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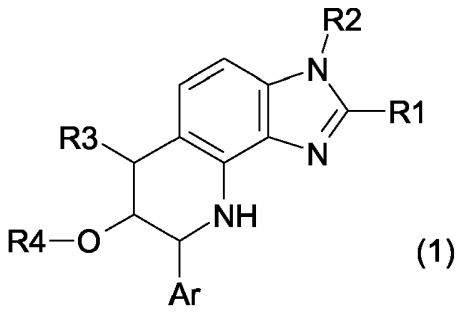
(54) Title: SUBSTITUTED TRICYCLIC BENZIMIDAZOLES



(1)

(57) Abstract: The invention relates to substituted tricyclic benzimidazoles of the formula (1) in which the substituents and symbols have the meanings indicated in the description. The compounds have gastric secretion inhibiting and excellent gastric and intestinal protective action properties.

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Novel substituted tricyclic Benzimidazoles

Technical field

The invention relates to novel compounds, which are used in the pharmaceutical industry as active compounds for the production of medicaments.

Prior art

In the international patent application WO 97/47603 (which corresponds to the US Patent 6,465,505), benzimidazole derivatives having a very specific substitution pattern are disclosed, which are said to be suitable for inhibition of gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases.

In the international patent applications WO 04/054984 (ALTANA Pharma AG) substituted, bicyclic benzimidazole derivatives are disclosed which have gastric secretion inhibiting and excellent gastric and intestinal protective action properties.

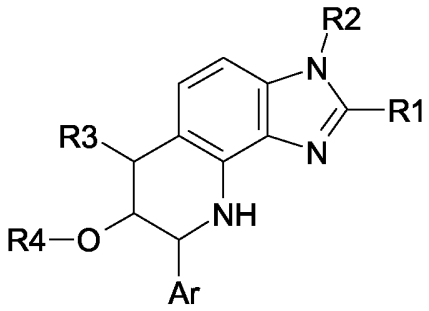
In the International Patent Applications WO 04/087701 and WO 05/058893 (ALTANA Pharma AG) tricyclic benzimidazole derivatives with a certain substitution pattern are disclosed. These compounds likewise have gastric secretion inhibiting and excellent gastric and intestinal protective action properties.

The International Patent Applications WO 98/42707, WO 00/17200, WO 00/26217, WO 00/63211, WO 01/72756, WO 01/72754, WO 02/34749 and WO 03/016310 (all ALTANA Pharma AG) disclose tricyclic imidazopyridine derivatives having a specific substitution pattern, which compounds are likewise said to be suitable for treating gastrointestinal disorders.

Kaminski et. al. describe in J. Med. Chem. 1989, 32, 1686 the synthesis and configurations of imidazo[1,2-a]pyridines and their anti-ulcer activity. In a latter publication by Kaminski et. al. (J. Med Chem., 1991, 34, 533), the inhibition of gastric H+/K+-ATPase by certain substituted imidazo[1,2-a]pyridines is described.

Summary of the invention

The invention relates to condensed benzimidazoles of the formula 1



(1)

in which

R1 is hydrogen, halogen, hydroxyl, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl, hydroxy-1-4C-alkyl or mono- or di-1-4C-alkylamino,

R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl, hydroxy-1-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, 2-4C-alkenyl, aryl-2-4C-alkenyl, cyano-1-4C-alkyl, or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, dihydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 3-7C-cycloalkyl, dihydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxy-pyrrolidino, azetidino, aziridino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl

Ar is a mono- or bicyclic aromatic residue, substituted by R5, R6, R7 and R8, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,

wherein

R5 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R6 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R7 is hydrogen, 1-4C-alkyl or halogen and

R8 is hydrogen, 1-4C-alkyl or halogen,

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and the salts of these compounds.

Halogen within the meaning of the invention is bromo, chloro and fluoro.

1-4C-Alkyl represents a straight-chain or branched alkyl group having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and the methyl group.

3-7C-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkyl-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned 3-7C-cycloalkyl groups. Examples which may be mentioned are the cyclopropylmethyl, the cyclohexylmethyl and the cyclohexylethyl group.

1-4C-Alkoxy represents a group, which in addition to the oxygen atom contains one of the aforementioned 1-4C-alkyl groups. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy group.

1-4C-Alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned 1-4C-alkoxy groups. Examples which may be mentioned are the methoxymethyl, the methoxyethyl group and the butoxyethyl group.

1-4C-Alkoxycarbonyl (1-4C-alkoxy-CO-) represents a carbonyl group, to which one of the aforementioned 1-4C-alkoxy groups is bonded. Examples which may be mentioned are the methoxycarbonyl (CH_3O-C(O)-) and the ethoxycarbonyl group (CH_3CH_2O-C(O)-) .

2-4C-Alkenyl represents a straight-chain or branched alkenyl group having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butenyl, 3-butenyl, 1-propenyl and the 2-propenyl group (allyl group).

2-4C-Alkynyl represents a straight-chain or branched alkynyl group having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butynyl, 3-butynyl, and preferably the 2-propynyl, group (propargyl group).

Fluoro-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one or more fluorine atoms. Examples which may be mentioned are the trifluoromethyl, the difluoromethyl, the 2-fluoroethyl, the 2,2-difluoroethyl or the 2,2,2-trifluoroethyl group.

Hydroxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by a hydroxy group. Examples which may be mentioned are the hydroxymethyl, the 2-hydroxyethyl and the 3-hydroxypropyl group. Hydroxy-1-4C-alkyl within the scope of the invention is understood to include 1-4C-alkyl groups with two or more hydroxy groups. Examples which may be mentioned are the 3,4-dihydroxybutyl and in particular the 2,3-dihydroxypropyl group.

Mono- or di-1-4C-alkylamino represents an amino group, which is substituted by one or by two - identical or different - groups from the aforementioned 1-4C-alkyl groups. Examples which may be mentioned are the dimethylamino, the diethylamino and the diisopropylamino group.

Mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl represents a 1-4C-alkylcarbonyl group, which is substituted by a mono- or di-1-4C-alkylamino group. Examples, which may be mentioned, are the dimethylamino-methyl-carbonyl and the diethylamino-methylcarbonyl group.

Fluoro-2-4C-alkyl represents a 2-4C-alkyl group, which is substituted by one or more fluorine atoms. An example which may be mentioned is the 2,2,2-trifluoroethyl group.

Aryl-2-4C-alkinyl represents a 2-4C-alkynyl group, which is substituted by one aryl group. Preferred groups of this type are aryl-ethinyl groups. Examples which may be mentioned are the phenyl-ethinyl, 4-methylphenyl-ethinyl, 2-fluorophenyl-ethinyl or the 4-fluorophenyl-ethinyl group.

Aryl-2-4C-alkenyl represents a 2-4C-alkenyl group, which is substituted by one aryl group. Preferred groups of this type are 2-aryl-vinyl groups. Examples which may be mentioned are the 2-phenyl-vinyl, 2-(4-methylphenyl)-vinyl, 2-(2-fluorophenyl)-vinyl or the 2-(4-fluorophenyl)-vinyl group.

Cyano-1-4C-alkyl represents a 1-4C-alkyl group, which is substituted by one cyano group. Examples which may be mentioned are the cyanomethyl, the 2-cyanoethyl and the 3-cyanopropyl group.

NR31R32-carbonyl-1-4C-alkyl represents a 1-4C-alkyl group, which is substituted by a carbonyl to which is bonded the nitrogen containing residue NR31R32 via its nitrogen atom. R31 and R32 are defined as described above. Preferred groups of this type are NR31R32-carbonyl-CH_2- groups.

Examples which may be mentioned are the carbamoyl (H_2N-C(O)-CH_2-), the $CH_3N(H)$-C(O)-CH_2-, the $(CH_3)_2N$-C(O)-CH_2-, the $CH_3OCH_2CH_2$-N(H)-C(O)-CH_2-, the $CH_3OCH_2CH_2$-$N(CH_3)$-C(O)-CH_2-, the $HOCH_2CH_2$-N(H)-C(O)-CH_2- or the $HOCH_2CH_2$-$N(CH_3)$-C(O)-CH_2- group.

1-7C-Alkyl represents a straight-chain or branched alkyl group having 1 to 7 carbon atoms. Examples which may be mentioned are the heptyl, isoheptyl (5-methylhexyl), hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethylbutyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and the methyl group.

Dihydroxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by two hydroxy groups. Examples which may be mentioned are the 3,4-dihydroxybutyl and in particular the 2,3-dihydroxypropyl group.

1-4C-Alkoxy-1-4C-alkyl-carbonyl represents a carbonyl group, to which one of the aforementioned 1-4C-alkoxy-1-4C-alkyl groups is bonded. Examples which may be mentioned are the methoxy-methyl-carbonyl (CH_3-O-CH_2-CO-) and the ethoxy-methyl-carbonyl group (CH_3CH_2-O-CH_2-CO-).

Groups Ar which may be mentioned are, for example, the following substituents: 4-acetoxyphenyl, 4-acetamidophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 3-benzyloxy-4-methoxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3,5-bis(trifluoromethyl)phenyl, 4-butoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-chloro-6-fluorophenyl, 3-chloro-4-fluorophenyl, 2-chloro-5-nitrophenyl, 4-chloro-3-nitrophenyl, 3-(4-chlorophenoxy)phenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 2,4-dihydroxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxy-5-hydroxyphenyl, 2,5-dimethylphenyl, 3-ethoxy-4-hydroxyphenyl, 2-fluorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2-hydroxy-5-nitrophenyl, 3-methoxy-2-nitrophenyl, 3-nitrophenyl, 2,3,5-trichlorophenyl, 2,4,6-trihydroxyphenyl, 2,3,4-trimethoxyphenyl, 2-hydroxy-1-naphthyl, 2-methoxy-1-naphthyl, 4-methoxy-1-naphthyl, 1-methyl-2-pyrrolyl, 2-pyrrolyl, 3-methyl-2-pyrrolyl, 3,4-dimethyl-2-pyrrolyl, 4-(2-methoxycarbonylethyl)-3-methyl-2-pyrrolyl, 5-ethoxycarbonyl-2,4-dimethyl-3-pyrrolyl, 3,4-dibromo-5-methyl-2-pyrrolyl, 2,5-dimethyl-1-phenyl-3-pyrrolyl, 5-carboxy-3-ethyl-4-methyl-2-pyrrolyl, 3,5-dimethyl-2-pyrrolyl, 2,5-dimethyl-1-(4-trifluoromethylphenyl)-3-pyrrolyl, 1-(2,6-dichloro-4-trifluoromethylphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(2-fluorophenyl)-2-pyrrolyl, 1-(4-trifluoromethoxyphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(4-ethoxycarbonyl)-2,5-dimethyl-3-pyrrolyl, 5-chloro-1,3-dimethyl-4-pyrazolyl, 5-chloro-1-methyl-3-trifluoromethyl-4-pyrazolyl, 1-(4-chlorobenzyl)-5-pyrazolyl, 1,3-dimethyl-5-(4-chlorphenoxy)-4-pyrazolyl, 1-methyl-3-trifluomethyl-5-(3-trifluoromethylphenoxy)-4-pyrazolyl, 4-methoxycarbonyl-1-(2,6-dichlorophenyl)-5-pyrazolyl, 5-allyloxy-1-methyl-3-trifluoromethyl-4-pyrazolyl, 5-chloro-1-phenyl-3-trifluoromethyl-4-pyrazolyl, 3,5-dimethyl-1-phenyl-4-imidazolyl, 4-bromo-1-methyl-5-imidazolyl, 2-butylimidazolyl, 1-phenyl-1,2,3-triazol-4-yl, 3-indolyl, 4-indolyl, 7-indolyl, 5-methoxy-3-indolyl, 5-benzyloxy-3-indolyl, 1-benzyl-3-indolyl, 2-(4-chlorophenyl)-3-indolyl, 7-benzyloxy-3-indolyl, 6-benzyloxy-3-indolyl, 2-methyl-5-nitro-3-

indolyl, 4,5,6,7-tetrafluoro-3-indolyl, 1-(3,5-difluorobenzyl)-3-indolyl, 1-methyl-2-(4-trifluorophenoxy)-3-indolyl, 1-methyl-2-benzimidazolyl, 5-nitro-2-furyl, 5-hydroxymethyl-2-furyl, 2-furyl, 3-furyl, 5-(2-nitro-4-trifluoromethylphenyl)-2-furyl, 4-ethoxycarbonyl-5-methyl-2-furyl, 5-(2-trifluoromethoxyphenyl)-2-furyl, 5-(4-methoxy-2-nitrophenyl)-2-furyl, 4-bromo-2-furyl, 5-dimethylamino-2-furyl, 5-bromo-2-furyl, 5-sulfo-2-furyl, 2-benzofuryl, 2-thienyl, 3-thienyl, 3-methyl-2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-nitro-2-thienyl, 5-methyl-2-thienyl, 5-(4-methoxyphenyl)-2-thienyl, 4-methyl-2-thienyl, 3-phenoxy-2-thienyl, 5-carboxy-2-thienyl, 2,5-dichloro-3-thienyl, 3-methoxy-2-thienyl, 2-benzothienyl, 3-methyl-2-benzothienyl, 2-bromo-5-chloro-3-benzothienyl, 2-thiazolyl, 2-amino-4-chloro-5-thiazolyl, 2,4-dichloro-5-thiazolyl, 2-diethylamino-5-thiazolyl, 3-methyl-4-nitro-5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 6-methyl-2-pyridyl, 3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl, 2,6-dichloro-4-pyridyl, 3-chloro-5-trifluoromethyl-2-pyridyl, 4,6-dimethyl-2-pyridyl, 4-(4-chlorophenyl)-3-pyridyl, 2-chloro-5-methoxycarbonyl-6-methyl-4-phenyl-3-pyridyl, 2-chloro-3-pyridyl, 6-(3-trifluoromethylphenoxy)-3-pyridyl, 2-(4-chlorophenoxy)-3-pyridyl, 2,4-dimethoxy-5-pyrimidinyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 2-chloro-3-quinolinyl, 2-chloro-6-methoxy-3-quinolinyl, 8-hydroxy-2-quinolinyl and 4-isoquinolinyl.

2-4C-Alkenyloxy represents a group, which in addition to the oxygen atom contains one of the above-mentioned 2-4C-alkenyl groups. Examples, which may be mentioned, are the 2-butenyloxy, 3-butenyloxy, 1-propenyloxy and the 2-propenyloxy group (allyloxy group).

1-4C-Alkylcarbonyl represents a group, which in addition to the carbonyl group contains one of the abovementioned 1-4C-alkyl groups. An example which may be mentioned is the acetyl group.

Carboxy-1-4C-alkyl represents a 1-4C-alkyl group which is substituted by a carboxyl group. Examples, which may be mentioned, are the carboxymethyl and the 2-carboxyethyl group.

1-4C-Alkoxycarbonyl-1-4C-alkyl represents a 1-4C-alkyl group, which is substituted by one of the abovementioned 1-4C-alkoxycarbonyl groups. Examples, which may be mentioned, are the Methoxycarbonylmethyl and the ethoxycarbonylmethyl group.

Aryl-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the abovementioned aryl groups. An exemplary preferred aryl-1-4C-alkyl group is the benzyl group.

Aryl-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the abovementioned aryl groups. An exemplary preferred aryl-1-4C-alkoxy group is the benzyloxy group.

1-4C-Alkylcarbonylamino represents an amino group to which a 1-4C-alkylcarbonyl group is bonded. Examples which may be mentioned are the propionylamino ($C_3H_7C(O)NH$-) and the acetylamino group (acetamido group) ($CH_3C(O)NH$-) .

1-4C-Alkoxycarbonylamino represents an amino group, which is substituted by one of the aforementioned 1-4C-alkoxycarbonyl groups. Examples, which may be mentioned, are the ethoxycarbonylamino and the methoxycarbonylamino group.

1-4C-Alkoxy-1-4C-alkoxycarbonyl represents a carbonyl group, to which one of the aforementioned 1-4C-alkoxy-1-4C-alkoxy groups is bonded. Examples which may be mentioned are the 2-(methoxy)ethoxycarbonyl (CH_3-O-CH_2CH_2-O-CO-) and the 2-(ethoxy)ethoxycarbonyl group (CH_3CH_2-O-CH_2CH_2-O-CO-).

1-4C-Alkoxy-1-4C-alkoxycarbonylamino represents an amino group, which is substituted by one of the aforementioned 1-4C-alkoxy-1-4C-alkoxycarbonyl groups. Examples which may be mentioned are the 2-(methoxy)ethoxycarbonylamino and the 2-(ethoxy)ethoxycarbonylamino group.

Possible salts of compounds of the formula 1 - depending on substitution - are especially all acid addition salts. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, where the acids are used in salt preparation - depending on whether a mono- or polybasic acid is concerned and on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can initially be obtained, for example, as process products in the production of the compounds according to the invention on the industrial scale, are converted into the pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to invention and their salts, if, for example, they are isolated in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula 1, and also all solvates and in particular all hydrates of the salts of the compounds of the formula 1.

The compounds of the formula 1 have at least three centers of chirality in the skeleton. The invention thus provides all feasible stereoisomers in any mixing ratio, including the pure stereoisomers, which are a preferred subject matter of the invention.

Compounds which are to be mentioned are those of the formula 1, where

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl or fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen or 1-7C-alkyl
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxy-pyrrolidino, azetidino, aziridino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,

Ar is a phenyl or thiazolyl residue, substituted by R5, R6, R7 and R8,
wherein
R5 is hydrogen, 1-4C-alkyl or halogen,
R6 is hydrogen, 1-4C-alkyl or halogen,
R7 is hydrogen, 1-4C-alkyl or halogen and
R8 is hydrogen, 1-4C-alkyl or halogen,
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and the salts of these compounds.

Compounds which are to be particularly mentioned are those of the formula 1, where

R1 is 1-4C-alkyl or 3-7C-cycloalkyl,

R2 is hydrogen, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl or 3-7C-cycloalkyl

R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,

Ar is a phenyl

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, halogen or trifluoromethyl

and the salts of these compounds.

Compounds which are also to be particularly mentioned are those of the formula 1, where

R1 is 1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl or 3-7C-cycloalkyl

R3 is 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,

Ar is a phenyl

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, halogen or trifluoromethyl

and the salts of these compounds.

Compounds which are to be emphasized are those of the formula 1, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen,

R32 is hydrogen,

R4 is hydrogen,

Ar is a phenyl

and wherein

aryl is phenyl

and the salts of these compounds.

Compounds which are to be particularly emphasized are those of the formula 1, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is 1-4C-alkyl, 3-7C-cycloalkyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group, where

R31 is hydrogen and

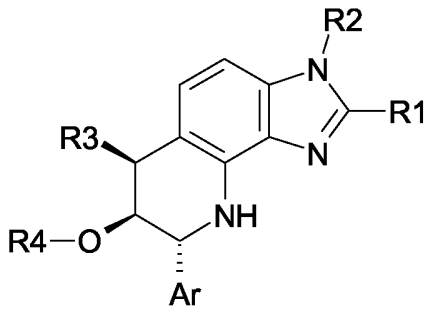
R32 is hydrogen,

R4 is hydrogen

Ar is a phenyl

and the salts of these compounds.

Among the compounds of the formula 1 according to the invention, emphasis is given to the compounds of the formula 1a,



(1a)

in which

R1 is hydrogen, halogen, hydroxyl, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl, hydroxy-1-4C-alkyl or mono- or di-1-4C-alkylamino,

R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl, hydroxy-1-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, 2-4C-alkenyl, aryl-2-4C-alkenyl, cyano-1-4C-alkyl, or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, dihydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 3-7C-cycloalkyl, dihydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino,

hydroxy-pyrrolidino, azetidino, aziridino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl

Ar is a mono- or bicyclic aromatic residue, substituted by R5, R6, R7 and R8, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,

wherein

R5 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R6 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R7 is hydrogen, 1-4C-alkyl or halogen and

R8 is hydrogen, 1-4C-alkyl or halogen,

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and the salts of these compounds.

Compounds which are to be mentioned are those of the formula 1a, where

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl or fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen or 1-7C-alkyl

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxy-pyrrolidino, azetidino, aziridino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,

Ar is a phenyl or thiazolyl residue, substituted by R5, R6, R7 and R8,
wherein
R5 is hydrogen, 1-4C-alkyl or halogen,
R6 is hydrogen, 1-4C-alkyl or halogen,
R7 is hydrogen, 1-4C-alkyl or halogen and
R8 is hydrogen, 1-4C-alkyl or halogen,
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and the salts of these compounds.

Compounds which are to be particularly mentioned are those of the formula 1, where

R1 is 1-4C-alkyl or 3-7C-cycloalkyl,

R2 is hydrogen, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl or 3-7C-cycloalkyl

R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,

Ar is a phenyl
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, halogen or trifluoromethyl

and the salts of these compounds.

Compounds which are also to be particularly mentioned are those of the formula 1a, where

R1 is 1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl or 3-7C-cycloalkyl

R3 is 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,
where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,

Ar is a phenyl
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, halogen or trifluoromethyl

and the salts of these compounds.

Compounds which are to be emphasized are those of the formula 1a, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or aryl-2-4C-alkinyl,
where
R31 is hydrogen,
R32 is hydrogen,

R4 is hydrogen,

Ar is a phenyl

and wherein

aryl is phenyl

and the salts of these compounds.

Compounds which are to be particularly emphasized are those of the formula 1a, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is 1-4C-alkyl, 3-7C-cycloalkyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen and
R32 is hydrogen,

R4 is hydrogen

Ar is a phenyl

and the salts of these compounds.

Compounds of the formula 1a which are to be particularly emphasized are those compounds, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

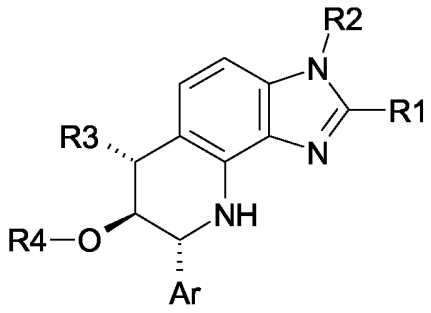
R3 is 1-4C-alkyl or 3-7C-cycloalkyl,

R4 is hydrogen

Ar is a phenyl

and the salts of these compounds.

Among the compounds of the formula 1 according to the invention, emphasis is also given to the compounds of the formula 1b,



(1b)

in which

R1 is hydrogen, halogen, hydroxyl, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl, hydroxy-1-4C-alkyl or mono- or di-1-4C-alkylamino,

R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl, hydroxy-1-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, 2-4C-alkenyl, aryl-2-4C-alkenyl, cyano-1-4C-alkyl, or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, dihydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 3-7C-cycloalkyl, dihydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxy-pyrrolidino, azetidino, aziridino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl

Ar is a mono- or bicyclic aromatic residue, substituted by R5, R6, R7 and R8, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl,

indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,

wherein

R5 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R6 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R7 is hydrogen, 1-4C-alkyl or halogen and

R8 is hydrogen, 1-4C-alkyl or halogen,

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and the salts of these compounds.

Compounds which are to be mentioned are those of the formula 1b, where

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl or fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen or 1-7C-alkyl

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxy-pyrrolidino, azetidino, aziridino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,

Ar is a phenyl or thiazolyl residue, substituted by R5, R6, R7 and R8,

wherein

R5 is hydrogen, 1-4C-alkyl or halogen,

R6 is hydrogen, 1-4C-alkyl or halogen,

R7 is hydrogen, 1-4C-alkyl or halogen and
R8 is hydrogen, 1-4C-alkyl or halogen,
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,
and the salts of these compounds.

Compounds which are to be particularly mentioned are those of the formula 1b, where
R1 is 1-4C-alkyl or 3-7C-cycloalkyl,
R2 is hydrogen, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl or 3-7C-cycloalkyl
R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen,
R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,
Ar is a phenyl
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, halogen or trifluoromethyl
and the salts of these compounds.

Compounds which are also to be particularly mentioned are those of the formula 1b, where
R1 is 1-4C-alkyl,
R2 is hydrogen, 1-4C-alkyl or 3-7C-cycloalkyl
R3 is 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen,
R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,
Ar is a phenyl
and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, halogen or trifluoromethyl

and the salts of these compounds.

Compounds which are to be emphasized are those of the formula 1b, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen,

R32 is hydrogen,

R4 is hydrogen,

Ar is a phenyl

and wherein

aryl is phenyl

and the salts of these compounds.

Compounds which are to be particularly emphasized are those of the formula 1b, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is 1-4C-alkyl, 3-7C-cycloalkyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen and

R32 is hydrogen,

R4 is hydrogen

Ar is a phenyl

and the salts of these compounds.

Compounds of the formula 1b which are to be particularly emphasized are those compounds, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen and

R32 is hydrogen,

R4 is hydrogen

Ar is a phenyl

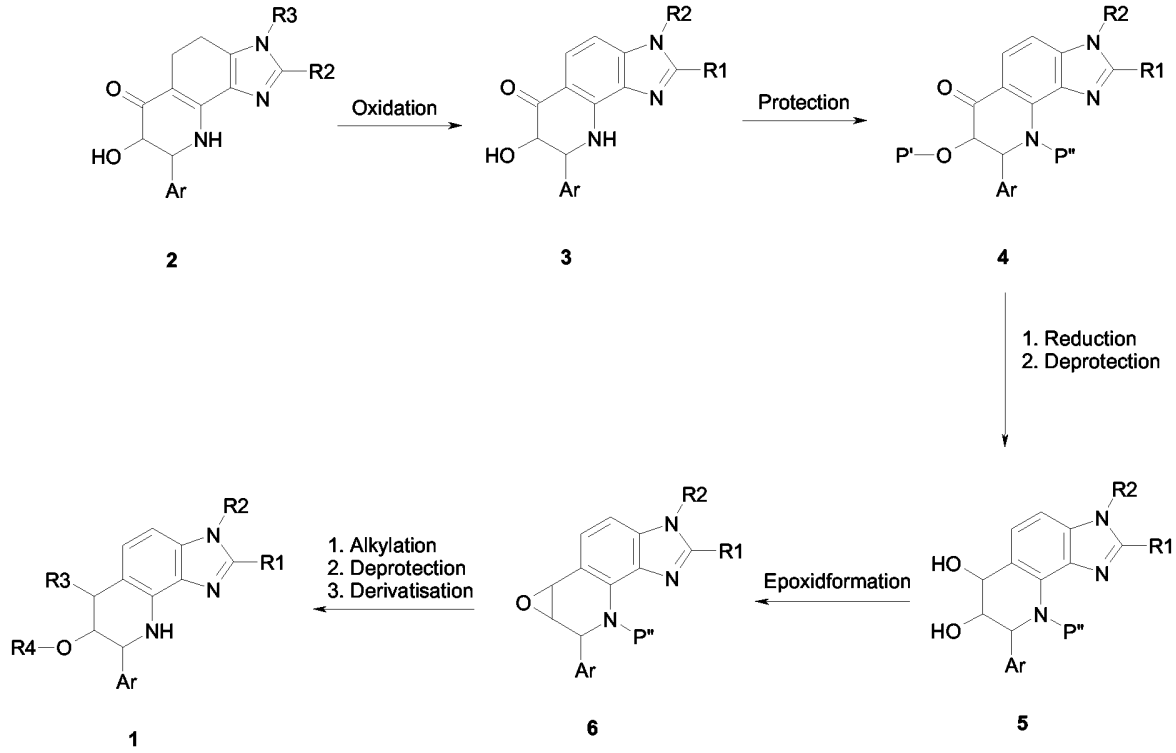
and the salts of these compounds.

Particularly preferred are the compounds given as final products of formula 1 in the examples, and the salts of these compounds.

The compounds according to the invention can be synthesised from corresponding starting compounds, for example according to the reaction schemes given below. The synthesis is carried out in a manner known to the expert, for example as described in more detail in the examples which follow the schemes. The synthesis of precursors described in the following schemes, for example of compounds of the formulae 2, 3, 4, 5, 6 and 7, is described inter alia in WO 05/058893 or can be performed in a similar way by a person skilled in the art.

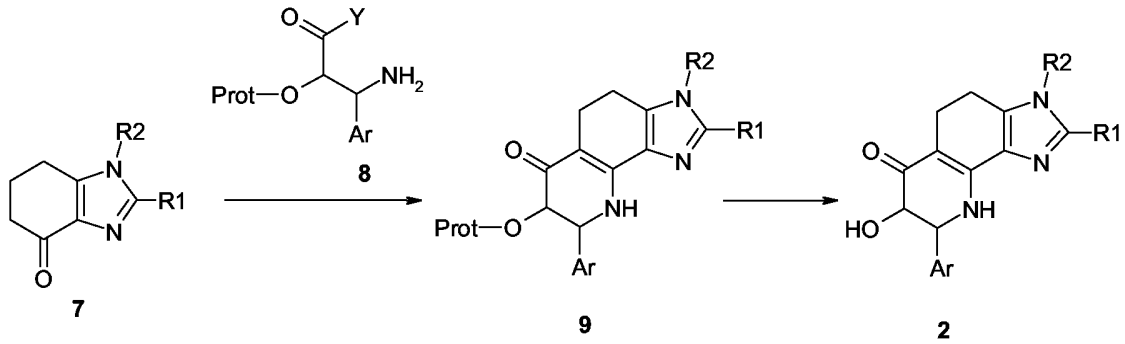
The compounds of the formula **1** can be obtained for example starting from compounds of the formula **2**. The reaction sequence is shown in scheme 1.
Oxidation of compounds of the formula **2** to compounds of the formula **3** is performed by standard procedures, for example using manganese dioxide. Protection of the hydroxyl group and of the amino group of compounds of formula **3** provides compounds of formula **4** and is performed by standard procedures and standard protection groups (P' and P"), like for example formyl, acetyl, pivaloyl or benzoyl. Reduction of the keto group of compounds of formula **4** by simultaneous or subsequent deprotection of the hydroxyl group leads to the corresponding diols of the formula **5** and can be carried out, for example, using sodium borohydride followed by treatment with potassium carbonate. Epoxid formation to yield epoxide compounds of the formula **6** is carried out, for example under Mitsunobu conditions or by other reaction conditions known to the expert. Alkylation of these epoxide compounds of the formula **6** by using suitable alkylation reagents like for example Grignard reagents or organolithium compounds, followed, if desired, by subsequent standard derivatisation reactions, like for example oxidation, reduction, etherification or further alkylation by simultaneous or subsequent deprotection leads to the desired compounds of the formula **1**.

Scheme 1:



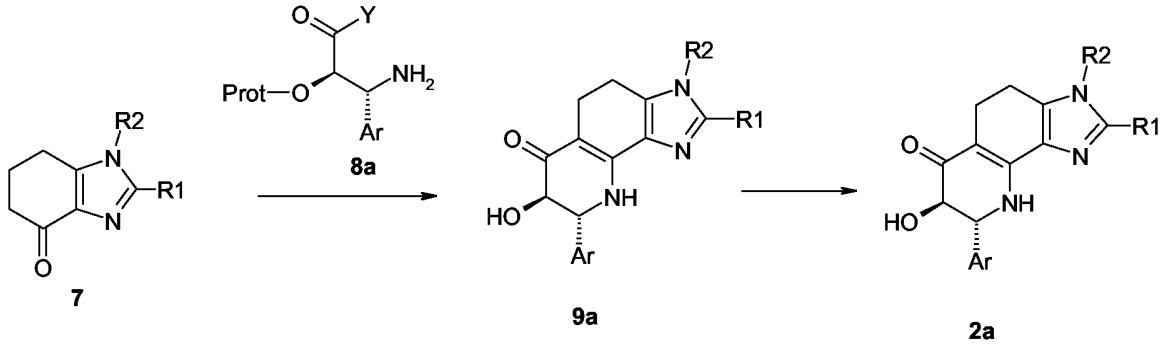
Compounds of the formula **2** can be prepared for example as outlined in scheme 2. In a first step ketones of the formula **7** are reacted with protected phenylisoserine derivatives of the formula **8** (wherein Y is a suitable leaving group, for example an ethoxy group and Prot is a suitable protecting group like a suitable silyl radical, for example a $^{t}BuMe_2Si$- radical) to give compounds of the formula **9** and/or compounds of the formula **2**. Compounds of the formula **9**, if obtained, can be deprotected by standard procedures to the desired compounds of the formula **2**.

Scheme 2:

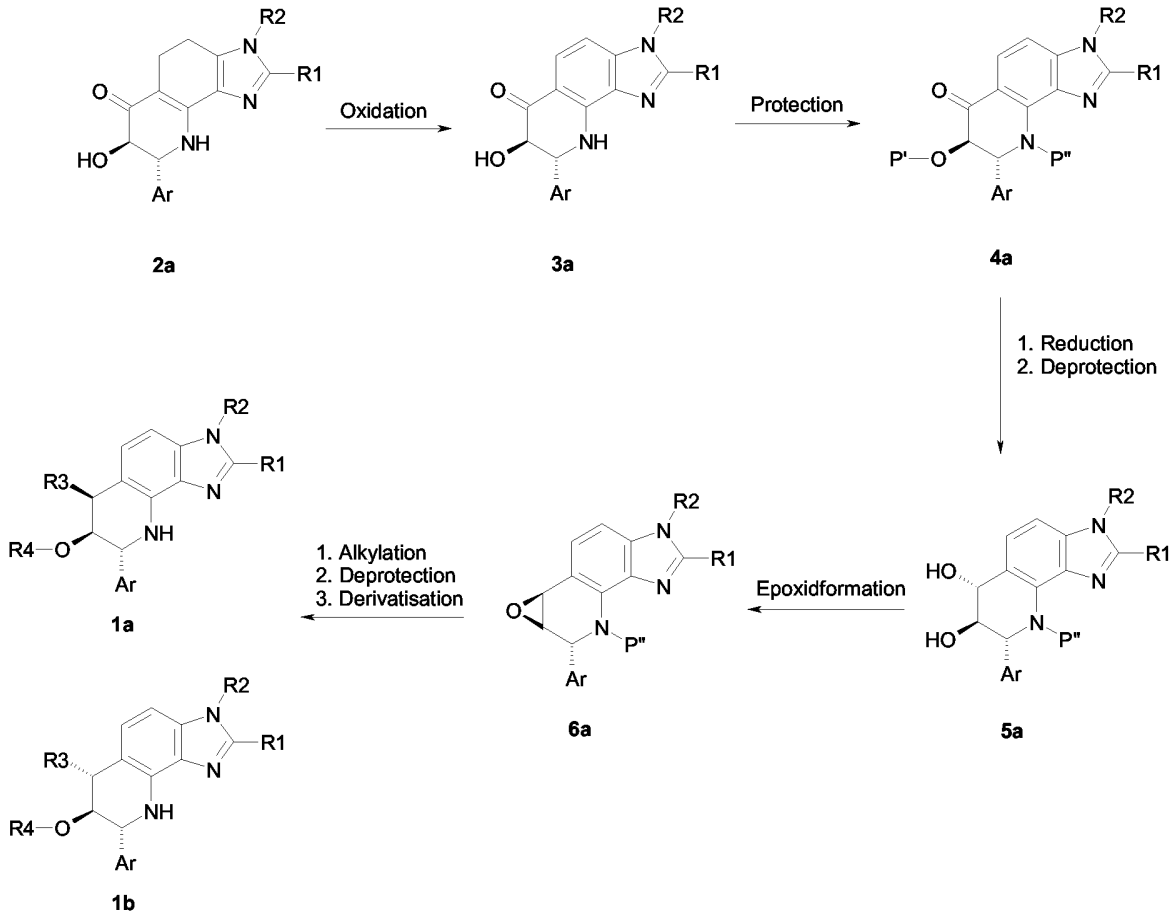


The synthesis as outlined in scheme **2a** and **1a** leads to the preferred optically pure compound of the formula **1a** and/or **1b** by reacting ketones of the formula **7** with optically pure phenylisoserin derivatives of the formula **8a** and further chemical transformations as described for scheme 1.

Scheme 2a:



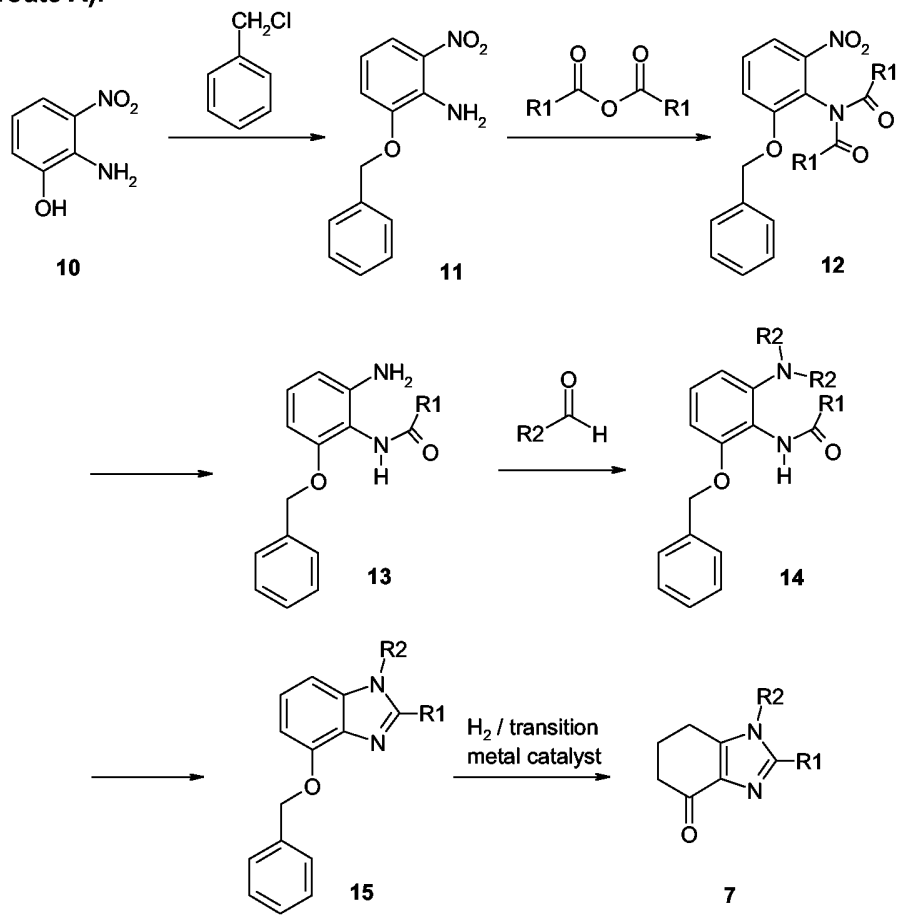
Scheme 1a:



The stereochemical outcome of the title compounds of formula 1 (**1a** and/or **1b**) depends on the alkylation condition and the alkylating reagent applied to the epoxide of the formula 6a. A person skilled in the art is able to adapt the reaction conditions and reagents accordingly.

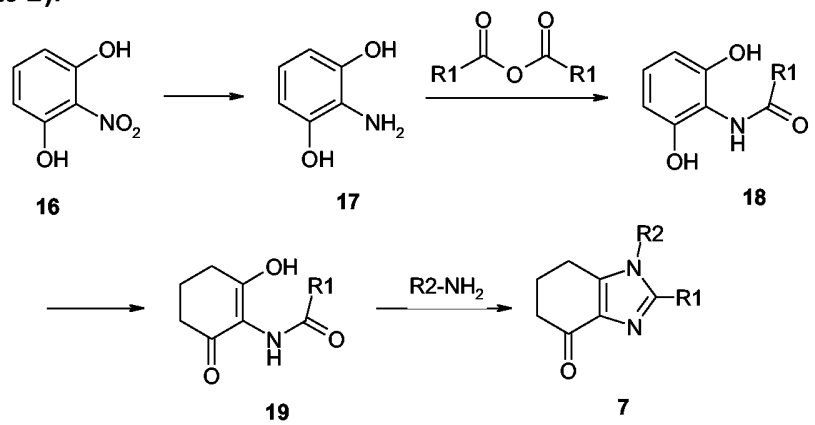
Ketones of the formula **7** are known, for example from Helvetica Chimica Acta (1979), 62, 507, or can be prepared in a manner as shown for example in scheme 3 (route A). 3-Nitro-2-aminophenol can be reacted in a first step with a suitable benzyl derivative, for example benzylchloride, and the amino group of the reaction product of the formula **11** (known from J. Heterocyclic Chem. (1983), 20, 1525) is converted to the di-amide of the formula **12**. Subsequent reduction under standard conditions, for example using hydrazine N_2H_4 in the presence of $FeCl_3$, leads to the formation of the primary amide of the formula **13**, whose amine functionality can be alkylated in a next step, for example under reductive alkylation conditions, to compounds of the formula **14**. The following cyclization step is performed under standard conditions, for example under acidic conditions using $POCl_3$, to give compounds of the formula **15** whose hydrogenation to the desired compounds of the formula **7** is performed in manner known to the expert, for example as described by H. Oelschlaeger and H. Giebenhain in Archiv der Pharmazie, 1973, 306, 485-489.

Scheme 3 (route A):



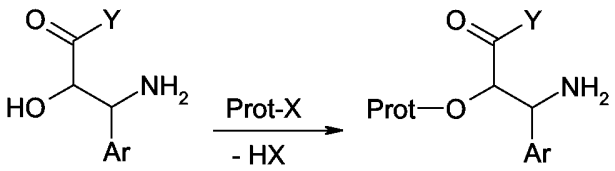
Alternatively, the ketones of the formula **7** can be prepared from compounds of the formula **19** by a cyclization reaction in the presence of a primary amine as shown in scheme 4 (route B). Compounds of the formula **19** are known, for example from H. Stetter and K. Hoehne, Chem. Ber., 1958, 91, 1123-1128, or can be prepared in an analogous manner starting from 2-nitroresorcin as shown in scheme 4.

Scheme 4 (route B):



Phenylisoserine derivatives of the formula **8** or **8a** can be prepared in analogy to methods known in literature (see for example J. Amer. Chem. Soc. (1998), 120, 431) or by methods known to the expert, for example by reaction under basic conditions of the corresponding unprotected phenylisoserine derivatives of the formula **20** with suitable protection group precursor Prot-X with a suitable leaving group X, like a suitable silyl chloride, for example $^{t}BuMe_2SiCl$, as shown in Scheme 5.

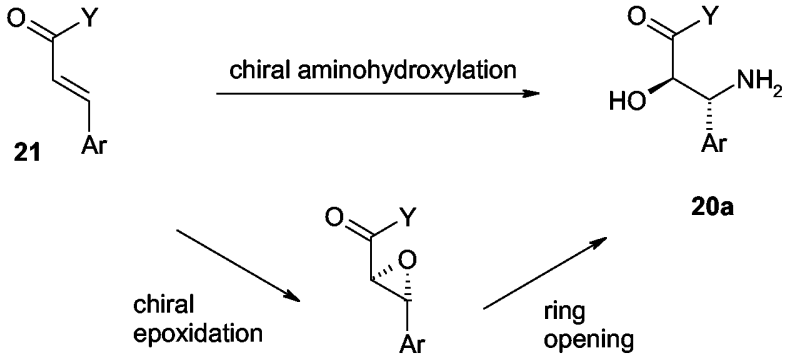
Scheme 5:



20 **8**

Compounds of the formula **20** are known or can be prepared by methods known to the expert, for example by epoxidation of the corresponding cinnamic acid derivatives of the formula **21**, followed by a ring opening reaction or directly by a aminohydroxylation reaction. Both variants can be performed in a stereoselective way, which leads for example to compounds of the formula **20a**, as shown in Scheme 6.

Scheme 6:



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The following examples serve to illustrate the invention in greater detail without restricting it. Likewise, further compounds of the formula **1** whose preparation is not described explicitly can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques. The abbreviation min stands for minute(s), h for hour(s) and m.p. for melting point.

Examples

I. Final Products of formula 1

1. (6S,7S,8R)-2,3,6-Trimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline

To a at –5°C cooled solution of 14.00 ml methylmagnesium bromide (42.0 mmol / 3.0 M solution in diethyl ether) in THF (40 ml) is added 2.00 g (6.00 mmol) of (6S,7R,8R)-9-acetyl-2,3-dimethyl-6,7-epoxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline dissolved in dichloromethane (40 ml) and the reaction mixture is stirred for 40 min at 0°C. Subsequently the mixture is poured into saturated ammonium chloride solution and extracted with ethyl acetate two times. The combined organic layers are concentrated in vacuo and the crude product is purified by column chromatography (ethyl acetate / methanol / ammonia solution: 97 / 2 / 1) to give 1.10 g (3.57 mmol / 60 %) of the title product with a melting point of 250°C (dichloromethane / methanol).

2. (6S,7S,8R)-6-Isobutyl-2,3-dimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline

To a at –5°C cooled solution of 15.00 ml isobutylmagnesium bromide (30.0 mmol / 2.0 M solution in diethyl ether) in THF (40 ml) is added 2.00 g (6.00 mmol) of (6S,7R,8R)-9-acetyl-2,3-dimethyl-6,7-epoxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline dissolved in dichloromethane (40 ml) and the reaction mixture is stirred for 50 min at 0°C. Subsequently the mixture is poured into saturated ammonium chloride solution and extracted with ethyl acetate three times. The combined organic layers are concentrated in vacuo and the crude product is purified by column chromatography (ethyl acetate / methanol / ammonia solution: 97 / 2 / 1) to give 0.40 g (1.15 mmol / 19 %) of the title compound.
^{1}H-NMR (200MHz, $CDCl_3$): δ = 0.74 (d, 3 H), 1.00 (d, 3 H), 1.50-2.06 (m, 3 H), 2.82-2.90 (m, 1 H), 3.64 (s, 3 H), 4.14 (dd, 1 H), 4.46 (dd, 1 H), 6.56 (d, 1 H), 6.99 (d, 1 H); 7.20-7.41 (m, 5 H).

3. (6S,7S,8R)-2,3-Dimethyl-7-hydroxy-8-phenyl-6-propyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline

To a at –5°C cooled solution of 41.00 ml n-propylmagnesium bromide (84.0 mmol / 2.0 M solution in diethyl ether) in THF (40 ml) is added 2.00 g (6.00 mmol) of (6S,7R,8R)-9-acetyl-2,3-dimethyl-6,7-epoxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline dissolved in dichloromethane (40 ml) and the reaction mixture is stirred for 1 h at 0°C. Subsequently the mixture is poured into saturated ammonium chloride solution and extracted with ethyl acetate three times. The combined organic

layers are concentrated in vacuo and the crude product is purified by column chromatography (ethyl acetate / ammonia solution: 9 / 1) to give 1.45 g (4.32 mmol / 72 %) of the title compound.
^{1}H-NMR (200MHz, $CDCl_3$): δ = 0.91 (t, 3 H), 1.22-2.04 (m, 4 H), 2.53 (s, 3 H), 2.76-2.85 (m, 1 H), 3.66 (s, 3 H), 4.15 (dd, 1 H), 4.62 (dd, 1 H), 6.59 (d, 1 H), 6.99 (d, 1 H); 7.26-7.43 (m, 5 H).

4. (6S,7S,8R)-6-Cyclopentyl-2,3-dimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline

To a at –5°C cooled solution of 17.9 ml cyclopentylmagnesium bromide (35.7 mmol / 2.0 M solution in diethyl ether) in THF (40 ml) is added 1.70 g (5.10 mmol) of (6S,7R,8R)-9-acetyl-2,3-dimethyl-6,7-epoxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline dissolved in dichloromethane (40 ml) and the reaction mixture is stirred for 18 h at 4°C. Subsequently the mixture is poured into saturated ammonium chloride solution and extracted with ethyl acetate three times. The combined organic layers are concentrated in vacuo and the crude product is purified by column chromatography (ethyl acetate / methanol / ammonia solution: 97 / 2 / 1) to give 0.30 g (0.83 mmol / 5 %) of the title compound.
^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.10-1.30 (m, 1 H), 1.31-1.89 (m, 6 H),1.91-2.15 (m, 1 H), 2.20-2.49 (m, 1 H), 2.55 (s, 3 H), 2.86 (dd, 1 H), 3.67 (s, 3 H), 4.19 (dd, 1 H), 4.60 (dd, 1 H), 6.59 (d, 1 H), 7.03 (d, 1 H); 7.26-7.46 (m, 5 H).

5. (6R,7S,8R)-6-Cyanomethyl-2,3-dimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline

To a at –60°C cooled solution of 24.6 ml lithium diisopropylamide (LDA) (12.3 mmol / 2.0 M solution in THF / hexane) is added 3.20 ml (61.3 mmol) acetonitrile. The reaction is stirred for further 30 min. Afterwards 2.00 g (6.00 mmol) of (6S,7R,8R)-9-acetyl-2,3-dimethyl-6,7-epoxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline dissolved in dichloromethane (6.0 ml) is added to the reaction mixture and is stirred for 0.5 h at –60°C and 0.5 h at –30°C. Subsequently the mixture is poured into saturated ammonium chloride solution and extracted with dichloromethane five times. The combined organic layers are concentrated in vacuo and the crude product is product by column chromatography (dichloromethane / methanol: 100 / 1 to 13 / 1) to give 0.40 g (1.20 mmol / 20 %) of the title product with a melting point of 261°C (dichloromethane / methanol).

6. (6R,7S,8R)-6-Carbamoylmethyl-2,3-dimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline

A mixture of 0.95 g (2.54 mmol) (6R,7S,8R)-6-cyanomethyl-2,3-dimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline in concentrated hydrochloric acid (4.5 ml) is stirred for 48 h at 25°C. Subsequently the mixture is poured into ice water and neutralized by using sodium hydroxide

solution (6 N) and saturated sodium hydrogen carbonate solution. The mixture is extracted with dichloromethane three times. The combined organic layers are concentrated in vacuo and the crude product is purified by column chromatography (dichloromethane / methanol: 13 / 1) to give 0.14 g (0.40 mmol / 15 %) of the title product with a melting point of 239°C (dichloromethane / methanol).

7. (6S,7S,8R)-2,3-Dimethyl-7-hydroxy-8-phenyl-6-(phenylethynyl)-6,7,8,9-tetrahydro-3H-imidazo[4,5-h]quinoline

To a at –5°C cooled solution of 42.00 ml phenylethynylmagnesium bromide (42.0 mmol / 1.0 M solution in THF) is added 2.00 g (6.00 mmol) of (6S,7R,8R)-9-acetyl-2,3-dimethyl-6,7-epoxy-8-phenyl-6,7,8,9-tetrahydro-3H-imidazo[4,5-h]quinoline dissolved in dichloromethane (40 ml) and the reaction mixture is stirred for 40 min at 0°C. Subsequently the mixture is poured into saturated ammonium chloride solution and extracted with ethyl acetate two times. The combined organic layers are concentrated in vacuo and the crude product is purified by column chromatography (ethyl acetate / methanol: 95 / 5 / and dichloromethane / methanol: 98 / 2) to give 0.07 g (0.178 mmol / 3 %) of the title product as a light brown foam.
1H-NMR (200MHz, CDCl3): δ = 2.53 (s,3 H), 3.62 (s, 3 H), 4.72-4.78 (m, 2 H), 6.53 (d, 1 H), 6.58 (s, 1 H), 6.71-6.76 (m, 2 H), 7.08-7.13 (m, 4 H), 7.29-7.36 (m, 5 H).

8. (6S,7S,8R)-6-Cyclopropyl-2,3-dimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline

To a solution of 75.00 ml cyclopropylmagnesium bromide (37.50 mmol / 0.5 M solution in THF) is added 2.00 g (6.00 mmol) of (6S,7R,8R)-9-acetyl-2,3-dimethyl-6,7-epoxy-8-phenyl-6,7,8,9-tetrahydro-3H-imidazo[4,5-h]quinoline dissolved in dichloromethane (20 ml) and the reaction mixture is stirred for 15 min at 25°C. Subsequently the mixture is poured into saturated ammonium chloride solution and extracted with ethyl acetate two times. The combined organic layers are concentrated in vacuo and the crude product is is purified by column chromatography (dichloromethane / methanol: 97 / 3). This product is crystallize out of pentane and petrol ether to give 0.95 g (2.85 mmol / 48 %) of the title product.
1H-NMR (200MHz, CDCl3): δ = 0.03-0.10 (m, 1 H), 0.25-0.34 (m, 1 H), 0.48-0.57(m, 1 H), 0.70-0.81 (m, 1 H), 1.10-1.27 (m, 1 H), 1.94 (dd, 1 H), 2.53 (s, 3 H), 3.65 (s, 3 H), 4.17 (t, 1 H), 4.75 (t, 1 H), 6.59 (d, 1 H), 7.18-7.38 (m, 6 H).

9. (7S,8R)-2,3-Dimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3H-imidazo[4,5-h]quinoline

A suspension of 1.20 (3.60 mmol) (7S,8R)-9-N-acetyl-2,3-dimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3H-imidazo[4,5-h]quinoline and 2.00 g (14.5 mmol) potassium carbonate in 2-aminoethanol

(12 ml) is stirred for 3 h at 100°C. Subsequently the mixture is poured into saturated ammonium chloride solution and the precipitate is filtered off to give 0.32 g (2.49 mmol / 31 %) of the title product as a beige solid.
1H-NMR (200MHz, CDCl3): δ = 2.46 (s, 3 H), 2.71 (d, 2 H), 3.64 (s, 3 H), 3.97 (q, 1 H), 4.32 (dd, 1 H), 6.58 (d, 1 H), 6.73 (d, 1 H), 7.23-7.32 (m, 5 H).

II. Starting Materials and Intermediates

A. 2-Benzyloxy-6-nitroaniline

To a solution of 50.0 g (0.31 mol) 2-amino-3-nitrophenol in ethanol (400 ml) is added 43.5 ml (0.38 mol) benzyl chloride, 47.8 g (0.35 mol) potassium carbonate and 2.00 g (13.3 mmol) sodium iodide and it is stirred at 80°C for 3.5 h. Subsequently the mixture is concentrated in vacuo, redissolved in dichloromethane, washed with water, dried over sodium sulfate, filtrated over sand and concentrated in vacuo again. The crude product is purified by column chromatography (cyclohexane / ethyl acetate: 8 / 2) to give 76.0 g (0.31 mol / 96 %) of the title product.
^{1}H-NMR (200MHz, $CDCl_3$): δ = 5.11 (s, 2 H), 6.57 (t, 1 H), 6.95 (d, 1 H), 7.35-7.44 (m, 5 H), 7.73 (d, 1 H).

B. N-Acetyl-2-benzyloxy-6-nitro-acetanilide

To a stirred reaction mixture of 76.0 g (0.31 mol) 2-benzyloxy-6-nitroaniline in acetic anhydride (469 ml) is added 7.60 ml (0.12 mol) methane sulfonic acid and is stirred for 2 h at 120°C. Afterwards the acetic anhydride is removed in vacuo and the residue is poured into ice water. This mixture is neutralised with concentrated ammonia solution and extracted with dichloromethane three times. The combined organic layers are concentrated and dried in vacuo to give 99.9 g (0.30 mol / 98 %) of the title product with a melting point of 113.8°C (dichloromethane).

C. 2-Amino-6-benzyloxy-acetanilide

To a stirred mixture of 99.6 g (0.30 mol) N-acetyl-2-benzyloxy-6-nitro-acetanilide, activated carbon (59.7 g) and 30.0 g (18.5 mmol) iron chloride in methanol (2.60 l) at 70°C is added dropewise 147 ml (3.03 mol) hydrazine hydrate and is stirred for further 5 h. Subsequently the mixture is filtrated over kieselgur and concentrated in vacuo. The crude mixture is suspended in a saturated ammonium chloride solution and extracted with dichloromethane twice. The combined organic layers are concentrated in vacuo and the crude product is reslurried in diethyl ether to give 50.5 g (0.20 mol / 65 %) of the title product with a melting point of 146.9°C (diethyl ether).

D. 4-Benzyloxy-1,2-dimethyl-1*H*-benzimidazole

To a stirred mixture of 4.00 g (17.0 mmol) 2-amino-6-benzyloxy-acetanilide in dichloromethane (8.0 ml) is added 4.00 ml (4.30 mmol) phoshoryl chloride and is stirred at 70°C for 5 h. Subsequently the mixture is poured into ice water, neutralised by adding sodium hydroxide solution (6 N) and extracted with dichloromethane three times. The combined organic layers are concentrated in vacuo and the crude product is product is purified by column chromatography (diethyl ether / petrol ether: 7 / 3) to give 3.09 g (12.2 mmol / 72 %) of the title product with a melting point of 130.9°C (diethyl ether / petrol ether).

E. 1,2-Dimethy-1,5,6,7-tetrahydro-benzoimidazol-4-one

Route A: A suspension of 2.00 g (7.93 mmol) 4-benzyloxy-1,2-dimethyl-1*H*-benzimidazole and 1.70 g palladium on carbon (10 %) in methanol (50 ml) is stirred in a autoclave by a hydrogen pressure of 150 bar at 70°C for 20 h. Afterwards the catalyst is filtered off and the methanol is removed in vacuo. The crude product is purified by column chromatography (dichloromethane / methanol: 100 / 3 to 13 / 1) to give 0.14 g (0.85 mmol / 11 %) of the title product with a melting point of 98.1°C (dichloromethane / methanol).

Route B: To a stirred mixture of 29.0 g (0.17 mol) 2-acetylamino-3-hydroxy-cyclohex-2-enone in xylene (580 ml) is added acetic acid (57 ml) and dropewise 116 ml (0.23 mol) methylamine (2 M in THF). The reaction mixture is heated to 155°C for 5 h, cooled down to 25°C and stirred for further 20 h. Afterwards the mixture is concentrated in vacuo and the crude product is purified by column chromatography (ethyl acetate / methanol: 8 / 2) to yield 21.4 g (0.13 mol / 77 %) of the title product with a melting point of 98.1°C (ethyl acetate / methanol).

F. (7R,8R)-7-Hydroxy-2,3-dimethyl-8-phenyl-5,7,8,9-tetrahydro-3*H*,4*H*-imidazo [4,5-h]quinolin-6-one

A mixture of 6.20 g (37.8 mmol) 1,2-dimethy-1,5,6,7-tetrahydro-benzoimidazol-4-one and 12.5 g (38.6 mmol) phenylisoserine is heated to 170°C and is stirred for 5.5 h. Afterwards the solid is purified by column chromatography (dichloromethane / methanol: 100 / 1 to 13 / 1) to give 6.35 g (20.5 mmol / 54 %) of the title product as a light brown solid with a melting point of 262.3°C (dichloromethane / methanol).

G. (7R,8R)-7-(tert-Butyl-dimethyl-silanyl-oxy)-2,3-dimethyl-8-phenyl-5,7,8,9-tetrahydro-3*H*,4*H*-imidazo[4,5-h]quinolin-6-one

A mixture of 6.20 g (37.8 mmol) 1,2-dimethy-1,5,6,7-tetrahydro-benzoimidazol-4-one and 12.5 g (38.6 mmol) phenylisoserine is heated to 170°C and is stirred for 5.5 h. Afterwards the solid is purified by column chromatography (dichloromethane / methanol: 100 / 1 to 13 / 1) to give 2.20 g (5.19 mmol / 14 %) of the title product. This compound is transformed by acetic standard condition without any characterisation into (7R,8R)-7-hydroxy-2,3-dimethyl-8-phenyl-5,7,8,9-tetrahydro-3*H*,4*H*-imidazo [4,5-h]quinolin-6-one.

H. (7R,8R)-7-Hydroxy-2,3-dimethyl-8-phenyl-8,9-dihydro-3*H*,7*H*-imidazo[4,5-h]quinolin-6-one

A reaction mixture of 6.20 g (20.0 mmol) (7R,8R)-7-hydroxy-2,3-dimethyl-8-phenyl-5,7,8,9-tetrahydro-3*H*,4*H*-imidazo[4,5-h]quinolin-6-one and 19.0 g (197 mmol) manganese dioxide in dichloromethane (250 ml) is stirred for 20 h at 25°C. Afterwards the manganese residues are filtered off by using kieselgur. The crude product is purified by column chromatography (dichloromethane / methanol: 100 / 1 to 13 / 1) and crystallized from acetone to give 4.70 g (15.3 mmol / 76 %) of the title product as a solid with a melting point of 235.1°C (acetone).

I. (7R,8R)-2,3-Dimethyl-8-phenyl-7-pivaloyloxy-8,9-dihydro-3*H*,7*H*-imidazo[4,5-h]quinolin-6-one

To a suspension of 98.6 g (0.32 mol) (7R,8R)-7-hydroxy-2,3-dimethyl-8-phenyl-8,9-dihydro-3*H*,7*H*-imidazo[4,5-h]quinolin-6-one in dichloromethane (500 ml) is added 110 ml (0.63 mol) n-ethyl-diisopropylamine and 15.5 g (0.12 mol) N-dimethyl-4-aminopyridine. The mixture is cooled to 0°C, 78.0 ml (0.63 mol) pivaloyl chloride is added dropwise and it is stirred for 18 h at 0-5°C. Subsequently the reaction is quenched by adding methanol (5.0 ml) and water (500 ml). The mixture is extracted with dichloromethane three times. The combined organic layers are concentrated in vacuo and the crude product is reslurried in petrol ether, filtered off and dried in vacuum to give 120 g (0.31 mol / 97 %) of the title product.
^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.08 (s, 9 H), 2.54 (s, 3 H), 3.69 (s, 3 H), 4.91 (d,1 H), 5.78 (d, 1 H), 6.72 (d, 1 H), 7.31-7.41 (m, 3 H), 7.50-7.57 (m, 2 H), 7.75 (d, 1 H).

J. (7R,8R)-9-Acetyl-2,3-dimethyl-8-phenyl-7-pivaloyloxy-8,9-dihydro-3*H*,7*H*-imidazo[4,5-h]quinolin-6-one

To a suspension of 154 g (0.39 mol) (7R,8R)-2,3-dimethyl-8-phenyl-7-pivaloyloxy -8,9-dihydro-3*H*,7*H*-imidazo[4,5-h]quinolin-6-one in acetic anhydride (300 ml) is added dropwise 43.7ml (0.79 mol) concentrated sulphuric acid and it is stirred for further 20 min. Subsequently the reaction mixture is poured in an ice saturated sodium hydrogen carbonate solution and is extracted with ethyl acetate three times. The combined organic layers are concentrated in vacuo. The crude product is redissolved

in dichoromethane / methanol (98 / 2) and filtered over silica gel to give 154 g (0.36 mol / 90 %) of the title product.
^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.23 (s, 9 H), 2.37 (s, 3 H), 2.66 (s, 3 H), 3.71 (s, 3 H), 5.78 (d,1 H), 6.62 (s, 1 H), 7.03-7.16 (m, 4 H), 7.25-7.29 (m, 2 H), 7.84 (d, 1 H).

K. (6R,7R,8R)-9-Acetyl-2,3-dimethyl-6-hydroxy-8-phenyl-7-pivaloyloxy-6,7,8,9-tetrahydro-3*H*,-imidazo[4,5-h]quinoline

To a at –50°C cooled suspension of 120 g (0.28 mol) (7R,8R)-9-acetyl-2,3-dimethyl-8-phenyl-7-pivaloyloxy-8,9-dihydro-3*H*,7*H*-imidazo[4,5-h]quinolin-6-one in methanol (950 ml) is added portionwise 14.7 g (0.37 mol) sodium borohydride and it is stirred for further 1 h. Subsequently the reaction mixture is acidified to pH 3 by adding ice and hydrochloric acid (2 N). The mixture is neutralized with sodium hydrogen carbonate and is extracted with dichloromethane three times. The combined organic layers are concentrated in vacuo to give 117 g (0.27 mol / 97 %) of the title product.
^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 1.97 (s, 3 H), 2.63 (s, 3 H), 3.77 (s, 3 H), 4.80 (d, 1 H), 5.09 (dd, 1 H), 5.87 (d, 1 H), 7.12-7.17 (m, 5 H), 7.31 (d, 1 H), 7.55 (d, 1 H).

L. (6R,7R,8R)-9-Acetyl-2,3-dimethyl-6,7-dihydroxy-8-phenyl-6,7,8,9-tetrahydro-3*H*,-imidazo[4,5-h]quinoline

A reaction mixture of 2.00 g (4.60 mmol) (6R,7R,8R)-9-acetyl-2,3-dimethyl-6-hydroxy-8-phenyl-7-pivaloyloxy-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline and 1.90 g (13.8 mmol) potassium carbonate in methanol (20 ml) is stirred for 3 h. Subsequently the reaction mixture is quenched by adding saturated ammonium chloride solution. The mixture is extracted with dichloromethane / methanol (13 / 1) three times. The combined organic layers are concentrated in vacuo. The crude product is redissolved in dichloromethane / methanol (9 / 1) and filtered over silica gel to give 1.20 g (3.41 mmol / 74 %) of the title product.
^{1}H-NMR (200MHz, D_6-DMSO): δ = 2.04 (s, 3 H), 2.59 (s, 3 H), 3.13-3.24 (m, 1 H), 3.74 (s, 3 H), 4.46 (dd,1 H), 5.35 (d, 1 H), 7.13-7.46 (m, 7 H).

M. (6S,7R,8R)-9-Acetyl-2,3-dimethyl-6,7-epoxy-8-phenyl-6,7,8,9-tetrahydro-3H-imidazo[4,5-h]quinoline

To a at 0°C cooled reaction mixture of 30.0 g (85.3 mmol) (6R,7R,8R)-9-acetyl-2,3-dimethyl-6,7-dihydroxy-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline in DMF (150 ml) is added dropwise 29.1 ml (111 mmol) tri-n-butylphosphine and 23.6 g (111 mmol) diisopropyl azodicarboxylate and it is stirred for further 1 h. Subsequently the reaction mixture is quenched by adding ice and saturated ammonium chloride solution. The crude product is filtered off to give 26.3 g (78.9 mmol / 92 %) of the title product with a melting point of 200-205°C (water).

N. (7S,8R)-9-N-acetyl-2,3-dimethyl-7-hydroxy-8-phenyl-6,7,8,9-tetrahydro-3H-imidazo[4,5-h]quinoline

A suspension of 2.00 g (6.00 mmol) of (6S,7R,8R)-9-acetyl-2,3-dimethyl-6,7-epoxy-8-phenyl-6,7,8,9-tetrahydro-3H-imidazo[4,5-h]quinoline and 0.50 g (0.47 mmol) palladium on carbon (10% of palladium) in dioxane (30 ml) is stirred in a hydrogenator by hydrogen overpressure (100 mbar of hydrogen) for 24 h at 25°C. Subsequently the mixture is filtered over kieselguhr. The filtrate is concentrated in vacuo and the crude product is reslurried in acetone and filtered off to give 0.45 g (1.34 mmol / 23 %) of the title product.
1H-NMR (200MHz, CDCl3): δ = 1.06 (s, 3 H), 2.59 (s, 3 H), 2.65-2.93 (m, 2 H), 3.73 (s, 3 H), 5.38 (d, 1 H), 7.08-7.21 (m, 4 H), 7.30-7.36 (m, 3 H).

Commercial utility

The compounds of the formulae 1, 1a and 2 and their pharmacologically acceptable salts (= active compounds according to the invention) have valuable pharmacological properties which make them commercially utilizable. In particular, they exhibit marked inhibition of gastric acid secretion and an excellent gastric and intestinal protective action in warm-blooded animals, in particular humans. In this connection, the active compounds according to the invention are distinguished by a high selectivity of action, an advantageous duration of action, a particularly good enteral activity, the absence of significant side effects and a large therapeutic range.

"Gastric and intestinal protection" in this connection is understood as meaning the prevention and treatment of gastrointestinal diseases, in particular of gastrointestinal inflammatory diseases and lesions (such as, for example, gastric ulcer, peptic ulcer, including peptic ulcer bleeding, duodenal ulcer, gastritis, hyperacidic or medicament-related functional dyspepsia), which can be caused, for example, by microorganisms (e.g. Helicobacter pylori), bacterial toxins, medicaments (e.g. certain antiinflammatories and antirheumatics, such as NSAIDs and COX-inhibitors), chemicals (e.g. ethanol), gastric acid or stress situations. "Gastric and intestinal protection" is understood to include, according to general knowledge, gastroesophageal reflux disease (GERD), the symptoms of which include, but are not limited to, heartburn and/or acid regurgitation.

In their excellent properties, the active compounds according to the invention surprisingly prove to be clearly superior to the compounds known from the prior art in various models in which the antiulcerogenic and the antisecretory properties are determined. On account of these properties, the active compounds according to the invention are outstandingly suitable for use in human and veterinary medicine, where they are used, in particular, for the treatment and/or prophylaxis of disorders of the stomach and/or intestine.

A further subject of the invention are therefore the active compounds according to the invention for use in the treatment and/or prophylaxis of the abovementioned diseases.

The invention likewise includes the use of the active compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the abovementioned diseases.

The invention furthermore includes the use of the active compounds according to the invention for the treatment and/or prophylaxis of the abovementioned diseases.

A further subject of the invention are medicaments which comprise one or more active compounds according to the invention.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the active compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries or excipients in the form of tablets, coated tablets, capsules, suppositories, patches (e.g. as TTS), emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and it being possible to obtain a pharmaceutical administration form exactly adapted to the active compound and/or to the desired onset and/or duration of action (e.g. a sustained-release form or an enteric form) by means of the appropriate selection of the auxiliaries and excipients.

The auxiliaries and excipients which are suitable for the desired pharmaceutical formulations are known to the person skilled in the art on the basis of his/her expert knowledge. In addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound excipients, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrins).

The active compounds can be administered orally, parenterally or percutaneously.

In general, it has proven advantageous in human medicine to administer the active compound(s) in the case of oral administration in a daily dose of approximately 0.01 to approximately 20, preferably 0.05 to 5, in particular 0.1 to 1.5, mg/kg of body weight, if appropriate in the form of several, preferably 1 to 4, individual doses to achieve the desired result. In the case of a parenteral treatment, similar or (in particular in the case of the intravenous administration of the active compounds), as a rule, lower doses can be used. The establishment of the optimal dose and manner of administration of the active compounds necessary in each case can easily be carried out by any person skilled in the art on the basis of his/her expert knowledge.

If the active compounds according to the invention and/or their salts are to be used for the treatment of the abovementioned diseases, the pharmaceutical preparations can also contain one or more pharmacologically active constituents of other groups of medicaments, for example: tranquillizers (for example from the group of the benzodiazepines, for example diazepam), spasmolytics (for example, bietamiverine or camylofine), anticholinergics (for example, oxyphencyclimine or phencarbamide), local anesthetics, (for example, tetracaine or procaine), and, if appropriate, also enzymes, vitamins or amino acids.

To be emphasized in this connection is in particular the combination of the active compounds according to the invention with pharmaceuticals which inhibit acid secretion, such as, for example, H_2

blockers (e.g. cimetidine, ranitidine), H^+/K^+ ATPase inhibitors (e.g. omeprazole, pantoprazole), or further with so-called peripheral anticholinergics (e.g. pirenzepine, telenzepine) and with gastrin antagonists with the aim of increasing the principal action in an additive or super-additive sense and/or of eliminating or of decreasing the side effects, or further the combination with antibacterially active substances (such as, for example, cephalosporins, tetracyclines, penicillins, macrolides, nitroimidazoles or alternatively bismuth salts) for the control of Helicobacter pylori. Suitable antibacterial co-components which may be mentioned are, for example, mezlocillin, ampicillin, amoxicillin, cefalothin, cefoxitin, cefotaxime, imipenem, gentamycin, amikacin, erythromycin, ciprofloxacin, metronidazole, clarithromycin, azithromycin and combinations thereof (for example clarithromycin + metronidazole).

In view of their excellent gastric and intestinal protection action, the active compounds according to the invention are suited for a free or fixed combination with those medicaments (e.g. certain antiinflammatories and antirheumatics, such as NSAIDs), which are known to have a certain ulcerogenic potency. In addition, the compounds of formula 1 are suited for a free or fixed combination with motility-modifying drugs.

Pharmacology

The excellent gastric protective action and the gastric acid secretion-inhibiting action of the compounds according to the invention can be demonstrated in investigations on animal experimental models. The compounds according to the invention investigated in the model mentioned below have been provided with numbers which correspond to the numbers of these compounds in the examples.

Testing of the secretion-inhibiting action on the perfused rat stomach

In Table A which follows, the influence of the compounds of the formula 1 according to the invention on the pentagastrin-stimulated acid secretion of the perfused rat stomach after intraduodenal administration in vivo is shown.

Table A

No.	Dose (μmol/kg) i.d.	Inhibition of acid secretion
1	3	> 25%
2	3	> 25%
5	3	> 25%
6	3	> 25%
7	3	> 25%
8	3	> 25%
9	1	> 25%

Methodology

The abdomen of anesthetized rats (CD rat, female, 200-250 g; 1.5 g/kg i.m. urethane) was opened after tracheotomy by a median upper abdominal incision and a PVC catheter was fixed transorally in the esophagus and another via the pylorus such that the ends of the tubes just projected into the gastric lumen. The catheter leading from the pylorus led outward into the right abdominal wall through a side opening.

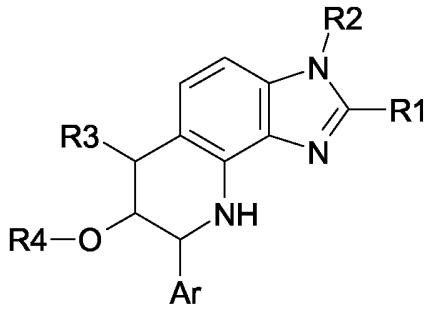
After thorough rinsing (about 50-100 ml), warm (37°C) physiological NaCl solution was continuously passed through the stomach (0.5 ml/min, pH 6.8-6.9; Braun-Unita I). The pH (pH meter 632, glass electrode EA 147; ϕ = 5 mm, Metrohm) and, by titration with a freshly prepared 0.01N NaOH solution to pH 7 (Dosimat 665 Metrohm), the secreted HCl were determined in the effluent in each case collected at an interval of 15 minutes.

The gastric secretion was stimulated by continuous infusion of 1 μg/kg (= 1.65 ml/h) of i.v. pentagastrin (left femoral vein) about 30 min after the end of the operation (i.e. after determination of 2 preliminary fractions). The substances to be tested were administered intraduodenally in a 2.5 ml/kg liquid volume
60 min after the start of the continuous pentagastrin infusion.

The body temperature of the animals was kept at a constant 37.8-38°C by infrared irradiation and heat pads (automatic, stepless control by means of a rectal temperature sensor).

Patent claims

1. A compound of the formula 1,



(1)

in which

R1 is hydrogen, halogen, hydroxyl, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl, hydroxy-1-4C-alkyl or mono- or di-1-4C-alkylamino,

R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl, hydroxy-1-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, 2-4C-alkenyl, aryl-2-4C-alkenyl, cyano-1-4C-alkyl, or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, dihydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 3-7C-cycloalkyl, dihydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxy-pyrrolidino, azetidino, aziridino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl

Ar is a mono- or bicyclic aromatic residue, substituted by R5, R6, R7 and R8, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,

wherein

R5 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl,

halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R6 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R7 is hydrogen, 1-4C-alkyl or halogen and

R8 is hydrogen, 1-4C-alkyl or halogen,

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and its salts.

2. A compound of the formula 1 as claimed in claim 1,

in which

R1 is 1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl or 3-7C-cycloalkyl

R3 is 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkyl-amino-1-4C-alkyl-carbonyl,

Ar is a phenyl

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, halogen or trifluoromethyl

and its salts.

3. A compound of the formula 1, as claimed in claim 1,

in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

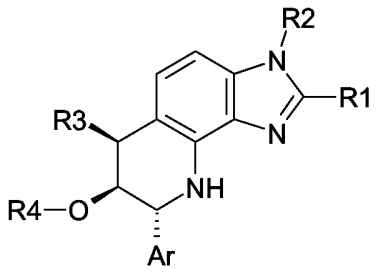
R3 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen,
R32 is hydrogen,
R4 is hydrogen,
Ar is a phenyl
and wherein
aryl is phenyl
and its salts.

4. A compound of the formula 1, as claimed in claim 1,
in which
R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,
R3 is 1-4C-alkyl, 3-7C-cycloalkyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen and
R32 is hydrogen,
R4 is hydrogen
Ar is a phenyl
and its salts.

5. A compound of the formula 1 as claimed in claim 1, characterized by the formula 1a,



(1a)

in which
R1 is hydrogen, halogen, hydroxyl, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl, hydroxy-1-4C-alkyl or mono- or di-1-4C-alkylamino,
R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl, hydroxy-1-4C-alkyl, fluoro-2-4C-alkyl,
R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, 2-4C-alkenyl, aryl-2-4C-alkenyl, cyano-1-4C-alkyl, or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, dihydroxy-1-4C-alkyl, or 1-4C-

alkoxy-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 3-7C-cycloalkyl, dihydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxy-pyrrolidino, azetidino, aziridino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl

Ar is a mono- or bicyclic aromatic residue, substituted by R5, R6, R7 and R8, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,
wherein
R5 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,
R6 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,
R7 is hydrogen, 1-4C-alkyl or halogen and
R8 is hydrogen, 1-4C-alkyl or halogen,
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

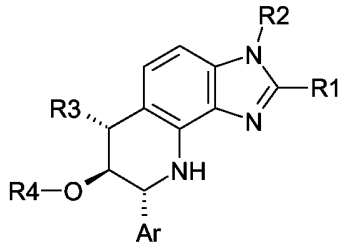
and its salts.

6. A compound of the formula 1a as claimed in claim 5,
in which
R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,
R3 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or aryl-2-4C-alkinyl,
R4 is hydrogen,
Ar is a phenyl
and wherein

aryl is phenyl
and its salts.

7. A compound of the formula 1a as claimed in claim 5,
in which
R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,
R3 is 1-4C-alkyl or 3-7C-cycloalkyl,
R4 is hydrogen
Ar is a phenyl
and its salts.

8. A compound of the formula 1 as claimed in claim 1, characterized by the formula 1b,



(1b)

in which
R1 is hydrogen, halogen, hydroxyl, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl, hydroxy-1-4C-alkyl or mono- or di-1-4C-alkylamino,
R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl, hydroxy-1-4C-alkyl, fluoro-2-4C-alkyl,
R3 is hydrogen, halogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkinyl, aryl-2-4C-alkinyl, 2-4C-alkenyl, aryl-2-4C-alkenyl, cyano-1-4C-alkyl, or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, dihydroxy-1-4C-alkyl, or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 3-7C-cycloalkyl, dihydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, hydroxy-pyrrolidino, azetidino, aziridino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, fluoro-1-4C-alkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl-carbonyl or mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl

Ar is a mono- or bicyclic aromatic residue, substituted by R5, R6, R7 and R8, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,

wherein

R5 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R6 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R7 is hydrogen, 1-4C-alkyl or halogen and

R8 is hydrogen, 1-4C-alkyl or halogen,

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and its salts.

9. A compound of the formula 1b as claimed in claim 8,

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, aryl-2-4C-alkinyl, cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,

where

R31 is hydrogen,

R32 is hydrogen,

R4 is hydrogen,

Ar is a phenyl

and wherein

aryl is phenyl

and its salts.

10. A compound of the formula 1b as claimed in claim 8,

in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is cyano-1-4C-alkyl or a NR31R32-carbonyl-1-4C-alkyl group,
where
R31 is hydrogen and
R32 is hydrogen,

R4 is hydrogen

Ar is a phenyl

and its salts.

11. A medicament comprising a compound as claimed in claim 1 and/or a pharmacologically acceptable salt thereof together with customary pharmaceutical auxiliaries and/or excipients

12. The use of a compound as claimed in claim 1 and its pharmacologically acceptable salts for the prevention and treatment of gastrointestinal disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/054898

A. CLASSIFICATION OF SUBJECT MATTER
C07D471/04 A61K31/4164 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/47603 A (ASTRA AKTIEBOLAG; AMIN, KOSRAT; DAHLSTROEM, MIKAEL; NORDBERG, PETER; S) 18 December 1997 (1997-12-18) cited in the application claim 1; examples 1.1,1.3,1.5,1.6,1.7,1.8	1-12
Y	WO 02/34749 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; BUHR, WILM; KOHL, BERNHARD;) 2 May 2002 (2002-05-02) claim 1; table a	1-12
Y	WO 01/72756 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; SENN-BILFINGER, JOERG; BUHR,) 4 October 2001 (2001-10-04) tables 1,a	1-12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2006	21/03/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Baston, E

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/054898

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 01/72754 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; SIMON, WOLFGANG-ALEXANDER; S) 4 October 2001 (2001-10-04) table 1	1-12
Y	WO 00/63211 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; SENN-BILFINGER, JOERG) 26 October 2000 (2000-10-26) table 1	1-12
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Y	WO 98/42707 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; SENN-BILFINGER, JOERG; GRUND) 1 October 1998 (1998-10-01) claim 1; table 1	1-12
A	KAMINSKI J J ET AL: "ANTIULCER AGENTS. 5. INHIBITION OF GASTRIC H+/K+-ATPASE BY SUBSITUTED IMIDAZOL1,2-A PYRIDINES AND RELATED ANALOGUES AND ITS IMPLICATION IN MODELING THE HIGH AFFINITY POTASSIUM ION BINDING SITE OF THE GASTRIC PROTON PUMP ENZYME" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, 1991, pages 533-541, XP000919185 ISSN: 0022-2623 table 1	1-12
A	KAMINSKI J J ET AL: "ANTIULCER AGENTS CONFORMATIONAL CONSIDERATIONS AND THE ANTIULCER ACTIVITY OF SUBSTITUTED IMIDAZO 1,2-A PYRIDINES AND RELATED ANALOGUES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 32, no. 8, January 1989 (1989-01), pages 1686-1700, XP002008622 ISSN: 0022-2623 tables 1,2	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/054898

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 12: The search for this claim was based on the alleged effects of the claimed compounds / compositions.Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/054898

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International application No
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