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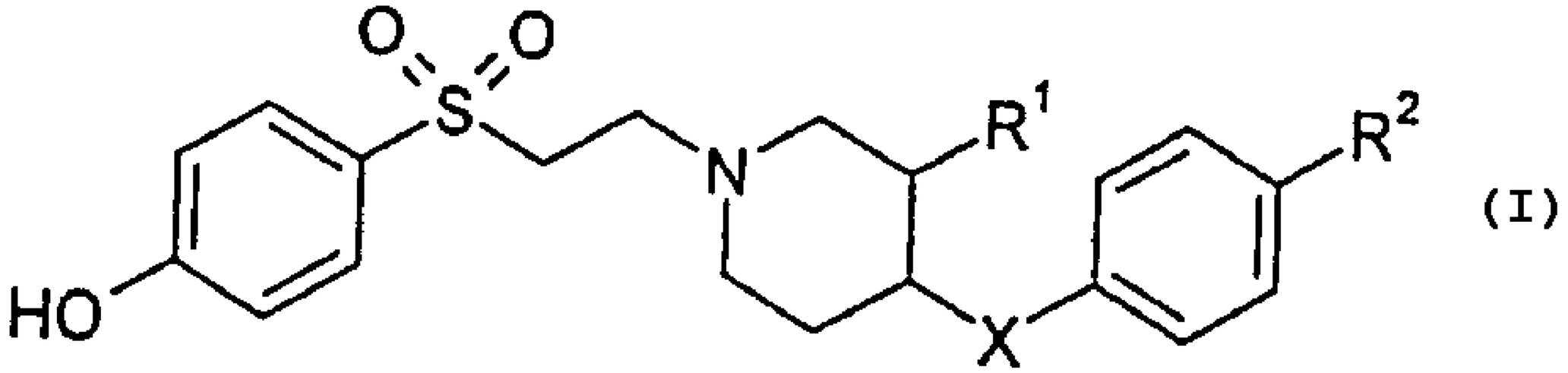
(54) Title: ETHANESULFONYL-PIPERIDINE DERIVATIVES



(I)

(57) Abrégé/Abstract:
The invention relates to compounds of general formula (I) wherein R signify hydrogen or hydroxy; R^2 signify hydrogen or methyl; and X signify -O- or -CH_2-; and their pharmaceutically acceptable acid addition salts. It has been shown that these compounds have a good affinity to the NMDA receptor and they are therefore useful in the treatment of diseases, 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, Parkinsons's disease, Huntington's disease or ALS (amyotrophic lateral sclerosis); neurodegeneration associated with bacterial or viral infections, and, diseases such as schizophrenia, anxiety, depression and chronic/acute pain.

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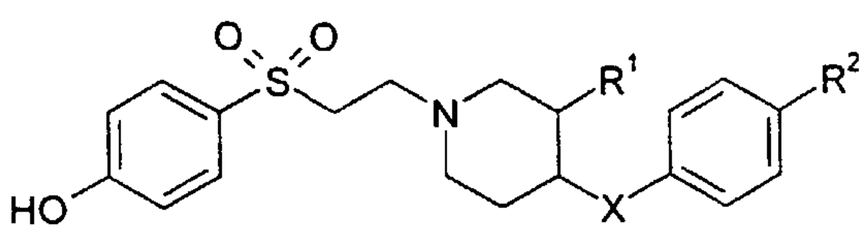
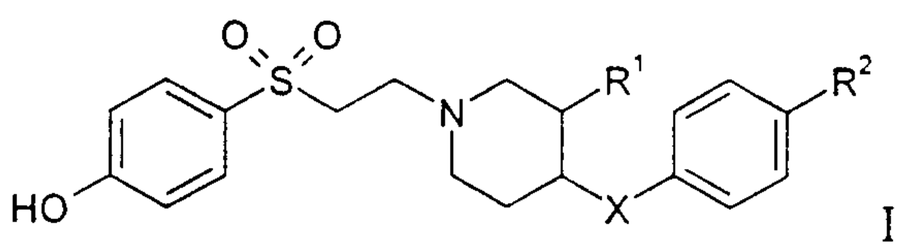


(I)

(57) Abstract: The invention relates to compounds of general formula (I) wherein R signify hydrogen or hydroxy; R^2 signify hydrogen or methyl; and X signify -O- or -CH_2-; and their pharmaceutically acceptable acid addition salts. It has been shown that these compounds have a good affinity to the NMDA receptor and they are therefore useful in the treatment of diseases, 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, Parkinsons's disease, Huntington's disease or ALS (amyotrophic lateral sclerosis); neurodegeneration associated with bacterial or viral infections, and, diseases such as schizophrenia, anxiety, depression and chronic/acute pain.

Ethanesulfonyl-piperidine derivatives

The present invention relates to compounds of the general formula



I

wherein

R^1 signify hydrogen or hydroxy;

R^2 signify hydrogen or methyl; and

X signify –O- or –CH_2-;

and to their pharmaceutically acceptable acid addition salts.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, lactic acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

The compounds of the invention relates to cis-isomeres.

The compounds of the present invention are NMDA (N-methyl-D-aspartate)-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 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 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 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); neurodegeneration associated with bacterial or viral infections, diseases such as schizophrenia, anxiety and depression and acute/chronic pain.

Objects of the present invention are novel compounds of formula I, the use in the treatment or prophylaxis of diseases caused by overactivation of respective NMDA receptor subtypes, 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, depression and acute/chronic pain, the use of these compounds for manufacture of corresponding medicaments, processes for the manufacture of these novel compounds and medicaments, containing them.

Compounds of formula I and their salts are generically, but not specifically, known compounds, described in WO 95/25721. They are described to possess activities on the glutamat receptor or AMPA receptor for the treatment of diseases which are related to these receptors. Furthermore similar compounds are described in EP 824 098, in which the piperidine ring is substituted by a hydroxy group in 4-position. These compounds are described to possess activities on the NMDA receptor and are useful in the treatment of acute forms of neurodegeneration caused, for example, by stroke and brain trauma, and chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, ALS (amyotrophic lateral sclerosis), neurodegeneration associated with bacterial or viral infections and acute/chronic pain.

It is known from EP 824 098 that these compounds are good NMDA receptor subtype specific blockers with a high affinity for NR2B subunit containing receptors and low affinity for NR2A subunit containing receptors.

Activity versus α_1-adrenergic receptors is also low and the compounds are active *in vivo* against audiogenic seizures in mice in the low mg/kg range. Importantly, these compounds were neuroprotective in an animal stroke model, namely, a permanent occlusion of the middle cerebral artery. However, *in vitro* and *in vivo* cardiotoxicity studies showed that these compounds had the propensity to prolong cardiac action potential duration *in vitro* and consequently the 'QT'-interval *in vivo* and thus, had a potential liability to produce cardiac arrhythmias. The ability of such compounds to prolong the cardiac action potential was identified as being due to an action at the hERG type

potassium channel, which is important for action potential repolarisation in humans and other species, and most compounds known to prolong the QT-interval in man are active at blocking this channel. Thus, the compounds of the prior art block recombinant human ERG potassium channels heterologously.

It has now surprisingly been found that the following compounds of formula I

4[-2-(4-benzyl-piperidine-1-yl)-ethanesulfonyl]-phenol (1),
4-[2-(4-p-tolyloxy-piperidin-1-yl)-ethanesulfonyl]-phenol (2),
(-)- (3R,4R)- or (3S,4S)-4-benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol (3),
(+)- (3S,4S)- or (3R,4R)-4-benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol (4),
(3RS,4RS)- 4-benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol (5),
(-)-(3R,4R)- or (3S,4S)-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-4-(4-methyl-benzyl)-piperidin-3-ol (6),
(+)-(3R,4R)- or (3S,4S)-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-4-(4-methyl-benzyl)-piperidin-3-ol (7) and
(3RS,4RS)-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-4-(4-methyl-benzyl)-piperidin-3-ol (8)

are NMDA NR2B subtype selective antagonists whilst they share the highly specific subtype selective blocking properties compounds of the prior art, for example of 1-[2-(4-hydroxy-phenoxy)-ethyl]-4-(4-methyl-benzyl)-piperidin-4-ol (9), and are neuroprotectants *in vivo*, they are less active as blockers of the hERG potassium channels and, thus, are much less likely to have pro-arrhythmic activity in man.

In the following table it is demonstrated the high selectivity of compounds of the present invention.

Selectivity profile of NMDA NR2B subtype selective antagonists

Compound	Inhibition of [3H]-Ro 25-6981 binding $IC_{50}(\mu M)$[a]	Inhibition of [3H]-Prazosin binding $IC_{50}(\mu M)$[b]	NMDA NR1+ NR2B IC_{50} (μM)[c]	NMDA NR1+ NR2A IC_{50} (μM)[c]	i.c.v. NMDA ED_{50} mg/kg i.v.[d]	hERG $IC_{50}(\mu M)$[e]
(9) comparison EP 824098	0.010	3.5	0.003	>100	2.3	0.69
(1)	0.018	42	<0.01	>10	1.1	4.0
(2)	0.024	16	<0.01	>10	0.84	4.7
(3)	0.014	55	0.038	>10	3.8	>10
(6)	0.011	88	0.008	>10	2.2	3.7

[a] Inhibition of [3H]-Ro 25-6981 binding indicates affinity for NMDA NR2B subunit containing receptors.

[b] Inhibition of [3H]-Prazosin binding indicates affinity for α_1-adrenergic receptors.

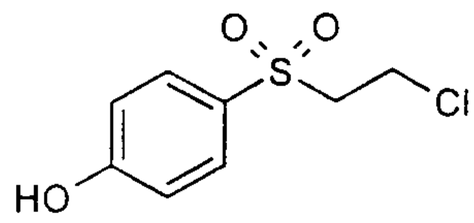
[c] NMDA NR1+NR2B and NMDA NR1+NR2A indicates the ability to block selectively recombinant NMDA receptor subtypes expressed in *Xenopus* oocytes.

[d] Indicates potency in mg/kg i.v. to block i.c.v. NMDA-induced convulsions in mice.

[e] Indicates potency for blockade of recombinant human ERG potassium channels expressed in a mammalian cell line (chinese hamster ovary cells, CHO).

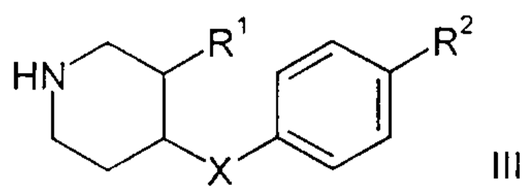
The novel compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example by processes described below, which comprises

a) reacting a compound of formula



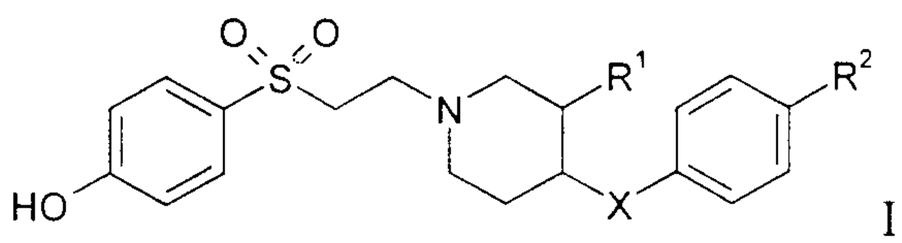
II

with a compound of formula



III

to a compound of formula



I

wherein the substituents are described above,

and, if desired,

b) converting the compound of formula I obtained into a pharmaceutically acceptable acid addition salts,

c) and, if desired,

converting a racemic mixture into its enantiomeric component thus obtaining optically pure compounds.

In accordance with process variant a) 4-(2-chloro-ethanesulfonyl)-phenol is dissolved in methylchloride and a compound of formula III, for example 4-p-tolyloxy-piperidine, 4-benzylpiperidine, (3R,4R)- or (3S,4S)-4-benzyl-piperidine-3-ol, (3R,4R)-or (3S,4S)-4-(4-methyl-benzyl)-piperidine-3-ol is added and in the presence of triethylamine or an excess of the piperidine the solution is stirred for some hours at room temperature. The reaction mixture is purified by chromatography over silica gel.

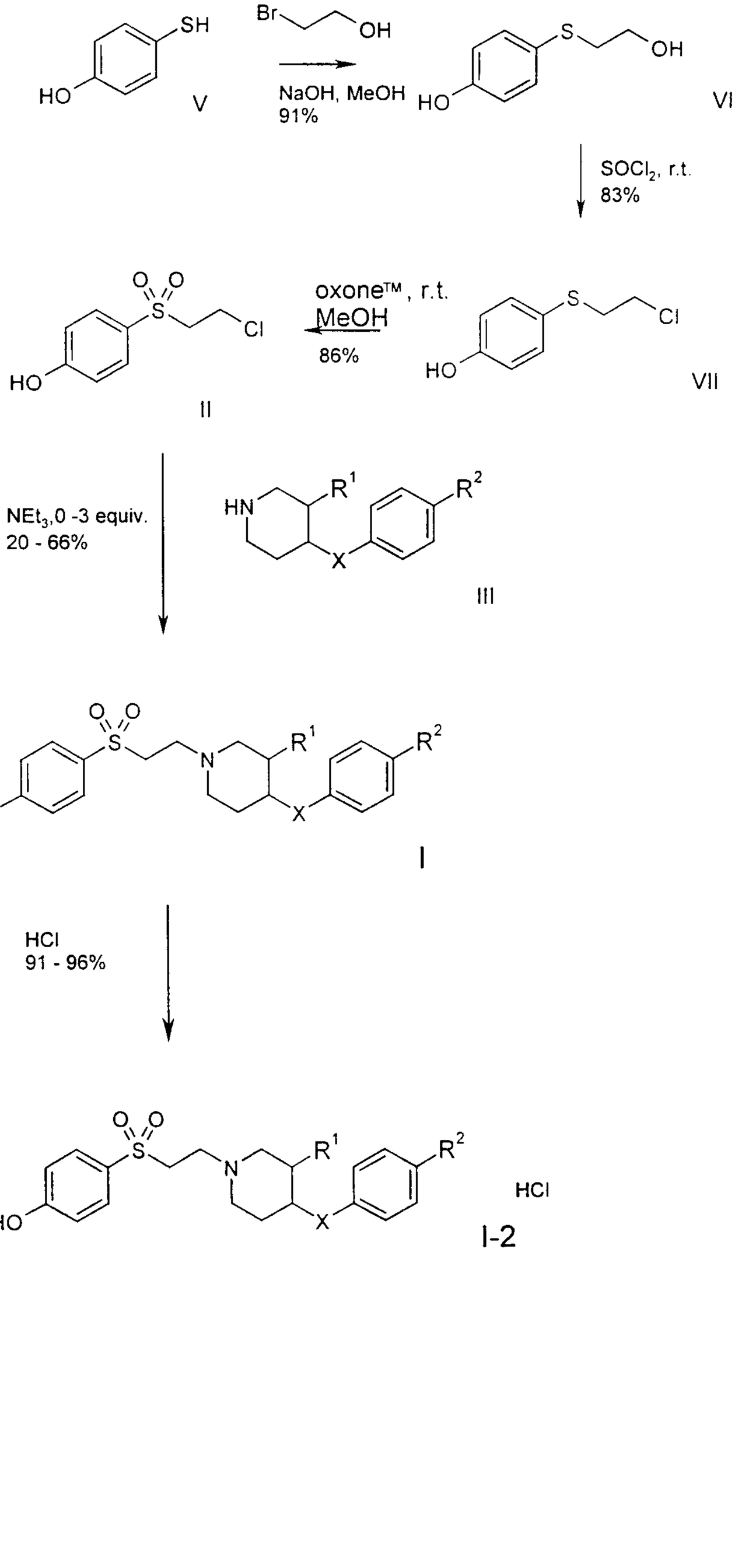
The acid addition salts of the compounds of formula I are especially well suited for pharmaceutical use.

The following schemes 1 – 3 describe the preparation of compounds of formula I and of compounds of formulae XIII, XIV and VIII, which are intermediates. The starting

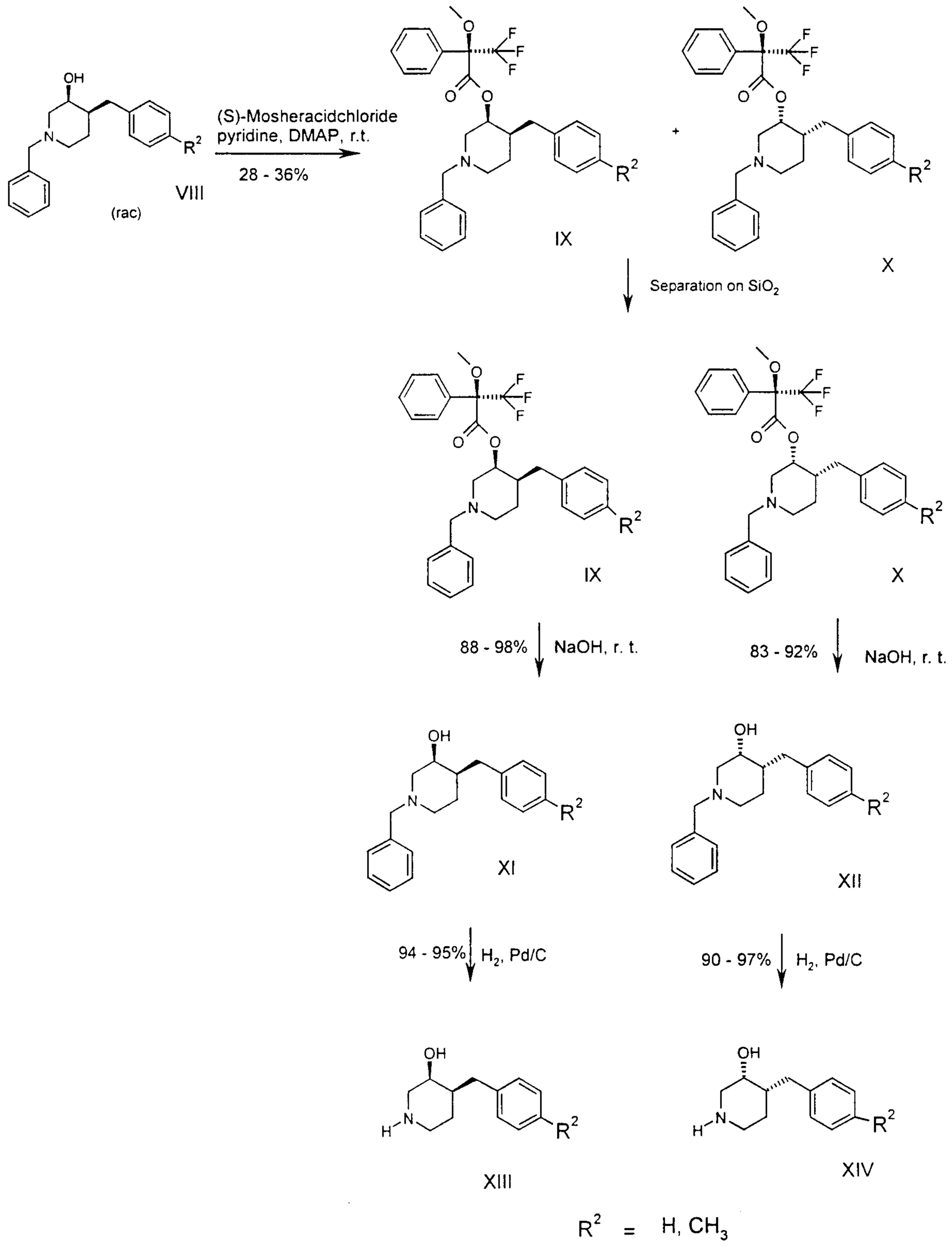
materials of formulae V and XV are known compounds or can be prepared by methods known in the art.

Scheme 1

Synthesis of sulfone derivatives and their salts



Scheme 2

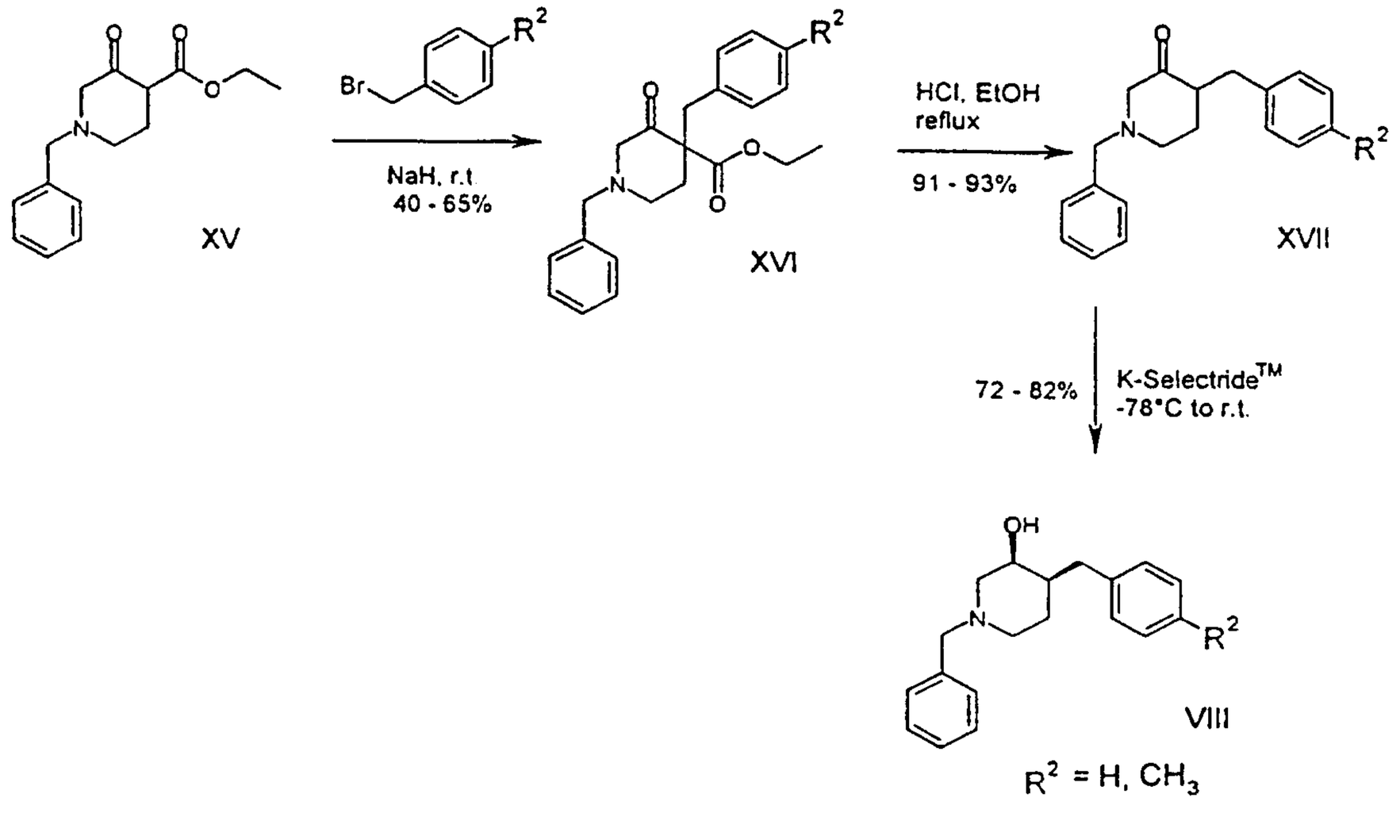


R^2 = H, CH_3

Synthesis of enantiomerically pure 3-hydroxy benzylpiperidines

Scheme 3

Synthesis of hydroxy benzyl piperidine derivatives



The detailed description of the above mentioned processes is described in Examples 1 - 31.

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.

Method 1

3H-Ro 25-6981 binding (Ro 25-6981 is [R-(R*,S*)]-α-(4-Hydroxy-phenyl)-β-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 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

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.

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 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).

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 IC_{50} with their relative upper and lower 95% confidence limits (RS1, BBN, USA).

Method 2

3H-Prazosin binding

Male Füllinsdorf albino rats weighing between 150-200 g were used. Membranes were prepared by homogenization of the whole brain minus cerebellum and medulla oblongata with a Polytron (10.000 rpm, 30 seconds), in 25 volumes of a cold Tris-HCl 50 mM, EDTA 10mM, 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 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 5mM, pH 7.4 cold buffer. The final pellet was resuspended in the same buffer and used at a final concentration of 200 mg of protein/ml.

3H-Prazosin binding experiments were performed using a Tris-HCl 50 mM, pH 7.4 buffer. For displacement experiments 0.2 nM of 3H-Prazosine were used and non specific binding was measured using 100 mM of chlorpromazine. The incubation time was 30 minutes at room temperature and the assay was stopped by filtration on Whatman GF/B

glass fiber filters (Unifilter-96, Canberra Packard S.A., 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). 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 IC_{50} with their relative upper and lower 95% confidence limits (RS1, BBN, USA).

The thus-determined activity of compounds of examples 1 – 3 and 6 in accordance with the invention is in the range of 0.011 – 0.024 (in μM), as described in the table above.

Method 3

Methods for studying the inhibition of the hERG K^+ channel.

CHO cells were stably transfected by a pcDNA3-hERG expression vector containing a SV40-neo cassette for selection. Cells were thinly plated into 35 mm dishes and used for the electrophysiological experiment ½-3 d later.

During the experiment the cells were continuously superfused with an extracellular saline containing (in mM): NaCl 150, KCl 10, $MgCl_2$ 1, $CaCl_2$ 3, HEPES 10 (pH = 7.3 by addition of NaOH). A 10-mM stock solution of the test compound was made from pure DMSO. Test solution were made by at least 1000-fold dilution of the stock solution into the extracellular saline. The glass micropipettes for whole-cell patch-clamp recording were filled with a containing (in mM): KCl 110, BAPTA 10, HEPES 10, $MgCl_2$ 4.5, Na_2ATP 4, Na_2-phosphocreatine 20, creatine kinase 200 μg/ml (pH = 7.3 by addition of KOH).

The whole-cell configuration of the patch-clamp technique was used for the experiments. Cells were clamped to –80 mV holding potential and repetitively (0.1 Hz) stimulated by a voltage pulse pattern consisting of a 1-s conditioning depolarisation to 20 mV immediately followed by a hyperpolarisation of 50 ms duration to –120 mV. The membrane current was recorded for at least 3 min (18 stimuli) before compound application (control), and then for another two 3-min intervals in presence of two different concentrations of the compound. The current amplitudes (I_{test}) at the end of each compound application interval were divided by the mean current amplitude ($I_{control}$) during the initial control period to calculate the percentage effect of the compound: effect (%) = $(1-I_{test}/I_{control})$ 100.

Compound concentrations were chosen in decade steps (usually 1 and 10 μM) around the expected 50% inhibitory concentration (IC_{50}). If after the first experiment the IC_{50} turned out to lie outside the range between the two chosen concentrations the

concentrations were changed to bracket the IC_{50} in the following experiments. The compound was tested on at least three cells. Its IC_{50} was then estimated from the population of all percent-effect values by non-linear regression using the function effect = 100 / (1 - IC_{50} / concentration)^{Hill}).

Concentrations higher than 10 µM were not tested. If 10 µM of the compound turned out to produce less than 50 % effect, IC50 was labelled as ">10 µM" and the compound was characterised by the average effect seen at 10 µM.

The compounds of formula I 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, 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 or to act as buffers. The pharmaceutical preparations can also contain other therapeutically active substances.

The daily dose of compounds of formula I to be administered varies with the particular compound employed, the chosen route of administration and the recipient. Representative of a method for administering the compounds of formula I is by the oral and parenteral type administration route. An oral formulation of a compound of formula I 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 5 to 500 mg per day.

The invention is further illustrated in the following examples.

Example 1

4[-2-(4-Benzyl-piperidine-1-yl)-ethanesulfonyl]-phenol

To a solution of 40.0 g 4-(2-chloro-ethanesulfonyl)-phenol (181 mmol) in 600 ml CH_2Cl_2 were added 69.9 g 4-benzylpiperidine (399 mmol). After stirring for 16 h at r. t. the reaction mixture was concentrated to 100 ml and directly purified by chromatography over silica gel (CH_2Cl_2/MeOH/NH_3 19/1/0.1). Recrystallization from ethyl acetate/hexane (2:1) yielded 25 g product (70 mmol, 38 %).

MS : m/e = 360.2 ($M+H^+$).

4[-2-(4-Benzyl-piperidine-1-yl)-ethanesulfonyl]-phenol hydrochloride (1:1)

To a solution of 1.15 g 4[-2-(4-benzyl-piperidine-1-yl)-ethanesulfonyl]-phenol (3.2 mmol) in EtOH (5 ml) was added ethanolic HCl (2.6 ml, 1.46 M, 3.8 mmol). The reaction mixture was cooled to 0 – 5°C and stirred for 10 min. Then diethyl ether was added until the product precipitated. After filtration 1.14 g of the product (2.9 mmol, 91 %) as a white solid was obtained.

MS : m/e = 360.2 ($M+H^+$).

Following the general procedure of example 1 the compounds of example 2 to example 8 were prepared

Example 2

4-[2-(4-p-Tolyloxy-piperidin-1-yl)-ethanesulfonyl]-phenol

The title compound was prepared from 4-(2-chloro-ethanesulfonyl)-phenol and 4-p-tolyloxy-piperidine (prepared according to J. Med. Chem., 1978, 21, 309) in 59 % yield as a white solid.

MS: m/e = 376.4 ($M+H^+$).

4-[2-(4-p-Tolyloxy-piperidin-1-yl)-ethanesulfonyl]-phenol hydrochloride (1:1)

The title compound was prepared from 4-[2-(4-p-tolyloxy-piperidin-1-yl)-ethanesulfonyl]-phenol in 96 % yield as a white solid.

MS : m/e = 376.4 ($M+H^+$).

Example 3

(-)-(3R,4R)- or (3S,4S)-4-Benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol

The title compound was prepared from 4-(2-chloro-ethanesulfonyl)-phenol and (3R,4R)- or (3S,4S)-4-benzyl-piperidine-3-ol in 66 % yield as a white solid.

MS : m/e = 376.4 ($M+H^+$), $[\alpha]_D^{20}$ = - 38.87 (c = 1.11, chloroform).

Example 4

(+)-(3S,4S)- or (3R,4R)-4-Benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol

The title compound was prepared from 4-(2-chloro-ethanesulfonyl)-phenol and (3S,4S)- or (3R,4R)-4-benzyl-piperidine-3-ol in 50 % yield as a white solid.

MS : m/e = 376.4 ($M+H^+$), $[\alpha]_D^{20}$ = + 39.81 (c = 1.66, chloroform).

Example 5

(3SR,4SR)-4-Benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol

The title compound was prepared from 4-(2-chloro-ethanesulfonyl)-phenol and (3SR,4SR)-4-benzyl-piperidine-3-ol in 20 % yield as a white foam.

MS : m/e = 376.4 ($M+H^+$).

Example 6

(-)-(3R,4R)- or (3S,4S)-1-[2-(4-Hydroxy-benzenesulfonyl)-ethyl]-4-(4-methyl-benzyl)-piperidin-3-ol

The title compound was prepared from 4-(2-chloro-ethanesulfonyl)-phenol and (3R,4R)- or (3S,4S)-4-(4-methyl-benzyl)-piperidin-3-ol in 51 % yield as a white foam.

MS : m/e = 390.2 ($M+H^+$), $[\alpha]_D^{20}$ = - 38.27 (c = 1.02, chloroform).

Example 7

(+)-(3S,4S)- or (3R,4R)-1-[2-(4-Hydroxy-benzenesulfonyl)-ethyl]-4-(4-methyl-benzyl)-piperidin-3-ol

The title compound was prepared from 4-(2-chloro-ethanesulfonyl)-phenol and (3S,4S)- or (3R,4R)-4-(4-methyl-benzyl)-piperidin-3-ol in 31 % yield as a white foam.

MS : m/e = 390.3 ($M+H^+$), $[\alpha]_D^{20}$ = + 39.01 (c = 1.05, chloroform).

Example 8

(3SR,4SR)-1-[2-(4-Hydroxy-benzenesulfonyl)-ethyl]-4-(4-methyl-benzyl)-piperidin-3-ol

The title compound was prepared from 4-(2-chloro-ethanesulfonyl)-phenol and (3SR,4SR)-4-(4-methyl-benzyl)-piperidin-3-ol in 30 % yield as a white solid.

MS : m/e = 390.3 ($M+H^+$).

Preparation of intermediates

Example 9

(3S,4S)- or (3R,4R)- 4-Benzyl-piperidine-3-ol

(3S,4S)- or (3R,4R)-1,4-Dibenzyl-piperidine-3-ol (320 mg, 1.1 mmol) was dissolved in 10 ml ethanol and hydrogenated in the presence of Pd on C (10%, 70 mg) under atmospheric pressure at 50°C for 2 h. The reaction mixture was filtrated and washed with ethanol to give 205 mg of the product (1.1 mmol, 94%) as a white solid.

MS : m/e = 191 ($M+H^+$), $[\alpha]_D^{20}$ = + 42.8 (c = 1.17, chloroform).

Following the general procedure of example 9 the compounds of example 10 to example 14 were prepared

Example 10

(3R,4R)- or (3S,4S)- 4-Benzyl-piperidine-3-ol

The title compound was prepared from (3R,4R)- or (3S,4S)-1,4-dibenzyl-piperidine-3-ol in 97 % yield as a colorless oil.

MS : m/e = 191 (M), $[\alpha]_D^{20}$ = - 41.1 (c = 1.14, chloroform).

Example 11

(3SR,4SR)-4-Benzyl-piperidine-3-ol

The title compound was prepared from (3SR,4SR)-1,4-dibenzyl-piperidine-3-ol in 88 % yield as a colorless oil.

MS : m/e = 191 (M).

Example 12

(3S,4S)- or (3R,4R)-4-(4-Methyl-benzyl)-piperidin-3-ol

The title compound was prepared from (3S,4S)- or (3R, 4R)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-ol in 95 % yield as a colorless oil.

MS : m/e = 206.2 ($M+H^+$), $[\alpha]_D^{20}$ = + 40.2 (c = 0.90, chloroform).

Example 13

(3R,4R)- or (3S,4S)-4-(4-Methyl-benzyl)-piperidin-3-ol

The title compound was prepared from (3R,4R)- or (3S, 4S)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-ol in 90 % yield as a colorless oil.

MS : m/e = 206.2 ($M+H^+$), $[\alpha]_D^{20}$ = - 38.1 (c = 0.93, chloroform).

Example 14

(3SR,4SR)-4-(4-Methyl-benzyl)-piperidin-3-ol

The title compound was prepared from (3SR,4SR)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-ol in quantitative yield as a colorless oil.

MS : m/e = 206.2 ($M+H^+$).

Example 15

(3S,4S)- or (3R,4R)-1,4-Dibenzyl-piperidine-3-ol

To a solution of 700 mg (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3S, 4S)-1,4-dibenzyl-piperidin-3-yl ester or (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3R, 4R)-1,4-dibenzyl-piperidin-3-yl ester (1.4 mmol) in 15 ml ethanol were added at r.t. 7 ml 4N NaOH (28 mmol). After 16 h the reaction mixture was poured to a 1:1 mixture of water and CH_2Cl_2 and the organic layer was separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were washed with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 350 mg of the product (12.4 mmol, 88%) as a yellow solid.

MS : m/e = 281 (M), $[\alpha]_D^{20}$ = + 45.1 (c = 1.11, chloroform).

Following the general procedure of example 15 the compounds of example 16 to example 18 were prepared

Example 16

(3R,4R)- or (3S,4S)-1,4-Dibenzyl-piperidine-3-ol

The title compound was prepared from (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3R, 4R)-1,4-dibenzyl-piperidin-3-yl ester or (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3S, 4S)-1,4-dibenzyl-piperidin-3-yl ester in 83 % yield as a yellow solid.

MS : m/e = 281 (M), $[\alpha]_D^{20}$ = - 44.8 (c = 1.13, chloroform).

Example 17

(3S, 4S)- or (3R,4R)-1-Benzyl-4-(4-methyl-benzyl)-piperidin-3-ol

The title compound was prepared from (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3S, 4S)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-yl ester or (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3R, 4R)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-yl ester in 98 % yield as a yellow oil.

MS : m/e = 296.4 ($M+H^+$), $[\alpha]_D^{20}$ = + 40.7 (c = 1.13, chloroform).

Example 18

(3R, 4R)- or (3S,4S)-1-Benzyl-4-(4-methyl-benzyl)-piperidin-3-ol

The title compound was prepared from (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3R, 4R)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-yl ester or (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3S, 4S)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-yl

ester in 92 % yield as a colorless oil.

MS : m/e = 296.4 ($M+H^+$), $[\alpha]_D^{20}$ = - 42.8 (c = 1.13, chloroform).

Example 19

(R)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (3S, 4S)-1,4-dibenzyl-piperidin-3-yl ester or (R)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic (3R, 4R)-1,4-dibenzyl-piperidin-3-yl ester

To a solution of 1.50 g (3SR,4SR)-1,4-dibenzyl-piperidine-3-ol (53 mmol) in 50 ml CH_2Cl_2 were added at 0°C 0.515 ml pyridine (506 mg, 64 mmol), 912 mg dimethylaminopyridine (74.6 mmol) and 1.19 ml (S)-(+)-alpha-methoxy-alpha-trifluoromethylphenylacetyl chloride (1.62 g, 64 mmol). The reaction mixture was stirred for 5 h at r.t., quenched by the addition of 50 ml water and stirred for 30 min. The organic phase was separated and washed twice with 50 ml saturated $NaHCO_3$-solution. The combined aqueous phases were extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by chromatography over silica gel (CH_2Cl_2/hexane/NH_3 50/50/1) to give 750 mg of the product (15.1 mmol, 28 %) as a yellow oil.

MS : m/e = 498.2 ($M+H^+$), $[\alpha]_D^{20}$ = + 106.0 (c = 1.02, chloroform).

Following the general procedure of example 19 the compounds of example 20 to example 22 were prepared

Example 20

(R)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (3R, 4R)-1,4-dibenzyl-piperidin-3-yl ester or (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3S, 4S)-1,4-dibenzyl-piperidin-3-yl ester

The title compound was prepared from (3SR,4SR)-1,4-dibenzyl-piperidin-3-ol and (S)-(+)-alpha-methoxy-alpha-trifluoromethylphenylacetyl chloride in 29 % yield as a yellow oil.

MS : m/e = 498.3 ($M+H^+$), $[\alpha]_D^{20}$ = - 65.8 (c = 0.89, chloroform).

Example 21

(R)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (3S, 4S)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-yl ester or (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3R, 4R)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-yl ester

The title compound was prepared from (3SR,4SR)-4-(4-methyl-benzyl)-piperidin-3-ol and (S)-(+)-alpha-methoxy-alpha-trifluoromethylphenylacetyl chloride in 33 % yield as a

yellow oil.

MS : m/e = 512.3 ($M+H^+$), $[\alpha]_D^{20}$ = + 102.0 (c = 0.98, chloroform).

Example 22

(R)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (3R, 4R)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-yl ester or (R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid (3S, 4S)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-yl ester

The title compound was prepared from (3SR,4SR)-4-(4-methyl-benzyl)-piperidine-3-ol and (S)-(+)-alpha-methoxy-alpha-trifluoromethylphenylacetyl chloride in 36 % yield as a yellow oil.

MS : m/e = 512.4 ($M+H^+$), $[\alpha]_D^{20}$ = - 63.1 (c = 1.06, chloroform).

Example 23

(3SR, 4SR)-1,4-Dibenzyl-piperidin-3-ol

To a solution of 9.0 g (SR)-1,4-dibenzyl-piperidin-3-one (32 mmol) in 200 ml dry THF were added at –78°C dropwise 48 ml K-selectride® (1 N in THF, 48 mmol). The reaction mixture was stirred for 1 h at -70°C and then warmed to r.t. The reaction was quenched by the addition of 100 ml $NaHCO_3$-solution and the aqueous phase was extracted twice with ethyl acetate (200 ml). The combined organic phases were washed with water (100 ml) and brine (100 ml). The organic phase was dried over $MgSO_4$, filtrated and the solvent was removed under reduced pressure to give the crude product. Purification by chromatography (ethyl acetate/hexane 1/2 to 2/1) yielded 6.5 g of the product (23 mmol, 72%) as a yellow oil.

MS : m/e = 281 (M).

Following the general procedure of example 23 the compound of example 24 was prepared.

Example 24

(3SR,4SR)-1-Benzyl-4-(4-methyl-benzyl)-piperidin-3-ol

The title compound was prepared from (SR)-1-benzyl-4-(4-methyl-benzyl)-piperidin-3-one in 82 % yield as an orange oil.

MS : m/e = 296.4 ($M+H^+$).

Example 25

(RS)-1,4-Dibenzyl-piperidin-3-one

To a solution of 13.5 g (SR)-1,4-dibenzyl-3-oxo-piperidine-4-carboxylic acid ethyl ester (38.4 mmol) in 20 ml ethanol were added 47.5 ml HCl (37%) and the yellow solution was refluxed for 48 h. The reaction mixture was cooled to 0°C and NaOH was added until pH 8 was reached. The aqueous phase was extracted three times with ethyl acetate (200 ml) and the combined organic phases were washed with water (2 × 100 ml) and brine (2 × 100 ml). The organic phase was dried over $MgSO_4$, filtrated and the solvent was removed under reduced pressure to give 9.8 g of the product (35 mmol, 91 %) as a brown oil.

MS : m/e = 279 (M).

Following the general procedure for example 25 the compound of example 26 was prepared.

Example 26

(SR)-1-Benzyl-4-(4-methyl-benzyl)-piperidin-3-one

The title compound was prepared from (SR)-1-benzyl-4-(4-methyl-benzyl)-3-oxo-piperidine-4-carboxylic acid ethyl ester in 77 % yield as a brown oil.

MS : m/e = 294 ($M+H^+$).

Example 27

(SR)-1,4-Dibenzyl-3-oxo-piperidine-4-carboxylic acid ethyl ester

To a suspension of 30.9 g NaH (55%, 772 mmol) in 1000 ml DMF was added under argon atmosphere portionwise 115 g ethyl (SR)-N-benzyl-3-oxo-4-piperidine-carboxylate hydrochloride (386 mmol, commercially available) at 0-5°C. The reaction mixture was stirred for 1h at r.t. and a solution of 45.9 ml benzylbromide (66.0 g, 386 mmol) in 200 ml DMF was added at 0°C. The reaction mixture was stirred for 1.5 h at r. t. and 200 ml sat. $NaHCO_3$ solution were added at 0-10°C. The reaction mixture was reduced to 500 ml and 1000 ml water were added. The aqueous phase was extracted three times with 1000 ml ethyl acetate and the combined organic phases were washed with water (3 × 200 ml) and brine (3 × 200 ml). The organic phase was dried over $MgSO_4$, filtrated and the solvent was removed under reduced pressure. The crude product was purified by chromatography over silica gel (ethyl acetate/hexane 1/8, then 1/4) to give 101 g of the product (290 mmol, 75 %) as a brown oil.

MS : m/e = 352.4 ($M+H^+$).

Following the general procedure for example 27 the compound of example 28 was prepared.

Example 28

(SR)-1-Benzyl-4-(4-methyl-benzyl)-3-oxo-piperidine-4-carboxylic acid ethyl ester

The title compound was prepared from (SR)-N-benzyl-3-oxo-4-piperidine-carboxylate hydrochloride and 4-methyl-benzylbromide in 73 % yield as a brown oil.

MS : m/e = 366.4 ($M+H^+$).

Example 29

4-(2-Chloro-ethanesulfonyl)-phenol

To a solution of 4.6 g 4-(2-chloro-ethylsulfanyl)-phenol (24.4 mmol) in 100 ml MeOH were added at r.t. 22.5 g oxone® (36.6 mmol). The reaction mixture was stirred for 16 h at r. t., filtrated and the solid was washed with MeOH. The filtrate was concentrated under reduced pressure, dissolved in ethyl acetate and washed twice with water. The combined aqueous phases were extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by chromatography over silica gel (ethyl acetate/hexane 1/3) to give 4.6 g of the product (20.9, 86%) as a white solid.

MS : m/e = 220 (M).

Example 30

4-(2-Chloro-ethylsulfanyl)-phenol

To a solution of 5.0 g 4-(2-hydroxy-ethylsulfanyl)-phenol (29 mmol) in 100 ml CH_2Cl_2 were added at 0°C 2.6 ml pyridine (32.3 mmol) and 2.34 ml $SOCl_2$ (32.3 mmol), dissolved in 10 ml CH_2Cl_2. The reaction mixture was stirred for 1 h at r.t. and then quenched by the addition of water. The organic phase was separated and washed twice with sat. $NaHCO_3$-solution. The combined aqueous phases were extracted with CH_2Cl_2 twice and the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 4.6 g product (24.3 mmol, 83%) as a yellow oil.

MS : m/e = 188 (M).

Example 31

4-(2-Hydroxy-ethylsulfanyl)-phenol

To a solution of 10.9 g 4-hydroxythiophenol (87 mmol) in 200 ml MeOH was added at 0-5 °C 87 ml 1N NaOH (87 mmol). After the reaction mixture was stirred for 10 min 6.1 ml bromoethanol (86 mmol) dissolved in 100 ml MeOH was added. The reaction mixture was stirred for 3 h at r.t. and the methanol was partly removed under reduced pressure. The residue was poured to a 1:1 mixture of ethyl acetate and saturated $NaHCO_3$-solution and

the organic phase was separated, dried over $MgSO_4$, filtrated and the solvent was removed under reduced pressure. The residue was purified by chromatography over silica gel (ethyl acetate/hexane 3/2 to 2/1) to give 13.4 g product (78.7 mmol, 91 %) as a white solid.
MS : m/e = 170 (M).

EXAMPLE A

Tablet Formulation (Wet Granulation)

Ingredients				mg / tablet	
1. Active compound		5	25	100	500
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

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.

Capsule Formulation

Ingredients				mg / capsule	
1. Active compound		5	25	100	500
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

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.

Tablet Formulation (Wet Granulation)

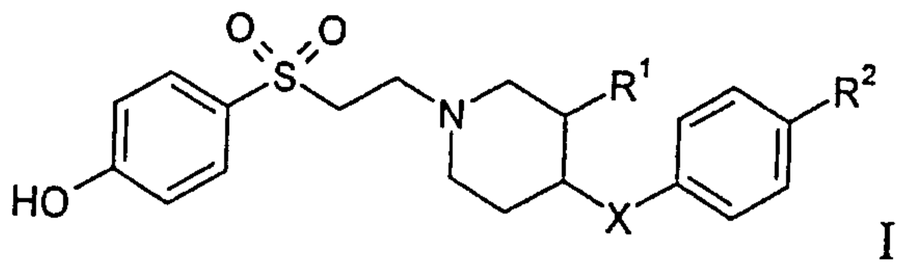
Ingredients	mg / tablet			
1. Active compound	5	25	100	500
2. Lactose Anhydrous	125	105	30	150
3. Sta-Rx 1500	6	6	6	30
4. Microcrystalline Cellulose	30	30	30	150
5. Magnesium Stearate	1	2	2	5
TOTAL	167	167	167	835

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.

CLAIMS:

1. Compounds of the general formula



I

wherein

R^1 signify hydrogen or hydroxy;

R^2 signify hydrogen or methyl; and

X signify –O- or $–CH_2$-;

and their pharmaceutically acceptable acid addition salts.

2. A compound of formula I in accordance with claim 1, which is
4[-2-(4-benzyl-piperidine-1-yl)-ethanesulfonyl]-phenol.

3. A compound of formula I in accordance with claim 1, which is
4-[2-(4-p-tolyloxy-piperidin-1-yl)-ethanesulfonyl]-phenol.

4. A compound of formula I in accordance with claim 1, which is
(-)-(3R,4R)- or (3S,4S)-4-benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol.

5. A compound of formula I in accordance with claim 1, which is
(+)- (3S,4S)- or (3R,4R)-4-benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol.

6. A compound of formula I in accordance with claim 1, which is
(3RS,4RS)- 4-benzyl-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-piperidin-3-ol.

7. A compound of formula I in accordance with claim 1, which is
(-)-(3R,4R)- or (3S,4S)-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-4-(4-methyl- benzyl)-piperidin-3-ol.

8. A compound of formula I in accordance with claim 1, which is
(+)-(3R,4R)- or (3S,4S)-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-4-(4-ethyl-benzyl)-piperidin-3-ol.

9. A compound of formula I in accordance with claim 1, which is (3RS,4RS)-1-[2-(4-hydroxy-benzenesulfonyl)-ethyl]-4-(4-methyl-benzyl)-piperidin-ol.

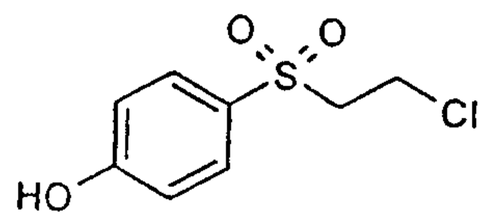
10. A medicament containing one or more compounds according to claims 1-9 and pharmaceutically inert excipients for the treatment of diseases associated with NMDA-receptor subtype selective antagonism.

11. A medicament in accordance with claim 10 for the treatment of acute forms of neurodegeneration caused by stroke or brain trauma; chronic forms of neurodegeneration; neurodegeneration associated with bacterial or viral infections, schizophrenia, anxiety, depression, chronic pain or acute pain.

12. The medicament according to claim 11, wherein the chronic forms of neurodegeneration are Alzheimer's disease, Parkinson's disease, Huntington's disease or ALS (amyotrophic lateral sclerosis).

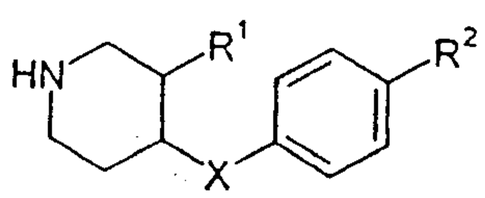
13. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



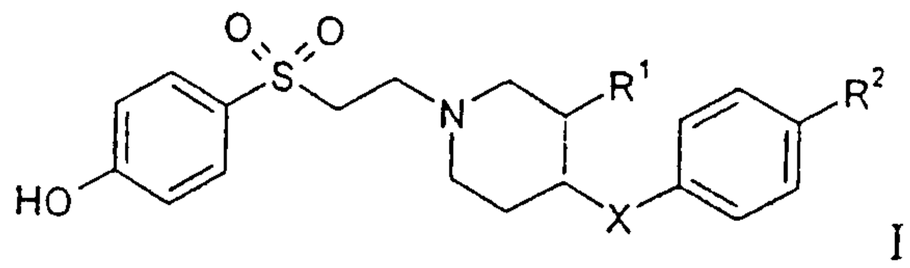
II

with a compound of formula



III

to produce a compound of formula



I

wherein R^1, R^2 and X are as defined in claim 1,

and,

b) converting the compound of formula I obtained into a pharmaceutically acceptable acid addition salts, and,

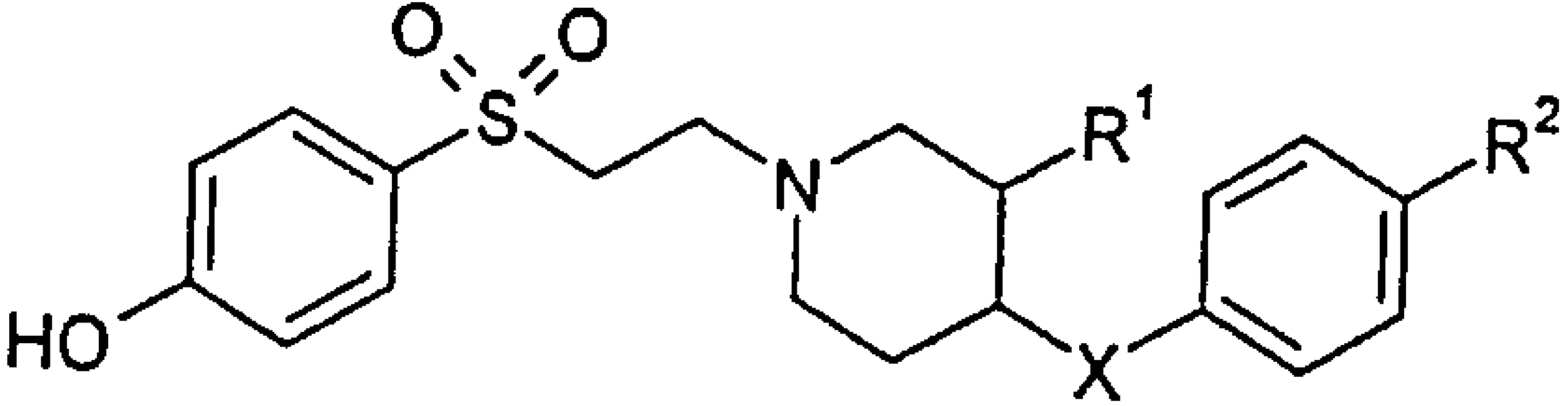
c) converting a racemic mixture into its enantiomeric component thus obtaining optically pure compounds.

14. The use of compounds of formula I according to claims 1 - 9 in the treatment of diseases associated with NMDA-receptor subtype selective antagonism.

15. The use of compounds of formula I according to claims 1 - 9 for the manufacture of medicaments containing one or more compounds of formula I in the treatment of diseases, wherein the therapeutic indications are acute forms of neurodegeneration; chronic forms of neurodegeneration; neurodegeneration associated with bacterial or viral infections, schizophrenia, anxiety, depression, chronic pain or acute pain.

16. The use according to claim 15, wherein the chronic forms of neurodegeneration are Alzheimer's disease, Parkinson's disease, Huntington's disease or ALS (amyotrophic lateral sclerosis).

17. The use according to claim 15,wherein the acute forms of neurodegeneration are caused by stroke or brain trauma.



(I)