl-H); 6.60 ppm (s, 1H, aryl-H); 6.65 ppm (s, 2H, aryl-H); 6.80 ppm (d, 1H, α-NH).

Further compounds prepared according to GWP 2 and GWP 3 are shown in Table 2.

Table 2

Example No.	Compound	Molar mass calculated	Molar mass found
106	(3,5-Dichloro-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid	412.3	410.2 (M-H) 366.2 (M-CO_2)
107	(3,5-Dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid	332.2	330.1 (M-H) 286.1 (M-CO_2)
108	(3,5-Dichloro-phenylamino)-(5-methyl-thiophen-2-yl)-acetic acid	316.2	314.0 (M-H) 270.2 (M-CO_2)
109	(3,5-Dichloro-phenylamino)-(5-hydroxymethyl-thiophen-2-yl)-acetic acid	332.2	331.9 (M-H) 286.1 (M-CO_2)
110	(5-Acetylsulfanylmethyl-furan-2-yl)-(3,5-dichloro-phenylamino)-acetic acid	374.2	372.3 (M-H) 327.6 (M-CO_2)
111	(3,5-Dichloro-phenylamino)-(5-ethyl-thiophen-2-yl)-acetic acid	330.2	328.0 (M-H) 284.2 (M-CO_2)
112	(3,5-Dichloro-phenylamino)-(5-n-propyl-thiophen-2-yl)-acetic acid	344.3	342.0 (M-H) 298.2 (M-CO_2)

General working procedure 4 (GWP 4)

The syntheses were carried out analogously to the synthesis process described by N.A. Petasis *et al.*, *Tetrahedron* (1997), 16463-16470: 10 mmol of glyoxalic acid hydrate were dissolved in 50 ml of dichloromethane; 10 mmol of aniline component (II) and 10 mmol of the boronic acid of the furan or thiophene derivative (IV-A) or (IV-B) were added, with stirring, and stirring was carried out overnight at room temperature. The precipitated product was filtered off with suction and then washed with a small amount of cold dichloromethane, and the substance was dried under a high vacuum. Colourless solids were obtained.

The ^{1}H-NMR data of some of the compounds prepared according to GWP 4 are shown hereinbelow; the NMR data were obtained at 300 MHz or 600 MHz, with d_6-DMSO being used as solvent:

(3,5-Dichlorophenylamino)-thiophen-3-yl)-acetic acid (**124**)

Molar mass (calc.): 302.18 g/mol; found 301.9

δ = 5.25 ppm (m, 1H, α-CH); 6.65 ppm (s, 1H, aryl-H); 6.70 ppm (s, 2H, aryl-H); 7.85 ppm (m, 1H, α-NH); 7.15 ppm (d, 1H, thiophene-H); 7.50-7.60 ppm (dd, 2H, thiophene-H); 13.00 (s (broad), 1H, COOH).

(3,5-Dichlorophenylamino)-(4-methylthiophen-2-yl)-acetic acid (**126**)

Molar mass (calc.): 358.18 g/mol; found 317.1

δ = 2.20 ppm (2, 3H, CH_3); 5.40 ppm (d, 1H, α-CH); 6.65 ppm (s, 1H, aryl-H); 6.75 ppm (s, 2H, aryl-H);

6.90 ppm (d, 1H, α-NH); 7.00-7.10 ppm (s, 2H, thiophene-H); 13.30 ppm (s (broad), 1H, COOH).

(3,5-Dichlorophenylamino)-(5-methylthiophen-2-yl)-acetic acid (**125**)

Molar mass (calc.): 358.18 g/mol; found 316.2

δ = 2.40 ppm (s, 3H, CH_3); 5.40 ppm (d, 1H, α-CH); 6.60-6.70 ppm (m, 2H, α-NH and aryl-H); 6.70 ppm (s, 2H, aryl-H); 6.90 ppm (d, 1H, thiophene-H); 6.95 ppm (d, 1H, thiophene-H); 13.30 ppm (s (broad), 1H, COOH).

(3,5-Dichlorophenylamino)-(5-methylthiophen-2-yl)-acetic acid sodium salt (**125-Na**)

δ = 2.40 ppm (s, 3H, CH_3); 5.30 ppm (d, 1H, α-CH); 6.60-6.80 ppm (m, 4H, α-NH and aryl-H); 6.85 ppm (d, 1H, thiophene-H); 6.90 ppm (d, 1H, thiophene-H).

(5-Chlorothiophen-2-yl)-(3,5-dichlorophenylamino)-acetic acid (**127**)

Molar mass (calc.): 336.63 g/mol; found 335.7

δ = 5.50 ppm (d, 1H, α-CH); 6.65 ppm (s, 1H, α-NH); 6.70 ppm (s, 1H, aryl-H); 6.80 ppm (s, 2H, aryl-H); 7.00 ppm (d, 1H, thiophene-H); 7.05 ppm (d, 1H, thiophene-H); 13.50 (s (broad), 1H, COOH).

(3,5-Dichlorophenylamino)-(5-chlorothiophen-2-yl)-acetic acid sodium salt (**127-Na**)

δ = 4.55 ppm (d, 1H, δ-CH); 6.55 ppm (s, 1H, aryl-H); 6.60 ppm (s, 2H, aryl-H); 6.75 ppm (d, 1H, thiophene-H); 6.85 ppm (d, 1H, thiophene-H).

Receptor binding studies (glycine binding site of the NMDA receptor channel)

The tests to determine the affinity of the compounds of formula (I) according to the invention for the glycine binding site of the NMDA receptor channel were carried out on brain membrane homogenates (homogenate of cortex and hippocampus areal from the brains of male rats, Wistar strain) (B.M. Baron, B.W. Siegel, B.L. Harrison, R.S. Gross, C. Hawes and P. Towers, Journal of Pharmacology and Experimental Therapeutics, (1996), Vol. 279, p. 62).

To that end, cortex and hippocampus from freshly removed rat brains were exposed and homogenised, while cooling with ice, in 5 mmol/l of TRIS acetate buffer, 0.32 mol/l of saccharose pH 7.4 (10 ml/g fresh weight) using a Potter homogeniser (Braun/Melsungen; 10 piston strokes at 500 rpm) and then centrifuged for 10 minutes at 1000 g and 4°C. The first supernatant was collected and the sediment was again homogenised, while cooling with ice, with 5 mmol/l of TRIS acetate buffer, 0.32 mol/l of saccharose pH 7.4 (5 ml/g original fresh weight) using the Potter homogeniser (10 piston strokes at 500 rpm) and centrifuged for 10 minutes at 1000 g and 4°C. The resulting supernatant was combined with the supernatant from the first centrifugation and centrifuged for 20 minutes at 17,000 g and 4°C. The supernatant from this centrifugation was discarded and the membrane sediment was taken up in 5 mmol/l of TRIS acetate buffer pH 8.0 (20 ml/g original fresh weight) and homogenised with 10 piston strokes at 500 rpm.

The membrane homogenate was then incubated for one hour at 4°C and centrifuged for 30 minutes at 50,000 g and 4°C. The supernatant was discarded and the centrifuge tube containing the membrane sediment was closed with Parafilm and frozen for 24 hours at -20°C. On the following day, the membrane sediment was thawed and taken up in 5 mmol/l of ice-cold TRIS acetate buffer, 0.1 % saponin (w/v) pH 7.0 (10 ml/g original fresh weight) and homogenised with 10 piston strokes at 500 rpm and then centrifuged for 20 minutes at 50,000 g and 4°C. The resulting supernatant was discarded and the sediment was taken up in a small volume in 5 mmol/l of TRIS acetate buffer pH 7.0 (about 2 ml/g original fresh weight) and again homogenised with 10 piston strokes at 500 rpm. After determination of the protein content, the membrane homogenate was adjusted to a protein concentration of 10 mg of protein/ml with 5 mmol/l TRIS acetate buffer pH 7.0, and was frozen in aliquots until testing.

For the receptor binding test, aliquots were thawed, diluted 1:10 with 5 mmol/l of TRIS acetate buffer pH 7.0, homogenised, while cooling with ice, with 10 piston strokes at 500 rpm using the Potter homogeniser (10 piston strokes at 500 rpm) and centrifuged for 60 minutes at 55,000 g and 4°C. The supernatant was decanted off and the membrane sediment was adjusted to a protein concentration of 1 mg/ml with 50 mmol/l of ice-cold TRIS acetate buffer pH 7.0 and again homogenised with 10 piston strokes at 500 rpm and maintained in suspension in an ice-bath while stirring with a magnetic

stirrer. Of that membrane homogenate, 100 µl per 1 ml batch were used in the receptor binding test (0.1 mg protein/ml in the final batch).

In the binding test, 50 mmol/l of TRIS acetate buffer pH 7.0 were used as the buffer, and 1 nmol/l of (^{3}H)-MDL 105,519 (B.M. Baron *et al.* 1996) was used as the radioactive ligand. The proportion of non-specific binding was determined in the presence of 1 mmol/l of glycine.

In further batches, the compounds according to the invention were added in series of concentrations and the displacement of the radioactive ligand from its specific binding to the glycine binding site of the NMDA receptor channel was determined. The respective triplicate batches were incubated for 120 minutes at 4°C and then harvested by means of filtration through glass fibre filter mats (GF/B) for determination of the radioactive ligand bonded to the membrane homogenate. The radioactivity retained on the glass fibre filters was measured after addition of scintillator in a β counter.

The affinity of the compounds according to the invention for the glycine binding site of the NMDA receptor channel was calculated as the IC_{50} (concentration with 50 % displacement of the radioactive ligand from its specific binding) by the law of mass action by means of non-linear regression and is shown in Table 3 after conversion (according to the Cheng-Prussoff equation) as the Ki value (mean +/- standard deviation of 3 independent tests) or as the percentage of the bonded radioactive

ligand, see above, which is displaced from its specific binding at a concentration of 10 µM of the substance to be tested.

Table 3

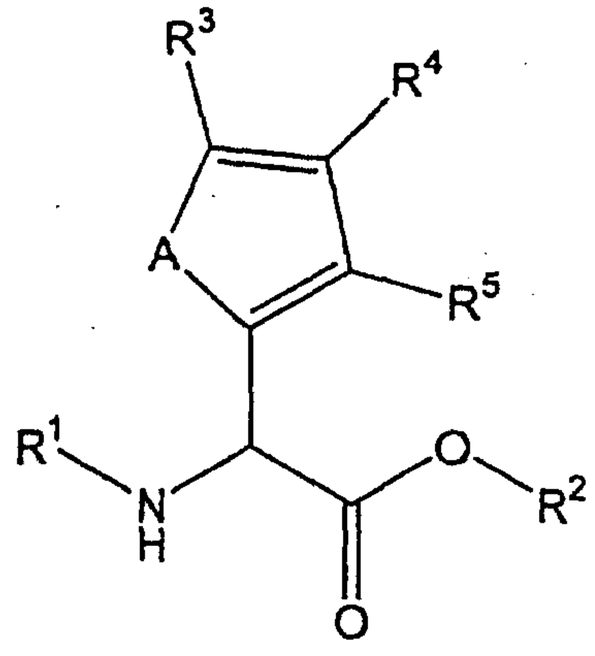
Example No. and Compound		Glycine binding site of the NMDA receptor channel	
		K_i (µmol)	Displacement (%, 10 µmol)
106	(3,5-Dichloro-phenylamino)-5-(methylsulfanylmethyl-furan-2-yl)-acetic acid		65
106-HCl	(3,5-Dichloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid hydrochloride		91
106-Na	(3,5-Dichloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid sodium	2.980	78
107	(3,5-Dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid		101
109	(3,5-Dichloro-phenylamino)-(5-hydroxymethyl-thiophen-2-yl)-acetic acid		66
110	(5-Acetylsulfanylmethyl-furan-2-yl)-(3,5-dichloro-phenylamino)-acetic acid	0.120	104
111	(3,5-Dichloro-phenylamino)-(5-ethyl-thiophen-2-yl)-acetic acid		44
113	(3-Chloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid		99
114	(3,4-Dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid		45
119-HCl	(5-tert-Butylfuran-2-yl)-(3,5-dichlorophenylamino)-acetic acid hydrochloride		91
120	(3,5-Dichlorophenylamino)-[5-(furan-2-ylmethyl-disulfanylmethyl)-furan-2-yl]-acetic acid	0.470	103
121	(3,5-Dichlorophenylamino)-(5-methyldisulfanyl-methyl-furan-2-yl)-acetic acid	0.290	106
123	(5-Acetoxymethylfuran-2-yl)-(3,5-dichlorophenyl-amino)-acetic acid	5.03	60
125-Na	(3,5-Dichlorophenylamino)-(5-methylthiophen-2-yl)-acetic acid sodium salt	5.03	63
126	(3,5-Dichlorophenylamino)-(4-methylthiophen-2-yl)-acetic acid	15.38	52
127	(5-Chlorothiophen-2-yl)-(3,5-dichlorophenylamino)-acetic acid	2.57	68
127-Na	(3,5-Dichlorophenylamino)-(5-chlorothiophen-2-yl)-acetic acid sodium salt		72

Pharmaceutical formulation of a medicament according to the invention

1 g of the hydrochloride of (3,5-dichlorophenylamino)-(5-methyldisulfanylmethylfuran-2-yl)-acetic acid (**121**) was dissolved at room temperature in 1 litre of water for injection purposes and then adjusted to isotonic conditions by addition of sodium chloride.

Claims

1. Compound having the general structure (I), or a pharmaceutically acceptable salt thereof,



I

wherein

A represents oxygen or sulfur,

R^1 represents aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl,

R^2 represents H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl,

R^3, R^4 and R^5 each independently of the others represents H, OH, SH, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl, $-SiR^6R^7R^8$, $-(CH_2)_n-O-(CH_2)_m-R^9$ wherein n = 1, 2, 3 or 4 and m = 0, 1, 2, 3 or 4, $-(CH_2)_o-S_p-(CH_2)_q-R^{10}$ wherein o = 1, 2, 3 or 4, p = 1 or 2

and q = 0, 1, 2, 3 or 4, $-(CH_2)_r-CO_2R^{11}$ wherein r = 0, 1, 2, 3 or 4, $-(CH_2)_s-OCOR^{12}$ wherein s = 0, 1, 2, 3 or 4, or $-C(=O)R^{13}$,

R^6, R^7 and R^8 each independently of the others represents C_{1-6}-alkyl or phenyl,

R^9 and R^{10} each independently of the other represents H, CH_3, aryl, heterocyclyl or $-C(=O)-C_{1-6}$-alkyl, $-C(=O)-(C_{1-6}$-alkyl)-aryl or $-C(=O)$-aryl,

R^{11} represents H, C_{1-6}-alkyl or CH_2-phenyl,

R^{12} represents C_{1-6}-alkyl or aryl,

R^{13} represents H, C_{1-6}-alkyl, aryl, heterocyclyl or $NR^{14}R^{15}$,

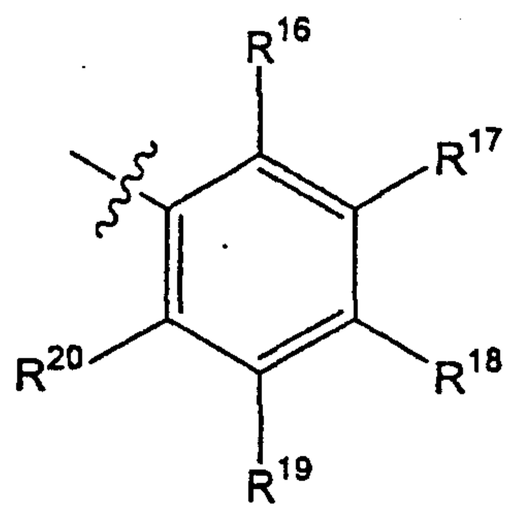
R^{14} and R^{15} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{14} and R^{15} together form $-(CH_2)_k-$ wherein k = 4, 5 or 6,

wherein

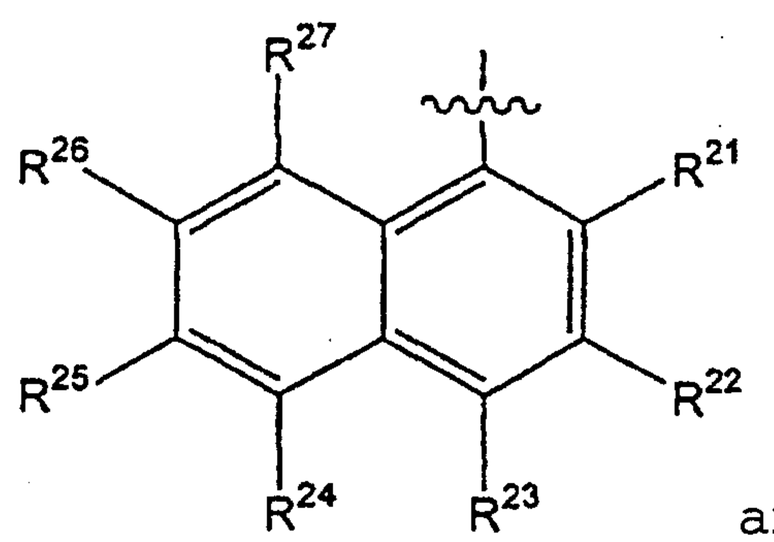
alkyl represents a non-cyclic hydrocarbon radical which is straight-chain or branched and is saturated or unsaturated and is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents,

cycloalkyl represents an alicyclic hydrocarbon radical which is saturated or unsaturated and is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents,

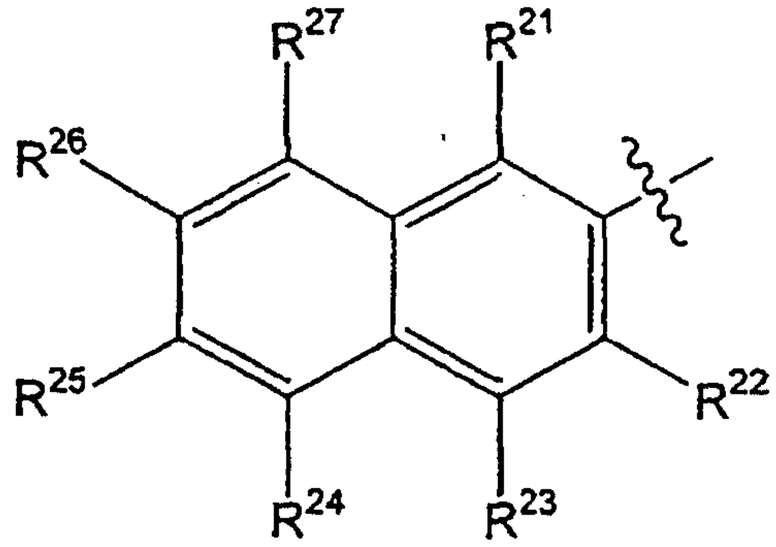
aryl is a radical selected from the group comprising



,



and



heterocyclyl represents a monocyclic or polycyclic organic radical in which at least one ring contains one hetero atom or 2, 3, 4 or 5 identical or different hetero atoms selected from the group containing N, O and S, the radical being saturated or unsaturated and being unsubstituted or monosubstituted or polysubstituted by identical or different substituents,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} and R^{27} each independently of the others represents H, OR^{28}, $S(O)_tR^{29}$ wherein t = 0, 1 or 2, SO_2OR^{30}, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl or (C_{1-6}-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl, $-CO_2R^{31}$ or $-NR^{32}R^{33}$,

R^{28}, R^{29}, R^{30} and R^{31} each independently of the others represents H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl or (C_{1-6}-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl or $-NR^{34}R^{35}$,

and

R^{32} and R^{33} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl, (C_{1-6}-alkyl)-phenyl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{32} and R^{33} together form $-(CH_2)_h-$ wherein h = 4, 5 or 6,

and

R^{34} and R^{35} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl, (C_{1-6}-alkyl)-phenyl,

heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{34} and R^{35} together form $-(CH_2)_g-$ wherein g = 4, 5 or 6,

with the exception of (4-methoxy-phenylamino)-thien-2-yl-acetic acid.

2. Compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the form of the racemate, in the form of the pure enantiomers or diastereoisomers or in the form of mixtures of the enantiomers or diastereoisomers in any desired mixing ratio.

3. Compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, characterised in that

R^1 represents aryl or heterocyclyl^1,

R^2 represents H, C_{1-12}-alkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl or (C_{1-6}-alkyl)-aryl,

R^3, R^4 and R^5 each independently of the others represents H, OH, SH, Cl, Br, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl^1, (C_{1-6}-alkyl)-heterocyclyl^1, $-SiR^6R^7R^8$, $-(CH_2)_n-O-(CH_2)_m-R^9$ wherein n = 1, 2, 3 or 4 and m = 0, 1 or 2, $-(CH_2)_o-S_p-(CH_2)_q-R^{10}$ wherein o = 1, 2, 3 or 4, p = 1 or 2 and q = 0, 1 or 2, $-(CH_2)_r-CO_2R^{11}$ wherein r = 0, 1, 2 or 3, $-(CH_2)_s-OC(=O)R^{12}$ wherein s = 0, 1 or 2, or $-C(=O)R^{13}$,

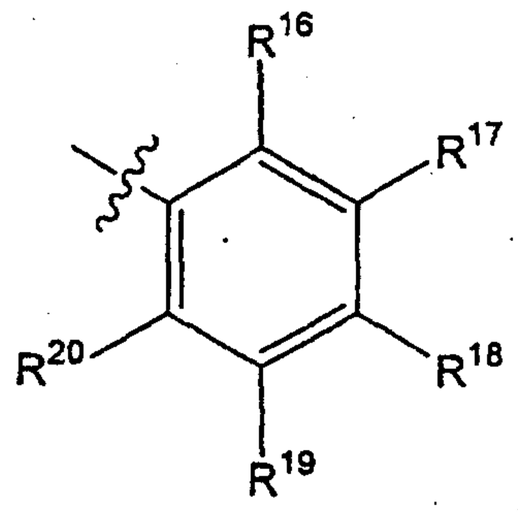
R^6, R^7 and R^8 each independently of the others represents C_{1-6}-alkyl or phenyl,

R^9 and R^{10} each independently of the other represents H, CH_3, aryl, heterocyclyl or $-C(=O)-C_{1-6}$-alkyl, $-C(=O)-(C_{1-6}$-alkyl)-aryl or $-C(=O)$-aryl,

R^{11} represents H, C_{1-6}-alkyl or CH_2-phenyl,

R^{12} represents C_{1-6}-alkyl or aryl,

R^{13} represents C_{1-6}-alkyl or aryl,



wherein aryl represents ,

heterocyclyl is as defined in claim 1,

heterocyclyl[1] represents a monocyclic or bicyclic organic radical in which at least one ring is 5- or 6-membered and contains one hetero atom or 2 identical or different hetero atoms selected from the group containing N, O and S, the radical being saturated or unsaturated and being unsubstituted or monosubstituted or polysubstituted by identical or different substituents,

R^{16}, R^{17}, R^{18}, R^{19} and R^{20} each independently of the others represents H, OR^{28}, $S(O)_tR^{29}$ wherein t = 0 or 2, SO_2OR^{30}, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, $(C_{1-6}$-alkyl)-C_{3-8}-cycloalkyl, phenyl or $(C_{1-6}$-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl[1], $(C_{1-6}$-alkyl)-heterocyclyl[1], $-CO_2R^{31}$ or $-NR^{32}R^{33}$,

R^{28}, R^{29}, R^{30} and R^{31} each independently of the others represents H, C_{1-6}-alkyl or phenyl,

and

R^{32} and R^{33} each independently of the other represents H, C_{1-6}-alkyl, $(C_{1-6}$-alkyl)-phenyl, or R^{32} and R^{33} together form $-(CH_2)_h-$ wherein h = 4, 5 or 6.

4. Compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof,

characterised in that

R^1 represents aryl or heterocyclyl^2,

R^2 represents H, methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl, n-hexyl,

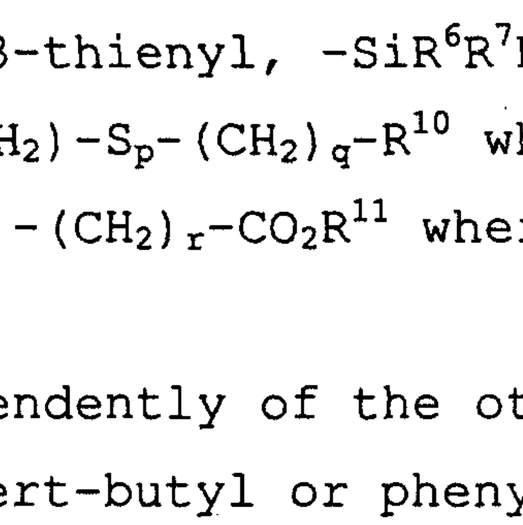
R^3, R^4 and R^5 each independently of the others represents H, OH, SH, Br, Cl, C_{1-6}-alkyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, $-SiR^6R^7R^8$, $-CH_2OH$, $-CH_2-O-(C=O)-CH_3$, $-(CH_2)-S_p-(CH_2)_q-R^{10}$ wherein p = 1 or 2 and q = 0 or 1, $-(CH_2)_r-CO_2R^{11}$ wherein r = 0 or 1, or $-COR^{13}$,

R^6, R^7 and R^8 each independently of the others represents methyl, tert-butyl or phenyl,

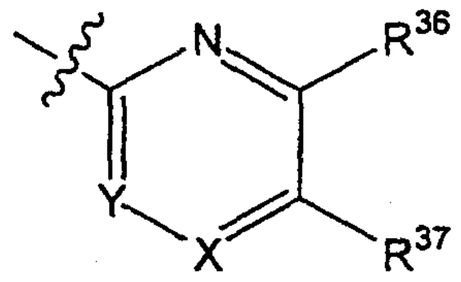
R^{10} represents H, methyl, ethyl, n-propyl, 2-furyl, 2-thienyl or $-C(=O)-CH_3$,

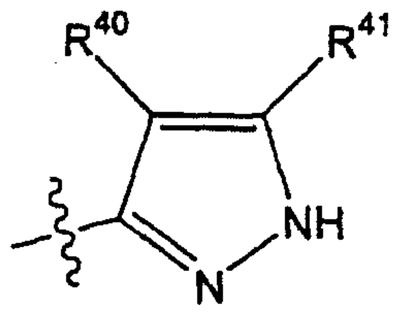
R^{11} represents H, methyl, ethyl or tert-butyl,

R^{13} represents methyl,

wherein aryl represents 

,

heterocyclyl^2 represents  or



,

R^{16}, R^{17}, R^{18}, R^{19} and R^{20} each independently of the others represents H, OR^{28}, $S(O)_tR^{29}$ wherein t = 0, F, Cl, Br, I, -CN, $-NO_2$, methyl, ethyl, n-propyl, 2-propyl, n-butyl, 2-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl, CF_3 or $-CO_2R^{31}$,

R^{28}, R^{29} and R^{31} each independently of the others represents H, methyl, ethyl, $-CF_3$ or phenyl,

X-Y represents CR^{38}-CR^{39}, CR^{38}-N or N-CR^{39},

R^{36}, R^{37}, R^{38} and R^{39} each independently of the others represents H, F, Cl, Br, I, -CN, $-NO_2$, -OH, -SH, C_{1-6}-alkyl or $-CF_3$,

and

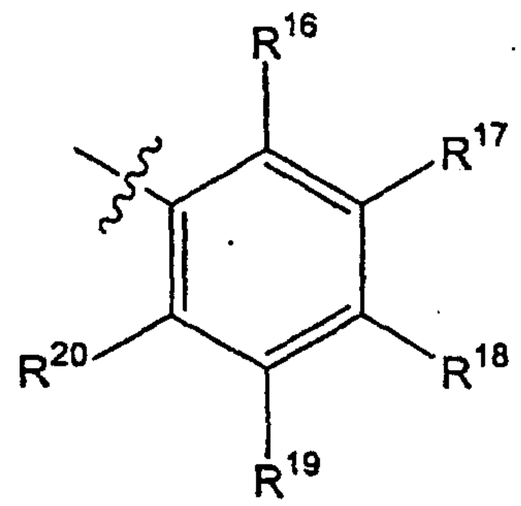
R^{40} and R^{41} each independently of the other represents H, F, Cl, Br, I, -CN, -OH, -O-C_{1-6}-alkyl, -SH, -S-C_{1-6}-alkyl, C_{1-8}-alkyl, CO_2-C_{1-6}-alkyl or -N=N-aryl.

5. Compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof,
characterised in that
R^1 represents aryl or heterocyclyl^2,
R^2 represents H, methyl, ethyl or tert-butyl,

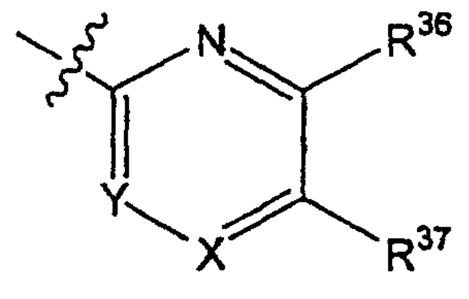
R^3 represents H, Cl, methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl, $-CH_2OH$, $-CH_2SH$, $-CH_2-S-CH_3$, $-CH_2-S-CH_2$-furan-2-yl, $-CH_2-O-(C=O)-CH_3$, $-CH_2-S-(C=O)-CH_3$, $-CH_2-S-S-CH_3$, $-CH_2-S-S-CH_2$-furan-2-yl, $-CH_2-CO_2$methyl or $-CH_2-CO_2$ethyl,

R^4 represents H, Br, methyl, ethyl, $-CH_2OH$, $-CO_2$methyl, $-CO_2$ethyl or $-C(=O)$methyl,

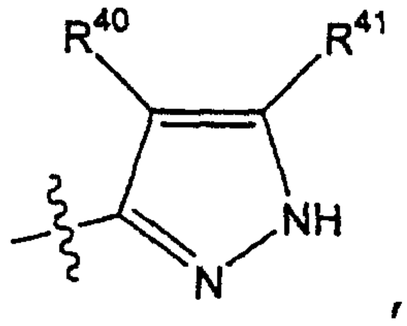
R^5 represents H, methyl or ethyl,



wherein aryl represents ,



heterocyclyl[2] represents or



,

R^{16} represents H, -O-phenyl, F, Cl, Br, methyl, ethyl, n-propyl, 2-propyl or tert-butyl,

R^{17} represents H, Cl, methyl, ethyl or CF_3,

R^{18} represents H, F, Cl, Br, I, -CN, $-O-CH_3$, $-O-CF_3$, -O-phenyl, methyl, ethyl, n-propyl, 2-propyl, n-butyl, 2-butyl or tert-butyl,

R^{19} represents H, Cl, Br, methyl or ethyl,

R^{20} represents H or methyl,

X-Y represents CR^{38}-CR^{39}, CR^{38}-N or N-CR^{39},

R^{36} represents H, methyl or ethyl,

R^{37} represents H, NO_2, Cl, Br, methyl or CF_3,

R^{38} represents H,

R^{39} represents H, Cl or Br,

R^{40} represents H, -N=N-phenyl, -CN, CO_2H, CO_2-methyl or CO_2-ethyl,

and

R^{41} represents H, OH, SH, S-methyl, methyl, ethyl, n-propyl, 2-propyl, n-butyl or tert-butyl.

6. Compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, characterised in that

R^1 represents 4-trifluoromethoxy-phenyl, 2-phenoxy-phenyl, 4-phenoxy-phenyl, 2-chloro-phenyl, 4-chloro-phenyl, 4-iodo-phenyl, 4-cyano-phenyl, 2-methyl-phenyl, 2-ethyl-phenyl, 4-ethyl-phenyl, 2-(2-propyl)-phenyl, 4-(2-butyl)-phenyl, 4-tert-butyl-phenyl, 2,4-dichlorophenyl, 2,3-dichloro-phenyl, 3,5-dichlorophenyl, 2,4-dibromo-phenyl, 4-chloro-2-fluoro-phenyl, 2-chloro-4-fluoro-phenyl, 4-bromo-2-chloro-phenyl, 2-chloro-4-iodo-phenyl, 3-chloro-2-methyl-phenyl, 4-chloro-2-methyl-phenyl, 5-chloro-2-methyl-phenyl, 2-chloro-4-methyl-phenyl, 4-chloro-3-trifluoromethyl-phenyl, 2,4-dibromo-5-methyl-phenyl, 5-nitro-pyridin-2-yl, 3,5-dibromo-pyridin-2-yl, 3,5-dichloro-pyridin-2-yl, 3-chloro-5-trifluoromethyl-pyridin-2-yl, 3,5-dibromo-6-methyl-pyridin-2-yl, pyrazin-2-yl, 5-bromo-pyrimidin-2-yl, 4-carboxyethyl-pyrazol-3-yl, 4-cyano-pyrazol-3-yl, 5-tert-butyl-pyrazol-3-yl,

5-hydroxy-4-(4-phenylazo)-pyrazol-3-yl or 4-cyano-5-methylsulfanyl-pyrazol-3-yl,

R^2 represents H or ethyl,

R^3 represents H, Cl, methyl, ethyl, n-propyl, tert-butyl, $-CH_2OH$, $-CH_2SH$, $-CH_2S-CH_3$, $-CH_2-S-CH_2$-furan-2-yl, $-CH_2-O-(C=O)-CH_3$, $-CH_2-S-(C=O)-CH_3-$, $-CH_2-S-S-CH_3$, $-CH_2-S-S-CH_2$-furan-2-yl or $-CH_2-CO_2$ethyl,

R^4 represents H, Br, methyl, $-CH_2OH$, $-CO_2$methyl, $-CO_2$ethyl or $-C(=O)CH_3$,

R^5 represents H or methyl.

7. Compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, characterised in that

R^1 represents 3,5-dichlorophenyl and

R^2 represents H.

8. Compound according to either claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, characterised in that the compound is selected from the group containing

- (5-methylsulfanylmethyl-furan-2-yl)-(5-nitro-pyridin-2-ylamino)-acetic acid
- (5-bromopyrimidin-2-ylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- 5-[carboxy-(3,5-dichloropyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(3,5-dibromopyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester

- 5-[carboxy-(3,5-dibromo-6-methyl-pyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- (3,5-dibromo-6-methyl-pyridin-2-ylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid
- (3,5-dichloro-pyridin-2-ylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (2,4-dibromo-5-methyl-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (4-methyl-thiophen-2-yl)-(5-nitro-pyridin-2-ylamino)-acetic acid
- (3,5-dichloro-pyridin-2-ylamino)-furan-2-yl-acetic acid
- (3,5-dibromopyridin-2-ylamino)-furan-2-yl-acetic acid
- (3,5-dibromo-6-methyl-pyridin-2-ylamino)-furan-2-yl-acetic acid
- (3-chloro-5-trifluoromethyl-pyridin-2-ylamino)-furan-2-yl-acetic acid
- (5-bromopyrimidin-2-ylamino)-furan-2-yl-acetic acid
- 5-[(3,5-dichloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- (5-hydroxy-4-phenylazo-1H-pyrazol-3-ylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid ethyl ester
- 3-{[ethoxycarbonyl-(4-ethoxycarbonyl-5-methyl-furan-2-yl)-methyl]-amino}-1H-pyrazole-4-carboxylic acid ethyl ester

- 5-[(4-cyano-5-methylsulfanyl-1H-pyrazol-3-ylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-cyano-1H-pyrazol-3-ylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-bromo-2-chloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-cyano-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- (4-hydroxymethyl-furan-2-yl)-(5-hydroxy-4-phenylazo-1H-pyrazol-3-ylamino)-acetic acid ethyl ester
- (4-cyano-5-methylsulfanyl-1H-pyrazol-3-ylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (4-bromo-2-chloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (3,5-dichloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (5-chloro-2-methyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid ethyl ester
- (2,4-dibromo-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (5-chloro-2-methyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (2-ethyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid

- (4-sec-butyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (5-methylsulfanylmethyl-furan-2-yl)-(4-trifluoro-methoxy-phenylamino)-acetic acid
- (2-isopropyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (2,4-dibromo-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (4-tert-butyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (5-chloro-2-methyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid
- (2-ethyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid
- (4-sec-butyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid
- [5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-(2-isopropyl-phenylamino)-acetic acid
- (4-tert-butyl-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid
- 5-[ethoxycarbonyl-(4-iodo-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[(4-chloro-2-methyl-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[ethoxycarbonyl-(4-phenoxy-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[ethoxycarbonyl-(4-iodo-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester

- 5-[(2-chloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-chloro-2-methyl-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(2-chloro-4-fluoro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[ethoxycarbonyl-(4-phenoxy-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[(2,3-dichloro-phenylamino)-ethoxycarbonyl-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- (4-hydroxymethyl-furan-2-yl)-(4-iodo-phenylamino)-acetic acid ethyl ester
- (2,4-dichloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (4-chloro-2-methyl-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (4-hydroxymethyl-furan-2-yl)-(4-phenoxy-phenylamino)-acetic acid ethyl ester
- (2,3-dichloro-phenylamino)-(4-hydroxymethyl-furan-2-yl)-acetic acid ethyl ester
- (2,3-dichloro-phenylamino)-furan-2-yl-acetic acid ethyl ester
- 5-[carboxy-(3,5-dibromo-6-methyl-pyridin-2-ylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- (5-methylsulfanylmethyl-furan-2-yl)-(pyrazin-2-ylamino)-acetic acid

- (3,5-dibromo-pyridin-2-ylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (3,5-dibromo-6-methyl-pyridin-2-ylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- 5-[(4-bromo-2-chloro-phenylamino)-carboxy-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[carboxy-(4-cyano-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[carboxy-(3,5-dichloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
- 5-[carboxy-(2-phenoxy-phenylamino)-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-bromo-2-chloro-phenylamino)-carboxy-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(4-cyano-phenylamino)-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(3,5-dichloro-phenylamino)-methyl]-2,4-dimethyl-furan-3-carboxylic acid ethyl ester
- 5-[(4-bromo-2-chloro-phenylamino)-carboxy-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(4-cyano-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(3,5-dichloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- (5-tert-butyl-1H-pyrazol-3-ylamino)-(4-hydroxy-methyl-furan-2-yl)-acetic acid
- (4-bromo-2-chloro-phenylamino)-(3-methyl-thiophen-2-yl)-acetic acid
- (4-cyano-phenylamino)-(3-methyl-thiophen-2-yl)-acetic acid

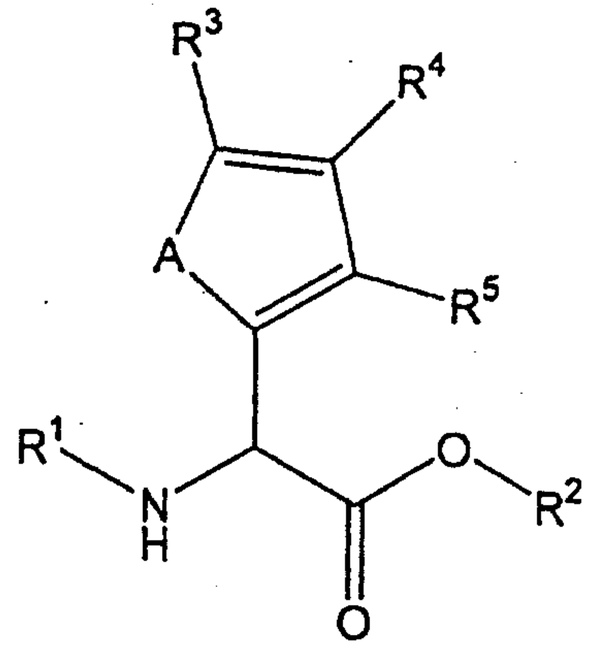
- (3,5-dichloro-phenylamino)-(3-methyl-thiophen-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-furan-2-yl-acetic acid
- [5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-(4-phenoxy-phenylamino)-acetic acid ethyl ester
- (5-ethoxycarbonylmethyl-thiophen-2-yl)-(5-hydroxy-4-phenylazo-1H-pyrazol-3-ylamino)-acetic acid ethyl ester
- {5-[1-(4-cyano-1H-pyrazol-3-ylamino)-3-methoxy-2-oxo-propyl]-thiophen-2-yl}-acetic acid ethyl ester
- (4-ethyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (3-chloro-2-methyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (4-chloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (5-methylsulfanylmethyl-furan-2-yl)-o-tolylamino-acetic acid
- 5-[carboxy-(4-chloro-3-trifluoromethyl-phenyl-amino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(2-chloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(2-chloro-4-fluoro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(4-chloro-2-fluoro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester
- 5-[carboxy-(2,3-dichloro-phenylamino)-methyl]-2-methyl-furan-3-carboxylic acid ethyl ester

- (2,4-dichloro-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-(4-methyl-thiophen-2-yl)-acetic acid
- (2,4-dichloro-phenylamino)-furan-2-yl-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-furan-2-yl-acetic acid
- (4-iodo-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (2,4-dichloro-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (2-chloro-phenylamino)-(5-methylsulfanylmethyl-furan-2-yl)-acetic acid
- (4-chloro-2-methyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (2-chloro-4-fluoro-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (2-chloro-4-methyl-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (2,3-dichloro-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- [5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-(4-iodo-phenylamino)-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid
- (4-chloro-2-methyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid

- (2-chloro-4-methyl-phenylamino)-[5-(furan-2-ylmethylsulfanylmethyl)-furan-2-yl]-acetic acid
- (4-chloro-3-trifluoromethyl-phenylamino)-(5-ethoxycarbonylmethyl-thiophen-2-yl)-acetic acid
- (4-acetyl-3,5-dimethyl-furan-2-yl)-(2-chloro-4-methyl-phenylamino)-acetic acid
- (4-acetyl-3,5-dimethyl-furan-2-yl)-(2,3-dichloro-phenylamino)-acetic acid
- (3,5-dichloro-phenylamino)-(5-methylsulfanyl-methyl-furan-2-yl)-acetic acid
- (3-chloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid
- (3,4-dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-(5-methyl-thiophen-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-(5-hydroxymethyl-thiophen-2-yl)-acetic acid
- (5-acetylsulfanylmethyl-furan-2-yl)-(3,5-dichloro-phenylamino)-acetic acid
- (3,5-dichloro-phenylamino)-(5-ethyl-thiophen-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-(5-n-propyl-thiophen-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid
- (3-chloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid

- (3,4-dichloro-phenylamino)-(5-mercaptomethyl-furan-2-yl)-acetic acid
- (3,5-dichloro-phenylamino)-(thiophen-2-yl)-acetic acid ethyl ester
- (4-bromofuran-2-yl)-(3,5-dichloro-phenylamino)-acetic acid ethyl ester
- (3,5-dichloro-phenylamino)-(5-propylthiophen-2-yl)-acetic acid ethyl ester
- (3,5-dichloro-phenylamino)-(3-methylthiophen-2-yl)-acetic acid ethyl ester
- (5-tert-butylfuran-2-yl)-(3,5-dichloro-phenyl-amino)-acetic acid
- (3,5-dichlorophenylamino)-[5-(furan-2-ylmethyl-disulfanylmethyl)-furan-2-yl]-acetic acid
- (3,5-dichlorophenylamino)-(5-methyldisulfanyl-methylfuran-2-yl)-acetic acid
- (3,5-dichlorophenylamino)-[5-(furan-2-ylmethyl-sulfanylmethyl)-furan-2-yl]-acetic acid
- 5-acetoxymethylfuran-2-yl-(3,5-dichlorophenyl-amino)-acetic acid
- (3,5-dichlorophenylamino)-thiophen-3-yl-acetic acid
- (3,5-dichlorophenylamino)-(5-methylthiophen-2-yl)-acetic acid
- (3,5-dichlorophenylamino)-(4-methylthiophen-2-yl)-acetic acid
- (5-chlorothiophen-2-yl)-(3,5-dichlorophenylamino)-acetic acid.

9. Process for the preparation of a compound having the general structure (I), or of a pharmaceutically acceptable salt thereof,



I

wherein

A represents oxygen or sulfur,

R^1 represents aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl,

R^2 represents H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl,

R^3, R^4 and R^5 each independently of the others represents H, OH, SH, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl, $-SiR^6R^7R^8$, $-(CH_2)_n-O-(CH_2)_m-R^9$ wherein n = 1, 2, 3 or 4 and m = 0, 1, 2, 3 or 4, $-(CH_2)_o-S_p-(CH_2)_q-R^{10}$ wherein o = 1, 2, 3 or 4, p = 1 or 2 and q = 0, 1, 2, 3 or 4, $-(CH_2)_r-CO_2R^{11}$ wherein r = 0, 1, 2, 3 or 4, $-(CH_2)_s-OCOR^{12}$ wherein s = 0, 1, 2, 3 or 4, or $-COR^{13}$,

R^6, R^7 and R^8 each independently of the others represents C_{1-6}-alkyl or phenyl,

R^9 and R^{10} each independently of the other represents H, CH_3, aryl, heterocyclyl or $-C(=O)-C_{1-6}$-alkyl, $-C(=O)-(C_{1-6}$-alkyl)-aryl or $-C(=O)$-aryl,

R^{11} represents H, C_{1-6}-alkyl or CH_2-phenyl,

R^{12} represents C_{1-6}-alkyl or aryl,

R^{13} represents H, C_{1-6}-alkyl, aryl, heterocyclyl or $NR^{14}R^{15}$,

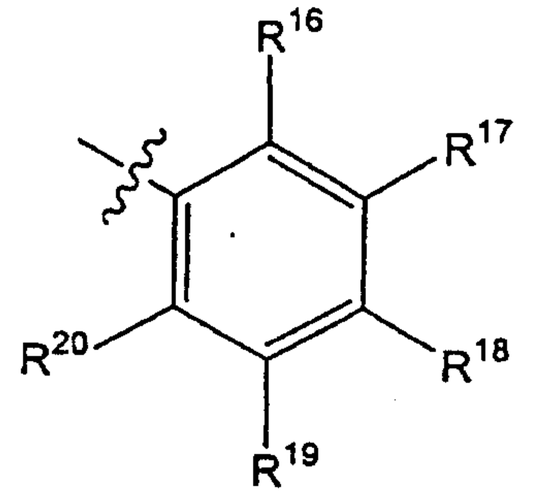
R^{14} and R^{15} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{14} and R^{15} together form $-(CH_2)_k-$ wherein k = 4, 5 or 6,

wherein

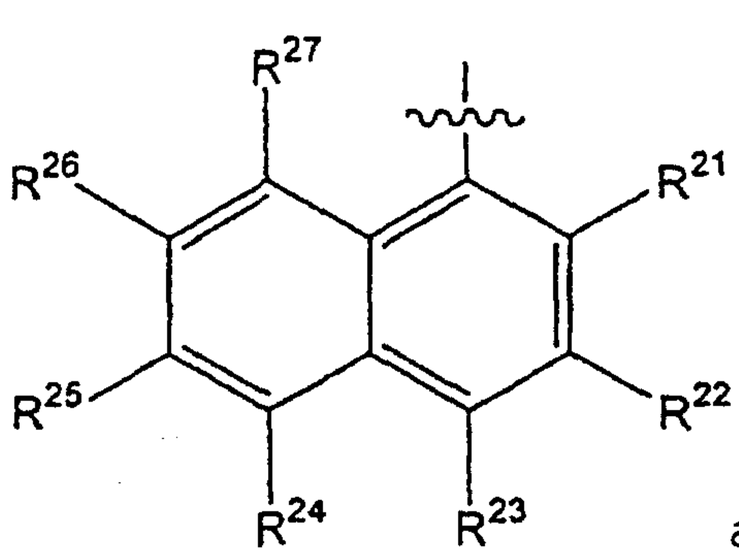
alkyl represents a non-cyclic hydrocarbon radical which is straight-chain or branched and is saturated or unsaturated and is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents,

cycloalkyl represents an alicyclic hydrocarbon radical which is saturated or unsaturated and is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents,

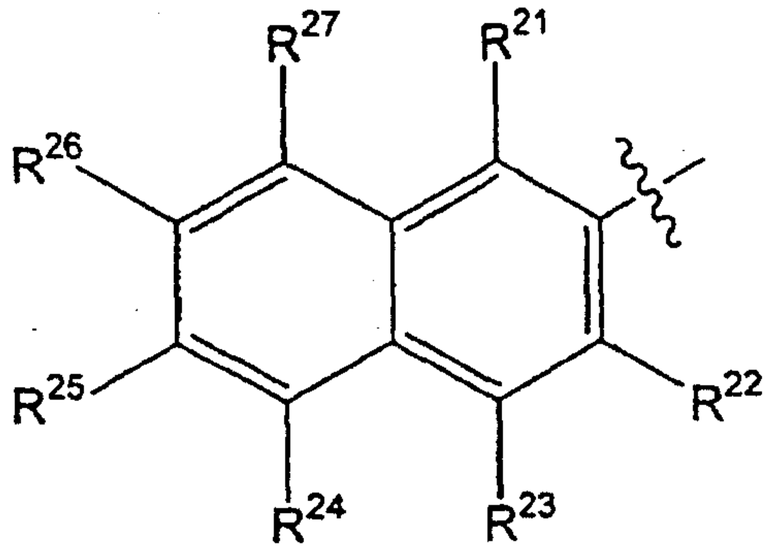
aryl is a radical selected from the group comprising



,



and



heterocyclyl represents a monocyclic or polycyclic organic radical in which at least one ring contains one hetero atom or 2, 3, 4 or 5 identical or different hetero atoms selected from the group containing N, O and S, the radical being saturated or unsaturated and being unsubstituted or monosubstituted or polysubstituted by identical or different substituents,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} and R^{27} each independently of the others represents H, OR^{28}, $S(O)_tR^{29}$ wherein t = 0, 1 or 2, SO_2OR^{30}, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl or (C_{1-6}-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl, $-CO_2R^{31}$ or $-NR^{32}R^{33}$,

R^{28}, R^{29}, R^{30} and R^{31} each independently of the others represents H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl or (C_{1-6}-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl or $-NR^{34}R^{35}$,

R^{32} and R^{33} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl, (C_{1-6}-alkyl)-phenyl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{32} and R^{33} together form $-(CH_2)_h-$ wherein h = 4, 5 or 6,

and

R^{34} and R^{35} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl, (C_{1-6}-alkyl)-phenyl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{34} and R^{35} together form $-(CH_2)_g-$ wherein g = 4, 5 or 6,

which process is characterised in that

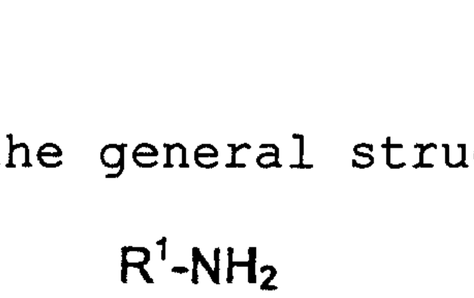
an amine having the general structure (II)

R^1-NH_2

II ,

wherein R^1 is as defined above in this claim,

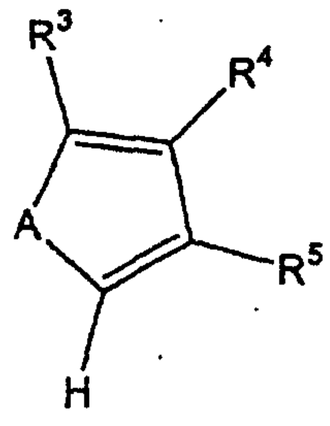
is reacted, under the action of an acid, with a glyoxalic acid derivative having the general structure (III)



III ,

wherein R^2 is as defined above in this claim,

and with a heterocycle having the general structure (IV)



IV ,

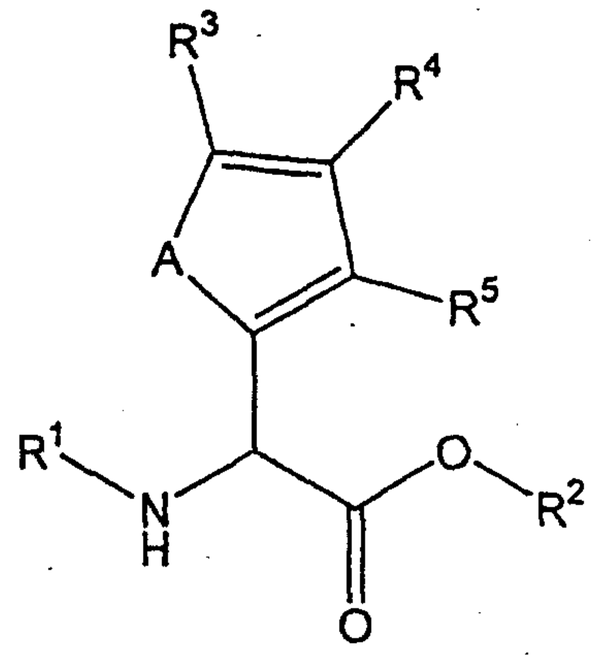
wherein A, R^3, R^4 and R^5 are as defined above in this claim.

10. Process according to claim 9, characterised in that it is carried out as a one-pot process.

11. Process according to either claim 9 or claim 10, characterised in that the reaction of the compounds (II), (III) and (IV) is carried out under the action of microwave radiation.

12. Process according to any one of claims 8 to 11, characterised in that the process is carried out in an organic solvent at a temperature of from 0°C to 100°C, especially from 15°C to 50°C.

13. Medicament containing a compound having the general structure (I), or a pharmaceutically acceptable salt thereof,



I

wherein

A represents oxygen or sulfur,

R^1 represents aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl,

R^2 represents H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl,

R^3, R^4 and R^5 each independently of the others represents H, OH, SH, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl, $-SiR^6R^7R^8$, $-(CH_2)_n-O-(CH_2)_m-R^9$ wherein n = 1, 2, 3 or 4 and m = 0, 1, 2, 3 or 4, $-(CH_2)_o-S_p-(CH_2)_q-R^{10}$ wherein o = 1, 2, 3 or 4, p = 1 or 2 and q = 0, 1, 2, 3 or 4, $-(CH_2)_r-CO_2R^{11}$ wherein r = 0, 1, 2, 3 or 4, $-(CH_2)_s-OCOR^{12}$ wherein s = 0, 1, 2, 3 or 4, or $-COR^{13}$,

R^6, R^7 and R^8 each independently of the others represents C_{1-6}-alkyl or phenyl,

R^9 and R^{10} each independently of the other represents H, CH_3, aryl, heterocyclyl or $-C(=O)-C_{1-6}$-alkyl, $-C(=O)-(C_{1-6}$-alkyl)-aryl or $-C(=O)$-aryl,

R^{11} represents H, C_{1-6}-alkyl or CH_2-phenyl,

R^{12} represents C_{1-6}-alkyl or aryl,

R^{13} represents H, C_{1-6}-alkyl, aryl, heterocyclyl or $NR^{14}R^{15}$,

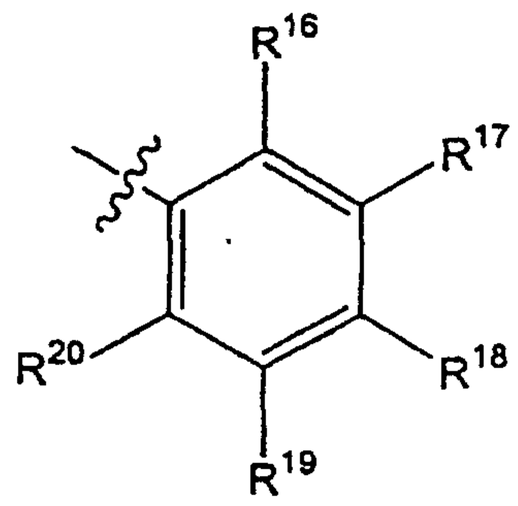
R^{14} and R^{15} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, aryl, (C_{1-6}-alkyl)-aryl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{14} and R^{15} together form $-(CH_2)_k-$ wherein k = 4, 5 or 6,

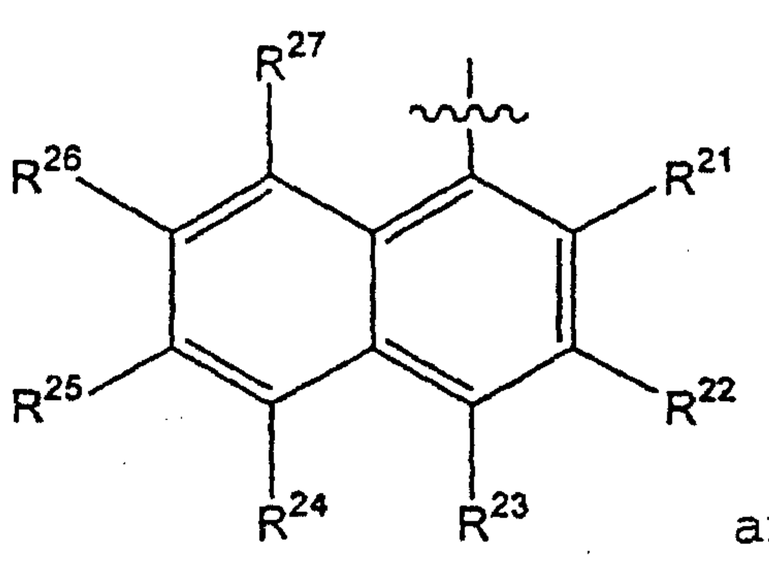
wherein

alkyl represents a non-cyclic hydrocarbon radical which is straight-chain or branched and is saturated or unsaturated and is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents,

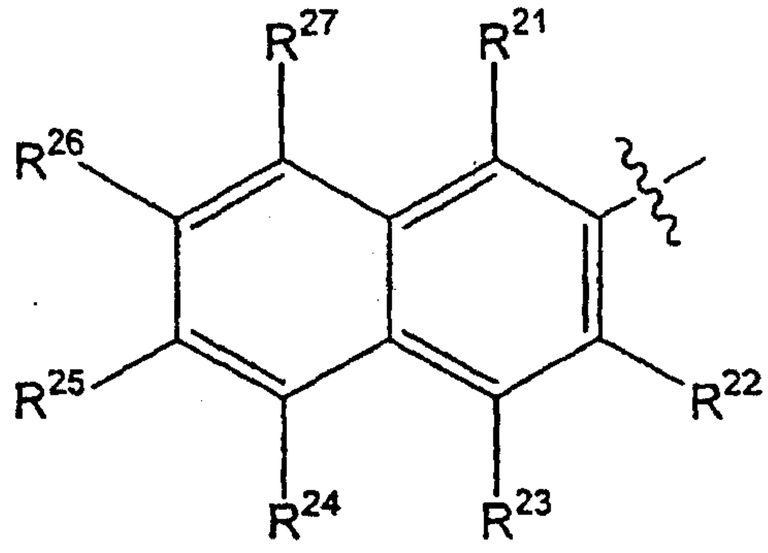
cycloalkyl represents an alicyclic hydrocarbon radical which is saturated or unsaturated and is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents,

aryl is a radical selected from the group comprising





and



heterocyclyl represents a monocyclic or polycyclic organic radical in which at least one ring contains one hetero atom or 2, 3, 4 or 5 identical or different hetero atoms selected from the group containing N, O and S, the radical being saturated or unsaturated and being unsubstituted or monosubstituted or polysubstituted by identical or different substituents,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} and R^{27} each independently of the others represents H, OR^{28}, $S(O)_tR^{29}$ wherein t = 0, 1 or 2, SO_2OR^{30}, F, Cl, Br, I, -CN, NO_2, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl or (C_{1-6}-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl, $-CO_2R^{31}$ or $-NR^{32}R^{33}$,

R^{28}, R^{29}, R^{30} and R^{31} each independently of the others represents H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl or (C_{1-6}-alkyl)-phenyl, wherein phenyl is unsubstituted or is monosubstituted or polysubstituted by identical or different substituents, heterocyclyl, (C_{1-6}-alkyl)-heterocyclyl or $-NR^{34}R^{35}$,

R^{32} and R^{33} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl, (C_{1-6}-alkyl)-phenyl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{32} and R^{33} together form $-(CH_2)_h-$ wherein h = 4, 5 or 6,

and

R^{34} and R^{35} each independently of the other represents H, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, (C_{1-6}-alkyl)-C_{3-8}-cycloalkyl, phenyl, (C_{1-6}-alkyl)-phenyl, heterocyclyl or (C_{1-6}-alkyl)-heterocyclyl, or R^{34} and R^{35} together form $-(CH_2)_g-$ wherein g = 4, 5 or 6.

14. Use of a compound having the general structure (I) as defined in claim 1, or of a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of pain.

15. Use of a compound having the general structure (I) as defined in claim 1, or of a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of migraine.

16. Pharmaceutical composition containing at least one compound having the general structure (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, as well as at least one pharmaceutical excipient.

17. Method of treating pain in a mammal and/or human, characterised in that a therapeutically effective

amount of a compound having the general structure (I) as defined in claim 1, or of a physiologically tolerable salt thereof, is administered.

18. Method of treating migraine in a mammal and/or human, characterised in that a therapeutically effective amount of a compound having the general structure (I) as defined in claim 1, or of a physiologically tolerable salt thereof, is administered.

Fetherstonhaugh &
Ottawa, Canada
Patent Agents