

**R(+)-2-AMINO-3-HYDROXYPROPANOIC ACID DERIVATIVES WITH
GLYCINERGIC ACTION**

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OBJECT OF THE INVENTION

The present invention concerns the use of R(+)-2-amino-3-hydroxypropanoic acid derivatives for preparing medicaments for the treatment of Central Nervous System (CNS) diseases due to reduced glycinergic transmission, pharmaceutical compositions comprising new R(+)-2-amino-3-hydroxypropanoic acid derivatives as active principles, as well as new R(+)-2-amino-3-hydroxypropanoic acid derivative compounds.

BACKGROUND OF THE INVENTION

Following the discovery of the glycine binding site coupled to the NMDA receptor at the level of CNS, it has been suggested that a deficiency in glycinergic and/or glutaminergic transmission at the level of the NMDA receptor is one of the causes of diseases that involve cognitive and memory disorders such as autism, children learning disorders, schizophrenia and Alzheimer's disease.

Substances which are capable of enhancing glycinergic transmission are thus able of improving the cognitive disorders and mnestic disorders accompanying these diseases.

PRIOR ART

It is known that glycine is one of the most powerful agonists of the NMDA glycine site receptor and that other D-aminoacids, including D-serine, are very good agonists, but with a weaker affinity than that of glycine. An abstract journal on the subject was published in CNS Drug Reviews, 1995, 1(2), 227-260.

It is also known that the negative and cognitive symptoms of schizophrenia can be treated with glycine or with its precursors or even with glycine reuptake antagonists. In particular, documents US 5,837,730 and US 5,854,286 teach that very high oral doses (> 30 g/day) of glycine or of compounds inducing elevations in CNS glycine level by serving as glycine precursors or which would substitute for glycine at the glycine site of the NMDA complex, lead to an improvement in the negative symptoms in schizophrenic

patients. Among these compounds, the documents mention glycinamide, threonine and D-serine.

US 6,228,875 shows that neuropsychiatric diseases characterized by a deficiency in neurotransmission by NMDA receptor can be alleviated by means of a composition acting as an agonist of the glycine site on NMDA receptor. Among these agonists, said document notably mentions D-serine, D-serine esters, alkylated D-serine or D-serine precursors. The same document describes a double-blind clinical trial in which D-serine, administrated at a dose of 2 g/day, is effective in the treatment of schizophrenia, even in patients having little response to conventional antipsychotic drug treatment. The results of the study described in this document lead to the conclusion that D-serine, which despite having a lower affinity than glycine is clinically active in a dose 15 times weaker than that expected for glycine, is undoubtedly not just a mere glycine substitute.

SUMMARY OF THE INVENTION

Now it has been discovered that D-serine derivatives, namely R(+)-2-amino-3-hydroxypropanoic acid derivatives, evaluated in predictive tests for an improvement in the activity of glycinergic transmission, have proven to be superior to D-serine.

More particularly, it has been found that R(+)-2-amino-3-hydroxypropanoic acid, substituted on nitrogen with a (C₃-C₆)alkenyl, 3-oxo(C₅-C₆)alkyl, 3-oxo(C₄-C₆)alken-2-yl, phenyl(C₁-C₆)alkyl, phenyl(C₂-C₆)alkenyl, gem-diphenyl(C₁-C₆)alkyl, gem-diphenyl(C₂-C₆)alkenyl, (C₁-C₆)alkanoyl, optionally N-substituted 2-aminopropionyl, optionally N,N'-disubstituted 2,6-diamino-*n*-hexanoyl, phenyl(C₁-C₆)alkylidene or gem-diphenyl(C₁-C₆)alkylidene group, notwithstanding its lower content in D-serine, is able to improve the glycinergic transmission in patients suffering from CNS diseases due to reduced glycinergic transmission, particularly patients suffering from autism, schizophrenia or Alzheimer's disease, in much weaker doses than those used for glycine and at the most as high as those used for D-serine.

It has also been found that, among said R(+)-2-amino-3-hydroxypropanoic acid derivatives, optionally esterified R(+)-2-amino-3-hydroxypropanoic acid, N-substituted by an alkyl group having at least one optionally substituted phenyl radical, has a higher in vivo activity than that of D-serine and of its alkylated derivatives.

$$\begin{array}{c} \text{Ra} \\ | \\ \text{Ra}' - \text{N} - \text{C}(\text{OH}) - \text{C}(=\text{O}) - \text{O} - \text{Ra}'' \\ | \\ \text{OH} \end{array} \quad (I)$$

Among the compounds of formula I wherein Ra' is a gem-diphenyl(C₁-C₆)alkyl group, those in which Ra' is a ?-diphenyl(C₂-C₆)alkyl group are particularly advantageous.

The activity of these products has been evaluated in a predictive test for this kind of activity that consists of evaluating animal locomotor activity. It is

carried out on groups of 10 mice having received the testing compounds *per os* (8mg/kg) 15 minutes before the injection of phencyclidine (4mg/kg). The animals are placed in an "open field" divided into 9 equal squares. A camera records their activity during 25 minutes, locomotor activity being expressed as the number of squares crossed per minute.

Among the above-mentioned derivatives, the following known compounds, with the Chemical Abstracts Service registry number (CAS No.) given in brackets,

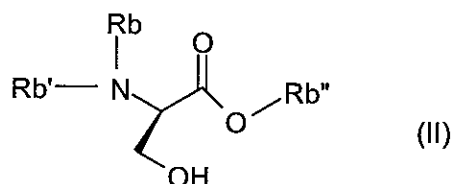
- isopropyl R(+)-2-amino-3-hydroxypropanoate (CAS No. 117426-05-8) and the pharmaceutically acceptable salts thereof, particularly hydrochloride (CAS No. 104055-30-3),
 - benzyl R(+)-2-amino-3-hydroxypropanoate (CAS No. 133099-79-3) and pharmaceutically acceptable salts thereof, particularly hydrochloride (CAS No. 151651-44-4),
 - N-[R(+)-2-aminopropionyl]-R(+)-2-amino-3-hydroxypropanoic acid (CAS No. 61427-68-7), and pharmaceutically acceptable salts thereof,
 - N-[S(-)-2-aminopropionyl]-R(+)-2-amino-3-hydroxypropanoic acid (CAS No. 1115-50-0), and pharmaceutically acceptable salts thereof,
 - N-[2-[S(-)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoic acid (CAS No. 17460-58-1), and pharmaceutically acceptable salts thereof,
 - N-acetyl-R(+)-2-amino-3-hydroxypropanoic acid (CAS No. 152612-69-6), and pharmaceutically acceptable salts thereof,
 - N-benzyl-R(+)-2-amino-3-hydroxypropanoic acid (CAS No. 106910-77-4), and pharmaceutically acceptable salts thereof,
 - ethyl R(+)-N-[(1-methyl-3-oxo)-1-buten-1-yl]-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
 - R(+)-N-(3-phenyl)propyl-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof,
 - ethyl R(+)-N-(3-phenyl)propyl-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
- are particularly advantageous for the intended use.

Compounds of formula I, particularly the above-mentioned specific compounds, are administered to patients in need of an increase of glycinergic transmission at a daily dose which does not exceed 10 g per day and which is advantageously between 200 and 7500 mg and more advantageously between

250 - 5000 mg. The preferred doses, 500 to 3000 mg or 750 to 2000 mg, allow a good improvement of glycinergic transmission and also improve the negative symptoms of schizophrenia, the symptoms of Alzheimer's disease and behavior in cases of autism.

For administration to patients, compounds which are useful as active principles destined to improve glycinergic transmission are included in pharmaceutical compositions formulated in unit dosages containing 10 mg to 1200 mg, advantageously 50 to 1000 mg of active principle.

According to another of its aspects, the present invention provides a pharmaceutical composition comprising, as active principle, a pharmacologically effective dose of a R(+)-2-amino-3-hydroxypropanoic acid derivative of formula II



wherein Rb is a hydrogen, Rb' is a hydrogen, a straight or branched chain (C₃-C₆)alkenyl, 3-oxo(C₄-C₆)alkyl or 3-oxo(C₄-C₆)alken-2-yl group, a phenyl(C₁-C₆)alkyl, phenyl(C₂-C₆)alkenyl, (C₂-C₆)alkanoyl, gem-diphenyl(C₁-C₆)alkyl, gem-diphenyl(C₂-C₆)alkenyl, (C₃-C₆)alkenoyl, N-(C₂-C₆)alkanoyl-R(+)-2-aminopropionyl, N-(C₂-C₆)alkanoyl-S(-)-2-aminopropionyl, N-benzyloxycarbonyl-R(+)-2-aminopropionyl, N-benzyloxycarbonyl-S(-)-2-aminopropionyl, R(+)-2,6-diamino-*n*-hexanoyl, S(-)-2,6-diamino-*n*-hexanoyl, N,N'-bis-(C₂-C₆)alkanoyl-R(+)-2,6-diamino-*n*-hexanoyl, N,N'-(C₂-C₆)alkanoyl-S(-)-2,6-diamino-*n*-hexanoyl, N,N'-bis-benzyloxycarbonyl-R(+)-2,6-diamino-*n*-hexanoyl, N,N'-bis-benzyloxycarbonyl-S(-)-2,6-diamino-*n*-hexanoyl group; or Rb and Rb' are together a phenyl(C₁-C₆)alkylidene or gem-diphenyl(C₁-C₆)alkylidene group; Rb'' is hydrogen, a straight or branched chain (C₁-C₆)alkyl group or a (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, phenyl(C₁-C₂)alkyl, phenacetyl or phenyl group, the phenyl group or groups present in the Rb, Rb' and Rb'' substituents being non-substituted or substituted by a halogen atom or by a hydroxy, (C₁-C₃)alkoxy, cyano, nitro or acetyl group, with the proviso that, when Rb and Rb' are both H, then Rb'' is other than hydrogen, methyl, ethyl or non-substituted benzyl and that, when Rb is hydrogen and Rb' is a non-substituted

benzyl, N-benzyloxycarbonyl-S(-)-2-aminopropionyl, R(+)-2-aminopropionyl or S(-)-2-aminopropionyl, then Rb" is different to hydrogen; or of a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier.

5 Among the compounds of formula II where Rb' is a gem-diphenyl(C₁-C₆)alkyl group, those in which Rb' is a ?-diphenyl(C₂-C₆)alkyl group, are particularly advantageous.

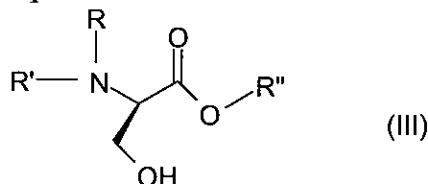
 Among the above-mentioned active principles of formula II,

- 2-oxo-2-phenylethyl R(+)-2-amino-3-hydroxypropanoate and
10 pharmaceutically acceptable salts thereof,
- cyclopropylmethyl R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
- 4-acetylphenyl R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
- 15 - N-[2-[R(+)-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof,
- N-[2-[S(-)-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoic acid, and pharmaceutically acceptable salts thereof,
- ethyl N-[S(-)-2-aminopropionyl]-R(+)-2-amino-3-hydroxypropanoate and
20 pharmaceutically acceptable salts thereof,
- methyl N-[2-[S(-)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
- ethyl N-[2-[S(-)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
- 25 - N-[2-[R(+)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof,
- methyl N-[2-[R(+)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
- N-[2-[S(-)-N,N'-bis-benzyloxycarbonyl-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof,
- 30 - methyl N-[2-[R(+)-N,N'-bis-benzyloxycarbonyl-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
- methyl N-[2-[S(-)-N,N'-bis-benzyloxycarbonyl-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
- 35 - ethyl N-[2-[R(+)-N,N'-bis-benzyloxycarbonyl-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,

- ethyl N-benzyl-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
 - ethyl R(+)-N-[(1-methyl-3-oxo)-1-buten-1-yl]-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
 - 5 - R(+)-N-(3-phenyl)propyl-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof,
 - ethyl R(+)-N-(3-phenyl)propyl-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof,
- are particularly interesting active principles.

10 In said pharmaceutical compositions for oral, sublingual, subcutaneous, intramuscular, transdermal or rectal administration, the active principle can be administrated in the most appropriate dosage unit in admixture with traditional pharmaceutical carriers in animals and humans. Suitable administration unit forms comprise oral forms such as tablets, capsules, powders, granulates and oral
15 solutions or suspensions, sublingual and buccal administration forms or parenteral or rectal administration forms.

According to a further of its aspects, the present invention provides new R(+)-2-amino-3-hydroxypropanoic acid derivatives of formula III



20 wherein R is a hydrogen; R' is a hydrogen, phenyl(C₂-C₆)alkenyl, gem-diphenyl(C₁-C₆)alkyl other than benzhydryl, gem-diphenyl(C₂-C₆)alkenyl; or R and R' are together a phenyl(C₁-C₆)alkylidene or gem-diphenyl(C₁-C₆)alkylidene group; R'' is a hydrogen or a (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, phenyl(C₁-C₂)alkyl, phenacetyl or phenyl group; the phenyl group or groups
25 being non-substituted or substituted by a halogen atom or by a hydroxy, (C₁-C₃)alkoxy, cyano, nitro or acetyl group, with the proviso that, when R and R' are both hydrogens, then R'' is other than hydrogen; and the pharmaceutically acceptable salts thereof.

Among the compounds of formula III in which R' is a gem-diphenyl(C₁-C₆)alkyl group other than benzhydryl, those in which R' is a ?-diphenyl(C₂-C₆)alkyl group are particularly advantageous.

Among the compounds of formula III,

- R(+)-N-(4,4-diphenyl)butyl-2-amino-3-hydroxypropanoic acid and

pharmaceutically acceptable salts thereof,
 - R(+)-N-[(4,4-diphenyl)-3-butenyl]-2-amino-3-hydroxypropanoic acid and
 pharmaceutically acceptable salts thereof, and
 - R(+)-N-[(α -phenyl-(2-hydroxy)benzylidene]-2-amino-3-hydroxypropanoic
 5 acid and pharmaceutically acceptable salts thereof
 are particularly advantageous.

The compounds of the invention, which are N-substitution derivatives of
 the R(+)-2-amino-3-hydroxypropanoic acid or of the esters thereof, and the
 pharmaceutically acceptable salts thereof, are synthesized according to the
 10 traditional preparation methods of amino acid esters or of N-substituted amino
 acid derivatives and of their esters.

R(+)-2-amino-3-hydroxypropanoic acid esters can be obtained by
 reacting a D-serine functional derivative with an esterifying alcohol or phenol or
 by saponification in position 4 of the methyl or ethyl (R)-3-*tert*-butoxycarbonyl-
 15 2,2-dimethyloxazolidine-4-carboxylate, esterification of the (R)-3-*tert*-
 butoxycarbonyl-2,2-dimethyloxazolidine-4-carboxylic acid by reaction of a
 functional derivative thereof with the esterifying alcohol or phenol in the
 presence of a proton acceptor, for example of a tertiary base such as 4-
 dimethylaminopyridine, methylmorpholine, ethylmorpholine or
 20 diisopropylamine, and saponification of *tert*-butyl ester with trifluoroacetic acid
 which concurrently affords the decomposition of the oxazolidine cycle and the
 formation of the desired R(+)-2-amino-3-hydroxypropanoic acid ester in form of
 its trifluoroacetic acid salt which, in its turn, can be neutralized or converted into
 another salt. The esters thus obtained can be transformed into N-substitution
 25 derivatives thereof and into pharmaceutically acceptable salts thereof.

N-monosubstitution can be carried out by reacting the R(+)-2-amino-3-
 hydroxypropanoic acid ester with an halide of formula:

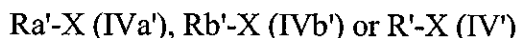


wherein Ra', Rb' and R' have the above stated meanings, in the presence of an
 30 organic tertiary base such as 4-dimethylaminopyridine, 4-methyl- or 4-
 ethylmorpholine, or of an inorganic base such as an alkaline bicarbonate such as
 sodium hydrogen carbonate.

When Ra', Rb' and R' are optionally substituted alcanoyl groups, the
 corresponding acyl halide can be replaced by another functional derivative such
 35 as a mixed anhydride, an active ester or the free acid form, appropriately
 activated for example by dicyclohexylcarbodiimide. If the alcanoyl group is

substituted on the alkyl with an amino group, the latter will be suitably protected by one of the conventional protecting groups of the peptide chemistry, for example by a benzyloxycarbonyl group.

In a similar way, the above halides, when Ra', Rb' or R' are other than an alkanoyl group, can be replaced by a compound of formula



wherein X represents a leaving group such as an alkanesulphonyloxy radical, such as a methanesulphonyloxy, or a benzenesulphonyloxy radical, the latter being non-substituted or substituted on the benzene cycle preferably with a methyl group, such as p-toluenesulphonyloxy.

Compounds of formula I, II or III, wherein Ra or Rb or R is hydrogen and Ra' or Rb' or R' is other than an alkanoyl group, can also be prepared by reductive amination by reacting the aldehyde or ketone corresponding to the compound Ra'-H or Rb'-H or R'-H with D-serine, preferably in the form of one of its esters, in the presence of a reducing agent such as sodium cyanoborohydride. If the ester has a group that is sensitive to reducing agents, for example a ketone, this group is suitably protected as a ketal or enol ether thereof.

The preparation of the compounds of formula I, II or III, wherein Ra and Ra', or Rb and Rb', or, respectively, R and R', together, form a phenyl(C₁-C₆)alkylidene group, is carried out by reacting D-serine or an ester thereof with a phenyl(C₁-C₆)carboxaldehyde under the preparation conditions of Schiff bases. In a similar way, the compounds of formula I, II or III, where Ra and Ra', or Rb and Rb', or R and R', together form a gem-diphenyl(C₁-C₆)alkylidene group, are prepared by reacting D-serine or one of the esters thereof with a benzophenone, if the desired product has the formula I, II or III where Ra and Ra', or Rb and Rb', or R and R' together form a gem-diphenyl(C₁)alkyl (diphenylmethyl) group; or with a gem-diphenyl(C₂-C₆)carboxaldehyde, if the desired product has the formula I, II or III where Ra and Ra', or Rb and Rb', or R and R' together form a gem-diphenyl(C₂-C₆)alkyl group, according to Schiff base preparation conditions.

The word "phenyl" used in the general description above, comprises any phenyl group that can be non-substituted or substituted by a halogen atom or by a hydroxy, (C₁-C₃)alkoxy, cyano, nitro or acetyl group.

When D-serine methyl or ethyl ester is used as starting compound, the N-substituted derivative thus obtained is an intermediate which is saponified in order to prepare a compound of formula I, II or III wherein Ra'', Rb'' or R'' is

hydrogen, whereas the N-substituted derivative thus obtained is the final product when an ester other than the methyl or ethyl ester is used as starting compound.

The R(+)-2-amino-3-hydroxypropanoic acid derivatives can be isolated in the free form or as chemically or pharmaceutically acceptable salts thereof.

5 Considering the amphoteric character of the compounds of the present invention, the salts can be those with mineral or organic bases, for example with sodium hydroxide or trometamol, or with mineral or organic acids such as the hydrochloride or the trifluoroacetate. In the case of the compounds of formula I, chemically or pharmaceutically acceptable salts are included in the invention.

10 The expression "chemically acceptable" refers to salts of formula I compounds that are useful for the isolation or purification of the new products.

The following non-limitative examples illustrate the invention.

EXAMPLE 1

Cyclopropylmethyl 2-(R)-amino-3-hydroxypropanoate hydrochloride

15 Cyclopropylcarbinol (15 ml) is cooled to 0°C and acetyl chloride (1.37 ml) is added. After being subjected to agitation for 10 minutes at 0°C, D-serine (750 mg) is added and the solution is brought to reflux for 2 hours. The reaction mixture is concentrated, recovered with a potassium carbonate saturated solution
20 and extracted with ethyl acetate. The organic phase is dried on MgSO₄, filtered and concentrated. The product is recovered in a minimum of methanol and a hydrochloric acid solution 1N is added in ether. The solvent is vacuum evaporated to obtain the desired product as a brown solid (250 mg). Melting point: 112-118°C.

25 RMN ¹H (CD₃OD) δ 4.07 (m, 5H); 1.18 (m, 1H); 0.64 (m, 2H); 0.37 (m, 2H).

EXAMPLE 2

4-acetylphenyl 2-(R)-amino-3-hydroxypropanoate trifluoroacetate

(a) methyl 3-tert-butoxycarbonyl-2,2-dimethyloxazolidine-4-(R)-carboxylate.

30 The product is prepared according to the method described in the article of P. Garner, J. M. Park, J. Org. Chem. 1987, 52, 2361-2364.

(b) 3-tert-butoxycarbonyl-2,2-dimethyloxazolidine-4-(R)-carboxylic acid.

Methyl 3-tert-butoxycarbonyl-2,2-dimethyloxazolidine-4-(R)-carboxylate (3.0 g) is dissolved in a mixture of tetrahydrofurane (THF)/H₂O (3/1; 30 ml), and
35 LiOH.H₂O (684 mg) is added. After being subjected to agitation for 3 hours at room temperature, the reaction mixture is acidified with citric acid 1N (11 ml).

THF is concentrated and the aqueous phase is extracted with ethyl acetate. The organic phase is dried on MgSO_4 , filtered and concentrated to obtain the expected product as a viscous orange oil (1.36 g).

(c) *4-acetylphenyl 3-tert-butoxycarbonyl-2,2-dimethyloxazolidine-4-(R)-carboxylate.*

At 0°C , 3-tert-butoxycarbonyl-2,2-dimethyloxazolidine-4-(R)-carboxylic acid (1.0 g) is dissolved in ethyl acetate (25 ml), dicyclohexylcarbodiimide (DCC; 1.26 g) is then added and the reaction mixture is subjected to agitation for 45 minutes at 0°C . Dimethylaminopyridine (DMAP; 100 mg) and 4'-hydroxyacetophenone (565 mg) are successively added, the reaction mixture is then left to return to room temperature. After 5 hours of agitation, the mixture is filtered and the filtrate is washed with a sodium hydrogen carbonate saturated solution, then with a sodium chloride saturated solution. The organic phase is dried on MgSO_4 , filtered and concentrated. The obtained orange oil is purified by chromatography on silica to obtain the desired product as a transparent oil (940 mg).

(d) *4-acetylphenyl 2-(R)-amino-3-hydroxypropanoate trifluoroacetate.*

Under nitrogen, 4-acetylphenyl 3-tert-butoxycarbonyl-2,2-dimethyloxazolidine-4-(R)-carboxylate (440 mg) is dissolved in dichloromethane (15 ml), and trifluoroacetic acid (TFA; 8 ml) is added. After being subjected to agitation for 1 hour, the reaction mixture is concentrated and ether is added. The formed precipitate is filtered, then vacuum dried to obtain the desired product as a white powder (280 mg). Melting point: $115\text{--}118^\circ\text{C}$.

RMN ^1H (CD_3OD) δ 8.12 (d, 2H); 7.39 (d, 2H); 4.49 (m, 1H); 4.25 (dd, 1H); 4.08 (dd, 1H); 2.56 (s, 3H).

EXAMPLE 3

Ethyl N-[2-[S(-)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoate

At 0°C , N-benzyloxycarbonyl-S(-)-alanine (3.0 g), R(+)-serine ethyl ester hydrochloride (2.28 g), 1-hydroxybenzotriazole hydrate ($\text{HOBt}\cdot\text{H}_2\text{O}$; 1.82 g) and N-ethylmorpholine (1.69 ml) are dissolved in tetrahydrofuran (THF; 30 ml). Then dicyclohexylcarbodiimide (DCC) (2.91 g) is added and the mixture is left to return to room temperature. After being subjected to agitation for 5 hours, the solution is filtered, rinsed with THF and the filtrate is concentrated. The residue is recovered in dichloromethane and the organic phase is successively washed

with a sodium carbonate saturated solution, water and a sodium chloride saturated solution. The organic phase is dried on MgSO_4 , filtered and concentrated. The obtained solid is purified by chromatography on silica to obtain the desired product as a white powder (2.5 g).

EXAMPLE 4

Ethyl N-[S(-)-2-aminopropionyl]-R(+)-2-amino-3-hydroxypropanoate hydrochloride

The ethyl N-[2-[S(-)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoate (1.0 g) obtained as described in example 3, is dissolved in ethanol (25 ml), and a concentrated hydrochloric acid solution (0.25 ml) and palladium on carbon (150 mg) are added. The reaction mixture is placed under hydrogen atmosphere ($P = 1.3$ bar) for 30 minutes, then filtered on kelite. The filtrate is dry evaporated to obtain the desired product as a beige powder (635 mg). Melting point: 163-168°C.

RMN ^1H (CD_3OD) δ 4.55 (m, 1H); 4.21 (q, 2H); 4.05 (m, 1H); 3.9 (m, 2H); 1.54 (d, 3H); 1.28 (t, 3H).

EXAMPLE 5

Ethyl N-[2-[R(+)-N,N'-bis-benzyloxycarbonyl-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoate

At 0°C, N,N'-bis-benzyloxycarbonyl-R(+)-lysine (2.51 g), R(+)-serine ethyl ester hydrochloride (1.03 g), HOBt. H_2O (0.82 g) and N-ethylmorpholine (0.76 ml) are dissolved in THF (30 ml). Then DCC (1.31 g) is added and the medium is left to return to room temperature for 4 hours. The reaction mixture is filtered on sintered material, washed with THF then the filtrate is dry concentrated. The residue is recovered in ethyl acetate and the organic phase is washed with a sodium carbonate saturated solution, then with a sodium chloride saturated solution. The organic phase is dried on MgSO_4 , filtrated and concentrated. The obtained solid is purified by chromatography on silica to obtain the desired product as a white solid (1.14 g). Melting point: 133-136°C.

RMN ^1H (CDCl_3) δ 7.28 (brs, 10H); 6.94 (brs, NH); 5.55 (brs, NH); 5.11 (s, 2H); 5.08 (s, 2H); 4.99 (brs, NH); 4.62 (m, 1H); 4.22 (q, 3H); 3.96 (brs, 2H); 3.21 (m, 2H); 1.72 (m, 6H); 1.27 (t, 3H).

EXAMPLE 6*Methyl R(+)-N-(4,4-diphenyl)butyl-2-amino-3-hydroxypropanoate*(a) *1,1-Diphenyl-4-bromobutene*.

At 0°C, cyclopropyl-diphenyl-carbinol (10.0 g) is dissolved in a hydrogen
bromide solution 48% (40 ml). After being subjected to agitation for 5 hours at
0°C, the medium is diluted with water and dichloromethane, then the organic
phase is washed three times with water. The organic phase is dried on MgSO₄,
filtered and concentrated to obtain the expected product as an orange oil (11.89
g).

(b) *1,1-Diphenyl-4-bromobutane*.

1,1-diphenyl-4-bromobutene (10.0 g) is dissolved in absolute ethanol (100 ml)
and palladium on carbon (400 mg) is added. The reaction mixture is placed
under hydrogen atmosphere (P = 3.3 bar) for 6 hours. The mixture is filtered on
kelite, the filtrate is concentrated to obtain the desired product as an orange oil
(9.24 g).

(c) *methyl R(+)-N-(4,4-diphenyl)butyl-2-amino-3-hydroxypropanoate*.

D-serine ethyl ester hydrochloride (1.5 g) is dissolved in dimethylformamide
(DMF; 20 ml), sodium hydrogen carbonate (1.78 g) is added and 1,1-diphenyl-4-
bromobutane (3.35 g) is dissolved in DMF (5 ml). The reaction mixture is raised
to 85°C for 1 hour, then vacuum concentrated. The residue is recovered with
ethyl acetate and water, then the organic phase is washed three times with a
sodium chloride saturated solution. The organic phase is dried on MgSO₄,
filtered and vacuum concentrated. Purification by chromatography on silica to
obtain the desired product as a loose yellow oil (1.38 g).

EXAMPLE 7*R(+)-N-(4,4-diphenyl)butyl-2-amino-3-hydroxypropanoic acid hydrochloride*

At 0°C, methyl R(+)-N-(4,4-diphenyl)butyl-2-amino-3-hydroxypropanoate (600
mg) is dissolved in a THF/H₂O mixture (3/1; 20 ml) and a sodium hydroxide
solution 5N (0.7 ml) is added. After 15 minutes at 0°C, the reaction mixture is
left to return to room temperature. After 45 minutes, the mixture is cooled again
to 0°C, a hydrochloric acid solution 1N (4 ml) is added, the mixture is then
vacuum concentrated. The solid obtained is triturated in boiling isopropanol and
the mixture is hot filtered. After evaporation of the filtrate, the desired product is
obtained as a clear yellow powder (303 mg). Melting point: 70-75°C.

RMN ¹H (CD₃OD) δ 7.18 (brs, 7H); 7.05 (m, 3H); 3.88 (m, 2H); 3.83 (m, 2H);

3.00 (m, 1H); 2.08 (m, 2H); 1.61 (m, 2H); 1.24 (m, 2H).

EXAMPLE 8

Methyl R(+)-N-[(4,4-diphenyl)-3-butenyl]-2-amino-3-hydroxypropanoate

5 R(+)-serine methyl ester hydrochloride (1.0 g) is dissolved in dimethylformamide (DMF), sodium hydrogen carbonate (1.08 g) and 1-(4-bromo-1-phenylbut-1-enyl) benzene (2.03 g) are added. After being subjected to agitation overnight at room temperature the medium is vacuum concentrated. The residue is recovered in ethyl acetate then the organic phase is washed three
10 times with water. The organic phase is dried on MgSO₄, filtered and concentrated. The desired product is obtained as a white powder (600 mg).

EXAMPLE 9

R(+)-N-[(4,4-diphenyl)-3-butenyl]-2-amino-3-hydroxypropanoic acid hydrochloride

15 At 0°C, methyl R(+)-N-[(4,4-diphenyl)-3-butenyl]-2-amino-3-hydroxypropanoate (600 mg) is dissolved in a mixture of THF/H₂O (3/1; 20 ml), then a sodium hydroxide solution 5N (700 µL) is added. After being subjected to agitation for 15 minutes at 0°C, the reaction mixture is left to return to room
20 temperature for 45 minutes and then the solution is cooled again to 0°C. A hydrochloric acid solution 1N (4 ml) is added and the medium is vacuum concentrated. The white solid obtained is triturated in boiling isopropanol, then filtered. After evaporation of the filtrate, the desired product is obtained as a clear yellow foam (303 mg). Melting point: 130-135°C.
25 RMN ¹H (CD₃OD) δ 7.31 (m, 3H); 7.15 (m, 6H); 6.00 (t, 1H); 3.79 (m, 3H); 3.08 (m, 2H); 2.44 (m, 2H).

EXAMPLE 10

Ethyl R(+)-N-(3-phenyl)propyl-2-amino-3-hydroxypropanoate

30 R(+)-serine ethyl ester hydrochloride (1.0 g) is left in suspension in anhydrous methanol, the molecular sieve 4 Å and sodium cyanoborohydride (NaBH₃CN, 267 mg) are added. After being subjected to agitation for 15 minutes, 3-phenylpropionaldehyde (705 µL) is added in one portion. After being subjected to agitation for 3h30 at room temperature, the reaction mixture is filtered on
35 sintered material and the filtrate is concentrated. The recovered viscous transparent oil (1.95 g) is purified by chromatography on silica to obtain a loose

clear yellow oil (900 mg). The residue is recovered with a minimum of ether and a hydrochloric acid solution 1N is added in ether (6 ml). The precipitate formed is filtered, then dried to obtain the desired product as a white solid (990 mg). Melting point: 102-107°C.

5 RMN ¹H (CD₃OD) δ 7.25 (m, 5H); 4.30 (q, 2H); 4.11 (m, 1H); 3.9 (m, 2H); 3.29 (m, 1H); 3.08 (m, 2H); 2.71 (t, 2H); 2.05 (m, 2H); 1.38 (t, 3H).

EXAMPLE 11

R(+)-N-(3-phenyl)propyl-2-amino-3-hydroxypropanoic acid hydrochloride

10 The ethyl *R(+)-N-(3-phenyl)propyl-2-amino-3-hydroxypropanoate* of example 10 (600 mg) is dissolved in a mixture of THF/ H₂O (3/1; 20 ml) and LiOH.H₂O (175 mg) is added. After being subjected to agitation overnight at room temperature, the THF is concentrated and a hydrochloric acid solution 1N (2 ml) is added. The precipitate formed is filtered, washed in water, then dried in a vacuum oven overnight to obtain the desired product as a white solid (290 mg). Melting point: 190-196°C.

15 RMN ¹H (DMSO) δ 7.25 (m, 5H); 3.73 (m, 1H); 3.62 (m, 1H); 3.20 (m, 1H); 2.85 (m, 2H); 2.58 (t, 2H); 1.90 (t, 2H).

EXAMPLE 12

Ethyl R(+)-N-[(1-methyl-3-oxo)-1-buten-1-yl]-2-amino-3-hydroxypropanoate

20 *R(+)-serine ethyl ester hydrochloride* (3.0 g) is dissolved in methanol (150 ml), 5 spatulas of molecular sieve 4 Å and then acetylacetone (2.55 ml) are added and the mixture is brought to reflux overnight. The solution is filtered on Kelite, rinsed with methanol and the filtrate is dry evaporated. The residue is recovered with ethyl acetate, ether is added, the filtrate is triturated, filtered and concentrated. Purification by chromatography on silica to obtain the desired product as a white solid (1.21 g). Melting point: 78°C.

25 RMN ¹H (CDCl₃) δ 11.00 (d, 1H); 5.00 (s, 1H); 4.23 (m, 4H); 3.94 (m, 2H); 1.95 (m, 6H); 1.27 (t, 3H).

EXAMPLE 13

R(+)-N-[α-phenyl-(2-hydroxy)benzylidene]-2-amino-3-hydroxypropanoic acid

35 Under nitrogen, *R(+)-serine* (1.0 g), *o*-hydroxybenzophenone (940 mg), sodium methanolate (512 mg) are dissolved in ethanol (50 ml) and the reaction mixture is brought to reflux for 3 hours. The medium is vacuum concentrated and

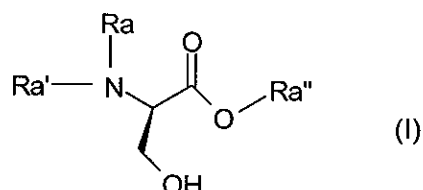
recovered in ether. A concentrated citric acid solution is added and the aqueous phase is extracted with ether. The organic phase is dried on MgSO_4 , filtered and concentrated. The residue is recovered in a minimum of ether, triturated and filtered to obtain the desired product as a yellow powder (610 mg). Melting point: 170°C .

5

RMN ^1H (CD_3OD) δ 7.58 (m, 3H); 7.34 (m, 3H); 6.95 (m, 1H); 6.82 (m, 1H); 6.67 (m, 1H); 4.17 (m, 1H); 3.95 (m, 2H).

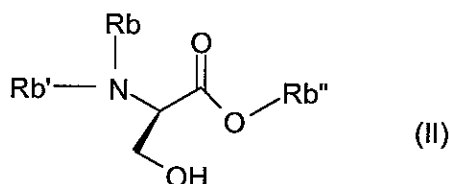
CLAIMS

1. Use of a R(+)-2-amino-3-hydroxypropanoic acid derivative of formula I



- 5
10
15
20
25
- wherein Ra is a hydrogen, Ra' is a hydrogen, a straight or branched chain (C₃-C₆)alkenyl, 3-oxo(C₄-C₆)alkyl or 3-oxo(C₄-C₆)alken-2-yl group, a phenyl(C₁-C₆)alkyl, phenyl(C₂-C₆)alkenyl, (C₂-C₆)alcanoyl, gem-diphenyl(C₁-C₆)alkyl, gem-diphenyl(C₂-C₆)alkenyl, (C₃-C₆)alkenoyl, R(+)-2-aminopropionyl, S(-)-2-aminopropionyl, N-(C₂-C₆)alcanoyl-R(+)-2-aminopropionyl, N-(C₂-C₆)alcanoyl-S(-)-2-aminopropionyl, N-benzyloxycarbonyl-R(+)-2-aminopropionyl, N-benzyloxycarbonyl-S(-)-2-aminopropionyl, R(+)-2,6-diamino-*n*-hexanoyl, S(-)-2,6-diamino-*n*-hexanoyl, N,N'-bis-(C₂-C₆)alcanoyl-R(+)-2,6-diamino-*n*-hexanoyl, N,N'-(C₂-C₆)alcanoyl-S(-)-2,6-diamino-*n*-hexanoyl, N,N'-bis-benzyloxycarbonyl-R(+)-2,6-diamino-*n*-hexanoyl, N,N'-bis-benzyloxycarbonyl-S(-)-2,6-diamino-*n*-hexanoyl group; or Ra and Ra' are together a phenyl(C₁-C₆)alkylydene or gem-diphenyl(C₁-C₆)alkylidene group; Ra'' is a hydrogen, a straight or branched chain (C₁-C₆)alkyl group or a (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, phenyl(C₁-C₂)alkyl, phenacetyl or phenyl group, the phenyl group or groups present in the substituents Ra, Ra' and Ra'' being non-substituted or substituted by a halogen atom or by a hydroxy, (C₁-C₃)alkoxy, cyano, nitro or acetyl group, with the proviso that, when Ra and Ra' are both H, then Ra'' is other than hydrogen, methyl or ethyl; or of one of its pharmaceutically acceptable salts, for preparation of drugs for the treatment of cognitive disorders or mnestic disorders which accompany CNS diseases due to reduced glycinergic transmission.
- 30
2. Use according to claim 1, wherein said CNS disease due to reduced glycinergic transmission is schizophrenia.
3. Use according to claim 1, wherein said CNS disease due to reduced glycinergic transmission is autism.
4. Use according to claim 1, wherein said CNS disease due to reduced glycinergic transmission is Alzheimer's disease.

5. Use according to any of claims 1 to 4, wherein said R(+)-2-amino-3-hydroxypropanoic acid derivative is selected from the group comprising isopropyl R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, benzyl R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, N-[R(+)-2-aminopropionyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof, N-[S(-)-2-aminopropionyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof, N-[2-[S(-)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof, N-acetyl-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof, N-benzyl-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof.
6. Use according to claim 5, wherein said R(+)-2-amino-3-hydroxypropanoic acid derivative is isopropyl R(+)-2-amino-3-hydroxypropanoate hydrochloride or benzyl R(+)-2-amino-3-hydroxypropanoate hydrochloride.
7. Pharmaceutical composition comprising, as active principle, a pharmaceutically effective dose of a R(+)-2-amino-3-hydroxypropanoic acid derivative of formula II

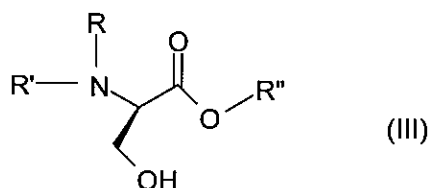


wherein Rb is a hydrogen, Rb' is a hydrogen, a straight or branched chain (C₃-C₆)alkenyl, 3-oxo(C₄-C₆)alkyl or 3-oxo(C₄-C₆)alken-2-yl group, a phenyl(C₁-C₆)alkyl, phenyl(C₂-C₆)alkenyl, (C₂-C₆)alkanoyl, gem-diphenyl(C₁-C₆)alkyl, gem-diphenyl(C₂-C₆)alkenyl, (C₃-C₆)alkenoyl, N-(C₂-C₆)alkanoyl-R(+)-2-aminopropionyl, N-(C₂-C₆)alkanoyl-S(-)-2-aminopropionyl, N-benzyloxycarbonyl-R(+)-2-aminopropionyl, N-benzyloxycarbonyl-S(-)-2-aminopropionyl, R(+)-2,6-diamino-*n*-hexanoyl, S(-)-2,6-diamino-*n*-hexanoyl, N,N'-bis-(C₂-C₆)alkanoyl-R(+)-2,6-diamino-*n*-hexanoyl, N,N'-(C₂-C₆)alkanoyl-S(-)-2,6-diamino-*n*-hexanoyl, N,N'-bis-benzyloxycarbonyl-R(+)-2,6-diamino-*n*-hexanoyl, N,N'-bis-

- benzyloxycarbonyl-S(-)-2,6-diamino-*n*-hexanoyl group; or Rb and Rb', are together a phenyl(C₁-C₆)alkyldene or gem-diphenyl(C₁-C₆)alkylidene group; Rb" is a hydrogen, a straight or branched chain (C₁-C₆)alkyl group or a (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, phenyl(C₁-C₂)alkyl, phenacetyl or phenyl group, the phenyl group or groups present in the Rb, Rb' and Rb" substituents being non-substituted or substituted by a halogen atom or by a hydroxy, (C₁-C₃)alkoxy, cyano, nitro or acetyl group, with the proviso that, when Rb and Rb' are both H, then Rb" is other than hydrogen, methyl, ethyl or non-substituted benzyl and that, when Rb is a hydrogen and Rb' is a non-substituted benzyl, a N-benzyloxycarbonyl-S(-)-2-aminopropionyl, a R(+)-2-aminopropionyl or S(-)-2-aminopropionyl, then Rb" is other than hydrogen; or one of its pharmaceutically acceptable salts, in admixture with a pharmaceutically acceptable carrier.
8. Pharmaceutical composition according to claim 7, wherein said active principle is selected from the group comprising 2-oxo-2-phenylethyl R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, cyclopropylmethyl R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, 4-acetylphenyl R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, N-[2-[R(+)-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof, N-[2-[S(-)-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof, ethyl N-[S(-)-2-aminopropionyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, methyl N-[2-[S(-)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, ethyl N-[2-[S(-)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, N-[2-[R(+)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof, methyl N-[2-[R(+)-benzyloxycarbonylamino]propionyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, N-[2-[S(-)-N,N'-bis-benzyloxycarbonyl-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoic acid and pharmaceutically acceptable salts thereof, methyl N-[2-[R(+)-N,N'-bis-benzyloxycarbonyl-2,6-diaminohexanoyl]-

R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, methyl N-[2-[S(-)-N,N'-bis-benzyloxycarbonyl-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, ethyl N-[2-[R(+)-N,N'-bis-benzyloxycarbonyl-2,6-diaminohexanoyl]-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof, ethyl N-benzyl-R(+)-2-amino-3-hydroxypropanoate and pharmaceutically acceptable salts thereof.

9. R(+)-2-amino-3-hydroxypropanoic acid derivative of formula III



wherein R is a hydrogen; R' is a hydrogen, a phenyl(C₂-C₆)alkenyl, gem-diphenyl(C₁-C₆)alkyl group other than benzhydryl, gem-diphenyl(C₂-C₆)alkenyl; or R and R' are together a phenyl(C₁-C₆)alkylidene or gem-diphenyl(C₁-C₆)alkylidene group; R'' is a hydrogen or a (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, phenyl(C₁-C₂)alkyl, phenacetyl or phenyl group; the phenyl group or groups being non-substituted or substituted by a halogen atom or by a hydroxy, (C₁-C₃)alkoxy, cyano, nitro or acetyl group, with the proviso that, when R and R' are both hydrogen, then R'' is other than hydrogen; or one of its pharmaceutically acceptable salts.

10. R(+)-2-amino-3-hydroxypropanoic acid derivative according to claim 9, of formula III, where R' is a ? -diphenyl(C₂-C₆)alkyl group.
11. R(+)-N-(4,4-diphenyl)butyl-2-amino-3-hydroxypropanoic acid or a pharmaceutically acceptable salts thereof.
12. R(+)-N-[(4,4-diphenyl)-3-butenyl]-2-amino-3-hydroxypropanoic acid or a pharmaceutically acceptable salts thereof.
13. R(+)-N-[a-phenyl-(2-hydroxy)benzylidene]-2-amino-3-hydroxypropanoic acid or a pharmaceutically acceptable salts thereof.