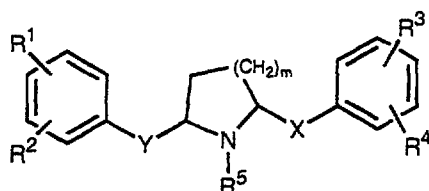


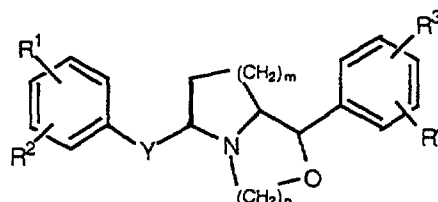
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REPLACED

9900363-4

The present invention relates to the use of pyrrolidine and piperidine derivatives of the general formulae



I and



II

wherein

5 R^1 and R^2 are, independently from each other, hydrogen, lower alkoxy, hydroxy, halogen, $-\text{CONH}_2$ or $-\text{C}(\text{O})\text{O}$ -lower alkyl; or taken together are $-\text{O}-\text{CH}_2-\text{O}-$;

R^3 and R^4 are, independently from each other, hydrogen, lower alkoxy, benzyloxy, halogen, hydroxy, $-\text{CONH}_2$ or $-\text{SCH}_3$; or taken
10 together are $-\text{O}-\text{CH}_2-\text{O}-$;

R^5 is hydrogen or lower alkyl;

X and Y are, independently from each other $-\text{CH}(\text{OH})-$, $-(\text{CH}_2)_n-$, $-\text{C}(\text{O})-$ or $-\text{CH}(\text{lower alkoxy})-$; and

m, n and p are 1 or 2;

15 and to their pharmaceutically acceptable addition salts for the treatment of diseases caused by overactivation of NMDA receptor subtypes.

Compounds of formula I and their salts are known compounds. They are described to possess activities for the treatment of the following diseases:

- ophthalmic diseases caused by increased intraocular pressure, such as
20 glaucoma (US 4,558,066),
- cardiovascular diseases (EP 114 758, US 4,548,951 and EP 115 413),
- hypertension, cardiac arrhythmia and vasal congestion (EP 71 399),

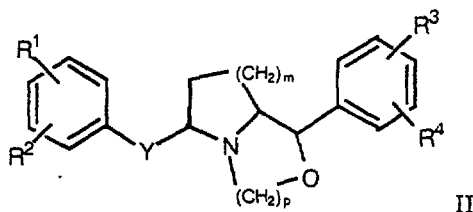


- hypertension, cardiac arrhythmia and allergic diseases (EP 50 370), and
- bronchodilator activity (US 3,941,796).

It has now surprisingly been found that compounds of the present invention are NMDA (N-methyl-D-aspartate)-receptor-subtype selective
5 blockers, which have a key function in modulating neuronal activity and plasticity which makes them key players in mediating processes underlying development of CNS including learning and memory formation and function.

Under pathological conditions of acute and chronic forms of neurodegeneration overactivation of NMDA receptors is a key event for
10 triggering neuronal cell death. NMDA receptors are composed of members from two subunit families, namely NR-1 (8 different splice variants) and NR-2 (A to D) originating from different genes. Members from the two subunit families show a distinct distribution in different brain areas. Heteromeric combinations of NR-1 members with different NR-2 subunits result in NMDA
15 receptors, displaying different pharmacological properties. Possible therapeutic indications for NMDA receptor subtype specific blockers include acute forms of neurodegeneration caused, e.g., by stroke or brain trauma; chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease or ALS (amyotrophic lateral sclerosis);
20 neurodegeneration associated with bacterial or viral infections, and, diseases such as schizophrenia, anxiety and depression.

Objects of the present invention are the use of compounds of formulae I and II in the treatment or prophylaxis of diseases caused by overactivation of respective NMDA receptor subtypes, which include acute forms of
25 neurodegeneration caused, e.g., by stroke or brain trauma; chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease or ALS (amyotrophic lateral sclerosis); neurodegeneration associated with bacterial or viral infections, and, diseases such as schizophrenia, anxiety and depression, the use of these compounds for
30 manufacture of corresponding medicaments, novel compounds of formula



wherein R^1 - R^4 , Y, m and p have the significances given above, processes for the manufacture of these novel compounds, medicaments, containing them, the use of these compounds in the above mentioned kind and for the

5 manufacture of corresponding medicaments.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a straight or branched-

10 chain alkyl group containing from 1 to 4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl and t-butyl.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "lower alkoxy" denotes a group wherein the alkyl residue is as defined above.

15 The compounds of the invention can be prepared in possible stereoisomeric forms, and may exist as stereochemically pure forms: as racemic mixtures containing both members of one enantiomeric pair from the total of four such pairs; or as mixture of some of all of the diastereomeric forms. The invention is intended to encompass all of these possibilities.

20 Preferred compounds of formula I are those, wherein

X is $-\text{CH}(\text{OH})-$, Y is $-(\text{CH}_2)_2-$ and m is 1, or

X is $-(\text{CH}_2)_2-$, Y is $-\text{CH}(\text{OH})-$ and m is 1, or

X is $-(\text{CH}_2)_2-$, Y is $-\text{CH}_2-$ and m is 1, or

X is $-\text{CH}_2-$. Y is $-(\text{CH}_2)_2-$ and m is 2, or

X is $-(CH_2)_2-$, Y is $-C(O)-$ and m is 1 and the other substituents are as described above.

Especially preferred are the following compounds:

- 4-[(RS)-hydroxy-[(2SR,5RS)-5-phenethyl-pyrrolidin-2-yl]-methyl]-phenol,
 5 2-fluoro-4-[(RS)-hydroxy-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-phenol,
 4-[(RS)-hydroxy-[(2SR,5RS)-5-phenethyl-pyrrolidin-2-yl]-methyl]-benzene-1,2-diol,
 4-[(RS)-hydroxy-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-phenol,
 10 4-[hydroxy-[(2RS,6SR)-6-[2-(4-methoxy-phenyl)-ethyl]-piperidin-2-yl]-methyl]-phenol,
 (2RS,5RS)-4-[5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-ylmethyl]-phenol,
 15 (2RS,5RS)-4-(5-phenethyl-pyrrolidin-2-yl-methyl)-benzene-1,2-diol.
 (2RS,6SR)-4-[6-[2-(4-methoxy-phenyl)-ethyl]-piperidin-2-ylmethyl]-phenol
 and
 Mixture of (2RS,5RS)- and (2RS,5SR)-(4-hydroxy-phenyl)-[5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methanone.

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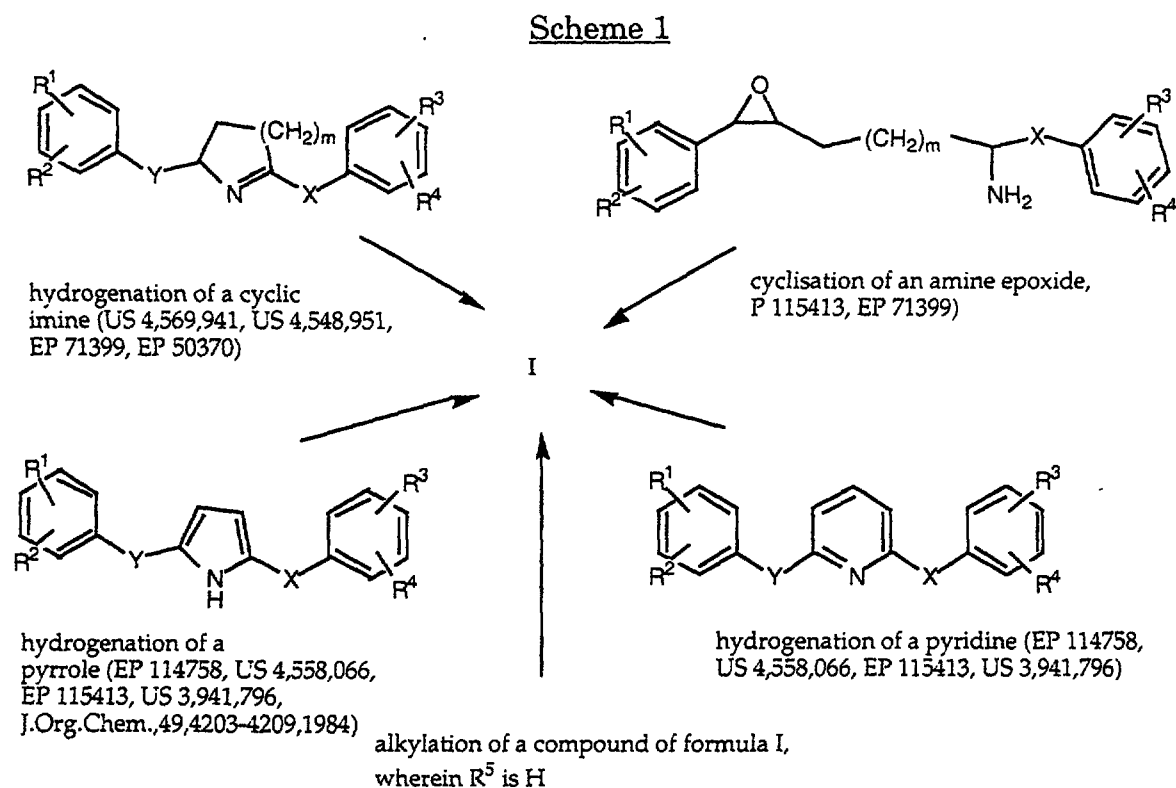
Preferred compounds of formula II are those, wherein

Y is $-(CH_2)_2-$, R^1 , R^2 and R^3 are hydrogen, R^4 is hydroxy and m and p are 1.

Especially preferred are the following compounds:

- 25 (1RS,5SR,7aRS)-4-(5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazol-1-yl)-phenol and
 (1RS,5RS,7aSR)-4-(5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazol-1-yl)-phenol.

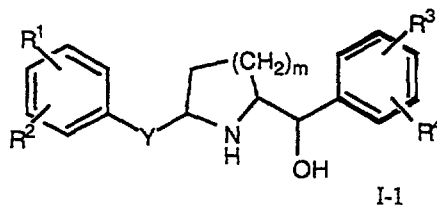
As mentioned earlier, compounds of formula I are known compounds. They can be prepared in accordance with the reactions of Scheme 1:



5

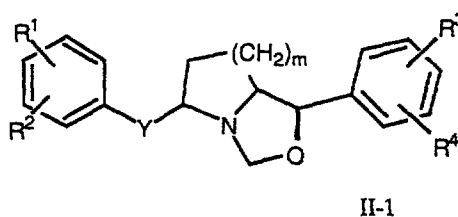
The novel compounds of formula II and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example by processes described below, which comprises

a) cyclizing a compound of formula

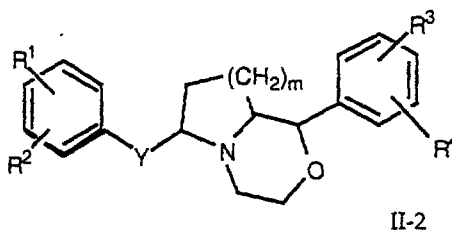


10

to a compound of formula



by reaction with a compound useful to form an oxazole ring, or to a compound of formula



by reaction with a compound useful to form a morpholine ring,
 5 wherein $R^1 - R^4$, Y and m have the significances given above, or

b) debenzylating a compound of formula II, wherein R^3 and/or R^4 are benzyloxy, or

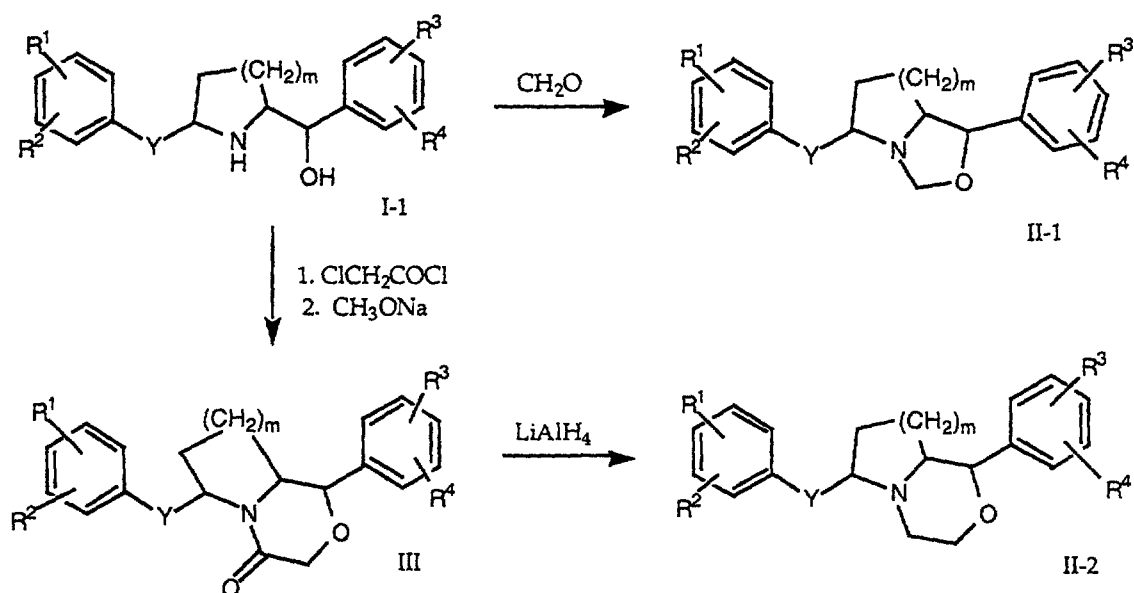
c) modifying one or more substituents $R^1 - R^4$ within the definitions given
 10 above, and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

Scheme 2 shows the processes for preparation of compounds of formula II from compounds of formula I.

15

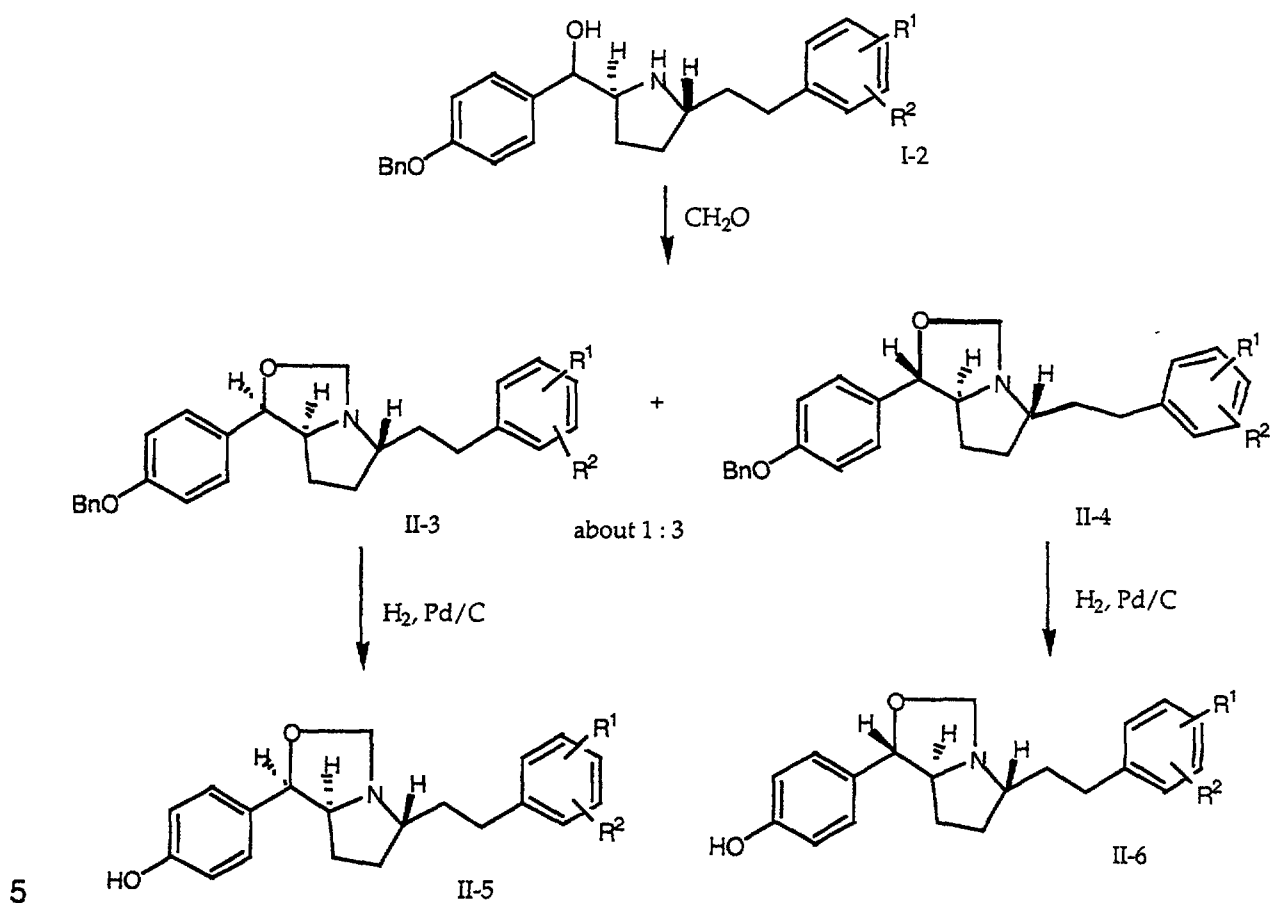
Scheme 2



wherein R^1 - R^4 , Y and m have the significances given above.

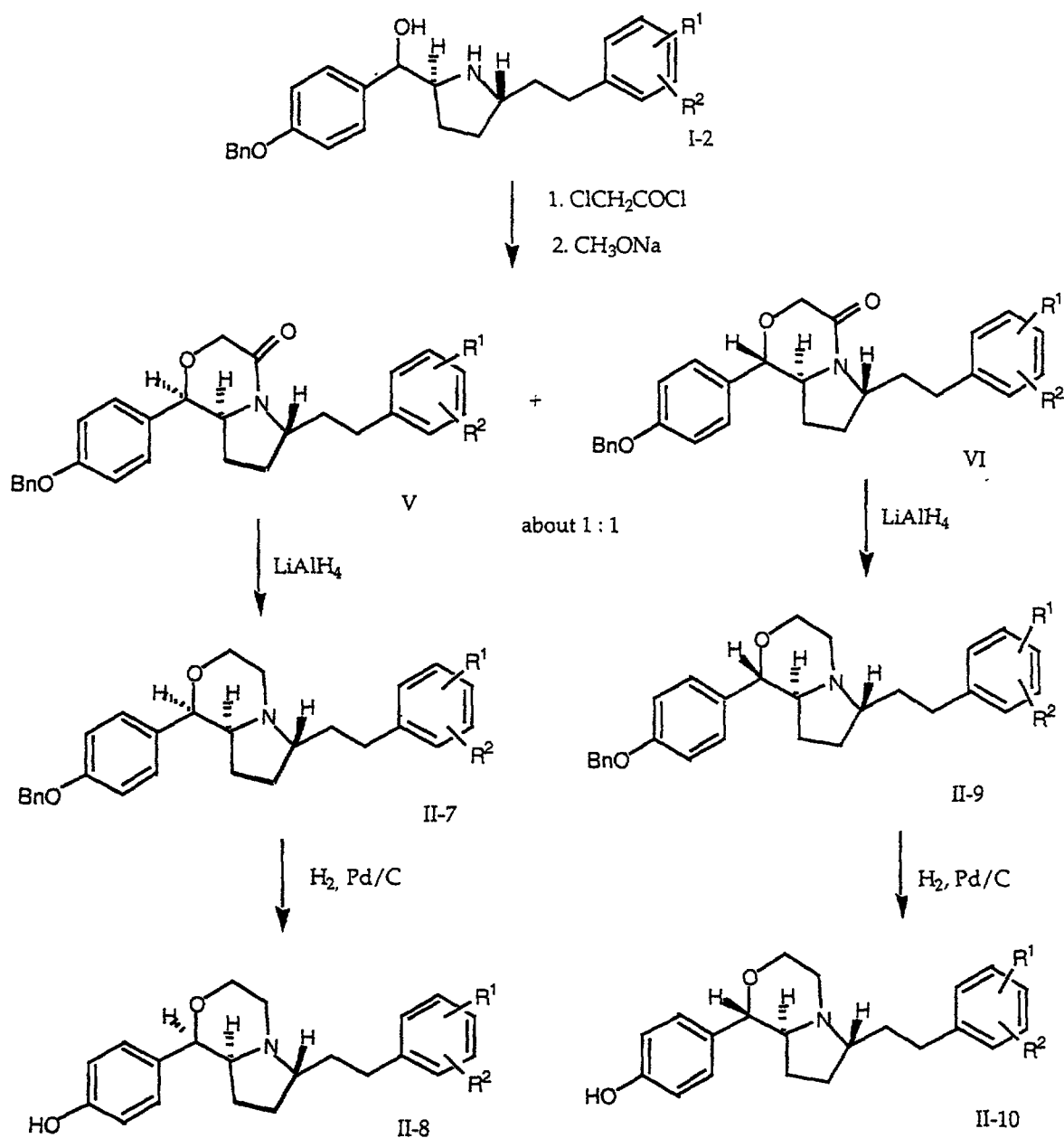
Specific isomers may be manufactured in accordance with schemes 3 and 4.

Scheme 3



wherein R^1 and R^2 have the significances given above.

Scheme 4



wherein R¹ and R² have the significances given above.

The detailed description of the above mentioned processes is described in

5 Examples 35 - 42.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable addition salts possess valuable pharmacodynamic properties. They are NMDA-receptor subtype selective blockers, which have a key function in modulating neuronal activity and plasticity which makes them key players in

mediating processes underlying development of CNS as well as learning and memory formation.

The compounds were investigated in accordance with the test given hereinafter.

5 Method

3H-Ro 25-6981 binding (Ro 25-6981 is [R-(R*,S*)]-a-(4-Hydroxy-phenyl)-b-methyl-4-(phenyl-methyl)-1-piperidine propanol)

Male Füllinsdorf albino rats weighing between 150-200 g were used. Membranes were prepared by homogenization of the whole brain minus
10 cerebellum and medulla oblongata with a Polytron (10.000 rpm, 30 seconds), in 25 volumes of a cold Tris-HCl 50 mM, EDTA 10 mM, pH 7.1 buffer. The homogenate was centrifuged at 48.000 g for 10 minutes at 4°C. The pellet was resuspended using the Polytron in the same volume of buffer and the homogenate was incubated at 37°C for 10 minutes. After centrifugation the
15 pellet was homogenized in the same buffer and frozen at -80°C for at least 16 hours but not more than 10 days. For the binding assay the homogenate was thawed at 37°C, centrifuged and the pellet was washed three times as above in a Tris-HCl 5 mM, pH 7.4 cold buffer. The final pellet was resuspended in the same buffer and used at a final concentration of 200 µg of protein/ml.

20 3H-Ro 25-6981 binding experiments were performed using a Tris-HCl 50 mM, pH 7.4 buffer. For displacement experiments 5 nM of 3H-Ro 25-6981 were used and non specific binding was measured using 10 µM of tetrahydroisoquinoline and usually it accounts for 10% of the total. The incubation time was 2 hours at 4°C and the assay was stopped by filtration on
25 Whatmann GF/B glass fiber filters (Unifilter-96, Packard, Zürich, Switzerland). The filters were washed 5 times with cold buffer. The radioactivity on the filter was counted on a Packard Top-count microplate scintillation counter after addition of 40 mL of microscint 40 (Canberra Packard S.A., Zürich, Switzerland).

30 The effects of compounds were measured using a minimum of 8 concentrations and repeated at least once. The pooled normalized values were

analyzed using a non-linear regression calculation program which provide IC₅₀ with their relative upper and lower 95% confidence limits (RS1, BBN, USA).

The thus-determined activity of the preferred compounds in accordance
5 with the invention is in the range of 0.02-0.1 (in μM).

The following compounds of formula I have been tested and are preferred compounds for use according to the present invention:

Ex. No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	m
1	H	H	4-OH	H	H	-CH(OH)-	-(CH ₂) ₂ -	1
2	4-OCH ₃	H	4-OH	3-F	H	-CH(OH)-	-(CH ₂) ₂ -	1
3	4-OH	H	4-OCH ₃	H	H	-(CH ₂) ₂ -	-CH(OH)-	2
4	4-OH	H	4-OCH ₃	H	H	-(CH ₂) ₂ -	-CH ₂ -	1
5	H	H	4-OH	3-OH	H	-CH(OH)-	-(CH ₂) ₂ -	1
6	4-OCH ₃	H	4-OH	H	H	-CH ₂ -	-(CH ₂) ₂ -	2
7	4-OH	H	4-OCH ₃	H	H	-(CH ₂) ₂ -	-C(O)-	1
8	4-OH	3-OH	H	H	H	-(CH ₂) ₂ -	-CH ₂ -	1
9	4-OCH ₃	H	4-OH	3-OH	H	-CH ₂ -	-(CH ₂) ₂ -	1
10	4-OH	3-OH	H	H	-(CH ₂) ₂ CH ₃	-(CH ₂) ₂ -	-CH ₂ -	1
11	4-OH	3-OH	H	H	-(CH ₂) ₃ CH ₃	-(CH ₂) ₂ -	-CH ₂ -	1
12	together -OCH ₂ O-		H	H	H	-CH(OH)-	-(CH ₂) ₂ -	1
13	4-OH	3-CONH ₂	together -OCH ₂ O-		H	-(CH ₂) ₂ -	-CH(OH)-	1
14	H	H	H	H	H	-CH ₂ -	-(CH ₂) ₂ -	1
15	H	H	H	H	H	-CH(OH)-	-(CH ₂) ₂ -	1
16	4-OCH ₃	H	4-OH	3-CONH ₂	H	-CH(OH)-	-(CH ₂) ₂ -	1

17	4-OH	3-CONH ₂	3-OCH ₃	H	H	-(CH ₂) ₂ -	-CH(OH)-	1
18	4-OH	H	4-OH	3-OH	H	-CH(OH)-	-(CH ₂) ₂ -	1
19	4-OCH ₃	H	H	H	H	-CH(OH)-	-(CH ₂) ₂ -	1
20	4-OH	H	4-OH	3-OH	H	-CH ₂ -	-(CH ₂) ₂ -	1
21	4-OCH ₃	H	4-OH	3-SCH ₃	H	-CH(OH)-	-(CH ₂) ₂ -	1
22	H	H	4-OH	H	H	-(CH ₂) ₂ -	-CH(OH)-	1
23	4-OH	3-OH	4-OH	H	(CH ₂) ₂ CH ₃	-(CH ₂) ₂ -	-CH ₂ -	1
24	4-OH	3-CONH ₂	2-OCH ₃	5-OCH ₃	H	-(CH ₂) ₂ -	-CH(OH)-	1
25	together -O-CH ₂ -O-		together -O-CH ₂ -O-		H	-CH(OH)-	-(CH ₂) ₂ -	1
26	together -O-CH ₂ -O-		H	H	H	-(CH ₂) ₂ -	-CH(OH)-	1
27	4-OCH ₃	3-OCH ₃	together -O-CH ₂ -O-		H	-(CH ₂) ₂ -	-CH(OH)-	1
28	4-OCH ₃	H	together -O-CH ₂ -O-		H	-(CH ₂) ₂ -	-CH(OH)-	1
29	4-OH	3-CONH ₂	2-OCH ₃	H	H	-(CH ₂) ₂ -	-CH(OH)-	1
30	4-OH	3-CONH ₂	2-OCH ₃	3-OCH ₃	H	-(CH ₂) ₂ -	-CH(OH)-	1
31	4-OCH ₃	H	4-OH	H	H	-CH(OH)-	-(CH ₂) ₂ -	1
32	4-OCH ₃	H	4-OH	3-OH	H	-CH(OH)-	-(CH ₂) ₂ -	1
33	4-OH	3-COOCH ₃	together -O-CH ₂ -O-		H	-(CH ₂) ₂ -	-CH(OH)-	1
34	together -O-CH ₂ -O-		4-OCH ₃	3-OCH ₃	H	-(CH ₂) ₂ -	-CH(OH)-	1

The preferred compounds are those of examples 1 - 26, 31 and 32, viz:

- (1) 4-[(RS)-hydroxy-[(2SR,5RS)-5-phenethyl-pyrrolidin-2-yl]-methyl]-phenol,
- (2) 2-fluoro-4-[(RS)-hydroxy-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-phenol,
- (3) 4-[hydroxy-[2RS,6SR)-6-[2-(4-methoxy-phenyl)-ethyl]-piperidin-2-yl]-

methyl)-phenol,

(4) (2RS,5RS)-4-[5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-ylmethyl]-phenol,

(5) 4-[(RS)-hydroxy-[(2SR,5RS)-5-phenethyl-pyrrolidin-2-yl]-methyl]-
5 benzene-1,2-diol,

(6) (2RS,6SR)-4-[6-[2-(4-methoxy-phenyl)-ethyl]-piperidin-2-ylmethyl]-phenol,

(7) Mixture of (2RS,5RS)- and (2RS,5SR)-(4-hydroxy-phenyl)-[5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methanone,

10 (8) (2RS,5RS)-4-(5-phenethyl-pyrrolidin-2-ylmethyl)-benzene-1,2-diol,

(9) (2RS,5RS)-4-[5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-ylmethyl]-benzene-1,2-diol,

(10) (2RS,5RS)-4-(1-butyl-5-phenethyl-pyrrolidin-2-ylmethyl)-benzene-1,2-diol,

15 (11) (2RS,5RS)-4-(5-phenethyl-1-propyl-pyrrolidin-2-ylmethyl)-benzene-1,2-diol,

(12) (RS)-[(2SR,5SR)-5-(2-benzo[1.3]dioxol-5-yl-ethyl)-pyrrolidin-2-yl]-phenyl-methanol,

(13) 5-[(RS)-[(2SR,5SR)-5-(2-benzo[1.3]dioxol-5-yl-ethyl)-pyrrolidin-2-yl]-
20 hydroxy-methyl]-2-hydroxy-benzamide,

(14) (2RS,5RS)-2-benzyl-5-phenethyl-pyrrolidine,

(15) (RS)-[(2SR,5SR)-5-phenethyl-pyrrolidin-2-yl]-phenyl-methanol,

(16) 2-hydroxy-5-[(RS)-hydroxy-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-benzamide,

25 (18) 4-[(RS)-hydroxy-[(2SR,5RS)-5-[2-(4-hydroxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-benzene-1,2-diol,

(19) (RS)-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-phenyl-methanol,

(20) 4-[2RS,5SR)-5-[2-(4-hydroxy-phenyl)-ethyl]-pyrrolidin-2-ylmethyl]-
30 benzene-1,2-diol,

(21) 4-[(RS)-hydroxy-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-2-methylsulfanyl-phenol,

(22) 4-[2-[(2RS,5RS)-5-[(SR)-hydroxy-phenyl-methyl]-pyrrolidin-2-yl]-ethyl]-phenol,

(23) (2RS,5RS)-4-[5-[2-(4-hydroxy-phenyl)-ethyl]-1-propyl-pyrrolidin-2-ylmethyl]-benzene-1,2-diol,

5 (24) 5-[(RS)-[(2SR,5SR)-5-[2-(2,5-dimethoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-hydroxy-methyl]-2-hydroxy-benzamide,

(25) (RS)-benzo[1.3]dioxol-5-yl-[(2SR,5SR)-5-(2-benzo[1.3]dioxol-5-yl-ethyl)-pyrrolidin-2-yl]-methanol,

10 (26) (RS)-benzo[1.3]dioxol-5-yl-[(2SR,5SR)-5-phenethyl-pyrrolidin-2-yl]-methanol,

(31) 4-[(RS)-hydroxy-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-benzene-1,2-diol,

(32) 4-[(RS)-hydroxy-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-phenol.

15 The following compounds of formula II have been tested:

Ex. No.	R ¹	R ²	R ³	R ⁴	Y	m	p
35	H	H	4-OH	H	-(CH ₂) ₂ -	1	2
36	H	H	4-OH	H	-(CH ₂) ₂ -	1	2
37	H	H	4-OH	H	-(CH ₂) ₂ -	1	1
38	H	H	4-OH	H	-(CH ₂) ₂ -	1	1

Compounds of Examples 35 - 38 are:

(35) (1RS,6SR,8aRS)-4-(6-phenethyl-hexahydro-pyrrolo[2,1-c][1,4]oxazin-1-yl)-phenol,

20 (36) (1RS,6RS,8aSR)-4-(6-phenethyl-hexahydro-pyrrolo[2,1-c][1,4]oxazin-1-yl)-phenol,

(37) (1RS,5RS,7aSR)-4-(5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazol-1-yl)-phenol and

(38) (1RS,5SR,7aRS)-4-(5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazol-1-yl)-phenol.

5 The compounds of formulae I and II and their salts, as herein described, together with pharmaceutically inert excipients can be incorporated into standard pharmaceutical dosage forms, for example, for oral or parenteral application with the usual pharmaceutical adjuvant materials, for example, organic or inorganic inert carrier materials, such as, water, gelatin, lactose,
10 starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene-glycols and the like. Examples of pharmaceutical preparations in solid form are tablets, suppositories, capsules, or in liquid form are solutions, suspensions or emulsions. Pharmaceutical adjuvant materials include preservatives, stabilizers, wetting or emulsifying agents, salts to change the osmotic pressure
15 or to act as buffers. The pharmaceutical preparations can also contain other therapeutically active substances.

The daily dose of compounds of formulae I and II to be administered varies with the particular compound employed, the chosen route of administration and the recipient. Representative of a method for
20 administering the compounds of formulae I and II is by the oral and parenteral type administration route. An oral formulation of a compound of formulae I and II is preferably administered to an adult at a dose in the range of 1 mg to 1000 mg per day. A parenteral formulation of a compound of formula I is preferably administered to an adult at a dose in the range of from
25 5 to 500 mg per day.

The invention is further illustrated in the following examples.

Example 35

(1RS,6SR,8aRS)-4-(6-Phenethyl-hexahydro-pyrrolo[2,1-c][1,4]oxazin-1-yl)-phenol

30 (1RS,6SR,8aRS)-1-(4-Benzoyloxy-phenyl)-6-phenethyl-hexahydro-pyrrolo[2,1-c][1,4]oxazine (0.09 g, 0.22 mmol) was dissolved in MeOH (5 ml)

and hydrogenated in the presence of Pd on C at room temperature and at atmospheric pressure for 4 hours. After filtration and evaporation of the solvent the residue was chromatographed over silica gel (CH₂Cl₂-MeOH 19:1) to provide (1RS,6SR,8aRS)-4-(6-phenethyl-hexahydro-pyrrolo[2,1-

5 c][1,4]oxazin-1-yl)-phenol (25 mg, 35%) as a pink solid, m.p. 170-172 °C.

MS: m/e= 324.3 (M+H⁺).

Following the general method of example 35 the compounds of examples 36 to example 38 were prepared.

Example 36

10 (1RS,6RS,8aSR)-4-(6-Phenethyl-hexahydro-pyrrolo[2,1-c][1,4]oxazin-1-yl)-phenol

The title compound, MS: m/e= 324.3 (M+H⁺), was prepared from (1RS,6RS,8aSR)-1-(4-benzyloxy-phenyl)-6-phenethyl-hexahydro-pyrrolo[2,1-c][1,4]oxazine.

15

Example 37

(1RS,5RS,7aSR)-4-(5-Phenethyl-tetrahydro-pyrrolo[1,2-c]oxazol-1-yl)-phenol

The title compound, MS: m/e= 310.3 (M+H⁺), was prepared from (1RS,5RS,7aSR)-1-(4-benzyloxy-phenyl)-5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazole.

20

Example 38

(1RS,5SR,7aRS)-4-(5-Phenethyl-tetrahydro-pyrrolo[1,2-c]oxazol-1-yl)-phenol

The title compound, m.p. 176 °C and MS: m/e= 310.2 (M+H⁺), was prepared from (1RS,5SR,7aRS)-1-(4-benzyloxy-phenyl)-5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazole.

25

Example 39

(1RS,5RS,7aSR)-1-(4-Benzyloxy-phenyl)-5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazole and (1RS,5SR,7aRS)-1-(4-Benzyloxy-phenyl)-5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazole

A mixture of (RS)- and (SR)-[(2RS,5SR)-4-benzyloxy-phenyl]-5-phenethyl-pyrrolidin-2-yl]-methanol (0.24 g, 0.62 mmol) was stirred in the presence of an aqueous solution of formaldehyde (36% in H₂O, 2 ml) for 2

30

hours at room temperature. Reaction mixture was then diluted with H₂O (10 ml), basified to pH 13 with 1N NaOH and extracted with ether (3x 20 ml). Combined organic phases were dried over Na₂SO₄, and concentrated. The residue was chromatographed over silica gel (hexane- ethyl acetate 1:1) to provide (1RS,5RS,7aSR)-1-(4-benzyloxy-phenyl)-5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazole (0.065 g, 26 %) as a yellowish solid, m.p. 101-103 °C. MS: m/e = 400.3 (M+H⁺) and (1RS,5SR,7aRS)-1-(4-benzyloxy-phenyl)-5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazole as a white solid, m.p. 94-95 °C. MS: m/e = 400.3 (M+H⁺).

10

Example 40

(1RS,6RS,8aSR)-1-(4-Benzyloxy-phenyl)-6-phenethyl-hexahydro-pyrrolo[2,1-cl[1,4]oxazine

A solution of (1RS,6RS,8aSR)-1-(4-Benzyloxy-phenyl)-6-phenethyl-tetrahydro-pyrrolo[2,1-cl[1,4]oxazin-4-one (0.12 g, 0.28 mmol) in THF (1 ml) was added dropwise to a 0 °C suspension of LiAlH₄ (0.021 g, 0.56 mmol) in THF (1 ml). Reaction mixture was stirred at room temperature for 2 hours then cooled to 0 °C and treated successively with H₂O (25 ml), 5N NaOH (25 ml), H₂O (75 ml). Reaction mixture was stirred at room temperature for 30 min. and Na₂SO₄ was added. After filtration, evaporation of the solvent provided (1RS,6RS,8aSR)-1-(4-benzyloxy-phenyl)-6-phenethyl-hexahydro-pyrrolo[2,1-cl[1,4]oxazine (90 mg, 78%) as a colorless oil.

20

MS: m/e = 414.5 (M+H⁺).

Following the general method of example 40 the compound of example 41 was prepared

25

Example 41

(1RS,6SR,8aRS)-1-(4-Benzyloxy-phenyl)-6-phenethyl-hexahydro-pyrrolo[2,1-cl[1,4]oxazine

The title compound, MS: m/e= 414.2 (M+H⁺), was prepared from (1RS,6SR,8aRS)-1-(4-benzyloxy-phenyl)-6-phenethyl-tetrahydro-pyrrolo[2,1-cl[1,4]oxazin-4-one.

30

Example 42

(1RS,6RS,8aSR)-1-(4-Benzoyloxy-phenyl)-6-phenethyl-tetrahydro-pyrrolo[2,1-c][1,4]oxazin-4-one and (1RS,6SR,8aRS)-1-(4-Benzoyloxy-phenyl)-6-phenethyl-tetrahydro-pyrrolo[2,1-c][1,4]oxazin-4-one

5 A mixture of (RS)- and (SR)-[(2RS,5SR)-4-Benzoyloxy-phenyl]-5-phenethyl-pyrrolidin-2-yl]-methanol (0.38 g, 1 mmol), and triethylamine (0.42 ml, 3 mmol) in dioxan (10 ml) was treated at 5 °C with chloroacetylchloride (96 ml, 1.2 mmol). After 1.2 hour stirring at room temperature, reaction mixture was quenched with H₂O (10 ml), acidified to pH 2 with 1N HCl and
10 extracted with CH₂Cl₂ (3 x 30 ml). Combined organic phases were washed with saturated NaCl (20 ml), dried over Na₂SO₄, and concentrated. Residue was dissolved in toluene (8 ml) and refluxed in the presence of sodium methylate (0.13 g, 2.4 mmol) for 4 hours. Reaction mixture was cooled to room temperature and solvent was evaporated. Residue was diluted with H₂O (10
15 ml), acidified to pH 2 with 1N HCl and extracted with CH₂Cl₂ (3 x 30 ml). Combined organic phases were washed with H₂O (20 ml), dried over Na₂SO₄, and concentrated. The residue was chromatographed over silica gel (hexane-ethyl acetate 4:1 then 1:1) to provide (1RS,6RS,8aSR)-1-(4-benzoyloxy-phenyl)-6-phenethyl-tetrahydro-pyrrolo[2,1-c][1,4]oxazin-4-one (0.125 g, 30 %) as a
20 yellow oil, MS: m/e = 428.4 (M+H⁺) and (1RS,6SR,8aRS)-1-(4-benzoyloxy-phenyl)-6-phenethyl-tetrahydro-pyrrolo[2,1-c][1,4]oxazin-4-one (0.127 g, 30 %) as a yellow oil.

MS: m/e = 428.3 (M+H⁺).

(RS)- and (SR)-[(2RS,5SR)-4-Benzoyloxy-phenyl]-5-phenethyl-pyrrolidin-
25 2-yl]-methanol can be prepared by hydrogenation of a pyrrole as described in J. Org. Chem. 1984, 49, 4203-4209.

EXAMPLE ATablet Formulation (Wet Granulation)

		ingredients		mg / tablet	
	1. Active compound	5	25	100	500
5	2. Lactose Anhydrous DTG	125	105	30	150
	3. Sta-Rx 1500	6	6	6	30
	4. Microcrystalline Cellulose	30	30	30	150
	5. Magnesium Stearate	1	1	1	1
	TOTAL	167	167	167	831

10

Manufacturing Procedure:

1. Mix Items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granulation at 50°C.
3. Pass the granulation through suitable milling equipment.
- 15 4. Add Item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

		Ingredients		mg / capsule	
	1. Active compound	5	25	100	500
20	2. Hydrous Lactose	159	123	148	---
	3. Corn Starch	25	35	40	70
	4. Talc	10	15	10	25
	5. Magnesium Stearate	1	2	2	5
	TOTAL	200	200	300	600

25

Manufacturing Procedure:

1. Mix Items 1, 2, and 3 in a suitable mixer for 30 minutes.
2. Add Items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.
- 30 2.

Tablet Formulation (Wet Granulation)

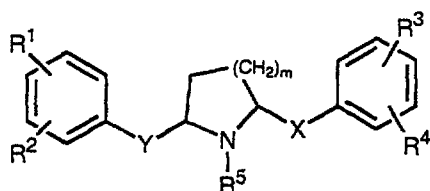
		Ingredients mg / tablet			
	1. Active compound	5	25	100	500
	2. Lactose Anhydrous	125	105	30	150
5	3. Sta-Rx 1500	6	6	6	30
	4. Microcrystalline Cellulose	30	30	30	150
	5. Magnesium Stearate	1	2	2	5
	TOTAL	167	167	167	835

10 Manufacturing Procedure:

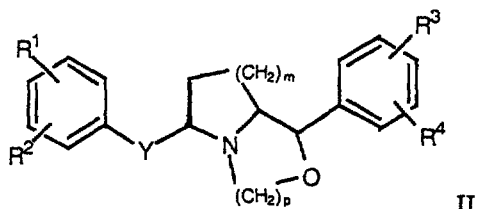
1. Mix Items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granulation at 50°C.
3. Pass the granulation through suitable milling equipment.
4. Add Item 5 and mix for three minutes; compress on a suitable press.

ClaimsTHIS SHEET HAS BEEN
REPLACED

1. The use of pyrrolidine and piperidine derivatives of the general formulae



I and



II

5

wherein

R^1 and R^2 are, independently from each other, hydrogen, lower alkoxy, hydroxy, halogen, $-\text{CONH}_2$ or $-\text{C}(\text{O})\text{O}$ -lower alkyl; or taken together are $-\text{O}-\text{CH}_2-\text{O}-$;

10 R^3 and R^4 are, independently from each other, hydrogen, lower alkoxy, benzyloxy, halogen, hydroxy, $-\text{CONH}_2$ or $-\text{SCH}_3$; or taken together are $-\text{O}-\text{CH}_2-\text{O}-$;

R^5 is hydrogen or lower alkyl;

X and Y are, independently from each other $-\text{CH}(\text{OH})-$, $-(\text{CH}_2)_n-$, $-\text{C}(\text{O})-$ or $-\text{CH}(\text{lower alkoxy})-$; and

15

m , n and p are 1 or 2;

and of their pharmaceutically acceptable addition salts for the treatment of diseases caused by overactivation of NMDA receptor subtypes and/or for the manufacture of corresponding medicaments.

20 2. The use of compounds of formulae I and II according to claim 1, wherein the therapeutic indications include acute forms of neurodegeneration caused, e.g., by stroke or brain trauma; chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease or ALS (amyotrophic lateral sclerosis); neurodegeneration associated with bacterial or

25 viral infections, and, diseases such as schizophrenia, anxiety and depression.

3. The use of compounds of formula I according to claim 1, wherein



X is -CH(OH)-, Y is -(CH₂)₂- and m is 1, or

X is -(CH₂)₂-, Y is -CH(OH)- and m is 1, or

X is -(CH₂)₂-, Y is -CH₂- and m is 1, or

X is -(CH₂)₂-, Y is -C(O)- and m is 1, or

5 X is -CH₂-. Y is -(CH₂)₂- and m is 2,

and the other substituents being as defined in claim 1.

4. The use of compounds of formula I according to claim 3, which compounds are

- 10 4-[(RS)-hydroxy-[(2SR,5RS)-5-phenethyl-pyrrolidin-2-yl]-methyl]-phenol,
2-fluoro-4-[(RS)-hydroxy-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-phenol,
4-[(RS)-hydroxy-[(2SR,5RS)-5-phenethyl-pyrrolidin-2-yl]-methyl]-benzene-1,2-diol,
15 4-[(RS)-hydroxy-[(2SR,5SR)-5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methyl]-phenol,
4-[hydroxy-[(2RS,6SR)-6-[2-(4-methoxy-phenyl)-ethyl]-piperidin-2-yl]-methyl]-phenol,
(2RS,5RS)-4-[5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-ylmethyl]-phenol,
20 (2RS,5RS)-4-(5-phenethyl-pyrrolidin-2-yl-methyl)-benzene-1,2-diol.
(2RS,6SR)-4-[6-[2-(4-methoxy-phenyl)-ethyl]-piperidin-2-ylmethyl]-phenol and
Mixture of (2RS,5RS)- and (2RS,5SR)-(4-hydroxy-phenyl)-[5-[2-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl]-methanone.

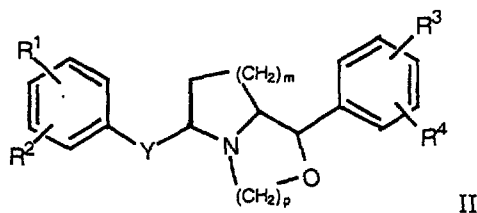
25 5. The use of compounds of formula II according to claim 1, wherein

Y is -(CH₂)₂-, R¹, R² and R³ are hydrogen, R⁴ is hydroxy and m and p are 1.

6. The use of compounds of formula II according to claim 5, which compounds are

- (1RS,5SR,7aRS)-4-(5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazol-1-yl)-phenol
30 and
(1RS,5RS,7aSR)-4-(5-phenethyl-tetrahydro-pyrrolo[1,2-c]oxazol-1-yl)-phenol.

7. Compounds of formula



wherein

R^1 and R^2 are, independently from each other, hydrogen, lower alkoxy, hydroxy, halogen, $-\text{CONH}_2$ or $-\text{C}(\text{O})\text{O}$ -lower alkyl; or taken together are $-\text{O}-\text{CH}_2-\text{O}-$;

R^3 and R^4 are, independently from each other, hydrogen, lower alkoxy, benzyloxy, halogen, hydroxy, $-\text{CONH}_2$ or $-\text{SCH}_3$; or taken together are $-\text{O}-\text{CH}_2-\text{O}-$;

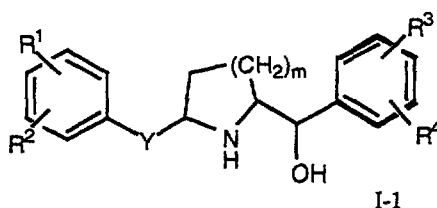
Y is $-\text{CH}(\text{OH})-$, $-(\text{CH}_2)_n-$, $-\text{C}(\text{O})-$ or $-\text{CH}(\text{lower alkoxy})-$; and

m , n and p are 1 or 2;

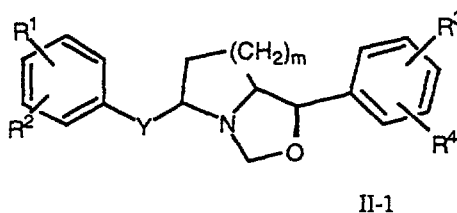
and their pharmaceutically acceptable addition salts.

8. A process for the manufacture of compounds of formula II, which process comprises

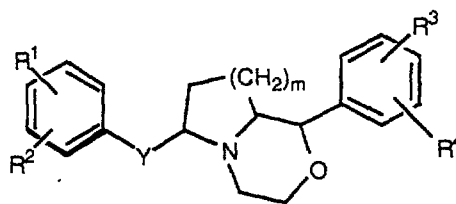
a) cyclizing a compound of formula



to a compound of formula



by reaction with a compound useful to form an oxazole ring, or to a compound of formula



II-2

by reaction with a compound useful to form a morpholine ring,
wherein $R^1 - R^4$, Y and m have the significances given above, or

5 b) debenzylating a compound of formula II, wherein R^3 and/or R^4 are
benzyloxy, or

c) modifying one or more substituents $R^1 - R^4$ within the definitions given
above, and

if desired, converting the compound obtained into a pharmaceutically

10 acceptable acid addition salt.

9. A medicament containing one or more compounds according to claim 7
and pharmaceutically inert excipients.

10. A medicament in accordance with claim 7 for the treatment of
diseases which include acute forms of neurodegeneration caused, e.g., by
15 stroke or brain trauma; chronic forms of neurodegeneration such as
Alzheimer's disease, Parkinson's disease, Huntington's disease or ALS
(amyotrophic lateral sclerosis); neurodegeneration associated with bacterial or
viral infections, and, diseases such as schizophrenia, anxiety and depression.

11. The use of compounds of formula II for the treatment of diseases
20 which include acute forms of neurodegeneration caused, e.g., by stroke or
brain trauma; chronic forms of neurodegeneration such as Alzheimer's disease,
Parkinson's disease, Huntington's disease or ALS (amyotrophic lateral
sclerosis); neurodegeneration associated with bacterial or viral infections, and,
diseases such as schizophrenia, anxiety and depression.

25 12. The invention as hereinbefore described.

