

Case 20359

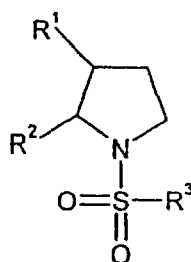


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1-Arenesulfonyl-2-aryl-pyrrolidine and piperidine derivatives

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The present invention is concerned with 1-arenesulfonyl-2-aryl-pyrrolidine and piperidine derivatives of the general formula



I

wherein

- R^1 signifies hydrogen or lower alkyl;
- R^2 signifies furyl, thienyl, pyridyl or phenyl, which is optionally substituted by 1 to 3 substituents, selected from lower alkyl, lower alkoxy, halogen, cyano, CF_3 or $-N(R^4)_2$;
- R^3 signifies naphthyl or phenyl, which is optionally substituted by 1 to 3 substituents, selected from lower alkyl, lower alkoxy, halogen, acetyl, cyano, hydroxy-lower alkyl, $-CH_2$ -morpholin-4-yl, lower alkyl-oxy-lower alkyl, lower alkyl- $N(R^4)_2$ or CF_3 ;
- R^4 signifies, independently from each other, hydrogen or lower alkyl, as well as their pharmaceutically acceptable salts.

Compounds of formula I are novel with the exception of (RS)-2-phenyl-1-(toluene-4-sulfonyl)-pyrrolidine, (RS)-1-(toluene-4-sulfonyl)-2-p-tolyl-pyrrolidine, N-tosyl-cis-3-methyl-2-phenyl pyrrolidine, 3-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]pyridine and N-tosyl-2-(3,4-dimethoxy-phenyl)-pyrrolidine. The manufacture of these compounds is described in J. Org. Chem., 51, (1986) 4089-4090. Furthermore, the preparation of (RS)-2-phenyl-1-(toluene-4-sulfonyl)-pyrrolidine is described in Liebigs Ann. Chem., 762, (1972) 93-105.

It has surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor antagonists and/or agonists. Compounds of formula I are distinguished by valuable therapeutic properties.

5 In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

L-glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays a critical role in a large number of physiological processes. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the
10 second main group and, furthermore, belong to the family of G-protein-coupled receptors.

At present, eight different members of these mGluR are known and of these some even have sub-types. On the basis of structural parameters, the different influences on the synthesis of secondary metabolites and the different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups:

15 mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as
20 well as chronic and acute pain.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Huntington's chorea, amyotrophic lateral sclerosis (ALS),
25 dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depressions.

30 Objects of the present invention are compounds of formula I and their pharmaceutically acceptable salts per se and as pharmaceutically active substances, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of the compounds in accordance with the invention in

the control or prevention of illnesses of the aforementioned kind, and, respectively, for the production of corresponding medicaments.

Preferred compounds of formula I in the scope of the present invention are those, in which R¹ signifies hydrogen or methyl; R² signifies phenyl, optionally substituted by halogen, lower alkyl, CF₃ or -N(CH₃)₂, with the exception of (RS)-2-phenyl-1-(toluene-4-sulfonyl)-pyrrolidine, (RS)-1-(toluene-4-sulfonyl)-2-p-tolyl-pyrrolidine, N-tosyl-cis-3-methyl-2-phenyl pyrrolidine, 3-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]pyridine and N-tosyl-2-(3,4-dimethoxy-phenyl)-pyrrolidine and their salts. The following are examples of such compounds:

(RS)-2-(3-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
(RS)-1-(4-chloro-benzenesulfonyl)-2-(3-fluoro-phenyl)-pyrrolidine,
(RS)-1-(4-chloro-benzenesulfonyl)-2-phenyl-pyrrolidine,
(RS)-2-(4-chloro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
(RS)-1-(4-chloro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
(RS)-2-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
(RS)-1-benzenesulfonyl-2-(4-chloro-phenyl)-pyrrolidine,
(RS)-1-(4-fluoro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
(RS)-2-(4-fluoro-phenyl)-1-(toluene-2-sulfonyl)-pyrrolidine,
(RS)-1-(4-chloro-benzenesulfonyl)-2-p-tolyl-pyrrolidine,
(RS)-1-(4-ethyl-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
(RS)-1-(toluene-4-sulfonyl)-2-m-tolyl-pyrrolidine,
(RS)-2-(3-chloro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
(RS)-2-(3,4-difluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
(RS)-2-(3-chloro-4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
(RS)-1-(4-fluoro-benzenesulfonyl)-2-(4-dimethylamino-3-chloro-phenyl)-pyrrolidine,
(RS)-1-(toluene-4-sulfonyl)-2-(4-trifluoromethyl-phenyl)-pyrrolidine,
(RS)-2-(4-chloro-3-methyl-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
(RS)-2-(4-fluoro-phenyl)-1-(4-trifluoromethyl-benzenesulfonyl)-pyrrolidine,
(RS)-2-(N,N-dimethylamino-phenyl)-1-(4-fluoro-benzenesulfonyl)-pyrrolidine,
(R)-1-(4-chloro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
(S)-1-(4-chloro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
(RS)-2-(4-ethyl-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
(RS)-2-(4-ethyl-phenyl)-1-(4-fluoro-benzenesulfonyl)-pyrrolidine,
(S)-2-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,

(R)-2-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (RS)-2-(4-fluoro-phenyl)-1-(4-methoxymethyl-benzenesulfonyl)-pyrrolidine and
 (2RS,3RS)-2-(4-fluoro-phenyl)-3-methyl-1-(toluene-4-sulfonyl)-pyrrolidine

Compounds of formula I, in which

- 5 R¹ signifies hydrogen; and
 R² signifies furyl, thienyl or pyridyl;
 are also preferred.

The following are examples of such compounds:

- (RS)-1-(4-chloro-benzenesulfonyl)-2-thien-2-yl-pyrrolidine,
 10 (RS)-2-thien-2-yl-1-(toluene-4-sulfonyl)-pyrrolidine and
 (RS)-2-thien-3-yl-1-(toluene-4-sulfonyl)-pyrrolidine.

The invention embraces all stereoisomeric forms in addition to the racemates.

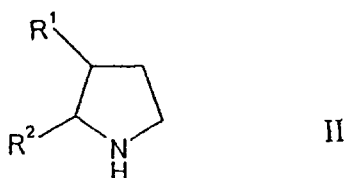
- The term "lower alkyl" used in the present description denotes straight-chain or
 branched saturated hydrocarbon residues with 1-7 carbon atoms, preferably with 1-4
 15 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and the like.

The term "lower alkoxy" denotes a lower alkyl residue in the sense of the foregoing
 definition bonded via an oxygen atom.

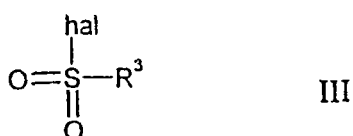
The term "halogen" embraces fluorine, chlorine, bromine and iodine.

- The compounds of general formula I and their pharmaceutically acceptable salts can
 20 be manufactured by

reacting a compound of the formula



with a compound of formula



and, if desired,

converting a functional group in a compound of formula I into another functional group

and, if desired,

converting a compound of formula I into a pharmaceutically acceptable salt.

- 5 In accordance with the invention, an appropriately substituted compound of formula II, for example (RS)-2-(3-fluoro-phenyl)-pyrrolidine, is reacted with a suitable compound of formula III, for example toluene-4-sulfonyl chloride. The reaction according to known methods takes place at room temperature within 16 hours in an inert solvent, for example in dichloromethane. After evaporating the solvent, the mixture is dissolved in water and
10 extracted with a suitable solvent, for example ethyl acetate and purified using known methods.

In particular, cyano groups can be hydrogenated to amino groups or halogen atoms in halogenated lower alkyl groups can be substituted with amines or converted to ethers.

- 15 The hydrogenation is preferably effected with Raney-nickel at room temperature under normal pressure and the amino group can be alkylated by known methods.

- The ether formation of benzylchloride derivatives can be conveniently carried out as follows: A compound of general formula I which contains a halogenated lower alkyl group, for example (RS)-2-(4-fluoro-phenyl)-1-(4-chloromethyl-benzenesulfonyl)-
20 pyrrolidine is reacted with sodium methanolate in MeOH for 80 hours at 50°C and purified using known methods.

- The substitution of a halogen atom in a halogenated lower alkyl group with an amine can be conveniently carried out as follows: A compound of general formula I which contains a halogenated lower alkyl group, for example (RS)-2-(4-fluoro-phenyl)-1-(4-
25 chloromethyl-benzenesulfonyl)-pyrrolidine is reacted with morpholine in DMF for 17 hours at 80°C and purified using known methods.

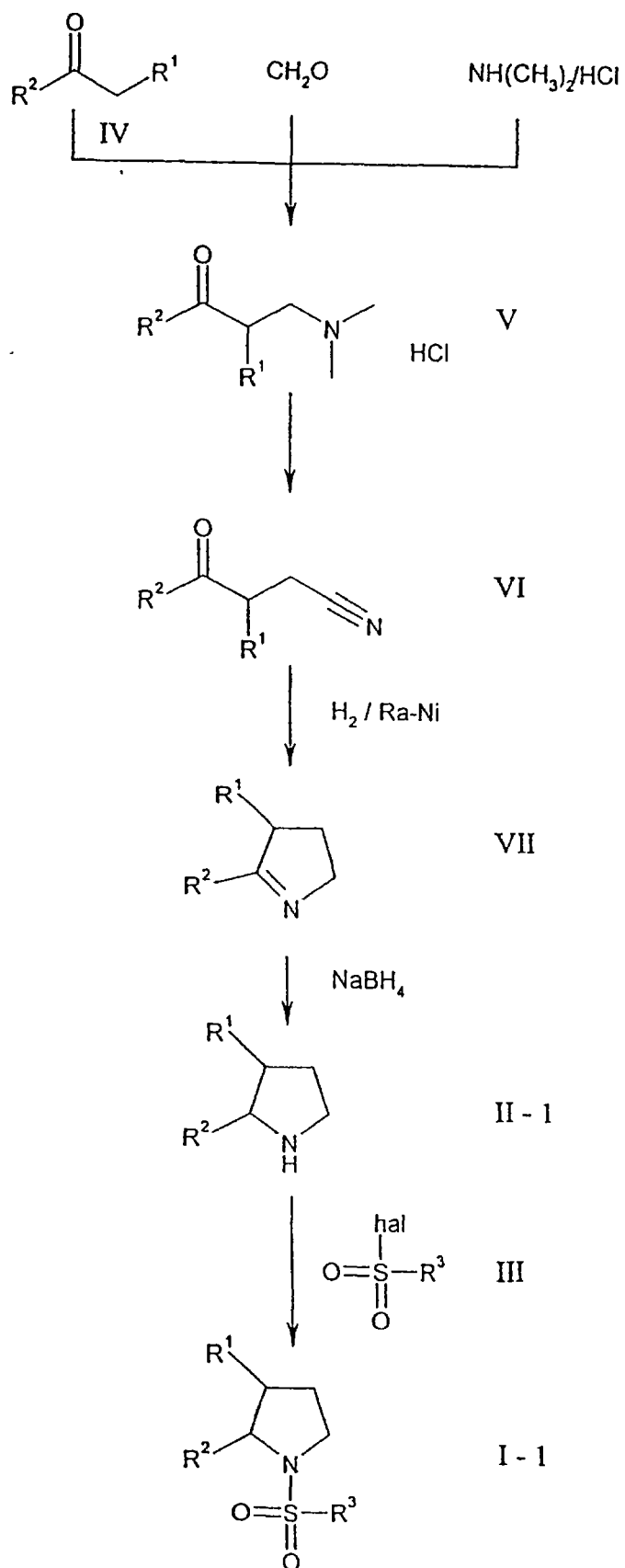
- The pharmaceutically acceptable salts can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid,
30 hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali

metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation or pharmaceutically acceptable salts of acidic compounds.

Scheme 1 gives an overview of the manufacture of the compounds of formula I
5 starting from known compounds. Substituents R^1 present in the compounds of formula I are introduced according to methods known to the person skilled in the art. The manufacture of representative compounds of formula I is described in detail in examples 1-91.

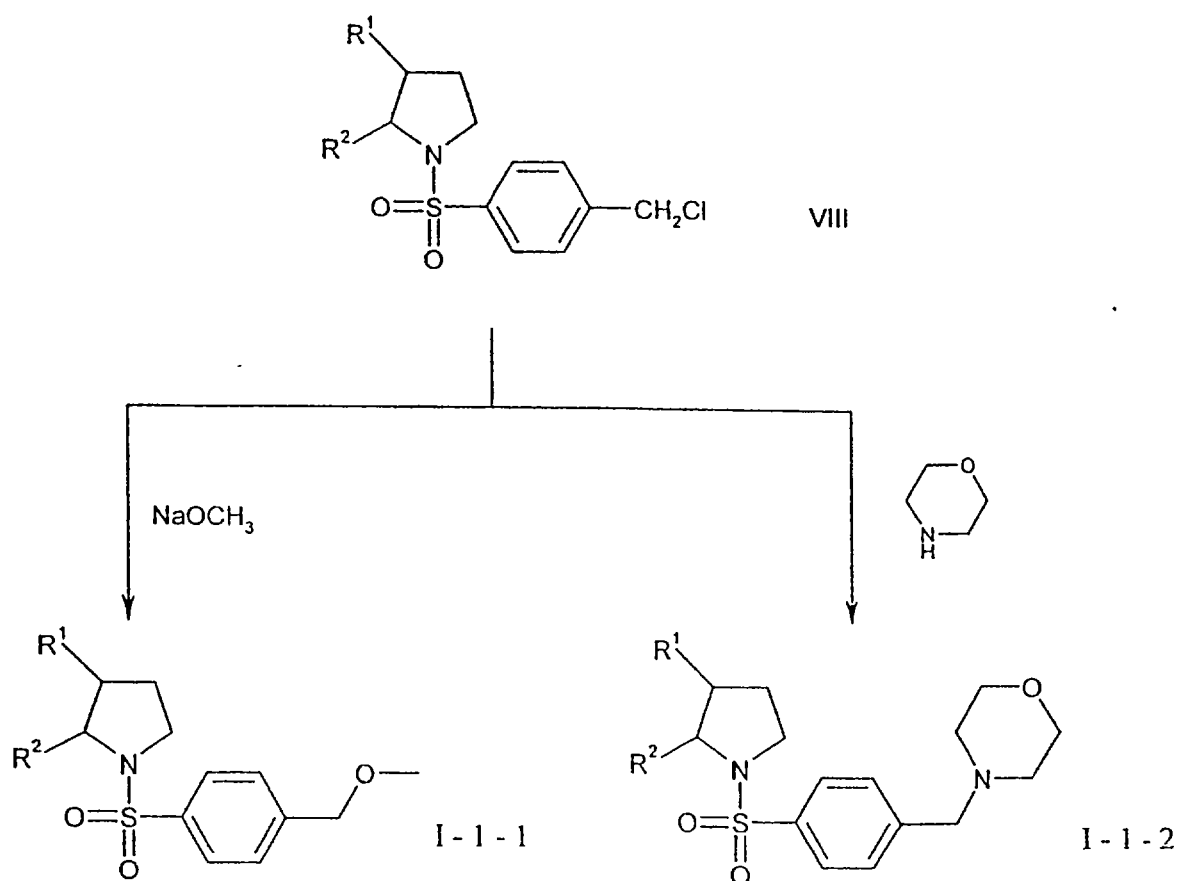
Scheme 2 and scheme 3 give an overview of the conversions of functional groups in
10 compounds of formula I described in detail in examples 85-87.

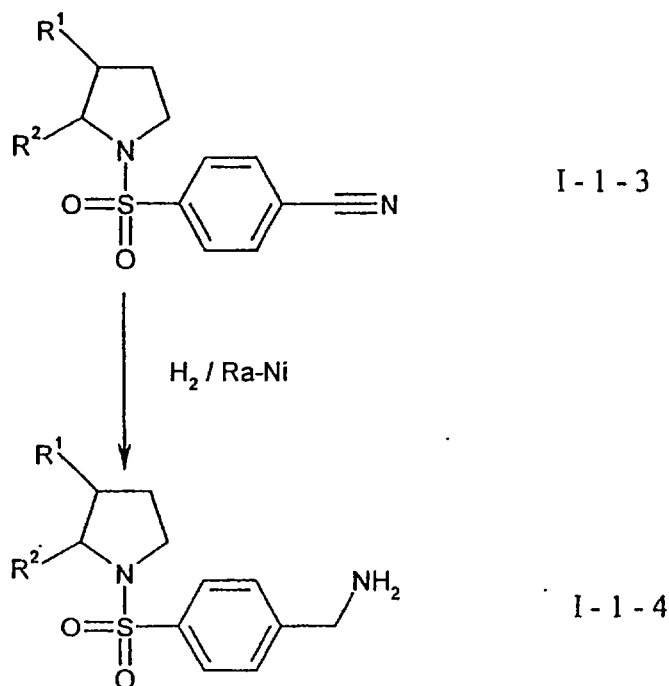
Scheme 1



R^1 is hydrogen or lower alkyl and the other substituents have the significances given earlier.

Scheme 2



Scheme 3

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, metabotropic glutamate receptor agonists and/or antagonists and can be used for the treatment or prevention of acute and/or chronic neurological disorders, such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as acute and chronic pain. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Alzheimer's disease, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression. The compounds of the present invention are group I mGlu receptor agonists and/or antagonists. It has been shown that the compounds of examples 1 - 4, 6, 8, 9, 11 - 14, 16, 19, 21, 25, 26, 28, 29, 31, 38, 39, 40, 42, 48, 55, 56, 58, 60, 69, 72, 76, 77, 78, 81, 82, 83, 84, 85, 88, 89 and 90 show agonistic activity, the other specific examples have an antagonistic activity to the mGlu receptor. The compounds show activities, as measured in

the assay described below, of 50 μM or less, typically 3 μM or less, and ideally of 0.5 μM or less.

In the table below are shown some specific activity-data:

Example No.	agonist/antagonist	IC ₅₀ (μM)
3	agonist	8.22
4	agonist	0.23
88	agonist	0.62
7	antagonist	8.00
18	antagonist	1.37
36	antagonist	0.56

5 cDNA encoding rat mGlu 1a receptor obtained from Prof. S. Nakanishi (Kyoto, Japan) was transiently transfected into EBNA cells using a procedure described by Schlaeger et. al, New Dev. New Appl. Anim. Cell Techn., Proc. ESACT Meet., 15th (1998), 105-112 and 117-120. $[\text{Ca}^{2+}]_i$ measurements were performed on mGlu 1a transfected EBNA cells after incubation of the cells with Fluo-3 AM (0.5 μM final concentration) for 1
10 hour at 37°C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES. $[\text{Ca}^{2+}]_i$ measurements were done using a fluorometric imaging plate reader (FLIPR, Molecular Devices Corporation, La Jolla, CA, USA). When compounds were evaluated as antagonists they were tested against 10 μM glutamate as agonist.

15 The inhibition (antagonists) or activation (agonists) curves were fitted with a four parameter logistic equation giving EC₅₀, IC₅₀, and Hill coefficient using the iterative non linear curve fitting software Origin (Microcal Software Inc., Northampton, MA, USA).

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical
20 preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the admini-

stration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid
5 or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case
10 of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats,
15 semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

20 As mentioned earlier, medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable
25 substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being
30 preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

Finally, as mentioned earlier, the use of compounds of formula I and of pharmaceutically acceptable salts thereof for the production of medicaments, especially for the control or prevention of acute and/or chronic neurological disorders of the aforementioned kind, is also an object of the invention.

5

Example 1

(RS)-2-(3-Fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

a) 3-Dimethylamino-1-(3-fluoro-phenyl)-propan-1-one hydrochloride (1:1)

- 10 A stirred mixture of 3-fluoro-acetophenone (10.5 g, 75.7 mmol), paraformaldehyde (3.79 g, 126 mmol), dimethylamine hydrochloride (6.17 g, 75.7 mmol), conc. HCl (0.2 ml) and ethanol (17 ml) was refluxed for 1.5 h. The clear solution was cooled to 0°C and diethyl ether (100 ml) was added. The formed white solid was collected, washed with diethyl ether and recrystallized from EtOH/diethyl ether to yield the product (10.2 g, 58 %) as a white
15 solid, m.p. 152°C and MS: m/e = 195 (M⁺).

b) 4-(3-Fluoro-phenyl)-4-oxo-butyronitrile

- A stirred mixture of 3-dimethylamino-1-(3-fluoro-phenyl)-propan-1-one hydrochloride (5.20 g, 22.4 mmol) and potassium cyanide (2.19 g, 33.6 mmol) was refluxed for 17 h, evaporated, dissolved in water (150 ml) and extracted with ethyl acetate (2 x 120 ml). The
20 combined organic layers were washed with water (120 ml), brine (120 ml), 3N sulfuric acid (100 ml) and brine (100 ml), dried (MgSO₄) and evaporated to give an orange oil (2.15 g) which was further purified by column chromatography on silica gel (ethyl acetate/hexane 1:3) to yield the product (1.68 g, 42%) as a pale yellow solid, m.p. 46°C and MS: m/e = 177 (M⁺).

25 c) 5-(3-Fluoro-phenyl)-3,4-dihydro-2H-pyrrole

- 4-(3-Fluoro-phenyl)-4-oxo-butyronitrile (1.60 g, 9.03 mmol) dissolved in MeOH (45 ml) and 3.5 N MeOH-NH₃ (45 ml) was hydrogenated on Ra-Ni at RT for 16 h. The catalyst was filtered off, the filtrate evaporated and the crude product purified by column chromatography on silica gel (ethyl acetate/toluene 1:2) to give the product (1.16 g, 79%)
30 as a colorless oil, MS: m/e = 163 (M⁺).

d) (RS)-2-(3-Fluoro-phenyl)-pyrrolidine

To a stirred solution of 5-(3-fluoro-phenyl)-3,4-dihydro-2H-pyrrole (1.10 g, 6.74 mmol) in methanol (40 ml) was added at 0°C sodium borohydride (0.51 g, 13.4 mmol) and the reaction mixture was stirred at RT for 1 h. Then additional sodium borohydride (0.25 g, 6.61 mmol) was added and stirring was continued for 1h. The mixture was evaporated,
5 dissolved in saturated NaHCO₃- solution (70 ml) and extracted with dichloromethane (2 x 70 ml). The combined organic layers were washed with brine (70 ml), dried (MgSO₄) and evaporated. The crude product was purified by column chromatography on silica gel (dichloromethane/MeOH/NH₄OH 15:1:0.1) to give the product (0.77 g, 69%) as a colorless oil, MS: m/e = 165 (M⁺).

10 e) (RS)-2-(3-Fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

To a stirred solution of (RS)-2-(3-fluoro-phenyl)-pyrrolidine (0.24 g, 1.45 mmol) and triethylamine (0.40 ml, 2.87 mmol) in dichloromethane (40 ml) was added at 0°C toluene-4-sulfonyl chloride (0.42 g, 2.20 mmol). The mixture was stirred at RT for 16 h, evaporated, dissolved in water (40 ml) and extracted with ethyl acetate (2 x 40 ml). The
15 combined organic layers were washed with water (40 ml), brine (40 ml), dried (MgSO₄) and evaporated. The crude product was purified by crystallization from ethyl acetate/hexane to give the product (0.38 g, 83%) as a white solid, m.p. 116°C and MS: m/e = 319 (M⁺).

Example 2

20

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(3-fluoro-phenyl)-pyrrolidine

The title compound, white solid, m.p. 126°C and MS: m/e = 339 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(3-fluoro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

25

Example 3

(RS)-4-[1-(Toluene-4-sulfonyl)-pyrrolidin-2-yl]-pyridine

The title compound, pale brown solid, m.p. 158°C and MS: m/e = 302 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-4-(2-pyrrolidinyl)-
30 pyridine and toluene-4-sulfonyl chloride.

Example 4

(RS)-2-Phenyl-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 109°C and MS: m/e = 301 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-phenyl-pyrrolidine and toluene-4-sulfonyl chloride.

Example 5

(RS)-1-Benzenesulfonyl-2-phenyl-pyrrolidine

The title compound, light pink solid, m.p. 116°C and MS: m/e = 287 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-phenyl-pyrrolidine and benzenesulfonyl chloride.

Example 6

(RS)-1-(4-Chloro-benzenesulfonyl)-2-phenyl-pyrrolidine

The title compound, pale pink solid, m.p. 119°C and MS: m/e = 321 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-phenyl-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 7

(RS)-1-Benzenesulfonyl-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, white solid, m.p. 100°C and MS: m/e = 305 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and benzenesulfonyl chloride.

Example 8

(RS)-2-(4-Chloro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 121°C and MS: m/e = 335 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-chloro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

Example 9

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(4-chloro-phenyl)-pyrrolidine

5 The title compound, white solid, m.p. 159°C and MS: m/e = 355 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-chloro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 10

(RS)-2-(4-Fluoro-phenyl)-1-(4-methoxy-benzenesulfonyl)-pyrrolidine

10 The title compound, white solid, m.p. 134°C and MS: m/e = 335 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-methoxy-benzenesulfonyl chloride.

Example 11

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(4-fluorophenyl)-pyrrolidine

The title compound, white solid, m.p. 118°C and MS: m/e = 339 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 12

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(RS)-2-(4-Fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, off-white solid, m.p. 128°C and MS: m/e = 319 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

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Example 13

(RS)-1-Benzenesulfonyl-2-(4-chloro-phenyl)-pyrrolidine

The title compound, white solid, m.p. 122°C and MS: m/e = 321 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-chloro-phenyl)-
30 pyrrolidine and benzenesulfonyl chloride.

Example 14

(RS)-4-[1-(4-Chloro-benzenesulfonyl)-pyrrolidin-2-yl]-pyridine

The title compound, white solid, m.p. 177°C and MS: m/e = 322 (M^+) was prepared in
5 accordance with the general method of example 1e from (RS)-4-(pyrrolidin-2-yl)-pyridine
and 4-chloro-benzenesulfonyl chloride.

Example 15

(RS)-1-Benzenesulfonyl-2-(3-fluoro-phenyl)-pyrrolidine

10 The title compound, white solid, m.p. 96°C and MS: m/e = 305 (M^+) was prepared in
accordance with the general method of example 1e from (RS)-2-(3-fluoro-phenyl)-
pyrrolidine and benzenesulfonyl chloride.

Example 16

15 (RS)-1-(4-Fluoro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, light brown solid, m.p. 121°C and MS: m/e = 324.2 ($M+H^+$) was
prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-
phenyl)-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 17

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(RS)-2-(4-Fluoro-phenyl)-1-(toluene-3-sulfonyl)-pyrrolidine

The title compound, light brown solid, m.p. 102°C and MS: m/e = 319 (M^+) was prepared
in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-
pyrrolidine and toluene-3-sulfonyl chloride.

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Example 18

(RS)-2-(4-Fluoro-phenyl)-1-(toluene-2-sulfonyl)-pyrrolidine

The title compound, colorless oil, MS: m/e = 319 (M^+) was prepared in accordance with
the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and toluene-
30 2-sulfonyl chloride.

Example 19

(RS)-1-(Toluene-4-sulfonyl)-2-p-tolyl-pyrrolidine

The title compound, white solid, m.p. 124°C and MS: m/e = 315 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-p-tolyl-pyrrolidine and toluene-4-sulfonyl chloride.

Example 20

(RS)-1-(4-Chloro-benzenesulfonyl)-2-p-tolyl-pyrrolidine

The title compound, white solid, m.p. 129°C and MS: m/e = 335 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-p-tolyl-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 21

(RS)-1-(4-Ethyl-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, white solid, m.p. 78°C and MS: m/e = 333 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-ethyl-benzenesulfonyl chloride.

Example 22

(RS)-2-(4-Fluoro-phenyl)-1-(4-isopropyl-benzenesulfonyl)-pyrrolidine

The title compound, white solid, m.p. 77°C and MS: m/e = 347 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-isopropyl-benzenesulfonyl chloride.

Example 23

(RS)-1-(4-Fluoro-benzenesulfonyl)-2-p-tolyl-pyrrolidine

The title compound, white solid, m.p. 112°C and MS: m/e = 319 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-p-tolyl-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 24

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(4-methoxy-phenyl)-pyrrolidine

The title compound, white solid, m.p. 133°C and MS: m/e = 352 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-methoxy-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 25

(RS)-2-(4-Methoxy-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 122°C and MS: m/e = 332 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-methoxy-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

Example 26

(RS)-1-(4-Bromo-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, off-white solid, m.p. 131°C and MS: m/e = 383 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-bromo-benzenesulfonyl chloride.

Example 27

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(RS)-1-{4-[2-(4-Fluoro-phenyl)-pyrrolidine-1-sulfonyl]-phenyl}-ethanone

The title compound, pale brown solid, m.p. 148°C and MS: m/e = 348 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-acetyl-benzenesulfonyl chloride.

25

Example 28

(RS)-1-(Toluene-4-sulfonyl)-2-m-tolyl-pyrrolidine

The title compound, off-white solid, m.p. 79°C and MS: m/e = 315 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-m-tolyl-pyrrolidine and toluene-4-sulfonyl chloride.

30

Example 29

(RS)-1-(4-Chloro-benzenesulfonyl)-2-m-tolyl-pyrrolidine

5 The title compound, off-white solid, m.p. 78°C and MS: m/e = 335 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-m-tolyl-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 30

(RS)-1-(4-Fluoro-benzenesulfonyl)-2-m-tolyl-pyrrolidine

10 The title compound, off-white solid, m.p. 80°C and MS: m/e = 319 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-m-tolyl-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 31

15 (RS)-2-(3-Chloro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, off-white solid, m.p. 107°C and MS: m/e = 335 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(3-chloro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

Example 32

20

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(3-chloro-phenyl)-pyrrolidine

The title compound, light brown solid, m.p. 99°C and MS: m/e = 355 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(3-chloro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

25

Example 33

(RS)-2-(4-Fluoro-phenyl)-1-(4-cyano-benzenesulfonyl)-pyrrolidine

30 The title compound, off-white solid, m.p. 147°C and MS: m/e = 330 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-cyano-benzenesulfonyl chloride.

Example 34

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(3-methoxy-phenyl)-pyrrolidine

The title compound, white solid, m.p. 95°C and MS: m/e = 351 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(3-methoxy-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 35

(RS)-1-(4-Fluoro-benzenesulfonyl)-2-thien-2-yl-pyrrolidine

The title compound, white solid, m.p. 97°C and MS: m/e = 312.1 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-thien-2-yl-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 36

(RS)-1-(4-Chloro-benzenesulfonyl)-2-thien-2-yl-pyrrolidine

The title compound, white solid, m.p. 84°C and MS: m/e = 328.1 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-thien-2-yl-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 37

20

(RS)-2-Thien-2-yl-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 108°C and MS: m/e = 308.2 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-thien-2-yl-pyrrolidine and toluene-4-sulfonyl chloride.

25

Example 38

(RS)-2-(3,4-Difluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 127°C and MS: m/e = 338.2 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(3,4-difluoro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

Example 39

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(3,4-difluoro-phenyl)-pyrrolidine

The title compound, white solid, m.p. 121°C and MS: m/e = 358.1 (M+H⁺) was prepared
5 in accordance with the general method of example 1e from (RS)-2-(3,4-difluoro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 40

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(4-dimethylamino-3-fluoro-phenyl)-pyrrolidine

10 The title compound, white solid, m.p. 99°C and MS: m/e = 383.2 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-dimethylamino-3-fluoro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 41

15 (RS)-1-(p-Toluenesulfonyl)-2-(4-dimethylamino-3-fluoro-phenyl)-pyrrolidine

The title compound, white solid, m.p. 66°C and MS: m/e = 363.1 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-dimethylamino-3-fluoro-phenyl)-pyrrolidine toluene-4-sulfonyl chloride.

Example 42

20

(RS)-2-(3-Chloro-4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, off-white solid, m.p. 96°C and MS: m/e = 354.2 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(3-chloro-4-fluoro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

25

Example 43

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(3-chloro-4-fluoro-phenyl)-pyrrolidine

The title compound, off-white solid, m.p. 119°C and MS: m/e = 374.2 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(3-chloro-4-
30 fluoro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 44

(RS)-2-(3-Chloro-4-fluoro-phenyl)-1-(4-fluoro-benzenesulfonyl)-pyrrolidine

The title compound, white solid, m.p. 116°C and MS: m/e = 358.1 (M^+) was prepared in
5 accordance with the general method of example 1e from (RS)-2-(3-chloro-4-fluoro-phenyl)-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 45

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(4-dimethylamino-3-chloro-phenyl)-pyrrolidine

10 The title compound, white solid, m.p. 103°C and MS: m/e = 398 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-dimethylamino-3-chloro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 46

15 (RS)-1-(4-fluoro-benzenesulfonyl)-2-(4-dimethylamino-3-chloro-phenyl)-pyrrolidine

The title compound, off-white solid, m.p. 119°C and MS: m/e = 382 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-dimethylamino-3-chloro-phenyl)-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 47

20

(RS)-2-(3,4-Dichloro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, off-white solid, m.p. 136°C and MS: m/e = 369 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(3,4-dichloro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

25

Example 48

(RS)-1-(Toluene-4-sulfonyl)-2-(4-trifluoromethyl-phenyl)-pyrrolidine

The title compound, white solid, m.p. 99°C and MS: m/e = 369 (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-trifluoromethyl-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.
30

Example 49

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(4-trifluoromethyl-phenyl)-pyrrolidine

The title compound, white solid, m.p. 107°C and MS: $m/e = 3$ (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-trifluoromethyl-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 50

(RS)-1-(4-Fluoro-benzenesulfonyl)-2-(4-trifluoromethyl-phenyl)-pyrrolidine

The title compound, white solid, m.p. 114°C and MS: $m/e = 373$ (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-trifluoromethyl-phenyl)-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 51

(RS)-2-(2-Chloro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 149°C and MS: $m/e = 336.2$ ($M+H^+$) was prepared in accordance with the general method of example 1e from (RS)-2-(2-chloro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

Example 52

20

(RS)-2-(2-Fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 143°C and MS: $m/e = 320.3$ ($M+H^+$) was prepared in accordance with the general method of example 1e from (RS)-2-(2-fluoro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

25

Example 53

(RS)-1-(4-Chloro-benzenesulfonyl)-2-(2-fluoro-phenyl)-pyrrolidine

The title compound, white solid, m.p. 134°C and MS: $m/e = 340.2$ ($M+H^+$) was prepared in accordance with the general method of example 1e from (RS)-2-(2-fluoro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 54

(RS)-1-(4-Fluoro-benzenesulfonyl)-2-(2-fluoro-phenyl)-pyrrolidine

5 The title compound, white solid, m.p. 108°C and MS: m/e = 324.2 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(2-fluoro-phenyl)-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 55

(RS)-2-Thien-3-yl-1-(toluene-4-sulfonyl)-pyrrolidine

10 The title compound, white solid, m.p. 114°C and MS: m/e = 308.2 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-thien-3-yl-pyrrolidine and toluene-4-sulfonyl chloride.

Example 56

15 (RS)-1-(4-Chloro-benzenesulfonyl)-2-thien-3-yl-pyrrolidine

The title compound, white solid, m.p. 120°C and MS: m/e = 328.1 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-thien-3-yl-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 57

20

(RS)-1-(4-Fluoro-benzenesulfonyl)-2-thien-3-yl-pyrrolidine

The title compound, white solid, m.p. 135°C and MS: m/e = 312.1 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-thien-3-yl-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

25

Example 58

(RS)-2-(4-Chloro-3-methyl-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

30 The title compound, white solid, m.p. 103°C and MS: m/e = 349 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-chloro-3-methyl-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

Example 59

(RS)-2-(4-Fluoro-phenyl)-1-(4-propyl-benzenesulfonyl)-pyrrolidine

The title compound, colorless oil, MS: $m/e = 347$ (M^+) was prepared in accordance with
5 the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-propyl-benzenesulfonyl chloride.

Example 60

(RS)-2-(4-Fluoro-phenyl)-1-(4-trifluoromethyl-benzenesulfonyl)-pyrrolidine

10 The title compound, white solid, m.p. 85°C and MS: $m/e = 373$ (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-trifluoromethyl-benzenesulfonyl chloride.

Example 61

15 (RS)-2-(4-Fluoro-phenyl)-1-(2,4,6-trimethyl-benzenesulfonyl)-pyrrolidine

The title compound, white solid, m.p. 111°C and MS: $m/e = 347$ (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 2,4,6-trimethyl-benzenesulfonyl chloride.

Example 62

20

(RS)-1-(3-Chloro-4-methyl-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, off-white solid, m.p. 134°C and MS: $m/e = 353$ (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 3-chloro-4-methyl-benzenesulfonyl chloride.

25

Example 63

(RS)-1-(2-Fluoro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, off-white solid, m.p. 91°C and MS: $m/e = 323$ (M^+) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-
30 pyrrolidine and 2-fluoro-benzenesulfonyl chloride.

Example 64

(RS)-1-(3-Fluoro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, off-white solid, m.p. 101°C and MS: m/e = 323 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 3-fluoro-benzenesulfonyl chloride.

Example 65

(RS)-1-(2-Cyano-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, light green solid, m.p. 101°C and MS: m/e = 330 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 2-cyano-benzenesulfonyl chloride.

Example 66

(RS)-2-(4-Fluoro-phenyl)-1-(naphthalene-2-sulfonyl)-pyrrolidine

The title compound, off-white solid, m.p. 166°C and MS: m/e = 355 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and naphthalene-2-sulfonyl chloride.

Example 67

20

(RS)-2-(2,4-Dimethyl-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 130°C and MS: m/e = 329 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(2,4-dimethyl-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

25

Example 68

(RS)-2-(2,4-Dimethyl-phenyl)-1-(4-fluoro-benzenesulfonyl)-pyrrolidine

The title compound, white solid, m.p. 134°C and MS: m/e = 333 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(2,4-dimethyl-phenyl)-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 69

(RS)-2-Furan-2-yl-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 58°C and MS: $m/e = 291$ (M^+) was prepared in
5 accordance with the general method of example 1e from (RS)-2-furan-2-yl-pyrrolidine and
toluene-4-sulfonyl chloride.

Example 70

(RS)-1-(4-Fluoro-benzenesulfonyl)-2-furan-2-yl-pyrrolidine

The title compound, white solid, m.p. 69°C and MS: $m/e = 295$ (M^+) was prepared in
10 accordance with the general method of example 1e from (RS)-2-furan-2-yl-pyrrolidine and
4-fluoro-benzenesulfonyl chloride.

Example 71

(RS)-1-(4-Chloro-benzenesulfonyl)-2-furan-2-yl-pyrrolidine

15 The title compound, yellow oil, MS: $m/e = 311$ (M^+) was prepared in accordance with the
general method of example 1e from (RS)-2-furan-2-yl-pyrrolidine and 4-chloro-
benzenesulfonyl chloride.

Example 72

20 (RS)-2-(4-N,N-Dimethylamino-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 132°C and MS: $m/e = 345.3$ ($M+H^+$) was prepared
in accordance with the general method of example 1e from (RS)-2-(4-N,N-
dimethylamino-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

Example 73

25

(RS)-2-(4-N,N-Dimethylamino-phenyl)-1-(4-fluoro-benzenesulfonyl)-pyrrolidine

The title compound, white solid, m.p. 109°C and MS: $m/e = 349.4$ ($M+H^+$) was prepared
in accordance with the general method of example 1e from (RS)-2-(4-N,N-
dimethylamino-phenyl)-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 74

(RS)-2-(4-N,N-Dimethylamino-phenyl)-1-(4-chloro-benzenesulfonyl)-pyrrolidine

The title compound, white solid, m.p. 117°C and MS: m/e = 365.2 (M+H⁺) was prepared
5 in accordance with the general method of example 1e from (RS)-2-(4-N,N-dimethylamino-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 75

(RS)-1-Benzenesulfonyl-2-(4-trifluoromethyl-phenyl)-pyrrolidine

10 The title compound, white solid, m.p. 95°C and MS: m/e = 355 (M⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-trifluoromethyl-phenyl)-pyrrolidine and benzenesulfonyl chloride.

Example 76

(R)-1-(4-Chloro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, white solid, m.p. 119°C and MS: m/e = 339 (M⁺) was prepared in accordance with the general method of example 1e from (R)-2-(4-fluoro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 77

20

(S)-1-(4-Chloro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine

The title compound, white solid, m.p. 120°C and MS: m/e = 339 (M⁺) was prepared in accordance with the general method of example 1e from (S)-2-(4-fluoro-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

25

Example 78

(RS)-2-(4-Ethyl-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 92°C and MS: m/e = 330.3 (M+H⁺) was prepared in accordance with the general method of example 1e from (RS)-2-(4-ethyl-phenyl)-
30 pyrrolidine and toluene-4-sulfonyl chloride.

Example 79

(RS)-2-(4-Ethyl-phenyl)-1-(4-chloro-benzenesulfonyl)-pyrrolidine

The title compound, white solid, m.p. 94°C and MS: $m/e = 350.3 (M^+)$ was prepared in
5 accordance with the general method of example 1e from (S)-2-(4-ethyl-phenyl)-pyrrolidine and 4-chloro-benzenesulfonyl chloride.

Example 80

(RS)-2-(4-Ethyl-phenyl)-1-(4-fluoro-benzenesulfonyl)-pyrrolidine

10 The title compound, white solid, m.p. 93°C and MS: $m/e = 334.2 (M+H^+)$ was prepared in accordance with the general method of example 1e from (S)-2-(4-ethyl-phenyl)-pyrrolidine and 4-fluoro-benzenesulfonyl chloride.

Example 81

15 (R)-2-(4-Fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 136°C, $[\alpha]_D^{20} = +174^\circ$ ($c = 0.1$ in $CHCl_3$) and MS: $m/e = 319 (M^+)$ was prepared in accordance with the general method of example 1e from (R)-2-(4-fluoro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

Example 82

20

(S)-2-(4-Fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, white solid, m.p. 136°C, $[\alpha]_D^{20} = -172^\circ$ ($c = 0.1$ in $CHCl_3$) and MS: $m/e = 319 (M^+)$ was prepared in accordance with the general method of example 1e from (S)-2-(4-fluoro-phenyl)-pyrrolidine and toluene-4-sulfonyl chloride.

25

Example 83

(RS)-3-[1-(Toluene-4-sulfonyl)-pyrrolidin-2-yl]-pyridine

The title compound, white solid, m.p. 112°C, and MS: $m/e = 302 (M^+)$ was prepared in accordance with the general method of example 1e from 3-(pyrrolidin-2-yl)-pyridine and
30 toluene-4-sulfonyl chloride.

Example 84

(RS)-2-(4-Fluoro-phenyl)-1-(4-hydroxymethyl-benzenesulfonyl)-pyrrolidine

The title compound, white solid, m.p. 107°C, and MS: m/e = 336.2 (M+H⁺) was prepared
5 in accordance with the general method of example 1e from (RS)-2-(4-fluoro-phenyl)-
pyrrolidine and 4-hydroxymethyl-benzenesulfonyl chloride.

Example 85

(RS)-2-(4-Fluoro-phenyl)-1-(4-methoxymethyl-benzenesulfonyl)-pyrrolidine

10 Reaction of (RS)-2-(4-fluoro-phenyl)-1-(4-chloromethyl-benzenesulfonyl)-pyrrolidine
(0.50 g, 1.41 mmol), which was prepared in accordance with the general method of
example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-bromomethyl-
benzenesulfonyl chloride, with sodium methanolate in MeOH for 80 h at 50°C yielded
after crystallization from EE/hexane 0.28 g (52%) of the title compound as a white solid,
15 m.p. 115°C, and MS: m/e = 349 (M⁺).

Example 86

(RS)-4-{4-[2-(4-Fluoro-phenyl)-pyrrolidine-1-sulfonyl]-benzyl}-morpholine fumarate (1:1)

20 Reaction of (RS)-2-(4-fluoro-phenyl)-1-(4-chloromethyl-benzenesulfonyl)-pyrrolidine
(0.50 g, 1.41 mmol), which was prepared in accordance with the general method of
example 1e from (RS)-2-(4-fluoro-phenyl)-pyrrolidine and 4-bromomethyl-
benzenesulfonyl chloride, with morpholine (K₂CO₃, DMF, 80°C, 17 h) and subsequent
formation of the fumarate (MeOH, diethyl ether) yielded the title compound as an off-
25 white solid, m.p. 136°C, and MS: m/e = 405.4 (M+H⁺).

Example 87

(RS)-4-[2-(4-Fluoro-phenyl)-pyrrolidine-1-sulfonyl]-benzylamine fumarate (1:0.5)

Hydrogenation of (RS)-2-(4-fluoro-phenyl)-1-(4-cyano-benzenesulfonyl)-pyrrolidine (Ra-
30 Ni, MeOH-NH₃) and subsequent formation of the fumarate (MeOH, diethyl ether) yielded
the title compound as a white solid, m.p. 207°C, and MS: m/e = 335.2 (M+H⁺).

Example 88

Mixture of (2RS,3RS)- and (2RS,3SR)-2-(4-fluoro-phenyl)-3-methyl-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, off-white solid, m.p. 94°C and MS: $m/e = 333$ (M^+) was prepared in accordance with the general method of example 1e from a mixture of (2RS,3RS)- and (2RS,3SR)-2-(4-fluoro-phenyl)-3-methyl-pyrrolidine and toluene-4-sulfonyl chloride.

Example 89

Mixture of (2RS,3RS)- and (2RS,3SR)-1-(4-chloro-benzenesulfonyl)-2-(4-fluoro-phenyl)-3-methyl-pyrrolidine

The title compound, off-white solid, m.p. 87°C and MS: $m/e = 354.2$ ($M+H^+$) was prepared in accordance with the general method of example 1e from a mixture of (2RS,3RS)- and (2RS,3SR)-2-(4-fluoro-phenyl)-3-methyl-pyrrolidine and 4-chlorobenzene-sulfonyl chloride.

Example 90

(2RS,3RS)-2-(4-Fluoro-phenyl)-3-methyl-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, off-white solid, m.p. 112°C and MS: $m/e = 333$ (M^+) was prepared in accordance with the general method of example 1e from (2RS,3RS)-2-(4-fluoro-phenyl)-3-methyl-pyrrolidine and toluene-4-sulfonyl chloride.

Example A

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
5 Active ingredient	100
Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
10 Magnesium stearate	2
Tablet weight	<u>250</u>

Example B

Tablets of the following composition are produced in a conventional manner:

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	<u>mg/Tablet</u>
Active ingredient	200
Powdered. lactose	100
White corn starch	64
20 Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	<u>400</u>

Example C

Capsules of the following composition are produced:

	<u>mg/Capsule</u>
Active ingredient	50
5 Crystalline. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	<u>150</u>

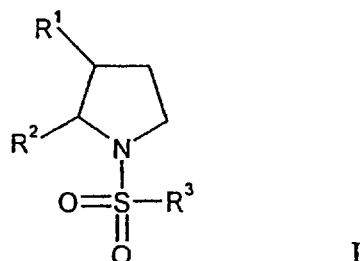
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The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

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Claims

1. Compounds of the general formula



wherein

- R^1 signifies hydrogen or (C_1-C_7) -alkyl;
- R^2 signifies furyl, thienyl, pyridyl or phenyl, which is optionally substituted by 1 to 3 substituents, selected from (C_1-C_7) -alkyl, (C_1-C_7) -alkoxy, halogen, cyano, CF_3 or $-N(R^4)_2$;
- R^3 signifies naphthyl or phenyl, which is optionally substituted by 1 to 3 substituents, selected from (C_1-C_7) -alkyl, (C_1-C_7) -alkoxy, halogen, acetyl, cyano, hydroxy- (C_1-C_7) -alkyl, $-CH_2$ -morpholin-4-yl, (C_1-C_7) -alkyl-oxy- (C_1-C_7) -alkyl, (C_1-C_7) -alkyl- $N(R^4)_2$ or CF_3 ;
- R^4 signifies, independently from each other, hydrogen or (C_1-C_7) -alkyl, with the exception of (RS)-2-phenyl-1-(toluene-4-sulfonyl)-pyrrolidine, (RS)-1-(toluene-4-sulfonyl)-2-p-tolyl-pyrrolidine, N-tosyl-cis-3-methyl-2-phenyl pyrrolidine, 3-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]pyridine and N-tosyl-2-(3,4-dimethoxy-phenyl)-pyrrolidine, as well as their pharmaceutically acceptable salts.

2. Compounds in accordance with claim 1, wherein

- R^1 signifies hydrogen or methyl;
- R^2 signifies phenyl, optionally substituted by halogen, (C_1-C_7) -alkyl, CF_3 or $-N(CH_3)_2$;

and pharmaceutically acceptable salts thereof.

3. Compounds in accordance with claims 1 and 2, which are

(RS)-2-(3-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,

(RS)-1-(4-chloro-benzenesulfonyl)-2-(3-fluoro-phenyl)-pyrrolidine,
 (RS)-1-(4-chloro-benzenesulfonyl)-2-phenyl-pyrrolidine,
 (RS)-2-(4-chloro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (RS)-1-(4-chloro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
 (RS)-2-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (RS)-1-benzenesulfonyl-2-(4-chloro-phenyl)-pyrrolidine,
 (RS)-1-(4-fluoro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
 (RS)-2-(4-fluoro-phenyl)-1-(toluene-2-sulfonyl)-pyrrolidine,
 (RS)-1-(4-chloro-benzenesulfonyl)-2-p-tolyl-pyrrolidine,
 (RS)-1-(4-ethyl-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
 (RS)-1-(toluene-4-sulfonyl)-2-m-tolyl-pyrrolidine,
 (RS)-2-(3-chloro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (RS)-2-(3,4-difluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (RS)-2-(3-chloro-4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (RS)-1-(4-fluorobenzenesulfonyl)-2-(4-dimethylamino-3-chloro-phenyl)-pyrrolidine,
 (RS)-1-(toluene-4-sulfonyl)-2-(4-trifluoromethyl-phenyl)-pyrrolidine,
 (RS)-2-(4-chloro-3-methyl-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (RS)-2-(4-fluoro-phenyl)-1-(4-trifluoromethyl-benzenesulfonyl)-pyrrolidine,
 (RS)-2-(N,N-dimethylamino-phenyl)-1-(4-fluoro-benzenesulfonyl)-pyrrolidine,
 (R)-1-(4-chloro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
 (S)-1-(4-chloro-benzenesulfonyl)-2-(4-fluoro-phenyl)-pyrrolidine,
 (RS)-2-(4-ethyl-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (RS)-2-(4-ethyl-phenyl)-1-(4-fluoro-benzenesulfonyl)-pyrrolidine,
 (S)-2-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (R)-2-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine,
 (RS)-2-(4-fluoro-phenyl)-1-(4-methoxymethyl-benzenesulfonyl)-pyrrolidine and
 (2RS,3RS)-2-(4-fluoro-phenyl)-3-methyl-1-(toluene-4-sulfonyl)-pyrrolidine.

4. Compounds in accordance with claim 1, wherein

R¹ signifies hydrogen; and

R² signifies furyl, thienyl or pyridyl.

5. Compounds in accordance with claims 1 and 4, which are

(RS)-1-(4-chloro-benzenesulfonyl)-2-thien-2-yl-pyrrolidine,

(RS)-2-thien-2-yl-1-(toluene-4-sulfonyl)-pyrrolidine and

(RS)-2-thien-3-yl-1-(toluene-4-sulfonyl)-pyrrolidine.

6. A medicament comprising a compound according to any one of claims 1-5 or

(RS)-2-phenyl-1-(toluene-4-sulfonyl)-pyrrolidine, (RS)-1-(toluene-4-sulfonyl)-2-p-

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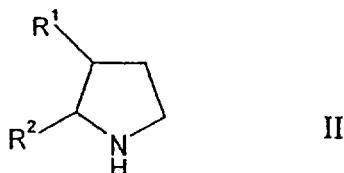
tolyl-pyrrolidine, N-tosyl-cis-3-methyl-2-phenyl pyrrolidine, 3-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]pyridine or N-tosyl-2-(3,4-dimethoxy-phenyl)-pyrrolidine as well as pharmaceutically acceptable salts thereof and pharmaceutically acceptable excipients.

7. A medicament in accordance with claim 6 for the control or prevention of acute and/or chronic neurological disorders such as restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest, hypoglycaemia, Alzheimer's disease, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, cognitive disorders, memory deficits as well as acute and chronic pain, schizophrenia, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

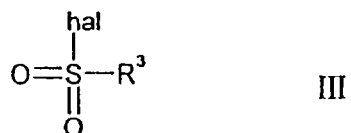
8. The use of compounds in accordance with any one of claims 1-5 or (RS)-2-phenyl-1-(toluene-4-sulfonyl)-pyrrolidine, (RS)-1-(toluene-4-sulfonyl)-2-p-tolyl-pyrrolidine, N-tosyl-cis-3-methyl-2-phenyl pyrrolidine, 3-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]pyridine or N-tosyl-2-(3,4-dimethoxy-phenyl)-pyrrolidine, as well as pharmaceutically acceptable salts thereof in the control or prevention of illness and, respectively, for the production of corresponding medicaments.

9. Compounds in accordance with claims 1-5 or (RS)-2-phenyl-1-(toluene-4-sulfonyl)-pyrrolidine, (RS)-1-(toluene-4-sulfonyl)-2-p-tolyl-pyrrolidine, N-tosyl-cis-3-methyl-2-phenyl pyrrolidine, 3-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]pyridine or N-tosyl-2-(3,4-dimethoxy-phenyl)-pyrrolidine as well as pharmaceutically acceptable salts thereof for the control or prevention of acute and/or chronic neurological disorders.

10. A process for the manufacture of compounds according to any one of claim 1-5 as well as of pharmaceutically acceptable salts thereof, which process reacting a compound of the formula



with a compound of formula



and, if desired,

converting a functional group in a compound of formula I into another functional group and, if desired,

converting a compound of formula I into a pharmaceutically acceptable salt.

11. Compounds in accordance with claims 1-5, when manufactured according to a process in accordance with claim 10.