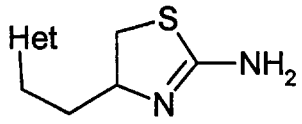
G00002

USE OF 2-AMINO-4-HETEROARYLETHYL-THIAZOLINE DERIVATIVES AS INHIBITORS OF INDUCIBLE NO SYNTHASE

The present invention relates to the use of 2-amino-4-heteroarylethyl-thiazoline derivatives of formula:



159159

(I)

or their pharmaceutically acceptable salts as inhibitors of inducible NO synthase.

The invention provides for the use of 2-amino-4-heteroarylethyl-thiazoline derivatives of formula (I) and their pharmaceutically acceptable salts for preparing pharmaceutical compositions intended for preventing and treating diseases involving abnormal production of nitrogen monoxide (NO) by induction of inducible NO synthase (NOS-2 or iNOS), the pharmaceutical compositions comprising the new 2-amino-4-heteroarylethyl-thiazoline derivatives and their pharmaceutically acceptable salts and the new 2-amino-4-heteroarylethyl-thiazoline derivatives and their pharmaceutically acceptable salts.

Nitrogen monoxide (NO) is a diffusible radical which is involved in numerous physiological and pathological processes. It is synthesized by oxidation of L-arginine, a reaction catalysed by a class of enzymes called nitrogen monoxide synthase or NO synthase (NOS), referenced in the international enzyme nomenclature system under the number E.C. 1.14.13.39.

Three isoforms of NOS, two of which are constitutive and one of which is inducible, are known:

- a neuronal NOS (NOS-1 or nNOS) was originally isolated and cloned from nerve tissue, where it is a constitutive enzyme. NOS-1 produces NO in response to various

physiological stimuli, such as the activation of membrane receptors in accordance with a mechanism dependent on calcium and on calmodulin.

- an inducible NOS (NOS-2 or iNOS) can be induced in response to immunological stimuli such as, for example, cytokines or bacterial antigens in various cells such as, for example, macrophages, endothelial cells, hepatocytes, glial cells, and a large number of other types of cells. The activity of this isoform is not regulated by calcium. Consequently, once induced, it produces large amounts of NO over prolonged periods.

- an endothelial NOS (NOS-3 or eNOS) is constitutive and calcium-calmodulin-dependent. It was originally identified in the cells of the vascular endothelium, where it generates NO in response to physiological stimuli such as the activation of membrane receptors.

The NO produced by the neuronal and endothelial constitutive isoforms (NOS-1 and NOS-3) is generally involved in intercellular signalling functions. For example, the endothelial cells which lie in the inner wall of blood vessels induce the relaxation of the underlying smooth muscle cells *via* the production of NO. It contributes in this way to the regulation of arterial pressure.

The NO produced in large amount by the inducible isoform, NOS-2, is involved *inter alia* in pathological phenomena associated with acute and chronic inflammatory processes in a wide variety of tissue and organs.

Excessive production of NO by induction of NOS-2 therefore plays a part in degenerative pathologies of the nervous system, such as, for example, multiple sclerosis, focal or global cerebral ischaemia, cerebral or spinal trauma, Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, migraine, depression, schizophrenia, anxiety and epilepsy. Likewise, aside from the central nervous system, the induction of NOS-2 is involved in numerous pathologies with inflammatory components, such as, for example, diabetes, atherosclerosis, myocarditis, arthritis, arthrosis, asthma, irritable bowel syndrome, Crohn's disease,

peritonitis, gastro-oesophageal reflux, uveitis, Guillain-Barré syndrome, glomerulonephritis, lupus erythematosus and psoriasis. NOS-2 has also been implicated in the growth of certain forms of tumours, such as, for example, epitheliomas, adenocarcinomas or sarcomas, and in infections by gram-positive or gram-negative intracellular or extracellular bacteria.

In all situations where overproduction of NO is deleterious it therefore appears to be desirable to reduce the production of NO by administering substances capable of inhibiting NOS-2. However, given the important physiological parts played by the constitutive isoform NOS-3, in particular in regulating arterial pressure, it is paramount that the inhibition of the NOS-2 isoform should have the least possible effect on the NOS-3 isoform. This is because it is known that the administration of unselective inhibitors of the NOS isoforms results in vasoconstriction and in an increase in arterial pressure (Moncada, S., Palmer, R.M.J. and Higgs, E.A., Biosynthesis of nitric oxide from L-arginine: a pathway for the regulation of cell function and communication, *Biochem. Pharmacol.*, 1989, 38: 1709-1715). These effects on the cardiovascular system are detrimental in that they reduce the supply of nutrients to the tissues. Consequently, the present invention relates to compounds whose inhibitory activity on NOS-2 is significantly greater than its inhibitory activity on NOS-3.

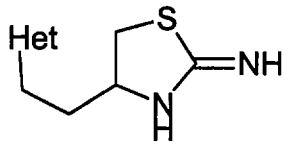
Thiazoline-derived NOS inhibitors are described in particular in patent applications WO94/12165, WO95/11231 and WO96/14842.

The present invention relates to the use of 2-amino-4-heteroarylethyl-thiazoline derivatives of formula (I) in which:

Het represents a 2-thienyl, 3-thienyl, 2-pyrimidyl, 5-pyrimidyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical for preparing medicaments useful for preventing or treating diseases involving abnormal production of nitrogen monoxide (NO) by induction of inducible NO synthase (NOS-2 or iNOS).

The compounds of formula (I) have one or more asymmetric carbons and can therefore be present in racemic form or in the form of enantiomers and of diastereoisomers; these also form part of the invention, along with their mixtures.

Furthermore, the compounds of formula (I) may be present in the tautomeric form (Ia):



(Ia)

These tautomers also form part of the invention.

Among the compounds of formula (I) which are useful according to the invention, mention may be made of the following compounds:

4-(2-pyridin-2-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(2-pyridin-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(2-pyridin-4-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(2-thien-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

their racemic mixtures, enantiomers, diastereoisomers and tautomers, and their pharmaceutically acceptable salts,

and more particularly the following compounds:

(+)-(4R)-4-(2-pyridin-2-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

(+)-(4R)-4-(2-pyridin-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

(+)-(4R)-4-(2-pyridin-4-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

(4R)-4-(2-thien-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

their tautomers and their pharmaceutically acceptable salts.

Among the compounds useful according to the invention and particularly preferred, mention may be made of the following compound:

4-(2-thien-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

its racemic mixture, its enantiomers and tautomers and their pharmaceutically acceptable salts,

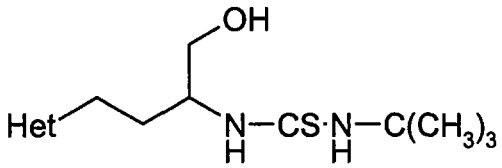
and more particularly the following compound:

(4R)-4-(2-thien-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

its tautomers and its pharmaceutically acceptable salts.

The invention likewise relates to pharmaceutical compositions comprising as active principle a derivative of formula (I) for which Het represents a 2-thienyl, 3-thienyl, 2-pyrimidyl, 5-pyrimidyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical and its racemic mixtures, enantiomers, diastereoisomers and mixtures thereof, its tautomers and its pharmaceutically acceptable salts.

The compounds of formula (I) can be prepared by cyclizing a derivative of formula:

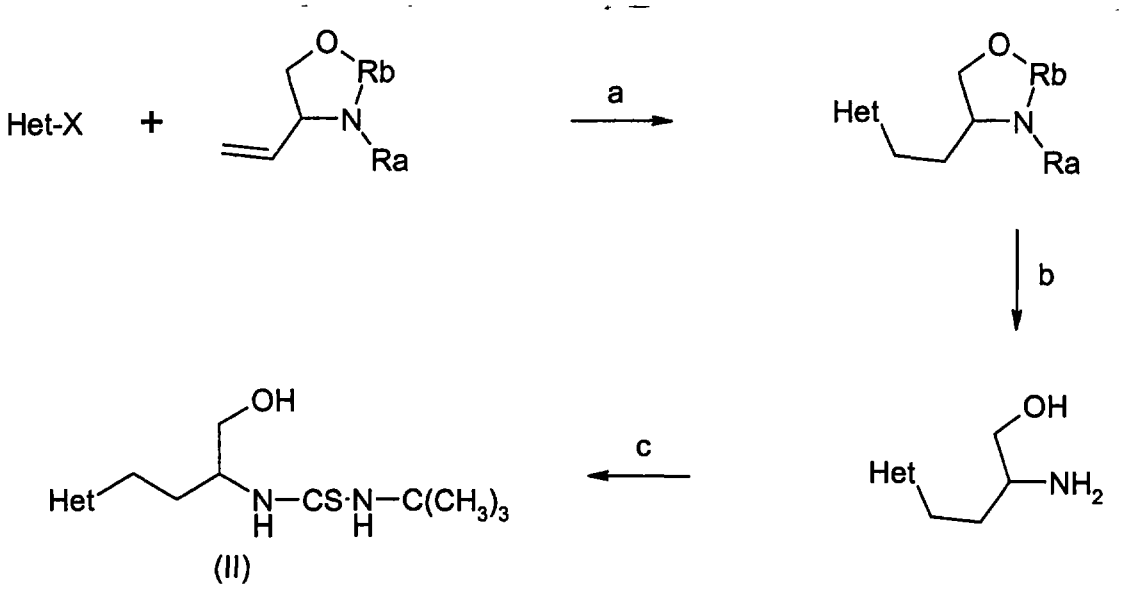


(II)

in which Het has the same meanings as in the formula (I).

This cyclization is generally effected by means of an acid such as hydrochloric acid in an aqueous medium at a temperature in the region of 100°C. 6N hydrochloric acid is generally used.

The derivatives of formula (II) can be obtained in accordance with the following reaction scheme:



(II)

in these formulae, Het has the same meanings as in the formula (I), Ra is a protective group for the amine function, such as those described by T.W. GREENE, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991), and Rb is a protective group for the β-amino alcohol function, such as those described by T.W. GREENE, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991). Preferably the protective group for the amine function is an acetyl or a *tert*-butyloxycarbonyl radical and the protective group for the β-amino alcohol function is an isopropylidene or benzylidene radical. X represents a halogen atom, preferably bromine or iodine, or else a perfluoroalkylsulphonate radical.

The reaction a is generally effected in the presence of a boron derivative such as 9-borabicyclononane or disiamylborane in an aromatic solvent such as toluene or else an ethereal solvent such as THF at a temperature between 10°C and the boiling temperature of the reaction mixture. Then the reaction mixture is admixed with an aqueous solution of an alkali metal hydroxide such as sodium or potassium hydroxide, followed by a transition metal complex such as palladium tetrakistriphenylphosphine or else palladium dichloride diphenylphosphinoferrocenyl,

followed by HetX. The resulting mixture is heated to the boiling temperature of the reaction mixture.

The deprotection reaction b is effected with a deprotection agent for the compounds for which Ra is a protective group for the amine function and Rb is a protective group for the β-amino alcohol function by all methods known to the person skilled in the art and in particular those described by T.W. GREENE, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991). Preferably when the protective group for the amine function is a *tert*-butyloxycarbonyl radical and the protective group for the β-amino alcohol function is an isopropylidene or benzylidene radical, this reaction is effected by means of an acid such as hydrochloric acid in aqueous medium at a temperature in the region of 25°C. 6N hydrochloric acid is generally used. When the protective group for the amine function is an acetyl radical and the protective group for the β-amino alcohol function is an isopropylidene or benzylidene radical, this reaction is effected by means of an acid such as hydrochloric acid in aqueous medium at a temperature close to the boiling point of the reaction mixture. 6N hydrochloric acid is generally used.

The reaction c is effected by the action of *tert*-butyl isothiocyanate in an inert solvent such as an aliphatic (1-4C) alcohol (methanol or ethanol for preference) in the presence of a tertiary amine such as triethylamine at a temperature between 20°C and the boiling temperature of the reaction medium.

The compounds of formula (I) are isolated and can be purified by the usual known methods, for example by crystallization, chromatography or extraction.

The enantiomers of the compounds of formula (I) can be obtained by resolving the racemic mixtures, for example by chromatography on a chiral column in accordance with PIRCKLE W.H. et al., asymmetric synthesis, vol. 1, Academic Press (1983), or by forming salts or by synthesis from chiral precursors. The diastereoisomers can be prepared according to the known conventional methods (crystallization, chromatography, or from chiral precursors).

The compounds of formula (I) can be optionally converted into addition salts with a mineral or organic acid by the action of such an acid in an organic solvent such as an alcohol, a ketone, an ether or a chlorinated solvent. These salts also form part of the invention.

As examples of pharmaceutically acceptable salts mention may be made of the following salts: benzenesulphonate, hydrobromide, hydrochloride, citrate, ethanesulphonate, fumarate, gluconate, iodate, isethionate, maleate, methanesulphonate, methylene-bis-b-oxynaphthoate, nitrate, oxalate, pamoate, phosphate, salicylate, succinate, sulphate, tartrate, theophyllineacetate and p-toluenesulphonate.

The compounds of formula (I) are inhibitors of inducible NO synthase or type-2 NO synthase (NOS-2) and thus are useful for preventing and treating disorders associated with excessive NO production, such as multiple sclerosis, focal or global cerebral ischaemia, cerebral or spinal trauma, Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, migraine, depression, schizophrenia, anxiety, epilepsy, diabetes, atherosclerosis, myocarditis, arthritis, arthrosis, asthma, irritable bowel syndrome, Crohn's disease, peritonitis, gastro-oesophageal reflux, uveitis, Guillain-Barré syndrome, glomerulo-nephritis, lupus erythematosus, psoriasis, the growth of certain forms of tumours, such as, for example, epitheliomas, adenocarcinomas or sarcomas, and infections with gram-positive or gram-negative intracellular or extracellular bacteria.

Their activities as NOS-2 and NOS-3 inhibitors were determined by measuring the conversion of [^{3}H]-L-arginine to [^{3}H]-L-citrulline with, respectively, an NOS-2 enzyme fraction extracted from lungs of rats or mice treated beforehand with lipopolysaccharides (10 mg/kg i.p. 6 hours before tissue harvesting) and with a commercial preparation of bovine recombinant NOS-3. The compounds were incubated at 37°C for 20 to 30 minutes in the presence of 5 μM (for NOS-2 activity) or 10 μM (for NOS-3 activity) of [^{3}H]-L-arginine, 1 mM of NADPH, 15 μM of tetrabiopterin, 1μM of FAD, 0.1 mM of DTT in a HEPES buffer (50 mM, pH 6.7)

containing 10 μg/ml of calmodulin and 1.25 mM of $CaCl_2$ when the NOS-3 activity was measured. Incubation was stopped by adding cold HEPES buffer (100 mM, pH 5.5) containing 10 mM of EGTA and 500 mg of a cationic ion exchange resin (AG50W-X8, counterion: Na^+) to separate the [^{3}H]-L-arginine from the [^{3}H]-L-citrulline. After 5 minutes, during which the phases settled out, the residual radioactivity of the liquid phase was measured in a scintillation counter in the presence of a suitable scintillation liquid. The yield of the recovery of the L-[^{3}H]citrulline formed was able to be estimated using L-[^{14}C-ureido]-citrulline as external standard.

The NOS-2 or NOS-3 activity was expressed in picomole(s) of [^{3}H]-L-citrulline formed per minute per milligram of protein present in the reaction mixture.

In this test on the NOS-2 enzyme, the IC_{50} of the compounds of formula (I) is less than or equal to 10 μM.

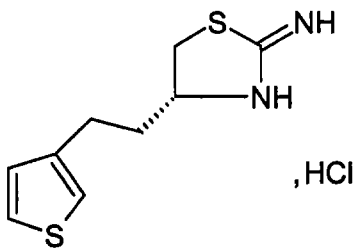
The selectivity is measured by the IC_{50} NOS-3 / IC_{50} NOS-2 ratio. This selectivity is greater than 30.

The compounds of formula (I) are of low toxicity. Administered subcutaneously to mice, their LD_{50} is greater than 40 mg/kg.

The example below illustrates the invention non-limitatively.

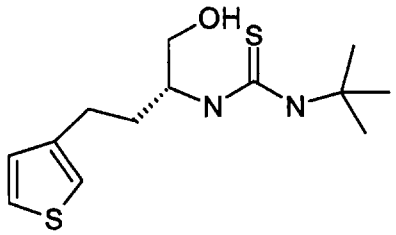
Example 1:

(4R)-4-(2-Thien-3-yl-ethyl)-4,5-dihydro-1,3-thiazol-2-ylamine hydrochloride



A mixture of 0.72 g of *N*-(*tert*-butyl)-*N'*-[(1R)-2-hydroxy-1-(2-thien-3-yl-ethyl)ethyl]-thiourea in 20 cm^3 of 5N aqueous hydrochloric acid solution is heated with magnetic stirring at a temperature in the region of 100°C for 18 hours. The reaction mixture is then evaporated under reduced pressure (2 kPa) at a temperature in the region of 40°C and the residue obtained is taken up in 20 cm^3 of ethanol and concentrated again in accordance with the conditions described above. The evaporation residue is triturated in 5 cm^3 of ethanol, filtered and washed with 2 times 2 cm^3 of ethanol and with 2 times 5 cm^3 of diethyl ether. The product is dried in an oven under vacuum (10 Pa) at a temperature in the region of 20°C. This gives 0.28 g of (4R)-4-(2-thien-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine hydrochloride in the form of a beige solid which melts at approximately 150°C. ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): from 1.85 to 2.10 (mt: 2H); 2.70 (mt: 2H); from 3.30 to 3.45 (mt: 1H); 3.69 (dd, J = 11 and 7.5 Hz: 1H); 4.21 (mt: 1H); 7.05 (dd, J = 5 and 1.5 Hz: 1H); 7.26 (mt: 1H); 7.50 (dd, J = 5 and 3 Hz: 1H); 9.10 (mf: 1H); 9.61 (mf: 1H); 10.27 (broad s: 1H).

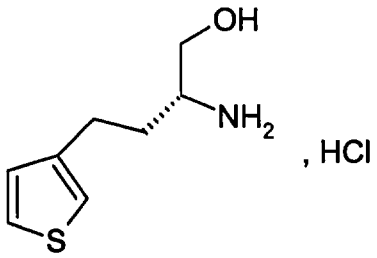
<u>*N*-(*tert*-Butyl)-*N'*-[(1R)-2-hydroxy-1-(2-thien-3-ylethyl)ethyl]-thiourea</u>



A solution of 1.2 g of (2R)-2-amino-4-(3-thienyl)-1-butanol hydrochloride in 40 cm^3 of ethanol admixed with 1.1 cm^3 of *tert*-butyl isothiocyanate and with 1 cm^3 of triethylamine is stirred magnetically under an inert atmosphere at a temperature in the region of 20°C then heated for 20 hours at a temperature in the region of 50°C. The reaction mixture is concentrated under reduced pressure (2 kPa) at a temperature in the region of 50°C. The evaporation residue is purified by chromatography under argon pressure (70 kPa) on a column of silica gel (particle size 60-200 μm; diameter 3.6 cm; height 20 cm), eluting with a cyclohexane-ethyl acetate mixture (60/40 by volume) and collecting fractions of 30 cm^3. The fractions containing the expected

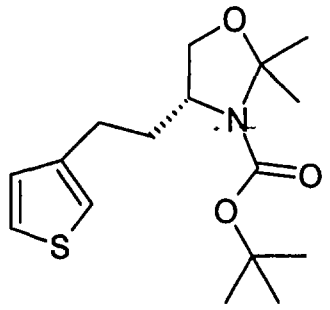
product are combined and evaporated under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 0.73 g of *N*-(*tert*-butyl)-*N'*-[(1R)-2-hydroxy-1-(2-thien-3-ylethyl)ethyl]thiourea in the form of a colourless oil. ^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.42 (s: 9H); from 1.60 to 1.95 (mt: 2H); 2.60 (broad t, J = 8 Hz: 2H); 3.38 (mt: 1H); 3.50 (mt: 1H); 4.26 (unresolved multiplet: 1H); 4.80 (unresolved multiplet: 1H); 7.01 (dd, J = 5 and 1.5 Hz: 1H); from 7.15 to 7.25 (mt: 2H); 7.20 (s: 1H); 7.46 (dd, J = 5 and 3 Hz: 1H).

(2R)-2-Amino-4-(3-thienyl)-1-butanol hydrochloride



A suspension of 1.8 g of *tert*-butyl 2,2-dimethyl-4-(2-thien-3-yl-ethyl)-oxazolidine-3-carboxylate in 5 cm^3 of a 5N aqueous hydrochloric acid solution and 5 cm^3 of dioxane is stirred at a temperature in the region of 20°C for 3 hours. The reaction mixture is then evaporated to dryness under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 1.3 g of (2R)-2-amino-4-(3-thienyl)-1-butanol hydrochloride in the form of a thick oil. ^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): from 1.70 to 1,95 (mt: 2H); 2.70 (broad t, J = 8 Hz: 2H); 3.05 (mt: 1H); 3,50 (dd, J = 11 and 6 Hz: 1H); 3.64 (dd, J = 11 and 4 Hz: 1H); 7.02 (dd, J = 5 and 1.5 Hz: 1H); 7.23 (broad d, J = 3 Hz: 1H); 7.49 (dd, J = 5 and 3 Hz: 1H); 8.02 (unresolved multiplet: 3H).

tert-Butyl (4R)-2,2-dimethyl-4-(2-thien-3-yl-ethyl)-oxazolidine-3-carboxylate



A suspension of 1.5 g of *tert*-butyl (4R)-2,2-dimethyl-4-vinyl-oxazolidine-3-carboxylate in 33 cm^3 of toluene, stirred under an inert atmosphere, is admixed with 26.4 cm^3 of a solution of 9-borabicyclo[3.3.1]nonane. The reaction mixture is heated at a temperature in the region of 70°C for 30 minutes. Heating is withdrawn momentarily for the addition of 5.3 cm^3 of a 5N aqueous solution of sodium hydroxide in 2 cm^3 of water, and after a minute 0.23 g of tetrakis(triphenylphosphine)palladium(0) and 0.81 cm^3 of 3-bromo-thiophene are added. Heating is then continued for 22 hours at a temperature in the region of 90°C. After the reaction mixture has been cooled to a temperature in the region of 20°C, 100 cm^3 of ethyl acetate are added. The organic phase is separated off after settling out, dried over magnesium sulphate, filtered and concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C. The evaporation residue is purified by chromatography (70 kPa) on a column of silica gel (particle size 60-200 μm; diameter 3.6 cm; height 30 cm), eluting with a cyclohexane-ethyl acetate mixture (90/10 by volume) and collecting fractions of 60 cm^3. The fractions containing the expected product are combined and evaporated to dryness under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 1.8 g of *tert*-butyl (4R)-2,2-dimethyl-4-(2-thien-3-yl-ethyl)oxazolidine-3-carboxylate in the form of a yellow oil. ^1H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 373 K, δ in ppm): 1.45 (s: 9H); 1.54 (s: 6H); from 1.75 to 2.10 (mt: 2H); 2.65 (mt: 2H); 3.75 (dd, J = 9 and 2 Hz: 1H); 3.85 (mt: 1H); 3.94 (dd, J = 9 and 6 Hz: 1H); 6.99 (broad d, J = 5 Hz: 1H); 7.14 (mt: 1H); 7.40 (dd, J = 5 and 3 Hz: 1H).

The pharmaceutical compositions according to the invention are composed of a compound of formula (I) or an isomer or a tautomer or a salt of such a compound, in the pure state or in the form of a composition in which it is combined with any other pharmaceutically compatible product, which may be inert or physiologically active. The medicaments according to the invention may be employed orally, parenterally, rectally or topically.

Solid compositions for oral administration which can be used include tablets, pills, powders (gelatin capsules, cachets) or granules. In these compositions the active principal according to the invention is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under a stream of argon. These compositions may also comprise substances other than the diluents, for example one or more lubricants such as magnesium stearate or talc, a dye, a coating (coated tablets) or a varnish.

Liquid compositions for oral administration which can be used include pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or liquid paraffin. These compositions may comprise substances other than the diluents, for example wetting products, sweeteners, thickeners, flavourings or stabilizers.

The sterile compositions for parenteral administration may preferably be aqueous or non-aqueous solutions or suspensions or emulsions. As the solvent or vehicle it is possible to employ water, propylene glycol, a polyethylene glycol, vegetable oils, especially olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents. These compositions may also contain adjuvants, especially wetting agents, isotonicity agents, emulsifiers, dispersants and stabilizers. Sterilization may be effected in a number of ways, for example by aseptic filtration, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other injectable sterile medium.

The compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active product, excipients such as cocoa butter, semi-synthetic glycerides or polyethylene glycols.

The compositions for topical administration may be, for example, creams, lotions, eye drops, mouth washes, nasal drops or aerosols.

In human therapy the compounds according to the invention are particularly useful for treating and/or preventing multiple sclerosis, focal or global cerebral ischaemia, cerebral or spinal trauma, Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, migraine, depression, schizophrenia, anxiety and epilepsy, diabetes, atherosclerosis, myocarditis, arthritis, arthrosis, asthma, irritable bowel syndrome, Crohn's disease, peritonitis, gastro-oesophageal reflux, uveitis, Guillain-Barré syndrome, glomerulo-nephritis, lupus erythematosus, psoriasis, the growth of certain forms of tumours, such as, for example, epitheliomas, adenocarcinomas or sarcomas, and infections by gram-positive or gram-negative intracellular or extracellular bacteria.

The doses depend on the desired effect, on the duration of treatment and on the administration route used; they are generally between 1 mg and 100 mg per day via the oral route for an adult, with unit doses ranging from 0.5 mg to 50 mg of active substance.

Generally speaking, the doctor will determine the appropriate dosage as a function of the age, weight and all the other factors specific to the individual to be treated.

The examples below illustrate compositions according to the invention:

EXAMPLE A

In accordance with the usual technique, gel capsules containing a 50 mg dose of active product and having the following composition are prepared:

- Compound of formula (I) ..... 50 mg

- Cellulose ..... 18 mg
- Lactose ..... 55 mg
- Colloidal silica ..... 1 mg
- Sodium carboxymethylstarch ..... 10 mg
- Talc ..... 10 mg
- Magnesium stearate ..... 1 mg

EXAMPLE B

In accordance with the usual technique, tablets containing a 50 mg dose of active product and having the following composition are prepared:

- Compound of formula (I) ..... 50 mg
- Lactose ..... 104 mg
- Cellulose ..... 40 mg
- Polyvidone ..... 10 mg
- Sodium carboxymethylstarch ..... 22 mg
- Talc ..... 10 mg
- Magnesium stearate ..... 2 mg
- Colloidal silica ..... 2 mg
- Mixture of hydroxymethylcellulose, glycerine and titanium oxide (72-3.5-24.5) q.s. for 1 finished film-coated tablet weighing 245 mg

EXAMPLE C

An injectable solution is prepared which contains 10 mg of active product and has the following composition:

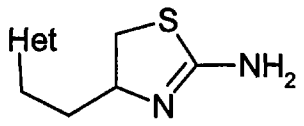
- Compound of formula (I) ..... 10 mg
- Benzoic acid ..... 80 mg
- Benzyl alcohol ..... 0.06 ml
- Sodium benzoate ..... 80 mg
- 95 % ethanol ..... 0.4 ml
- Sodium hydroxide ..... 24 mg
- Propylene glycol ..... 1.6 ml

- Water. ..... q.s. 4 ml

The present invention also relates to the method of preventing and treating diseases involving abnormal production of nitrogen monoxide (NO) by induction of inducible NO synthase (NOS-2 or iNOS) by administering a compound of formula (I), its racemic mixtures, enantiomers, diastereoisomers and mixtures thereof, its tautomer and its pharmaceutically acceptable salts.

CLAIMS

1 Compounds of formula (I)



(I)

in which Het represents a 2-thienyl, 3-thienyl, 2-pyrimidyl, 5-pyrimidyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical

their racemic mixtures, enantiomers, diastereoisomers and mixtures thereof, their tautomers and their pharmaceutically acceptable salts.

2 Compound according to Claim 1 characterized in that it is selected from:

4-(2-pyridin-2-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(2-pyridin-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(2-pyridin-4-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(2-thien-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

their racemic mixtures, enantiomers, diastereoisomers and mixtures thereof, their tautomers and their pharmaceutically acceptable salts.

3 Compound according to any one of Claims 1 to 2 characterized in that it is selected from:

(+)-(4R)-4-(2-pyridin-2-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

(+)-(4R)-4-(2-pyridin-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

(+)-(4R)-4-(2-pyridin-4-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

(4R)-4-(2-thien-3-ylethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

their tautomers and their pharmaceutically acceptable salts.

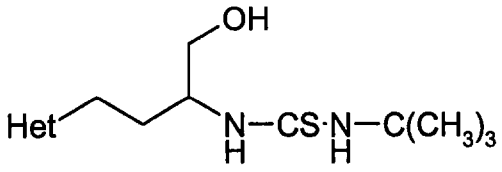
4 Compound according to any one of Claims 1 to 3 used to prepare a medicament.

5 Pharmaceutical composition characterized in that it comprises in a pharmaceutically acceptable medium a compound according to any one of Claims 1 to 3.

6 Medicament according to Claim 4 characterized in that it contains at least one compound according to any one of Claims 1 to 3 for its therapeutic application in the treatment of diseases involving abnormal production of nitrogen monoxide (NO) by induction of inducible NO synthase (NOS-2).

7 Medicament characterized in that it contains at least one compound according to any one of Claims 1 to 3 for its therapeutic application in the treatment of Parkinson's disease.

8 Process for preparing compounds of formula (I) as defined in Claim 1 characterized in that a derivative of formula:



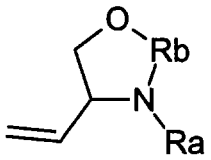
(II)

in which Het has the same meanings as in Claim 1 is cyclized.

9 Preparation process according to Claim 8 characterized in that the cyclization takes place in an acidic medium at a temperature in the region of 100°C.

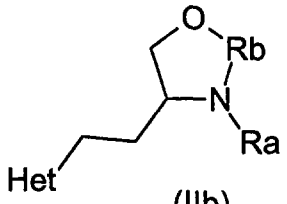
10 Preparation process according to Claim 9 characterized in that the acidic medium is preferably 6N hydrochloric acid

11 Process for preparing compounds of formula (II) as defined in Claim 8 and in which Het has the same meaning as in Claim 1 characterized in that a compound of formula (IIa)



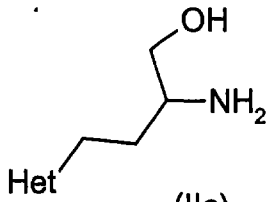
(IIa)

Ra [lacuna] a protective group for the amine formation and Rb is a protective group for the β-amino alcohol function is subjected to the action of a boron derivative and X-Het so as to give a compound of formula (IIb)



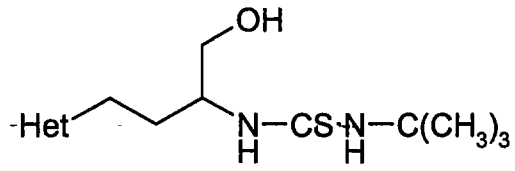
(IIb)

which is subjected to the action of a deprotection agent so as to give a compound of formula (IIc)



(IIc)

which is subjected to the action of *tert*-butyl isothiocyanate so as to give a compound of formula (II)



(II)

12 As intermediates, the compounds *N-(tert*-butyl)-*N'*-[(1R)-2-hydroxyl-1-(2-thien-3-ylethyl)ethyl]thiourea; (2R)-2-amino-4-(3-thienyl)-1-butanol hydrochloride; *tert*-butyl (4R)-2,2-dimethyl-4-(2-thien-3-ylethyl)oxazolidine-3-carboxylate