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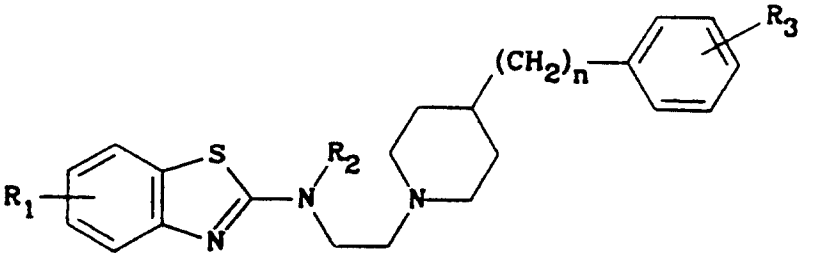
(54) **DERIVES DE N-(BENZOTHIAZOL-2-YL)PIPERIDINE-1-ETHANAMINE, LEUR PREPARATION ET LEUR APPLICATION EN THERAPEUTIQUE**

(54) **N-(BENZOTHIAZOL-2-YL) PIPERIDINE-1-ETHANAMINE DERIVATIVES, THEIR PREPARATION AND APPLICATION IN THERAPEUTICS**



(I)

(57) Composés répondant à la formule générale (I) dans laquelle n représente le nombre 0, 1, 2 ou 3, R_1 représente un atome d'hydrogène ou d'halogène ou un groupe méthyle ou méthoxy, R_2 représente un atome d'hydrogène ou un groupe méthyle, et R_3 représente un atome d'hydrogène ou un ou deux atomes d'halogène. Application en thérapeutique.

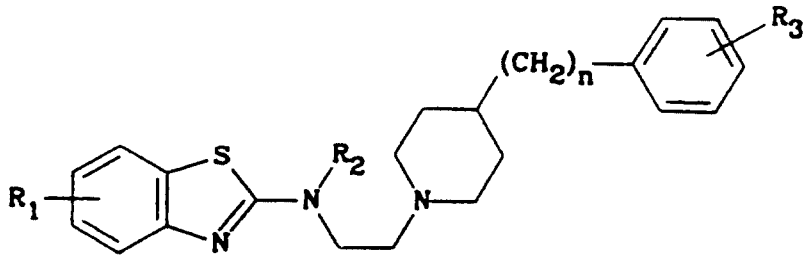
(57) The invention discloses compounds complying with general formula (I) in which n represents number 0, 1, 2 or 3, R_1 represents one hydrogen or halogen atom or a methyl or methoxy group, R_2 represents one hydrogen atom or one methyl group, and R_3 represents one hydrogen atom or one or two halogen atoms. The invention is applicable in therapeutics.

N-(2-BENZOTHIAZOLYL)-1-PIPERIDINEETHANAMINE DERIVATIVES, THEIR PREPARATION AND THEIR USE IN THERAPY

SYNTHÉLABO

Abstract

Compounds corresponding to the general formula (I)



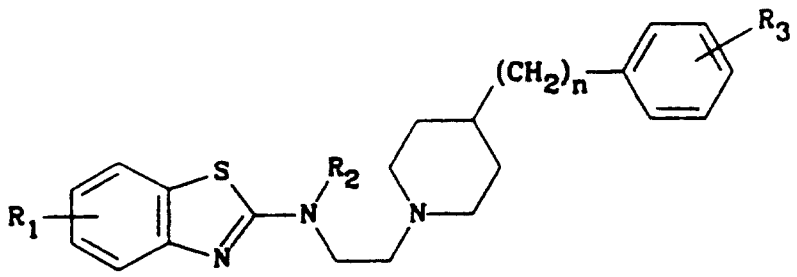
(I)

in which n represents the number 0, 1, 2 or 3, R_1 represents a hydrogen or halogen atom or a methyl or methoxy group, R_2 represents a hydrogen atom or a methyl group and R_3 represents a hydrogen atom or one or two halogen atoms.

Use in therapy.

N-(2-Benzothiazolyl)-1-piperidineethanamine derivatives, their preparation and their use in therapy.

The compounds of the invention correspond to the general formula (1)



(I)

in which

n represents the number 0, 1, 2 or 3,

R_1 represents a hydrogen or halogen atom or a methyl or methoxy group,

R_2 represents a hydrogen atom or a methyl group, and

R_3 represents a hydrogen atom or one or two halogen atoms.

The compounds of the invention can exist in the free base state or in the state of addition salts with acids.

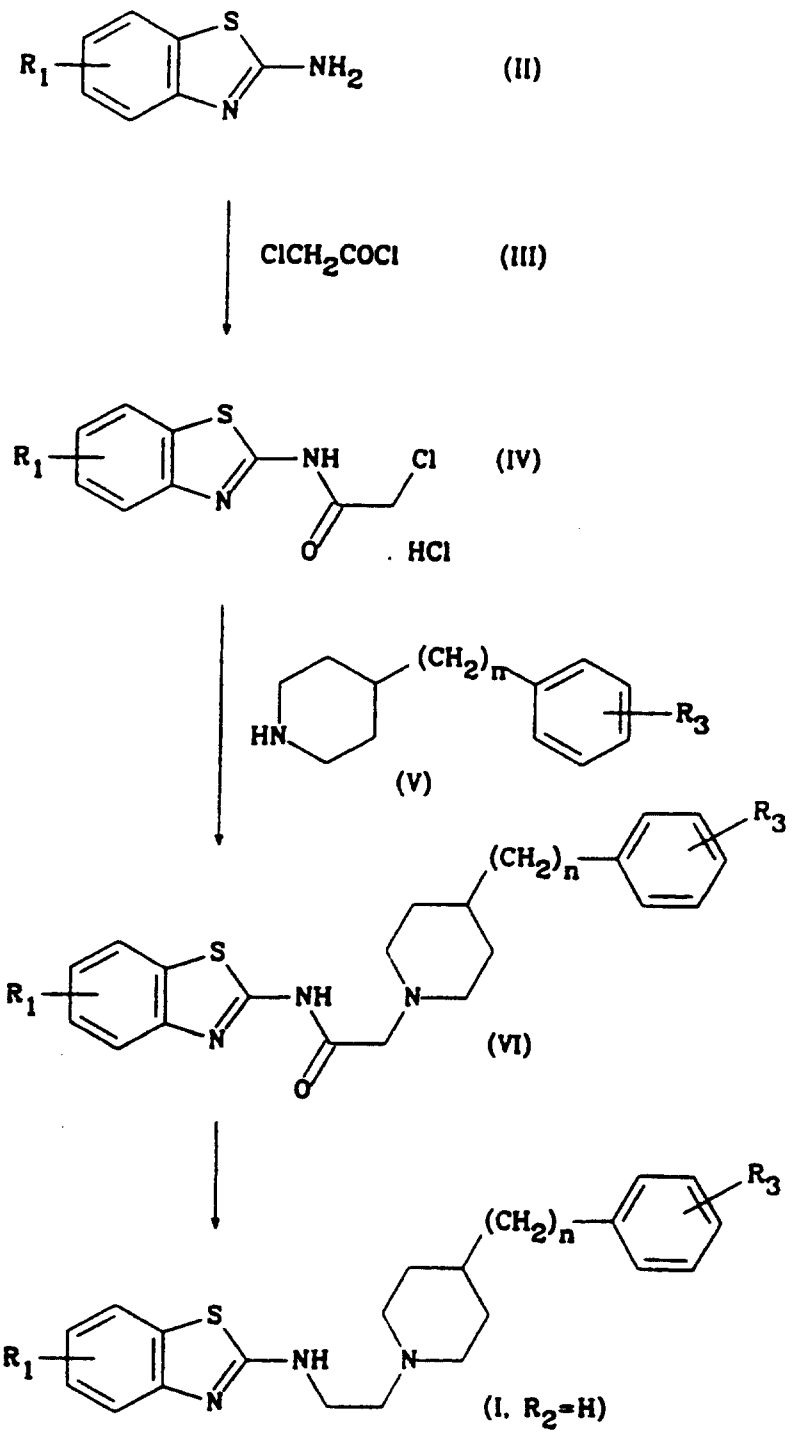
In accordance with the invention, the compounds of general formula (I) may be prepared according to processes illustrated by the schemes which follow.

In the case of the compounds in which R_2 represents a hydrogen atom, and according to Scheme 1, a compound of general formula (II), in which R_1 is as

defined above, is reacted with chloroacetyl chloride of formula (III) under conditions similar to the ones described in *Bull. Soc. Chim.* France (1962) 736-737, that is to say in an aprotic solvent, for example dioxane, at a temperature of 20 to 100°C.

An amide of general formula (IV) is obtained, which is reacted with a piperidine of general formula (V), in which n and R_3 are as defined above, in an aprotic polar solvent, for example *N,N*-dimethylformamide, at a temperature of 50 to 80°C and in the presence of an inorganic base, for example potassium carbonate. An amide of general formula (VI) is obtained, which is finally reduced to an amine of general formula (I, with R_2=H) by means of a simple or complex reducing agent such as an alkali metal hydride or other metal hydride, for example lithium aluminium hydride, boron hydride, the boron hydride/tetrahydrofuran or boron hydride/methyl sulphide complex or aluminium hydride, in an aromatic or ethereal inert solvent, for example toluene, xylene, diethyl ether, tetrahydrofuran or dioxane, at a temperature of 30 to 140°C depending on the solvent.

Scheme 1

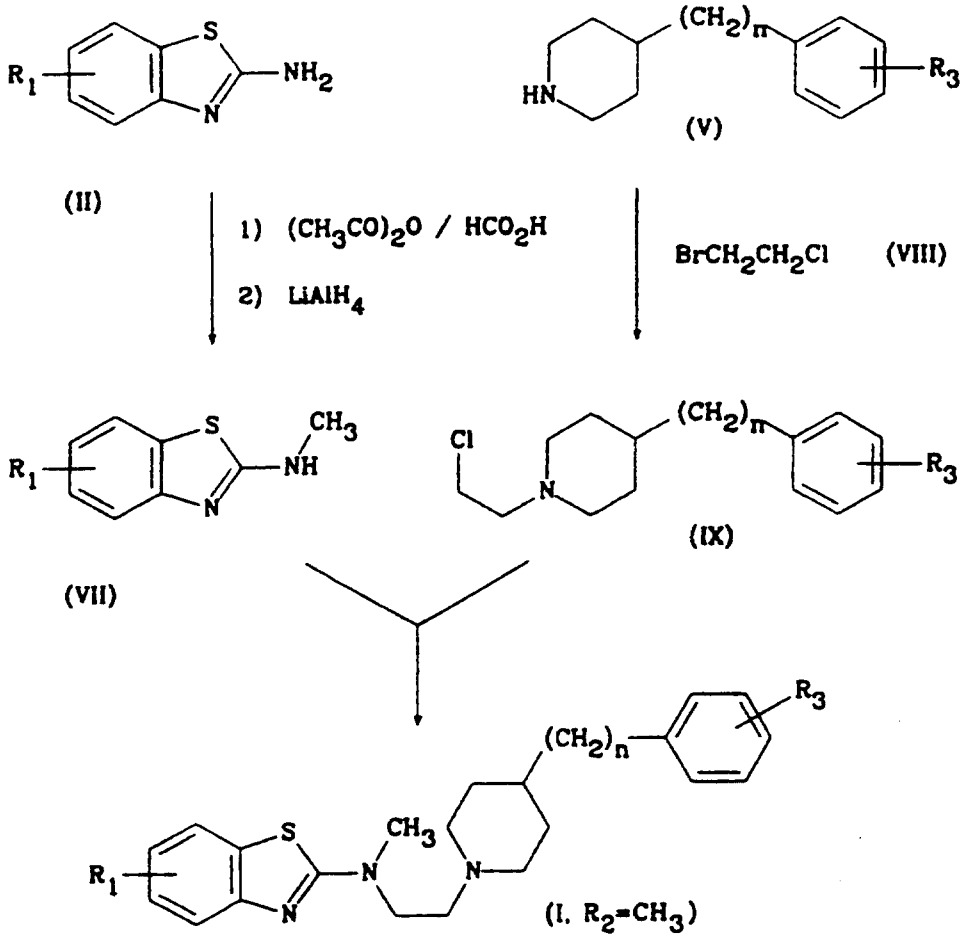


In the case of the compounds in which R_2 represents a methyl group, and according to Scheme 2, a compound of general formula (II), in which R_1 is as defined above, is reacted first with a mixture of acetic anhydride and formic acid under conditions similar to the ones described in *Tetrahedron Letters* (1982) 23 (33) 3315-3318 and in *J. Med. Chem.* (1966) 9 830-832, that is to say in an inert solvent, for example tetrahydrofuran, at a temperature of 20 to 40°C, and the *N*-formyl intermediate thereby obtained is then reduced as indicated above in relation to the compound of general formula (VI) to obtain an *N*-methyl-2-benzothiazolamine of general formula (VII).

Separately, a piperidine of general formula (V), in which n and R_3 are as defined above, is reacted with 1-bromo-2-chloroethane under the standard conditions for a reaction of this kind, that is to say in a polar solvent, for example *N,N*-dimethylformamide, in the presence of an inorganic base, for example potassium carbonate, at a temperature of 50 to 80°C.

A chlorinated derivative of general formula (IX) is obtained, which is finally reacted with the *N*-methyl-2-benzothiazolamine of general formula (VII) in a polar solvent, for example *N,N*-dimethylformamide, in the presence of an inorganic base, for example potassium carbonate, at a temperature of 80 to 100°C, to obtain a compound of general formula (I, R_2=CH_3).

Scheme 2



The starting compounds of general formula (II) are available on the market.

The starting compounds of general formula (V) are available on the market or are described in Patent Applications EP-0109317 and EP-0524846.

The examples which follow illustrate in detail the preparation of a few compounds according to the invention. The elemental microanalyses and the IR and NMR spectra confirm the structures of the compounds obtained.

The numbers of the compounds shown in brackets in the titles correspond to those in the table given later.

Example 1 (Compound No. 1)

N-(2-Benzothiazolyl)-4-phenyl-1-piperidineethanamine.

1.1. *N*-(2-Benzothiazolyl)-2-chloroacetamide hydrochloride.

15 g (0.1 mol) of 2-benzothiazolamine and 200 ml of dioxane are introduced into a 1-l round-bottomed flask, the mixture is stirred until dissolution is complete, a solution of 11.3 g (0.1 mol) of chloroacetyl chloride is added and the mixture is heated on an oil bath at 50°C for 24 h.

A further 5.6 g (0.05 mol) of chloroacetyl chloride dissolved in 50 ml of dioxane are added and heating is continued at 50°C overnight.

The mixture is allowed to cool, and the precipitate is separated by filtration, washed with a little dioxane and then with petroleum ether and dried in the presence of phosphorus pentoxide.

25.49 g of product are obtained, which product is used without further treatment in the next step.

1.2. *N*-(2-Benzothiazolyl)-4-phenyl-1-piperidineacetamide.

2.63 g (0.01 mol) of *N*-(2-benzothiazolyl)-2-chloroacetamide hydrochloride, 1.61 g (0.01 mol) of

4-phenylpiperidine, 2.76 g of potassium carbonate and 80 ml of *N,N*-dimethylformamide are introduced into a 500-ml round-bottomed flask, and the mixture is heated to 50°C for 3 h 30 min.

The mixture is allowed to cool, 160 ml of water are added, and the precipitate is collected by filtration and dried.

3.15 g of product are obtained, which product is used without further treatment in the next step.

1.3. *N*-(2-Benzothiazolyl)-4-phenyl-1-piperidineethanamine.

430 mg (0.0112 mol) of lithium aluminium hydride and then 60 ml of tetrahydrofuran are introduced into a 500-ml round-bottomed flask, and the suspension is heated to reflux. 2 g (0.0056 mol) of *N*-(2-benzothiazolyl)-4-phenyl-1-piperidineacetamide dissolved in 30 ml of tetrahydrofuran are added dropwise, and heating is maintained for a further 15 min.

The mixture is cooled, 56 ml of ethyl acetate and 22 ml of water are added, the organic phase is separated after settling has taken place, the solvents are evaporated off under reduced pressure and the oily residue is dried under reduced pressure.

2.48 g of crude product are obtained, which product is purified by chromatography on a column of silica gel, eluting with a 9:1 mixture of

dichloromethane and methanol to obtain 1.6 g of a pale yellow oil which crystallizes.

After recrystallization in 2-propanol and drying under reduced pressure, 0.81 g of compound is finally isolated.

Melting point: 140-141°C.

Example 2 (Compound No. 3)

N-(2-Benzothiazolyl)-4-[(4-fluorophenyl)methyl]-1-piperidineethanamine ethanedioate.

2.1. *N*-(2-Benzothiazolyl)-4-[(4-fluorophenyl)methyl]-1-piperidineacetamide.

2.26 g (0.0086 mol) of *N*-(2-benzothiazolyl)-2-chloroacetamide hydrochloride, 2.29 g (0.01 mol) of 4-[(4-fluorophenyl)methyl]piperidine hydrochloride, 4.14 g (0.03 mol) of potassium carbonate and 80 ml of *N,N*-dimethylformamide are introduced into a 500-ml round-bottomed flask, and the mixture is heated to 50°C for 2 h 30 min.

The mixture is allowed to cool, 240 ml of water are added, the mixture is cooled in an ice bath, and the white precipitate is collected by filtration, washed copiously with water and dried in the presence of phosphorus pentoxide.

2.9 g of product are obtained, which product is recrystallized in 30 ml of ethanol. After drying, 2.42 g of compound are obtained.

Melting point: 141-142°C.

2.2. *N*-(2-Benzothiazolyl)-4-[(4-fluorophenyl)methyl]-1-piperidineethanamine ethanedioate.

1.3 g (0.00349 mol) of *N*-(2-benzothiazolyl)-4-[(4-fluorophenyl)methyl]-1-piperidineacetamide dissolved in 25 ml of dry tetrahydrofuran are introduced under a nitrogen atmosphere into a 250-ml three-necked round-bottomed flask, 1.09 ml, that is to say 3 equivalents, of borane/methyl sulphide complex are added and the mixture is heated to reflux for 4 h. The mixture is allowed to cool to room temperature, a mixture of 53 ml of 2N hydrochloric acid and 25 ml of methanol is added, and the mixture is heated to reflux again for 1 h 30 min and left standing overnight.

Concentrated sodium hydroxide is added to the mixture until the pH is alkaline and the mixture is extracted three times with ethyl acetate. The organic phase is washed with water, dried over sodium sulphate and filtered and the filtrate is evaporated under reduced pressure.

1.6 g of oily product are obtained, which product is purified by chromatography on a column of silica gel, eluting with a 95:5 mixture of dichloromethane and methanol.

0.83 g of opaque oil is obtained, which oil is dissolved in 2-propanol with one equivalent of oxalic acid.

After recrystallization, filtration and drying, 0.73 g of compound is finally isolated.

Melting point: 155-156°C.

Example 3 (Compound No. 4)

N-(2-Benzothiazolyl)-*N*-methyl-4-(phenylmethyl)-1-piperidineethanamine ethanedioate.

3.1. *N*-Methyl-2-benzothiazolamine.

10.2 ml of acetic anhydride are introduced into a round-bottomed flask, 4.3 ml of formic acid are added dropwise and while stirring and the mixture is then heated to 50°C for 2 h. The mixture is cooled to room temperature, 10 ml of dry tetrahydrofuran are added, a solution of 11.25 g (0.075 mol) of 2-benzothiazolamine in 30 ml of dry tetrahydrofuran is then added dropwise and without the temperature exceeding 40°C and the mixture is left standing for 2 days.

The solvent is evaporated off under reduced pressure, and the crystalline residue is washed twice with petroleum ether and dried in the presence of phosphorus pentoxide.

13 g of intermediate *N*-(2-benzothiazolyl)formamide are obtained.

A suspension of 0.854 g (0.0224 mol) of lithium aluminium hydride in 50 ml of tetrahydrofuran is prepared and heated to reflux, a solution of 2 g (0.0112 mol) of formyl intermediate in 100 ml of tetrahydrofuran is added and heating is continued for

30 min.

The mixture is cooled, 100 ml of ethyl acetate are added, 38 ml of water are added dropwise, the organic phase is separated after settling has taken place and evaporated under reduced pressure, and the crystallized residue is ground in petroleum ether, filtered off and dried in the presence of phosphorus pentoxide.

1.5 g of compound are obtained.

3.2. 1-(2-Chloroethyl)-4-(phenylmethyl)piperidine.

3.5 g (0.02 mol) of 4-(phenylmethyl)piperidine dissolved in 50 ml of *N,N*-dimethylformamide are introduced into a round-bottomed flask, 2.86 g (0.02 mol) of 1-bromo-2-chloroethane and 2.76 g (0.02 mol) of potassium carbonate are added and the mixture is stirred vigorously at room temperature for 1 h.

The mixture is poured into 250 ml of ice-cold water and extracted with 2 times 150 ml of ethyl acetate. The organic phase is washed with saline solution and the solvent is evaporated off under reduced pressure. 7 g of oily product are obtained, which product is purified by chromatography on a column of silica gel, eluting with ethyl acetate.

2.1 g of purified product are obtained in the form of an oil.

3.3. *N*-(2-Benzothiazolyl)-*N*-methyl-4-(phenylmethyl)-1-piperidineethanamine ethanedioate.

1 g (0.00421 mol) of 1-(2-chloroethyl)-4-(phenylmethyl)piperidine is dissolved in 25 ml of *N*,*N*-dimethylformamide, 0.7 g (0.00426 mol) of *N*-methyl-2-benzothiazolamine and 0.8 g of potassium carbonate are added and the mixture is heated to 100°C for 1 h.

It is cooled in an ice bath, 50 ml of water are added, the mixture is extracted with 2 times 100 ml of ethyl acetate, and the organic phase is washed with saline solution and evaporated. An oily residue is obtained, which is purified by two successive chromatographic runs on a column of silica gel, the first eluting with a 90:10 mixture of dichloromethane and methanol and the second eluting with ethyl acetate.

0.3 g of compound is obtained, 0.1 g of which is removed to form the oxalate in ethanol.

Melting point: 164-166°C.

Example 4 (Compound No. 11)

N-(2-Benzothiazolyl)-4-[2-(4-fluorophenyl)ethyl]-1-piperidineethanamine.

4.1. *N*-(2-Benzothiazolyl)-4-[2-(4-fluorophenyl)ethyl]-1-piperidineacetamide.

2.63 g (0.01 mol) of *N*-(2-benzothiazolyl)-2-chloroacetamide hydrochloride, 2.44 g (0.01 mol) of 4-[2-(4-fluorophenyl)ethyl]piperidine hydrochloride,

4.14 g (0.03 mol) of potassium carbonate and 80 ml of *N,N*-dimethylformamide are introduced into a 500-ml round-bottomed flask, and the mixture is heated to 50°C for 3 h 30 min.

It is allowed to cool, 240 ml of water are added and the mixture is extracted with 300 ml of ethyl acetate.

The organic phase is washed with water and then with saturated sodium chloride solution, dried over sodium sulphate and filtered and the filtrate is evaporated under reduced pressure. A brown oily product is obtained, which is used without further treatment in the next step.

4.2. *N*-(2-Benzothiazolyl)-4-[2-(4-fluorophenyl)ethyl]-1-piperidineethanamine.

0.96 g (0.025 mol) of lithium aluminium hydride and 140 ml of dry tetrahydrofuran are introduced under a nitrogen atmosphere into a 500-ml three-necked round-bottomed flask, the suspension is heated to reflux, 5.0 g (0.01 mol) of *N*-(2-benzothiazolyl)-4-[2-(4-fluorophenyl)ethyl]-1-piperidineacetamide dissolved in 60 ml of dry tetrahydrofuran are added dropwise and heating is continued for 30 min.

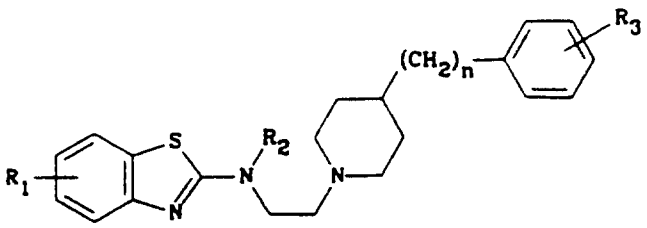
The mixture is cooled, 140 ml of ethyl acetate and 51 ml of water are added, the organic phase is separated, the solvents are evaporated off under

reduced pressure and the residue is purified by chromatography on a column of silica gel, eluting with a 9:1 mixture of dichloromethane and methanol. 1.6 g of an oil which crystallizes are obtained. After recrystallization in a mixture of ethanol and water, followed by drying under reduced pressure, 1.23 g of compound are isolated.

Melting point: 107-108°C.

The table which follows illustrates the chemical structures and the physical properties of a few compounds according to the invention. In the "salt" column, "-" denotes a compound in the base state, "ox." denotes an oxalate or ethanedioate, and "fum." denotes a fumarate or (*E*)-2-butenedioate. The acid/base mole ratio is shown in brackets.

Table



(I)

No.	n	R_1	R_2	R_3	Salt		M.p.(°C)
1	0	H	H	H	-		140-141
2	1	H	H	H	ox.	(1.05:1)	141-142
3	1	H	H	4-F	ox.	(1:1)	155-156
					fum.	(1.2:1)	150-151
4	1	H	CH_3	H	ox.	(1.15:1)	164-166
5	1	H	CH_3	4-F	fum.	(1.9:1)	137-140
6	1	6-Cl	H	4-F	-		118-119
7	1	6-CH_3	H	4-F	-		148-149
8	1	6-OCH_3	H	H	-		123-124
9	1	6-OCH_3	H	4-F	-		107-108
10	2	H	H	H	ox.	(2:1)	189-190
11	2	H	H	4-F	-		107-108
12	2	6-OCH_3	H	H	-		129-130
13	3	H	H	H	ox.	(2:1)	179-180
14	2	H	H	2-F	fum.	(1:2)	159-160
15	2	H	H	3-F	fum.	(1:2)	168-169
16	2	H	H	2,4-F	fum.	(2:1)	156-158
17	2	H	H	3,4-F	fum.	(1.2:1)	100-138
18	2	H	H	3,5-F	fum.	(1:2)	158-159

The compounds of the invention were subjected to tests which demonstrated their value as therapeutic active substances.

Thus, they were subjected to a study in relation to their neuroprotective activity in a model of permanent focal ischaemia produced by intraluminal occlusion of the middle cerebral artery in rats, according to a method similar to the one described in *Stroke* (1989) 20 84-91.

Under methohexitone sodium anaesthesia, the pterygopalatine artery, common carotid artery and the left external carotid artery are ligated, and a polyamide thread is introduced into the internal carotid artery over a length of approximately 18 mm, corresponding to the distance separating the point of origin of the internal carotid artery from that of the middle cerebral artery.

The compounds under study are administered intravenously after the occlusion.

24 h after occlusion of the middle cerebral artery, the animals are sacrificed and the brain is removed.

The volume of the cerebral infarction is evaluated from the measurement of the area of necrosis on 6 coronal sections stained with 2,3,5-triphenyltetrazolium chloride. As an example, Compound No. 11 in the table above significantly reduces the volume of the infarction by approximately 48% at a dose

of 1 mg/kg administered intravenously at times 10 min, 1 h 30 min, 3 h and 6 h after occlusion.

The compounds of the invention were also subjected to the global cerebral ischaemia test in mice.

The ischaemia is due to a cardiac arrest induced by rapid intravenous injection of magnesium chloride. In this test, the "survival time", that is to say the interval between the time of injection of magnesium chloride and the last observable respiratory movement of each mouse, is measured. This last movement is considered to be the final sign of functioning of the central nervous system. Respiratory arrest occurs approximately 19 seconds after the injection of magnesium chloride.

Male mice (Charles River CD1) are studied in groups of 10. They are supplied with food and water ad libitum before the tests. The survival time is measured 10 minutes after the intraperitoneal administration of the compounds of the invention. The results are given in the form of the difference between the survival time measured in a group of 10 mice which have received the compound, and the survival time measured in a group of 10 mice which have received the vehicle liquid. The relationships between the modifications in the survival term and the dose of the compound are recorded graphically according to a semi-logarithmic curve.

This curve enables the "3-seconds effective

dose" ($ED_{3,,}$), that is to say the dose (in mg/kg) which produces an increase of 3 seconds in the survival time relative to the control group of 10 untreated mice, to be calculated. An increase of 3 seconds in the survival time is both statistically significant and reproducible. The $ED_{3,,}$ of the most active compounds of the invention are less than 5 mg/kg via the intraperitoneal route.

The compounds according to the invention were also subjected to an *in vitro* study in relation to their affinity for the D_4 dopaminergic receptors, obtained by transfection of human $D_{4.4}$ receptors into CHO cells, essentially as described by Van Tol. et al., *Nature* (1991) 350 610-614 and Van Tol. et al., *Nature* (1992) 358 149-152.

On the day of the experiment, the membrane preparation (Receptor Biology, Inc., Glen Echo, MD20812, USA), stored at -80°C, is thawed rapidly and then diluted in 20 volumes of incubation buffer (50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 5 mM $MgCl_2$, pH = 7.5).

The membrane suspension (100 µl, 78 µg of membrane) is incubated at 25°C for 60 min in the presence of 0.5 nM [^{3}H]spiperone (specific activity 17 to 20 Ci/mmol, New England Nuclear/Du Pont de Nemours, Boston, MA, USA) in a final volume of 1 ml of incubation buffer in the presence or absence of the test compound.

Incubation is completed by filtration, with the use of Whatman GF/B® filters treated beforehand with polyethylenimine (0.5%). Each reaction tube is rinsed three times with 3 ml of Tris-NaCl buffer (50 mM Tris-HCl, 120 mM NaCl, pH = 7.5).

The filters are dried in an oven at 120°C for 5 min. The radioactivity retained on the filters is determined by liquid scintigraphy. Non-specific binding is determined in the presence of 1 μM haloperidol.

For each concentration of compound under study, the percentage inhibition of the specific binding of [^{3}H]spiperone is calculated, and then the IC_{50}, the concentration which inhibits 50% of the binding, is determined.

The IC_{50} values of the compounds of the invention are of the order of 3 to 30 nM.

The results of the tests show that, *in vivo*, the compounds according to the invention have neuroprotective properties, and that, *in vitro*, they displace the specific binding of [^{3}H]spiperone to human $D_{4.4}$ dopaminergic receptors.

Consequently they may be used, on the one hand, for the treatment and prevention of cerebrovascular disorders of ischaemic or hypoxic origin (cerebral infarction, cranial or cord trauma, cardiac or respiratory arrest, transient ischaemic attack, perinatal asphyxia), glaucoma, progressive neurodegenerative disorders (senile dementia such as

Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, olivopontocerebellar atrophy, amyotrophic lateral sclerosis, neurodegenerative disorders of viral origin, and the like), and in the prevention of cerebral ischaemic accidents associated with cardiac and vascular surgery or with endovascular therapy.

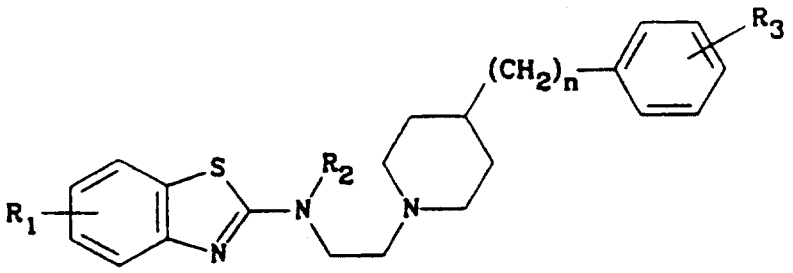
They may be used, on the other hand, for the treatment of psychoses, especially schizophrenia (deficiency and productive forms) and the acute and chronic extrapyramidal symptoms induced by neuroleptics or resulting from Parkinson's disease, for the treatment of the various forms of anxiety, panic attacks, phobias, compulsive obsessional disorders, for the treatment of the different forms of depression, including psychotic depression, for the treatment of narcotic- and alcohol-induced dependency and disorders of hypothalamohypophyseal function, and for the treatment of cognitive disorders associated with age or Alzheimer's disease.

To this end, they may be presented in all pharmaceutical dosage forms, in combination with suitable excipients, for enteral, parenteral or transdermal administration, for example in the form of tablets, dragées, capsules including hard gelatin capsules, solutions or suspensions for oral administration or for injection, suppositories, patches, and the like, containing doses that permit a

daily administration of 1 to 500 mg of active substance.

Claims

1. Compound corresponding to the general formula (1)



(I)

in which

n represents the number 0, 1, 2 or 3,

R_1 represents a hydrogen or halogen atom or a methyl or methoxy group,

R_2 represents a hydrogen atom or a methyl group, and

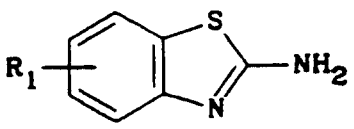
R_3 represents a hydrogen atom or one or two halogen atoms,

in the free base state or in the state of an addition salt with an acid.

2. Process for preparing a compound according to Claim 1, characterized in that

- to prepare a compound in the formula of which R_2 represents a hydrogen atom,

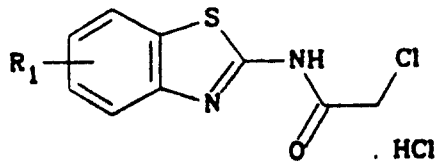
a compound of general formula (II)



(II)

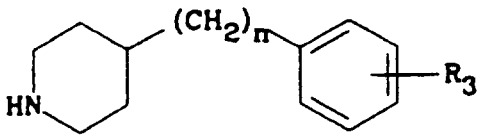
in which R_1 is as defined in Claim 1, is reacted with

chloroacetyl chloride to obtain an amide of general formula (IV)



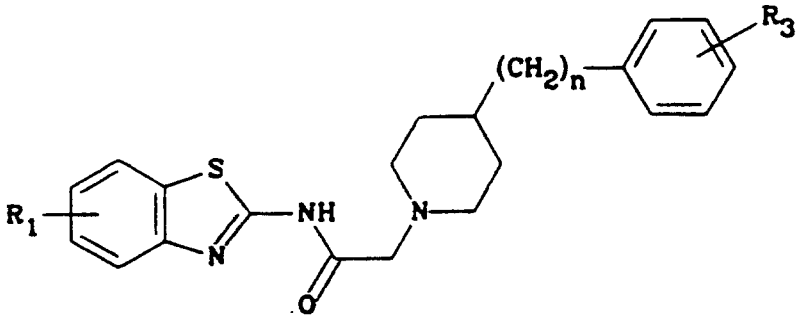
(IV)

which is reacted with a piperidine of general formula (V)



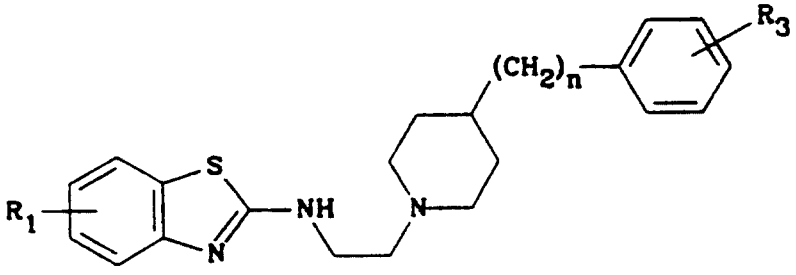
(V)

in which n and R_3 are as defined in Claim 1, to obtain an amide of general formula (VI)



(VI)

which is finally reduced to an amine of general formula (I, with R_2=H)

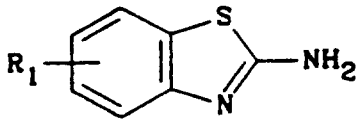


(I, R_2=H)

or alternatively,

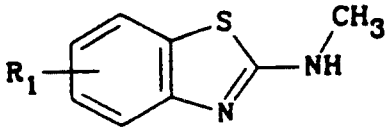
- to prepare a compound in the formula of which R_2 represents a methyl group,

a compound of general formula (II)



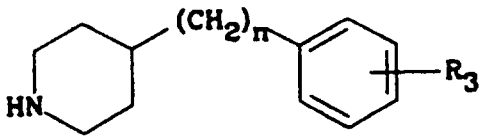
(II)

in which R_1 is as defined in Claim 1, is reacted first with a mixture of acetic anhydride and formic acid, and the *N*-formyl intermediate thereby obtained is then reduced to obtain an *N*-methyl-2-benzothiazolamine of general formula (VII)



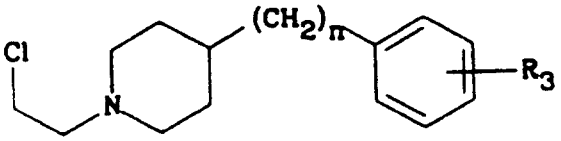
(VII)

and, separately, a piperidine of general formula (V)



(V)

in which n and R_3 are as defined in Claim 1, is reacted with 1-bromo-2-chloroethane to obtain a chlorinated derivative of general formula (IX)

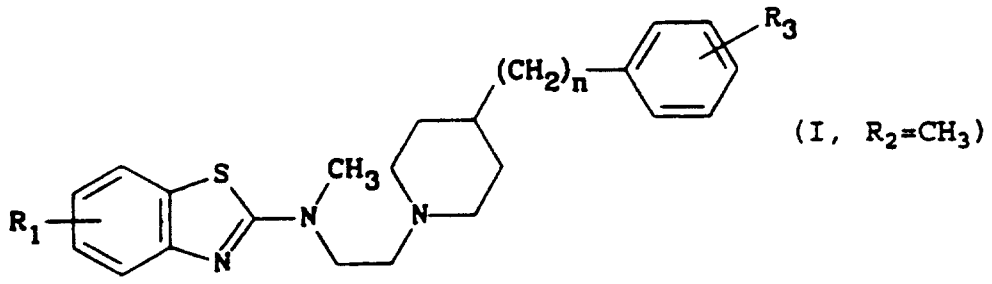


(IX)

which is finally reacted with the *N*-methyl-2-

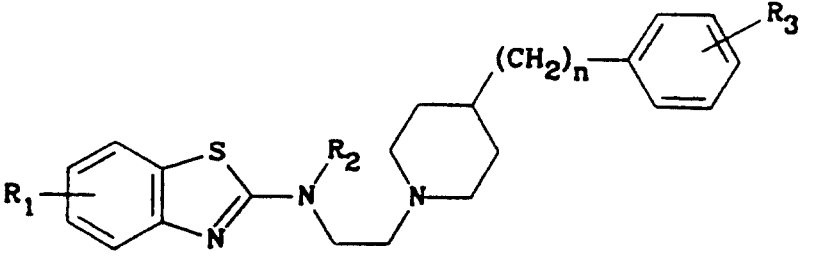
benzothiazolamine of general formula (VII)

to obtain a compound of general formula (I, with $R_2=CH_3$)



3. Medicament, characterized in that it consists of a compound according to either of Claims 1 and 2.

4. Pharmaceutical composition, characterized in that it contains a compound according to either of Claims 1 and 2, in combination with an excipient.



(I)