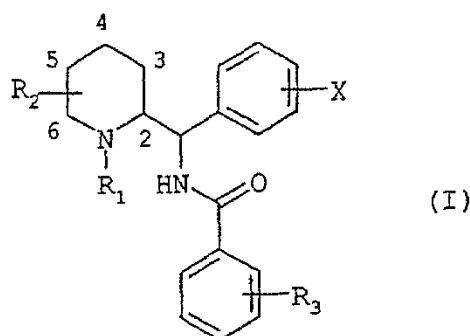


N-[Phenyl(alkyl-2-piperidyl)methyl]benzamide
 derivatives, preparation thereof and therapeutic use
 thereof

- 5 The compounds of the invention correspond to the
 general formula (I)



10 in which

R_1 represents either a hydrogen atom, or a linear or
 branched (C_1 - C_7)alkyl group optionally substituted with
 one or more fluorine atoms, or a (C_3 - C_7)cycloalkyl
 group, or a (C_3 - C_7)cycloalkyl(C_1 - C_3)alkyl group, or a
 15 phenyl(C_1 - C_3)alkyl group optionally substituted with one
 or two methoxy groups, or a (C_2 - C_4)alkenyl group, or a
 (C_2 - C_4)alkynyl group;

R_2 represents either a linear or branched (C_1 - C_7)alkyl
 or (C_3 - C_7)cycloalkyl group, or a (C_3 - C_7)cycloalkyl(C_1 -
 20 C_3)alkyl group;

X represents either a hydrogen atom or one or more
 substituents chosen from halogen atoms and trifluoro-
 methyl, linear or branched (C_1 - C_6)alkyl and
 (C_1 - C_6)alkoxy groups;

25 R_3 represents either a hydrogen atom or one or more
 substituents chosen from halogen atoms and
 trifluoromethyl, linear or branched (C_1 - C_6)alkyl,
 (C_3 - C_7)cycloalkyl, (C_1 - C_6)alkoxy, phenyl, cyano, acetyl,
 benzoyl, (C_1 - C_6)thioalkyl, (C_1 - C_6)alkylsulfonyl,
 30 carboxyl and (C_1 - C_6)alkoxycarbonyl groups, or a group of
 general formula NR_4R_5 or $SO_2NR_4R_5$ or $CONR_4R_5$ in which R_4
 and R_5 each independently represent a hydrogen atom or

a linear or branched (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group, or R₄ and R₅ form, with the nitrogen atom that bears them, a pyrrolidine, piperidine or morpholine ring.

5

The compounds of formula (I) contain two or three asymmetric centers depending on whether R₂ is in position 2, 3, 4, 5 or 6. They may thus exist in the form of enantiomers or diastereoisomers. These
10 enantiomers and diastereoisomers, and also mixtures thereof, including racemic mixtures, form part of the invention.

More particularly, the compounds of formula (I) may
15 exist in the form of threo ((1S, 2S) and (1R, 2R)) or erythro ((1S, 2R) and (1R, 2S)) enantiomers or diastereoisomers with a cis or trans stereochemistry of the piperidine substituents, or as a mixture of such isomers.

20

The compounds of formula (I) may exist in the form of bases or of acid-addition salts. Such addition salts form part of the invention.

25 The salts are advantageously prepared with pharmaceutically acceptable acids, but the salts of other acids that are useful, for example, for purifying or isolating the compounds of formula (I) also form part of the invention.

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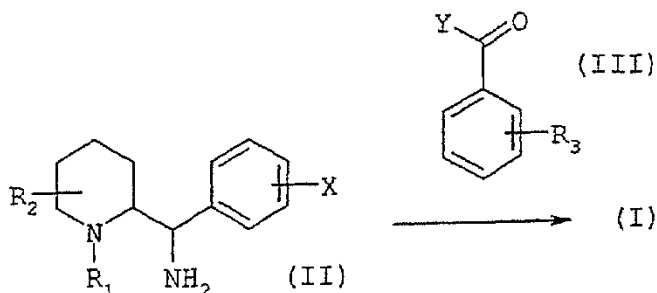
The compounds of formula (I) may also exist in the form of hydrates or solvates, i.e. in the form of associations or combinations with one or more water molecules or with a solvent. Such hydrates and solvates
35 also form part of the invention.

The compounds of the invention show particular activity as specific inhibitors of the glycine transporters glyt1 and/or glyt2.

The compounds of general formula (I) in which R_1 is other than a hydrogen atom may be prepared via a process illustrated by Scheme 1 below.

5

Scheme 1



- 10 Coupling of a diamine of general formula (II), in which R_1 , R_2 and X are as defined above (with R_1 other than a hydrogen atom), with an activated acid or an acid chloride of general formula (III) in which Y represents an activated OH group or a chlorine atom and R_3 is as
 15 defined above, is performed using the methods known to those skilled in the art.

The diamine of general formula (II) with R_2 in position 3, 4, 5 or 6 may be prepared via a process illustrated
 20 by Scheme 2 below.

According to a first route, the α -lithiation of the piperidine of general formula (IV), in which R_2 is as defined above and Boc represents a 1,1-dimethylethoxy-carbonyl group, is performed with *sec*-butyllithium in
 25 the presence of TMEDA (*N,N,N',N'*-tetramethylethylenediamine) in an ether solvent such as diethyl ether at -78°C , to react the lithioamine formed *in situ* with the benzaldehyde derivative of general formula (VI), in which X is as defined above. A mixture of alcohol of
 30 general formula (VIII) and of cyclic carbamate of general formula (IX) is thus obtained.

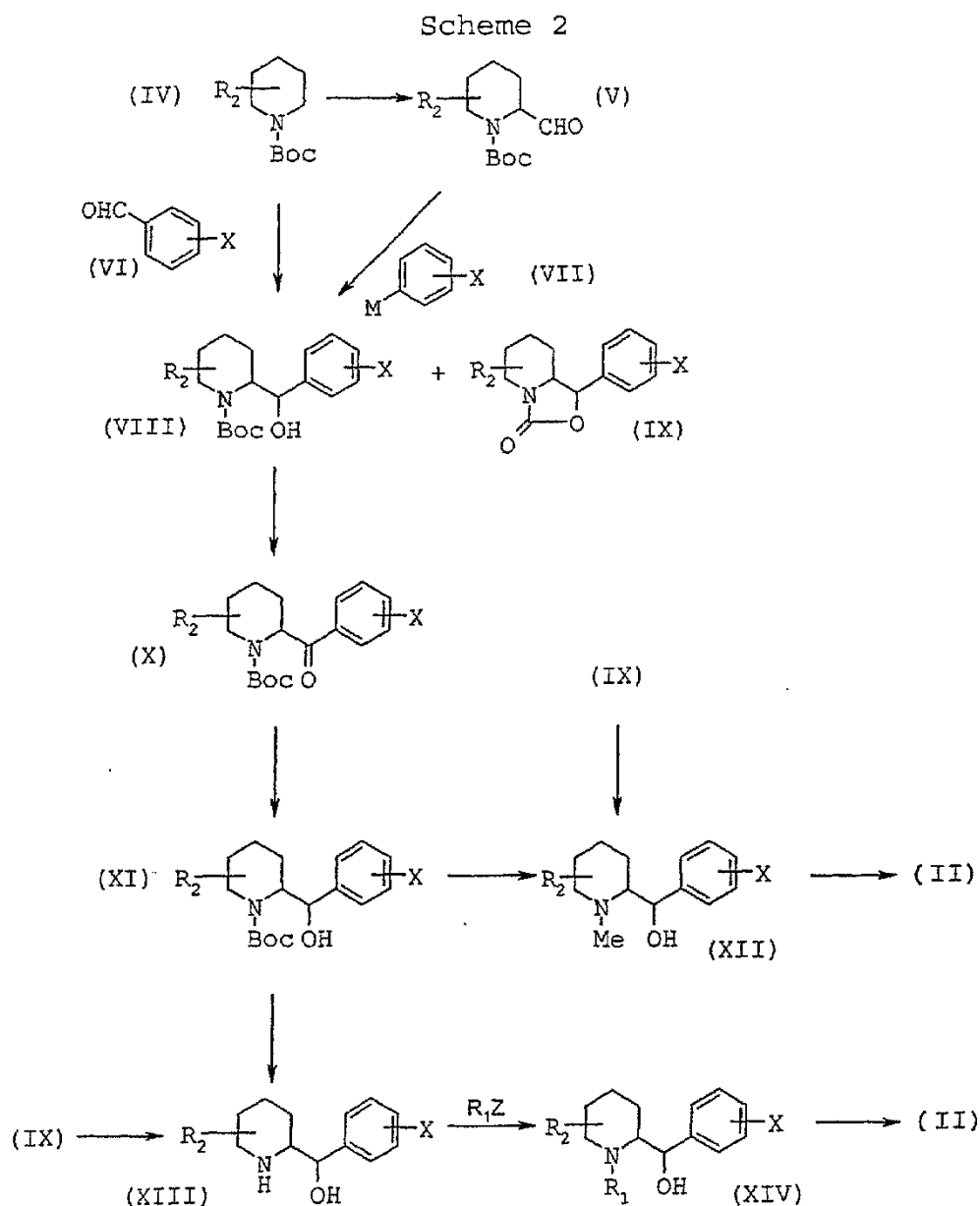
These compounds may also be obtained according to a second route in the following manner: the aldehyde of general formula (V) is either prepared according to methods described in the literature, or prepared from the piperidine of general formula (IV) after lithiation and condensation with the dimethylformaldehyde under the conditions described above. It is then reacted with the derivative of general formula (VII), in which X is as defined above and M represents a metal such as lithium, in an ether solvent such as diethyl ether, between -30°C and room temperature, to give the compounds of general formulae (VIII) and (IX). The alcohol of general formula (VIII) of threo/erythro configuration is converted into the alcohol of general formula (XI) of threo configuration in two steps in the following manner: the alcohol is oxidized to the ketone of general formula (X) with an oxidizing agent such as pyridinium chlorochromate in a chlorinated solvent such as dichloromethane at room temperature, and the ketone is then diastereoselectively reduced to an alcohol of threo configuration of general formula (XI) with a reducing agent such as K-Selectride® or L-Selectride® (potassium or lithium tri-sec-butylborohydride), in an ether solvent such as tetrahydrofuran, between -78°C and room temperature.

The carbamate of general formula (XI) of threo configuration may then be reduced to the threo N-methylamino alcohol of general formula (XII) via the action of a mixed hydride such as lithium aluminum hydride, in an ether solvent such as tetrahydrofuran, between room temperature and the reflux temperature. Under the same reduction conditions, the threo cyclic carbamate of general formula (IX) also leads to the threo N-methylamino alcohol derivative of general formula (XII).

The threo/erythro cyclic carbamate mixture of general formula (IX) leads to the mixture of threo/erythro

derivatives of general formula (XII), which may be purified and separated by chromatography on silica gel to give the pure threo compound and the pure erythro compound.

5



10

The threo alcohol of general formula (XII) is then converted into the threo intermediate of general formula (II) in which R_1 represents a methyl group, in two steps: the alcohol function is first converted into an electrophilic group, for example a methanesulfonate group, via the action of methanesulfonyl chloride, in a chlorinated solvent such as dichloromethane, and in the

15

presence of a base such as triethylamine, between 0°C and room temperature, and the electrophilic group is then reacted with liquefied ammonia at -50°C, in an alcohol such as ethanol, in a closed medium such as an autoclave, between -50°C and room temperature.

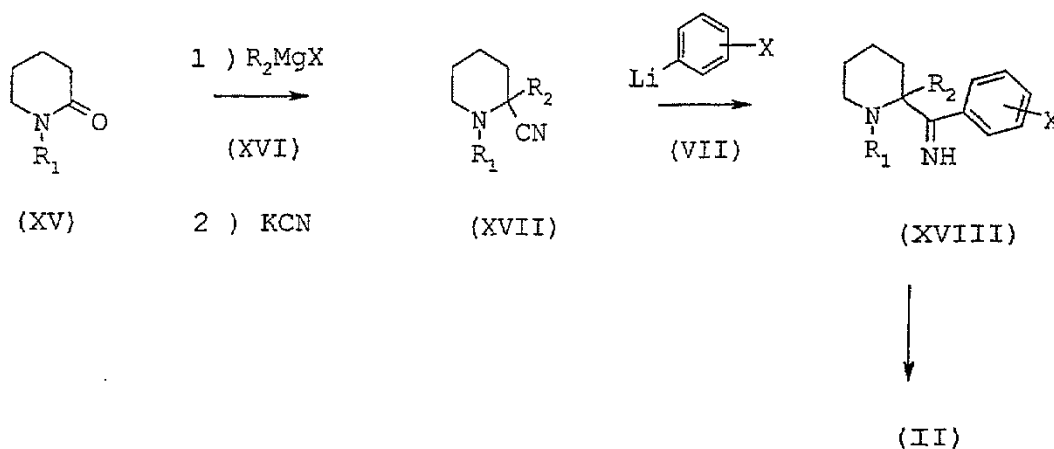
The carbamate of general formula (XI) of threo configuration may also be deprotected using a strong base such as aqueous potassium hydroxide, in an alcohol such as methanol to obtain the threo amino alcohol of general formula (XIII). Under the same hydrolysis conditions, the cyclic carbamate of general formula (IX) leads to the amino alcohol of general formula (XIII).

An *N*-alkylation is then performed using a halogenated derivative of formula R_1Z , in which R_1 is as defined above, but other than a hydrogen atom, and Z represents a halogen atom, in the presence of a base such as potassium carbonate, in a polar solvent such as *N,N*-dimethylformamide, between room temperature and 100°C, to give the alkylated derivative of general formula (XIV). The alkylated derivative of general formula (XIV) is then transformed into the intermediate of general formula (II) as described with respect to the alcohol of general formula (XII).

The process may be performed in the same manner as above with the erythro derivatives of general formula (IX) to obtain the erythro compounds of general formula (I).

The diamine of general formula (II) with R_2 in position 2 may be prepared via a process illustrated by Scheme 3 below.

Scheme 3



5 A piperidinone of general formula (XV), in which R_1 is as defined above, is reacted with an organometallic reagent of general formula (XVI), in refluxing tetrahydrofuran, and the reaction medium is treated with potassium cyanide solution to give the amino
10 nitrile of general formula (XVII). This product is then reacted with a lithiated derivative of general formula (VII), in which X is as defined above, in an ether solvent such as diethyl ether or tetrahydrofuran, between $-90^\circ C$ and $-30^\circ C$; an intermediate imine of
15 general formula (XVIII) is obtained, which is reduced to the threo primary amine of general formula (II) with a reducing agent such as sodium borohydride, in a protic solvent such as methanol, between $0^\circ C$ and room temperature.

20

The compounds of general formula (I) in which R_1 represents a hydrogen atom may be prepared from a compound of general formula (I) in which R_1 represents:
- either an optionally substituted phenylmethyl group,
25 by deprotecting the nitrogen of the piperidine ring, for example with an oxidizing agent or with a Lewis acid such as boron tribromide, or by hydrogenolysis,
- or an alkenyl group, preferably an allyl group, by deprotecting the nitrogen of the piperidine ring, for

example with a Pd^0 complex, to obtain a compound of general formula (I) in which R_1 represents a hydrogen atom.

- 5 The piperidinone of general formula (XV) is commercially available.

Moreover, the chiral compounds of general formula (I) may be obtained by separation of the racemic compounds
10 via high-performance liquid chromatography (HPLC) on a chiral column, or by resolution of the racemic amine of general formula (II) by using a chiral acid, such as tartaric acid, camphorsulfonic acid, dibenzoyltartaric acid or N-acetylleucine, via fractional and
15 preferential recrystallization of a diastereoisomeric salt in a solvent of alcohol type.

The piperidines of general formula (IV) are prepared by protection, for example with a Boc group, of the
20 nitrogen of the corresponding piperidines, which are commercially available or described in the literature, according to methods known to those skilled in the art. The method for forming the lithiopiperidine from the piperidine of general formula (IV) and its reaction
25 with the benzaldehyde of general formula (VI) is similar to that described in *J.O.C.*, **55**, (1990), 2578-2580. The phenyllithium compound of general formula (VII) in which X represents a hydrogen atom is commercially available. Its substituted derivatives may
30 be prepared according to a method similar to that described in *Tetrahedron Lett.*, **57**, 33, (1996), 5905-5908. The aldehydes of general formula (V) in which R_2 represents a methyl group in positions 2, 4, 5 and 6 are described in *J.O.C.*, **58**, (1993), 1109-117 and *J. Chem. Soc., Perkin Trans. 1*, (2002), 1438-1443. The
35 halo derivatives of formula R_1Z are commercially available. Certain acids and acid chlorides of general formula (III) are commercially available or, when they are novel, may be obtained according to methods similar

to those described in patents EP-0 556 672 and US-3 801 636 and in *J. Chem. Soc.*, (1927), 25, *Chem. Pharm. Bull.*, (1992), 1789-1792, *Aust. J. Chem.*, (1984), 1938-1950 and *J.O.C.*, (1980), 527.

5

The examples that follow illustrate the preparation of a number of compounds of the invention. The elemental microanalyses, the IR and NMR spectra and the HPLC on a chiral column confirm the structures and the enantiomeric purities of the compounds obtained.

10

The numbers given in parentheses in the example titles correspond to those in the first column of the table given later.

15

In the compound names, the hyphen "-" forms part of the word, and the underscore mark "_" serves merely to indicate a line break; it should be deleted if a line break does not occur at that point, and should not be replaced either with a normal hyphen or with a space.

20

Example 1 (Compound 1)

Cis-threo-2-chloro-N-[(1,6-dimethyl-2-piperidyl)-(phenyl)methyl]-3-(trifluoromethyl)benzamide hydrochloride 1:1

25

1.1. 1,1-Dimethylethyl cis-[2-hydroxy(phenyl)methyl-6-methyl]piperidine-1-carboxylate

1 g (4.4 mmol) of 1,1-dimethylethyl cis-2-formyl-6-methylpiperidine-1-carboxylate is introduced into 15 ml of anhydrous tetrahydrofuran in a 50 ml round-bottomed flask, under a nitrogen atmosphere, the medium is cooled to -78°C, 4.4 ml (4.4 mmol) of a 1M solution of phenylmagnesium bromide in tetrahydrofuran are added dropwise and the mixture is allowed to warm to -50°C with stirring for 2 hours.

30

35

After hydrolysis with saturated aqueous ammonium chloride solution, the aqueous phase is separated out and extracted with ethyl acetate. The combined organic phases are dried over sodium sulfate, filtered and concentrated under reduced pressure, and the residue is purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane. 1.15 g of alcohol are obtained in the form of a threo/erythro diastereoisomer mixture.

1.2. 1,1-Dimethylethyl cis-2-methyl-6-(phenylcarbonyl)-piperidine-1-carboxylate

0.12 g (1.5 mmol) of sodium acetate suspended in 20 ml of dichloromethane, and 1.2 g (5.5 mmol) of pyridinium chlorochromate are successively introduced into a 100 ml round-bottomed flask, followed by addition of a solution of 1.15 g (3.76 mmol) of 1,1-dimethylethyl cis-[2-hydroxy(phenyl)methyl-6-methyl]piperidine-1-carboxylate in 20 ml of dichloromethane. The mixture rapidly turns black, and is left stirring for 4 hours at room temperature.

30 ml of ethyl ether are added, the mixture is filtered, rinsed and concentrated under reduced pressure, and the residue is purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane.

0.46 g of ketone is obtained in the form of a white solid.

Melting point: 92-93°C.

1.3. 1,1-Dimethylethyl cis-threo-[2-hydroxy(phenyl)-methyl-6-methyl]piperidine-1-carboxylate

0.46 g (1.5 mmol) of 1,1-dimethylethyl cis-2-methyl-6-(phenylcarbonyl)piperidine-1-carboxylate is introduced into 40 ml of anhydrous tetrahydrofuran in a 100 ml

round-bottomed flask, the solution is cooled to -78°C , and 4.6 ml (4.6 mmol) of a 1M solution of L-Selectride® (lithium tri-sec-butylborohydride) in tetrahydrofuran are added dropwise, and the mixture is stirred at -78°C for 5 hours.

The resulting mixture is hydrolyzed slowly under cold conditions with 3.2 ml of water and 3.2 ml of aqueous 35% hydrogen peroxide solution, and the mixture is allowed to return to room temperature with stirring for 2 hours.

The resulting mixture is diluted with water and ethyl acetate, the phases are separated and the aqueous phase is extracted with ethyl acetate. After washing the combined organic phases, drying over sodium sulfate, filtering and evaporating, the residue is purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane.

0.38 g of threo-cis isomer is obtained in the form of a colorless oil.

1.4. Cis-threo-(1,6-dimethyl-2-piperidyl)phenylmethanol

0.24 g (6.3 mmol) of lithium aluminum hydride is introduced into 7 ml of anhydrous tetrahydrofuran in a 25 ml two-necked flask, under a nitrogen atmosphere, the mixture is heated to reflux, 0.38 g (1.2 mmol) of a solution of 1,1-dimethylethyl cis-threo-[2-hydroxy(phenyl)methyl-6-methyl]piperidine-1-carboxylate in 3 ml of tetrahydrofuran is added and the mixture is maintained at reflux for 3.5 hours.

The resulting mixture is cooled and hydrolyzed slowly with 0.1M potassium sodium tartrate solution, and the mixture is stirred overnight. The resulting mixture is filtered, the precipitate is rinsed with tetrahydrofuran, the filtrate is concentrated under

reduced pressure and the residue is purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol.

5 0.11 g of a colorless oily product is obtained.

1.5 Cis-threo-(1,6-dimethyl-2-piperidyl)phenyl-methanamine

10 0.11 g (0.52 mmol) of cis-threo-(1,6-dimethyl-2-piperidyl)phenylmethanol and 0.11 ml (0.78 mmol) of triethylamine are introduced into 7 ml of anhydrous dichloromethane in a 25 ml round-bottomed flask under a nitrogen atmosphere, the medium is cooled to 0°C,
15 0.06 ml (0.78 mmol) of methanesulfonyl chloride is added and the mixture is allowed to return slowly to room temperature over 2 hours and concentrated under reduced pressure.

20 Liquefied ammonia is introduced into an autoclave equipped with a magnetic stirrer and cooled to -50°C, a solution of the crude methanesulfonate prepared above dissolved in 30 ml of absolute ethanol is added, the autoclave is closed and the mixture is stirred for
25 48 hours. The mixture is transferred into a round-bottomed flask and concentrated to dryness, the residue is diluted with water and dichloromethane, the phases are separated and the aqueous phase is extracted with dichloromethane. After washing the combined organic
30 phases, drying over sodium sulfate, filtering and evaporating, 0.1 g of amine is isolated in the form of an oily compound, which is used without further purification in the following step.

35 1.6. Cis-threo-2-chloro-N-[(1,6-dimethyl-2-piperidyl)-(phenyl)methyl]-3-(trifluoromethyl)benzamide hydrochloride 1:1

0.13 g (0.58 mmol) of 2-chloro-3-trifluoromethane-benzoic acid, 0.11 g (0.59 mmol) of 1-[3-(dimethylamine)propyl]-3-ethylcarbodiimide hydrochloride and 0.03 g (0.24 mmol) of dimethylaminopyridine dissolved
5 in 4 ml of dichloromethane are successively introduced into a 25 ml round-bottomed flask, 0.10 g (0.48 mmol) of cis-threo-(1,6-dimethyl-2-piperidyl)phenylmethan-amine dissolved in 1 ml of dichloromethane is added and the mixture is left stirring for 5 hours.

10

The resulting mixture is treated with water and extracted several times with dichloromethane. After washing the organic phases with water and then with aqueous 1N sodium hydroxide solution, drying over
15 magnesium sulfate, filtering and evaporating off the solvent under reduced pressure, the residue is purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol.

20 0.18 g of oily product is obtained, which is isolated in hydrochloride form from a 0.1N solution of hydrogen chloride in 2-propanol.

0.12 g of hydrochloride is finally isolated in the form
25 of white solid.

Melting point: 208-209°C.

Example 2 (Compound 9)

Cis-threo-2-chloro-N-[(1,4-dimethyl-2-piperidyl)-(phenyl)methyl]-3-(trifluoromethyl)benzamide hydro-
30 chloride 1:1

2.1. Cis-7-methyl-1-phenylhexahydro[1,3]oxazolo[3,4-a]pyridin-3-one

35

14.2 g (71.2 mmol) of 1,1-dimethylethyl 4-methyl-piperidine-1-carboxylate dissolved in 130 ml of anhydrous diethyl ether are introduced into a 1 l round-bottomed flask, under an argon atmosphere, and

the medium is cooled to -70°C . 14 ml (92.5 mmol) of TMEDA (*N,N,N',N'*-tetramethylethylenediamine) are added, followed by addition of 70 ml (92.5 mmol) of a 1.3M solution of *sec*-butyllithium in cyclohexane, and the
5 mixture is allowed to return to -30°C with stirring over 0.5 hour.

A solution of 11.33 ml (106.8 mmol) of benzaldehyde (distilled beforehand) in 40 ml of anhydrous diethyl
10 ether is then added and the mixture is allowed to return to room temperature with stirring over 12 hours.

After hydrolysis with water, the aqueous phase is separated out and extracted with ethyl acetate. The
15 combined organic phases are dried over sodium sulfate, filtered and concentrated under reduced pressure, and the residue is purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol.

20 3.3 g of a colorless oil of a mixture of *cis* threo/erythro isomers are obtained.

2.2 *Cis*-threo-(1,4-dimethyl-2-piperidyl)phenylmethanol
25

2.71 g (71.5 mmol) of lithium aluminum hydride are introduced into 120 ml of anhydrous tetrahydrofuran in a 500 ml two-necked flask, under a nitrogen atmosphere, the mixture is heated to reflux, 3.33 g (14.3 mmol) of
30 a solution of *cis*-7-methyl-1-phenylhexahydro[1,3]oxazolo[3,4-*a*]pyridin-3-one in 40 ml of tetrahydrofuran are added and refluxing is continued for 5.5 hours.

35 The mixture is cooled, hydrolyzed slowly with 0.1M potassium sodium tartrate solution and stirred overnight.

The resulting mixture is filtered, the precipitate is rinsed with tetrahydrofuran, the filtrate is concentrated under reduced pressure and the residue is purified by column chromatography on silica gel,
5 eluting with a mixture of dichloromethane and methanol.

0.95 g of a product is obtained in the form of a colorless oil.

10 2.3. Cis-threo-(1,4-dimethyl-2-piperidyl)phenylmethan-amine

0.95 g (4.3 mmol) of cis-threo-(1,4-dimethyl-2-piperidyl)phenylmethanol and 0.9 ml (6.5 mmol) of triethyl-
15 amine are introduced into 40 ml of anhydrous dichloromethane in a 10 ml round-bottomed flask, under a nitrogen atmosphere, the medium is cooled to 0°C, 0.5 ml (6.5 mmol) of methanesulfonyl chloride is added and the mixture is allowed to return slowly to room
20 temperature over 2 hours and is concentrated under reduced pressure.

Liquefied ammonia is introduced into an autoclave equipped with a magnetic stirrer and cooled to -50°C, a
25 solution of the crude methanesulfonate prepared above dissolved in 30 ml of absolute ethanol is added, and the autoclave is closed and stirred for 48 hours. The mixture is transferred into a round-bottomed flask and concentrated to dryness, the residue is diluted with
30 water and dichloromethane, the phases are separated and the aqueous phase is extracted with dichloromethane. After washing the combined organic phases, drying over sodium sulfate, filtering and evaporating, 0.8 g of amine is isolated in the form of an oily compound,
35 which is used without further purification in the following step.

2.4. Cis-threo-2-chloro-N-[(1,4-dimethyl-2-piperidyl)-(phenyl)methyl]-3-(trifluoromethyl)benzamide hydrochloride 1:1

5 0.98 g (4.38 mmol) of 2-chloro-3-trifluoromethane-benzoic acid, 0.85 g (4.46 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and 0.22 g (1.83 mmol) of dimethylamino-pyridine dissolved in 20 ml of dichloromethane are
10 successively introduced into a 50 ml round-bottomed flask, 0.8 g (3.66 mmol) of cis-threo-(1,4-dimethyl-2-piperidyl)phenylmethanamine dissolved in 4 ml of dichloromethane is added and the mixture is stirred for 12 hours.

15

The resulting mixture is treated with water and extracted several times with dichloromethane. After washing the organic phases with water and then with aqueous 1N sodium hydroxide solution, drying over
20 magnesium sulfate, filtering and evaporating off the solvent under reduced pressure, the residue is purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol.

25 0.32 g of oily product is obtained, which is isolated in hydrochloride form from a 0.1N solution of hydrogen chloride in 2-propanol.

0.28 g of hydrochloride is finally isolated in the form of a white solid.

30 Melting point: 209-211°C.

Example 3 (Compound 5)

Trans-threo-2-chloro-N-[(1,5-dimethyl-2-piperidyl)-(4-fluorophenyl)methyl]-3-(trifluoromethyl)benzamide

35 hydrochloride 1:1

By working in the same manner as in Example 2 and replacing the 1,1-dimethylethyl 4-methylpiperidine-1-carboxylate with 1,1-dimethylethyl 5-methylpiperidine-

1-carboxylate and the benzaldehyde with 4-fluoro-benzaldehyde, a mixture of corresponding alcohol and isoxazolidone is obtained. Reduction of the isoxazolidone obtained with lithium aluminum hydride gives the trans-threo amino alcohol compound, which is used according to the methods described in steps 2.3 and 2.4 of Example 2 using 2-chloro-3-trifluoromethanebenzoic acid.

Melting point: 220-222°C.

10

Example 4 (Compound 10)

Threo-2-chloro-N-[(1,2-dimethyl-2-piperidyl)(phenyl)-methyl]-3-(trifluoromethyl)benzamide hydrochloride 1:1

15 4.1. 1,2-Dimethylpiperidine-2-carbonitrile

22 ml (31 mmol) of a 1.4M solution of methylmagnesium bromide in tetrahydrofuran are introduced into a 500 ml three-necked flask equipped with a condenser and a magnetic stirrer, under a nitrogen atmosphere, followed by addition of a solution of 5 g (44.2 mmol) of 1-methylpiperidin-2-one in 20 ml of tetrahydrofuran, and the mixture is refluxed with stirring for 2 hours.

25 The mixture is allowed to cool, 50 ml of 2N hydrochloric acid solution are added and the resulting mixture is extracted with ethyl acetate. The aqueous phase is then adjusted to pH 6 with sodium bicarbonate and 2.9 g (2.8 mmol) of potassium cyanide are added. 30 The mixture is then stirred at 25°C for 12 hours.

10% sodium bicarbonate solution is added and the mixture is extracted with ethyl acetate. After washing the combined organic phases, drying over sodium sulfate, filtering and evaporating, 3 g of product are obtained in the form of an oily compound, which is used without further purification in the following step.

35

4.2. 1-(1,2-Dimethyl-2-piperidyl)-1-phenylmethanamine.

A solution of phenyllithium is prepared at -78°C starting with 6.8 g (43.4 mmol) of bromobenzene in 50 ml of tetrahydrofuran and 17.4 ml of butyllithium (2.5M in hexane), in a 250 ml round-bottomed flask equipped with a magnetic stirrer and under an argon atmosphere. A solution of 3 g (21.71 mmol) of 1,2-dimethylpiperidine-2-carbonitrile in 50 ml of tetrahydrofuran is introduced at 78°C and the mixture (yellow solution) is stirred and allowed to return to room temperature over 1 hour. Water is added and the resulting mixture is extracted with ethyl acetate. The combined organic phases are dried over sodium sulfate and filtered, and the imine is concentrated under reduced pressure. The residue is taken up in a 250 ml round-bottomed flask with 50 ml of methanol. The mixture is cooled to 0°C and 4 g (108 mmol) of sodium borohydride are added slowly. Stirring is continued while allowing the temperature of the mixture to return to room temperature over 1 hour. The mixture is concentrated under reduced pressure and the residue is taken up in water and ethyl acetate. The phases are separated and the aqueous phase is extracted with ethyl acetate. After washing the combined organic phases, drying over sodium sulfate, filtering and evaporating, 3.2 g of product are obtained in the form of an oily compound, which is used without further purification in the following step.

4.3. Threo-2-chloro-*N*-[(1,2-dimethyl-2-piperidyl)-(phenyl)methyl]-3-(trifluoromethyl)benzamide hydrochloride 1:1

0.41 g (1.8 mmol) of 1-(1,2-dimethyl-2-piperidyl)-1-phenylmethanamine, 0.3 ml (2.25 mmol) of triethylamine and 0.54 g (2.25 mmol) of 2-chloro-3-(trifluoromethyl)-benzoyl chloride are successively introduced into 20 ml of dichloromethane in a 100 ml round-bottomed flask,

and the mixture is stirred at room temperature for 1 hour.

5 The resulting mixture is treated with water and extracted several times with dichloromethane. After washing the organic phases with water and then with aqueous 1N sodium hydroxide solution, drying over magnesium sulfate, filtering and evaporating off the solvent under reduced pressure, the residue is purified
10 by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol.

0.36 g of oily product is obtained.

15 This product is converted into the hydrochloride using a 0.1N solution of hydrogen chloride in 2-propanol.

0.14 g of hydrochloride is finally isolated in the form of a white solid.

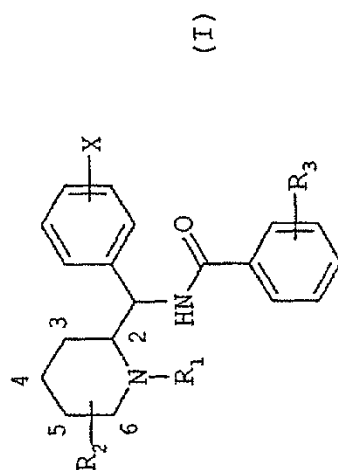
20 Melting point: 239-241°C.

The table that follows illustrates the chemical structures and the physical properties of a number of compounds of the invention.

25

In the "salt" column, "HCl" denotes a hydrochloride.

Table



No.	R ₁	X	R ₂	R ₃	Salt	M.p. (°C)	Stereochemistry
1	CH ₃	H	Cis 6-CH ₃	2-Cl, 3-CF ₃	HCl	208-209	Threo
2	CH ₃	H	Trans 6-CH ₃	2-Cl, 3-CF ₃	HCl	128-129	Threo
3	CH ₃	H	Trans 6-CH ₂ -C6H11	2-Cl, 3-CF ₃	HCl	127-129	Threo
4	CH ₃	H	Trans 6-CH ₃	3,5-Cl, 4-NH ₂	HCl	270-271	Threo
5	CH ₃	4-F	Trans 5-CH ₃	2-Cl, 3-CF ₃	HCl	220-222	Threo
6	CH ₃	4-F	Trans 5-CH ₃	3-Cl, 4-NH ₂	HCl	169-171	Threo
7	CH ₃	H	Cis 5-CH ₃	2-CH ₃ , 3-CF ₃	HCl	131-133	Threo
8	CH ₃	4-F	Cis 6-CH ₃	3,5-Cl, 4-NH ₂	HCl	254-256	Threo
9	CH ₃	H	Cis 4-CH ₃	2-Cl, 3-CF ₃	HCl	209-211	Threo
10	CH ₃	H	2-CH ₃	2-Cl, 3-CF ₃	HCl	239-241	Threo
11	CH ₃	H	2-CH ₃	2-Cl, 3-CH ₃ , 6-F	HCl	227-229	Threo
12	CH ₃	H	2-CH ₃	2-CH ₃ , 3-CF ₃	HCl	149-151	Threo

No.	R ₁	X	R ₂	R ₃	Salt	M.p. (°C)	Stereochemistry
13	CH ₃	H	2-CH ₃	2-CH ₃ , 3-OCH ₃	HCl	170-172	Threo
14	CH ₃	H	2-CH ₃	2-CH ₃ , 3-Cl	HCl	177-179	Threo
15	CH ₃	H	2-CH ₃	2-Cl, 5-CF ₃	HCl	213-215	Threo
16	CH ₃	H	2-CH ₃	2,6-Cl, 3-CF ₃	HCl	253-255	Threo
17	CH ₂ CH:CH ₂	H	2-CH ₃	2-Cl, 3-CF ₃	HCl	244-246	Threo
18	H	H	2-CH ₃	2-Cl, 3-CF ₃	HCl	278-280	Threo

The compounds of the invention were subjected to a series of pharmacological tests that demonstrated their value as therapeutically active substances.

5 Study of glycine transportation in SK-N-MC cells
 expressing the native human transporter glyt1

 The uptake of [14 C]glycine is studied in SK-N-MC cells
 (human neuroepithelial cells) expressing the native
 human transporter glyt1 by measuring the radioactivity
10 incorporated in the presence or absence of the test
 compound. The cells are cultured as a monolayer for
 48 hours in plates pretreated with 0.02% fibronectin.
 On the day of the experiment, the culture medium is
 removed and the cells are washed with Krebs-HEPES
15 buffer ([4-(2-hydroxyethyl)-1-piperazineethanesulfonic
 acid) at pH 7.4. After preincubation for 10 minutes at
 37°C in the presence either of buffer (control batch)
 or of test compound at various concentrations or of
 10 mM glycine (determination of the nonspecific
20 uptake), 10 μ M of [14 C]glycine (specific activity
 112 mCi/mmol) are then added. Incubation is continued
 for 10 minutes at 37°C, and the reaction is quenched by
 washing twice with pH 7.4 Krebs-HEPES buffer. The
 radioactivity incorporated by the cells is then
25 estimated after adding 100 μ l of liquid scintillant and
 stirring for 1 hour. Counting is performed on a
 Microbeta Tri-LuxTM counter. The efficacy of the
 compound is determined by means of the IC₅₀, which is
 the concentration of compound that reduces by 50% the
30 specific uptake of glycine, defined by the difference
 in radioactivity incorporated by the control batch and
 the batch that received 10 mM of glycine.

 The compounds of the invention that are the most
35 active, in this test, have an IC₅₀ of about from 0.001
 to 10 μ M.

 The individual results of a few compounds are as

follows (IC₅₀ in μ M):

	Compound 1	0.51
	Compound 5	0.1
	Compound 9	0.09
5	Compound 10	0.008

ex-vivo study of the inhibitory activity of a compound on the uptake of [¹⁴C]glycine in mouse cortex homogenate

Increasing doses of the compound to be studied are administered orally (preparation by trituration of the test molecule in a mortar in a 0.5% solution of Tween/MethocelTM in distilled water) or intraperitoneally (dissolution of the test molecule in physiological saline or preparation by trituration in a mortar in a 0.5% solution of Tween/Methocel in water, according to the solubility of the molecule) on male OF1 Iffa Credo mice weighing 20 to 25 g on the day of the experiment. The control group is treated with the vehicle. The doses in mg/kg, the route of administration and the treatment time are determined as a function of the molecule to be studied. After euthanasia by decapitation of the animals at a given time after the administration, the cortex of each animal is rapidly removed onto ice, weighed and stored at 4°C or frozen at -80°C (in both cases the samples are stored for a maximum of 1 day). Each sample is homogenized in pH 7.4 Krebs-HEPES buffer in a proportion of 10 ml/g of tissue. 20 μ l of each homogenate are incubated for 10 minutes at room temperature in the presence of 10 mM of L-alanine and of buffer. The nonspecific uptake is determined by addition of 10 mM of glycine to the control group. The reaction is quenched by vacuum filtration and the radioactivity retained is estimated by solid scintillation by counting using a Microbeta Tri-luxTM counter. An inhibitor of the uptake of [¹⁴C]glycine will reduce the amount of radioligand incorporated into each homogenate. The activity of the compound is evaluated by means of its ED₅₀, the dose

that inhibits 50% of the uptake of [14 C]glycine relative to the control group.

The compounds of the invention that are the most powerful in this test have an ED_{50} of from 0.1 to 5 mg/kg intraperitoneally or orally.

Study of the glycine transportation in mouse spinal cord homogenate

10 The uptake of [14 C]glycine by the transporter glyt2 is studied in mouse spinal cord homogenate by measuring the radioactivity incorporated in the presence or absence of test compound.

15 After euthanizing the animals (male OF1 Iffa Credo mice weighing 20 to 25 g on the day of the experiment), the spinal cord of each animal is rapidly removed, weighed and stored on ice. The samples are homogenized in pH 7.4 Krebs-HEPES buffer ([4-(2-hydroxyethyl)-
20 1-piperazineethanesulfonic acid), in a proportion of 25 ml/g of tissue.

50 μ l of homogenate are preincubated for 10 minutes at 25°C in the presence of pH 7.4 Krebs-HEPES buffer and
25 of test compound at various concentrations, or of 10 mM of glycine to determine the nonspecific uptake. [14 C]glycine (specific activity = 112 mCi/mmol) is then added over 10 minutes at 25°C to a final concentration of 10 μ M. The reaction is quenched by vacuum filtration
30 and the radioactivity is estimated by solid scintillation by counting on a Microbeta Tri-LuxTM counter. The efficacy of the compound is determined by means of the IC_{50} , the concentration capable of reducing by 50% the specific uptake of glycine, defined by the
35 difference in radioactivity incorporated by the control batch and the batch that received 10 mM of glycine.

The compounds of the invention that are the most active in this test have an IC_{50} of about from 0.001 to 10 μ M.

The individual results of a few compounds are as follows (IC₅₀ in μ M):

	Compound 1	0.12
5	Compound 9	0.07

ex-vivo study of the inhibitory activity of a compound on the uptake of [¹⁴C]glycine in mouse spinal homogenate
Increasing doses of the compound to be studied are
10 administered orally (preparation by triturating the test compound in a mortar, in a 0.5% solution of Tween/MethocelTM in distilled water) or intra-peritoneally (test compound dissolved in physiological saline, or triturated in a mortar, in a 0.5% solution
15 of Tween/MethocelTM in distilled water) to male OF1 Iffa Credo mice weighing 20 to 25 g on the day of the experiment. The control group is treated with the vehicle. The doses in mg/kg, the route of administration, the treatment time and the euthanasia
20 time are determined as a function of the compound to be studied.

After euthanasia by decapitation of the animals at a given time after the administration, the spinal cords
25 are rapidly removed, weighed and introduced into glass scintillation flasks, stored in crushed ice or frozen at -80°C (in both cases the samples are stored for a maximum of 1 day). Each sample is homogenized in pH 7.4 Krebs-HEPES buffer, in a proportion of 25 ml/g of
30 tissue. 50 μ l of each homogenate are incubated for 10 minutes at room temperature in the presence of buffer.

The nonspecific uptake is determined by adding 10 mM of
35 glycine to the control group.

The reaction is quenched by vacuum filtration and the radioactivity is estimated by solid scintillation by counting on a Microbeta Tri-luxTM counter.

An inhibitor of the uptake of [^{14}C]glycine will reduce the amount of radioligand incorporated into each homogenate. The activity of the compound is evaluated
5 by means of its ED_{50} , the effective dose that inhibits 50% of the uptake of [^{14}C]glycine relative to the control group.

The compounds of the invention that are the most active
10 in this test have an ED_{50} of from 1 to 20 mg/kg intraperitoneally or orally.

The results of the tests performed on the compounds of the invention show that they are inhibitors of the
15 glycine transporters glyt1 present in the brain and glyt2 present in the brain or the spinal cord.

The compounds according to the invention may thus be used for the preparation of medicaments, in particular
20 of medicaments that inhibit the glycine transporters glyt1 and/or glyt2.

Thus, according to another of its aspects, a subject of the invention is medicaments comprising a compound of
25 formula (I), or an addition salt thereof with a pharmaceutically acceptable acid, or alternatively a hydrate or a solvate of the compound of formula (I).

The compounds of the invention may be used especially
30 for behavioral disorders associated with dementia, psychoses, in particular schizophrenia (deficient form and productive form) and acute or chronic extrapyramidal symptoms induced by neuroleptics, for the treatment of various forms of anxiety, panic
35 attacks, phobia, obsessive compulsive disorders, for treating various forms of depression, including psychotic depression, for treating disorders caused by alcohol abuse or weaning from alcohol, sexual behavior disorders, eating disorders and for treating migraine.

Moreover, the compounds of the invention may be used for treating painful muscle contracture in rheumatology and in acute spinal pathology, for treating spastic
5 contractures of medullary or cerebral origin, for the symptomatic treatment of acute and subacute pain of light to moderate intensity, for treating intense and/or chronic pain, neurogenic pain and intractable pain, for treating Parkinson's disease and Parkinson-
10 like symptoms of neurodegenerative origin or induced by neuroleptics, for treating partial primary and secondary generalized epilepsy of simple or complex symptomatology, mixed forms and other epileptic syndromes in addition to another antiepileptic
15 treatment, or in monotherapy, for the treatment of sleep apnea, and for neuroprotection.

A subject of the present invention is also pharmaceutical compositions containing an effective
20 dose of at least one compound according to the invention, in the form of base or of pharmaceutically acceptable salt or solvate, and as a mixture, where appropriate, with suitable excipients. Said excipients are chosen according to the pharmaceutical form and the
25 desired mode of administration.

The pharmaceutical compositions according to the invention may thus be intended for oral, sublingual, subcutaneous, intramuscular, intravenous, topical,
30 intratracheal, intranasal, transdermal, rectal or intraocular administration.

The unit administration forms may be, for example, tablets, gel capsules, granules, powders, oral or
35 injectable solutions or suspensions, transdermal patches or suppositories. Pomades, lotions and eyedrops may be envisioned for topical administration.

By way of example, a unit form of administration of a compound according to the invention in the form of a tablet may comprise the following components:

5	Compound according to the invention	50.0 mg
	Mannitol	223.75 mg
	Sodium croscarmellose	6.0 mg
	Corn starch	15.0 mg
	Hydroxypropylmethylcellulose	2.25 mg
10	Magnesium stearate	3.0 mg

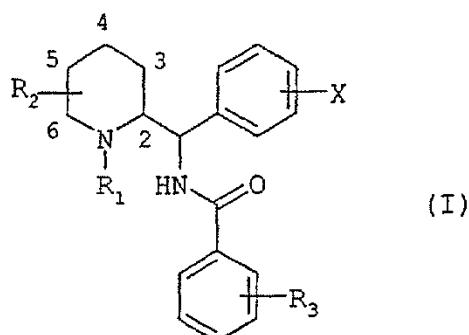
Said unit forms are dosed to allow a daily administration of from 0.01 to 20 mg of active principle per kg of body weight, according to the
15 galenical form.

There may be special cases in which higher or lower doses are appropriate; such doses do not depart from the context of the invention. According to the usual
20 practice, the dosage that is appropriate to each patient is determined by the medical practitioner according to the mode of administration, the weight and the response of said patient.

25 According to another of its aspects, the present invention also relates to a method for treating the pathologies indicated above, which comprises the administration, to a patient, of an effective dose of a compound according to the invention, or of a
30 pharmaceutically acceptable salt or hydrates or solvates thereof.

Claims

1. A compound corresponding to the general formula (I)



5

in which

R_1 represents either a hydrogen atom, or a linear or branched (C_1-C_7) alkyl group optionally substituted with one or more fluorine atoms, or a (C_3-C_7) cycloalkyl group, or a (C_3-C_7) cycloalkyl (C_1-C_3) alkyl group, or a phenyl (C_1-C_3) alkyl group optionally substituted with one or two methoxy groups, or a (C_2-C_4) alkenyl group, or a (C_2-C_4) alkynyl group;

R_2 represents either a linear or branched (C_1-C_7) alkyl or (C_3-C_7) cycloalkyl group, or a (C_3-C_7) cycloalkyl (C_1-C_3) alkyl group;

X represents either a hydrogen atom or one or more substituents chosen from halogen atoms and trifluoromethyl, linear or branched (C_1-C_6) alkyl and (C_1-C_6) alkoxy groups;

R_3 represents either a hydrogen atom or one or more substituents chosen from halogen atoms and trifluoromethyl, linear or branched (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkoxy, phenyl, cyano, acetyl, benzoyl, (C_1-C_6) thioalkyl, (C_1-C_6) alkylsulfonyl, carboxyl and (C_1-C_6) alkoxycarbonyl groups, or a group of general formula NR_4R_5 or $SO_2NR_4R_5$ or $CONR_4R_5$ in which R_4 and R_5 each independently represent a hydrogen atom or a linear or branched (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl group, or R_4 and R_5 form, with the nitrogen atom that

bears them, a pyrrolidine, piperidine or morpholine ring; in the form of free base or acid-addition salt, hydrate or solvate.

5 2. The compound as claimed in claim 1, characterized in that it is of threo configuration; in the form of free base or acid-addition salt, hydrate or solvate.

3. The compound as claimed in claim 2, characterized
10 in that it is of (1*S*, 2*S*) or (1*R*, 2*R*) configuration; in the form of free base or acid-addition salt, hydrate or solvate.

4. The compound as claimed in claim 1, characterized
15 in that it is of erythro configuration; in the form of free base or acid-addition salt, hydrate or solvate.

5. The compound as claimed in claim 4, characterized in that it is of (1*S*, 2*R*) or (1*R*, 2*S*) configuration; in
20 the form of free base or acid-addition salt, hydrate or solvate.

6. A medicament, characterized in that it comprises a compound as claimed in one of claims 1 to 5, or an
25 addition salt of this compound with a pharmaceutically acceptable acid or alternatively a hydrate or a solvate of the compound of formula (I).

7. A pharmaceutical composition, characterized in
30 that it comprises a compound as claimed in one of claims 1 to 5, or a pharmaceutically acceptable salt, a hydrate or a solvate of this compound, and also at least one pharmaceutically acceptable excipient.

8. The use of a compound of formula (I) as claimed in
35 one of claims 1 to 5, for the preparation of a medicament for treating behavioral disorders associated with dementia, psychoses, various forms of anxiety, panic attacks, phobias, obsessive compulsive disorders,

various forms of depression, disorders caused by alcohol abuse or weaning from alcohol, sexual behavior disorders, eating disorders and migraine.

- 5 9. The use of a compound of formula (I) as claimed in
one of claims 1 to 5 for the preparation of a
medicament for treating contracture, pain, Parkinson's
disease and Parkinson-like symptoms, epilepsy, mixed
forms and other epileptic syndromes in addition to
10 another antiepileptic treatment, or in monotherapy, and
sleep apnea, and for neuroprotection.