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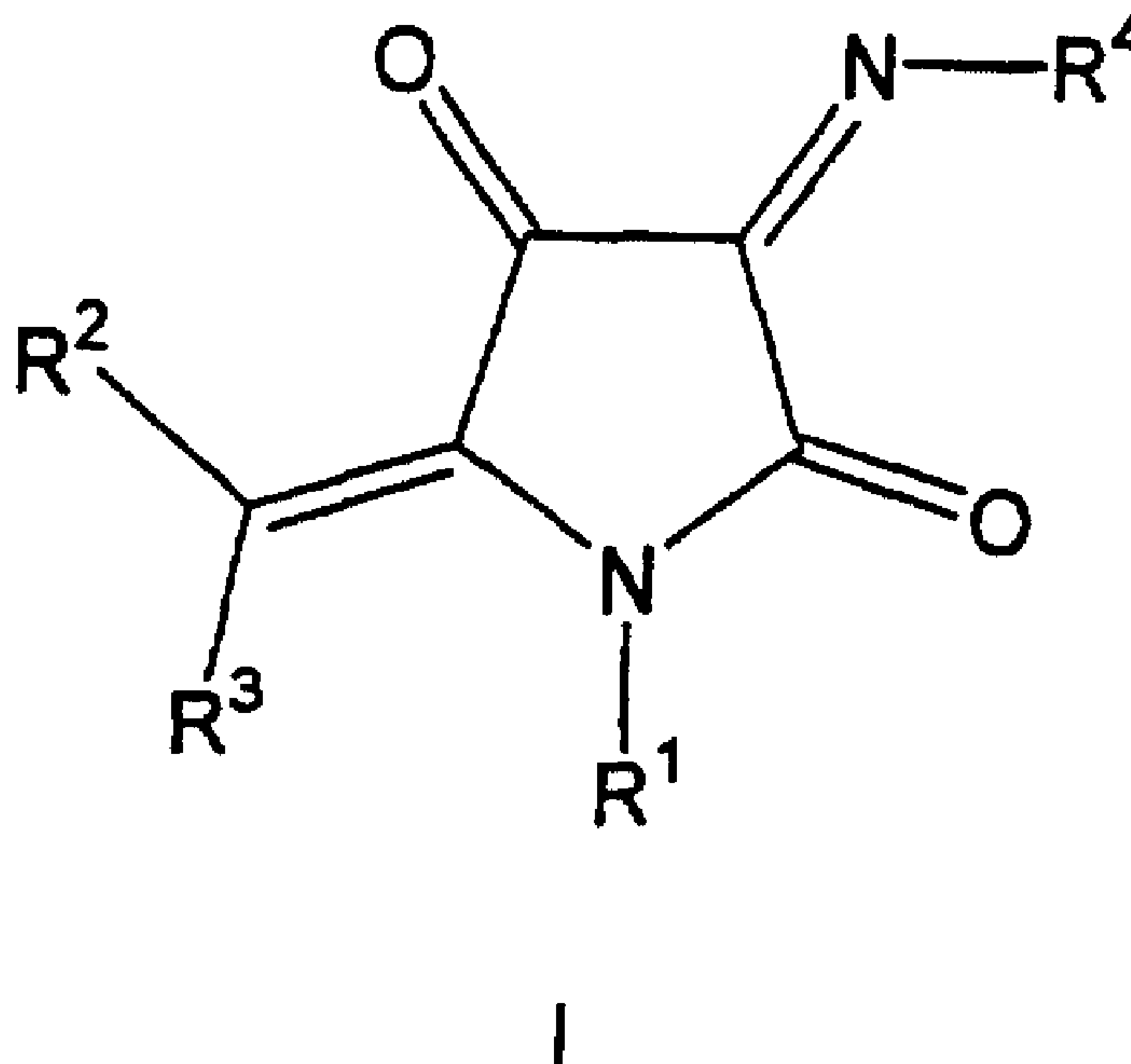
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(54) Titre : DERIVES SUBSTITUES DE PYRROLIDINE-2,3,4-TRION-3-OXIME AGISSANT EN TANT
QU'ANTAGONISTES DU RECEPTEUR NMDA

(54) Title: SUBSTITUTED PYRROLIDINE-2-3,4-TRIONE 3-OXIME DERIVATIVES WHICH ARE ACTIVE AS NMDA
RECEPTOR ANTAGONISTS



(57) **Abrégé/Abstract:**

The invention relates to substituted pyrrolidin-2,3,4-trione-3-oxime derivatives of formula (I), a method for the preparation thereof and the use thereof for the production of drugs for the treatment of pain.



(57) Abstract: The invention relates to substituted pyrrolidin-2,3,4-trione-3-oxime derivatives of formula (I), a method for the preparation thereof and the use thereof for the production of drugs for the treatment of pain.

Substituted pyrrolidine-2,3,4-trione 3-oxime derivatives
which are active as NMDA receptor antagonists

The invention relates to substituted pyrrolidine-2,3,4-
5 trione 3-oxime derivatives, processes for their
preparation, medicaments comprising these compounds, and
the use of these compounds for the preparation of
medicaments.

10 The treatment of chronic and non-chronic states of pain is
of great importance in medicine. There is a worldwide
demand for pain treatments which have a good efficacy. The
urgent need for action in respect of patient-relevant and
target-orientated treatment of chronic and non-chronic
15 states of pain, this being understood as meaning successful
and satisfactory pain treatment for the patient, is
documented in the large number of scientific works which
have recently appeared in the field of applied analgesia
and fundamental research into nociception.

20

Conventional opioids, such as e.g. morphine, have a good
action in the treatment of severe to very severe pain.
However, their use is limited due to the known side
effects, e.g. respiratory depression, vomiting, sedation,
25 constipation, addiction, dependency and development of
tolerance. They can therefore be administered over a
relatively long period of time or in relatively high
dosages only with particular safety precautions, such as
e.g. specific prescription instructions (Goodman, Gilman,
30 The Pharmacological Basis of Therapeutics, Pergamon Press,
New York 1990). Furthermore, they have a relatively low
efficacy for some states of pain, in particular neuropathic
and incidental pain.

35 Opioids display their analgesic action by binding to
receptors on the membrane which belong to the family of so-
called G protein-coupled receptors. In addition, there are
further receptors and ion channels which are considerably
involved in the system of pain formation and pain

conduction, such as e.g. the N-methyl-D-aspartate (NMDA) ion channel, via which a considerable part of the communication of synapses proceeds and through which the calcium ion exchange between a neuronal cell and its
5 environment is controlled.

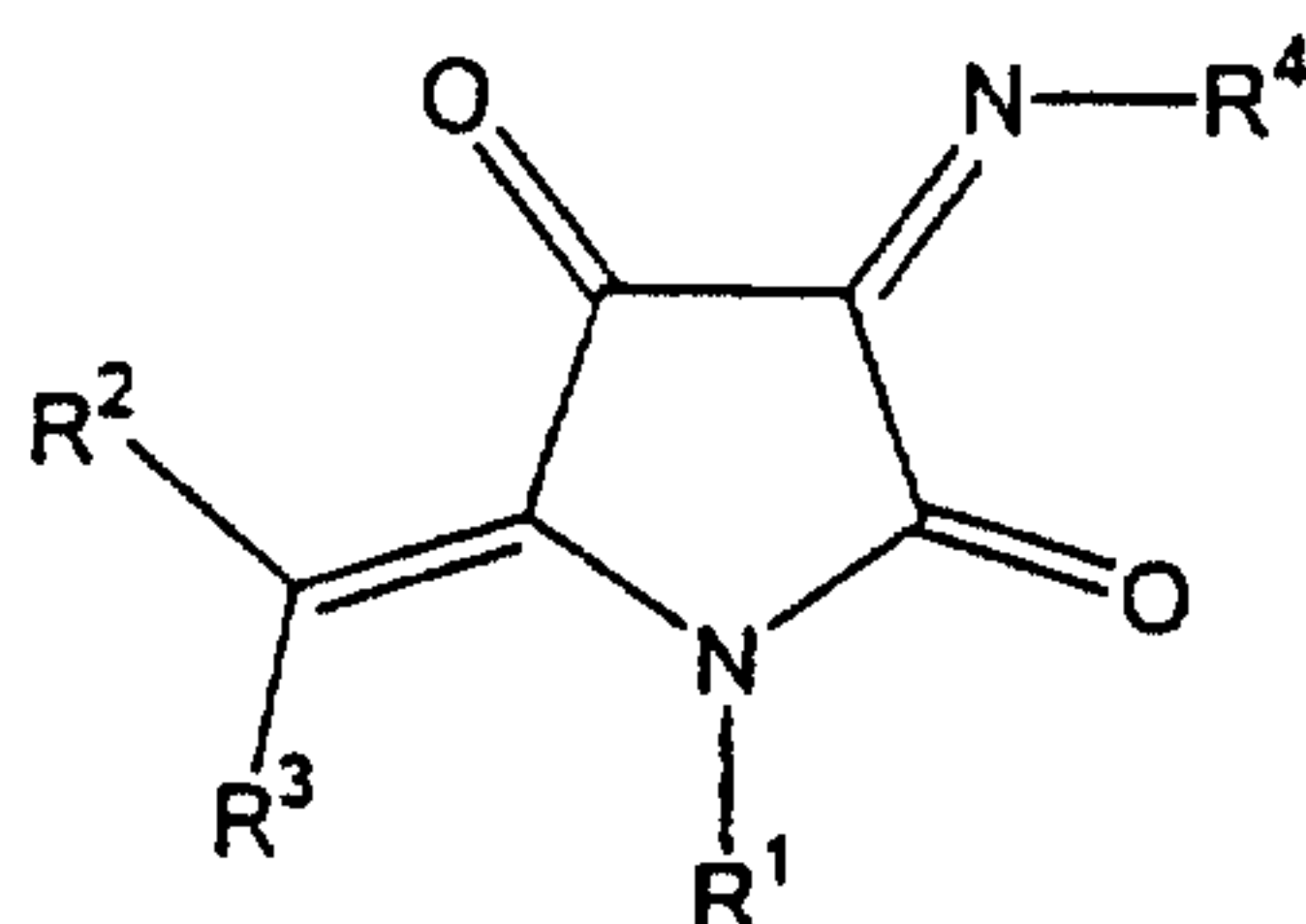
Knowledge of the physiological importance of ion channel-selective substances has been acquired by the development of the patch clamp technique, with which the action of NMDA
10 antagonists on the calcium balance inside the cell can be demonstrated.

An object on which the invention is based was to provide new compounds which are suitable for pain treatment or for
15 anxiolysis. Furthermore, these compounds should have as few as possible of the side effects of opioid analgesics, such as e.g. nausea, vomiting, dependency, respiratory depression or constipation. Further objects were to provide new active compounds for treatment of inflammatory and/or
20 allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses, epilepsy, schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, cerebral
25 ischaemias, cerebral infarctions, psychoses caused by increased amino acid levels, apoplexies, cerebral oedemas, hypoxia, anoxia, AIDS dementia, encephalomyelitis, Tourette's syndrome or perinatal asphyxia.

30 It has now been found that substituted pyrrolidine-2,3,4-trione 3-oxime derivatives of the following general formula I, as NMDA antagonists, selectively attack the glycine binding site and are suitable for treatment of inflammatory and/or allergic reactions, depressions, drug and/or alcohol
35 abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses, epilepsy, schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's

disease, cerebral ischaemias, cerebral infarctions, psychoses caused by increased amino acid levels, apoplexies, cerebral oedemas, hypoxia, anoxia, AIDS dementia, encephalomyelitis, Tourette's syndrome or
 5 perinatal asphyxia, and which moreover have a pronounced analgesic or anxiolytic action.

The present invention therefore provides compounds of the general formula I



I

10

wherein

the radical R^1 represents H, OR^8 , COR^5 , CSR^5 , NR^6R^7 , $COOR^5$, $CONR^6R^7$, $CSNR^6R^7$, a C_{1-10} -alkyl, preferably a C_{1-6} -alkyl, an
 15 aryl or a heteroaryl radical or represents an aryl radical bonded via a C_{1-6} -alkylene group, preferably an aryl radical bonded via a C_{1-3} -alkylene group,

the radicals R^2 , R^3 , which are identical or different,
 20 represent H, F, Cl, Br, CF_3 , OR^8 , SR^8 , a C_{1-10} -alkyl, preferably a C_{1-6} -alkyl, an aryl or a heteroaryl radical or represent an aryl radical bonded via a C_{1-6} -alkylene group, preferably an aryl radical bonded via a C_{1-3} -alkylene group,

25 the radical R^4 represent [sic] H, OH, OR^8 , SR^8 , COR^5 , $COOR^5$, $COCOR^5$, $CONR^6R^7$, $CSNR^6R^7$, preferably OH or OR^8 , a C_{1-10} -alkyl, preferably a C_{1-6} -alkyl, an aryl or a heteroaryl radical or represents an aryl radical bonded via a C_{1-6} -alkylene group, preferably an aryl radical bonded via a

30 C_{1-3} -alkylene group,

the radical R^5 represents H, a C_{1-10} -alkyl, preferably a C_{1-6} -alkyl, an aryl or a heteroaryl radical or represents an aryl radical bonded via a C_{1-6} -alkylene group, preferably an
5 aryl radical bonded via a C_{1-3} -alkylene group,

the radicals R^6 , R^7 , which are identical or different, represent H, OR^8 , COR^5 , $COOR^5$, a C_{1-10} -alkyl, preferably a C_{1-6} -alkyl, an aryl or a heteroaryl radical or represent an
10 aryl radical bonded via a C_{1-6} -alkylene group, preferably an aryl radical bonded via a C_{1-3} -alkylene group,

the radical R^8 represents a C_{1-10} -alkyl, preferably a C_{1-6} -alkyl, an aryl or a heteroaryl radical or represents an
15 aryl radical bonded via a C_{1-6} -alkylene group, preferably an aryl radical bonded via a C_{1-3} -alkylene group,

in the form of their racemates, enantiomers, diastereomers or a corresponding base or a corresponding physiologically
20 tolerated salt.

Alkyl radicals are also understood as meaning branched, unbranched or cyclic hydrocarbons which are unsubstituted or at least monosubstituted, preferably by F, Cl, Br, CN,
25 NO_2 , CHO, SO_2C_{1-6} -alkyl, SO_2CF_3 , OR^5 , NR^6R^7 , COR^5 , $COOR^5$, $COCOR^5$, $CONR^6R^7$ or $CSNR^6R^7$, where the radicals R^5 to R^7 have the meaning according to the general formula I. If these alkyl radicals contain more than one substituent, these can be identical or different. The alkyl radicals are
30 preferably methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, neopentyl, n-hexyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

An aryl radical is also understood as meaning phenyl
35 radicals which are unsubstituted or at least monosubstituted by OH, F, Cl, Br, CF_3 , CN, NO_2 , CHO, SO_2C_{1-6} -alkyl, SO_2CF_3 , OR^5 , NR^6R^7 , COR^5 , $COOR^5$, $COCOR^5$, $CONR^6R^7$, $CSNR^6R^7$, a C_{1-6} -alkyl radical, a C_{1-6} -alkoxy radical, a C_{2-6} -

alkylene radical, a heterocyclyl radical and/or a phenyl radical, wherein the radicals R^5 to R^7 have the meaning according to the general formula I. The term can also denote an optionally substituted naphthyl radical. The
5 phenyl radicals can also be fused with further rings.

A heteroaryl radical is also understood as meaning 5- or 6-membered unsaturated heterocyclic compounds which are optionally provided with a fused-on aryl radical and
10 contain at least one heteroatom, preferably nitrogen and/or oxygen and/or sulfur.

The heteroaryl radical is preferably furan, thiophene, pyrrole, pyridine, pyrimidine, quinoline, isoquinoline, phthalazine or quinazoline.

15

The following substituted pyrrolidine-2,3,4-trione 3-oxime derivatives are particularly preferred:

20

5-(methoxyphenylmethylene)-pyrrolidine-2,3,4-trione 3-oxime

5-(bromophenylmethylene)-pyrrolidine-2,3,4-trione 3-oxime

5-benzylidene-pyrrolidine-2,3,4-trione 3-oxime,

25

5-(2-chlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

5-(4-chlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

30

5-(2,3-dichlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

5-(2,4-dichlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

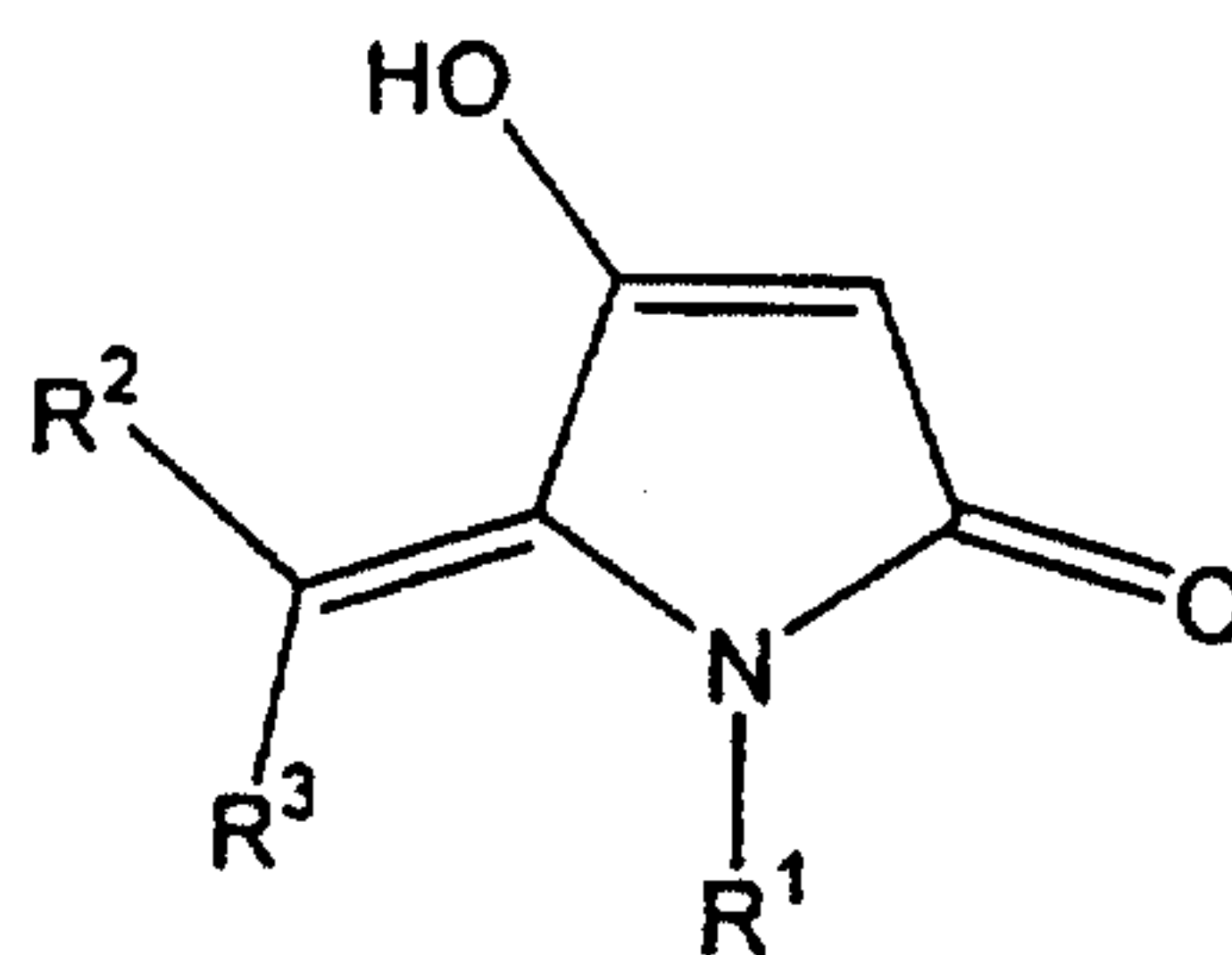
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5-(2,6-dichlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

and

5-(3-chlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

The present invention also provides processes for the
5 preparation of substituted pyrrolidine-2,3,4-trione 3-oxime
derivatives of the general formula I, in which tetramic
acids of the general formula II



wherein the radicals R^1 to R^3 have the meaning according to
10 the general formula I, are reacted with an aqueous solution
of sodium nitrite in an ice-cooled solution, preferably in
an ice-cooled solution of glacial acetic acid, to give
compounds of the general formula I wherein the radical R^4
represents OH and the radicals R^1 to R^3 have the meaning
15 according to the general formula I, and these are
preferably purified by recrystallization, preferably from
ethanol, and isolated.

The synthesis of the starting compounds, the tetramic acids
20 of the general formula II, can be carried out in accordance
with H. Poschenrieder et al. (Arch. Pharm. Pharm. Med.
Chem. 1998, vol. 331, pages 389-394) and Stachel et al. (J.
Heterocycl. Chem. 1980, vol. 17, pages 1195-1199 and
Liebigs Ann. Chem. 1985, pages 1692-1696) and the
25 literature references cited therein. They are included
herewith as reference and are therefore part of the
disclosure.

The compounds of the general formula I wherein the radical
30 R^4 represents OH and the radicals R^1 to R^3 have the meaning
according to the general formula I are reacted with C_{1-10} -

alkyl halides, preferably with C₁₋₆-alkyl halides, with aryl halides, heteroaryl halides or with aryl-C₁₋₆-alkyl halides, preferably with aryl-C₁₋₃-alkyl halides, preferably under an inert gas atmosphere in absolute solvents, preferably in
5 open-chain and/or cyclic ethers, at low temperatures in the presence of strong bases, preferably alkali metal hydroxides and/or alkaline earth metal hydroxides and/or organometallic bases, to give compounds of the general formula I wherein the radical R⁴ represents OR⁸ and the
10 radicals R¹ to R³ and R⁸ have the meaning according to the general formula I.

The compounds of the general formula I wherein the radical R⁴ represents OR⁸ and the radicals R¹ to R³ and R⁸ have the
15 meaning according to the general formula I can be derivatized still further in that they are reacted with acid chlorides of the general formula R⁵-(C=O)-Cl and/or acid bromides of the general formula R⁵-(C=O)-Br or chloroformic acid esters of the general formula Cl-(C=O)-O-
20 R⁵ or fluoroformic acid esters of the general formula F-(C=O)-O-R⁵ or with open-chain carbonates of the general formula R⁵-O-(C=O)-O-R⁵ or with correspondingly substituted cyclic carbonates, preferably with correspondingly substituted cyclic carbonates which contain 5 or 6 atoms in
25 the ring, wherein in each case the radical R⁵ has the meaning according to the general formula I, preferably under an inert gas atmosphere in an absolute solvent, preferably in open-chain and/or cyclic ethers, to give compounds of the general formula I wherein the radical R⁴
30 represents COR⁵ and COOR⁵ and the radicals R¹ to R³ and the radical R⁵ have the meaning according to the general formula I, and ... [sic] are purified and isolated by conventional processes.

35 The compounds of the general formula I wherein the radical R⁴ represents OH and the radicals R¹ to R³ have the meaning according to the general formula I can also be reacted with aliphatic, aromatic and heteroaromatic isocyanates or

isothiocyanates at low temperatures in aprotic, polar solvents to give compounds of the general formula I wherein the radical R^4 represents CONR^6R^7 or CSNR^6R^7 , the radical R^6 or R^7 denotes H and the radicals R^1 to R^3 and R^6 and R^7 have
5 the meaning according to the general formula I, and ...
[sic] are purified and isolated by conventional processes.

The preparation of the compounds of the general formula I in which the radical R^4 represents a C_{1-10} -alkyl radical, an
10 aryl radical or a heteroaryl radical or represents an aryl radical bonded via a C_{1-6} -alkylene group can be carried out by the method described in Maruoka and Yamamoto, Angew. Chem., vol. 97, pp. 670-683, 1985, Maruoka et al. J. Am. Chem. Soc., vol. 105, p. 2831, 1985 or Maruoka et al. Org.
15 Synth., vol. 66, p. 185. The corresponding disclosures are included herewith as reference.

The preparation of the compounds of the general formula I wherein the radical R^4 represents H, SR^8 or COCOR^5 and the
20 radicals R^5 and R^8 have the meaning according to the general formula I can be carried out by the various methods known to the expert. The preparation of the compounds of the general formula I wherein the radical R^4 represents CONR^6R^7 or CSNR^6R^7 and the radicals R^6 and R^7 either each denote H or
25 each have the meaning of the general formula I but are not H can also be carried out by the various methods known to the expert.

Analyses by means of ^1H -NMR spectroscopy show that the
30 pyrrolidine-2,3,4-trione 3-oxime derivatives of the general formula I obtained by the abovementioned processes can be present as a mixture of syn and anti isomers, which it has not been possible to separate further.

35 The compounds of the general formula I according to the invention can be converted with acids, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid,

oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, aspartic acid or a mixture of at least two of these acids into the corresponding physiologically tolerated salts in the manner known per se. The salt formation is preferably carried out in a solvent, such as, for example, diethyl ether, diisopropyl ether, acetic acid alkyl esters, acetone, 2-butanone or a mixture of at least two of these solvents. Trimethylchlorosilane in aqueous solution is moreover suitable for preparation of the corresponding hydrochlorides.

The substituted pyrrolidine-2,3,4-trione 3-oxime derivatives of the general formula I according to the invention are toxicologically acceptable and therefore represent suitable pharmaceutical active compounds.

The invention therefore also provides medicaments which comprise, as the active compound, at least one substituted pyrrolidine-2,3,4-trione 3-oxime derivative of the general formula I and/or a corresponding base and/or a corresponding physiologically tolerated salt, and optionally further active compounds and/or auxiliary substances. The medicament can also comprise a mixture of at least two enantiomers and/or the corresponding bases and/or the corresponding physiologically tolerated salts of a compound of the general formula I according to the invention, wherein the enantiomers are not present in equimolar amounts.

The medicaments are preferably employed for treatment/control for/of pain, inflammatory and/or allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses, neurodegenerative diseases, epilepsy, schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, cerebral ischaemias, cerebral infarctions, psychoses caused by increased amino acid

levels, apoplexies, cerebral oedemas, deficiency states of the central nervous system, hypoxia, anoxia, AIDS dementia, encephalomyelitis, Tourette's syndrome, perinatal asphyxia or for anxiolysis.

5

The invention also provides the use of at least one substituted pyrrolidine-2,3,4-trione 3-oxime derivative of the general formula I and/or a corresponding base and/or a corresponding physiologically tolerated salt for the
10 preparation of a medicament for treatment/control for/of pain, inflammatory and/or allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses, neurodegenerative
15 diseases, epilepsy, schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, cerebral ischaemias, cerebral infarctions, psychoses caused by increased amino acid levels, apoplexies, cerebral oedemas, deficiency states of the central nervous system, hypoxia,
20 anoxia, AIDS dementia, encephalomyelitis, Tourette's syndrome, perinatal asphyxia or for anxiolysis.

To prepare corresponding pharmaceutical formulations, in addition to at least one substituted pyrrolidine-2,3,4-
25 trione 3-oxime derivative of the general formula I, conventional auxiliary substances, such as e.g. carrier materials, fillers, solvents, diluents, dyestuffs or binders, are additionally employed. The choice of auxiliary substances and the amounts thereof to be employed depends
30 on the mode of administration, such as e.g. oral, intravenous, intraperitoneal, intradermal, intramuscular, intranasal, buccal or local, for example on infections on the skin, the mucous membranes and on the eyes, and is known to the expert. Formulations in the form of tablets,
35 coated tablets, capsules, granules, drops, juices and syrups and multiparticulate formulations, for example pellets or granules, which can optionally also be filled in capsules or pressed to tablets, are suitable, for example,

for oral administration, and solutions, suspensions, easily reconstitutable dry formulations and sprays e.g. are suitable for parenteral, topical and inhalatory administration. Compounds of the general formula I according to the invention in a depot, in dissolved form or in a patch, optionally with the addition of agents which promote penetration of the skin, are suitable percutaneous administration formulations. Formulation forms which can be used orally or percutaneously can also release the compounds of the general formula I according to the invention in a retarded manner.

The amount of active compound to be administered to the patient varies according to the weight of the patient, the mode of administration, the indication and the severity of the illness. 2 to 500 mg/kg of body weight of the patient of at least one pyrrolidine-2,3,4-trione 3-oxime derivative of the general formula I are usually administered.

Pharmacological studies

a) Studies of the receptor binding

Studies for determination of the affinity of the substituted pyrrolidine-2,3,4-trione 3-oxime derivatives of the general formula I according to the invention for the glycine binding site of the NMDA receptor channel was [sic] carried out on cerebral membrane homogenates (homogenate of the cortex and hippocampus area from the brain of male rats, Wistar strain, Charles River, WIGA GmbH, Sulzbach, Germany) by the method of Baron B.M. et al, J. Pharmacol. Exp. Ther., vol. 279, pp.62-68 (1996).

For this, the cortex and hippocampus was [sic] dissected free from freshly removed rat brains and homogenized in 5 mmol/l TRIS-acetate buffer, 0.32 mol/l sucrose pH 7.4 (10 ml/g fresh weight) with a Potter homogenizer (Braun/Melsungen, Germany, 10 plunger strokes at 500

revolutions per minute (rpm)), while cooling with ice, and the homogenate was then centrifuged for 10 minutes at 1,000 g and 4°C. The first supernatant was collected and the sediment was homogenized again with 5 mmol/l TRIS-acetate buffer, 0.32 mol/l sucrose pH 7.4 (5 ml/g original fresh weight of rat brain cortex and hippocampus) with the Potter homogenizer (10 plunger strokes at 500 rpm), while cooling with ice, and the homogenate was centrifuged for 10 minutes at 1,000 g and 4°C. The resulting supernatant was combined with the supernatant from the first centrifugation and the mixture was centrifuged at 17,000 g for 20 minutes at 4°C. The supernatant after this centrifugation was discarded, the membrane sediment was taken up in 5 mmol/l TRIS-acetate buffer pH 8.0 (20 ml/g original fresh weight) and the mixture was homogenized with 10 plunger strokes at 500 rpm. The membrane homogenate was then incubated for 1 hour at 4°C and centrifuged for 30 minutes at 50,000 g and 4°C. The supernatant was discarded and the centrifuge tube with the membrane sediment was closed with Parafilm and frozen at -20°C for 24 hours. The membrane sediment was then thawed and taken up in ice-cold 5 mmol/l TRIS-acetate buffer, 0.1% saponin (weight/volume) pH 7.0 (10 ml/g original fresh weight) and homogenized with 10 plunger strokes at 500 rpm and the homogenate was 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 of 5 mmol/l TRIS-acetate buffer pH 7.0 (approx. 2 ml/g original fresh weight) and the mixture was homogenized again with 10 plunger strokes at 500 rpm. After determination of the protein content, the membrane homogenate was brought to a protein concentration of 10 mg protein/ml with 5 mmol/l TRIS-acetate buffer pH 7.0 and frozen in aliquots until the analysis was carried out.

For the receptor binding test, aliquots were thawed, diluted 1:10 with 5 mmol/l TRIS-acetate buffer pH 7.0, homogenized with 10 plunger strokes at 500 rpm with the Potter homogenizer, while cooling with ice, and centrifuged

for 60 minutes at 55,000 g at 4°C. The supernatant was decanted and the membrane sediment was brought to a protein concentration of 1 mg/ml with ice-cold 50 mmol/l TRIS-acetate buffer pH 7.0, and the mixture was homogenized
5 again with 10 plunger strokes at 500 rpm and kept in suspension while stirring on a magnetic stirrer in an ice-bath. 100 µl portions of this membrane homogenate were employed per 1 ml batch in the receptor binding test (0.1 mg protein/ml in the final batch).

10

In the binding test, 50 mmol/l TRIS-acetate buffer pH 7.0 was employed as the buffer and 1 nmol/l (³H)-MDL 105.519 (Baron B.M. et al, J. Pharmacol. Exp. Ther., vol. 279, pp. 62-68 (1996)) was employed as the radioactive ligand. The
15 proportion of non-specific binding was determined in the presence of 1 mmol/l glycine.

In further batches, the compounds according to the invention were added in concentration series and the
20 displacement of the radioactive ligand from its specific binding to the glycine binding site of the NMDA receptor channel was determined. The particular triplicate batches were incubated for 120 minutes at 4°C and then harvested by means of filtration through glass fibre filter mats (type
25 Whatman GF/B, Adi Hassel, Munich, Germany) for determination of the radioactive ligand bonded to the membrane homogenate. The radioactivity retained on the glass fibre filters was measured in a β-counter (Packard TRI-CARB Liquid Scintillation Analyzer 2000CA, Packard
30 Instrument [sic], Meriden, CT 06450, USA) after addition of scintillator (Ready Protein, Beckamnn [sic] Coulter GmbH, Krefeld, Germany).

The affinity of the compounds according to the invention
35 for the glycine binding site of the NMDA receptor channel was calculated as the IC₅₀ (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 stated as the K_i value after conversion (by the Cheng-Prusoff equation (Y. Cheng, W.H. Prusoff, 1973, Biochem. Pharmacol., vol. 22, pp. 3099-3108))

- 5 b) NMDA/glycine-induced ion currents in *Xenopus* oocytes injected with RNA

The study for determination of function changes of the NMDA receptor channel by the compounds of the general formula I
10 according to the invention was carried out on oocytes of the South African clawed toad *Xenopus laevis*. For this, neuronal NMDA receptor channels were formed in oocytes after injection of RNA from mouse brains, and ion currents induced by co-application of NMDA and glycine were
15 measured.

Xenopus oocytes of stages V and VI (Dumont, J.N., J. Morphol. 136, pp. 153-180 (1972)) were microinjected with complete RNA from brain tissue of adult mice (100-
20 130 ng/cell) and were kept for up to 10 days in culture medium (composition: 88.0 mmol/l NaCl, 1.0 mmol/l KCl, 1.5 mmol/l CaCl_2 , 0.8 mmol/l MgSO_4 , 2.4 mmol/l NaHCO_3 , 5 mmol/l HEPES, 100 IU/ml penicillin, 100 $\mu\text{g/ml}$ streptomycin, pH 7.4) at 20°C. Transmembrane ion currents were recorded with
25 the aid of the conventional two-electrode voltage clamping technique at a holding potential of -70 mV (Bloms-Funke P. et al, (1996) Neurosci. Lett. 205, pp. 115-118 (1996)). The OTC interface and Cellworks software (npi, Federal Republic of Germany) were used for recording data and controlling
30 the test apparatus. The compounds according to the invention were added to a nominally Mg^{2+} -free medium (composition: 89.0 mmol/l NaCl, 1.0 mmol/l KCl, 1.8 mmol/l CaCl_2 , 2.4 mmol/l NaHCO_3 , 5 mmol/l HEPES, pH 7.4) and applied to the system with the aid of a concentration clamp
35 (npi, Federal Republic of Germany). To test substance effects mediated via the glycine B-binding site of the NMDA receptor channel, the glycine dose/effect curve with and without the particular compound according to the invention

was plotted. For this, NMDA was co-applied cumulatively in a fixed concentration of 100 $\mu\text{mol/l}$ with glycine in increasing concentrations (0-100 $\mu\text{mol/l}$). Thereafter, the experiment was repeated in the same manner with a fixed concentration of the compound according to the invention. The current amplitudes were standardized to those of the control response to co-application of NMDA (100 $\mu\text{mol/l}$) with glycine (10 $\mu\text{mol/l}$). The data were analysed with the Igor-Pro software (version 3.1, WaveMetrics, USA). All the results were stated as the mean from at least 3 experiments on different oocytes of at least two toads. The significance for non-paired measurement parameters is determined with the aid of the Mann-Whitney U test and that for paired measurement parameters by the Wilcoxon test (Sysstat, SPSS Inc., USA). The EC_{50} values are calculated according to the following equation:

$$Y = Y_{\min} + (Y_{\max} - Y_{\min}) / (1 + (X/\text{EC}_{50})^{-p})$$

($Y_{\min}$ = minimum test value, $Y_{\max}$ = maximum test value, Y = relative current amplitude, X = concentration of the test substance, p = slope factor). With a right-hand shift of the glycine dose/effect curve, the pA_2 value of the compound according to the invention was determined graphically with the aid of a Schild regression. Concentration ratios were calculated with the aid of the EC_{50} values, which were calculated independently for each dose/effect curve.

c) Formalin test in mice

30

The studies for determination of the antinociceptive action of the compounds according to the invention were carried out in the formalin test in male albino mice (NMRI, 25 - 35 g, Iffa Credo, Belgium).

35

In the formalin test, a distinction is made between the first (early) phase (0 - 15 min after formalin injection) and the second (late) phase (15 - 60 min after formalin

injection) (D. Dubuisson et al, Pain, vol. 4, pp. 161 - 174 (1977)). The early phase represents a model for acute pain, as a direct reaction to the formalin injection, while the late phase is regarded as a model for persistent (chronic) pain (T.J.Coderre et al, Pain, vol. 52, pp. 259 - 285 (1993)).

The compounds according to the invention were investigated in the second phase of the formalin test to obtain information on the actions of the compounds according to the invention on chronic/inflammatory pain.

By a single subcutaneous formalin injection (20 µl, 1% aqueous solution) into the dorsal side of the right hind paw of freely mobile test animals, a nociceptive reaction was induced, which manifests itself in significant licking and biting of the paw affected.

For the investigation period in the second (late) phase of the formalin test, the nociceptive behaviour was recorded continuously by observing the animals. The pain properties were quantified by adding up the seconds in which the animals showed licking and biting of the paw affected in the investigation period. After injection of substances which have an antinociceptive action in the formalin test, the modes of behaviour described for the animals are reduced, and possibly even eliminated. In a manner corresponding to the experiments in which the animals had received an injection of the compounds according to the invention before the administration of formalin, the control animals were injected with the vehicle, i.e. solvent (e.g. 0.9% NaCl solution) before the administration of formalin. The behaviour of the rats after administration of the substance was compared with a control group (10 mice per substance dose).

On the basis of the quantification of the pain properties, the action of the substance in the formalin test was determined as a change from the control in per cent. The ED₅₀ calculations were made by means of regression analysis. The administration time before the formalin injection was

chosen according to the mode of administration of the compounds according to the invention (intraperitoneal: 15 min, intravenous: 5 min).

5 d) Writhing test in the mouse

The study of the analgesic activity was also carried out in the phenylquinone-induced writhing in the mouse (modified by I.C. Hendershot et al, (1959) J. Pharmacol. Exp. Ther.,
10 vol. 125, pp. 237-240). Male NMRI mice weighing 25 to 30 g (Iffa, Credo, Belgium, were used for this. Groups of 10 animals per substance dose received 0.3 ml/mouse of a 0.02% aqueous solution of phenylquinone (phenylbenzoquinone, Sigma, Deisenhofen; preparation of the solution with the
15 addition of 5% ethanol and storage in a water bath at 45°C) administered intraperitoneally 10 minutes after intravenous administration of the particular compound. The animals were placed individually in observation cages. The number of pain-induced stretching movements (so-called writhing
20 reactions = straightening of the body with stretching of the hind extremities) was counted by means of a push-button counter for 5 to 20 minutes after the administration of phenylquinone. Animals which received only physiological saline solution were also run as a control. All the
25 substances were tested in the standard dosage of 10 mg/kg of body weight of the mouse. The percentage inhibition (% inhibition) of the writhing reaction by a substance was calculated according to the following equation:

$$\begin{aligned} 30 \quad & \text{writhing reactions} \\ \% \text{ inhibition} = 100 - & \frac{\text{of the treated animals}}{\text{writhing reactions}} * 100 \\ & \text{of the control animals} \end{aligned}$$

35 For some of the compounds according to the invention the ED₅₀ values with the 95% confidence range of the writhing reaction was [sic] calculated by means of regression analysis (evaluation program from Martens EDV Service,

Eckental) from the dose-dependent decrease in the writhing reactions compared with phenylquinone control groups investigated in parallel.

- 5 The following examples serve to illustrate the invention, but do not limit the general inventive idea.

Examples

- 10 The yields of the compounds prepared are not optimized.

The melting points determined are uncorrected.

- 15 Example 1:

5-(Methoxyphenylmethylene)-pyrrolidine-2,3,4-trione 3-oxime

- An aqueous solution of 1.1 mmol (0.075 g) sodium nitrite
20 was added dropwise to an ice-cooled solution of 2 mmol 4-hydroxy-5-(methoxyphenyl-methylene)-1,5-dihydropyrrol-2-one (prepared in accordance with H. Poschenrieder et al (Arch. Pharm. Pharm. Med. Chem. 1998, 331, 389-394) and H.-D. Stachel et al (J. Heterocycl. Chem. 1980, vol. 17, pp.
25 1195-1199 and Liebigs Ann. Chem. 1985, pp. 1692-1696)) in 5 ml glacial acetic acid, while stirring. The resulting solution was then stirred at room temperature for 30 minutes and concentrated in vacuo. The residue is purified by recrystallization from ethanol. The yield of 5-
30 (methoxyphenylmethylene)-pyrrolidine-2,3,4-trione 3-oxime was 60%, with a melting point of 174°C.

Analysis of this compounds [sic] by means of ¹H-NMR spectroscopy gave the following signals:

- 35 (d6-DMSO, δ in ppm): 11.95 (s, 1 H); 10.74 (s, 0.66 H); 10.71 (s, 0.33 H); 7.46 (m, 5 H); 3.42 (s, 1 H); 3.41 (s, 2 H).

Example 2:

5-(Bromophenylmethylene)-pyrrolidine-2,3,4-trione 3-oxime

5

An aqueous solution of 1.1 mmol (0.075 g) sodium nitrite was added dropwise to an ice-cooled solution of 2 mmol 5-(bromophenyl-methylene)-4-hydroxy-1,5-dihydropyrrol-2-one (prepared in accordance with H. Poschenrieder et al (Arch. Pharm. Pharm. Med. Chem. 1998, 331, 389-394) and H.-D. Stachel et al (J. Heterocycl. Chem. 1980, vol. 17, pp. 1195-1199 and Liebigs Ann. Chem. 1985, pp. 1692-1696)) in 5 ml glacial acetic acid, while stirring. The resulting solution was then stirred at room temperature for 30 minutes and concentrated in vacuo. The residue is purified by recrystallization from ethanol. The yield of 5-(bromophenylmethylene)-pyrrolidine-2,3,4-trione 3-oxime was 65%, with a melting point of 158°C.

20 Analysis of this compounds [sic] by means of ¹H-NMR spectroscopy gave the following signals:

(d6-DMSO, δ in ppm): 14.46 (s, 1 H); 11.06 (s, 0.70 H); 11.00 (s, 0.30 H); 7.40-7.26 (m, 5 H).

25 Example 3:

5-Benzylidene-pyrrolidine-2,3,4-trione 3-oxime

An aqueous solution of 1.1 mmol (0.075 g) sodium nitrite was added dropwise to an ice-cooled solution of 2 mmol 5-benzylidene 4-hydroxy-1,5-dihydropyrrol-2-one (prepared in accordance with H. Poschenrieder et al (Arch. Pharm. Pharm. Med. Chem. 1998, 331, 389-394) and H.-D. Stachel et al (J. Heterocycl. Chem. 1980, vol. 17, pp. 1195-1199 and Liebigs Ann. Chem. 1985, pp. 1692-1696)) in 5 ml glacial acetic acid, while stirring. The resulting solution was then stirred at room temperature for 30 minutes and concentrated in vacuo. The residue is purified by recrystallization from

ethanol. The yield of 5-benzylidene-pyrrolidine-2,3,4-trione 3-oxime was 65%, with a melting point of 205°C.

Analysis of this compounds [sic] by means of ¹H-NMR spectroscopy gave the following signals:
(d6-DMSO, δ in ppm): 14.66 (s, 1 H); 11.25 (s, 0.66 H); 11.18 (s, 0.33 H); 7.64-7.31 (m, 5 H); 6.42 (s, 0.33 H); 6.36 (s, 0.66 H).

10 Example 4:

5-(2-Chlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

An aqueous solution of 1.1 mmol (0.075 g) sodium nitrite was added dropwise to an ice-cooled solution of 2 mmol 5-(2-chlorobenzylidene)-4-hydroxy-1,5-dihydropyrrol-2-one (prepared in accordance with H. Poschenrieder et al (Arch. Pharm. Pharm. Med. Chem. 1998, 331, 389-394) and H.-D. Stachel et al (J. Heterocycl. Chem. 1980, vol. 17, pp. 1195-1199 and Liebigs Ann. Chem. 1985, pp. 1692-1696)) in 5 ml glacial acetic acid, while stirring. The resulting solution was then stirred at room temperature for 30 minutes and concentrated in vacuo. The residue is purified by recrystallization from ethanol. The yield of 5-(2-chlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime was 60%, with a melting point of 176°C.

Analysis of this compounds [sic] by means of ¹H-NMR spectroscopy gave the following signals:
(d6-DMSO, δ in ppm): 11.40 (s, 0.66 H); 11.34 (s, 0.33 H); 7.46-7.21 (m, 4 H); 6.52 (s, 0.33 H); 6.47 (s, 0.66 H).

Example 5:

5-(4-Chlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

- 5 An aqueous solution of 1.1 mmol (0.075 g) sodium nitrite was added dropwise to an ice-cooled solution of 2 mmol 5-(4-chlorobenzylidene)-4-hydroxy-1,5-dihydropyrrol-2-one (prepared in accordance with H. Poschenrieder et al (Arch. Pharm. Pharm. Med. Chem. 1998, 331, 389-394) and H.-D. Stachel et al (J. Heterocycl. Chem. 1980, vol. 17, pp. 1195-1199 and Liebigs Ann. Chem. 1985, pp. 1692-1696)) in 5 ml glacial acetic acid, while stirring. The resulting solution was then stirred at room temperature for 30 minutes and concentrated in vacuo. The residue is purified by recrystallization from ethanol. The yield of 5-(4-chlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime was 50%, with a melting point of 190°C.

- Analysis of this compounds [sic] by means of ¹H-NMR spectroscopy gave the following signals:
(d6-DMSO, δ in ppm): 11.35 (s, 0.66 H); 11.28 (s, 0.33 H); 7.67-7.64 (m, 2 H); 7.45-7.35 (m, 2 H); 6.40 (s, 0.33 H); 6.35 (s, 0.66 H).

25 Example 6:

5-(2,3-Dichlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

- 30 An aqueous solution of 1.1 mmol (0.075 g) sodium nitrite was added dropwise to an ice-cooled solution of 2 mmol 5-(2,3-dichlorobenzylidene)-4-hydroxy-1,5-dihydropyrrol-2-one (prepared in accordance with H. Poschenrieder et al (Arch. Pharm. Pharm. Med. Chem. 1998, 331, 389-394) and H.-D. Stachel et al (J. Heterocycl. Chem. 1980, vol. 17, pp. 1195-1199) and Liebigs Ann. Chem. 1985, pp. 1692-1696)) in 5 ml glacial acetic acid, while stirring. The resulting solution was then stirred at room temperature for 30

minutes and concentrated in vacuo. The residue is purified by recrystallization from ethanol. The yield of 5-(2,4-dichlorobenzylidene)-pyrrolidine-2,3,4-trione [sic] 3-oxime was 55%, with a melting point of 180°C.

5

Analysis of this compounds [sic] by means of ¹H-NMR spectroscopy gave the following signals:

(d6-DMSO, δ in ppm): 11.43 (s, 0.66 H); 11.37 (s, 0.33 H); 7.63-7.37 (m, 3 H); 6.50 (s, 0.33 H); 6.45 (s, 0.66 H).

10

Example 7:

5-(2,4-Dichlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

15

An aqueous solution of 1.1 mmol (0.075 g) sodium nitrite was added dropwise to an ice-cooled solution of 2 mmol 5-(2,4-dichlorobenzylidene)-4-hydroxy-1,5-dihydropyrrol-2-one (prepared in accordance with H. Poschenrieder et al (Arch. Pharm. Pharm. Med. Chem. 1998, 331, 389-394) and H.-D. Stachel et al (J. Heterocycl. Chem. 1980, vol. 17, pp. 1195-1199 and Liebigs Ann. Chem. 1985, pp. 1692-1696)) in 5 ml glacial acetic acid, while stirring. The resulting solution was then stirred at room temperature for 30 minutes and concentrated in vacuo. The residue is purified by recrystallization from ethanol. The yield of 5-(2,4-dichlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime was 55%, with a melting point of 180°C.

30 Analysis of this compounds [sic] by means of ¹H-NMR spectroscopy gave the following signals:

(d6-DMSO, δ in ppm): 11.38 (s, 0.66 H); 11.32 (s, 0.33 H); 7.68 -7.65 (m, 2 H); 7.45-7.43 (m, 1 H); 6.42 (s, 0.33 H); 6.36 (s, 0.66 H).

Example 8:

5-(2,6-Dichlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

5

An aqueous solution of 1.1 mmol (0.075 g) sodium nitrite was added dropwise to an ice-cooled solution of 2 mmol 5-(2,6-dichlorobenzylidene)-4-hydroxy-1,5-dihydropyrrol-2-one (prepared in accordance with H. Poschenrieder et al (Arch. Pharm. Pharm. Med. Chem. 1998, 331, 389-394) and H.-D. Stachel et al (J. Heterocycl. Chem. 1980, vol. 17, pp. 1195-1199 and Liebigs Ann. Chem. 1985, pp. 1692-1696)) in 5 ml glacial acetic acid, while stirring. The resulting solution was then stirred at room temperature for 30 minutes and concentrated in vacuo. The residue is purified by recrystallization from ethanol. The yield of 5-(2,6-dichlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime was 65%, with a melting point of 232°C.

20 Analysis of this compounds [sic] by means of ¹H-NMR spectroscopy gave the following signals:

(d6-DMSO, δ in ppm): 11.12 (s, 0.66 H); 11.08 (s, 0.33 H); 7.50-7.48 (m, 2 H); 7.39-7.35 (m 1 H); 6.27 (s, 0.33 H); 6.22 (s, 0.66 H).

25

Example 9:

5-(3-Chlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime

30 An aqueous solution of 1.1 mmol (0.075 g) sodium nitrite was added dropwise to an ice-cooled solution of 2 mmol 5-(3-chlorobenzylidene)-4-hydroxy-1,5-dihydropyrrol-2-one (prepared in accordance with H. Poschenrieder et al (Arch. Pharm. Pharm. Med. Chem. 1998, 331, 389-394) and H.-D. Stachel et al (J. Heterocycl. Chem. 1980, vol. 17, pp. 1195-1199 and Liebigs Ann. Chem. 1985, pp. 1692-1696)) in 5 ml glacial acetic acid, while stirring. The resulting solution was then stirred at room temperature for 30

minutes and concentrated in vacuo. The residue is purified by recrystallization from ethanol. The yield of 5-(3-chlorobenzylidene)-pyrrolidine-2,3,4-trione 3-oxime was 50%, with a melting point of 185°C.

5

Analysis of this compounds [sic] by means of ^1H -NMR spectroscopy gave the following signals:

(d6-DMSO, δ in ppm): 14.69 (s, 0.66 H); 14.53 (s, 0.33 H); 11.47 (s, 0.66 H), 11.40 (s, 0.33 H); 7.72-7.20 (m, 4 H);
10 6.38 (s, 0.33 H); 6.33 (s, 0.66 H).

Pharmacological studies

a) Studies of the receptor binding

15

The studies to determine the affinity of the compounds according to the invention according to example 1 and 2 for the glycine binding site of the NMDA receptor channel were carried out as described above.

20

The affinity ... [sic] 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
25 non-linear regression and is stated in the following table 1 as the K_i value after conversion (by the Cheng-Prusoff equation (Y. Cheng, W.H. Prusoff, 1973, Biochem. Pharmacol., vol. 22, pp. 3099-3108))

30 **Table 1**

Example	Glycine binding site of the NMDA receptor channel K_i ($\mu\text{mol/l}$)
1	0.116
2	0.430

b) NMDA/glycine-induced ion currents on RNA-injected *Xenopus* oocytes.

The study to determine function changes in the NMDA receptor channel due to the compound according to the invention according to example 1 was carried out as described above.

The result of the study of the effect of the compound according to the invention according to example 1 on ion currents induced by NMDA/glycine on RNA-injected oocytes is shown in the following table 2.

Table 2:

15

Example no.	Ion currents		
	relative current amplitudes		
	NMDA	NMDA + glycine (0.3 μ M)	NMDA + glycine (10 μ M)
Control	1.42%	70.23%	100%
Example 1	-0.58%	0.08%	59.93%

The studies show the antagonistic action of the compound according to example 1.

20 c) Formalin test in mice

The studies to determine the antinociceptive action of the compounds according to the invention was [sic] carried out as described above.

The corresponding results in the formalin test in mice are summarized in the following table 3.

5 **Table 3:**

Example	% change from the control at 10 mg/kg
1	63.9
2	36.3
3	47.6

d) Writhing test in mice

- 10 The study of the analgesic activity was carried out in the phenylquinone-induced writhing in mice as described above. All the compounds according to the invention investigated showed a pronounced analgesic action. The results are summarized in the following table 4.

Table 4:

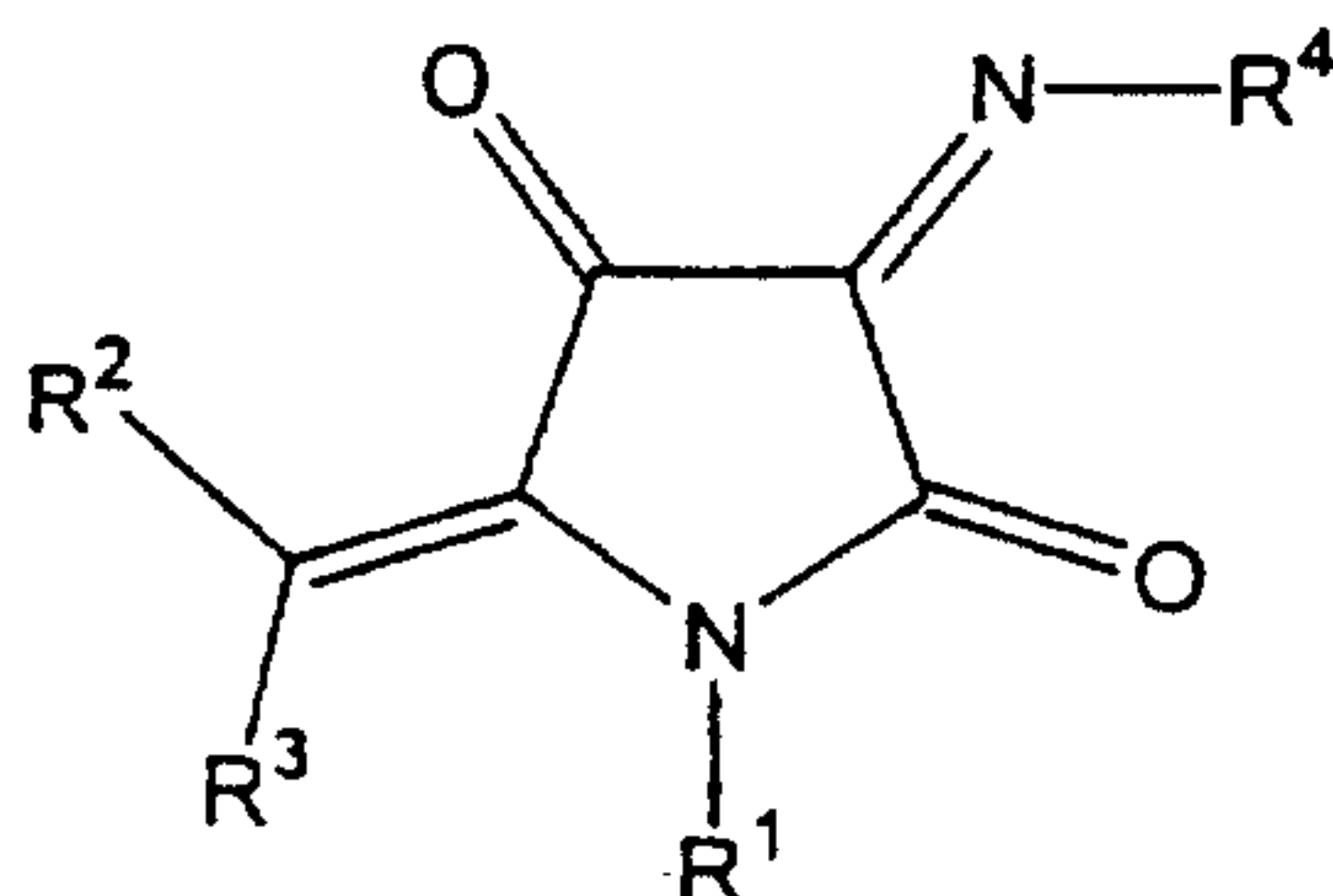
Example	% inhibition of the writhing reaction at 10 mg/kg intravenously
3	25
4	55
5	50
6	52
7	46
8	51
9	81

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Patent Claims:

1. Substituted pyrrolidine-2,3,4-trione derivatives of the general formula I



I

5

wherein

the radical R^1 represents H, OR^8 , COR^5 , CSR^5 , NR^6R^7 , $COOR^5$, $CONR^6R^7$, $CSNR^6R^7$, a C_{1-10} -alkyl radical or an unsubstituted phenyl radical,

10

the radicals R^2 , R^3 , which are identical or different, represent H, F, Cl, Br, CF_3 , OR^8 , SR^8 , a C_{1-10} -alkyl, an aryl or a heteroaryl radical or represent an aryl radical bonded via a C_{1-6} -alkylene group,

15

the radical R^4 represents H, OH, OR^8 , SR^8 , COR^5 , $COOR^5$, $COCOR^5$, $CONR^6R^7$, $CSNR^6R^7$ or a C_{1-10} -alkyl radical,

20

the radical R^5 represents H or a C_{1-10} -alkyl radical,

the radicals R^6 , R^7 , which are identical or different, represent H, OR^8 , COR^5 , $COOR^5$ or a C_{1-10} -alkyl radical,

25

the radical R^8 represents a C_{1-10} -alkyl radical,

in the form of their racemates, enantiomers, diastereomers or a corresponding base or a corresponding physiologically tolerated salt.

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G2916PCT

PCT/EP00/07101

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2. Substituted pyrrolidine-2,3,4-trione derivatives according to claim 1, characterized in that the radical R^1 represents a C_{1-6} -alkyl radical and the other radicals R^2 to R^8 have the meaning according to the general formula I.
3. Substituted pyrrolidine-2,3,4-trione derivatives according to claim 1 or 2, characterized in that the radical R^2 and/or R^3 represents a C_{1-6} -alkyl radical and the other radicals R^4 to R^8 and where appropriate R^2 or R^3 have the meaning according to the general formula I.
4. Substituted pyrrolidine-2,3,4-trione derivatives according to claim 1 or 2, characterized in that the radical R^2 and/or R^3 represents an aryl radical bonded via a C_{1-3} -alkylene group and the other radicals R^4 to R^8 and where appropriate R^2 or R^3 have the meaning according to the general formula I.
5. Substituted pyrrolidine-2,3,4-trione derivatives according to one of claims 1 to 4, characterized in that the radical R^4 represents OH and the other radicals R^5 to R^8 have the meaning according to the general formula I.
6. Substituted pyrrolidine-2,3,4-trione derivatives according to one of claims 1 to 4, characterized in that the radical R^4 represents OR^8 and the other radicals R^5 to R^8 have the meaning according to the general formula I.
7. Substituted pyrrolidine-2,3,4-trione derivatives according to one of claims 1 to 4, characterized in that the radical R^4 represents a C_{1-6} -alkyl radical and the other radicals R^5 to R^8 have the meaning according to the general formula I.

G2916PCT

PCT/EP00/07101

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8. Substituted pyrrolidine-2,3,4-trione derivatives
according to one of claims 1 to 7, characterized in
that the radical R^5 represents a C_{1-6} -alkyl radical and
the other radicals R^6 to R^8 have the meaning according
to the general formula I.
9. Substituted pyrrolidine-2,3,4-trione derivatives
according to one of claims 1 to 8, characterized in
that the radical R^6 and/or R^7 represents a C_{1-6} -alkyl
radical and the radical R^8 and where appropriate R^6 or
 R^7 has [sic] the meaning according to the general
formula I.
10. Substituted pyrrolidine-2,3,4-trione derivatives
according to one of claims 1 to 9, characterized in
that the radical R^8 represents a C_{1-6} -alkyl radical.
11. Substituted pyrrolidine-2,3,4-trione derivatives
according to claim 1
- 5-(methoxyphenylmethylene)-pyrrolidine-2,3,4-
trione 3-oxime
- 5-(bromophenylmethylene)-pyrrolidine-2,3,4-trione
3-oxime
- 5-benzylidene-pyrrolidine-2,3,4-trione 3-oxime,
- 5-(2-chlorobenzylidene)-pyrrolidine-2,3,4-trione
3-oxime
- 5-(4-chlorobenzylidene)-pyrrolidine-2,3,4-trione
3-oxime
- 5-(2,3-dichlorobenzylidene)-pyrrolidine-2,3,4-
trione 3-oxime

G2916PCT

PCT/EP00/07101

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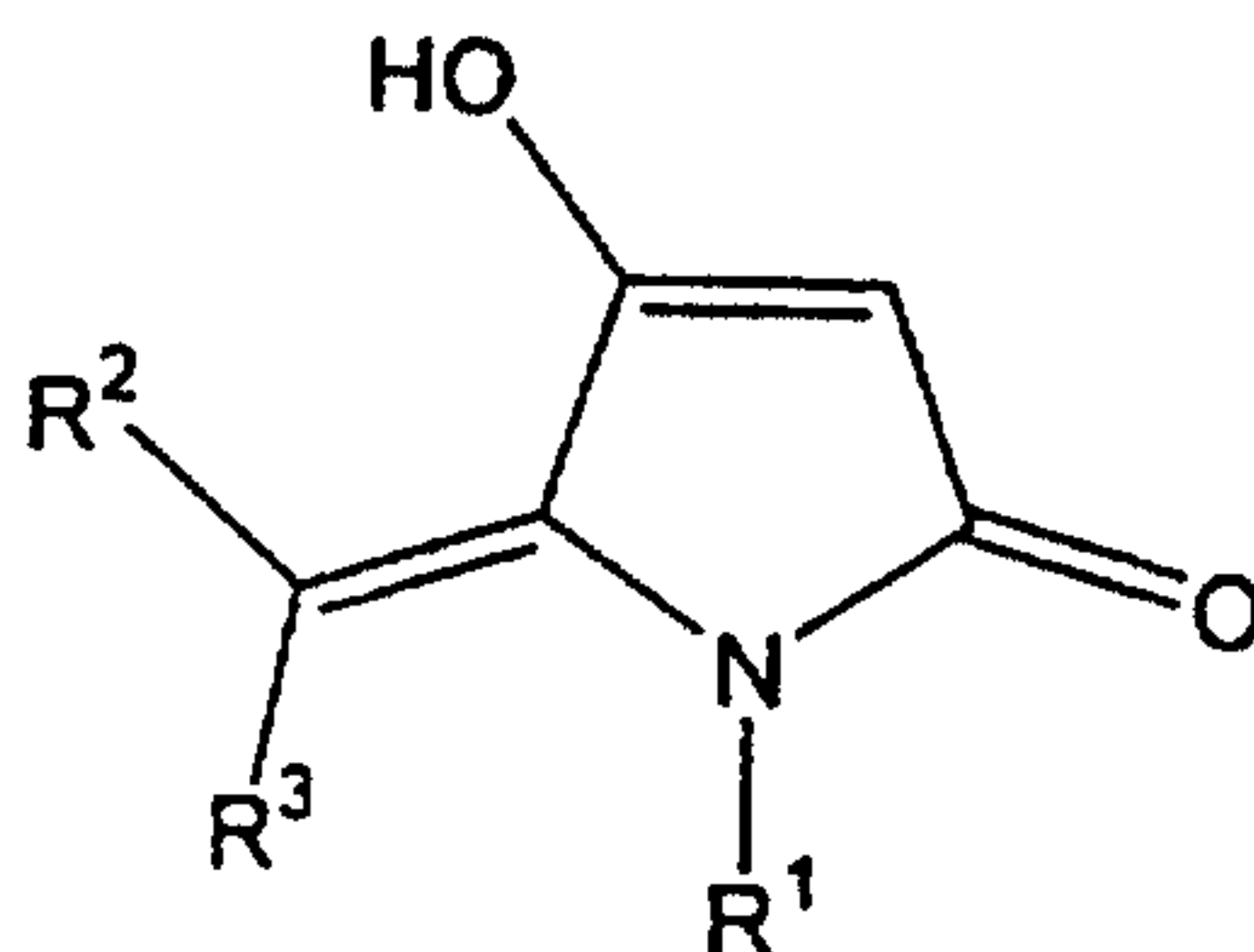
5- (2,4-dichlorobenzylidene) -pyrrolidine-2,3,4-trione 3-oxime

5- (2,6-dichlorobenzylidene) -pyrrolidine-2,3,4-trione 3-oxime

and

5- (3-chlorobenzylidene) -pyrrolidine-2,3,4-trione 3-oxime

12. Process for the preparation of substituted pyrrolidine-2,3,4-trione derivatives of the general formula I according to claim 1, characterized in that tetramic acids of the general formula II



II

wherein the radicals R^1 to R^3 have the meaning according to the general formula I, are reacted with an aqueous solution of sodium nitrite in an ice-cooled solution, to give compounds of the general formula I wherein the ... [sic] R^4 represents OH and the radicals R^1 to R^3 have the meaning according to the general formula I, and these are purified and isolated.

13. Process for the preparation of substituted pyrrolidine-2,3,4-trione derivatives of the general formula I according to claim 1, characterized in that the compounds of the general formula I wherein the radical R^4 represents OH and the radicals R^1 to R^3 have

G2916PCT

PCT/EP00/07101

32

the meaning according to the general formula I are reacted with C₁₋₁₀-alkyl halides in absolute solvents at low temperatures in the presence of strong bases to give compounds of the general formula I wherein the radical R⁴ represents OR⁸ and the radicals R¹ to R³ and R⁸ have the meaning according to the general formula I.

14. Process for the preparation of substituted pyrrolidine-2,3,4-trione derivatives of the general formula I according to claim 1, characterized in that the compounds of the general formula I wherein the radical R⁴ represents OR⁸ and the radicals R¹ to R³ and R⁸ have the meaning according to the general formula I are reacted with acid chlorides of the general formula R⁵-(C=O)-Cl and/or acid bromides of the general formula R⁵-(C=O)-Br or chloroformic acid esters of the general formula Cl-(C=O)-O-R⁵ or fluoroformic acid esters of the general formula F-(C=O)-O-R⁵ or with open-chain carbonates of the general formula R⁵-O-(C=O)-O-R⁵ or with correspondingly substituted cyclic carbonates, wherein in each case the radical R⁵ has the meaning according to the general formula I, in an absolute solvent to give compounds of the general formula I wherein the radical R⁴ represents COR⁵ or COOR⁵ and the radicals R¹ to R³ and R⁵ have the meaning according to the general formula I, and ... [sic] are purified and isolated by conventional processes.

15. Process for the preparation of substituted pyrrolidine-2,3,4-trione derivatives of the general formula I according to claim 1, characterized in that the compounds of the general formula I wherein the radical R⁴ represents OH and the radicals R¹ to R³ have the meaning according to the general formula I are reacted with aliphatic isocyanates or isothiocyanates at low temperatures in aprotic polar solvents to give

G2916PCT

PCT/EP00/07101

33

compounds of the general formula I wherein R^4 represents CONR^6R^7 or CSNR^6R^7 , the radical R^6 or R^7 denotes H and the radicals R^1 to R^3 and R^6 or R^7 have the meaning according to the general formula I, and
5 ... [sic] are purified and isolated by conventional processes.

16. Process according to claim 12, characterized in that the tetramic acids of the general formula II are
10 reacted with an aqueous solution of sodium nitrite in an ice-cooled solution of glacial acetic acid.

17. Process according to claim 12 or 16, characterized in that the compounds of the general formula I wherein
15 the radical R^4 represents OH and the radicals R^1 to R^3 have the meaning according to the general formula I are purified and isolated by recrystallization, preferably by recrystallization from ethanol.

20 18. Process according to claim 13, characterized in that the compounds of the general formula I wherein R^4 represents OH and the radicals R^1 to R^3 have the meaning according to the general formula I are reacted under an inert gas atmosphere.

25 19. Process according to claim 13 or 18, characterized in that the compounds of the general formula I wherein R^4 represents OH and the radicals R^1 to R^3 have the meaning according to the general formula I are reacted
30 in open-chain and/or cyclic ethers.

20. Process according to one of claims 13, 18 or 19, characterized in that the compounds of the general formula I wherein the radical R^4 represents OH and the
35 radicals R^1 to R^3 have the meaning according to the general formula I are reacted in the presence of

G2916PCT

PCT/EP00/07101

34

alkali metal hydroxides and/or alkaline earth metal hydroxides and/or organometallic bases.

21. Process according to one of claims 13 or 18 to 20,
5 characterized in that the compounds of the general formula I wherein the radical R^4 represents OH and the radicals R^1 to R^3 have the meaning according to the general formula I are reacted with C_{1-6} -alkyl halides.
- 10 22 Process according to claim 14, characterized in that the compounds of the general formula I wherein the radical R^4 represents OR^8 and the radicals R^1 to R^3 and R^8 have the meaning according to the general formula I are reacted under an inert gas atmosphere.
- 15 23. Process according to claim 14 or 22, characterized in that the compounds of the general formula I wherein the radical R^4 represents OR^8 and the radicals R^1 to R^3 and R^8 have the meaning according to the general
20 formula I are reacted in open-chain and/or cyclic ethers.
24. Process according to one of claims 14, 22 or 23,
25 characterized in that the cyclic carbonates employed contain 5 or 6 atoms in the ring.
25. Medicaments comprising, as the pharmaceutical active compound, at least substituted pyrrolidine-2,3,4-trione derivative of the general formula I according
30 to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt, and optionally further active compounds and/or auxiliaries.
- 35 26. Medicaments according to claim 25 for treatment/control for/of pain, inflammatory and/or

G2916PCT

PCT/EP00/07101

35

allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses and/or epilepsy.

5

27. Medicaments according to claim 25 for treatment/prophylaxis of/for schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, cerebral ischaemias, cerebral infarctions, psychoses caused by increased amino acid levels, apoplexies, cerebral oedemas, hypoxia, anoxia, AIDS dementia, encephalomyelitis, Tourette's syndrome, perinatal asphyxia or for anxiolysis.
- 10
- 15 28. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for controlling pain.
- 20
29. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of inflammatory reactions.
- 25
30. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of allergic reactions
- 30
- 35 31. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according

G2916PCT

PCT/EP00/07101

36

to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of depressions.

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32. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of drug and/or alcohol abuse.

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33. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of gastritis.

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34. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for the preparation of a medicament [sic] for treatment of diarrhoea.

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35. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for the preparation of a medicament [sic] for treatment of urinary incontinence.

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36. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according

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G2916PCT

PCT/EP00/07101

37

- 5 to claim 1 and/or a corresponding base and/or a
corresponding physiologically tolerated salt for the
preparation of a medicament for the preparation of a
medicament [sic] for treatment of cardiovascular
diseases.
- 10 37. Use of at least one substituted pyrrolidine-2,3,4-
trione derivative of the general formula I according
to claim 1 and/or a corresponding base and/or a
corresponding physiologically tolerated salt for the
preparation of a medicament for treatment of
respiratory tract diseases.
- 15 38. Use of at least one substituted pyrrolidine-2,3,4-
trione derivative of the general formula I according
to claim 1 and/or a corresponding base and/or a
corresponding physiologically tolerated salt for the
preparation of a medicament for treatment of coughing.
- 20 39. Use of at least one substituted pyrrolidine-2,3,4-
trione derivative of the general formula I according
to claim 1 and/or a corresponding base and/or a
corresponding physiologically tolerated salt for the
preparation of a medicament for treatment of mental
25 illnesses.
- 30 40. Use of at least one substituted pyrrolidine-2,3,4-
trione derivative of the general formula I according
to claim 1 and/or a corresponding base and/or a
corresponding physiologically tolerated salt for the
preparation of a medicament for treatment of epilepsy.
- 35 41. Use of at least one substituted pyrrolidine-2,3,4-
trione derivative of the general formula I according
to claim 1 and/or a corresponding base and/or a
corresponding physiologically tolerated salt for the

G2916PCT

PCT/EP00/07101

38

preparation of a medicament for treatment of schizophrenia.

42. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of Alzheimer's disease.
43. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of Huntington's disease.
44. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of Parkinson's disease.
45. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of cerebral ischaemias.
46. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the

G2916PCT

PCT/EP00/07101

39

preparation of a medicament for treatment of cerebral infarctions.

47. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of psychoses caused by increased amino acid levels.
48. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for prophylaxis of apoplexies.
49. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of cerebral oedemas.
50. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of hypoxia.
51. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of anoxia.

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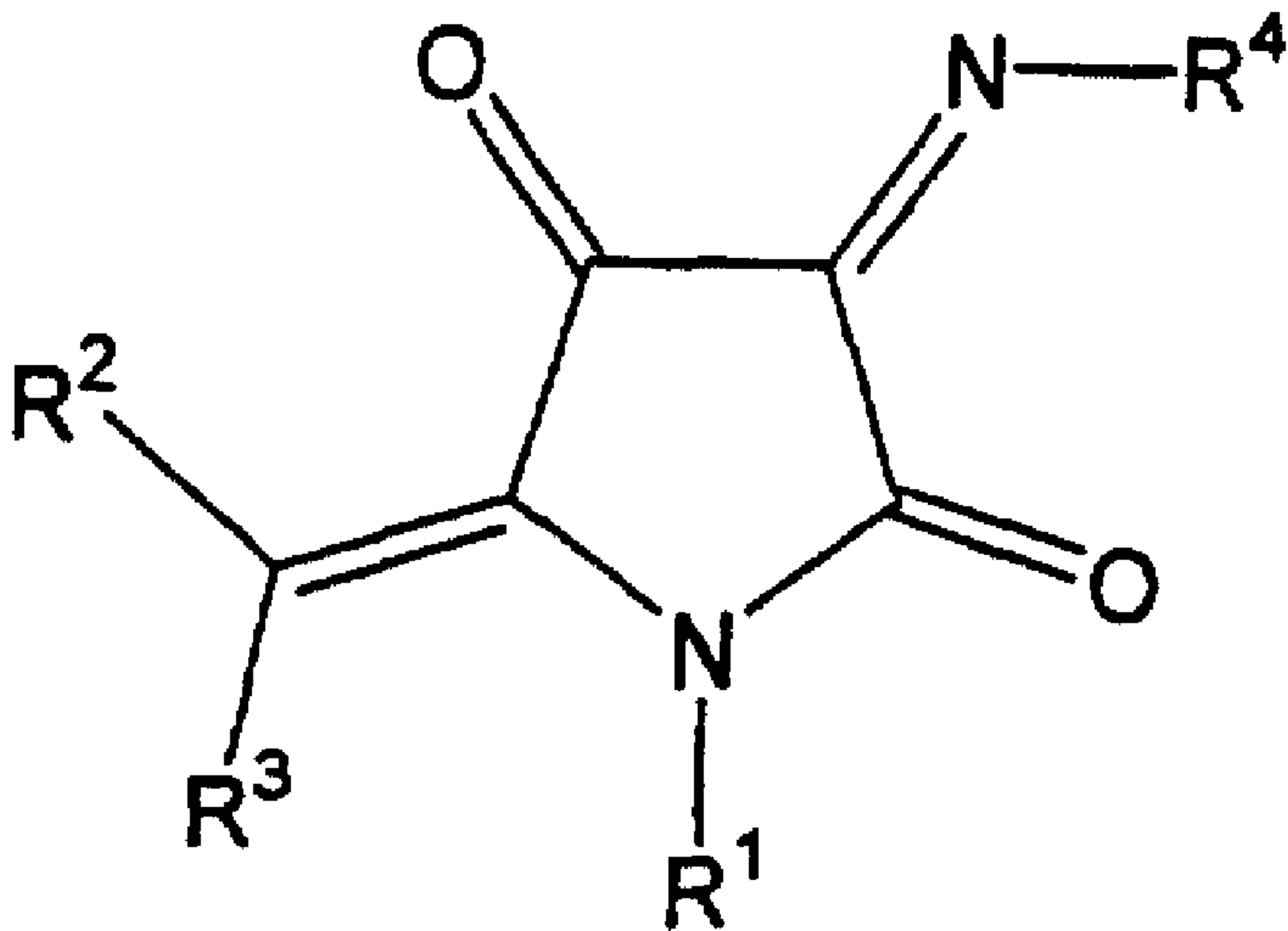
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52. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of AIDS dementia.
53. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of encephalomyelitis.
54. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment in cases of Tourette's syndrome.
55. Use of at least one substituted pyrrolidine-2,3,4-trione derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for treatment of perinatal asphyxia.
56. Use of at least one substituted pyrrolidine-2,3,4-trione 3-oxime derivative of the general formula I according to claim 1 and/or a corresponding base and/or a corresponding physiologically tolerated salt for the preparation of a medicament for anxiolytic treatment.

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