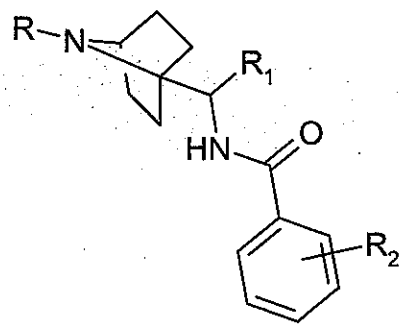
DERIVATIVES *OF N*-[(7-AZABICYCLO[2.2.1]HEPT-1-YL)-ARYL-METHYL]BENZAMIDE, PREPARATION THEREOF AND THERAPEUTIC USE THEREOF

The present invention relates to *N*-[(7-azabicyclo[2.2.1]hept-1-yl)-aryl-methyl]benzamide derivatives, to the preparation thereof and to the therapeutic use thereof in the treatment or prevention of diseases involving Glyt1 glycine transporters.

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



(I)

in which:

- R represents a hydrogen atom or a group chosen from the groups (C_1-C_6)alkyl and (C_3-C_7)cycloalkyl, optionally substituted with one or more groups chosen, independently of one another, from halogen atoms and (C_3-C_7)cycloalkyl, (C_2-C_4)alkenyl, phenyl, (C_1-C_6)alkoxy and hydroxyl groups; the phenyl group being optionally substituted with one or more (C_1-C_6)alkoxy groups;
- R_1 represents a phenyl or naphthyl group, optionally substituted with one or more substituents chosen, independently of one another, from halogen atoms and (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo-(C_1-C_6)alkyl, hydroxyl, halo-(C_1-C_6)alkoxy, (C_1-C_6)alkyl-thio, (C_1-C_6)alkyl-SO and (C_1-C_6)alkyl-SO_2 groups;
- R_2 represents one or more substituents chosen from a hydrogen atom, halogen atoms and halo-(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_3)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-thio, (C_1-C_6)alkyl-SO and (C_1-C_6)alkyl-SO_2 groups;

in the form of a base or of an addition salt with an acid.

The compounds of formula (I) comprise an asymmetric carbon atom. They can therefore exist in the form of enantiomers. These enantiomers, including racemic mixtures, belong to the invention.

The compounds of formula (I) can exist in the form of bases or of addition salts with acids. Such addition salts belong to the invention.

These salts are advantageously prepared with pharmaceutically acceptable acids, but the salts of other acids that are of use, for example, for purifying or isolating the compounds of formula (I) also belong to the invention.

In the context of the invention:

- the expression "C_t-C_z where t and z can take the values of 1 to 6" is intended to mean a carbon-based chain that can contain from t to z carbon atoms, for example the term "C_1-C_6" is intended to mean a carbon-based chain that can contain from 1 to 6 carbon atoms;
- the term "alkyl" is intended to mean a linear or branched, saturated aliphatic group; for example, a C_1-C_6-alkyl group represents a linear or branched carbon-based chain containing from 1 to 6 carbon atoms, for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl or hexyl;
- the term "alkylene" is intended to mean a linear or branched, saturated divalent alkyl group; for example, a C_{1-6}-alkylene group represents a linear or branched, divalent carbon-based chain containing from 1 to 6 carbon atoms, for example a methylene, ethylene, 1-methylethylene or propylene;
- the term "alkoxy" is intended to mean an -O-alkyl group;
- the term "hydroxyl" is intended to mean an -OH group;
- the term "alkyl-thio" is intended to mean a sulphur atom substituted with an alkyl group;
- the term "halogen atom" is intended to mean a fluorine, a chlorine, a bromine or an iodine;
- the term "halo-alkyl" is intended to mean an alkyl group in which one or more hydrogen atoms have been substituted with halogen. By way of example, mention may be made of trifluoromethyl, trifluoroethyl or pentafluoroethyl groups;
- the term "halo-alkoxy" is intended to mean an alkoxy group in which one or more hydrogen atoms have been substituted with halogen.

Among the compounds of general formula (I) which are subjects of the invention, a first group of compounds is constituted of the compounds for which:

- R represents a hydrogen atom or a (C_1-C_6)alkyl or benzyl group;
- $R_1$and R_2 being as defined above.

Among the compounds of general formula (I) which are subjects of the invention, a second group of compounds is constituted by the compounds for which:
- R_1 represents a phenyl group;
- R and R_2 being as defined above.

Among the compounds of general formula (I) which are subjects of the invention, a third group of compounds is constituted of the compounds for which:
- R_2 represents one or more substituents chosen from a hydrogen atom, halogen atoms and halo-(C_1-C_6)alkyl or (C_1-C_6)alkyl groups;
- R and R_1 being as defined above.

Among the compounds of general formula (I) which are subjects of the invention, a fourth group of compounds is constituted of the compounds for which:
- R represents a hydrogen atom or a (C_1-C_6)alkyl or benzyl group;
- R_1 represents a phenyl group;
- R_2 represents one or more substituents chosen from a hydrogen atom, halogen atoms and halo-(C_1-C_6)alkyl or (C_1-C_6)alkyl groups.

Among the compounds of general formula (I) which are subjects of the invention, a fifth group of compounds is constituted of the compounds for which:
- R represents a hydrogen atom or a methyl, ethyl or benzyl group;
- R_1 represents a phenyl group;
- R_2 represents one or more substituents chosen from a hydrogen atom, a chlorine atom and methyl, ethyl or trifluoromethyl groups, in the form of a base or of an addition salt with an acid.

The combinations of groups one to five as defined above also belong to the invention.

Among the compounds of general formula (I) which are subjects of the invention, mention may in particular be made of the following compounds:

•*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylméthyl](2-methyl-3-trifluoromethyl)benzamide;

•*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2,6-dichloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;

•(-)-*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2,6-dichloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;

•*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2-chloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;

•2-chloro-*N*-[(7-ethyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](3-trifluoromethyl)benzamide, and the hydrochloride thereof;

•(+)-*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2,6-dichloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;

•2-chloro-*N*-[(7-methyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl]-3-trifluoromethyl-benzamide, and the hydrochloride thereof;

•*N*-[(7-benzyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl]-(2-methyl-3-trifluoro-methyl)benzamide, and the hydrochloride thereof;

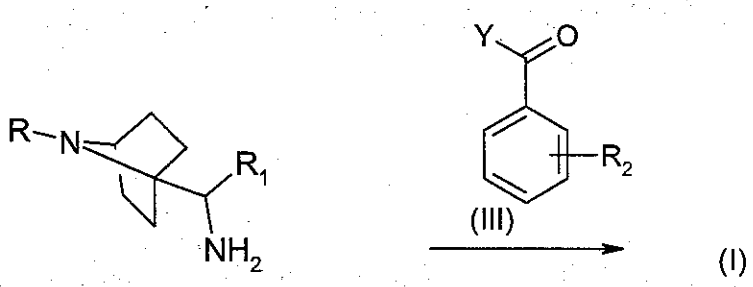
•*N*-[(7-benzyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2-chloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;

•N-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2-chloro-3-ethyl)benzamide, and the hydrochloride thereof.

The compounds of the invention exhibit a particular activity as inhibitors of Glyt1 glycine transporters, in particular an improved activity and improved safety profile.

The compounds of general formula (I) can be prepared by means of a process illustrated by scheme 1 which follows:

SCHEME 1



(II) (I)

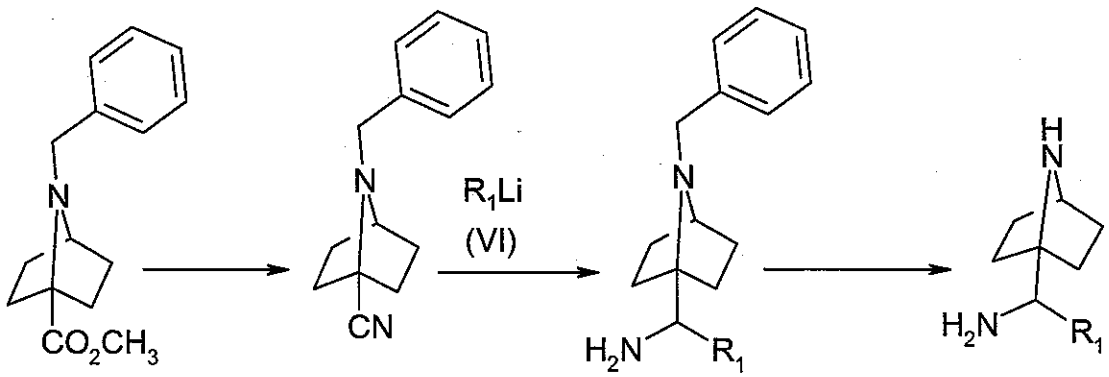
A diamine of general formula (II), in which R and R_1 are as defined above, in particular when R represents a hydrogen atom or a phenylmethyl group, is coupled with an acid that is activated, for example via a mixed anhydride or an acid chloride of general formula (III) in which Y represents a leaving group derived, for example, from benzotriazole, from acylurea or a halogen atom and R_2 is as defined above, using the methods known to those skilled in the art.

The compounds of general formula (I) in which R represents a hydrogen atom can also be prepared from compounds of general formula (I) in which R represents:
- either a phenylmethyl group, by deprotecting the nitrogen by hydrogenolysis,
- or an alkenyl group, preferably allyl group, by deprotecting the nitrogen, for example with a complex of palladium "zero" according to the methods known to those skilled in the art,
- or a dimethoxybenzyl group, by deprotecting using oxidation methods known to those skilled in the art.

The compounds of general formula (I) in which R is other than a hydrogen atom can also be prepared from compounds of general formula (I) in which R represents a hydrogen atom, either by alkylation of said compound of general formula (I) with a halide or mesylate of the RX type, in which R is as defined above and X is a mesylate or halogen, in the presence of an inorganic base, for example potassium carbonate in acetonitrile; or by means of an Eschweiler-Clarke reaction or reductive amination with a suitable aldehyde or a suitable ketone according to the methods known to those skilled in the art; or with a suitable epoxide derivative, according to the methods known to those skilled in the art.

The diamine of general formula (II) can be prepared by means of the process illustrated by scheme 2 for the amine of general formula (IIa) and for the amine of general formula (IIb) which follows:

SCHEME 2



(IV) (V) (IIa) (IIb)

According to scheme 2, the ester of formula (IV) is converted to the nitrile of formula (V) by heating at the reflux of xylene in the presence of the previously formed complex of trimethylaluminium and of ammonium chloride, according to a method described in *Synthetic Commun., 1982,12 (13), 989-993* and in *Tetrahedron Lett., 1979, (51), 4907-4910*. The nitrile of formula (V) is then reacted with the lithiated aromatic compound of general formula (VI), in which R_1 is as defined above, in an ethereal solvent such as tetrahydrofuran or ether, at low temperature, for example -70°C. An imine is thus obtained, which is reduced with a reducing agent such as sodium borohydride in a protic solvent such as methanol, so as to give the amine of general formula (IIa). The amine (IIa) can be debenzylated by hydrogenation in the presence of a palladium catalyst, so as to give the deprotected amine of general formula (IIb).

For the compounds of formulae (IV) and (V), the benzyl group could in particular be replaced with another protective group, for example with an allyl group or a dimethoxybenzyl group, either:

- by debenzylating and then reprotecting, for example via an alkylation reaction with the appropriate electrophilic agent, for example an allyl bromide or a dimethoxybenzyl bromide, according to the methods known to those skilled in the art;

- or according to the method described in *Tetrahedron: Asymmetry, 2006 (17), 252-258* by replacing the benzylamine with allylamine or a dimethoxybenzylamine, in particular 2,4-dimethoxybenzylamine.

Moreover, the chiral compounds of general formula (I) corresponding to the *S* or *R* enantiomers can be obtained by separation of the racemic compounds by chiral-column high performance liquid chromatography (HPLC), or could be obtained by resolving of the racemic amine of general formula (II) using a chiral acid, such as dibenzoyltartaric acid, or by fractionated and preferential recrystallization of a diastereoisomeric salt.

The ester of formula (IV) is prepared according to a method described in *Tetrahedron, 2002 (58), 10167-10171.*

The nitrile of formula (V) could also be prepared according to a method described in *Tetrahedron: Asymmetry, 2006 (17), 252-258.*

The lithiated derivatives of general formula (VI) can be prepared according to methods known to those skilled in the art.

The acids and acid chlorides of general formula (III) are commercially available or prepared by analogy with methods known to those skilled in the art.

The examples which follow illustrate the preparation of some compounds of the invention. In these examples:

- the elemental microanalyses, the IR and NMR spectra and the chiral-column HPLC confirm the structures and the enantiomeric purities of the compounds obtained,
- For the NMR descriptions, "m" means multiplet, "s" singlet, "t" triplet, "d" doublet, "q" quadruplet, dxd means double doublet, txt means triple triplet, dxt means double triplet, etc.,
- The numbers indicated between parentheses in the titles of the examples correspond to those of the 1st column of the table given later,
- "decomp." means "decomposition",
- The nomenclature used is the nomenclature according to the IUPAC (International Union of Pure and Applied Chemistry) recommendations.

In the names of the compounds, the dash "-" is part of the word and the dash "_" is only used for the break at the end of a line; it should be deleted in the absence of a break and should not be replaced by a normal dash nor by a space.

Example 1 (Compound No. 4): *N*-[(7-Azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2-chloro-3-trifluoromethyl)benzamide hydrochloride (1:1)

1.1. (7-Benzyl-7-azabicyclo[2.2.1]heptane)-1-carbonitrile

In a 250 ml three-necked flask under nitrogen, the complex of trimethylaluminium and of ammonium chloride (approximately 0.67M), hereinafter referred to as complex A, is prepared by placing 1.5 g of dry ammonium chloride (28 mmol) in 30 ml of anhydrous toluene, adding thereto, after cooling, 15 ml of a 2N solution of trimethylaluminium in toluene (30 mmol), and leaving the mixture at ambient temperature until no more gas is given off.

In a 250 ml three-necked flask under nitrogen, fitted with a condenser, 1.27 g of methyl (7-benzyl-7-azabicyclo[2.2.1]heptane)-1-carboxylate (5.18 mmol) are placed in 100 ml of anhydrous xylene.

20 ml of the complex A (13 mmol) are added dropwise and the mixture is refluxed overnight.

After cooling, the medium is acidified to pH 4-5 with a 1N hydrochloric acid solution and is then extracted successively with ethyl acetate (100 ml) and then dichloromethane (100 ml).

The organic phases are dried over sodium sulphate, filtered, combined, and then evaporated under reduced pressure.

The residue is purified by silica gel column chromatography, elution being carried out with a mixture of petroleum ether and ethyl acetate. 210 mg of (7-benzyl-7-azabicyclo[2.2.1]heptane)-1-carbonitrile are thus obtained in the form of an oil.

^{1}H NMR (200 MHz,$CDCl_3$) δ ppm 7.5 (m, 5H), 3.75 (s, 2H), 3.40 (m, 1H), 2.25 (m, 2H), 2.0 (m, 4H), 1.4 (m, 2H).

1.2. (7-Benzyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethylamine

In a 50 ml three-necked flask under argon, 0.45 g of (7-benzyl-7-azabicyclo[2.2.1]heptane)-1-carbonitrile (2.12 mmol) is placed, at -70°C, in 15 ml of

anhydrous tetrahydrofuran. 5.65 ml of a 0.75M solution (cyclohexane/ether) of phenyllithium (4.24 mmol) are added dropwise.

The mixture is left at -70°C for two and a half hours and then hydrolysed at -20°C with 10 ml of water.

After extraction with ethyl acetate, the organic phase is concentrated under reduced pressure and the residue is then taken up in 20 ml of methanol. 0.40 g of sodium borohydride (10.6 mmol) is added thereto portionwise. The reaction medium is left to stir overnight at ambient temperature.

After evaporation under reduced pressure, the residue is taken up with 25 ml of ether and 25 ml of water. The medium is acidified with a 1N hydrochloric acid solution and then extracted. The aqueous phase is basified with aqueous ammonia and then reextracted twice with 50 ml of dichloromethane. The organic phases are combined, dried over sodium sulphate, filtered, and evaporated under reduced pressure. The residue is purified by silica gel column chromatography, elution being carried out with a mixture of dichloromethane and ammoniacal methanol. 0.5 g of (7-benzyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethylamine is thus obtained in the form of an oil which crystallizes.

^{1}H NMR (400 MHz,$CDCl_3$) δ ppm 7.56 -7.22 (m, 10H), 4.31 (s, 1H), 3.86 (d, J = 13.3 Hz, 1H), 3.37 (d, J = 13.3 Hz, 1H), 3.19 (t, J = 4.5 Hz, 1H), 2.23 (m, 1H), 2.00 (m, 1H), 1.80-1.56 (m, 2H), 1.37 (m, 1H), 1.22 -1.06 (m, 2H), 0.97 (m, 1H).

Mp = 87-88°C

1.3. (7-azabicyclo[2.2.1]hept-1-yl)phenylmethylamine

In an autoclave, 0.5 g of (7-benzyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethylamine (1.71 mmol) in solution in 20 ml of ethanol and 3.4 ml of 1N hydrochloric acid in the presence of a spatula tip of palladium on carbon at 10% are placed under a pressure of 7 atmospheres of hydrogen at 50°C for 6 hours. After the catalyst has been filtered off and the filtrate has been concentrated under reduced pressure, the residue is taken up in 25 ml of dichloromethane and 25 ml of water basified with aqueous ammonia. After extraction, the organic phase is dried over sodium sulphate, filtered, and evaporated under reduced pressure. 0.28 g of (7-azabicyclo[2.2.1]hept-1-yl)phenylmethylamine is thus obtained in the form of an oil which solidifies in the cold and which is used as it is in the next stage.

^{1}H NMR (400 MHz,$CDCl_3$) δ ppm 7.36 -7.13 (m, 5H), 4.24 (s, 1H), 3.49 (t, J = 4.8 Hz, 1H), 1.74-1.15 (m, 8H).

Mp = 62-63°C

1.4. *N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2-chloro-3-trifluoromethyl)benzamide hydrochloride (1:1)

In a 25 ml round-bottomed flask, 0.26 g of (2-chloro-3-trifluoromethyl)benzoic acid (1.19 mmol), 0.16 g of hydroxybenzotriazole (1.19 mmol) and 0.23 g of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.19 mmol) are dissolved in 5 ml of dichloromethane and the mixture is stirred at ambient temperature for 15 minutes. 0.2 g (1.0 mmol) of (7-azabicyclo[2.2.1]hept-1-yl)phenylmethylamine in solution in 2 ml of dichloromethane is added and the mixture is stirred at ambient temperature overnight.

The reaction medium is then diluted with 2 ml of dichloromethane and then washed successively with water (3 ml), with 1N sodium hydroxide (3 ml) and with a saturated solution of sodium chloride (3 ml).

The organic phase is dried over sodium sulphate, filtered, and evaporated under reduced pressure. The residue is purified by silica gel column chromatography, elution being carried out with a mixture of dichloromethane and ammoniacal methanol. 260 mg of *N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2-chloro-3-trifluoromethyl)benzamide are thus obtained, said compound being salified in hydrochloride form by solubilisation of the base in ether, addition of an excess of 1N hydrochloric acid in ether and then concentration under reduced pressure.

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 9.52 (d, J = 9 Hz, 1H), 9.32 (m, 1H), 8.92 (m, 1H), 7.96 (m, 2H), 7.65 (m, 1H), 7.55-7.30 (m, 5H), 5.69 (d, J = 9.1 Hz, 1H), 4.07 (m, 1H), 2.30-0.65 (m, 8H).

Mp = 146.5-147.5°C.

Example 2 (Compound No. 5): 2-Chloro-*N*-[(7-ethyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](3-trifluoromethyl)benzamide hydrochloride (1:1)

In a 25 ml round-bottomed flask fitted with a condenser, 95 mg of *N*-[(2-azabicyclo[2.1.1]hex-1-yl)phenylmethyl](2-chloro-3-trifluoromethyl)benzamide (0.23 mmol) are placed in 2 ml of acetonitrile and 64 mg of potassium carbonate, to which 30 µl of iodoethane (0.36 mmol) are added. The reaction medium is stirred overnight at 45°C and then for 3 hours at 50°C and is then concentrated under

reduced pressure. The residue is then diluted with 10 ml of dichloromethane and then washed with water (5 ml). After extraction, the organic phase is dried over sodium sulphate, filtered, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography, elution being carried out with a mixture of dichloromethane and ammoniacal methanol. 90 mg of 2-chloro-*N*-[(7-ethyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](3-trifluoromethyl)benzamide are thus obtained, said compound being salified in hydrochloride form by solubilisation of the base in dichloromethane, addition of an excess of 1N hydrochloric acid in ether, and then concentration under reduced pressure.

^{1}H NMR (400 MHz,DMSO-d6) δ ppm 10.29 (m, 1H), 9.48 (d, J = 9.1 Hz, 1H), 8.12 (m, J = 8 Hz, 1H), 7.94 (m, J = 7.6 Hz, 1H), 7.71-7.31 (m, 6H), 5.68 (d, J = 9.3 Hz, 1H), 4.21 (m, 1H), 3.41-3.03 (m, 2H), 2.39-1.15 (m, 11H).
Mp = 189.5-191.5°C.

Example 3 (Compound No. 7): 2-Chloro-*N*-[(7-methyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](3-trifluoromethyl)benzamide hydrochloride (1:1)

In a 25 ml round-bottomed flask fitted with a condenser, 0.09 g of *N*-[(2-azabicyclo[2.1.1]hex-1-yl)phenylmethyl](2-chloro-3-trifluoromethyl)benzamide (0.22 mmol) and 2 ml of formaldehyde are placed in 2 ml of formic acid. The reaction mixture is heated at 100°C for 72 hours. After cooling, the medium is hydrolysed, basified to pH 9 with aqueous ammonia, and then extracted with dichloromethane. The organic phase is dried over sodium sulphate, filtered, and evaporated under reduced pressure. 70 mg of 2-chloro-*N*-[(7-ethyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](3-trifluoromethyl)benzamide are thus obtained, said compound being salified in hydrochloride form by solubilisation of the base in dichloromethane, addition of an excess of 1N hydrochloric acid in ether and then concentration under reduced pressure.

^{1}H NMR (400 MHz,DMSO-d6) δ ppm 10.58 (m, 1H), 9.54 (d, J = 9.6 Hz, 1H), 8.26 (m, J = 7.4 Hz, 1H), 7.97 (m, J = 7.6 Hz, 1H), 7.75-7.33 (m, 7H), 5.71 (d, J = 9.4 Hz, 1H), 4.05 (m, 1H), 2.87 (m, 3H), 2.44-1.18 (m, 8H).
Mp = 244-246°C.

The other compounds listed in the table are obtained according to the methods

described in Examples 1 to 3 using amines of general formula (IIa) or (IIb), lithium compounds of general formula (VI), carboxylic acid derivatives of general formula (III) or alkylating agents that are appropriate.

Table 1 which follows illustrates the chemical structures of some compounds of the invention.

In the "salts" column, "-" denotes a compound in the form of a base, "HCl" denotes a hydrochloride, the number between parentheses indicating the (acid:base) ratio;

In the columns R, R_1 and R_2:

- "Cl" stands for chlorine,
- "CH_3" stands for methyl,
- "Ph" stands for phenyl,
- "Bn" stands for benzyl,
- "CF_3" stands for trifluoromethyl,
- in the column "R_2", the number before the substituents indicates the position in general formula (I),
- The compounds in the table are in the form of hydrochloride solvated with one or more molecules of water.

Compounds No. 3 and 6 in Table 1 form a pair of enantiomers which are separated by preparative HPLC, using a Chirobiotic® T2 5 µm column and a 100/0.1/0.05 methanol/triethylamine/acetic acid mixture as solvent. The absolute stereochemistry was determined by X-ray diffraction.

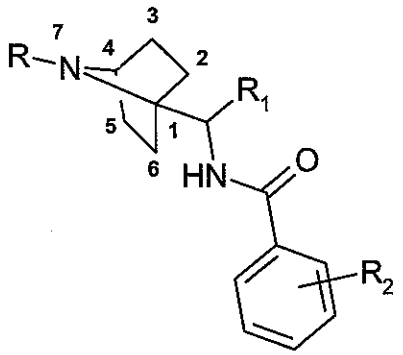
Table 2 gives the physical properties, melting points and optical rotations of the compounds of Table 1.

In Table 2:

- the column $[\alpha_D]_{20°C}$ gives information on the result of analysis of the optical rotation of the compounds of the table at the wavelength of 589 nM and the temperature of 20°C. The solvent indicated between parentheses corresponds to the solvent used to carry out the measurement of optical rotation in degrees, and the letter "c" indicates the concentration of the solvent in g/100 ml. "N.A." means that the optical rotation measurement is not applicable,
- the column "m/z" gives information on the molecular ion $(M+H^+)$ or (M^+) observed by analysis of the products by mass spectrometry, either by LC-MS (liquid

chromatography coupled to mass spectroscopy) carried out on an Agilent LC-MSD Trap instrument in positive ESI mode, or by direct introduction by MS (mass spectroscopy) on an Autospec M (EBE) instrument using the DCI-NH_3 technique or using the electron impact technique on a Waters GCT instrument.

TABLE 1



(I)

No.	R	R_1	R_2	Salts	stereochemistry
1	H	Ph	2-CH_3,3-CF_3	-	racemic
2	H	Ph	2,6-$(Cl)_2$,3-CF_3	HCl (1:1)	racemic
3	H	Ph	2,6-$(Cl)_2$,3-CF_3	HCl (1:1)	Chiral laevorotatory R
4	H	Ph	2-Cl,3-CF_3	HCl (1:1)	racemic
5	C_2H_5	Ph	2-Cl,3-CF_3	HCl (1:1)	racemic
6	H	Ph	2,6-$(Cl)_2$,3-CF_3	HCl (1:1)	Chiral dextrorotatory S
7	CH_3	Ph	2-Cl,3-CF_3	HCl (1:1)	racemic
8	Bn	Ph	2-CH_3,3-CF_3	HCl (1:1)	racemic
9	Bn	Ph	2-Cl,3-CF_3	HCl (1:1)	racemic
10	H	Ph	2-Cl,3-C_2H_5	HCl (1:1)	racemic

TABLE 2

No.	Mp °C	$[\alpha_D]_{20°C}$ °	LCMS MH^+
1	62-63	N.A	389
2	210-211	N.A	443
3	185-186	-50.73 (MeOH, c=0.466 g/100 ml)	443
4	146.5-147.5	N.A	409
5	189.5-191.5	N.A	437
6	181.5-182.5	+34.41 (MeOH, c=0.732g/100 ml)	443
7	244-246	N.A	423
8	153-154	N.A	479
9	159.5-160.5	N.A	499
10	234.2-235.2	N.A	369

The compounds of the invention were subjected to a series of pharmacological tests which demonstrated their advantage as substances having therapeutic activities.

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

[^{14}C]glycine uptake is studied in SK-N-MC cells (human neuroepithelial cells) expressing the native human transporter glyt1, by measuring the radioactivity incorporated in the presence or absence of the test compound. The cells are cultured in a monolayer for 48 h in plates pretreated with 0.02% fibronectin. On the day of the experiment, the culture medium is removed and the cells are washed with a Krebs-HEPES ([4-(2-hydroxyethyl)piperazine]-1-ethanesulphonic acid) buffer at pH 7.4. After preincubation for 10 min 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 nonspecific uptake), 10 µM [^{14}C]glycine (specific activity 112 mCi/mmol) is then added. The incubation is continued for 10 min at 37°C, and the reaction is stopped by means of 2 washes with a Krebs-HEPES buffer at pH 7.4. The radioactivity incorporated by the cells is then estimated after adding 100 µl of liquid scintillant and

stirring for 1 h. The counting is performed on a Microbeta Tri-lux™ counter. The effectiveness of the compound is determined by means of the IC_{50}, which is the concentration of the compound which reduces by 50% the specific uptake of glycine, defined by the difference in radioactivity incorporated by the control batch and the batch which received the glycine at 10 mM.

The compounds of the invention, in this test, have an IC_{50} of the order of 0.001 to 10 µM.

Table 3 indicates some examples of IC_{50} results for compounds according to the invention.

TABLE 3

Compound	IC_{50} (µM)
1	0.038
2	0.003
3	0.023
4	0.027
6	0.0016

The results of the tests carried out on the chiral compounds of the invention and the racemates thereof in general formula (I) show that they are inhibitors of the glyt1 glycine transporter present in the brain.

These results suggest that the compounds of the invention can be used for the treatment of cognitive and/or behavioural disorders associated with neurodegenerative diseases, with dementia; for the treatment of psychoses, in particular of schizophrenia (deficient form and productive form), acute or chronic extrapyramidal symptoms induced by neuroleptics; for the treatment of various forms of anxiety, panic attacks, phobias, obsessive-compulsive disorders; for the treatment of various forms of depression, including psychotic depression; for the treatment of bipolar disorders, manic disorders, mood disorders; for the treatment of disorders due to alcohol abuse or to alcohol withdrawal, sexual behaviour disorders, eating disorders, migraine; pain; sleep disorders.

The compounds according to the invention can therefore be used for the preparation

of medicaments, in particular medicaments which inhibit the glyt1 glycine transporter.

Thus, according to another of the aspects of the invention, a subject thereof is medicaments which comprise a compound of formula (I), or an addition salt of the latter with a pharmaceutically acceptable acid or else a hydrate or a solvate of the compound of formula (I).

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

Said excipients are chosen according to the pharmaceutical form and the method of administration desired.

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

The unit administration forms may be, for example, tablets, gel capsules, granules, powders, oral or injectable solutions or suspensions, patches or suppositories. For topical administration, ointments, lotions and collyria can be envisaged.
Said unit forms contain doses so as to allow a daily administration of 0.01 to 20 mg of active ingredient per kg of body weight, according to the galenical form.

In order to prepare tablets, a pharmaceutical carrier which may be composed of diluents, for example lactose, microcrystalline cellulose or starch, and formulation additives such as binders (polyvinylpyrrolidone, hydroxypropylmethylcellulose, etc.), flow agents such as silica, and lubricants such as magnesium stearate, stearic acid, glyceryl tribehenate or sodium stearylfumarate, are added to the active ingredient, which may or may not be micronized. Wetting agents or surfactants such as sodium lauryl sulphate can also be added.
The preparation techniques may be direct compression, dry granulation, wet granulation or the hot-melt process.
The tablets may be uncoated, sugar-coated, for example with sucrose, or coated with

various polymers or other suitable materials. They can be designed so as to allow rapid, delayed or sustained release of the active ingredient by virtue of polymer matrices or of specific polymers used in the coating.

In order to prepare gel capsules, the active ingredient is mixed with dry pharmaceutical carriers (simple mixing, dry or wet granulation, or the hot-melt process), or liquid or semi-solid pharmaceutical carriers.
The gel capsules may be hard or soft, and optionally film-coated, so as to have a rapid, sustained or delayed activity (for example, for an enteric form).

A composition in the form of a syrup or an elixir or for administration in the form of drops can contain the active ingredient together with a sweetener, preferably a calorie-free sweetener, methylparaben or propylparaben as antiseptic, a flavour enhancer and a colorant.

The water-dispersible powders and granules can contain the active ingredient as a mixture with dispersing agents or wetting agents, or dispersing agents, such as polyvinylpyrrolidone, as well as with sweeteners and flavour-correcting agents.

For rectal administration, recourse is had to suppositories prepared with binders which melt at the rectal temperature, for example cocoa butter or polyethylene glycols.

For parenteral administration, use is made of aqueous suspensions, isotonic saline solutions or injectable sterile solutions comprising pharmacologically compatible dispersing agents and/or wetting agents, for example propylene glycol or butylene glycol.

The active ingredient can also be formulated in the form of microcapsules, optionally with one or more supports or additives, or else with a polymer matrix or with a cyclodextrin (patches, sustained-release forms).

The topical compositions according to the invention comprise a medium compatible with the skin. They can be provided in particular in the form of aqueous, alcoholic or aqueous-alcoholic solutions, of gels, of water-in-oil or oil-in-water emulsions having the appearance of a cream or of a gel, of microemulsions or of aerosols, or else in the

form of vesicular dispersions containing ionic and/or nonionic lipids. These galenical forms are prepared according to the usual methods in the fields under consideration.

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

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

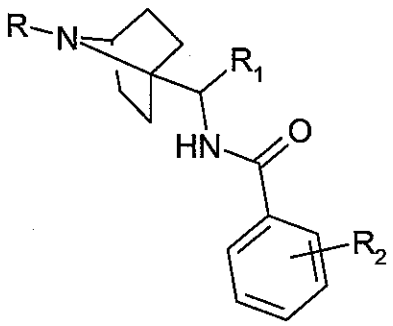
When given orally, the dose of active ingredient administered per day can reach 0.1 to 20 mg/kg, in one or more intakes.

There may be particular cases where higher or lower dosages are appropriate; such dosages do not depart from the context of the invention. Depending on the usual practice, the dosage appropriate for each patient is determined by the physician according to the method of administration and the weight and response of said patient.

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 a pharmaceutically acceptable salt thereof.

CLAIMS

1. Compound of general formula (I)



(I)

in which:

- R represents a hydrogen atom or a group chosen from the groups (C_1-C_6)alkyl and (C_3-C_7)cycloalkyl, optionally substituted with one or more groups chosen, independently of one another, from halogen atoms and (C_3-C_7)cycloalkyl, (C_2-C_4)alkenyl, phenyl, (C_1-C_6)alkoxy and hydroxyl groups; the phenyl group being optionally substituted with one or more (C_1-C_6)alkoxy groups;
- R_1 represents a phenyl or naphthyl group, optionally substituted with one or more substituents chosen, independently of one another, from halogen atoms and (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo-(C_1-C_6)alkyl, hydroxyl, halo-(C_1-C_6)alkoxy, (C_1-C_6)alkyl-thio, (C_1-C_6)alkyl-SO and (C_1-C_6)alkyl-SO_2 groups;
- R_2 represents one or more substituents chosen from a hydrogen atom, halogen atoms and halo-(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_3)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-thio, (C_1-C_6)alkyl-SO and (C_1-C_6)alkyl-SO_2 groups;

in the form of a base or of an addition salt with an acid.

2. Compound of general formula (I) according to Claim 1, characterized in that R represents a hydrogen atom or a (C_1-C_6)alkyl or benzyl group; R_1 and R_2 being as defined in Claim 1, in the form of a base or of an addition salt with an acid.

3. Compound of general formula (I) according to Claim 1, characterized in that

R_1 represents a phenyl group;
R and R_2 being as defined in Claim 1, in the form of a base or of an addition salt with an acid.

4. Compound of general formula (I) according to Claim 1, characterized in that
R_2 represents one or more substituents chosen from a hydrogen atom, halogen atoms and halo-(C_1-C_6)alkyl or (C_1-C_6)alkyl groups;
R and R_1 being as defined in Claim 1, in the form of a base or of an addition salt with an acid.

5. Compound of general formula (I) according to Claim 1, characterized in that
R represents a hydrogen atom or a (C_1-C_6)alkyl or benzyl group;
R_1 represents a phenyl group;
R_2 represents one or more substituents chosen from a hydrogen atom, halogen atoms and halo-(C_1-C_6)alkyl or (C_1-C_6)alkyl groups,
in the form of a base or of an addition salt with an acid.

6. R represents a hydrogen atom or a methyl, ethyl or benzyl group;
R_1 represents a phenyl group;
R_2 represents one or more substituents chosen from a hydrogen atom, a chlorine atom and methyl, ethyl or trifluoromethyl groups, in the form of a base or of an addition salt with an acid.

7. Compound according to Claim 1 or 2, characterized in that it is chosen from:
•*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylméthyl](2-methyl-3-trifluoromethyl)benzamide;
•*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2,6-dichloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;
•(-)-*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2,6-dichloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;
•*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2-chloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;
•2-chloro-*N*-[(7-ethyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](3-trifluoromethyl)benzamide, and the hydrochloride thereof;

•(+)-*N*-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2,6-dichloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;

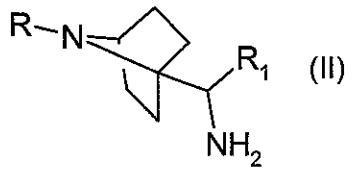
•2-chloro-*N*-[(7-methyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl]-3-trifluoromethyl-benzamide, and the hydrochloride thereof;

•*N*-[(7-benzyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl]-(2-methyl-3-trifluoro-methyl)benzamide, and the hydrochloride thereof;

•*N*-[(7-benzyl-7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2-chloro-3-trifluoromethyl)benzamide, and the hydrochloride thereof;

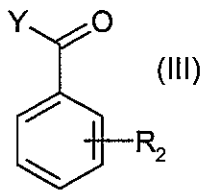
•N-[(7-azabicyclo[2.2.1]hept-1-yl)phenylmethyl](2-chloro-3-ethyl)benzamide, and the hydrochloride thereof.

8. Process for preparing a compound of general formula (I) according to Claim 1, characterized in that a compound of general formula (II)



(II)

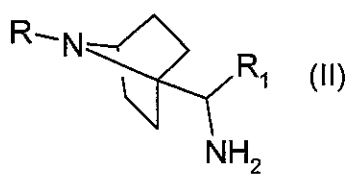
in which R and R_1 are as defined according to Claim 1, reacts with a compound of general formula (III)



(III)

in which Y represents a leaving group or a halogen atom and R_2 is as defined according to Claim 1.

9. Compound of general formula (II)



(II)

in which R and R_1 are as defined in Claim 1.

10. Medicament, characterized in that it comprises a compound of formula (I)

according to any one of Claims 1 to 7, or an addition salt of this compound with a pharmaceutically acceptable acid.

11. Pharmaceutical composition, characterized in that it comprises a compound of formula (I) according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt of this compound, and also at least one pharmaceutically acceptable excipient.

12. Use of a compound of formula (I) according to any one of Claims 1 to 7, for the preparation of a medicament for the treatment of cognitive and/or behavioural disorders associated with neurodegenerative diseases; with dementia.

13. Use of a compound of formula (I) according to any one of Claims 1 to 7, for the preparation of a medicament for the treatment of psychoses, of schizophrenia (deficient form and productive form) and of acute or chronic extrapyramidal symptoms induced by neuroleptics.

14. Use of a compound of formula (I) according to any one of Claims 1 to 7, for the preparation of a medicament for the treatment of various forms of anxiety, panic attacks, phobias and obsessive-compulsive disorders.

15. Use of a compound of formula (I) according to any one of Claims 1 to 7, for the preparation of a medicament for the treatment of various forms of depression, including psychotic depression; for the treatment of bipolar disorders, manic disorders, mood disorders; for the treatment of disorders due to alcohol abuse or alcohol withdrawal, sexual behaviour disorders, eating disorders, and migraine.

16. Use of a compound of formula (I) according to any one of Claims 1 to 7, for the preparation of a medicament for the treatment of pain.

17. Use of a compound of formula (I) according to any one of Claims 1 to 7, for the preparation of a medicament for the treatment of sleep disorders.

18. Compound according to any one of Claims 1 to 7, for the treatment of cognitive and/or behavioural disorders associated with neurodegenerative diseases; with dementia.

19. Compound according to any one of Claims 1 to 7, for the treatment of psychoses, of schizophrenia (deficient form and productive form) and of acute or chronic extrapyramidal symptoms induced by neuroleptics.

20. Compound according to any one of Claims 1 to 7, for the treatment of various forms of anxiety, panic attacks, phobias and obsessive-compulsive disorders.

21. Compound according to any one of Claims 1 to 7, for the treatment of various forms of depression, including psychotic depression; for the treatment of bipolar disorders, manic disorders, mood disorders; for the treatment of disorders due to alcohol abuse or alcohol withdrawal, sexual behaviour disorders, eating disorders, and migraine.

22. Compound according to any one of Claims 1 to 7, for the treatment of pain.

23. Compound according to any one of Claims 1 to 7, for the treatment of sleep disorders.