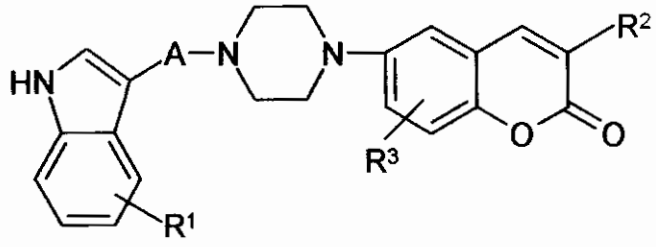
Chromenoneindoles

The invention relates to chromenoneindole derivatives of the formula I



I

in which

- R^1 is H, OH, CN, Hal, CONHR, OB, CO_2B, CF_3, NR_2, NRCOR, NRCOOR or $NRCONR_2$,
- R^2 is NR_2, NRCOR, NRCOOR, $NRCONR_2$, NO_2, $NRSO_2R_2$, NRCSR or $NRCSNR_2$,
- R^3 is H, OH, CN, Hal, CONHR, OB, CO_2B, CF_3, NO_2, NR_2, NRCOR, NRCOOR or $NRCONR_2$,
- R, independently of one another, are H, B, Het or Ar,
- A is a straight-chain or branched, mono- or polyunsaturated carbon chain having 2, 3, 4, 5 or 6 C atoms,
- B is a straight-chain or branched alkyl radical having 1, 2, 3, 4, 5 or 6 C atoms,

and pharmaceutically usable prodrugs, derivatives, solvates, stereoisomers and salts thereof, including mixtures thereof in all ratios.

The invention had the object of finding novel compounds which have high bioavailability and are capable of significantly increasing the serotonin level in the brain.

It has been found that the compounds of the formula I and pharmaceutically usable prodrugs, derivatives, solvates, stereoisomers and salts thereof have valuable pharmacological properties. The compounds of the formula I exhibit particular actions on the central nervous system, in particular 5-HT reuptake-inhibiting and 5-HT_x-agonistic and/or -antagonistic actions, where HT_x is taken to mean HT_{1A}, HT_{1D}, HT_{2A} and/or HT_{2C}.

Compounds having a similar structure are described in DE 197 30 989. It has now been found that a group of certain chromenoneindoles, more precisely those in which R^2 is one of the radicals NR_2, NRCOR, NRCOOR, $NRCONR_2$, NO_2, $NRSO_2R_2$, NRCSR or $NRCSNR_2$, have significantly higher bioavailability compared with other chromenoneindoles and/or cause a significantly higher serotonin level in the brain (see Figs. 1, 2 and 3). The compounds according to the invention should thus be regarded as a selection invention with respect to the said application.

Since the compounds inhibit serotonin reuptake, they are particularly suitable as antipsychotics, neuroleptics, antidepressants, anxiolytics and/or antihypertonics. The compounds exhibit serotonin-agonistic and -antagonistic properties. They inhibit the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol. 140 (1987), 143–155) and synaptosomal serotonin reuptake (Sherman et al., Life Sci. 23 (1978) , 1863–1870). In addition, changes in DOPA accumulation in the striatum and 5-HT accumulation in various regions of the brain occur (Seyfried et al., European J. Pharmacol. 160 (1989), 31-41). The 5-HT_{1A}-antagonistic action is demonstrated in vitro, for example by inhibition of the abolition of electrically induced contraction of the guinea pig ileum caused by 8-OH-DPAT (Fozard and Kilbinger, Br. J.

Pharmacol. 86 (1985) 601P). The 5-HT_{1A}-antagonistic action is detected ex vivo by inhibition of 5-HTP accumulation reduced by 8-OH-DPAT (Seyfried et al., European J. Pharmacol. 160 (1989), 31-41) and the antagonisation of 8-OH-DPAT-induced effects in the ultrasound vocalisation test (DeVry, Psychpharmacol. 121 (1995), 1–26). Inhibition of serotonin reuptake can be detected ex vivo using syntaptosomal uptake inhibition (Wong et al., Neuropsychopharmacol. 8 (1993), 23–33) and p-chloroamphetamine antagonism (Fuller et al., J. Pharmacol. Exp. Ther. 212 (1980), 115–119). Furthermore, analgesic and hypotensive actions occur.

The compounds are therefore suitable for the treatment of schizophrenia, cognitive deficits, anxiety, depression, nausea, tardive dyskinesia, gastrointestinal tract disorders, learning disorders, age-related memory disorders, psychoses and for positively influencing obsessive-compulsive disorder (OCD) and eating disorders (for example bulimia). They exhibit actions on the central nervous system, in particular additional 5-HT_{1A}-agonistic and 5-HT reuptake-inhibiting actions. They are likewise suitable for the prophylaxis and the combating of the consequences of cerebral infarction (apoplexia cerebri), such as strokes and cerebral ischaemia, and for the treatment of extrapyramidal motor side effects of neuroleptics and of Parkinson's disease.

The compounds of the formula I are therefore suitable both in veterinary and in human medicine for the treatment of dysfunctions of the central nervous system and of inflammation. They can be used for the prophylaxis of and for combating the consequences of cerebral infarction (apoplexia cerebri), such as strokes and cerebral ischaemia, and for the treatment of extrapyramidal motor side effects of neuroleptics and of Parkinson's disease, for the acute and symptomatic therapy of Alzheimer's disease and for the treatment of amyotrophic lateral sclerosis. They are likewise

suitable as therapeutic agents for the treatment of brain and spinal cord trauma. However, they are also suitable as medicament active ingredients for anxiolytics, antidepressants, antipsychotics, neuroleptics, antihypertonics and/or for positively influencing obsessive-compulsive disorder, sleeping disorders, tardive dyskinesia, learning disorders, age-related memory disorders, eating disorders, such as bulimia, and/or sexual dysfunctions.

The invention preferably relates to compounds of the formula I in which the radical R^1 is CN or Hal, where CN is preferred, and R, R^2, R^3, A and B are as defined above and below for the compounds of the formula I.

Preference is furthermore given to compounds of the formula I in which the radical R^3 is H, where R, R^1, R^2, A and B are as defined above and below for the compounds of the formula I.

Preference is likewise given to compounds of the formula I in which the radical R^2 is NRCOR or NRCOOR, where R, independently of one another, can be H, B, Het or Ar, and R^1, R^3, A and B are as defined above and below for the compounds of the formula I.

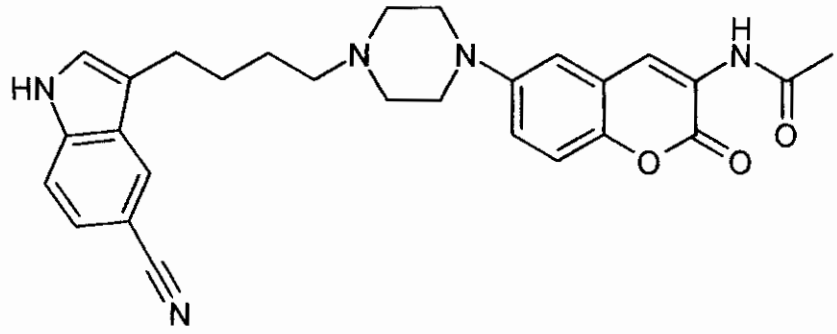
Preference is also given to the compounds of the formula I in which A is $(CH_2)_m$, where m = 2, 3, 4, 5 or 6, particularly preferably 4, and R, R^1, R^2, R^3 and B are as defined above and below for the compounds of the formula I.

Particular preference is given to the compounds of the formula I in which R^1 is CN or Hal, where CN is preferred, and R^3 is H, where R, R^2, A and B are as defined above and below for the compounds of the formula I.

Very particular preference is given to the compounds of the formula I in which R^1 is CN, R^3 is H, and A is $(CH_2)_m$, where m = 4, and R, R^2 and B are as defined above and below for the compounds of the formula I.

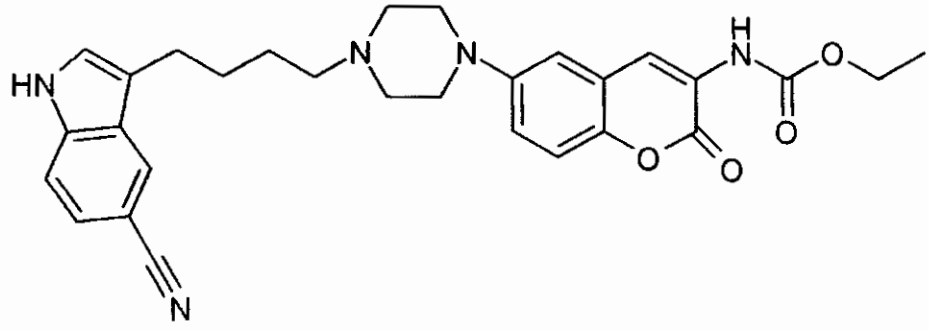
In particularly preferred embodiments, the indole radical is substituted by R^1 in the 5-position, furthermore also in the 6- or 7-position.

In a very particularly preferred embodiment of the present invention, the compounds of the formula I are selected from the following sub-formulae Ia to Ie:



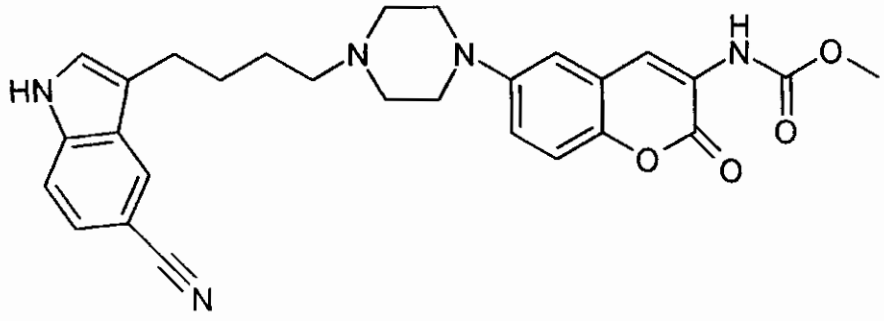
*HCl a

N-(6-{4-[4-(5-Cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)methylamide (HCl) (EMD 391987)



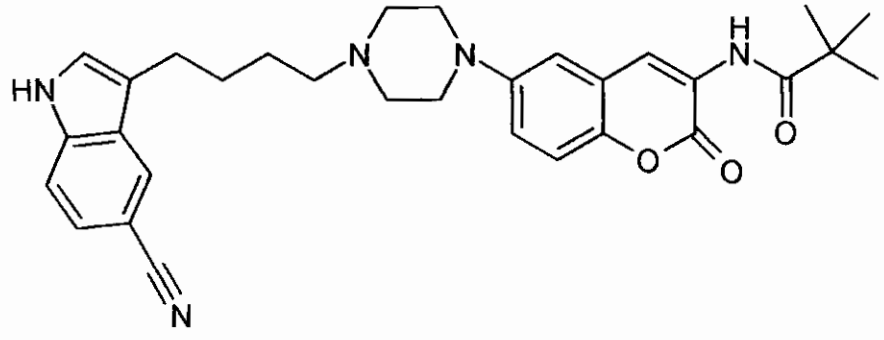
b

Ethyl (6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)carbamate (EMD 480247)



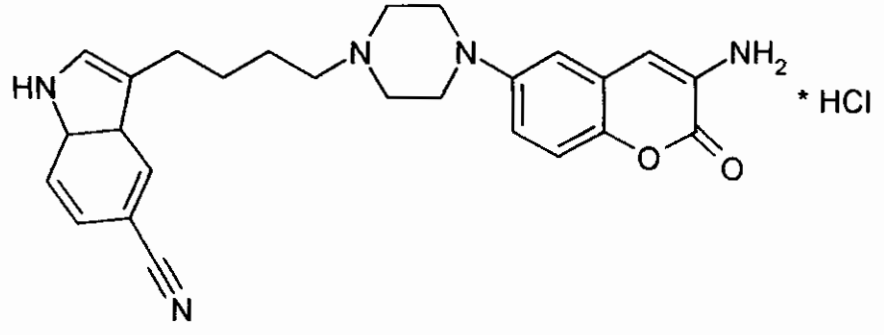
c

Methyl N-(6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)carbamate (EMD 487535)



d

N-(6-{4-[4-(5-Cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)-2,2-dimethylpropionamide (EMD 480248)



e

3-{4-[4-(3-Amino-2-oxo-2H-chromen-6-yl)piperazin-1-yl]butyl}-1H-indole-5-carbonitrile (HCl) (EMD 480246)

For all radicals which occur more than once, such as, for example, R or B, their meanings are independent of one another.

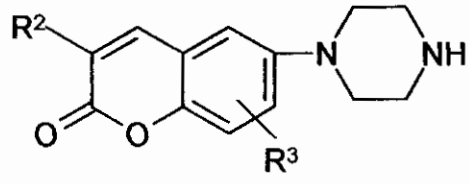
The radical B is alkyl and has 1, 2, 3, 4, 5 or 6, in particular 1, 2, 3 or 4, C atoms. Alkyl is a linear or branched alkyl radical, preferably an unbranched alkyl radical, and may be mono- or poly- by halogen (Hal), for example perfluorinated. If an alkyl radical is substituted by halogen, it preferably, depending on the number of carbon atoms in the alkyl radical, has 1, 2, 3, 4 or 5 halogen atoms. If an alkyl radical is substituted by halogen, it preferably, depending on the number of carbon atoms in the alkyl radical, has 1, 2, 3, 4 or 5 halogen atoms. Examples of alkyl groups are therefore methyl, ethyl or isopropyl, furthermore n-propyl, 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, furthermore also fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trichloroethyl or pentafluoroethyl.

The term "aryl" covers an unsubstituted or mono- or polysubstituted aromatic mono-, bi- or tricyclic hydrocarbon radical, such as, for example, a benzene ring or anthracene, phenanthrene or naphthalene ring systems. Examples of suitable substituents include NO_2-, F-, Cl-, Br-, I-, HO-, H_2N-, R^3HN-, $(R^3)_2N$-, alkyl-, alkyl-O-, CF_3-O-, alkyl-CO-, aryl-, aryl-O-, aryl-CO-, aryl-CONH-, $arylSO_2$- or $arylSO_2$-HN-, where the substituents may occur, independently of one another, 0 to 5 times.

The term "Het" covers an unsubstituted or mono- or polysubstituted, saturated, unsaturated or aromatic mono-, bi- or tricyclic heterocyclic radical. As hetero atoms, S, N or O may occur once to three times. Examples of suitable substituents include NO_2-, F-, Cl-, Br-, I-, HO-, H_2N-, R^3HN-, $(R^3)_2N$-, alkyl-, alkyl-O-, CF_3-O-, alkyl-CO-, aryl-, aryl-O-, aryl-CO-,

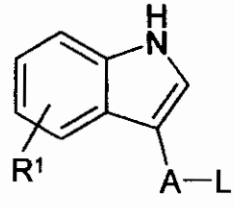
aryl-CONH-, aryl-SO_2- and aryl-SO_2-HN-, where the substituents may occur, independently of one another, 0 to 5 times.

The invention furthermore relates to a process for the preparation of the compounds of the formula I and pharmaceutically usable prodrugs, derivatives, solvates, stereoisomers and salts thereof, characterised in that a compound of the formula II



II

in which R^2 and R^3 are as defined above and below for the compounds of the formula I, is reacted with a compound of the formula III

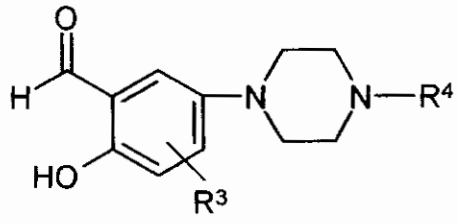


III

in which R^1 and A are as defined above and below for the compounds of the formula I, and L is Cl, Br, I, OH or a reactively esterified OH group or another readily nucleophilically substitutable leaving group, such as alkylsulfonyloxy having 1-6 C atoms (for example methanesulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (for example benzenesulfonyloxy, p-toluenesulfonyloxy or 1- or 2- naphthalenesulfonyloxy), where I is preferred.

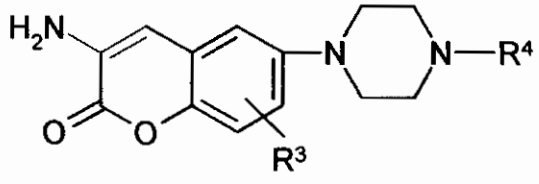
The present invention likewise relates to a process for the preparation of the compounds of the formula I and pharmaceutically usable prodrugs,

derivatives, solvates, stereoisomers and salts thereof, characterised in that a compound of the formula IV



IV

in which R^3 is as defined above and below for the compounds of the formula I, and R^4 is an amino-protecting group or H, is reacted, in a Michael-analogous reaction, with ethyl nitroacetate and diethylammonium chloride, and the nitro group is subsequently reduced, to give the compound of the formula V



V

and the compound of the formula V is reacted with a compound conforming to the formula III.

In addition, the compounds of the formula I are prepared by methods known per se, as described, for example, in Houben-Weyl (Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York) or in DE 197 30 989, to be precise under reaction conditions as are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

The starting materials for the claimed process may also, if desired, be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I.

The majority of the piperazine derivatives of the formula III are known. If they are not commercially available or known, they can be prepared by methods known per se. For example, they can be prepared by reaction of bis(2-chloroethyl)amine or bis(2-chloroethyl)ammonium chloride with amino-substituted benzopyran compounds.

The majority of the indole derivatives of the formula II are known and some are also commercially available. Furthermore, the compounds can be prepared from known compounds by electrophilic or in certain cases also nucleophilic aromatic substitutions. The starting substance used is preferably a corresponding indole-3-alkanoic acid (which can be prepared analogously to a Japp-Klingemann-type Fischer indole synthesis, cf. in this respect Böttcher et al., J. Med. Chem. 1992, 35, 4020–4026 or Iyer et al., J. Chem. Soc. Perkin Trans. II 1973, 872–878).

Primary alcohols of the formula III in which L is an OH group are obtainable, for example, by reduction of the corresponding carboxylic acids or esters thereof. Treatment with thionyl chloride, hydrogen bromide, phosphorus tribromide or similar halogen compounds gives the corresponding halides of the formula III in which L is a halogen. The corresponding sulfonyloxy compounds are obtainable from the alcohols by reaction with the corresponding sulfonyl chlorides. The iodine compounds of the formula III (L = I) are obtainable, for example, by the action of potassium iodide on the associated p-toluenesulfonic acid esters or corresponding chlorides.

Some of the starting materials of the formula IV are known. If they are not known, they can be prepared by methods known per se.

The reaction of the compounds II and III as well as V and III proceeds by methods as are known from the literature for the alkylation or acylation of amines. The components can be melted with one another without the presence of a solvent, if desired in a sealed tube or in an autoclave. However, it is also possible to react the compounds in the presence of an inert solvent. Suitable solvents are, for example, hydrocarbons, such as benzene, toluene or xylene; ketones, such as acetone or butanone; alcohols, such as methanol, ethanol, isopropanol or N-butanol; ethers, such as tetrahydrofuran (THF) or dioxane; amides, such as dimethylformamide (DMF) or N-methylpyrrolidone; nitriles, such as acetonitrile, if desired also mixtures of these solvents with one another or mixtures with water. The addition of an acid-binding agent, for example an alkali 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 an excess of piperazine derivative of the formula II may be favourable. Depending on the conditions used, the reaction time is between a few minutes and 14 days, and the reaction temperature is between about 0 and 150°, normally between 20 and 130°.

Where appropriate, it is necessary to protect further amino groups present against alkylation or acylation by introducing suitable protecting groups before these reactions are carried out. The term "amino-protecting group" is known in general terms and relates to groups which are suitable for protecting an amino group against chemical reactions, but are easily removable after the desired chemical reaction has been carried out elsewhere in the molecule. Since protecting groups of this type and the introduction and removal thereof are well known to the person skilled in the art from numerous references and textbooks, this need not be discussed in greater detail at this point.

It is furthermore possible to obtain a compound of the formula I by treating a precursor containing one or more reducible group(s) instead of hydrogen atoms and/or one or more additional C-C and/or C-N bond(s) with a reducing agent, preferably at temperatures between -80 and +250° in the presence of at least one inert solvent. Reducible (hydrogen-replaceable) groups are, in particular, oxygen in a carbonyl group, hydroxyl, aryl-sulfonyloxy (for example p-toluenesulfonyloxy), N-benzenesulfonyl, N-benzyl or O-benzyl.

It is in principle possible to convert compounds containing only one or those simultaneously containing two or more of the above-mentioned groups or additional bonds into a compound of the formula I by reduction; at the same time, substituents in the group I which are present in the starting compound can be reduced. This is preferably carried out using nascent hydrogen or complex metal hydrides, furthermore the Wolff-Kishner reduction or reduction is preferably carried out using hydrogen gas with transition-metal catalysis.

If the reducing agent used is nascent hydrogen, this can be generated, for example, by treatment of metals with weak acids or with bases. Thus, for example, a mixture of zinc with alkali metal hydroxide solution or of iron with acetic acid can be used. Also suitable is the use of sodium or another alkali metal dissolved in an alcohol, such as ethanol, isopropanol, butanol, amyl alcohol, isoamyl alcohol or phenol. It is furthermore possible to use an aluminium/nickel alloy in alkaline/aqueous solution, if desired with addition of ethanol. Sodium amalgam or aluminium amalgam in aqueous/alcoholic or aqueous solution is also suitable for generation of the nascent hydrogen. The reaction can also be carried out in the heterogeneous phase, in which case it is advantageous to use an aqueous phase and a benzene or toluene phase.

Reducing agents which can be employed are furthermore particularly advantageously complex metal hydrides, such as $LiAlH_4$, $NaBH_4$, diisobutylaluminium hydride or $NaAl(OCH_2CH_2OCH_3)_2H_2$ as well as diborane, if desired with addition of catalysts, such as BF_3, $AlCl_3$ or LiBr. Suitable solvents for this purpose are, in particular, ethers, such as diethyl ether, di-n-butyl ether, THF, dioxane, diglyme or 1,2-dimethoxyethane, and hydrocarbons, such as benzene. For the reduction using $NaBH_4$, suitable solvents are primarily alcohols, such as methanol or ethanol, furthermore water, and aqueous alcohols. By these methods, the reduction is preferably carried out at temperatures between -80 and +150°, in particular between about 0 and about 100°.

In addition, it is possible to carry out certain reductions through the use of H_2 gas with the catalytic action of transition metals, such as, for example, Raney Ni or Pd. In this way, for example, Cl, Br, I, SH or in certain cases also OH groups can be replaced by hydrogen. The NH_2 group in the compound of the formula V can likewise be obtained from the nitro group by catalytic hydrogenation using Pd/H_2 in methanol.

Compounds which otherwise conform to the formula I, but contain one or more solvolysable group(s) instead of one or more H atoms can be solvolysed, in particular hydrolysed, to the compounds of the formula I.

Furthermore, a compound of the formula I can be converted into another compound of the formula I by methods known per se.

Compounds of the formula I in which R^1 is a CONHR radical can be obtained by derivatisation of corresponding substituted compounds of the formula I by partial hydrolysis. It is furthermore possible firstly to hydrolyse cyano-substituted compounds of the formula I to acids and to amidate the acids using primary or secondary amines. Preference is given to the

reaction of the free carboxylic acid with the amine under the conditions of a peptide synthesis. This reaction preferably succeeds in the presence of a dehydrating agent, for example a carbodiimide, such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N-ethylcarbodiimide, furthermore propanephosphonic anhydride (cf. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, for example a halogenated hydrocarbon, such as dichloromethane, an ether, such as THF or dioxane, an amide, such as DMF or dimethylacetamide, or a nitrile, such as acetonitrile, at temperatures between about -10 and 40°, preferably between 0 and 30°. Instead of the acid or amide, it is also possible to employ reactive derivatives of these substances in the reaction, for example those in which reactive groups are temporarily blocked by protecting groups.
The acids can also be used in the form of their activated esters, which are advantageously formed in situ, for example by addition of 1-hydroxybenzotriazole or N-hydroxysuccinimide. Thus, it is also possible, for example, for cyano-substituted indole radicals to be hydrolysed to carboxyindole or carboxamidoindole radicals.

However, it is also particularly favourable to prepare the nitriles in the reverse manner, by elimination of water, starting from the amides, for example by means of trichloroacetyl chloride/Et_3N [Synthesis (2), 184 (1985)] or using $POCl_3$ (J. Org. Chem. 26, 1003 (1961)).

A resultant base of the formula I can be converted into the associated acid-addition salt using an acid. Suitable acids for this reaction are those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example 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-hydroxyethane-sulfonic acid; benzenesulfonic acid, p-toluenesulfonic acid, naphthalene-mono- and -disulfonic acids, 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 hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate, so long as no further acidic groups are present in the molecule. In those cases where the compounds of the formula I contain 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 pharmacological properties of the compounds of the formula I according to the invention were tested as follows:

The bioavailability was determined by a standard method described in many textbooks of pharmacokinetics with the aid of the AUC (area under the concentration/time curves) measured after po and iv administration. For the determination of the absolute bioavailability, the plasma concentration curve of the said substances was determined after intravenous (iv) and oral (po) administration to Wistar rats (male; N = 3 animals/administration). The following experiment design was selected:

Administration method: iv and po

Dose: iv - 0.2 mg/kg; po - 0.5 mg/kg

Time of blood sampling for the determination of the plasma concentrations:

iv: 0.1, 0.5, 1, 2, 4, 6 and 24 h

po: 0.25, 0.5, 1, 2, 4, 6 and 24 h

The plasma concentrations were determined with the aid of LC/MS/MS.

The plasma concentrations were used to calculate the AUC (area under the concentration/time curve) in accordance with the so-called trapezium formula.

The bioavailability is obtained from the AUC in accordance with the following formula:

Bioavailability [%] = 100 x (AUC po) / AUC iv) / (dose iv / dose po)

This measurement gave a bioavailability of 10% for the compound 3-(4-(4-(2-oxo-2H-1-benzopyran-6-yl)-1-piperazinyl)butyl)indole-5-carbonitrile (EMD 135894) described in DE 197 30 989.

By contrast, the bioavailability of the compound ethyl (6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)carbamate (see formula Ib; EMD 480247) was significantly higher, namely about 20%.

In order to determine the effect of the substances on the cortical serotonin level in rats in vivo, a microdialysis probe with a semipermeable membrane was implanted into the brain tissue and perfused with a solution matched to the composition of cerebrospinal fluid (see in this respect, for example, Di Chiara, Trends Pharmacol. Sci. 11, 117 – 121, 1990). The molecules of the extracellular space, such as, for example, also of the neurotransmitter serotonin, diffuse via this membrane into the interior of the probe in accordance with their concentration gradient. From there, they are transported with the perfusion stream to a collecting vessel. The

serotonin concentration in the dialysate obtained in this way is subsequently determined by means of high-sensitivity analytical methods. The fractions obtained at regular intervals (of, for example, 15 – 20 minutes) thus reflect the concentration changes of the transmitter in question in the brain tissue over a period of several hours. The concentration of the serotonin in the dialysate is firstly measured without any influence. The substance to be tested is then applied, and the serotonin concentrations before and after administration of the substances are compared.

As can be seen from Fig. 1, the administration of the compound EMD 391987 (see formula Ia) results in a significantly higher serotonin level in the brain than administration of the same concentration (1 mg/kg i.p.) of the compound 3-(4-(4-(2-oxo-2H-1-benzopyran-6-yl)-1-piperazinyl)butyl)-indole-5-carbonitrile (EMD 135894), which is described in DE 197 30 989 and has been selected as comparative substance.

Vilazodone (5-{4-[4-(5-cyano-3-inolyl)butyl]-1-piperanzinyl}benzofuran-2-carboxamide; EMD 68843), which is described in EP 0 648 767 B1 and is already in clinical trials, was also employed as comparative compound since it likewise has 5-HT reuptake-inhibiting and 5-HT_x-agonistic and/or -antagonistic properties. EMD 391987 also results in a significantly higher serotonin level in the brain compared with this compound, which causes a comparable increase in the concentration of serotonin in the brain to EMD 135894.

As shown by Figure 2, a further substance of the formula I according to the invention, 3-{4-[4-(3-amino-2-oxo-2H-chromen-6-yl)piperazin-1-yl]butyl}-1H-indole-5-carbonitrile (EMD 480246, see formula Ie), results in an even higher serotonin level than EMD 391987, which is itself superior to the comparative compounds EMD 68843 and EMD 135894.

Ethyl (6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)carbamate (EMD 480247, see formula Ib) also exhibits a clearly superior action to vilazodone (EMD 68843) (see Fig. 3).

Consequently, the compounds of the formula I according to the invention are clearly superior to the other compounds described in DE 197 30 989 and EP 0 648 767 B1 with respect to bioavailability and the increase in serotonin levels or inhibition of serotonin reuptake.

The invention furthermore relates to the use of the compound of the formula I and pharmaceutically usable prodrugs, derivatives, solvates, stereoisomers and salts thereof, including mixtures thereof in all ratios, for the preparation of pharmaceutical preparations, in particular by non-chemical methods. They can be converted here, for example, into a suitable dosage form together with a solid, liquid or semi-liquid excipient or adjuvant and optionally in combination with one or more further active ingredient(s).

The invention furthermore relates to compositions, in particular pharmaceutical preparations, comprising at least one compound of the formula I and/or one of its pharmaceutically usable prodrugs, derivatives, solvates, stereoisomers and salts. These preparations can be employed as medicaments in human and veterinary medicine. Suitable carrier substances are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or Vaseline. Suitable for enteral administration are, in particular, tablets, coated tablets, capsules, syrups, juices, drops or suppositories, suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments,

creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations.

The stated preparations may be sterilised and/or comprise adjuvants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, colorants, flavours and/or aroma substances. If desired, they may also comprise one or more further active ingredients, for example one or more vitamins.

The compounds of the formula I and pharmaceutically usable prodrugs, derivatives, solvates, stereoisomers and salts thereof can be used in the therapeutic treatment of the human or animal body and in the combating of diseases. They are suitable for the treatment of diseases of the central nervous system, such as states of tension, depression, anxiety states, schizophrenia, gastrointestinal tract disorders, nausea, tardive dyskinesia, Parkinson's disease and/or psychoses and of side effects in the treatment of hypertonia (for example using α-methyldopa). The compounds can furthermore be used in endocrinology and gynaecology, for example for the therapy of acromegalia, hypogonadism, secondary amenorrhoea, premenstrual syndrome, undesired puerperal lactation, furthermore for the prophylaxis and therapy of cerebral disorders (for example migraine), in particular in geriatrics, in a similar way to certain ergot alkaloids.

They can also particularly preferably be employed as therapeutic agents for combating the consequences of cerebral infarction (apoplexia cerebri), such as strokes and cerebral ischaemia, and for the treatment of brain and spinal cord trauma.

However, they are particularly suitable as medicament active ingredients for anxiolytics, antidepressants, antipsychotics, neuroleptics,

antihypertonics and/or for positively influencing obsessive-compulsive disorder (OCD), sleeping disorders, tardive dyskinesia, learning disorders, age-related memory disorders, eating disorders, such as bulimia, and/or sexual dysfunctions.

The substances according to the invention are generally administered analogously to known commercially available preparations (for example citalopram and fluoxetine), preferably in doses of between about 0.2 and 500 mg, in particular between 0.2 and 50 mg, per dosage unit. The daily dose is preferably between about 0.001 and 10 mg/kg of body weight. The low doses are between about 0.2 and 500 mg, in particular between 0.2 and 50 mg, per dosage unit. The low doses (about 0.2 to 1 mg per dosage unit; about 0.001 to 0.005 mg/kg of body weight) are particularly suitable for use as migraine agents; for the other indications, doses of between 10 and 50 mg per dosage unit are preferred. However, the specific dose for each particular patient depends on a very wide variety 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 method of administration, on the excretion rate, medicament combination and severity of the particular disease to which the therapy applies. Oral administration is preferred.

Figures:

Fig. 1: Change in the serotonin concentration (5-hydroxytryptamine, 5-HT) in the dialysate as a function of time before and after administration (i.p.) of EMD 135894, EMD 68843 and EMD 391987 (concentration in each case: 1 mg/kg of body weight).

Fig. 2: Change in the serotonin concentration (5-hydroxytryptamine, 5-HT) in the dialysate as a function of time before and after

administration (i.p.) of EMD 480246 and EMD 391987 (each 0.3 mg/kg of body weight).

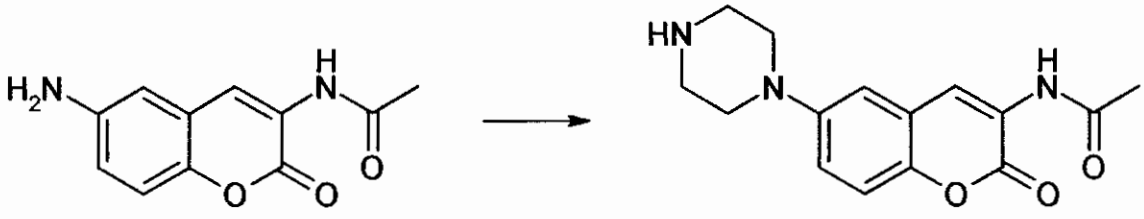
Fig. 3: Change in the serotonin concentration (5-hydroxytryptamine, 5-HT) in the dialysate as a function of time before and after administration (i.p.) of 0.3 mg/kg of body weight or 1.0 mg/kg of body weight of EMD 480247 compared with vilazodone (EMD 68843; 1 mg/kg of body weight).

Examples:

Example 1

Synthesis of N-(6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)methylamide

a)



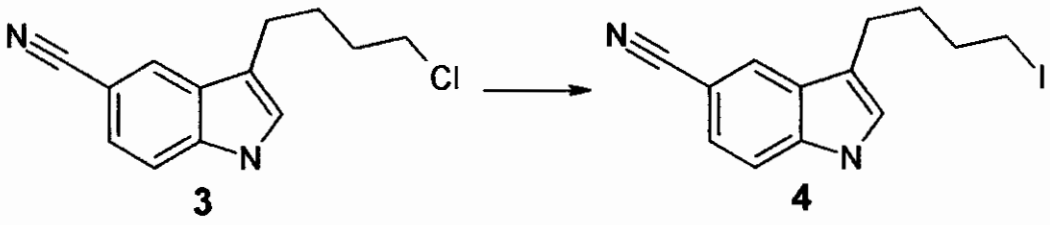
1 **2**

20.0 g (91.7 mmol) of **1** were initially introduced in chlorobenzene (600 ml), 16.4 g (91.7 mmol) of bis(2-chloroethyl)ammonium chloride and 12.7 g mg (92.0 mmol) of potassium carbonate were added, and the mixture was refluxed for 4 days. The residue was filtered off, washed with copious water and dried in a vacuum drying cabinet.

Yield: 14 g of colourless solid (**2**)

$[M+H]^+$ 288 (HPLC-MS)

b)

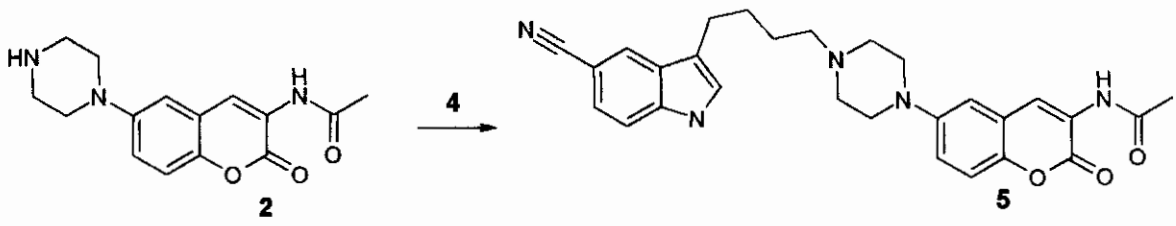


3 (150 g, 0.65 mol) was dissolved in 500 ml of acetone (dried), and sodium iodide (580 g, 3.87 mol) was stirred in. The suspension was stirred at RT. After 118 hours, a further 18 g of NaI (0.12 mol) were added, and the mixture was stirred at RT for a further 3 days. The suspension was filtered off with suction, rinsed with acetone (dried), and 100 g of NaI (ground in a mortar) were added, and the mixture was stirred at RT. After 24 hours, a further 100 g of NaI (ground in a mortar) were added, and the mixture was stirred for a further 72 hours. A further 100 g of NaI (ground in a mortar) were subsequently added, and the mixture was stirred for a further 5 days. The suspension was filtered off with suction and rinsed well with acetone, the filter cake was discarded, and the filtrate was evaporated to dryness. The residue was stirred with water and extracted by shaking with ethyl acetate, and the ethyl acetate solution was dried, filtered and evaporated to dryness. The residue was stirred with a mixture of 300 ml of petroleum ether and 200 ml of diethyl ether and filtered off with suction. The crystals were rinsed on the suction filter with 50 ml of cold diethyl ether and dried in air.

Yield: 184 g of brownish crystals (**4**)

$[M+H]^+$ 325 (HPLC-MS)

c)



12.4 g (43.0 mmol) of **2** were taken up in *N*-methylpyrrolidone (150 ml), 13.9 g (43.0 mmol) of **4** and 11.1 g (85.8 mmol) of diisopropyldiethylamine were added, and the mixture was stirred at 140°C for 3 days. The reaction solution was poured into ice-water, and the brown precipitate was filtered off. The residue was purified by column chromatography (ethyl acetate/-MeOH, 9:1), and the virtually clean fraction was recrystallised from tert-butyl methyl ether/hexane. The solid was converted into the hydrochloride in the usual manner.

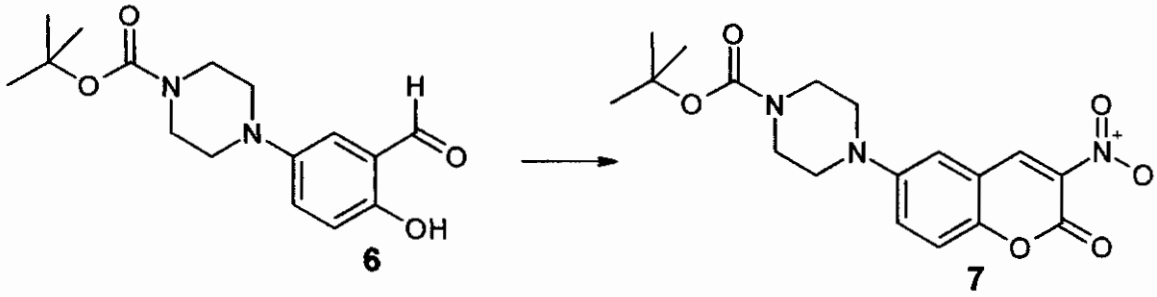
Yield: 3.8 g of colourless solid, HCl salt (**5**)

$[M+H]^+$ 484 (HPLC-MS)

Example 2

Synthesis of N-(6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)ethylamide

a)

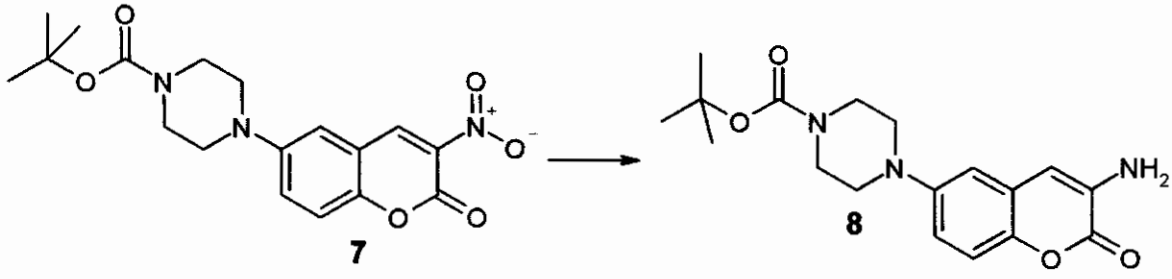


6 (20.0 g, 65.1 mmol), ethyl nitroacetate (9.00 ml, 78.3 mmol) and diethylammonium chloride (8.58 g, 78.3 mmol) were heated on a water separator for 3 days in toluene (500 ml). The cooled reaction solution was washed with water and dried, the drying agent was filtered off, and the solvent was removed. The residue was purified by column chromatography (ethyl acetate/cyclohexane).

Yield: 13.2 g of yellowish solid (**7**)

$[M+H]^+$ 376, $[M-55]^+$ 320 (HPLC-MS)

b)



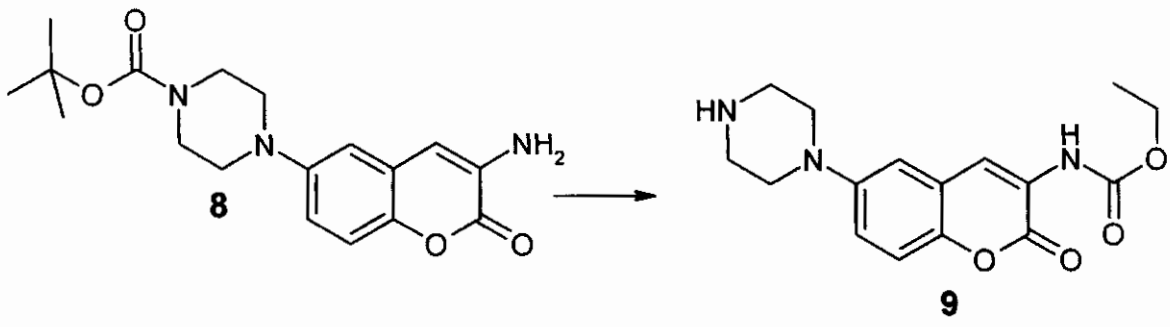
7 **8**

7 (3.00 g, 7.99 mmol) was dissolved in MeOH (50 ml), Pd/C.5% (1 g) was added, and the mixture was stirred for 24 hours in a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was purified by column chromatography (ethyl acetate/ methanol).

Yield: 1.50 g of brownish solid (**8**)

$[M+H]^+$ 346, $[M-55]^+$ 290 (HPLC-MS)

c)



8 (375 mg, 1.09 mmol) was dissolved in dichloromethane (10 ml), pyridine (0.11 ml, 1.1 mmol) was added, and the mixture was cooled to 0°C. Ethyl chloroformate (141 mg, 1.10 mmol) was added dropwise at this temperature, and the mixture was stirred overnight at room temperature. The batch was evaporated and purified by column chromatography (ethyl acetate/ cyclohexane, 1:1).

Yield: 320 mg of colourless solid

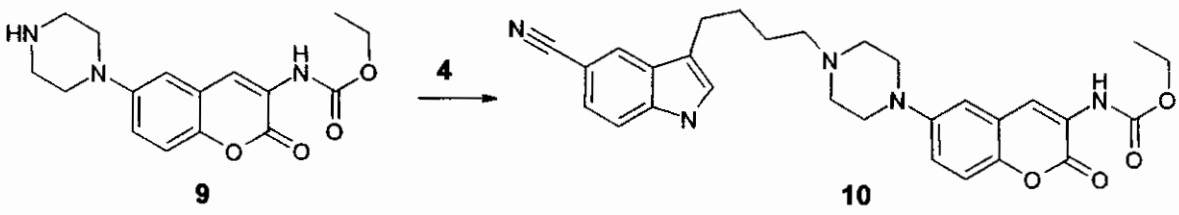
$[M+H]^+$ 418, $[M-55]^+$ 362 (HPLC-MS)

The substance obtained in this way was stirred for 60 minutes at room temperature in saturated ethanolic HCl solution (10 ml), and the solvent was stripped off.

Yield: 270 mg of colourless solid, di-HCl salt (**9**)

$[M+H]^+$ 355 (HPLC-MS)

d)



9 (200 mg, 0.51 mmol), **4** (see Example 1; 166 mg, 0.51 mmol) and diisopropylethylamine (0.26 ml, 1.53 mmol) were refluxed for 18 hours in acetonitrile (5 ml). The solvent was removed, and the residue and purified by column chromatography (ethyl acetate/methanol). The solid was converted into the hydrochloride in the usual manner.

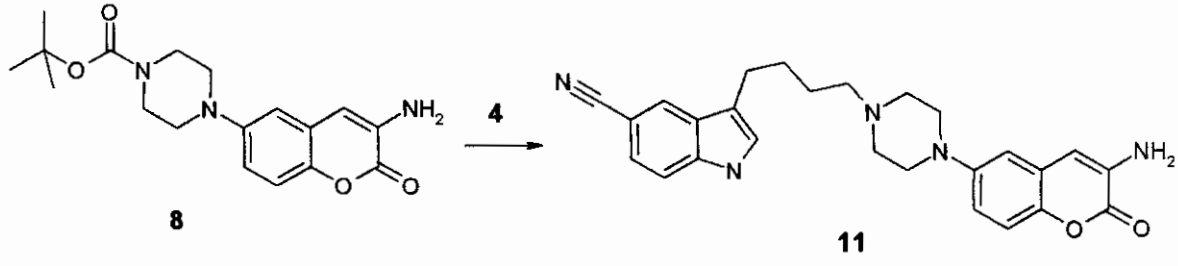
Yield: 70 mg of colourless solid, HCl salt (**10**)

$[M+H]^+$ 514 (HPLC-MS)

Example 3

Synthesis of **N**-(6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)amine

a)



8 **11**

Compound **8** was prepared analogously to steps a) and b) in Example 2. **8** (1.00 g, 2.90 mmol) was subsequently stirred at room temperature for 60 minutes in saturated ethanolic HCl solution (10 ml), and the solvent was stripped off.

Yield: 880 mg of colourless solid, di-HCl salt (**8**)

$[M+H]^+$ 246 (HPLC-MS)

Compound **8** obtained in this way (50 mg, 0.16 mmol) was refluxed for 18 hours with **4** (77 mg, 0.24 mmol) and diisopropylethylamine (0.08 ml, 0.47 mmol) in acetonitrile (2 ml). The solvent was removed, and the residue and purified by column chromatography (ethyl acetate/methanol). The solid was converted into the hydrochloride in the usual manner.

Yield: 25 mg of colourless solid, HCl salt (**11**)

$[M+H]^+$ 442 (HPLC-MS)

Example A: Suppositories

A mixture of 20 g of an active ingredient of the formula I is melted 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 ingredient.

Example B: Solution

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

Example C: Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of Vaseline under aseptic conditions.

Example D: Tablets

A mixture of 1 kg of active ingredient 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 pressed to give tablets in a conventional manner in such a way that each tablet comprises 10 mg of active ingredient.

Example E: Coated tablets

Tablets are pressed analogously to Example D and are subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example F: Capsules

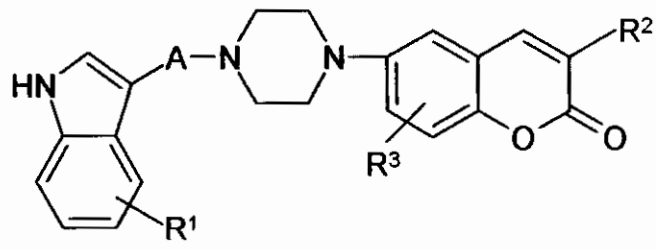
2 kg of active ingredient of the formula I are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

Example G: Ampoules

A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is transferred into ampoules, lyophilised under aseptic conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

Patent Claims

1) Compounds of the formula I



I

in which

R^1 is H, OH, CN, Hal, CONHR, OB, CO_2B, CF_3, NR_2, NRCOR, NRCOOR or $NRCONR_2$,

R^2 is NR_2, NRCOR, NRCOOR, $NRCONR_2$, NO_2, $NRSO_2R_2$, NRCSR or $NRCSNR_2$,

R^3 is H, OH, CN, Hal, CONHR, OB, CO_2B, CF_3, NO_2, NR_2, NRCOR, NRCOOR or $NRCONR_2$,

R, independently of one another, are H, B, Het or Ar,

A is a straight-chain or branched, mono- or polyunsaturated carbon chain having 2, 3, 4, 5, or 6 C atoms,

B is a straight-chain or branched alkyl radical having 1, 2, 3, 4, 5 or 6 C atoms,

and pharmaceutically usable prodrugs, derivatives, solvates, stereoisomers and salts thereof, and mixtures thereof in all ratios.

2) Compounds of the formula I according to Claim 1, characterised in that the radical R^1 is CN or Hal, preferably CN.

3) Compounds of the formula I according to Claim 1 and/or 2, characterised in that the radical R^3 is H.

4) Compounds of the formula I according to one or more of Claims 1 to 3, characterised in that the radical R^2 is NRCOR or NRCOOR.

5) Compounds of the formula I according to one or more of Claims 1 to 4, characterised in that A is $(CH_2)_m$, where m = 2, 3, 4, 5 or 6, preferably 4.

6) Compounds of the formula I according to one or more of Claims 1 to 5, characterised in that the radical R^1 is CN or Hal, where CN is preferred, and R^3 is H.

7) Compounds of the formula I according to one or more of Claims 1 to 6, characterised in that R^1 is CN, R^3 is H, and A is $(CH_2)_m$, where m = 4.

8) Compounds of the formula I according to one or more of Claims 1 to 7, characterised in that the radical R^1 is in position 5 of the indole radical.

9) Compounds of the formula I selected from the group
N-(6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)methylamide,

ethyl (6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)carbamate,

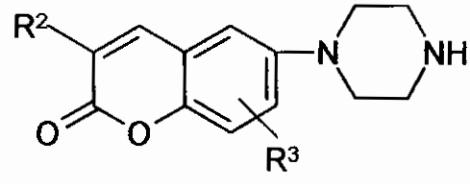
methyl N-(6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)carbamate,

N-(6-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-2-oxo-2H-chromen-3-yl)-2,2-dimethylpropionamide,

3-{4-[4-(3-amino-2-oxo-2H-chromen-6-yl)piperazin-1-yl]butyl}-1H-indole-5-carbonitrile,

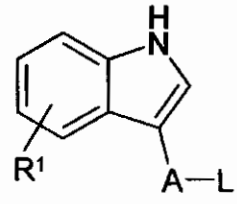
and pharmaceutically usable prodrugs, derivatives, solvates, stereoisomers and salts thereof.

10) Process for the preparation of compounds of the formula I according to one or more of Claims 1 to 9, characterised in that a compound of the formula II



II

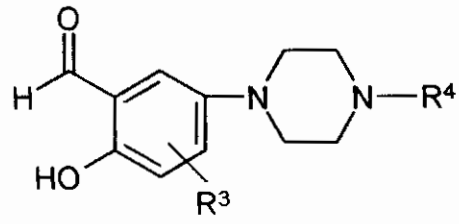
in which R^2 and R^3 are as defined in Claim 1, is reacted with a compound of the formula III



III

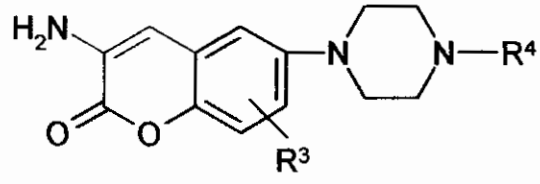
in which R^1 and A are as defined in Claim 1, and L is Cl, Br, I, OH or a reactively esterified OH group or another readily nucleophilically substitutable leaving group.

11) Process for the preparation of compounds of the formula I according to one or more of Claims 1 to 9, characterised in that a compound of the formula IV



IV

in which R^3 is as defined in Claim 1, and R^4 is an amino-protecting group or H, is reacted, in a Michael-analogous reaction, with ethyl nitroacetate and diethylammonium chloride, and the nitro group is subsequently reduced, to give the compound of the formula V



V

and the compound of the formula V is reacted with a compound conforming to the formula III.

12) Compounds of the formula I according to one or more of Claims 1 to 7 as medicaments.

13) Medicament comprising an effective amount of a compound of the formula I according to one or more of Claims 1 to 9, optionally in addition to one or more inert excipients, adjuvants and/or diluents.

14) Medicament according to Claim 13, characterised in that at least one further medicament active ingredient is present.

15) Process for the preparation of a medicament according to Claim 13 or 14, characterised in that a compound of the formula I according to one or more of Claims 1 to 9 and, if desired, a further medicament active ingredient is incorporated into one or more inert excipients and/or diluents by non-chemical methods.

16) Use of the compounds of the formula I according to one or more of Claims 1 to 9 for the preparation of a medicament for the prophylaxis and/or therapy of diseases in which 5-HT plays a role.

17) Use of the compounds of the formula I according to Claim 16, characterised in that the diseases are selected from the group depression, strokes, cerebral ischaemia, extrapyramidal motor side effects of neuroleptics and of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, brain and spinal cord trauma, obsessive-compulsive disorder, sleeping disorders, tardive dyskinesia, learning disorders, age-related memory disorders, eating disorders, such as bulimia, and/or sexual dysfunctions.

18) Medicament kit consisting of separate packs of

a) an effective amount of a compound of the formula I according to one or more of Claims 1 to 9 and
b) an effective amount of a further medicament active ingredient.