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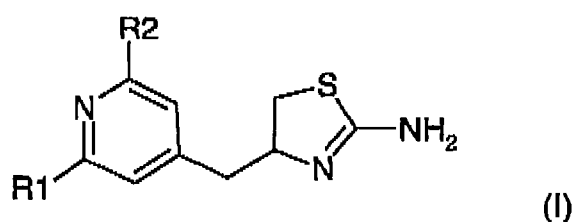


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## USE OF 2-AMINO-4-PYRIDYLMETHYL-THIAZOLINE DERIVATIVES AS INHIBITORS OF INDUCIBLE NO SYNTHASE

5 The present invention relates to the use of 2-amino-4-pyridylmethyl-thiazoline derivatives of formula (I):



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

10 The invention provides for the use of 2-amino-4-pyridylmethyl-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-pyridylmethyl-thiazoline derivatives and their pharmaceutically acceptable salts and the new 2-amino-4-pyridylmethyl-thiazoline derivatives and their  
15 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  
20 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  
5 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  
10 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  
15 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.

20 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-pyridylmethyl-thiazoline derivatives of formula (I) in which:

either R1 and R2 are identical and represent a hydroxyl or (C1-C4)alkyl radical, a  
25 chlorine or a (C1-C4)alkoxy;

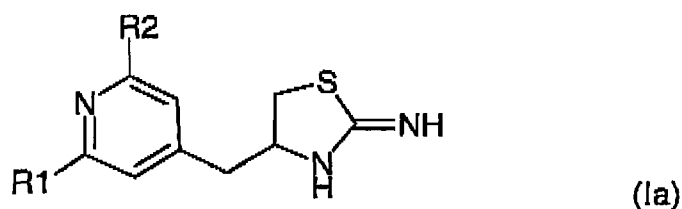
or at least one of the two, R1, R2, is a hydrogen and the other is a (C1-C4)alkyl or (C1-C4)alkoxy radical, a hydroxyl or a chlorine

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).

In the definitions above and below, the (C1-C4)alkyl and (C1-C4)alkoxy radicals  
5 contain 1 to 4 carbon atoms in a straight or branched chain.

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  
10 (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:

15 4-(2-hydroxy-pyridin-4-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

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

4-(2,6-dichloro-pyridin-4-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

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

20 and more particularly the following compounds:

(+)-4-(2-hydroxy-pyridin-4-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

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

4-(2,6-dichloro-pyridin-4-ylmethyl)-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,  
5 mention may be made of the following compound:

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

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

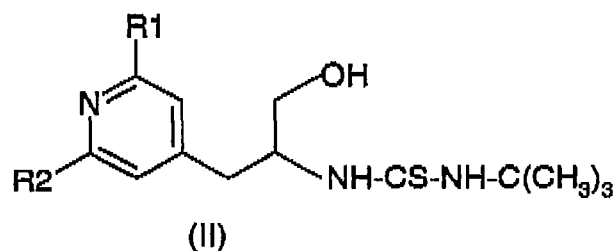
and more particularly the following compound:

10 (+)-4-(2-hydroxy-pyridin-4-ylmethyl)-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 either R<sub>1</sub> and R<sub>2</sub> are identical and represent a hydroxyl or (C<sub>1</sub>-C<sub>4</sub>)alkyl radical, a chlorine or a (C<sub>1</sub>-C<sub>4</sub>)alkoxy; or at  
15 least one of the two, R<sub>1</sub>, R<sub>2</sub>, is a hydrogen and the other is a (C<sub>1</sub>-C<sub>4</sub>)alkyl or (C<sub>1</sub>-C<sub>4</sub>)alkoxy radical, a hydroxyl or a chlorine, and its racemic mixtures, enantiomers, diastereoisomers and mixtures thereof, their tautomers and its pharmaceutically acceptable salts.

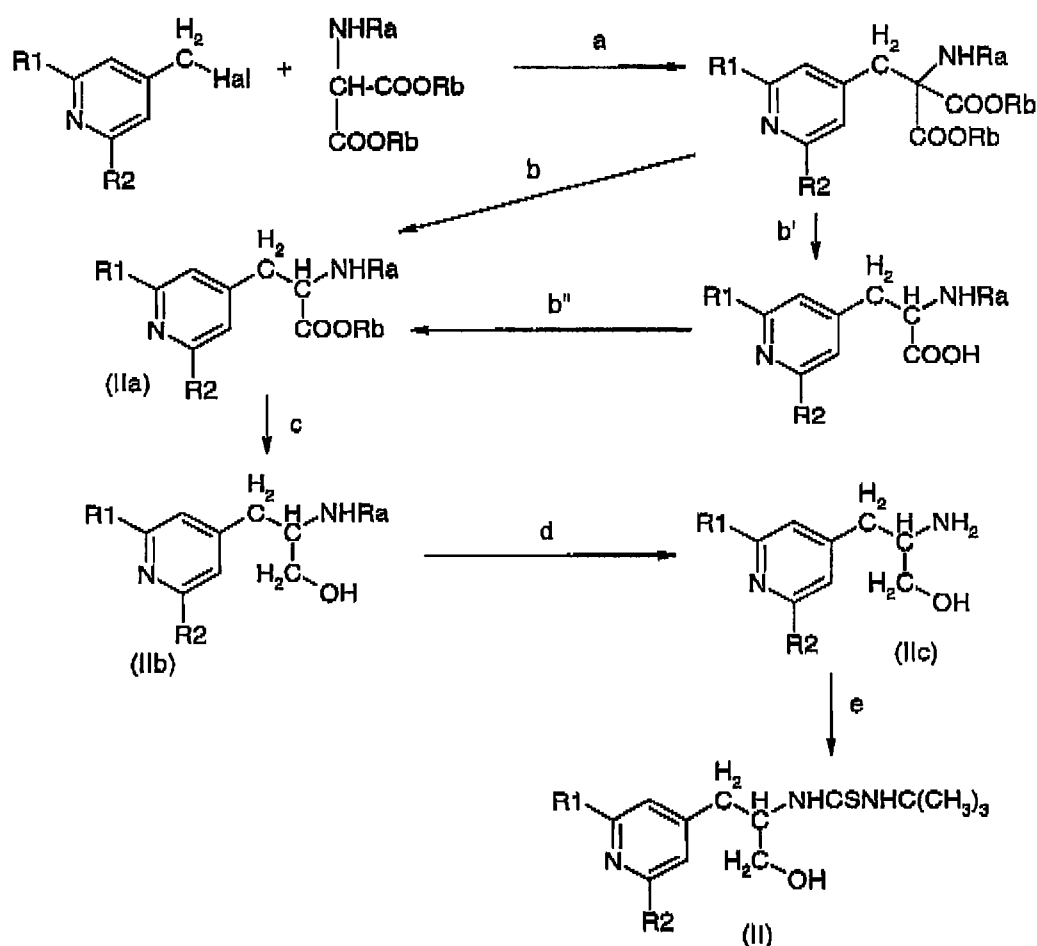
The compounds of formula (I) can be prepared by cyclizing a derivative of formula:



in which  $R_1$  and  $R_2$  have 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  $100^\circ\text{C}$ . Preference is given to using 6N hydrochloric acid.

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



in these formulae,  $R_a$  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), preferably an acetyl or *tert*-butoxycarbonyl radical,  $R_b$  is a (1-4C)alkyl or alkoxycarbonyl radical, preferably methyl, ethyl or

isobutyloxycarbonyl, and Hal is a halogen atom, preferably chlorine, bromine or iodine.

The reaction a is generally effected in the presence of sodium (1-4C)alkoxide (preferably sodium ethoxide) in the corresponding alcohol at a temperature between  
5 10°C and the boiling temperature of the reaction mixture.

The reaction b is generally effected in an inert solvent such as dimethylformamide in the presence of lithium iodide at a temperature of between 100°C and the boiling temperature of the reaction mixture or else in an aliphatic (1-4C) alcohol, in the presence of sodium hydroxide, at a temperature of 10 to 30°C followed by  
10 neutralization with aqueous HCl (preferably 6N to 12N) with subsequent heating in a solvent such as dioxane or an aliphatic (1-4C) alcohol at the boiling temperature of the reaction mixture.

The reaction b' is preferably effected by means of 12N hydrochloric acid at a temperature in the region of 100°C.

15 Reaction b'' for the derivatives for which Rb is an alkyl radical is generally effected by the action of an aliphatic (1-4C) alcohol (methanol or ethanol for preference) in the presence of a mineral acid such as sulphuric acid at a temperature between 50°C and the boiling temperature of the reaction mixture. For the derivatives for which Rb is an isobutyloxycarbonyl radical this reaction is generally effected by the action of  
20 isobutyl chloroformate in the presence of a base such as triethylamine in an inert solvent such as tetrahydrofuran at a temperature between -20°C and 0°C.

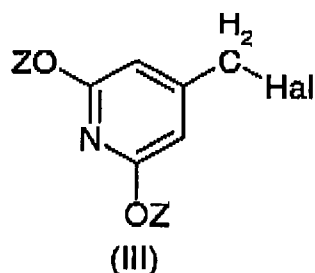
Compound IIa is converted to IIb by the action of a reducing agent. The reduction reaction c is effected preferably by means of a hydride such as sodium borohydride or lithium aluminium hydride in an aliphatic (1-4C) alcohol or tetrahydrofuran at a  
25 temperature between 10°C and 30°C.

The compound IIb is converted to IIc by the action of a deprotection agent. The deprotection reaction d for the compounds for which Ra is a protective group for the

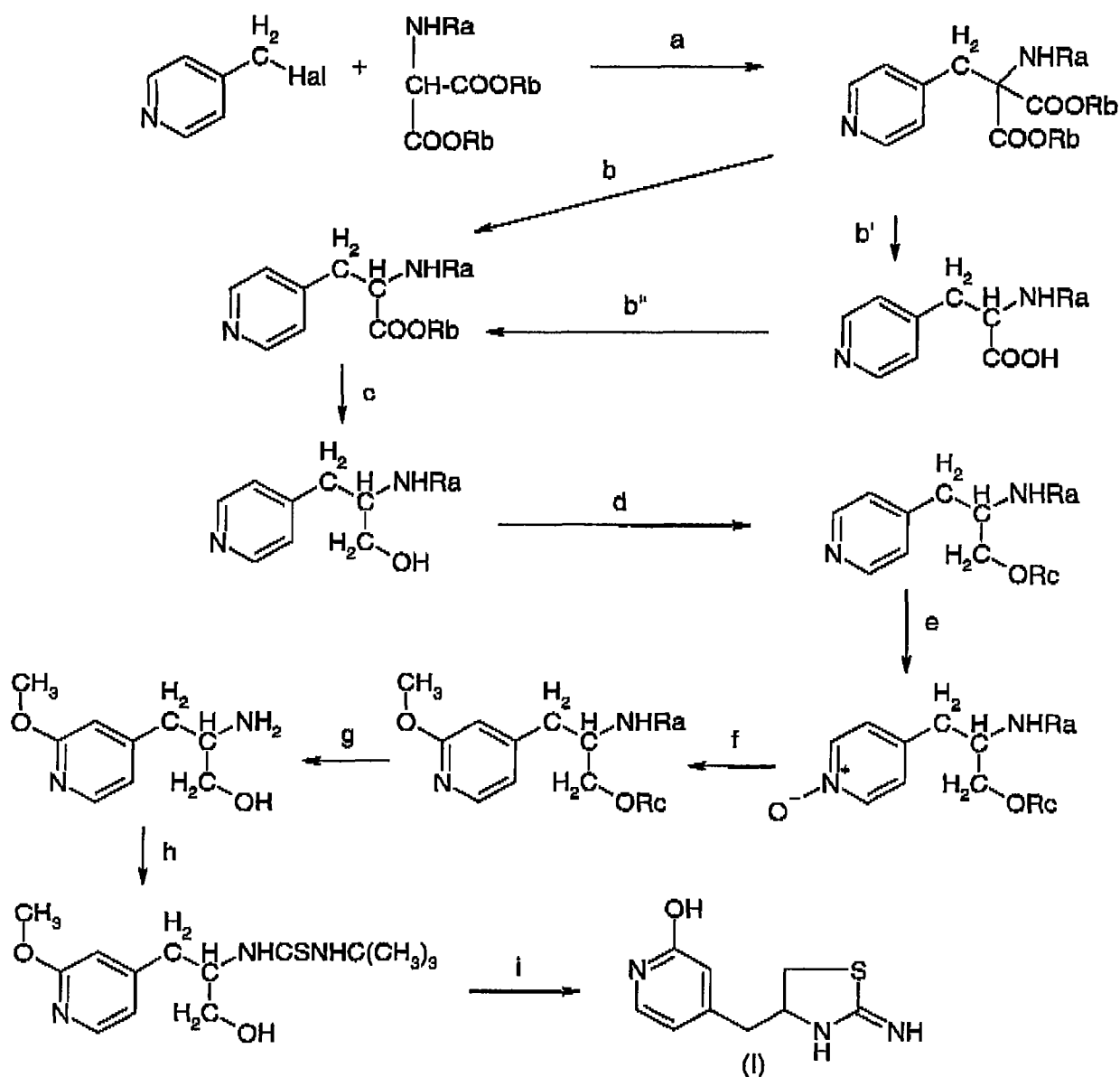
amine function is effected by any deprotection method known to the person skilled in the art, and in particular those described by T.W. GREENE, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991). Preferably, when the protective group is an acetyl radical, this reaction is effected by means of aqueous hydrochloric acid at a temperature in the region of 100°C. When the protective group is a *tert*-butoxycarbonyl radical this reaction is effected by means of hydrochloric acid in dioxane, at a temperature in the region of 20°C.

The reaction e 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), optionally in the presence of a tertiary amine such as triethylamine at a temperature between 20°C and the boiling temperature of the reaction mixture.

The compound of formula (II) for which R<sub>1</sub> and R<sub>2</sub> are OH can be prepared in the same way from compounds of formula (III) for which Z is a silyl radical, preferably *tert*-butyldimethylsilyl, whose preparation is described in Synthesis 1994, 486 and Tetrahedron 1986, 42, 2725.



The compound of formula (I) for which R<sub>1</sub> is OH and R<sub>2</sub> is hydrogen can be prepared in accordance with the following reaction scheme:



- in these formulae 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), preferably an acetyl or *tert*-butoxycarbonyl radical, and Rb is a (1-4C) alkyl or an alkoxycarbonyl radical, preferably methyl, ethyl or isobutyloxycarbonyl. Rc is a protective group of the alcohol function such as those described by T.W. GREENE, Protective groups in Organic Synthesis, J. Wiley-
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Interscience Publication (1991), preferably a silyl radical and more particularly *tert*-butyldimethylsilyl.

The reaction a is effected generally in the presence of sodium (1-4C) alkoxide (preferably sodium ethoxide) in the corresponding alcohol at a temperature between  
5 10°C and the boiling temperature of the reaction mixture.

The reaction b is effected generally in an inert solvent such as dimethylformamide in the presence of lithium iodide at a temperature between 100°C and the boiling temperature of the reaction mixture or else in an aliphatic (1-4C) alcohol in the presence of sodium hydroxide at a temperature of 10 to 30°C followed by  
10 neutralization with 6N HCl with subsequent heating in a solvent such as dioxane or an alcohol such as ethanol at the boiling temperature of the reaction mixture.

The reaction b' is effected preferably by means of 12N hydrochloric acid at a temperature in the region of 100°C.

The reaction b" for the derivatives for which Rb is an alkyl radical is effected  
15 generally by the action of an aliphatic (1-4C) alcohol (methanol or ethanol for preference) in the presence of a mineral acid such as sulphuric acid at a temperature between 50°C and the boiling temperature of the reaction mixture. For the derivatives for which Rb is an isobutyloxycarbonyl radical this reaction is effected generally by the action of isobutyl chloroformate in the presence of a base such as triethylamine in  
20 an inert solvent such as tetrahydrofuran at a temperature between -20°C and 0°C.

The reduction reaction c is effected preferably by means of a hydride such as sodium borohydride or lithium borohydride in an aliphatic (1-4C) alcohol and/or tetrahydrofuran at a temperature between 10°C and 30°C.

The protection reaction d is effected by any method of protecting the alcohol function  
25 such as those described by T.W. GREENE, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991), preferably by means of *tert*-butyldimethylsilyl chloride in the presence of a base such as a tertiary amine (diisopropylethylamine for

preference) in an inert solvent such as dichloromethane at a temperature between 0°C and 30°C.

The reaction e is effected in the presence of 3-chloroperoxybenzoic acid in a solvent such as dichloromethane at a temperature between 0°C and the boiling temperature of the reaction mixture.

The reaction f is effected in the presence of *para*-toluenesulphonyl chloride in the presence of a base such as a tertiary amine (triethylamine for preference) in a solvent such as an alcohol (methanol for preference) at a temperature between 10°C and the boiling temperature of the reaction mixture.

10 The deprotection reaction g for the compounds for which R<sub>a</sub> is a protective group for the amine function and R<sub>c</sub> is a protective group for the alcohol function is effected by any deprotection method 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 R<sub>a</sub> is an acetyl radical and when the protective group R<sub>c</sub> is a silyl radical and more particularly *tert*-butyldimethylsilyl, this reaction is effected by means of aqueous hydrochloric acid (6N HCl for preference) at the boiling temperature of the reaction mixture.

20 The reaction h 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) optionally 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 reaction i is effected generally by means of an acid such as hydrochloric acid in aqueous medium at the boiling temperature, in the region of 100°C, of the reaction mixture. Preference is given to using 6N hydrochloric acid.

25 The compounds of formula (I) for which either R<sub>1</sub> is OAlk and R<sub>2</sub> is hydrogen or R<sub>1</sub> and R<sub>2</sub> are OAlk can be prepared, respectively, from compounds of formula (I) for which either R<sub>1</sub> is OH and R<sub>2</sub> is hydrogen or R<sub>1</sub> and R<sub>2</sub> are OH by alkylation with a

compound of structure Hal-Alk. Hal represents a halogen atom (preferably chlorine, bromine or iodine) and Alk has the same meaning as in the formula (I). This reaction is generally effected in an inert solvent such as dimethylformamide, dimethyl sulphoxide, dioxane or tetrahydrofuran in the presence of an acid acceptor such as a trialkylamine (triethylamine for example), an alkali metal hydroxide (sodium or potassium hydroxide for example) or an alkali metal hydride (sodium hydride for example) at a temperature between 20°C and the boiling temperature of the reaction mixture.

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.
- 10 Their activities as NOS-2 and NOS-3 inhibitors were determined by measuring the conversion of [ $^3\text{H}$ ]-L-arginine to [ $^3\text{H}$ ]-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
- 15 incubated at 37°C for 20 to 30 minutes in the presence of 5  $\mu\text{M}$  (for NOS-2 activity) or 10  $\mu\text{M}$  (for NOS-3 activity) of [ $^3\text{H}$ ]-L-arginine, 1 mM of NADPH, 15  $\mu\text{M}$  of tetrahydropterin, 1  $\mu\text{M}$  of FAD, 0.1 mM of DTT in a HEPES buffer (50 mM, pH 6.7) containing 10  $\mu\text{g/ml}$  of calmodulin and 1.25 mM of  $\text{CaCl}_2$  when the NOS-3 activity was measured. Incubation was stopped by adding cold HEPES buffer (100 mM, pH
- 20 5.5) containing 10 mM of EGTA and 500 mg of a cationic ion exchange resin (AG50W-X8, counterion:  $\text{Na}^+$ ) to separate the [ $^3\text{H}$ ]-L-arginine from the [ $^3\text{H}$ ]-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
- 25 L-[ $^3\text{H}$ ]citrulline formed was able to be estimated using L-[ $^{14}\text{C}$ -ureido]-citrulline as external standard.

The NOS-2 or NOS-3 activity was expressed in picomole(s) of [ $^3\text{H}$ ]-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  $\mu$ M.

The selectivity is measured by the  $IC_{50}$  NOS-3 /  $IC_{50}$  NOS-2 ratio. This selectivity is greater than 45.

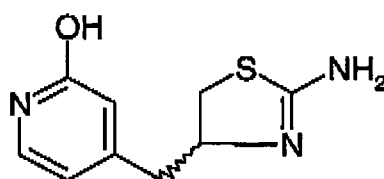
- 5 The compounds of formula (I) are of low toxicity. Administered subcutaneously to mice, their  $LD_{50}$  is greater than 40 mg/kg.

The example below illustrates the invention non-limitatively.

Example 1:

(+)-4-(2-Hydroxy-pyridin-4-ylmethyl)-4,5-dihydro-thiazol-2-ylamine

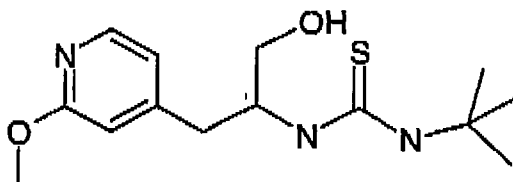
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- A suspension of 0.4 g of *N*-(*tert*-butyl)-*N'*-[2-hydroxy-1-(3-methoxy-pyridin-4-yl-methyl)ethyl]thiourea in 4 cm<sup>3</sup> of 6N aqueous hydrochloric acid solution is heated at a temperature in the region of 100°C for 18 hours. The reaction mixture is subsequently concentrated to dryness under reduced pressure (2 kPa) at a temperature in the region of 40°C. The residue obtained is taken up in 25 cm<sup>3</sup> of distilled water and the mixture is washed with 2 times 20 cm<sup>3</sup> of dichloromethane. The aqueous phase is evaporated under reduced pressure (2 kPa) at a temperature in the region of 40°C. The residue is taken up with 2 times 15 cm<sup>3</sup> of ethanol and concentrated to dryness under the conditions described above, then dried in an oven under reduced pressure (10 Pa) at a temperature in the region of 40°C for 4 hours. This gives 0.31 g of racemic 4-(2-amino-4,5-dihydro-thiazol-4-ylmethyl)-1H-pyridin-2-one hydrochloride, in the form of a pale yellow solid which melts at approximately 124°C. This product is purified by chromatography on a CHIRALCEL OD 20 $\mu$
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- 20
- 25

column in a heptane-ethanol-triethylamine mixture (80/20/0.1 by volume). The fractions containing the expected product are combined and concentrated under reduced pressure (1 kPa) at a temperature in the region of 40°C and then the residue is dried in an oven under reduced pressure (10 Pa) at a temperature in the region of 40°C. This gives 0.0131 g of (+)-4-(2-hydroxy-pyridin-4-ylmethyl)-4,5-dihydro-thiazol-2-ylamine, ( $\alpha_D^{20} = +12.1^\circ \pm 0.7$  in DMSO at 0.5%).  $^1\text{H}$  NMR spectrum (300 MHz,  $(\text{CD}_3)_2\text{SO}-d_6$ ,  $\delta$  in ppm): 2.73 (dd,  $J = 13.5$  and  $7$  Hz: 1H); 2.80 (dd,  $J = 13.5$  and  $7$  Hz: 1H); 3.27 (dd,  $J = 11.5$  and  $5.5$  Hz: 1H); 3.62 (dd,  $J = 11.5$  and  $7.5$  Hz: 1H); 4.53 (mt: 1H); 6.13 (dd,  $J = 6.5$  and  $1.5$  Hz: 1H); 6.24 (broad s: 1H); 7.34 (d,  $J = 6.5$  Hz: 1H); from 8.90 to 9.40 (very extensive unresolved mt: 2H); from 9.60 to 10.40 (very extensive unresolved mt: 1H).

*N*-(*tert*-Butyl)-*N'*-[2-hydroxy-1-(3-methoxy-pyridin-4-yl-methyl)ethyl]-thiourea

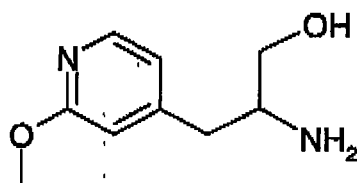


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A solution of 0.3 g of 2-amino-3-(3-methoxy-pyridin-4-yl)-1-propanol in 50 cm<sup>3</sup> of absolute ethanol is admixed with 0.337 cm<sup>3</sup> of *tert*-butyl isothiocyanate and then the reaction mixture is stirred under an inert atmosphere at a temperature in the region of 20°C for 18 hours. Then 0.337 cm<sup>3</sup> of *tert*-butyl isothiocyanate is added again and the reaction mixture is heated at a temperature in the region of 60°C for 4 hours. After cooling, the reaction mixture is concentrated to dryness under reduced pressure (2 kPa) at a temperature in the region of 40°C. The oil obtained is purified by chromatography under argon pressure (50 kPa) on a column of silica gel (particle size 40-63  $\mu\text{m}$ ; diameter 4 cm; height 22 cm), eluting with a dichloromethane-methanol-20% ammonia mixture (90/10/0.5 by volume) and collecting fractions of 10 cm<sup>3</sup>. The fractions containing the expected product are combined and concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 0.4 g of

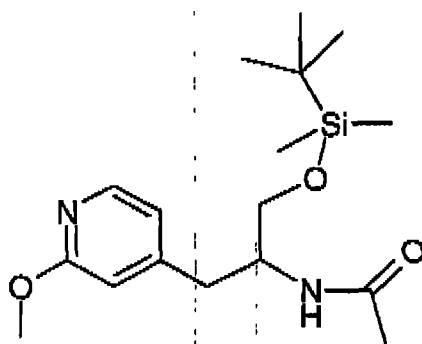
*N*-(*tert*-butyl)-*N'*-[2-hydroxy-1-(3-methoxy-pyridin-4-yl-methyl)ethyl]thiourea in the form of a yellow oil. CH<sub>2</sub>Cl<sub>2</sub> infrared spectrum 3620; 3411; 2972; 1614; 1561; 1532; 1400; 1319; 1161; 1041 and 815 cm<sup>-1</sup>.

5 2-Amino-3-(3-methoxy-pyridin-4-yl)-1-propanol



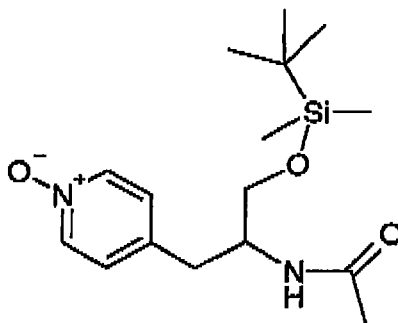
A mixture of 1.2 g of *N*-[1-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-(3-methoxy-pyridin-4-yl)ethyl]acetamide in 60 cm<sup>3</sup> of 6N aqueous hydrochloric acid solution is heated at a temperature in the region of 100°C for 30 minutes. After it has cooled to a temperature in the region of 20°C, a sufficient volume of 30% aqueous sodium hydroxide solution to give a pH close to 10 is run in dropwise. The mixture is extracted with 3 times 100 cm<sup>3</sup> of ethyl acetate and the organic extracts are combined, dried over magnesium sulphate and then concentrated to dryness under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 0.3 g of 2-amino-3-(3-methoxy-pyridin-4-yl)-1-propanol in the form of a yellow-coloured oil. CH<sub>2</sub>Cl<sub>2</sub> infrared spectrum 3628; 3335; 2948; 1614; 1561; 1400; 1319; 1162; 1044 and 815 cm<sup>-1</sup>.

20 *N*-[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-(3-methoxy-pyridin-4-yl)ethyl]-acetamide



- A mixture of 5.12 g of *N*-[1-(*tert*-butyl-dimethyl-silyloxymethyl)-2-(1-oxypyridin-4-yl)ethyl]acetamide in 150 cm<sup>3</sup> of anhydrous methanol is admixed with 6 g of *p*-toluenesulphonyl chloride and then with 8.9 cm<sup>3</sup> of triethylamine. The reaction mixture is heated at a temperature in the region of 60°C for 96 hours and then concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C. The residue is taken up in 200 cm<sup>3</sup> of dichloromethane and washed with 3 times 150 cm<sup>3</sup> of distilled water and with 100 cm<sup>3</sup> of saturated aqueous sodium chloride solution. The organic phase is dried over magnesium sulphate, filtered and then concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C.
- The residue is purified by chromatography under argon pressure (50 kPa) on a column of silica gel (particle size 40-63 µm; diameter 7 cm; height 30 cm), eluting with a dichloromethane-methanol-20% ammonia mixture (95/5/0.5 by volume) and collecting fractions of 10 cm<sup>3</sup>. The fractions containing the expected product are combined and concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 1.24 g of *N*-[1-(*tert*-butyl-dimethyl-silyloxymethyl)-2-(3-methoxy-pyridin-4-yl)ethyl]acetamide, in the form of a yellow oil. CCl<sub>4</sub> infrared spectrum 3446; 2954; 2930; 2858; 1684; 1614; 1562; 1499; 1399; 1255; 1117; 1043 and 837 cm<sup>-1</sup>.

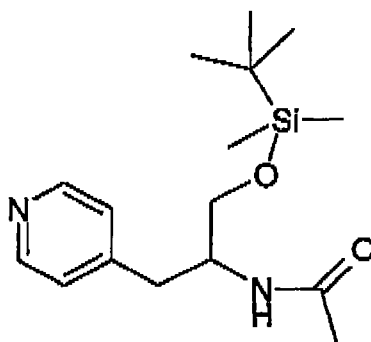
20 *N*-[1-(*tert*-Butyl-dimethyl-silyloxymethyl)-2-(1-oxy-pyridin-4-yl)-ethyl]acetamide



- A mixture of 21 g of *N*-[1-(*tert*-butyl-dimethyl-silyloxymethyl)-2-(pyridin-4-yl)-ethyl]acetamide in 250 cm<sup>3</sup> of dichloromethane, with stirring and under an inert atmosphere, is admixed gradually with 9.4 g of 3-chloroperoxybenzoic acid and then is heated at a temperature in the region of 40°C for 30 minutes. The reaction mixture

is subsequently cooled and then washed with 3 times 200 cm<sup>3</sup> of saturated sodium hydrogencarbonate solution and then with 150 cm<sup>3</sup> of distilled water. The organic phase is dried over magnesium sulphate and then concentrated to dryness under reduced pressure (2 kPa) at a temperature in the region of 40°C. The oil obtained is purified by chromatography under argon pressure (50 kPa) on a column of silica gel (particle size 40-63 µm; diameter 7 cm; height 37 cm), eluting with successive dichloromethane-methanol-20% ammonia mixtures (97/3/0.5, 95/5/0.5, 90/10/0.5 by volume) and collecting fractions of 50 cm<sup>3</sup>. The fractions containing the expected product are combined and concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 4.5 g of *N*-[1-(*tert*-butyldimethyl-silyloxymethyl)-2-(1-oxy-pyridin-4-yl)ethyl]acetamide in the form of a yellow oil. <sup>1</sup>H NMR spectrum (300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO d<sub>6</sub>, δ in ppm): 0.07 (s: 6H); 0.90 (s: 9H); 1.65 (s: 3H); 2.57 (dd, J = 13.5 and 9.5 Hz: 1H); 2.85 (dd, J = 13.5 and 4.5 Hz: 1H); from 3.40 to 3.60 (mt: 2H); 3.96 (mt: 1H); 7.22 (d, J = 7 Hz: 2H); 7.73 (d, J = 8 Hz: 1H); 8.12 (d, J = 7 Hz: 2H).

*N*-[1-(*tert*-Butyl-dimethyl-silyloxymethyl)-2-(pyridin-4-yl)ethyl]acetamide

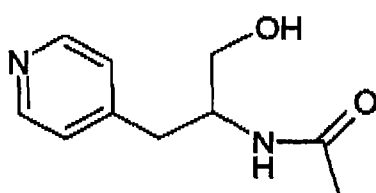


A suspension of 25 g of *N*-(1-hydroxymethyl-2-(pyridin-4-yl)ethyl)acetamide in 700 cm<sup>3</sup> of dichloromethane, with stirring, is admixed with 87 g of *tert*-butyldimethylsilyl chloride and then 112 cm<sup>3</sup> of diisopropylethylamine are run in dropwise. The reaction mixture is stirred for 24 hours at a temperature in the region of 20°C, and then distilled water is run in. The organic phase is separated by settling and then washed with 3 times 250 cm<sup>3</sup> of distilled water and with 200 cm<sup>3</sup> of saturated aqueous sodium chloride solution. It is subsequently dried over magnesium sulphate,

filtered and concentrated to dryness under reduced pressure (2 kPa) at a temperature in the region of 40°C. The oil obtained is purified by chromatography under argon pressure (50 kPa) on a column of silica gel (particle size 40-63  $\mu\text{m}$ ; diameter 11 cm; height 40 cm), eluting with a dichloromethane-methanol-20% ammonia mixture (95/15/0.5 by volume) and collecting fractions of 100  $\text{cm}^3$ . The fractions containing the expected product are combined and concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 21 g of *N*-[1-(*tert*-butyl-dimethyl-silyloxymethyl)-2-(pyridin-4-yl)ethyl]acetamide in the form of a white solid. Mass spectrum DCI  $m/z=309 \text{ MH}^+$

10

*N*-(1-Hydroxymethyl-2-(pyridin-4-yl)ethyl)acetamide

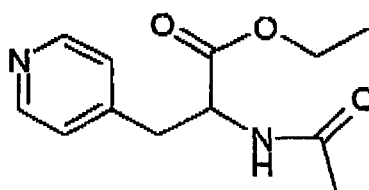


A solution of 21.5 g of ethyl 2-(acetylamino)-3-(4-pyridinyl)propanoate in 800  $\text{cm}^3$  of anhydrous methanol, with stirring and under an inert atmosphere, is admixed gradually with 8.7 g of sodium borohydride, during which the temperature is kept below 30°C. The reaction mixture is stirred at a temperature in the region of 20°C for 24 hours and then is subsequently concentrated under reduced pressure (2 kPa) at a temperature in the region of 30°C. The residue is taken up in 450  $\text{cm}^3$  of water and extracted with 4 times 150  $\text{cm}^3$  of dichloromethane. The aqueous phase is concentrated under reduced pressure (2 kPa) at a temperature in the region of 50°C. The residue is purified by chromatography under argon pressure (50 kPa) on a column of silica gel (particle size 40-63  $\mu\text{m}$ ; diameter 7.5 cm; height 40 cm), eluting with a dichloromethane-methanol-20% ammonia mixture (90/10/0.5 by volume) and collecting fractions of 50  $\text{cm}^3$ . The fractions containing the expected product are combined and concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 2.6 g of *N*-(1-hydroxymethyl-2-(pyridin-4-

yl)ethyl)acetamide in the form of an oil, which solidifies. IR spectrum (KBr) 3279; 3200; 2865; 1647; 1609; 1560; 1374; 1080; 1057; 1005; 907; 806; 566 and 517  $\text{cm}^{-1}$ .

Ethyl 2-(acetylamino)-3-(4-pyridinyl)propanoate

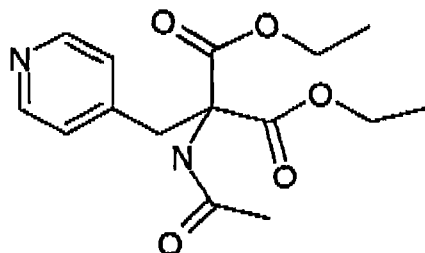
5



A solution of 49.4 g of diethyl 2-(acetylamino)-2-(4-pyridinylmethyl)malonate in 600  $\text{cm}^3$  of absolute ethanol is admixed dropwise with 51.2  $\text{cm}^3$  of 5N aqueous sodium hydroxide solution. The mixture is stirred for 1 hour at a temperature in the region of 20°C and then 21.3  $\text{cm}^3$  of 12N aqueous hydrochloric acid solution are run in dropwise and the reaction mixture is heated at a temperature in the region of 70°C for 5 hours. After it has been cooled to a temperature in the region of 20°C, the reaction mixture is concentrated under reduced pressure (2 kPa) at a temperature in the region of 50°C. The residue is taken up in 200  $\text{cm}^3$  of cold ethanol and the precipitate obtained is washed with 2 times 30  $\text{cm}^3$  of cold ethanol. The filtrate is evaporated under the conditions described above. This operation is carried out a number of times in order to remove the sodium chloride from the reaction mixture. This gives 43,1 g of ethyl 2-(acetylamino)-3-(4-pyridinyl)propanoate in the form of an orange-yellow oil. Mass spectrum EI  $m/z=236$   $\text{M}^+$   $m/z=178$   $\text{M} - \text{NHAc}$   $m/z=121$   $\text{C}_7\text{H}_9\text{N}_2^+$   $m/z=93$   $\text{C}_6\text{H}_7\text{N}^+$  base peak  $m/z=43$   $\text{C}_2\text{H}_3\text{O}^+$ .

20

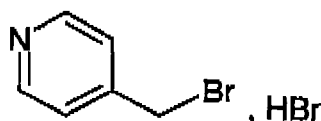
Diethyl 2-(acetylamino)-2-(4-pyridinylmethyl)malonate



750 cm<sup>3</sup> of ethanol are admixed in small portions with 9 g of sodium, with stirring and under an inert atmosphere. After all of the sodium has been consumed and the temperature has returned to a figure in the region of 20°C, 42 g of diethyl acetamidomalonate are added slowly and the mixture is then left with stirring at a temperature in the region of 20°C for 1 hour 30 minutes. A suspension of 61.5 g of 4-bromomethylpyridine hydrobromide in 250 cm<sup>3</sup> of ethanol is subsequently run in rapidly and the resulting suspension is stirred at a temperature in the region of 20°C for 18 hours. The reaction mixture is subsequently concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C. The residue is taken up in 200 cm<sup>3</sup> of distilled water and is neutralized with 1N aqueous hydrochloric acid solution until the pH is equal to 7. The suspension obtained is cooled to a temperature in the region of 0°C and filtered and the insoluble product is washed with 2 times 50 cm<sup>3</sup> of ice-water, isolated with suction and then dried in an oven under reduced pressure (10 Pa) at a temperature in the region of 40°C for 18 hours. This gives 49.4 g of diethyl 2-(acetylamino)-2-(4-pyridinylmethyl)malonate in the form of a pinky-white solid.

CH<sub>2</sub>Cl<sub>2</sub> infrared spectrum 3409; 2895; 1741; 1681; 1603; 1496; 1302; 1198; 1057; 855; 557 and 524 cm<sup>-1</sup>.

20 4-Bromoethylpyridine hydrobromide



A suspension of 140 g of triphenylphosphine bromide in 750 cm<sup>3</sup> of dichloromethane, with stirring and under an inert atmosphere, is admixed dropwise with a solution of 30 g of 4-pyridylcarbinol in 250 cm<sup>3</sup> of dichloromethane, the temperature being kept at less than 27°C. The reaction mixture is stirred at a temperature in the region of 20°C for 4 hours and then the insoluble product obtained is filtered off, rinsed with 100 cm<sup>3</sup> of dichloromethane and isolated with suction. This gives 61.5 g of 4-

bromoethylpyridine hydrobromide in the form of a white solid. Mass spectrum EI  $m/z=171$   $M^+$   $m/z=92$   $C_6H_6N$  base peak  $m/z=65$   $C_5H_5^+$ .

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,  
5 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  
10 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,  
15 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  
20 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 |
| 5  | - Cellulose .....                 | 18 mg |
|    | - Lactose .....                   | 55 mg |
|    | - Colloidal silica .....          | 1 mg  |
|    | - Sodium carboxymethylstarch..... | 10 mg |
|    | - Talc .....                      | 10 mg |
| 10 | - 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  |
| 15 | - Lactose .....                                                                                                                           | 104 mg |
|    | - Cellulose .....                                                                                                                         | 40 mg  |
|    | - Polyvidone .....                                                                                                                        | 10 mg  |
|    | - Sodium carboxymethylstarch.....                                                                                                         | 22 mg  |
|    | - Talc .....                                                                                                                              | 10 mg  |
| 20 | - Magnesium stearate .....                                                                                                                | 2 mg   |
|    | - Colloidal silica .....                                                                                                                  | 2 mg   |
|    | - Mixture of hydroxymethylcellulose, glycerine and titanium oxide<br>(72-3.5-24.5) q.s. for 1 finished film-coated tablet weighing 245 mg |        |

**EXAMPLE C**

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

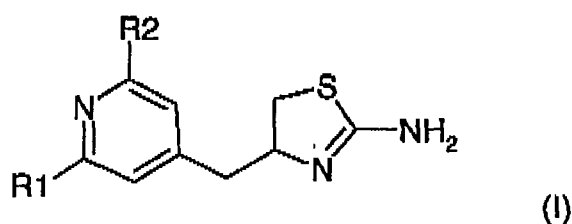
|  |                                |       |
|--|--------------------------------|-------|
|  | - Compound of formula (I)..... | 10 mg |
|--|--------------------------------|-------|

|   |                          |         |
|---|--------------------------|---------|
|   | - Benzoic acid.....      | 80 mg   |
|   | - Benzyl alcohol .....   | 0.06 ml |
|   | - Sodium benzoate.....   | 80 mg   |
|   | - 95 % ethanol .....     | 0.4 ml  |
| 5 | - 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)



in which

5 either R1 and R2 are identical and represent a hydroxyl or (C1-C4)alkyl radical, a chlorine or a (C1-C4)alkoxy;

or at least one of the two, R1, R2, is a hydrogen and the other is a (C1-C4)alkyl or (C1-C4)alkoxy radical, a hydroxyl or a chlorine

10 with the proviso that the (C1-C4)alkyl and (C1-C4)alkoxy radicals contain 1 to 4 carbons in a straight or branched chain

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-hydroxy-pyridin-4-ylmethyl)-4,5-dihydro-thiazol-2-ylamine

15 4-(2-chloro-pyridin-4-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(2,6-dichloro-pyridin-4-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

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

20 3 Compound according to any one of Claims 1 to 2 characterized in that it is selected from:

(+)-4-(2-hydroxy-pyridin-4-ylmethyl)-4,5-dihydro-thiazol-2-ylamine

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

4-(2,6-dichloro-pyridin-4-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

their tautomers and their pharmaceutically acceptable salts.

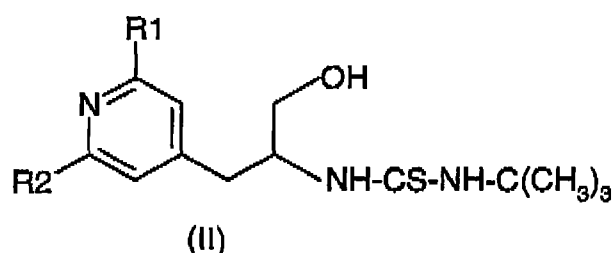
5 4 Compound according to any one of Claims 1 to 3 used to prepare a medicament.

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

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

7 Medicaments according to Claim 4 characterized in that it contains at least one compound defined according to any one of Claims 1 to 3 for its therapeutic application in the treatment of Parkinson's disease.

15 8 Process for preparing compounds of formula (I) as defined in Claim 1 characterized in that a derivative of formula:

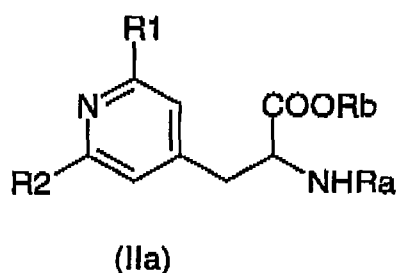


in which R1 and R2 have the same meanings as in Claim 1 is cyclized and is converted optionally into a pharmaceutically acceptable salt.

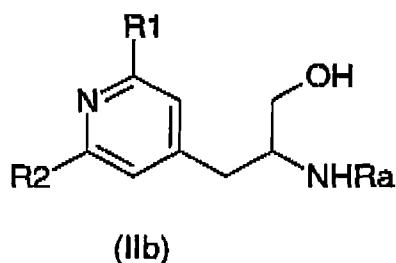
20 9 Preparation process according to Claim 8 characterized in that the cyclization takes place in an acidic medium at a temperature in the region of 100°C.

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 R1 and R2 have the same meaning as in Claim 1 characterized in that a  
5 compound of formula (IIa)

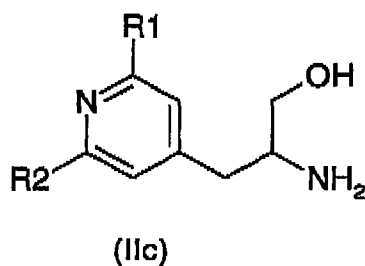


Ra is a protective group for the amine function such as CO<sub>2</sub> tBu or Ac and Rb being either a (1-4C) alkyl radical or an alkoxy carbonyl radical is subjected to the action of a reducing agent so as to give the compound of formula (IIb)

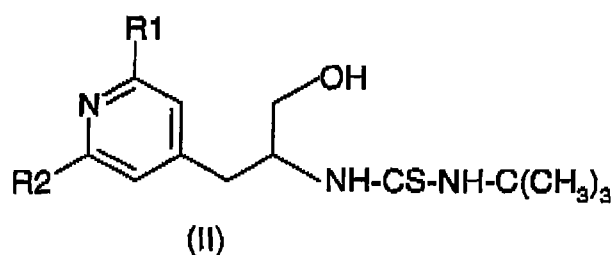


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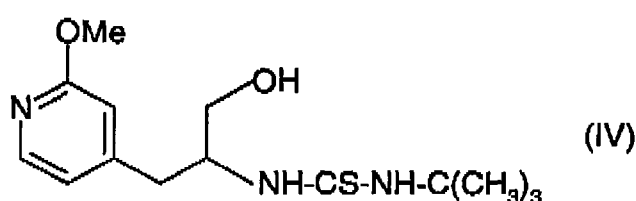
which is subjected to the action of a deprotection agent so as to give a compound of formula (IIc)



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



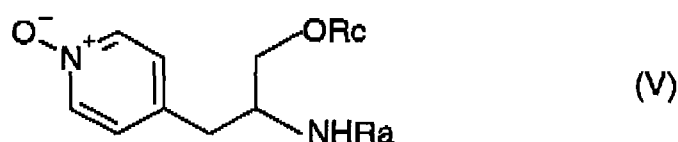
- 12 Process for preparing compounds of formula (I) as defined in Claim 1 for which  
 5 R1 is OH and R2 is H characterized in that a derivative of formula:



is cyclized and is converted optionally into a pharmaceutically acceptable salt.

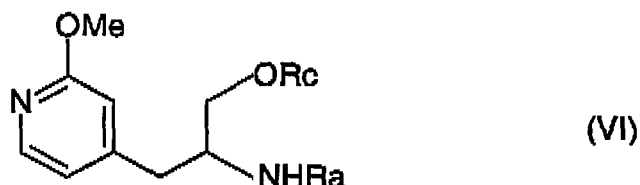
- 13 Preparation process according to Claim 12, characterized in that the cyclization takes place in an acidic medium at a temperature in the region of 100°C.  
 10 14 Preparation process according to Claim 13 characterized in that the acidic medium is preferably 6N hydrochloric acid.

15 Process for preparing compounds of formula (IV) according to Claim 12 characterized in that a compound of formula (V):

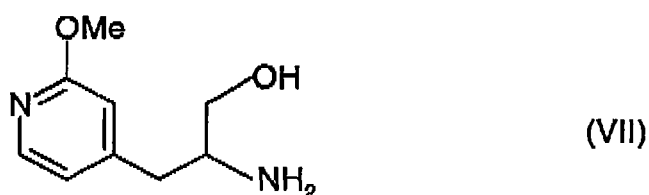


- 15 in which Ra is a protective group for the amine function and Rc is a protective group for the alcohol function such as an acetyl or *tert*-butoxycarbonyl radical for Ra and

such as *tert*-butyldimethylsilyl for R<sub>c</sub>, is subjected to the action of *para*-toluenesulphonyl chloride in the presence of a base in an alcoholic solvent so as to give a compound of formula (VI)



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



which is subjected to the action of *tert*-butyl isothiocyanate so as to give a compound of formula (IV) as defined in Claim 12.

- 10 16 As intermediates, the compounds of formulae IV, V, VI and VII as defined in Claim 15.

17 - As intermediates, the compounds of formulae II, IIa, IIb and IIc as defined in Claim 11 with the exception of ethyl 2-acetylamino-3-(2-ethoxypyridin-4-yl)propionate.

- 15 18 As intermediates, the compounds *N*-(*tert*-butyl)-*N'*-[2-hydroxy-1-(3-methoxypyridin-4-yl-methyl)ethyl]thiourea; 2-amino-3-(3-methoxypyridin-4-yl)-1-propanol; *N*-[1-(*tert*-butyldimethyl-silanyloxymethyl)-2-(3-methoxypyridin-4-yl)ethyl]-acetamide; *N*-[1-(*tert*-butyldimethyl-silanyloxymethyl)-2-(1-oxypyridin-4-yl)ethyl]-acetamide.