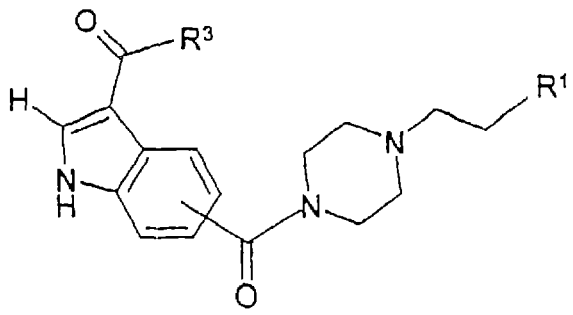
# Indole derivatives

The invention relates to compounds of the formula I



I

in which

$R^1$ is a phenyl radical which is unsubstituted or substituted by $R^2$ and/or $R^4$ or is $Het^1$,

$R^2$, $R^4$,

$R^5$, $R^6$ in each case independently of one another are Hal, A, OA, OH, CN or acyl,

$R^3$ is a phenyl radical which is unsubstituted or substituted by $R^5$ and/or $R^6$ or is $Het^2$,

$Het^1$ is a mono- or binuclear unsaturated heterocyclic ring system, which is unsubstituted or mono- or disubstituted by Hal, A, OA or OH and contains one, two or three identical or different heteroatoms such as nitrogen, oxygen and sulfur,

$Het^2$ is an unsaturated heterocyclic ring system which is unsubstituted or mono- or disubstituted by Hal, A, OA and contains one or two identical or different heteroatoms such as nitrogen, oxygen and sulfur,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

and their physiologically acceptable salts and solvates.

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The invention was based on the object of finding novel compounds having valuable properties, in particular those which can be used for the production of medicaments.

It has been found that the compounds of the formula I and their physiologically acceptable salts and solvates have valuable pharmacological properties together with good tolerability, as they have actions on the central nervous system. The compounds have a strong affinity for 5-$HT_{2A}$ receptors; they furthermore exhibit 5-$HT_{2A}$ receptor-antagonistic properties.

For the in-vitro detection of the affinity for 5-$HT_{2A}$ receptors, it is possible to use, for example, the following test (Example A1). The 5-$HT_{2A}$ receptors are exposed to both [$^3$H]ketanserin (a substance known for its affinity for the receptor) and the test compound. The decrease in the affinity of [$^3$H]ketanserin for the receptor is a sign of the affinity of the test substance for the 5-$HT_{2A}$ receptor. Detection is carried out analogously to the description of J.E. Leysen et al., Molecular Pharmacology, 1982, 21: 301-314 or as also described, for example, in EP 0320983.

The efficacy of the compounds according to the invention as 5-$HT_{2A}$ receptor antagonists can be measured in vitro analogously to W. Feniuk et al., Mechanisms of 5-hydroxytryptamine-induced vasoconstriction, in: The Peripheral Actions of 5-Hydroxytryptamine, ed. Fozard JR, Oxford University Press, New York, 1989, p. 110. Thus the contractility of the rat tail artery, caused by 5-hydroxytryptamine, is mediated by 5-$HT_{2A}$ receptors. For the test system, vessel rings, prepared from the ventral rat tail artery, are subjected to perfusion with an oxygen-saturated solution in an organ bath. By introduction of increasing concentrations of 5-hydroxytryptamine into the solution, a response to the cumulative concentration of 5-HT is obtained. The test

compound is then added to the organ bath in suitable concentrations and a second concentration curve is measured for 5-HT. The strength of the test compound on the shift of the 5-HT-induced concentration curve to higher 5-HT concentrations is a measure of the 5-$HT_{2A}$ receptor-antagonistic property in vitro.

The 5-$HT_{2A}$-antagonistic property can be determined in vivo analogously to M.D. Serdar et al., Psychopharmacology, 1996, 128: 198-205.

Other compounds which likewise exhibit 5-$HT_2$-antagonistic actions are described, for example, in EP 0320983.
Similar piperazine derivatives having antiarrhythmic properties are disclosed, for example, in EP 0431945. Other indolecarbonyl derivatives having analgesic properties are described in EP 0599240. EP 0624584 describes piperazine derivatives as calmodolin [sic] inhibitors. The compounds according to the invention are to be considered as a selection invention with respect to the last-mentioned document.
WO 99/11641 describes phenylindole derivatives having 5-$HT_2$-antagonistic properties.

The compounds of the formula I are therefore suitable both in veterinary and in human medicine for the treatment of functional disorders of the central nervous system and also of inflammation. They can be used for the prophylaxis and for the control of the sequelae of cerebral infarcts (cerebral apoplexy) such as stroke and cerebral ischaemias and for the treatment of extrapyramidal motor side effects of neuroleptics and also of Parkinson's disease, for the acute and symptomatic therapy of Alzheimer's disease and the treatment of amyotrophic lateral sclerosis. They are likewise suitable as therapeutics for the treatment of brain and spinal cord traumata. In particular, however, they are suitable as pharmaceutical active compounds

for anxiolytics, antidepressants, antipsychotics, neuroleptics, antihypertensives and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD; e.g. WO 9524194), anxiety states and also physiological changes which accompany anxiety states such as, for example, tachycardia, tremors or sweating (e.g. EP 319962), panic attacks, psychoses, schizophrenia, anorexia, delusional obsessions, agoraphobia, migraine, Alzheimer's disease, sleep disorders and also sleep apnoea, tardive dyskinesias, learning disorders, age-dependent memory disorders, eating disorders such as bulimia, drug abuse such as, for example, of alcohol, opiates, nicotine, psychostimulants such as, for example, cocaine or amphetamines (e.g. US 6004980), sexual functional disorders, states of pain of all types and fibromyalgia (e.g. WO 9946245).

The compounds of the formula I are suitable for the treatment of extrapyramidal side effects (EPS) in neuroleptic drug therapy. EPS is characterized by Parkinson-like syndromes, acathisia and dystonic reactions (e.g. EP 337136). They are further suitable for the treatment of anorexia nervosa, angina, Reynaud's phenomenon, coronary vasospasms, in the prophylaxis of migraine (e.g. EP 208235), pain and neuralgia (e.g. EP 320983), for the treatment of the Rett syndrome with autistic traits, of the Asperger syndrome, or autism and autistic disorders, in concentration deficiency states, developmental diseases, hyperactivity - states with - mental underdevelopment and stereotypic behavioural states (e.g. WO 9524194).

In addition, they are suitable for the treatment of endocrine disorders such as hyperprolactinaemia, furthermore in vasospasms, thrombotic disorders (e.g. WO 9946245), hypertension and gastrointestinal disorders.

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They are furthermore suitable for the treatment of cardiovascular disorders and also extrapyramidal symptoms as described in WO 99/11641 on page 2, lines 24-30.

The compounds according to the invention are further suitable for decreasing intraocular pressure and for the treatment of glaucoma. They are also suitable in animals for the prophylaxis and treatment of symptoms of intoxication on the administration of ergovaline.

The compounds are furthermore suitable for the treatment of disorders of the cardiovascular system (WO 99/11641, page 3, lines 14-15).

The compounds according to the invention can also be employed together with other active compounds in the treatment of schizophrenia. Possible other active compounds are the compounds mentioned in WO 99/11641 on page 13, lines 20-26.

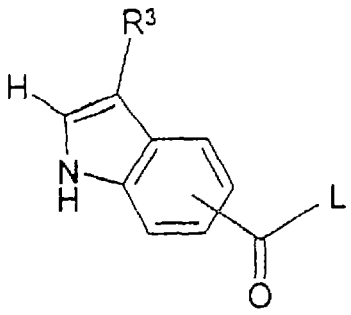
They can furthermore be employed as intermediates for the production of further pharmaceutical active compounds.

The invention relates to the N-(indolecarbonyl)-piperazine derivatives of the formula I and to their physiologically acceptable acid addition salts. The invention also relates to the solvates, e.g. hydrates or alcoholates, of these compounds.

The invention accordingly relates to the compounds of the formula I and a process for the preparation of compounds of the formula I according to Claim 1.

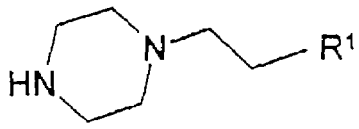
The process for the preparation of compounds of the formula I according to Claim 1 is characterized in that

a) a compound of the formula II



II

in which L is Cl, Br, I or a free or reactively functionally modified OH group,
and $R^3$ has the meaning indicated in Claim 1,
is reacted with a compound of the formula III

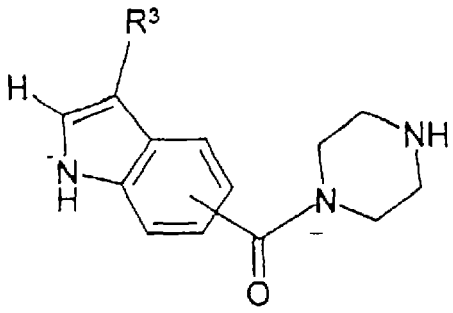


III

in which $R^1$ has the meaning indicated in Claim 1,

or

b) a compound of the formula IV



IV

in which $R^3$ has the meaning indicated in Claim 1,
is reacted with a compound of the formula V

$$L\text{-}CH_2\text{-}CH_2\text{-}R^1 \qquad V$$

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in which L is Cl, Br, I or a free or reactively functionally modified OH group, and $R^1$ has the meaning indicated in Claim 1,

or

c) if appropriate, one of the radicals $R^1$ and/or $R^3$ is converted into another radical $R^1$ and/or $R^3$ by cleaving, for example, an OA group with formation of an OH group and/or converting a CHO group into a CN group,

and/or a base of the formula I which is obtained is converted into one of its salts by treating with an acid.

The invention also relates to the compounds of the formula I according to Claim 1, and to their physiologically acceptable salts and solvates as medicaments.

The invention relates in particular to the compounds of the formula I according to Claim 1, and also their physiologically acceptable salts and solvates as medicaments having 5-$HT_{2A}$ receptor-antagonistic action.

The invention also relates to the compounds of the formula I, and their enantiomers and diastereomers, and their salts.

For all radicals which occur a number of times, such as, for example, A or Hal, it holds true that their meanings are independent of one another.

The radical A is alkyl and has 1 to 6, preferably 1, 2, 3 or 4, in particular 1 or 2, C atoms. Alkyl is therefore in particular, for example, methyl, furthermore ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-

ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl.

Acyl preferably has 1-6 C atoms and is, for example, formyl, acetyl, propionyl, butyryl, furthermore trifluoroacetyl.

Alkylene is propylene, butylene or pentylene.
OA is preferably methoxy, furthermore also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy.

Hal is fluorine, chlorine, bromine or iodine, in particular fluorine or chlorine.

$R^1$ is unsubstituted, preferably - as indicated - monosubstituted phenyl, specifically preferably phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-trifluoromethoxyphenyl, o-, m- or p-cyanophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-difluoromethoxyphenyl, o-, m- or p-fluoromethoxyphenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2-chloro-3-methyl-, 2-chloro-4-methyl-, 2-chloro-5-methyl-, 2-chloro-6-methyl-, 2-methyl-3-chloro-, 2-methyl-4-chloro-, 2-methyl-5-chloro-, 2-methyl-6-chloro-, 3-chloro-4-methyl-, 3-chloro-5-methyl- or 3-methyl-4-chlorophenyl, 2-bromo-3-methyl-, 2-bromo-4-methyl-, 2-bromo-5-methyl-, 2-bromo-6-methyl-, 2-methyl-3-bromo-, 2-methyl-4-bromo-, 2-methyl-5-bromo-, 2-methyl-6-bromo-,

3-bromo-4-methyl-, 3-bromo-5-methyl- or 3-methyl-4-bromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-tri-tert-butylphenyl, furthermore preferably 2-nitro-4-trifluoromethylphenyl, 3,5-ditrifluoromethylphenyl, 2,5-dimethylphenyl, 2-hydroxy-3,5-dichlorophenyl, 2-fluoro-5- or 4-fluoro-3-trifluoromethylphenyl, 4-chloro-2- or 4-chloro-3-trifluoromethyl-, 2-chloro-4- or 2-chloro-5-trifluoromethylphenyl, 4-bromo-2- or 4-bromo-3-trifluoromethylphenyl, p-iodophenyl, 2-nitro-4-methoxyphenyl, 2,5-dimethoxy-4-nitrophenyl, 2-methyl-5-nitrophenyl, 2,4-dimethyl-3-nitrophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3,5-dimethylphenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 2,4-dichloro-5-methylphenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 2-methoxy-5-methylphenyl or 2,4,6-triisopropylphenyl.

$R^1$ is also $Het^1$.

$Het^1$ is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2,4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4-H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-,

6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl.

$R^1$ is very particularly preferably phenyl, p-chlorophenyl, p-fluorophenyl, thiophen-2-yl, 5-chlorothiophen-2-yl, 2,5-dichlorothiophen-3-yl and 2- or 3-furyl.

$R^3$ is preferably unsubstituted, preferably - as indicated - monosubstituted phenyl, specifically preferably phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-trifluoromethoxyphenyl, o-, m- or p-cyanophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-difluoromethoxyphenyl, o-, m- or p-fluoromethoxyphenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2-chloro-3-methyl-, 2-chloro-4-methyl-, 2-chloro-5-methyl-, 2-chloro-6-methyl-, 2-methyl-3-chloro-, 2-methyl-4-chloro-, 2-methyl-5-chloro-, 2-methyl-6-chloro-, 3-chloro-4-methyl-, 3-chloro-5-methyl- or 3-methyl-4-chlorophenyl, 2-bromo-3-methyl-, 2-bromo-4-methyl-, 2-bromo-5-methyl-, 2-bromo-6-methyl-, 2-methyl-3-bromo-, 2-methyl-4-bromo-, 2-methyl-5-bromo-, 2-methyl-6-bromo-, 3-bromo-4-methyl-, 3-bromo-5-methyl- or 3-methyl-4-bromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-tri-tert-butylphenyl, furthermore preferably 2-nitro-4-trifluoromethylphenyl, 3,5-di-trifluoromethylphenyl, 2,5-dimethylphenyl, 2-hydroxy-3,5-dichlorophenyl, 2-fluoro-5- or 4-fluoro-3-trifluoro-

methylphenyl, 4-chloro-2- or 4-chloro-3-trifluoromethyl-, 2-chloro-4- or 2-chloro-5-trifluoromethylphenyl, 4-bromo-2- or 4-bromo-3-trifluoromethylphenyl, p-iodophenyl, 2-nitro-4-methoxyphenyl, 2,5-dimethoxy-4-nitrophenyl, 2-methyl-5-nitrophenyl, 2,4-dimethyl-3-nitrophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3,5-dimethylphenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 2,4-dichloro-5-methylphenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 2-methoxy-5-methylphenyl or 2,4,6-triisopropylphenyl.

$R^3$ is also $Het^2$.

$Het^2$ is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2,4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl,

$R^3$ is very particularly preferably phenyl, p-chlorophenyl, p-fluorophenyl, thiophen-2-yl, 5-chlorothiophen-2-yl, 2,5-dichlorothiophen-3-yl and 2- or 3-furyl.

$R^2$, $R^4$, $R^5$, $R^6$ are in each case independently of one another preferably H, Hal, alkyl having 1-6 C atoms, alkoxy having 1-6 C atoms or hydroxyl, very particularly preferably H, Hal or alkyl having 1-4 C atoms.

Accordingly, the invention relates in particular to those compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following subformulae Ia to Ig, which correspond to the formula I and in which the radicals not designated in greater detail have the meaning indicated in formula I, but in which

in Ia $R^1$ is phenyl;

in Ib $R^1$ is phenyl which is unsubstituted or monosubstituted by Hal;

in Ic $R^1$ is phenyl which is monosubstituted by Hal, or $Het^1$;

in Id $R^1$ is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^1$;

in Ie $R^1$ is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^1$,

$Het^1$ is an unsaturated heterocyclic ring system which is unsubstituted or mono- or disubstituted by Hal or A and contains one or two identical or different heteroatoms such as nitrogen, oxygen and sulfur;

in If $R^1$ is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^1$,

$Het^1$ is an unsaturated heterocyclic ring system which is unsubstituted or mono- or disubstituted by Hal or A and contains one or two identical or different heteroatoms such as nitrogen, oxygen and sulfur,

$R^3$ is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^2$;

in Ig $R^1$ is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^1$,

$Het^1$ is an unsaturated heterocyclic ring system which is unsubstituted or mono- or disubstituted by Hal or A and contains one or two identical or

different heteroatoms such as nitrogen, oxygen and sulfur,

$R^3$ is phenyl which is unsubstituted or monosubstituted by Hal, or $Het^2$,

$Het^2$ is an unsaturated heterocyclic ring system which is mono- or disubstituted by Hal or A and contains a heteroatom such as nitrogen, oxygen and sulfur.

The compounds of the formula I and also the starting substances for their preparation are otherwise prepared by methods known per se, such as are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York), namely under reaction conditions such as are known and suitable for the reactions mentioned. Use can also be made in this case of variants which are known per se, but not mentioned here in greater detail.

If desired, the starting substances for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture, but immediately reacted further to give the compounds of the formula I. On the other hand, it is possible to carry out the reaction stepwise.

In the compounds of the formula II and V, the radical L is preferably Cl or Br; however, it can also be I, OH or otherwise preferably a reactively functionally modified OH group, in particular alkylsulfonyloxy having 1-6 (e.g. methanesulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, 1- or 2-naphthalenesulfonyloxy) or otherwise trichloromethoxy, alkoxy, such as, for example, methoxy, ethoxy, propoxy or butoxy, furthermore also phenoxy.

The compounds of the formula I can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.

As a rule, the starting substances of the formulae II and III are known; the unknown compounds of the formulae II and III can easily be prepared analogously to the known compounds.

The reaction of the compounds II and III proceeds according to methods such as are known from the literature for the alkylation or acylation of amines. However, it is also possible to react the compounds in the presence of an indifferent solvent. Suitable solvents are, for example, hydrocarbons, such as benzene, toluene, xylene; ketones such as acetone, butanone; alcohols such as methanol, ethanol, isopropanol, N-butanol [sic]; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; nitriles such as acetonitrile, and, if appropriate, also mixtures of these solvents with one another or mixtures with water. The addition of an acid-binding agent, for example of an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline earth metals, preferably of potassium, sodium or calcium, or the addition of an organic base such as triethylamine, dimethylaniline, pyridine or quinoline or of an excess of piperazine derivative of the formula II can be favourable. Depending on the conditions used, the reaction time is between a few minutes and 14 days; the reaction temperature between approximately 0 and 150°, normally between 20 and 130°.

In addition, compounds of the formula I can be prepared by reacting amines of the formula IV with a component of the formula V comprising the radical $R^1$.

As a rule, the respective components are known or can be prepared by known processes as already described.

A base of the formula I obtained can be converted into the associated acid addition salt using an acid. For this reaction, suitable acids are those which yield physiologically acceptable salts. Thus inorganic acids can be used, e.g. sulfuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid, sulfamic acid, furthermore organic acids, specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxy-ethanesulfonic acid, benzenesulfonic acid, p-toluene-sulfonic acid, naphthalenemono- and -disulfonic acids and laurylsulfuric acid.

The free bases of the formula I can, if desired, be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide, or sodium or potassium carbonate, if no further acidic groups are present in the molecule. In those cases where the compounds of the formula I have free acid groups, salt formation can likewise be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

The invention furthermore relates to the medicaments according to the invention having 5-$HT_{2A}$ receptor-antagonistic action for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic

lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, anorexia nervosa, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

The invention also relates to a pharmaceutical preparation comprising at least one medicament according to the invention and also, if appropriate, vehicles and/or excipients and, if appropriate, other active compounds.
In this case, the medicaments can be brought into a suitable dose form together with at least one solid, liquid and/or semiliquid vehicle or excipient and, if appropriate, in combination with one or more further active compound(s).

The invention furthermore relates to the use of the compounds according to the invention and/or of their physiologically acceptable salts and solvates for the production of a medicament having 5-$HT_{2A}$ receptor-antagonistic action.

The invention also relates to the use of the compounds according to the invention and/or of their physiologically acceptable salts and solvates for the production of a medicament having 5-$HT_{2A}$ receptor-antagonistic action for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, anorexia nervosa, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

The pharmaceutical preparations can be employed as medicaments in human and veterinary medicine. Suitable carrier substances are organic or inorganic substances

which are suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. In particular, tablets, coated tablets, capsules, syrups, suspensions, drops or suppositories are used for enteral administration, solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the lyophilizates obtained can be used, for example, for the production of injection preparations.

The preparations indicated can be sterilized and/or can contain excipients such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colorants, flavourings and/or aromatizers. They can, if desired, also contain one or more further active compounds, e.g. one or more vitamins.

In this case, the substances according to the invention are as a rule administered in analogy to known preparations, preferably in doses between approximately 0.1 and 500 mg, in particular between 5 and 300 mg, per dose unit. The daily dose is preferably between approximately 0.01 and 250 mg/kg, in particular between 0.02 and 100 mg/kg, of body weight.

In this case, the substances according to the invention as a rule are preferably administered in doses of between approximately 1 and 500 mg, in particular between 5 and 100 mg, per dose unit. The daily dose is preferably between approximately 0.02 and 10 mg/kg of body weight. The specific dose for each intended

patient depends, however, on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and route of administration, on the excretion rate, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

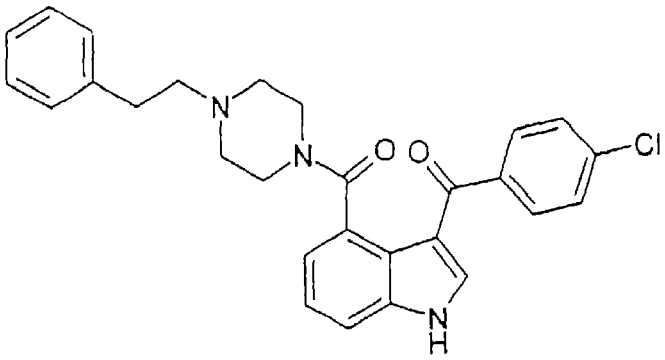
Above and below, all temperatures are indicated in °C. In the examples below, "customary working up" means: if necessary, the solvent is removed, if necessary, water is added, if necessary, the mixture is adjusted, depending on the constitution of the final product, to a pH of between 2 and 10 and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate, filtered and concentrated, and the residue is purified by chromatography on silica gel and/or by crystallization.

Example A1

Preparation of a suspension of 5-$HT_{2A}$ receptors:
Frontal rat cortex is homogenized in ice-cold buffer. The homogenate is centrifuged for 10 minutes at 4°C and 50,000 X [sic]. The pellet is resuspended in 2.5 ml of ice-cold tris buffer, made up with 10 ml of additional buffer and centrifuged as described. The pellet is then resuspended in buffer and diluted to give a homogenate which contains 60 mg of material/ml.
0.1 ml of the suspension, 100 µl of a 5 nM solution of [$^3$H]ketanserin, 100 µl of a solution of the test compound (concentration in the range from $10^{-5}$ to $10^{-10}$ mol per litre) are added to the incubation tubes and made up to 1 ml with buffer. The tubes are incubated for 15 minutes at 37°C. After termination of the incubation by immersing the tubes in an ice bath, the cooled suspension is filtered through a glass filter in vacuo. The filters are washed 3 × with 5 ml of cold buffer and then transferred to scintillation tubes. The filters are analysed by means of liquid scintillation spectrometry in 8 ml of Triton X scintillator fluid.

Example 1

A solution of 4-carboxy-3-(4-chlorobenzoyl)indole and 2-chloro-1-methylpyridinium iodide in N-methyl-pyrrolidone (NMP) is treated with a solution of 4-phenethylpiperazine and ethyldiisopropylamine (EDIPA) in NMP and subsequently stirred at room temperature for 3 hours. The mixture is worked up in the customary manner and the crude product is obtained. This is dissolved in acetone and the hydrochloride is precipitated using aqueous hydrochloric acid. After drying, [3-(4-chlorobenzoyl)-1*H*-indol-4-yl]-4-phenethylpiperazin-1-ylmethanone, hydrochloride hydrate, m.p. 187.4°, is obtained.



The compounds below are obtained analogously

[3-(4-chlorobenzoyl)-1*H*-indol-4-yl]-[4-(4-fluorophenethyl)piperazin-1-yl]methanone,
[3-(4-chlorobenzoyl)-1*H*-indol-4-yl]-[4-(thiophen-2-yl)piperazin-1-yl]methanone,
[3-(4-chlorobenzoyl)-1*H*-indol-4-yl]-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
[3-(4-chlorobenzoyl)-1*H*-indol-4-yl]-[4-(thiophen-3-yl)piperazin-1-yl]methanone,
[3-(4-chlorobenzoyl)-1*H*-indol-4-yl]-[4-(2,5-dichlorothiophen-3-yl)piperazin-1-yl]methanone,
[3-(4-chlorobenzoyl)-1*H*-indol-4-yl]-[4-(furan-2-yl)-piperazin-1-yl]methanone,

[3-(4-fluorobenzoyl)-1*H*-indol-4-yl]-(4-phenethylpiperazin-1-yl)methanone, hydrochloride, m.p. 139-141°;
[3-(4-fluorobenzoyl)-1*H*-indol-4-yl]-[4-(4-fluorophenethyl)piperazin-1-yl]methanone,
[3-(4-chlorobenzoyl)-1*H*-indol-4-yl]-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 232°;
[3-(4-fluorobenzoyl)-1*H*-indol-4-yl]-[4-(thiophen-2-yl)-piperazin-1-yl]methanone,
[3-(4-fluorobenzoyl)-1*H*-indol-4-yl]-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
[3-(4-fluorobenzoyl)-1*H*-indol-4-yl]-[4-(thiophen-3-yl)piperazin-1-yl]methanone,
[3-(4-fluorobenzoyl)-1*H*-indol-4-yl]-[4-(2,5-dichlorothiophen-3-yl)piperazin-1-yl]methanone,

[3-(4-fluorobenzoyl)-1*H*-indol-4-yl]-[4-(furan-2-yl)piperazin-1-yl]methanone,

[3-(4-fluorobenzoyl)-1*H*-indol-5-yl]-(4-phenethyl-piperazin-1-yl)methanone, hydrochloride, m.p. 139-141°;
[3-(4-chlorobenzoyl)-1*H*-indol-5-yl]-(4-phenethylpiperazin-1-yl)methanone, m.p. 168.5°;
[3-(4-fluorobenzoyl)-1*H*-indol-5-yl]-[4-(4-fluorophen-ethyl)piperazin-1-yl]methanone, hydrochloride, m.p. 198-200°;
[3-(4-fluorobenzoyl)-1*H*-indol-5-yl]-[4-(thiophen-2-yl)piperazin-1-yl]methanone,
[3-(4-fluorobenzoyl)-1*H*-indol-5-yl]-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
[3-(4-fluorobenzoyl)-1*H*-indol-5-yl]-[4-(thiophen-3-yl)piperazin-1-yl]methanone,
[3-(4-fluorobenzoyl)-1*H*-indol-5-yl]-[4-(2,5-dichlorothiophen-3-yl)piperazin-1-yl]methanone,
[3-(4-fluorobenzoyl-2-yl)-1*H*-indol-5-yl]-[4-(furan-2-yl)piperazin-1-yl]methanone,

[3-(furan-2-yl)-1*H*-indol-4-yl]-(4-phenethylpiperazin-1-yl)methanone,
[3-(furan-2-yl)-1*H*-indol-4-yl]-[4-(4-fluorophenethyl)-piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-4-yl]-[4-(thiophen-2-yl)-piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-4-yl]-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-4-yl]-[4-(thiophen-3-yl)-piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-4-yl]-[4-(2,5-dichloro-thiophen-3-yl)piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-4-yl]-[4-(furan-2-yl)-piperazin-1-yl]methanone,

[3-(furan-2-yl)-1*H*-indol-5-yl]-(4-phenethylpiperazin-1-yl)methanone, hydrochloride, m.p. 268-269°;

[3-(furan-2-yl)-1*H*-indol-5-yl]-[4-(4-fluorophenethyl)-piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-5-yl]-[4-(thiophen-2-yl)-piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-5-yl]-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-5-yl]-[4-(thiophen-3-yl)-piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-5-yl]-[4-(2,5-dichloro-thiophen-3-yl)piperazin-1-yl]methanone,
[3-(furan-2-yl)-1*H*-indol-5-yl]-[4-(furan-2-yl)-piperazin-1-yl]methanone,

[3-(thiophen-2-yl)-1*H*-indol-4-yl]-(4-phenethyl-piperazin-1-yl)methanone,
[3-(thiophen-2-yl)-1*H*-indol-4-yl]-[4-(4-fluorophen-ethyl)piperazin-1-yl]methanone,
[3-(thiophen-2-yl)-1*H*-indol-4-yl]-[4-(thiophen-2-yl)-piperazin-1-yl]methanone,
[3-(thiophen-2-yl)-1*H*-indol-4-yl]-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
[3-(thiophen-2-yl)-1*H*-indol-4-yl]-[4-(thiophen-3-yl)-piperazin-1-yl]methanone,
[3-(thiophen-2-yl)-1*H*-indol-4-yl]-[4-(2,5-dichloro-thiophen-3-yl)piperazin-1-yl]methanone,
[3-(thiophen-2-yl)-1*H*-indol-4-yl]-[4-(furan-2-yl)-piperazin-1-yl]methanone,

[3-(thiophen-2-yl)-1*H*-indol-5-yl]-(4-phenethyl-piperazin-1-yl)methanone, hydrochloride, m.p. 191-192°;
[3-(thiophen-2-yl)-1*H*-indol-5-yl]-[4-(4-fluorophen-ethyl)piperazin-1-yl]methanone,
[3-(thiophen-2-yl)-1*H*-indol-5-yl]-[4-(thiophen-2-yl)-piperazin-1-yl]methanone,
[3-(thiophen-2-yl)-1*H*-indol-5-yl]-[4-(5-chlorothiophen-2-yl)piperazin-1-yl]methanone,
[3-(thiophen-2-yl)-1*H*-indol-5-yl]-[4-(thiophen-3-yl)-piperazin-1-yl]methanone,

[3-(thiophen-2-yl)-1*H*-indol-5-yl]-[4-(2,5-dichloro-thiophen-3-yl)piperazin-1-yl]methanone,
[3-(thiophen-2-yl)-1*H*-indol-5-yl]-[4-(furan-2-yl)-piperazin-1-yl]methanone.

Example 2

By catalytic hydrogenation with hydrogen and Pd/C in methanol, from [3-(4-chlorobenzoyl)-1*H*-indol-4-yl]-[4-(4-fluorophenethyl)piperazin-1-yl]methanone, the compound
[3-benzoyl-1*H*-indol-4-yl]-[4-(4-fluorophenethyl)-piperazin-1-yl]methanone, hydrochloride, m.p. 257°, is obtained.

The following examples relate to pharmaceutical preparations:

**Example A: Injection vials**

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile-filtered, filled into injection vials, lyophilized and aseptically sealed. Each injection vial contains 5 mg of active compound.

**Example B: Suppositories**

A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

**Example C: Solution**

A solution is prepared from 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \times 2H_2O$, 28.48 g of $NaH_2PO_4 \times 12H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

**Example D: Ointment**

500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

**Example E: Tablets**

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed in a customary manner to give tablets such that each tablet contains 10 mg of active compound.

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**Example F: Coated tablets**

Analogously to Example E, tablets are pressed and are then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colorant.

**Example G: Capsules**

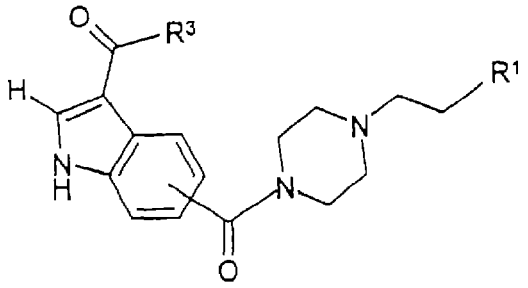
2 kg of active compound of the formula I are filled into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

**Example H: Ampoules**

A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is filled into ampoules, lyophilized under aseptic conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

# Patent Claims

1. Compounds of the formula I



I

in which

$R^1$ is a phenyl radical which is unsubstituted or substituted by $R^2$ and/or $R^4$ or is $Het^1$,

$R^2$, $R^4$, $R^5$, $R^6$ in each case independently of one another are Hal, A, OA, OH, CN or acyl,

$R^3$ is a phenyl radical which is unsubstituted or substituted by $R^5$ and/or $R^6$ or is $Het^2$,

$Het^1$ is a mono- or binuclear unsaturated heterocyclic ring system, which is unsubstituted or mono- or disubstituted by Hal, A, OA or OH and contains one, two or three identical or different heteroatoms such as nitrogen, oxygen and sulfur,

$Het^2$ is an unsaturated heterocyclic ring system which is unsubstituted or mono- or disubstituted by Hal, A, OA and contains one or two identical or different heteroatoms such as nitrogen, oxygen and sulfur,

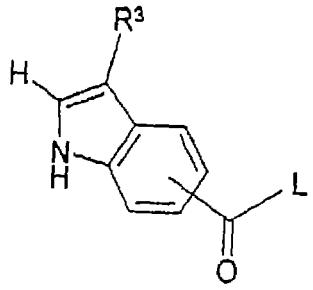
A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

and their physiologically acceptable salts and solvates.

2. Process for the preparation of compounds of the formula I according to Claim 1, characterized in that

a) a compound of the formula II



II

in which L is Cl, Br, I or alkylsulfonyloxy having 1-6 or arylsulfonyloxy having 6-10 C atoms or trichloromethoxy, alkoxy or phenoxy

and $R^3$ has the meaning indicated in Claim 1,

is reacted with a compound of the formula III

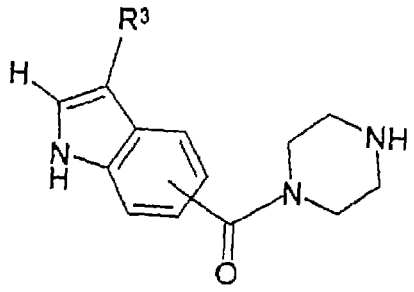


III

in which $R^1$ has the meaning indicated in Claim 1,

or

b) a compound of the formula IV



IV

in which $R^3$ has the meaning indicated in Claim 1,

is reacted with a compound of the formula V

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$L\text{-}CH_2\text{-}CH_2\text{-}R^1$ V

in which L is Cl, Br, I or a free or reactively functionally modified OH group, and $R^1$ has the meaning indicated in Claim 1,

or

c) if appropriate, one of the radicals $R^1$ and/or $R^3$ is converted into another radical $R^1$ and/or $R^3$ by cleaving, for example, an OA group with formation of an OH group and/or converting a CHO group into a CN group,

and/or
a base of the formula I which is obtained is converted into one of its salts by treating with an acid.

3. Compounds of the formula I according to Claim 1, and their physiologically acceptable salts and solvates as medicaments.

4. Compounds of the formula I according to Claim 1, and their physiologically acceptable salts and solvates as medicaments having 5-$HT_{2A}$ receptor-antagonistic action.

5. Medicament according to Claim 4 for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, anorexia nervosa, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).

6. Pharmaceutical preparation, comprising at least one medicament according to Claim 5, and optionally vehicles and/or excipients and optionally other active compounds.

7. Use of compounds according to Claim 1 and/or of their physiologically acceptable salts and solvates for the production of a medicament having 5-$HT_{2A}$ receptor-antagonistic action.

8. Use according to Claim 7 for the production of a medicament for the treatment of psychoses, schizophrenia, depression, neurological disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia, anorexia nervosa, premenstrual syndrome and/or for positively affecting compulsive behaviour (obsessive-compulsive disorder, OCD).