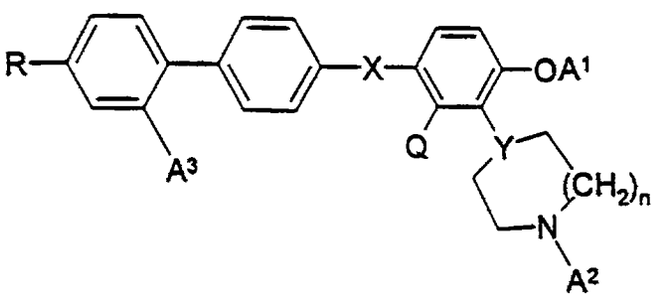
Biphenyl derivatives

The invention relates to novel Biphenyl derivatives of formula I



I

wherein

R	is -C(=NH)-NH_2, -C(=NH)-NHA^3, -C(=NH)-NHAc, -C(=NH)-$NHSO_2CH_3$, R^2, -CO-NH-Z-R^3 or -CO-R^1,
X	is -CONH-, -SO_2NH-, -NHCO- or -$NHSO_2$-,
Y	is CH or N,
A^1	H, alkyl having 1 to 6 C atoms wherein 1 to 7 H atoms can be replaced by F, SO_2CH_3 or SO_2CF_3,
A^2	H or alkyl having 1 to 6 C atoms,
A^3, A^5	in each case independently of one another are alkyl having 1 to 6 C atoms,
A^6, A^7	in each case independently of one another are H or $(CH_2)_pCH_3$,
Q	H or OA^1,
R^1	is 4-A^5-piperazin-1-yl, 4-A^5-homopiperazinyl, 1-pyrrolidinyl which is substituted once by R^4 or -Z-R^4, 1-piperidinyl which is substituted once by R^4 or -Z-R^4, N-A^5-pyrrolidinyl-amino, N-A^5-piperidinyl-amino, N-A^5-pyrrolidinyl-Z-amino or N-A^5-piperidinyl-Z-amino, -N(A^6)(ZR^3) or NA^6A^7,
R^2	is 5-methyl-1,3,4-oxadiazol-2-yl or 5-methyl-1,2,4-oxadiazol-3-yl,

R^3, R^4		in each case independently of one another are NHA^5, $N(A^5)_2$, 4-morpholinyl, 1-pyrrolidinyl or 1-piperidinyl,
Z		is alkylene having 1 to 6 C atoms,
n		is 0 or 1,
p		is 0, 1 or 2,

with the proviso that, if Y is N, X = -CONH- and n =1, then $R \neq R^2$ or $R \neq -CONA^6A^7$,

including the racemate and the enantiomers,
and the physiologically acceptable salts and solvates thereof.

Biphenylamide derivatives are disclosed, for example, in WO 96/31508 or as described by P.J. Pauwels in Gen. Pharmac. Vol. 29, No. 3, 293-303 (1997).
Benzanilide derivatives are known from EP 0 533 267, EP 0 533 268 or from WO 94/15920.

The invention was based on the object of finding novel compounds which have valuable properties, in particular those which can be used for the preparation of pharmaceuticals.
It has been found that the compounds of the formula I and their salts have very valuable pharmacological properties combined with good tolerance.

Thus, in particular, they are active on the central nervous system, especially as serotonin (5-hydroxytryptamine) antagonists.

Serotonin is distributed in the central nervous system (CNS), platelets and the gastrointestinal tract. There are multiple types of receptors for serotonin such as $5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, $5\text{-}HT_{1C}$ or $5\text{-}HT_{1D}$.
The $5\text{-}HT_{1C}$ receptor recently has been renamed to $5\text{-}HT_{2C}$.
Changes in transmission of serotonin in the CNS can modify e.g. mood, psychomotor activity, appetite, memory and blood pressure. Release of

serotonin from platelets can mediate vasospasm while changes in free serotonin levels in the gastrotestinal tract can modify sectretion and motility.

Pharmacological studies have suggested that activation of 5-HT_{1B} receptors might lead to an increase in anxiety and locomotion and to a decrease in food intake, sexual activity and agressive behaviour. Furthermore, selective blockade of central 5-$HT_{1B/D}$ autoreceptors should facilitate 5-HT transmission and may therefore offer a novel antidepressant therapy (P.J. Pauwels in Gen. Pharmac. Vol. 29, No. 3, 293-303 (1997)). Other studies suggest that supersensitive 5-$HT_{1B/D}$ receptors may have a role in the pathophysiology of obsessive-compulsive disorder (OCD) (O.T. Dolberg et al., Eur. Neuropsychopharmac. 5, 161-162 (1995)). Another observation offers new possibilities for application of 5-$HT_{1B/D}$ receptor antagonists in 5-HT-dependent tumor cell growth.

Compounds of the formula I can be used in the treatment of diseases which are related to interferences in the serotoninergic systems. Compounds show potent 5-HT_{1B} and/or 5-HT_{1D} antagonistic properties.

Compounds showing 5-HT_{1D} antagonistic properties may be identified by a high level of affinity in the in vitro human cortex and guinea-pig striatum radioligand binding assays described by Hoyer et al., Neuroscience Letters, 1988, 85, 357-362. The affinity of a compound for a 5-HT_{1A} receptor is measured using the in vitro test described by Gozlan et al., Nature, 1983, 305, 140-142.

The affinity of the compounds for the 5-HT_{1D} receptors in calf caudate membranes (mainly constituting the homologous bovine 5-HT_{1B} receptor) as well as the 5-HT_{1B} antagonistic properties in the K^+-stimulated release of [^{3}H]-5-HT from preloaded rat occipital cortical slices, can be determined analogous to S.Berg et al. in J. Med. Chem. **1998**, 41, 1934-1942.

The effect of the compounds on the 5-HT turnover in rat brain in vivo can be determined by using the 5-HTP accumulation technique (S.Berg et al.)

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/or of cardiovascular disorders. They can be used in the treatment or prophylaxis of various CNS disorders such as mood disorders, including depression and dysthymia, anxiety disorder including generalized anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, memory disorders, including dementia, amnestic disorders and age-associated memory impairment. They can be used for treating Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced parkinson and tardive dyskinesias. Moreover, they can be used in the treatment of 5-HT-dependent tumor cell growth, of disorders of eating behaviors, including anorexia nervosa and bulimia. Furthermore, they can be used in the treatment of cardiovascular disorders characterized by the malfunction of peripheral 5-$HT_{1B/D}$ receptors, in the treatment or prophylaxis of endocrine disorders, vasospasm, hypertension, disorders of the gastrointestinal tract where changes in motility and secretion are involved, and sexual dysfunction.

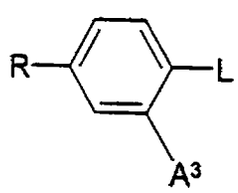
In particular, however, they are suitable as pharmaceutical active compounds for anxiolytics, antidepressants, antipsychotics and/or positively influencing obsessive-compulsive behaviour, sleep disorders, tardive dyskinesias, learning disorders, age-dependent memory disorders, eating disorders such as bulimia, and/or sexual functional disorders.

The compounds of the formula I and their physiologically acceptable salts can therefore be used as pharmaceutical active compounds for anxiolytics, antidepressants, antipsychotics, neuroleptics and/or antihypertensives, and for positively affecting obsessive-compulsive behaviour, eating disorders such as bulimia, tardive dyskinesias, learning disorders and age-dependent memory disorders.

The compounds of the formula I can be employed as pharmaceutical active compounds in human and veterinary medicine. They can further be employed as intermediates for the preparation of further pharmaceutical active compounds.

The invention accordingly relates to the compounds of the formula I and to a process for the preparation of compounds of formula I according to Claim 1 and salts and solvates thereof, characterized in that

a) a compound of formula II

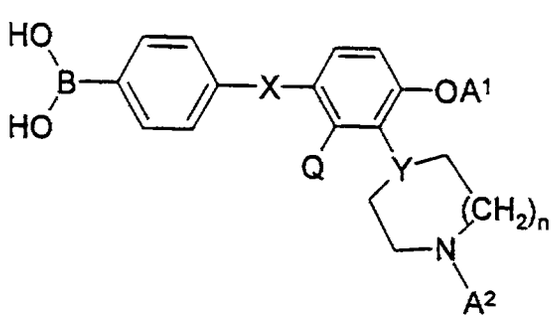


II

wherein

L is Cl, Br, I or an OH group functionally modified to form a reactive group, especially a suitable leaving group, and R and A^3 are as defined,

is reacted with a boronic acid derivative of formula III



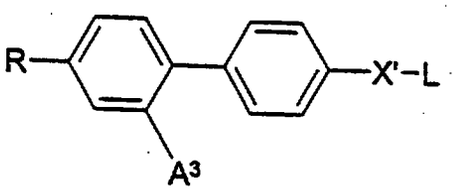
III

wherein

X, Y, A^1, A^2, Q and n are as defined,

or

b) a compound of the formula IV



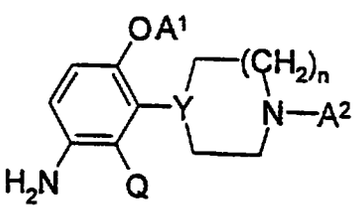
IV

wherein

R and A^3 are as defined, X' is CO or SO_2 and

L is Cl, Br, I or an OH group functionally modified to form a reactive group, especially a suitable leaving group,

is reacted with a compound of formula V



V

wherein

Y, A^1, A^2, Q and n are as defined,

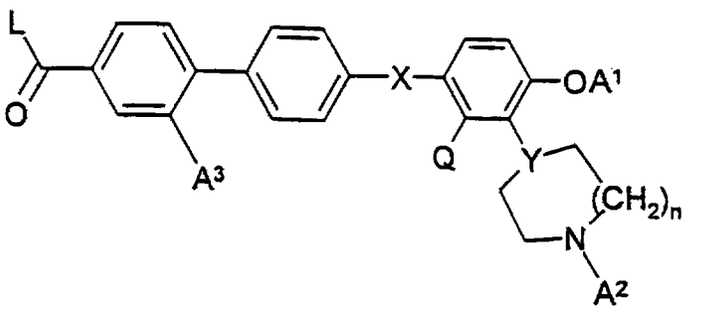
or

c) for the preparation of a compound of the formula I

wherein

R is -CO-NH-Z-R^3 or -CO-R^1

a compound of the formula VI



VI

wherein

L is Cl, Br, I or a free or reactive functionally modified OH group,

and X, Y, A^1, A^2, A^3, Q and n are as defined,

is reacted with a compound of formula VII

H-R' VII

wherein

R' is NH-Z-R^3 or R^1

and Z, R^3 and R^1 are as defined,

and/or in that in a compound of the formula I one or more radicals R, Q, A^1 and/or A^2 is converted into one or more other radicals R, Q, A^1 and/or A^2,

by

i) converting a group R^2 into an amidino group,

ii) hydrolysing an ether group to a hydroxyl group,

iii) converting a hydroxy group into a sulfonyloxy group

and/or a basic compound of the formula I is converted into a salt thereof by treatment with an acid.

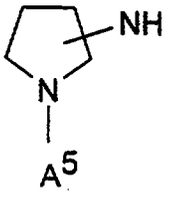
Above and below, the radicals R, X, Y, X', R', A^1, A^2, A^3, A^5, Q, L and n have the meanings indicated in the formulae I, II, III, IV, V, VI and VII if not expressly stated otherwise.

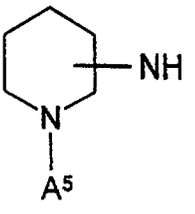
The invention likewise relates to medicaments of the formula I and their physiologically acceptable salts and solvates having serotonin (5-HT_{1B} and/or 5-HT_{1D}) antagonistic action.

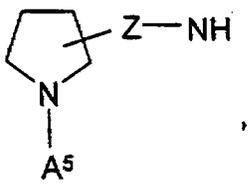
The invention relates to the compounds of the formula I according to Claim 1 and to their salts and solvates.

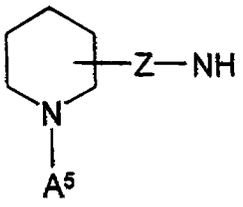
Solvates means addition compounds of the compounds of formula I according to Claim 1 with inert solvents. Solvates are e.g. the mono- or dihydrates or alcoholates, e.g. with methanol or ethanol.

A^1 preferably is H, methyl, ethyl, CH_2CH_2F, CF_3, SO_2CH_3 or SO_2CF_3.
A^2 preferably is H, methyl or ethyl.
A^3 and A^5 are by preference in each case independently of one another alkyl having 1-6 C atoms.
A^3 preferably is methyl, ethyl or propyl.
A^5 preferably is methyl, ethyl or propyl.
Q preferably is H, furthermore preferably methoxy or ethoxy.
X preferably is -CONH- or -SO_2NH-.
Z preferably means methylene, ethylene or propylene.

N-A^5-pyrrolidinyl-amino means 

N-A^5-piperidinyl-amino means 

N-A^5-pyrrolidinyl-Z-amino means 

N-A^5-piperidinyl-Z-amino 

-$N(A^6)(ZR^3)$ preferably means -$NH(CH_2NHCH_3)$, -$NH(CH_2CH_2NHCH_3)$, -$NH(CH_2CH_2NMe_2)$, -$NMe(CH_2CH_2NMe_2)$, -$NH(CH_2CH_2CH_2\,NMe_2)$, -$NMe(CH_2CH_2CH_2\,NMe_2)$. NA^6A^7 preferably means NH_2, $NHCH_3$, NHC_2H_5, $N(CH_3)_2$ or $N(C_2H_5)_2$.

R^1 preferably means 4-methyl-piperazin-1-yl, morpholin-4-yl, 4-methyl-homopiperazinyl, 2-dimethylaminomethyl-pyrrolidin-1-yl, 2-dimethylamino-methyl-piperidin-1-yl, N-methyl-pyrrolidin-2-yl-amino, N-methyl-piperidin-3- or -4-yl-amino, N-methyl-pyrrolidin-2-yl-methylamino or N-methyl-piperidinyl-methyl-amino.

Ac is acyl and preferably means acetyl, propionyl or benzoyl.
me or Me is methyl, et or Et is ethyl.

In the above formulae, alkyl has 1, 2, 3, 4, 5 or 6 C atoms, preferably 1, 2, 3, 4 or 5 C atoms, and is preferably methyl, ethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl or isopentyl.

NHA^5 is preferably methylamino and also ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino or tert.-butylamino. $N(A^5)_2$ is preferably dimethylamino and also diethylamino, *di*-n-propylamino, diisopropylamino or di-n-butylamino.

Alkylene preferably means unbranched methylene, ethylene, propylene, butylene, pentylene or hexylene. Furthermore, alkylene means branched alkylene residues.

Accordingly, the invention relates in particular to those compounds of the formula I in which at least one of the abovementioned radicals has one of the meanings given above as being preferred. Some preferred groups of compounds can be expressed by the following sub-formulae Ia to Ih, which correspond to the formula I and in which the radicals which are not described in greater detail have the meanings given for formula I, but in which

in Ia	R	is -C(=NH)-NH_2 or R^2,
in Ib	X	is SO_2NH,
in Ic	R	is -C(=NH)-NH_2 or R^2,
	A^3	is alkyl having 1 to 6 C atoms,
in Id	R	is -C(=NH)-NH_2, R^2 or 4-methyl-piperazinyl,
in Ie	R	is -C(=NH)-NH_2, R^2 or -CO-R^1,
	A^3	is alkyl having 1 to 6 C atoms,
in If	R	is -C(=NH)-NH_2, R^2 or -CO-R^1,
	A^3	is alkyl having 1 to 6 C atoms,
	A^1	is H or alkyl having 1 to 6 C atoms,
	A^2	is alkyl having 1 to 6 C atoms,
	A^5	is alkyl having 1 to 6 C atoms,
in Ig	R	is -C(=NH)-NH_2, R^2 or -CO-R^1,
	A^3	is alkyl having 1 to 6 C atoms,
	A^1	is H or alkyl having 1 to 6 C atoms,
	A^2	is alkyl having 1 to 6 C atoms,

	A^5	is alkyl having 1 to 6 C atoms,
	X	is SO_2NH,
in Ih	R	is $-C(=NH)-NH_2$, R^2 or $-CO-R^1$,
	A^3	is alkyl having 1 to 6 C atoms,
	A^1	is H or alkyl having 1 to 6 C atoms,
	A^2	is alkyl having 1 to 6 C atoms,
	A^5	is alkyl having 1 to 6 C atoms,
	X	is SO_2NH,
	Y	is CH,
in Ii	R	is $-C(=NH)-NH_2$, R^2 or $-CO-R^1$,
	A^3	is alkyl having 1 to 6 C atoms,
	A^1	is H or alkyl having 1 to 6 C atoms,
	A^2	is alkyl having 1 to 6 C atoms,
	A^5	is alkyl having 1 to 6 C atoms,
	X	is CONH,
	Y	is CH.

Besides, the compounds of the formula I and also the starting materials for their preparation are prepared by methods known per se and they are described in the literature (for example in the standard publications such as Houben-Weyl, Methoden der organischen Chemie [Methods in Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), under reaction conditions which are known and suitable for the abovementioned reactions. It is also possible to make use of variants which are known per se and not mentioned in greater detail in the present text.

In the derivatives of formula II, IV, and VI L is preferably Cl or Br, but it can also be I or an OH group functionally modified to form a reactive group. If L is a reactive esterified OH group, then this is by preference alkyl-sulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy or trifluoro-

methylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolyl-sulfonyloxy, furthermore also 2-naphthalenesulfonyl-oxy).

If desired, the starting materials may also be formed in situ, so 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.

The compounds of the formula I can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.
The starting substances of the formulae II and III are known in some cases. If they are not known, they can be prepared by methods known per se.
Compounds of the formula III can be obtained e.g. by treatment of the corresponding halo-derivatives with e.g. $B(O^iPr)_3$ or $B(OMe)_3$ and n-BuLi (butyl lithium) at temperatures between approximately -80 and 30°.

In detail, the reaction of the compounds II and III is carried out in the presence or absence of an inert solvent at temperatures between approximately -20 and approximately 180°, preferably between 40 and 130° and the presence of e.g. $Pd(PPh_3)_4$ (Suzuki-reaction).
Addition of an acid-binding agent, for example an alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, alkaline earth metal hydroxide, alkaline earth metal carbonate or alkaline earth metal bicarbonate, or of another salt of a weak acid of the alkali metal or alkaline earth metals, preferably of potassium, sodium or calcium, or an addition of an organic base such as triethylamine, dimethylamine or pyridine or quinoline or of an excess of the amine component may be advantageous.
Examples of suitable inert solvents are hydrocarbons such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols such as methanol, ethanol,

isopropanol, n-propanol, n-but-anol or tert-butanol; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers such as ethylene glycol monomethyl ether, ethylene glycol monoethyl ether (methylglycol or ethylglycol) or ethylene glycol dimethyl ether (diglyme); ketones such as acetone or butanone; amides such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles such as acetonitrile; sulfoxides such as dimethyl sulfoxide (DMSO); nitro compounds such as nitromethane or nitrobenzene; esters such as ethyl acetate, or mixtures of the abovementioned solvents with water.

It is also possible to obtain a compound of formula I by reacting a compound of formula IV with a compound of formula V.

Some of the compounds of formula IV and V, especially of formula V, are known; the unknown compounds can easily be prepared analogously to the known compounds. Thus, compounds of formula IV can be prepared by reacting the corresponding carboxylic acid or the sulfonic acid with $SOCl_2$.

The reaction of compounds IV and V proceeds according to methods which are known from the literature for the formation of amides or sulfonamides. The components can be melted with one another directly, without the presence of a solvent, at normal pressure or at elevated pressure, an inert gas such as e.g. N_2 being added to increase the pressure. However, it is also possible to react the compounds in the presence of an inert solvent. Suitable solvants are those mentioned previously. The addition of an acid-binding agent to the reaction mixture can also have a favourable effect. The same bases are suitable as those described above.

Depending on the reaction conditions chosen, the optimum reaction time is between a few minutes and 14 days, and the reaction temperature is between about 0° and 150°, usually between 20° and 130°.

Furthermore, it is possible to obtain compounds of formula I, wherein R is

-CO-NH-Z-R^3 or -CO-R^1, by reacting a compound of formula VI with a compound of formula VII.

The reaction of compounds VI and VII proceeds according to methods which are known from the literature for the formation of amides.

Examples for the N-acylation of compounds of formula VII of suitable derivatives of the compounds of formula VI are acid halides, preferably chlorides, azides, anhydrides, imidazolides (which can be obtained, for example, from carbodiimidazoles), activated esters or O-acylureas, which are obtained from suitable carboximides, such as dialkylcarbodiimides, e.g. cyclohexyl-carbodiimide. It may be necessary, before carrying out this reaction, to exclude further amino groups contained in the compound of the formula VII from the acylation reaction by introduction of suitable protective groups.

The reaction is generally carried out in an inert solvent, in the presence of an acid-binding agent, preferably of an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or of another salt of a weak acid of the alkali metals or alkaline earth metals, preferably of potassium, sodium, calcium or caesium. The addition of an organic base such as triethylamine, dimethylaniline, pyridine or quinoline or of an excess of the compound of the formula VII or of the alkylating derivative of the formula VI may also be favourable. The reaction time, depending on the conditions used, is between a few minutes and 14 days, and the reaction temperature is between approximately 0° and 150°, normally between 20° and 130°. Suitable solvants are those mentioned previously.

The expression "amino protective group" is generally known and relates to groups which are suitable for protecting (for blocking) an amino group from chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at another position in the molecule. Typical of such groups are, in particular, unsubstituted or substituted acyl, aryl (e.g. dinitrophenyl (DNP), aralkoxymethyl (e.g. benzoxymethyl (BOM)) or aralkyl groups (e.g. benzyl, 4-nitrobenzyl, triphenylmethyl). As the amino

protective groups are removed after the desired reaction (or reaction sequence), their nature and size is otherwise uncritical; however, those having 1-20, in particular 1-8, C atoms are preferred. The expression "acyl group" in this connection is to be interpreted in the widest sense. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and in particular alkoxy-carbonyl, aryloxycarbonyl and especially aralkoxycarbonyl groups. Examples of acyl groups of this type are alkanoyl such as acetyl, propionyl, butyryl; aralkanoyl such as phenacetyl; aroyl such as benzoyl or tolyl; aryloxyalkanoyl such as phenoxy-acetyl; alkoxycarbonyl such as methoxy-carbonyl, ethoxycarbonyl; 2,2,2-trichloroethoxycarbonyl, iso-propoxy-carbonyl, tert-butoxycarbonyl (BOC), 2-iodo-ethoxycarbonyl; aralkyl-oxycarbonyl such as benzyloxy-carbonyl (CBZ), 4-methoxybenzyl-oxycarbonyl and 9-fluorenylmethoxycarbonyl (FMOC).
Preferred amino protective groups are BOC, DNP and BOM, and further CBZ, benzyl and acetyl. A crucial factor in the choice of the protective group employed is the possibility of being able to remove this selectively again after the actual reaction.

Preferably, the amides of formula I, wherein R is -CO-NH-Z-R^3 or -CO-R^1, can be prepared e.g. by coupling the amine and the carboxylic acid using P-EDC (polymer-bound 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide according to M. Desai et al., Tetrahedron Letters **1993**, 34 (48), 7685-7688) an inert solvent at temperatures between approximately -20 and approximately 100°, preferably between -10 and 60°. Suitable solvants are those mentioned previously.

Compounds of the formula I can furthermore preferably be obtained by reductive amination of compounds of the formula I. The starting substances are known in some cases. If they are not known, they can be prepared by methods known per se.

The reducing amination can be carried out in the presence of reducing agents such as, for example, $NaBH_3CN$, $NaBH_4$ and $NaBH(OAc)_3$. The reaction is carried out in solvents and at temperatures as described above.

It is further possible to convert a compound of the formula I into another compound of the formula I by converting one or more radicals R, Q, A^1, and/or A^2 into one or more other radicals R, A^1, and/or A^2, e.g. by converting a group R^2 for example by hydrogenation on Raney Nickel or Pd-carbon in an inert solvent such as methanol or ethanol, to an amidino group and/or hydrolysing an ether group to a hydroxyl group.

Free amino groups can further be acylated in a customary manner using an acid chloride or anhydride or alkylated using an unsubstituted or substituted alkyl halide, expediently in an inert solvent such as dichloromethane or THF and/or in the presence of a base such as triethylamine or pyridine at temperatures between -60 and +30°.
If desired, a functionally modified amino and/or hydroxyl group in a compound of the formula I can be liberated by solvolysis or hydrogenolysis according to customary methods. For example, a compound of the formula I which contains an NHCOOalkyl group can thus be converted into the corresponding compound of the formula I which, instead of this, contains an NH_2 group.

A base of the formula I may be converted with an acid to give the corresponding acid addition salt, for example by reacting equivalent amounts of the base and of the acid in an inert solvent such as acetone, followed by evaporation. Particularly suitable acids for this reaction are those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphorus acids such as orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or

polybasic carboxylic, sulfonic or sulfuric acids, e.g. 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, 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. Salts with acids which are physiologically not acceptable, e.g. picrates, can be used for isolating and/or purifying the compounds of the formula I.

On the other hand, the free bases of the formula I may, if desired, be liberated from their salts by using bases (e.g. sodium hydroxide, sodium carbonate, potassum hydroxide or potassium carbonate).

The invention further relates to the use of the compounds of the formula I and/or their physiologically acceptable salts or solvates for the preparation of pharmaceutical products, in particular by non-chemical routes. They can be brought into a suitable pharmaceutical form together with at least one solid, liquid and/or semi-liquid excipient or auxiliary and, if appropriate, in combination with one or more other active ingredients.

The invention furthermore relates to pharmaceutical products comprising at least one compound of the formula I and/or a physiologically acceptable salt thereof.

These products can be used as pharmaceuticals in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (e.g. oral), parenteral or topical adminstration and which do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc, petroleum jelly. Forms which are used for oral administration are, in particular, tablets, pills, sugar-coated tablets, capsules, powders, granules, syrups, liquids or drops, forms for rectal

administration are, in particular suppositories, forms for parenteral administration are, in particular, solvents, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, and forms for topical administration are ointments, creams or powders. The novel compounds may also be lyophilized and the resulting lyophilisates used for example for the preparation of injectable products. The abovementioned products can be in sterilized form and/or comprise auxiliaries such as glidants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, colourings, flavourings and/or other active ingredients, e.g. one or more vitamins.

The invention also relates to compounds of the formula I according to Claim 1 and the physiologically acceptable salts and solvates thereof as serotonin (5-$HT_{1B/D}$) antagonists.

The invention relates to the compounds of the formula I according to Claim 1 and the physiologically acceptable salts and solvates thereof for the treatment or prophylaxis of mood disorders, including depression and dysthymia, anxiety disorder including generalized anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, memory disorders, including dementia, amnestic disorders and age-associated memory impairment, Parkinson's disease, 5-HT-dependent tumor cell growth, disorders of eating behaviors, including anorexia nervosa and bulimia, cardiovascular disorders characterized by the malfunction of peripheral 5-$HT_{1B/D}$ receptors, endocrine disorders, vasospasm, hypertension, disorders of the gastrointestinal tract where changes in motility and secretion are involved, and sexual dysfunction.

Most preferably the invention relates to the compounds of the formula I according to Claim 1 and the physiologically acceptable salts and solvates thereof for the treatment or prophylaxis of depression, generalized anxiety, obsessive compulsive disorder and bulimia.

In this case, the substances according to the invention are preferably administered in analogy to other known commercially available preparations for the indications claimed (e.g. imipramine, fluoxetine, clomipramine), preferably in doses of 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 10 mg/kg of body weight. However, the specific dose for each patient depends on all sorts of factors, for example on the activity 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 substance combination and severity of the particular disorder to which the therapy relates. Oral administration is preferred.

The invention additionally relates to the use of compounds of the formula I according to Claim 1 and/or of the physiologically acceptable salts or solvates thereof for the preparation of a pharmaceutical for the treatment or prophylaxis of depression, generalized anxiety, obsessive compulsive disorder and bulimia.

The invention also relates to the use of compounds of the formula I according to Claim 1 and/or of the physiologically acceptable salts or solvates thereof for the treatment or prophylaxis , generalized anxiety, obsessive compulsive disorder and bulimia.

Compounds of the formula I according to the invention can be chiral on account of their molecular structure and can accordingly occur in two enantiomeric forms. They can therefore be present in racemic or in optically active form.

As the pharmaceutical activity of the racemates or of the stereoisomers of the compounds according to the invention can differ, it may be desirable to use the enantiomers. In these cases, the final product or else even the

intermediates can be resolved into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed in the synthesis as such.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active resolving agent. Suitable resolving agents are, for example, optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitably N-protected amino acids (e.g. N-benzoyl-proline or N-benzenesulfonylproline) or the various optically active camphorsulfonic acids. Also advantageous is a chromatographic resolution of enantiomers with the aid of an optically active resolving agent (e.g. dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatized methacrylate polymers attached to silica gel). Suitable eluents for this purpose are aqueous or alcoholic solvent mixtures such as, for example, hexane/isopropanol/acetonitrile, e.g. in the ratio 82:15:3.

Under particular conditions, however, it is also even possible during the synthesis to employ appropriate enantiomerically pure intermediates which have been prepared by one of the abovementioned processes. In this case, the chirality is maintained in the course of further synthesis.

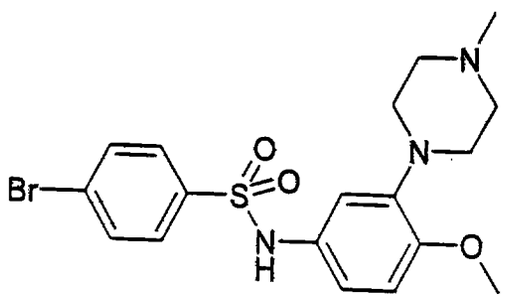
Above and below, all the temperatures are indicated in °C. In the following examples, "customary working up" means: if necessary, water is added, the mixture is adjusted, if necessary, depending on the constitution of the final product, to a pH of between 2 and 10, extracted with ethyl acetate or dichloromethane, and the organic phase is separated off, dried over sodium sulfate, evaporated and purified by chromatography on silica gel and/or by crystallization. Rf on silica gel; eluant: ethyl acetate/methanol 9:1.

Mass spectrometry (MS): EI (electron impact ionization)M^+

FAB (fast atom bombardment) $(M+H)^+$

Example 1

To a mixture of 511 mg 4-bromo-phenylsulfonic chloride ("A") and 588 mg 4-methoxy-3-(N-methylpiperazino)aniline dihydrochloride in 10 ml THF was added 2 ml of triethylamine at room temperature. The mixture was stirred for 15 hours. After filtration and customary working up N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-4-bromo-benzosulfonamide



is obtained: 850 mg, m.p. 180-182°; IR (KBr) 3005, 2946, 2830, 1594, 1574, 1510, 1334, 1153, 998 cm^{-1}; EI m/z 439.

Analogously, from

4-methoxy-3-(N-methyl-pyrrolidine-3-yl)aniline

with "A", the compound below is obtained

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-4-bromo-benzosulfonamide.

Analogously, from
4-methoxy-3-(N-methylpiperazino)aniline,
4-methoxy-3-(N-methyl-pyrrolidine-3-yl)aniline

with 4-bromo-benzoic acid chloride the compounds below are obtained

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-4-bromo-benzamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-4-bromo-benzamide.

Example 2

2.1 ml Tri-isopropyloxyboron was added to a solution of 329 mg of N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-4-bromo-benzosulfonamide in 15 ml dry THF which was cooled to -80° under nitrogen. 3.8 ml n-BuLi (2.5 M in hexane) was added dropwise to the solution. The mixture was stirred for 3 h at that temperature followed by stirring for 15 hours at room temperature. After adding 5 ml water, stirring for 1 hour, the solvents were removed. The residue was preadsorbed onto 10 ml of silica gel, and purified by flash chromatography [SiO_2, CH_2Cl_2: EtOH: 25 % aq NH_4OH (90:10:1 to 70:30:3) as eluents] to afford 220 mg 4-{N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-aminosulfonyl}benzeneboronic acid ("B"), white foam, m.p. > 217°, Rf 0.20 (CH_2Cl_2/EtOH/25 % aq. NH_4OH 60:40:3).

Analogously, the following compounds are obtained

4-{N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-amino-sulfonyl}benzeneboronic acid,

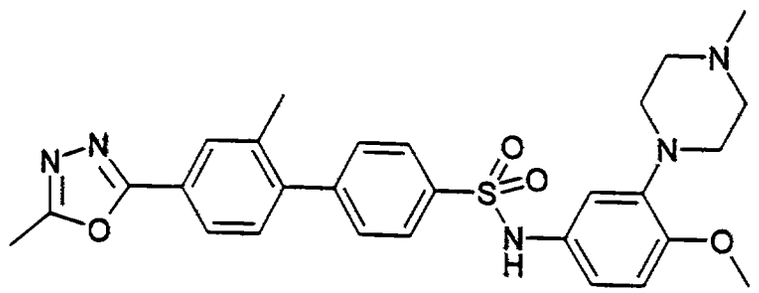
4-{N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-amino-carbonyl}benzeneboronic acid,

4-{N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-amino-carbonyl}benzeneboronic acid.

Example 3

18 mg Tetrakis [triphenylphosphine]palladium(0) was added under nitrogen atmosphere to a mixture of 180 mg "B", 189 mg 2-(4-bromo-3-methyl-phenyl)-5-methyl-1,3,4-oxadiazole ("C") and 230 mg $Na_2CO_3 \cdot 10\ H_2O$ in 10 ml DME (dimethoxyethane). The mixture was refluxed for 15 hours and the solvent removed. The residue was preadsorbed onto 5 g of SiO_2, and purified by flash chromatography (SiO_2, THF; 90:10:1 then 70:30:3 CH_2Cl_2:

EtOH: 25% aq NH_4OH) to afford N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,3,4-oxadiazole-2-yl)-biphenyl-4-sulfonamide



which was recrystallized from ethylacetate: 200 mg, m.p. 242-244°; IR (KBr) 2984, 2824, 1584, 1503, 1339, 1236, 1166 cm^{-1}; EI m/z 533.

Analogously, by reacting "B" with 3-(4-bromo-3-methyl-phenyl)-5-methyl-1,2,4-oxadiazole ("D")

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazole-3-yl)-biphenyl-4-sulfonamide is obtained.

Analogously, by reaction of

4-{N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-amino-sulfonyl}benzeneboronic acid,

4-{N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-amino-carbonyl}benzeneboronic acid,

4-{N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-amino-carbonyl}benzeneboronic acid

with "C" the following compounds are obtained

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,3,4-oxadiazole-2-yl)-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,3,4-oxadiazole-2-yl)-biphenyl-4-carboxamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,3,4-oxadiazole-2-yl)-biphenyl-4-carboxamide.

Analogously, by reaction of

4-{N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-amino-sulfonyl}benzeneboronic acid,

4-{N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-amino-carbonyl}benzeneboronic acid,

4-{N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-amino-carbonyl}benzeneboronic acid

with "D" the following compounds are obtained

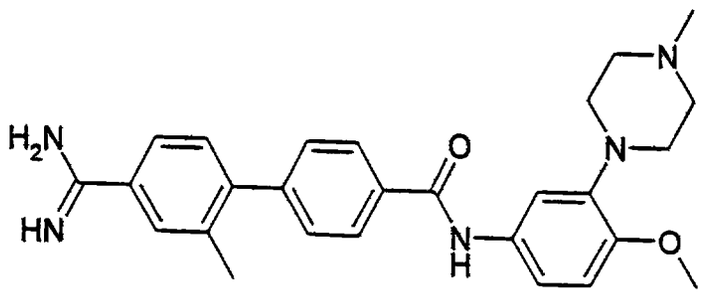
N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazole-3-yl)-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazole-3-yl)-biphenyl-4-carboxamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazole-3-yl)-biphenyl-4-carboxamide, m.p. 97-99°.

Example 4

200 mg N-[4-Methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-carboxamide was dissolved into a mixture of 50 ml of methanol and 10 ml of acetic acid, followed by the addition of Raney-Ni slurry in water. The mixture was hydrogenated for 12 hours. Filtration, washing with acetic acid and evaporation of the filtrate afforded an oil residue. After customary working up N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-amidinyl-biphenyl-4-carboxamide



is obtained: 140 mg, m.p. 159-162°; IR (KBr) 3300, 2935, 2801, 1645, 1607, 1508 cm^{-1}; FAB m/z 458.

Analogously, by hydrogenation of

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazole-3-yl)-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazole-3-yl)-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazole-3-yl)-biphenyl-4-carboxamide

the following compounds are obtained

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-amidinyl-biphenyl-4-sulfonamide,

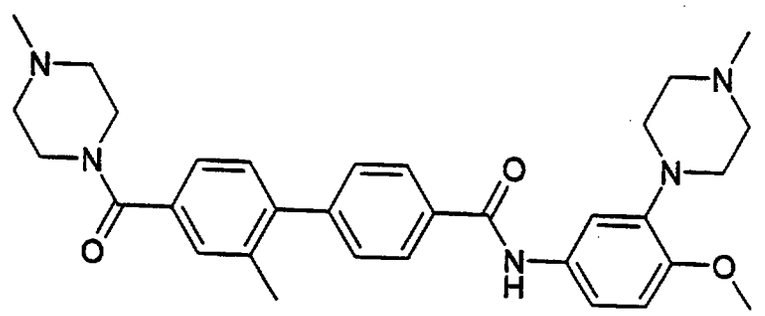
N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-amidinyl-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-amidinyl-biphenyl-4-carboxamide.

Example 5

3 ml $SOCl_2$ was added to a solution of 338 mg of 2'-Methyl-4'-(4-methyl-piperazine-1-carbonyl)-biphenyl-4-carboxylic acid [obtainable by reacting 4-carboxy-phenylboronic acid with (4-bromo-3-methyl-phenyl)-(4-methyl-

piperazine-1-yl)-methanone under Suzuki conditions] and 1 ml triethylamine in 15 ml CH_2Cl_2. The solution was refluxed for 30 minutes. The solvents were removed and 10 ml CH_2Cl_2 was added. The solution was cooled to 0° and 2 ml triethylamine was added followed by addition of 265 mg 4-methoxy-3-(N-methylpiperazino)aniline. After stirring for 15 hours and customary working up 210 mg of N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(4-methyl-piperazine-1-carbonyl)-biphenyl-4-carboxamide,



is obtained, m.p. 195-197°; MS (APCI) 524 [M+1]; IR: 3430, 1663 cm^{-1}.

Analogously, by reacting 2'-Methyl-4'-(4-methyl-piperazine-1-carbonyl)-biphenyl-4-carboxylic acid with 2,4-dimethoxy-3-(N-methylpiperazino)-aniline the compound N-[2,4-dimethoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(4-methyl-piperazine-1-carbonyl)-biphenyl-4-carboxamide is obtained, EI 571; FAB 572; Rf 0.14 (CH_2Cl_2/EtOH 4:1).

Example 5'

Analogously to example 5, by reacting 2'-methyl-4'-(4-methyl-piperazine-1-yl-carbonyl)-biphenyl-4-carboxylic acid with 4-methoxy-3-(N-methyl-pyrrolidin-3-yl)-aniline the compound N-[4-methoxy-3-(N'-methylpyrrolidin-3-yl)-phenyl]-2'-methyl-4'-(4-methyl-piperazin-1-yl-carbonyl)-biphenyl-carboxamide is obtained; Rf 0.25 (CH_2Cl_2/EtOH/25% aq. NH_4OH 80:20:1).

Example 6

7.9 g 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) was stirred with 50 g chloromethylated polystyrene-divinylbenzene 2 % resin in 400 ml

DMF at 100° for 24 hours. Filtration, washing and drying provided 53 g P-EDC.

A suspension of 0.3 mmol methylpiperazine, 0.45 mmol N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-carboxy-biphenyl-4-carboxamide ("E") [obtainable by reaction of 4-carboxy-2-methyl-phenylboronic acid with N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-4-brom-phenyl-carboxamide under Suzuki conditions], and 1.0 g P-EDC in 8 ml $CHCl_3$/THF (7:1) was stirred at room temperature for 48 hours. After filtration the polymer was washed with $CHCl_3$. After removing of the solvents N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(4-methyl-piperazine-1-carbonyl)-biphenyl-4-carboxamide, m.p. 195-197°, is obtained.

Analogously, by reacting "E" with

N^1,N^1-dimethyl-ethane-1,2-diamine,
N^1,N^1-dimethyl-propane-1,3-diamine,
4-amino-N-methyl-piperidine,
3-amino-N-methyl-pyrrolidine,
4-dimethylamino-piperidine,
3-dimethylamino-piperidine,
morpholine

the following compounds are obtained

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(2-dimethylamino-ethyl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(3-dimethylamino-propyl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(N-methyl-piperidine-4-yl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(N-methyl-pyrrolidine-3-yl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(4-dimethylamino-piperidine-1-yl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(3-dimethylamino-piperidine-1-yl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(morpholin-4-ylcarbonyl)-biphenyl-4-carboxamide.

Analogously, by reacting N-[4-Methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-carboxy-biphenyl-4-carboxamide with

N^1,N^1-dimethyl-ethane-1,2-diamine,
N^1,N^1-dimethyl-propane-1,3-diamine,
4-amino-N-methyl-piperidine,
3-amino-N-methyl-pyrrolidine,
4-dimethylamino-piperidine,
3-dimethylamino-piperidine,
morpholine

the following compounds are obtained

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(2-dimethylamino-ethyl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(3-dimethylamino-propyl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(N-methyl-piperidine-4-yl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(N-methyl-pyrrolidine-3-yl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(4-dimethylamino-piperidine-1-yl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(3-dimethylamino-piperidine-1-yl)-aminocarbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(morpholin-4-ylcarbonyl)-biphenyl-4-carboxamide,

Example 7

Analogously to Example 6, by reacting N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-carboxy-biphenyl-4-sulfonamide [obtainable by reaction of 4-carboxy-2-methyl-phenylboronic acid with N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-4-brom-phenyl-sulfonamide under Suzuki conditions],
with

N^1,N^1-dimethyl-ethane-1,2-diamine,
N^1,N^1-dimethyl-propane-1,3-diamine,
4-amino-N-methyl-piperidine,
3-amino-N-methyl-pyrrolidine,
4-dimethylamino-piperidine,
3-dimethylamino-piperidine,
morpholine,
1-methyl-piperazine

the following compounds are obtained

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(2-dimethylamino-ethyl)-aminocarbonyl]-biphenyl-4-sulfonamide, mp. 117-120°,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(3-dimethylamino-propyl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(N-methyl-piperidine-4-yl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(N-methyl-pyrrolidine-3-yl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(4-dimethylamino-piperidine-1-yl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(3-dimethylamino-piperidine-1-yl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(morpholin-4-ylcarbonyl)-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(1-methyl-piperazin-4-ylcarbonyl)-biphenyl-4-sulfonamide, EI 577.

Analogously, by reacting N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-carboxy-biphenyl-4-sulfonamide with

N^1,N^1-dimethyl-ethane-1,2-diamine,
N^1,N^1-dimethyl-propane-1,3-diamine,
4-amino-N-methyl-piperidine,
3-amino-N-methyl-pyrrolidine,
4-dimethylamino-piperidine,
3-dimethylamino-piperidine,
morpholine

the following compounds are obtained

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(2-dimethylamino-ethyl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(3-dimethylamino-propyl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(N-methyl-piperidine-4-yl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(N-methyl-pyrrolidine-3-yl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(4-dimethylamino-piperidine-1-yl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-[(3-dimethylamino-piperidine-1-yl)-aminocarbonyl]-biphenyl-4-sulfonamide,

N-[4-methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(morpholin-4-ylcarbonyl)-biphenyl-4-sulfonamide.

Example 8

Analogously to Example 6, by reacting "E" with

1-methylhomopiperazine,
2-(N,N-dimethylaminomethyl)-pyrrolidine,
C-(N-methyl-pyrrolidin-2-yl)-methylamine,
2-(pyrrolidin-1-ylmethyl)-pyrrolidine,
2-(N,N-diethylaminomethyl)-piperidine,
2-(morpholin-4-yl)-ethylamine

the following compounds are obtained

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(1-methyl-homopiperazin-4-yl)-carbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(2-(N,N-dimethylaminomethyl)-pyrrolidin-1-yl)-carbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(N-methyl-pyrrolidin-2-yl)-methylaminocarbonyl]-biphenyl-4-carboxamide,

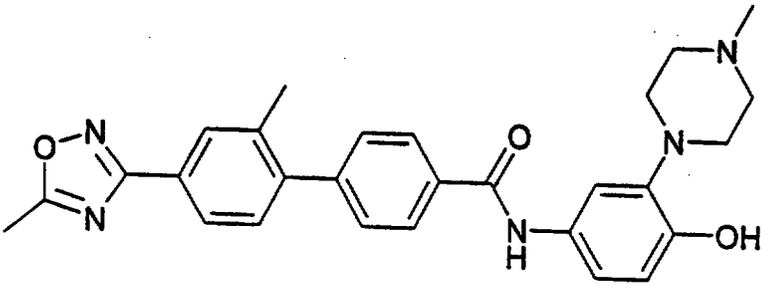
N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(2-(pyrrolidin-1-ylmethyl)-pyrrolidin-1-yl)-carbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(2-(N,N-diethylaminomethyl)-piperidin-1-yl)-carbonyl]-biphenyl-4-carboxamide,

N-[4-methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-[(2-(morpholin-4-yl)-ethylamino)-carbonyl]-biphenyl-4-carboxamide.

Example 9

A solution of 200 mg N-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-carboxamide in 3.0.ml EtSH and 2 ml CH_2Cl_2 is cooled to 0°. 1.0 g $AlCl_3$ is added and the mixture is stirred for 15 hours at rt. 20 ml ice-water is added, neutralized with $NaHCO_3$ (powder) until the pH of the solution is about 8, and extracted with CH_2Cl_2 (4 x 30 ml). The combined organic layers are dried ($MgSO_4$), filtered by suction and evaporated to give 200 mg N-[4-hydroxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-carboxamide, which is purified by flash chromatography and recrystallized from 1:2 ethylacetate/hexane to afford 140 mg: m.p. 140-142°; IR (KBr) 3296 (brs), 1504 (s), 1425 (s), 1261 (s) cm^{-1}; EI 483

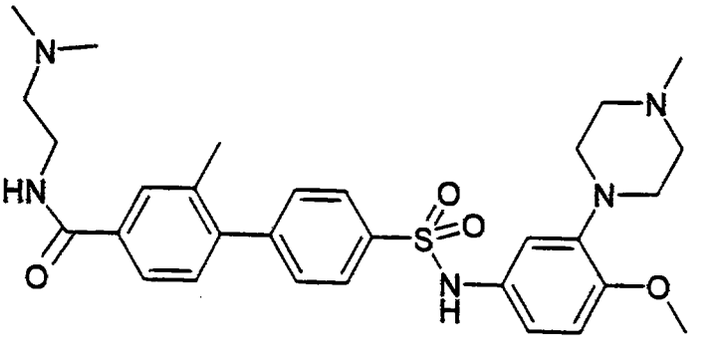


Analogously, N-[4-hydroxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-carboxamide is obtained: m.p. 149-152°; IR (KBr) 3504, 3350, 3294, 1646, 1505, 1262, 1241 cm^{-1}.

Example 10

Analogously to example 3, by reacting 180 mg "B" with 143 mg of N-[2-(N,N-dimethylamino)-ethyl]-4-bromo-3-methyl-benzene-carboxamide [obtained from 4-bromo-3-methyl-benzene-carboxylic acid with N',N'-dimethyl-ethane-1,2-diamine] the compound N-[4-methoxy-3-(4-methyl-

piperazin-1-yl)-phenyl]-2'-methyl-4'-[(2-dimethylamino-ethyl)-aminocarbonyl]-biphenyl-4-sulfonamid



is obtained: 120 mg; m.p. 117-120°; Rf: 0.22 (CH_2Cl_2/EtOH/ 25% aq. NH_4OH 90:10:1); IR (KBr) 1642 cm^{-1}.

Analogously, by reacting "B" with

N-methyl-N-(2-dimethylamino-ethyl)-4-bromo-3-methyl-benzene-carboxamide,
N-(3-dimethylamino-propyl)-4-bromo-3-methyl-benzene-carboxamide,
N-methyl-N-(3-dimethylamino-propyl)-4-bromo-3-methyl-benzene-carboxamide,

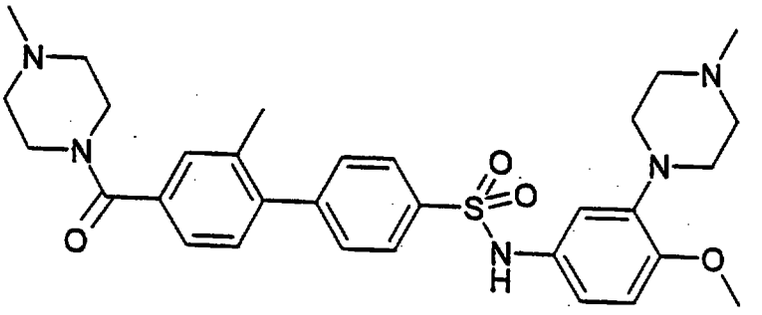
the following compounds are obtained

N-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-[N'-methyl-N'-(2-dimethylamino-ethyl)-aminocarbonyl]-biphenyl-4-sulfonamide,
N-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-[N'-(3-dimethylamino-propyl)-aminocarbonyl]-biphenyl-4-sulfonamide,
N-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-[N'-methyl-N'-(3-dimethylamino-propyl)-aminocarbonyl]-biphenyl-4-sulfonamide.

Example 11

Analogously to example 3, by reacting 350 mg "B" with 230 mg of 4-methyl-1-(4'-bromo-3'-methyl-phenyl-1'-carbonyl)-piperazine the compound

N-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(4-methyl-piperazine-1-carbonyl)-biphenyl-4-sulfonamid



is obtained: 300 mg; m.p. 106-108°.

Analogously, by reacting "B" with

1-(4'-N,N-dimethylamino-piperidine-1'-carbonyl)-4-bromo-3-methyl-benzene,
N-(N-methyl-piperidin-4-yl)-4-bromo-3-methyl-benzene-carboxamide

the following compounds are obtained

N-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(4-dimethylamino-piperidine-1-yl-carbonyl)-biphenyl-4-sulfonamide,
N-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(1-methyl-piperidine-4-yl-aminocarbonyl)-biphenyl-4-sulfonamide.

Example 12

Analogously to example 6, by reacting 2'-methyl-4'-(4-methyl-piperazine-1-yl-carbonyl)-biphenyl-4-carboxylic acid with 2,4-dimethoxy-3-(4-methyl-piperazin-1-yl)-aniline the compound N-[2,4-dimethoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(4-methyl-piperazin-1-yl-carbonyl)-biphenyl-4-carboxamide is obtained, Rf 0.14 (CH_2Cl_2/EtOH 4:1); FAB 572.

Example 13

A solution of 40 mg N-[4-hydroxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-carboxamide and 0.1 ml triethylamine in 3 ml CH_2Cl_2 is cooled to 0° and treated with 0.06 ml methylsulfonyl chloride for 1 hour. To the mixture is added 0.1 ml 2N NaOH and 2 g SiO_2. After evaporation, the residue is purified by flash chromatography and recrystallized from EtOAc-hexane. 40 mg of N-[4-methanesulfonyloxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-carboxamide is obtained, m.p. 194-197°; IR (KBr) 3420 (brm), 2977 (s), 2941 (s), 2603 (vs), 2496 (vs), 1655 (s), 1397 (s), 1186 (s), 1037 (s) cm^{-1}; EI 561.

Analogously, N-[4-trifluoromethanesulfonyloxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-carboxamide is obtained, m.p. 140°; IR (KBr) 3416 (brm), 1676 (m), 1595 (s), 1422 (s), 1212 (brs), 1139 (s) cm^{-1}.

Example 14

A solution of 120 mg N-[4-hydroxy-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-carboxamide, 52 mg $BrCH_2CH_2F$ and 600 mg $CsCO_3$ in 15 ml acetonitrile is refluxed for 3 hours. Acetonitrile is removed and after customary working-up 94 mg N-[4-(2-fluoroethyl)-3-(4-methyl-piperazin-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-carboxamide is obtained, m.p. 128-130°, IR (KBr) 3417 (brm), 1654 (m), 1643 (m), 1607 (m), 1507 (m), 1257 (s), 1230 (s) cm^{-1}; EI 529.

The examples which follow relate to pharmaceutical products:

Example A: Vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogen phosphate in 3 l of twice-distilled water is brought to pH 6.5 with 2N hydrochloric acid, filter-sterilized, filled into vials, lyophilized under sterile conditions and sealed in sterile form. Each vial comprises 5 mg of active ingredient.

Example B: 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, and the mixture is poured into moulds and left to cool. Each suppository comprises 20 mg of active ingredient.

Example C: Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of twice-distilled water. The pH is brought to 6.8, and the solution is made up to 1 l and sterilized by irradiation. This solution can be used in the form of eyedrops.

Example D: Ointment

500 mg of an active ingredient 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 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 tableted in the customary manner in such a way that each tablet comprises 10 mg of active ingredient.

Example F: Sugar-coated tablets

A mixture is tableted analogously to Example E, and the tablets are subsequently coated in the customary manner with a coating of sucrose, potato starch, talc, tragacanth and colouring.

Example G: capsules

2 kg of active ingredient of the formula I are filled into hard gelatin capsules in the customary manner so that each capsule comprises 20 mg of the active ingredient.

Example H: Ampoules

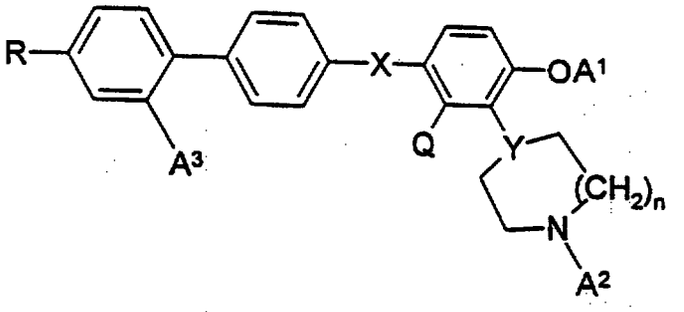
A solution of 1 kg of active ingredient of the formula I in 60 l of twice-distilled water is filter-sterilized, filled into ampoules, lyophilized under sterile conditions and sealed in sterile form. Each ampoule comprises 10 mg of active ingredient.

Example I: Spray for inhalation

14 g of active ingredient of the formula I are dissolved in 10 l of isotonic NaCl solution, and the solution is filled into commercially available pump-operated spray containers. The solution can be sprayed into mouth or nose. One actuation (approximately 0.1 ml) corresponds to a dose of approximately 0.14 mg.

Patent Claims

1. Biphenyl derivatives of formula I



I

wherein

R is -C(=NH)-NH_2, -C(=NH)-NHA^3, -C(=NH)-NHAc, -C(=NH)-$NHSO_2CH_3$, R^2, -CO-NH-Z-R^3 or -CO-R^1,

X is -CONH-, -SO_2NH-, -NHCO- or -$NHSO_2$-,

Y is CH or N,

A^1 H, alkyl having 1 to 6 C atoms wherein 1 to 7 H atoms can be replaced by F, SO_2CH_3 or SO_2CF_3,

A^2 H or alkyl having 1 to 6 C atoms,

A^3, A^5 in each case independently of one another are alkyl having 1 to 6 C atoms,

A^6, A^7 in each case independently of one another are H or $(CH_2)_pCH_3$,

Q H or OA^1,

R^1 is 4-A^5-piperazin-1-yl, 4-A^5-homopiperazinyl, 1-pyrrolidinyl which is substituted once by R^4 or -Z-R^4, 1-piperidinyl which is substituted once by R^4 or -Z-R^4, N-A^5-pyrrolidinyl-amino, N-A^5-piperidinyl-amino, N-A^5-pyrrolidinyl-Z-amino, N-A^5-piperidinyl-Z-amino, -N(A^6)(ZR^3) or NA^6A^7,

R^2 is 5-methyl-1,3,4-oxadiazol-2-yl or 5-methyl-1,2,4-oxadiazol-3-yl,

R^3, R^4 in each case independently of one another are NHA^5, $N(A^5)_2$, 4-morpholinyl, 1-pyrrolidinyl or 1-piperidinyl,

Z is alkylene having 1 to 6 C atoms,

n is 0 or 1

p is 0, 1 or 2,

with the proviso that, if Y is N, X = -CONH- and n =1,
then $R \neq R^2$ or $R \neq -CONA^6A^7$,

including the racemate and the enantiomers,
and the physiologically acceptable salts and solvates thereof.

2. Compounds of the formula I according to Claim 1

a) N-[4-Methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-amidinyl-biphenyl-4-carboxamide;

b) N-[4-Methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-sulfonamide;

c) N-[4-Methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-carboxamide;

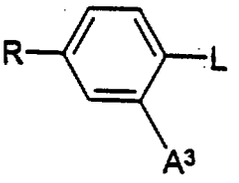
d) N-[4-Methoxy-3-(N-methyl-pyrrolidine-3-yl)-phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-sulfonamide;

e) N-[4-Methoxy-3-(4-methyl-piperazine-1-yl)-phenyl]-2'-methyl-4'-(4-methyl-piperazin-1-carbonyl)-biphenyl-4-carboxamide;

and the physiologically acceptable salts and solvates thereof.

3. A process for the preparation of compounds of formula I according to Claim 1 and salts and solvates thereof, characterized in that

a) a compound of formula II

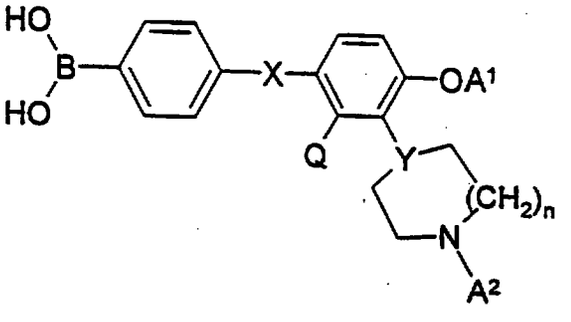


II

wherein

L is Cl, Br, I or an OH group functionally modified to form a reactive group, especially a suitable leaving group, and R and A^3 are as defined,

is reacted with a boronic acid derivative of formula III



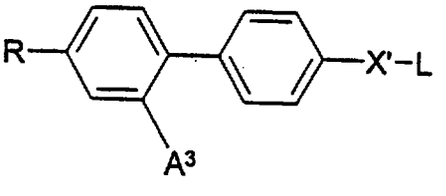
III

wherein

X, Y, A^1, A^2, Q and n are as defined,

or

b) a compound of the formula IV



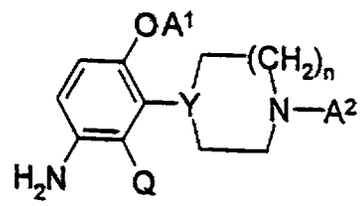
IV

wherein

R and A^3 are as defined, X' is CO or SO_2 and

L is Cl, Br, I or an OH group functionally modified to form a reactive group, especially a suitable leaving group,

is reacted with a compound of formula V



V

wherein

Y, A^1, A^2 and n are as defined,

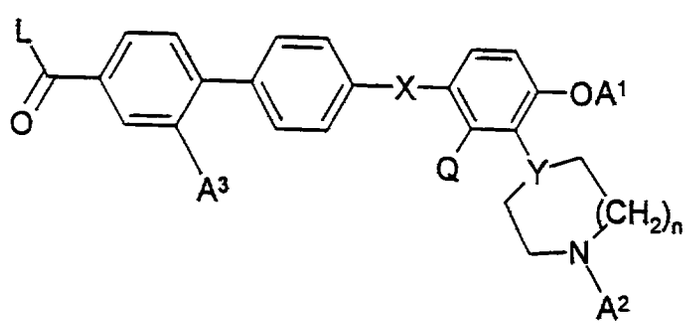
or

c) for the preparation of a compound of the formula I

wherein

R is -CO-NH-Z-R^3 or -CO-R^1

a compound of the formula VI



VI

wherein

L is Cl, Br, I or a free or reactive functionally modified OH group,

and X, Y, A^1, A^2, A^3, Q and n are as defined,

is reacted with a compound of formula VII

H-R' VII

wherein

R' is NH-Z-R^3 or R^1,

and Z, R^3 and R^1 are as defined,

and/or in that in a compound of the formula I one or more radicals R, Q, A^1 and/or A^2 is converted into one or more other radicals R, Q, A^1 and/or A^2,

by

i) converting a group R^2 into an amidino group,

ii) hydrolysing an ether group to a hydroxyl group,

iii) converting a hydroxy group into a sulfonyloxy group

and/or a basic compound of the formula I is converted into a salt thereof by treatment with an acid.

4. Process for the preparation of pharmaceutical products, characterized in that a compound of the formula I according to Claim 1 and/or a physiologically acceptable salt or solvate thereof is brought into a suitable pharmaceutical form together with at least one solid, liquid or semi-liquid excipient or auxiliary.

5. Pharmaceutical preparation, characterized in that it comprises at least one compound of the formula I according to Claim 1 and/or a physiologically acceptable salt or solvate thereof.

6. Compounds of the formula I according to Claim 1 and the physiologically acceptable salts and solvates thereof as serotonin ($5\text{-}HT_{1B/D}$) antagonists.

7. Compounds of the formula I according to Claim 1 and the physiologically acceptable salts and solvates thereof for the

treatment or prophylaxis of mood disorders, including depression and dysthymia, anxiety disorder including generalized anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, memory disorders, including dementia, amnestic disorders and age-associated memory impairment, Parkinson's disease, 5-HT-dependent tumor cell growth, disorders of eating behaviors, including anorexia nervosa and bulimia, cardiovascular disorders characterized by the malfunction of peripheral 5-$HT_{1B/D}$ receptors, endocrine disorders, vasospasm, hypertension, disorders of the gastrointestinal tract where changes in motility and secretion are involved, and sexual dysfunction.

8. Use of compounds of the formula I according to Claim 1 and/or of the physiologically acceptable salts or solvates thereof for the preparation of a pharmaceutical having serotonin antagonistic properties for the treatment or prophylaxis of depression, generalized anxiety, obsessive compulsive disorder and bulimia.

9. Use of compounds of the formula I according to Claim 1 and/or of the physiologically acceptable salts or solvates thereof for the treatment or prophylaxis of depression, generalized anxiety, obsessive compulsive disorder and bulimia.

* C L M S *