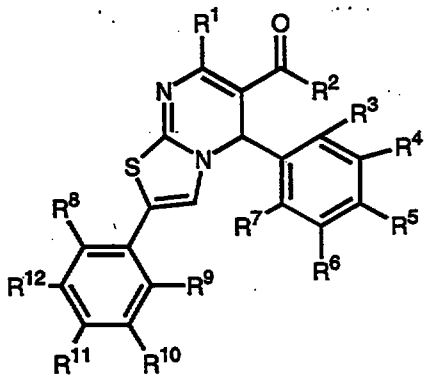
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The present invention is concerned with 5H-thiazolo[3,2-a]pyrimidine derivatives of the general formula



I

wherein

R^1	signifies hydrogen, lower alkyl, phenyl or benzyl,	
R^2	signifies lower alkyl, lower alkoxy, $-O(CH_2)_nN(R^{13})(R^{14})$, $-(CH_2)_nN(R^{13})(R^{14})$ or $-N(R^{15})(CH_2)_nN(R^{13})(R^{14})$,	
R^3-R^{12}	signify hydrogen, halogen, trifluoromethyl, lower alkyl, cycloalkyl, lower alkoxy, hydroxy, nitro, cyano, $-N(R^{13})_2$, phenyl, phenyloxy, benzyl or benzyloxy, or	
R^6 and R^7	together signify a benzene ring,	
R^{13}-R^{15}	signify hydrogen, lower alkyl or cycloalkyl and	
n	signifies 1-5,	

as well as their pharmaceutically acceptable salts.

These compounds and their salts are novel and are distinguished by valuable therapeutic properties.

It has been found that the compounds of general formula I are metabotropic glutamate receptor-antagonists and/or agonists.

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 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:

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

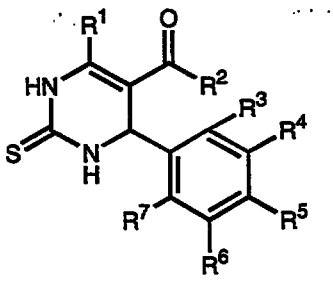
Metabotropic glutamate receptors belonging to the second group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia.

Other treatable indications in this connection are Alzheimer's disease,Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, cognitive disorders, 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, chronic pain, dyskinesia, depressions and pains.

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.

Objects of the invention are, furthermore, the novel compounds of the formula



II

wherein R^1-R^7 have the significances given earlier,

which are intermediates in the manufacture of the compounds of formula I.

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 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and the like.

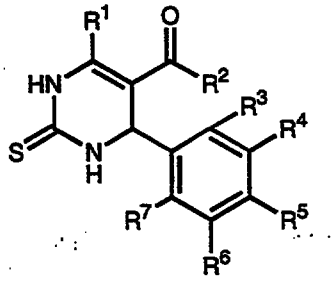
The term "cycloalkyl" denotes cyclic saturated hydrocarbon residues with 3-7 ring carbon atoms, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

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.

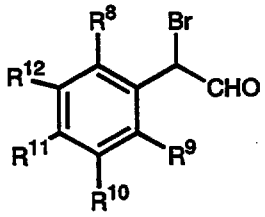
The compounds of general formula I and their pharmaceutically acceptable salts can be manufactured by

reacting a compound of the formula



II

with an α-bromo-acetaldehyde of the formula



III

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.

In particular, nitro groups of compounds of formula I can be hydrogenated to amino groups or amino groups can be alkylated to lower alkylamino or di-lower-alkylamino groups or hydroxy groups can be alkylated.

In accordance with the invention an appropriately substituted α-bromoacetaldehyde of formula III, for example α-bromo-2,6-dichlorophenyl-acetaldehyde, is reacted with a suitable thioxopyrimidine of formula II, for example (RS)-1-[4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]ethanone. The reaction takes place at room temperature within 60-70 hours in an inert solvent, for example in tetrahydrofuran (THF), or in acetonitrile. After cooling the reaction mixture to about 0°C the separated solid is heated with concentrated acetic acid for several hours and purified using known methods.

Nitro groups present can be hydrogenated to amino groups according to methods known per se. The hydrogenation is preferably effected with Raney-nickel at room temperature under normal pressure, where no chlorine is present in the molecule.

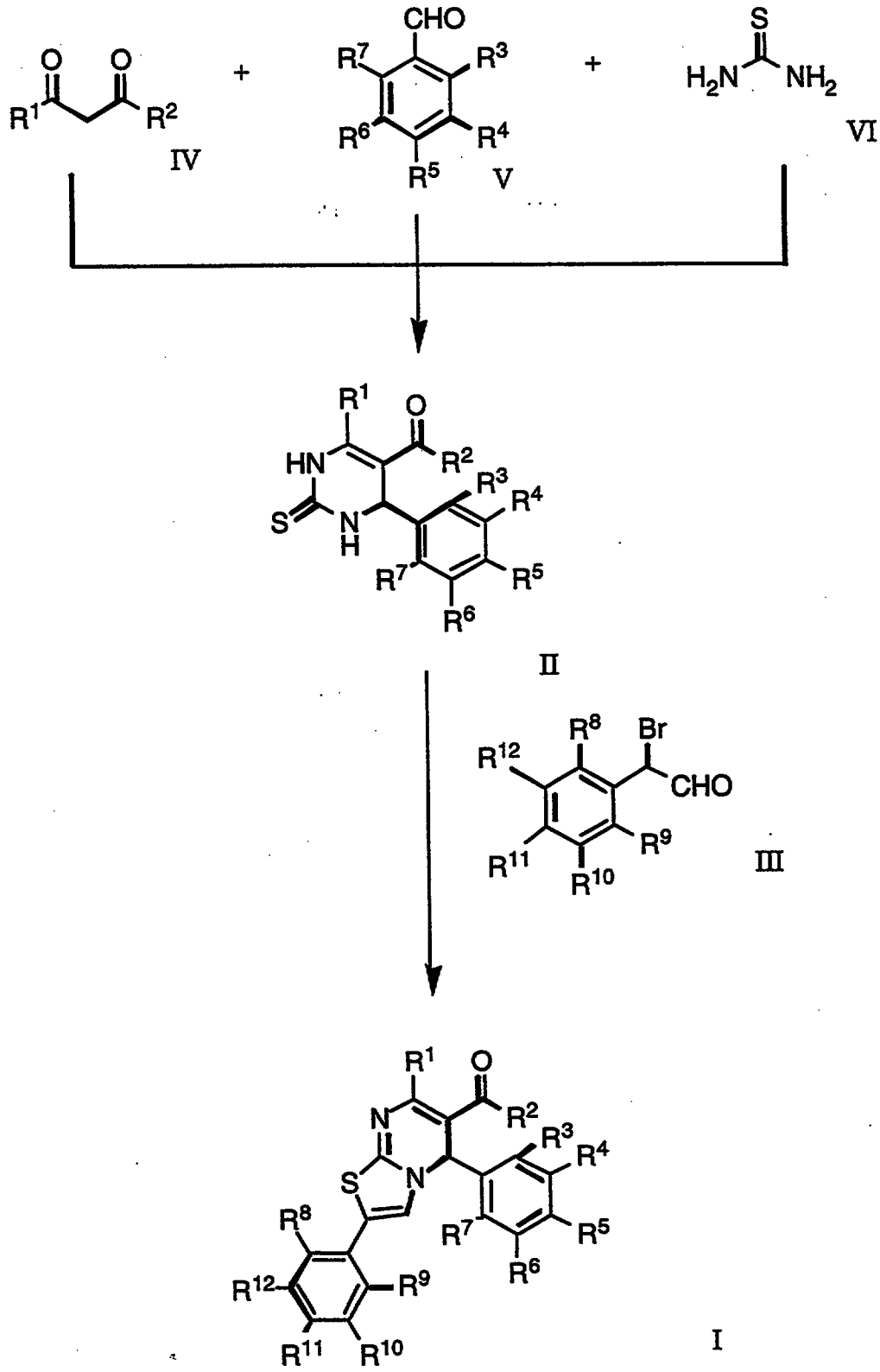
The alkylation of amino groups can be conveniently carried out as follows: A compound of general formula I which contains an amino group is, for example, dissolved in acetonitrile and treated with formaldehyde and $NaBH_3CN$. After adjustment to pH 6 with, for example, glacial acetic acid this procedure is repeated, with a methylamino compound of formula I being obtained after a reaction period of about 2 hours. Another method comprises treatment of a compound of formula I which contains an amino group with, for example, formic acid esters and subsequent hydrogenation in a BH_3-THF solution.

The alkylation of a hydroxy group can be carried out according to generally familiar methods. Dimethyl sulphate can be conveniently used as the alkylating agent for a methylation. This can be carried out by dissolving the compound to be alkylated in a suitable solvent, e.g. toluene, treating with dimethyl sulphate, tetrabutylammonium hydrogen sulphate and a sodium hydroxide solution and stirring intensively. The reaction conditions can be varied according to alkylating agent and, respectively, compound to the alkylated.

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, 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.

The following Scheme gives an overview of the manufacture of the compounds of formula I starting from the compounds of formulae IV, V and VI. The intermediates of formula II are novel. The α-bromoacetyldehydes can be prepared according to US 3,660,418. The manufacture of representative compounds of formula I is described in detail in Examples 1-27.

Scheme 1



The substituents have the significances given earlier.

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, metabotropic glutamate receptor antagonists and can be used for the treatment 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 and hypoglycaemia. Other treatable indications are Alzheimer's disease,Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, cognitive illnesses, 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, chronic pain, dyskinesia, depressions and pains.

The binding of the compounds of formula I in accordance with the invention to group II metabotropic glutamate receptors was determined in vitro. The preparations were investigated in accordance with the test given hereinafter.

The GTP $\gamma^{35}S$ test was used to determine the affinity of a compound to the group II mGluR. These were stimulated with 10 µM 1S,3R-ACPD.

The Ki values of the compounds tested are given. The Ki value is defined by the following formula:

$$K_i = \frac{IC_{50}}{1 + \frac{[L]}{EC_{50}}}$$

in which the IC_{50} values are those concentrations of the compounds tested in µM by which 50% of the effect of 1S,3R-ACPD are antagonised. [L] is the concentration of 1S,3R-ACPD and the EC_{50} value is the concentration of 1S,3R-ACPD in µM which brings about 50% stimulation.

The compounds described in Examples 1-27 have activities of Ki = 1-20 µM.

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 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 administration 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 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 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, 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.

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

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 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.

Example 1

(RS)-1-[2-(2,6-Dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidin-6-yl]ethanone

a) A solution of 12.1 ml (0.1 mol) of 4-methoxybenzaldehyde, 10.3 ml (0.1 mol) of acetylacetone and 9.13 g (0.12 mol) of thiourea in 30 ml of ethanol was treated with 10 drops of conc. hydrochloric acid and boiled under reflux while stirring for 4 h. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (dichloromethane- methanol 98:2). Subsequent crystallization from ethanol gave 6.2 g (22%) of (RS)-1-[4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]ethanone as a red-brown solid with m.p. 175°C.

b) A mixture of 1.9 g (7.09 mmol) of α-bromo-2,6-dichlorophenyl-acetaldehyde and 1.78 g (6.45 mmol) of (RS)-1-[4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]ethanone in 50 ml of tetra- hydrofuran was stirred at RT for 65 h. Subsequently, the mixture was cooled to 0°C and the precipitated solid was filtered off, dissolved in 75 ml of conc. acetic acid and heated at reflux while stirring for 8 h. The

reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (dichloromethane/methanol 95:5). There were obtained 1.95 g (68%) of (RS)-1-[2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl]ethanone as a yellow foam.

c) 1.95 g (4.38 mmol) of (RS)-1-[2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl]ethanone were dissolved in 20 ml of methanolic hydrochloric acid solution (2.6N) while stirring and treated with 100 ml of diethyl ether. After 1 h the crystals were filtered off. There were obtained 1.54 g (73%) of (RS)-1-[2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl]ethanone hydrochloride as a beige solid with m.p. 165°C.

Example 2

(RS)-1-[2-(2,6-Dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo-[3,2-a]pyrimidin-6-yl]ethanone

Analogously to Example 1a-c, starting from 2-methoxybenzaldehyde, thiourea, acetylacetone and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, (RS)-1-[2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl]ethanone hydrobromide as a white solid with m.p. 290°C.

Example 3

Ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo-[3,2-a]pyrimidine-6-carboxylate

a) A mixture of 2.0 g (7.5 mmol) of α-bromo-2,6-dichlorophenyl-acetaldehyde and 2.08 g (6.8 mmol) of ethyl (RS)-4-(2-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate in 40 ml of tetrahydrofuran was stirred at RT for 17 h. Subsequently, the mixture was cooled to 0°C and the precipitated solid was filtered off, dissolved in 75 ml of conc. acetic acid and heated at reflux while stirring for 24 h. The reaction mixture was concentrated and the residue was purified by column chromatography

on silica gel (ethyl acetate). There were obtained 1.82 g (51%) of ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate as a yellow foam.

b) 1.82 g (3.83 mmol) of ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate were dissolved in 20 ml of methanolic hydrochloric solution (2.6N) while stirring and treated with 100 ml of diethyl ether. After 15 h. the crystals were filtered off. There were obtained 1.55 g (79%) of ethyl (RS)-2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate hydrochloride as a light yellow solid with m.p. 233°C.

Example 4

(RS)-2-(2,6-Dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-6-carboxylate

Analogously to Example 3a-b, starting from ethyl (RS)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, ethyl (RS)-2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate hydrochloride as a white solid with m.p. 201°C.

Example 5

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

a) A solution of 3.0 g (17.3 mmol) of 2-dimethylaminoethyl 3-oxo-butanoate, 2.1 ml (17.3 mmol) of 4-methoxybenzaldehyde and 1.58 g (20.8 mmol) of thiourea in 15 ml of conc. acetic acid was heated under reflux for 4 h. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (dichloromethane/-methanol/- ammonium hydroxide solution 8:1:0.1). There were obtained 2.76 g (46%) of

2-dimethyl-amino-ethyl (RS)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate as a light yellow solid with m.p. 80°C.

b) 0.9 g (2.6 mmol) of 2-dimethylamino-methyl (RS)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate was dissolved in 10 ml of methanolic hydrochloric acid solution and concentrated. The hydrochloride obtained and 0.77 g (2.86 mmol) of α-bromo-2,6-dichlorophenyl-acetaldehyde dissolved in 50 ml of acetonitrile were boiled under reflux while stirring for 16 h. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (dichloromethane/methanol/- ammonium hydroxide solution 8:1:0.1). There was obtained 0.83 g (61%) of 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate as a greenish foam.

c) 0.83 g (1.6 mmol) of 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate was dissolved in 10 ml of methanolic hydrochloric acid solution (2.6N) while stirring and treated with 50 ml of diethyl ether. After 3 h. the crystals were filtered off. There was obtained 0.87 g (79%) of 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p. >240°C.

Example 6

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-methoxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate dihydrobromide as a pale yellow solid with m.p. 237°C.

Example 7

3-Dimethylamino-propyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-methoxybenzaldehyde, 3-dimethylamino-propyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 3-dimethylamino-propyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p. 175°C (dec.)

Example 8

2-Dimethylamino-ethyl (RS)-2-(4-chlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-methoxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-4-chlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(4-chlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate dihydrochloride as a pale green solid with m.p. 178°C.

Example 9

2-Dimethylamino-ethyl (RS)-2-(2,4-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-methoxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,4-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,4-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a pale yellow solid with m.p. 191°C.

Example 10

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(3-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 3-methoxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(3-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p. 155°C (dec.).

Example 11

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(4-chlorophenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 4-chlorobenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(4-chlorophenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p. 190°C.

Example 12

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-chlorobenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p 169°C.

Example 13

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-*iso*-propyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-methoxybenzaldehyde, 2-dimethylamino-ethyl 4-methyl-3-oxo-pentanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-*iso*-propyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p. 165°C (dec.).

Example 14

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-ethyl-5H-thiazolo[3,2-a]pyrimidine 6-carboxylate

Analogously to Example 5a-c, starting from 2-methoxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-pentanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-ethyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p. 167°C (dec.).

Example 15

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-benzyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-methoxybenzaldehyde, 2-dimethylamino-ethyl 4-phenyl-3-oxo-butanate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-benzyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p. 170°C (dec.).

Example 16

(RS)-2-(2,6-Dichlorophenyl)-5-(2-methoxyphenyl)-7-benzyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylic acid N-(2-dimethylamino-ethyl)-amide

Analogously to Example 5a-c, starting from 2-methoxybenzaldehyde, N-(2-dimethylamino-ethyl)-3-oxo-butanamide, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-benzyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid N-(2-dimethylamino-ethyl)-amide dihydrochloride as a beige solid with m.p. 232°C.

Example 17

(RS)-2-(2,6-Dichlorophenyl)-5-(2-methoxyphenyl)-7-benzyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylic acid N-(2-dimethylamino-ethyl)-N-methyl-amide

Analogously to Example 5a-c, starting from 2-methoxybenzaldehyde, N-(2-dimethylamino-ethyl)-N-methyl-3-oxo-butanamide, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-benzyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid N-(2-dimethylamino-ethyl)-N-methyl-amide dihydrochloride as a beige solid with m.p. 170°C (dec.).

Example 18

(RS)-2-(2,6-Dichlorophenyl)-5-(4-methoxyphenyl)-7-benzyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylic acid N-(2-dimethylamino-ethyl)-amide

Analogously to Example 5a-c, starting from 4-methoxybenzaldehyde, N-(2-dimethylamino-ethyl)-3-oxo-butanamide, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, (RS)-2-(2,6-dichlorophenyl)-5-(4-methoxyphenyl)-7-benzyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic

acid N-(2-dimethylamino-ethyl)-amide dihydrochloride as a light yellow solid with m.p. 180°C (dec.).

Example 19

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2,3-dimethoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2,3-dimethoxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2,3-dimethoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a light brown solid with m.p. 144°C.

Example 20

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2,6-dimethoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2,6-dimethoxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2,6-dimethoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a light green solid with m.p. 171°C (dec.).

Example 21

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-fluorophenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-fluorobenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-

ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-fluorophenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p. 169°C (dec.).

Example 22

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methylphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-methylbenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methylphenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a beige solid with m.p. 157°C (dec.).

Example 23

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-ethoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-ethoxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-ethoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a white solid with m.p. 188°C (dec.).

Example 24

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-*iso*-propyloxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-*iso*-propyloxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-

ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-*iso*-propyloxyphenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidin-6-carboxylate dihydrochloride as a pale brown solid with m.p. 172°C (dec.).

Example 25

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxynaphthyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-methoxynaphthaldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxynaphthyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate dihydrochloride as a brown solid with m.p. 174°C (dec.).

Example 26

2-Dimethylamino-ethyl (RS)-2-(2,4-dichlorophenyl)-5-(2-methoxyphenyl)-7-ethyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5 a-c, starting from 2-methoxybenzaldehyde, 2-dimethylamino-ethyl 3-oxo-pentanoate, thiourea and α-bromo-2,4-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-ethyl (RS)-2-(2,4-dichlorophenyl)-5-(2-methoxyphenyl)-7-ethyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a yellow solid with m.p. 199°C (dec.).

Example 27

2-Dimethylamino-ethyl 12 (RS)-2-(2,6-dichlorophenyl)-5-(2-benzyloxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

Analogously to Example 5a-c, starting from 2-benzyloxybenzyldehyde, 2-dimethylamino-ethyl 3-oxo-butanoate, thiourea and α-bromo-2,6-dichlorophenyl-acetaldehyde there was obtained, after salt formation and crystallization, 2-dimethylamino-

ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-benzyloxyphenyl)-7-methyl-5H-thiazolo[3,2-a]-pyrimidine-6-carboxylate dihydrochloride as a light brown solid with m.p. 147°C (dec.).

Example A

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

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

Example B

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

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

Example C

Capsules of the following composition are produced:

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

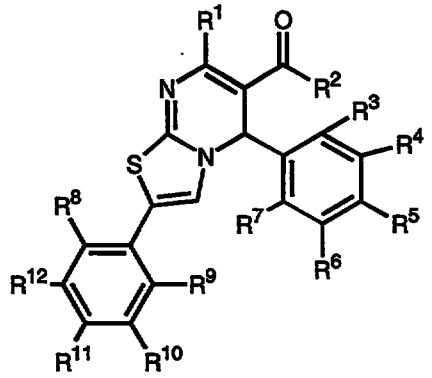
The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

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Claims

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1. Compounds of the general formula



I

wherein

R^1	signifies hydrogen, lower alkyl, phenyl or benzyl,
R^2	signifies lower alkyl, lower alkoxy, $-O(CH_2)_nN(R^{13})(R^{14})$, $-(CH_2)_nN(R^{13})(R^{14})$ or $-N(R^{15})(CH_2)_nN(R^{13})(R^{14})$,
R^3-R^{12}	signify hydrogen, halogen, trifluoromethyl, lower alkyl, cycloalkyl, lower alkoxy, hydroxy, nitro, cyano, $-N(R^{13})_2$, phenyl, phenyloxy, benzyl or benzyloxy, or
R^6 and R^7	together signify a benzene ring,
R^{13}-R^{15}	signify hydrogen, lower alkyl or cycloalkyl and
n	signifies 1-5,

as well as their pharmaceutically acceptable salts.

2. Compounds in accordance with claim 1, wherein

R^1	signifies lower alkyl or benzyl;
R^2	signifies lower alkyl, lower alkoxy, $-O(CH_2)_2N(CH_3)_2$, $-O(CH_2)_3N(CH_3)_2$, $-NH(CH_2)_2N(CH_3)_2$ or $-N(CH_3)(CH_2)_2N(CH_3)_2$;
R^3	signifies hydrogen, lower alkoxy, halogen or benzyloxy;
R^4	signifies hydrogen or lower alkoxy;

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R^5	signifies hydrogen, halogen or lower alkoxy;	
R^6	signifies hydrogen;	
R^7	signifies hydrogen or lower alkoxy; or	
R^6 and R^7	together signify a benzene ring; and	
R^8-R^{12}	signify hydrogen or halogen.	

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3. Compounds in accordance with claims 1 and 2, wherein

R^1	signifies methyl or ethyl;	
R^2	signifies $-O(CH_2)_2N(CH_3)_2$;	
R^3	signifies methoxy, chlorine or i-propoxy;	
R^4-R^7	signify hydrogen; and	
R^8-R^{12}	ignify hydrogen or chlorine.	

4. The following compounds in accordance with claim 3:

2-Dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate,

2-dimethylamino-ethyl (RS)-2-(2,4-dichlorophenyl)-5-(2-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate,

2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate,

2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-methoxyphenyl)-7-ethyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate,

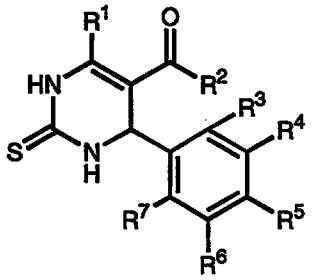
2-dimethylamino-ethyl (RS)-2-(2,6-dichlorophenyl)-5-(2-isopropyloxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate and

2-dimethylamino-ethyl (RS)-2-(2,4-dichlorophenyl)-5-(2-methoxyphenyl)-7-ethyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate.

5. Compounds of the general formula



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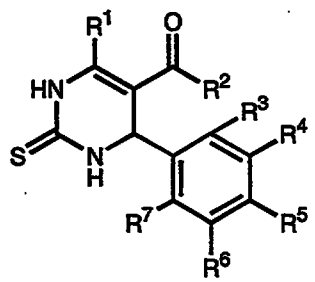
wherein R^1-R^7 have the significances set forth in claim 1.

6. A medicament containing a compound according to any one of claims 1-4 and a therapeutically inert excipient.

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 cause by pregnancy, cardiac arrest, hypoglycaemia, Alzheimer's disease, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries,retinopathy, cognitive disorders, 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, chronic pain, dyskinesia and depressions.

8. A process for the manufacture of compounds according to any one of claim 1-4 as well as of pharmaceutically acceptable salts thereof, which process comprises

reacting a compound of the formula



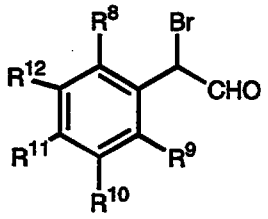
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with an α-bromo-acetaldehyde of the formula

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III

wherein R^1-R^{12} have the significances given in claim 1,

and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

9. Compounds in accordance with claims 1-4, when manufactured according to a process in accordance with claim 8.

10. Compounds in accordance with claims 1-4 for the control or prevention of acute and/or chronic neurological disorders.

11. The use of compounds in accordance with any one of claims 1-4 in the control or prevention of illnesses and, respectively, for the production of corresponding medicaments.

12. The invention as herein described.

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