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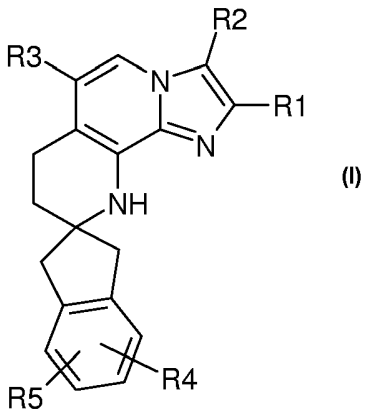
(54) Title: SPIRO-IMIDAZNAPHTHYRIDINE DERIVATIVES AS GASTRIC ACID SECRETION INHIBITORS



(I)

(57) Abstract: The invention provides compounds of the formula (I), in which the substituents and symbols are as defined in the description. The compounds inhibit the secretion of gastric acid.

WO 2006/134112 A1

Description

Title

SPIRO-IMIDAZONAPHTHYRIDINE DERIVATIVES AS GASTRIC ACID SECRETION INHIBITORS

Technical field

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

Background Art

U.S. Patent 4,468,400 describes tricyclic imidazo[1,2-a]pyridines having different ring systems fused to the imidazopyridine skeleton, which compounds are said to be suitable for treating peptide ulcer disorders. The International Patent Applications WO98/42707 (which corresponds to US patent 6,197,783), WO98/54188 (which corresponds to US patent 6,160,119), WO00/17200 (which corresponds to US patent 6,436,953 and 6,696,460), WO00/26217 (which corresponds to US patent 6,384,048), WO 00/63211 (which corresponds to US patent 6,503,923), WO 01/72756, WO 01/72754 (which corresponds to US patent 6,916,825), WO 01/72755 (which corresponds to US patent 6,936,623), WO 01/72757 (which corresponds to US patent 6,696,461), WO 02/34749 (which corresponds to US patent 6,869,949), WO 03/014120, WO 03/016310, WO 03/014123, WO 03/068774, WO 03/091253, WO 05/058325, WO 05/090358 and WO 05/077949 disclose tricyclic imidazopyridine derivatives having a very specific substitution pattern, which compounds are likewise said to be suitable for treating gastrointestinal disorders.

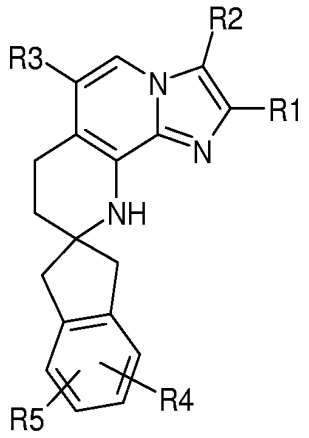
Disclosure of Invention

Technical problem

A whole series of compounds are known from the prior art which inhibit gastric acid secretion by blockade of the H+/K+-ATPase. The compounds designated as proton pump inhibitors (PPI´s), for example omeprazole, esomeprazole, lansoprazole, pantoprazole or rabeprazole, bind irreversibly to the H+/K+-ATPase. PPI´s are available as therapeutics for a long time already. A new class of compounds designated as reversible proton pump inhibitors (rPPI´s), as acid pump antagonists (APA´s) or as potassium competitive acid blockers (P-CAB´s) bind reversibly to the H+/K+-ATPase. Although rPPI´s, APA´s and P-CAB´s are known for more than 20 years and many companies are engaged in their development, no rPPI, APA or P-CAB is at present available for therapy. The technical problem underlying the present invention is therefore to provide acid pump antagonists which can be used in therapy.

Technical solution

The invention relates to compounds of the formula 1



(1)

in which

R1 is hydrogen, 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 or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-carbonyl, hydroxy-1-4C-alkyl, halogen, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl, mono- or di-1-4C-alkylamino-1-4C-alkyl or cyanomethyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl or 1-4C-alkoxycarbonyl
and
R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, fluorazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, trifluoromethyl, halo-1-4C-alkoxy, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alk-

ylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

and their salts.

1-4C-Alkyl represents straight-chain or branched alkyl groups 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 groups, which in addition to the oxygen atom contain a straight-chain or branched alkyl group having 1 to 4 carbon atoms. 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 group, the methoxyethyl group, in particular the 2-methoxyethyl group, the ethoxyethyl group, in particular the 2-ethoxyethyl group, and the butoxyethyl group, in particular the 2-butoxyethyl group.

1-4C-Alkoxycarbonyl (-CO-1-4C-alkoxy) 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 straight-chain or branched alkenyl groups 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 straight-chain or branched alkynyl groups 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 group, 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, the 3-hydroxypropyl, the (2S)-2-hydroxypropyl and the (2R)-2-hydroxypropyl group. Hydroxy-1-4C-alkyl within the scope of the invention is understood to include 1-4C-alkyl groups substituted by two or more hydroxy groups. Examples which may be mentioned are the 3,4-dihydroxybutyl and in particular the 2,3-dihydroxypropyl groups.

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

Mono- or di-1-4C-alkylamino radicals contain, in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preference is given to di-1-4C-alkylamino and in particular to dimethyl-, diethyl- or diisopropylamino.

Mono- or di-1-4C-alkylamino-1-4C-alkyl denotes one of the abovementioned 1-4C-alkyl radicals which is substituted by one of the abovementioned mono- or di-1-4C-alkylamino radicals. Preferred mono- or di-1-4C-alkylamino-1-4C-alkyl radicals are the mono- or di-1-4C-alkylaminomethyl radicals. An Example which may be mentioned is the dimethylaminomethyl $(CH3)_2N\text{-}CH_2$ radical.

1-4C-Alkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by a further 1-4C-alkoxy group. Examples which may be mentioned are the groups 2-(methoxy)ethoxy ($CH_3\text{-}O\text{-}CH_2\text{-}CH_2\text{-}O$-) and 2-(ethoxy)ethoxy ($CH_3\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2$ -O-).

1-4C-Alkoxy-1-4C-alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkoxy1-4C-alkyl groups, which is substituted by one of the aforementioned 1-4C-alkoxy groups. An example which may be mentioned is the group 2-(methoxy)ethoxymethyl ($CH_3\text{-}O\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_2$-).

Fluoro-1-4C-alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by a fluoro-1-4C-alkoxy group. Fluoro-1-4C-alkoxy in this case represents one of the aforementioned 1-4C-alkoxy groups, which substituted by one or more fluorine atoms. Examples of fluoro-substituted 1-4C-alkoxy groups which may be mentioned are the 2-fluoroethoxy, 1,1,1,3,3,3-hexafluoro-2-propoxy, the 2-trifluoromethyl-2-propoxy, the 1,1,1-trifluoro-2-propoxy, the perfluoro-tert-butoxy, the 2,2,3,3,4,4,4-heptafluoro-1-butoxy, the 4,4,4-trifluoro-1-butoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and prefera-

bly the difluoromethoxy group. Examples of fluoro-1-4C-alkoxy-1-4C-alkyl radicals which may be mentioned are, 1,1,2,2-tetrafluoroethoxymethyl, the 2,2,2-trifluoroethoxymethyl, the trifluoromethoxymethyl, 2-fluoroethoxyethyl, the 1,1,2,2-tetrafluoroethoxyethyl, the 2,2,2-trifluoroethoxyethyl, the trifluoromethoxyethyl and preferably the difluoromethoxymethyl and the difluoromethoxyethyl radicals.

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

1-4C-Alkylcarbonyl-1-4C-alkyl represents aforementioned 1-4C-alkyl groups which are substituted by 1-4C-alkylcarbonyl group. Examples which may be mentioned are the 2-oxo-propyl, the 2-oxo-butyl, the 2-oxo-pentyl, the 3-oxo-butyl or the 3-oxo-pentyl radicals.

Hydroxy-1-4C-alkoxy represents aforementioned 1-4C-alkoxy groups, which are substituted by a hydroxy group. A preferred example which may be mentioned is the 2-hydroxyethoxy group.

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

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

Halo-1-4C-alkoxy represents 1-4C-alkoxy groups which are completely or mainly substituted by halogen. "Mainly" in this connection means that more than half of the hydrogen atoms in the 1-4C-alkoxy groups are replaced by halogen atoms. Halo-1-4C-alkoxy groups are primarily chloro- and/or in particular fluoro-substituted 1-4C-alkoxy groups. Examples of halogen-substituted 1-4C-alkoxy groups which may be mentioned are the 2,2,2-trichloroethoxy, the hexachloroisopropoxy, the pentachloroisopropoxy, the 1,1,1-trichloro-3,3,3-trifluoro-2-propoxy, the 1,1,1-trichloro-2-methyl-2-propoxy, the 1,1,1-trichloro-2-propoxy, the 3-bromo-1,1,1-trifluoro-2-propoxy, the 3-bromo-1,1,1-trifluoro-2-butoxy, the 4-bromo-3,3,4,4-tetrafluoro-1-butoxy, the chlorodifluoromethoxy, the 1,1,1,3,3,3-hexafluoro-2-propoxy, the 2-trifluoromethyl-2-propoxy, the 1,1,1-trifluoro-2-propoxy, the perfluoro-tert-butoxy, the 2,2,3,3,4,4,4-heptafluoro-1-butoxy, the 4,4,4-trifluoro-1-butoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-tri-

fluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy 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.

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

Hydroxypyrrolidino represents a pyrrolidino group, which is substituted by a hydroxy group. Examples which may be mentioned are the 2-hydroxypyrrolidino and the 3-hydroxypyrrolidino groups.

Hydroxyazetidino represents an azetidino group, which is substituted by a hydroxy group. An which may be mentioned is the 3-hydroxyazetidino group.

Fluorazetidino represents an azetidino group, which is substituted by a fluoro atom. Examples which may be mentioned are the (2S)-and the (2R)-fluoroazetidino and in particular the 3-fluoroazetidino group.

N-1-4C-alkylpiperazino represents a piperazino group, in which one of the piperazino nitrogen atoms is substituted by one of the aforementioned 1-4-C-alkyl groups. Examples which may be mentioned are the 4-methylpiperazino, the 4-ethylpiperazino and the 4-iso-propylpiperazino groups.

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, malonic 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.

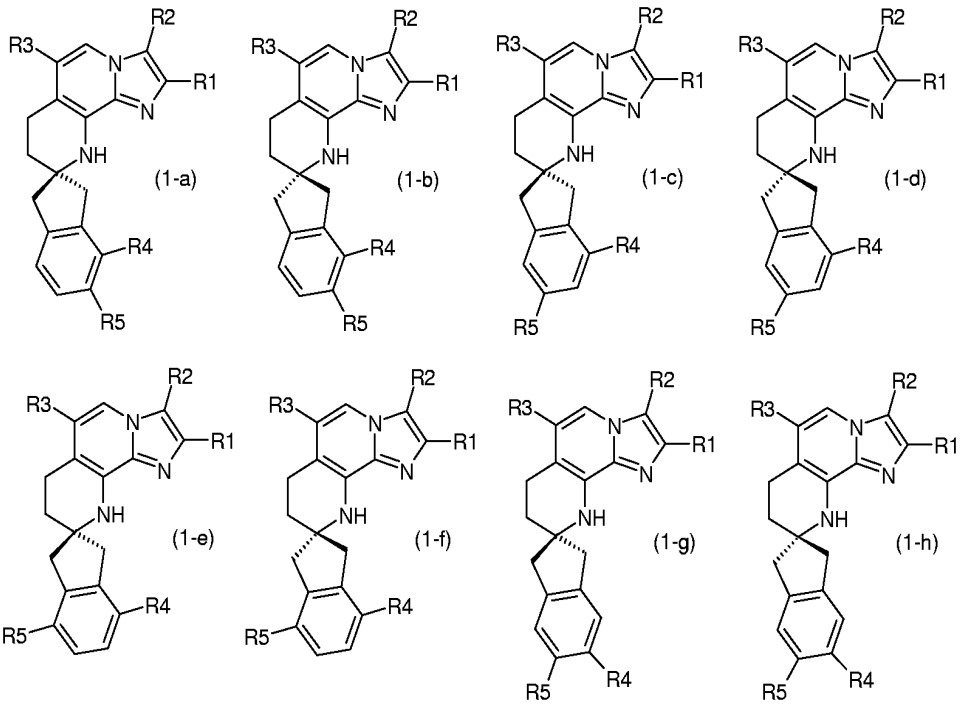
Salts of the compounds of formula I according to the invention can be obtained by dissolving, the free compound in a suitable solvent (for example a ketone such as acetone, methylethylketone or methylisobutylketone, an ether such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as methanol, ethanol or isopropanol) which contains the desired acid or to which the desired acid is then added, if necessary upon heating. The acid can be employed in salt preparation, depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired, in an equimolar quantitative ratio or one differing therefrom. The salts are obtained for example by evaporating the solvent or by precipitating upon cooling, by re-precipitating, or by precipitating with a non-solvent for the salt and separation, for example by filtration, of the salt after precipitation.

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 the 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 can have a center of chirality at the spiro carbon atom in 8-postion of the basic skeleton. The occurance of such a center of chirality depends on the nature and the position of the substituents R4 and R5. A center of chirality arises for example if R4 is different from R5. The invention thus relates to all feasible stereoisomers in any desired mixing ratio to another, including the pure stereoisomers, which are a preferred subject of the invention.

The invention therefore relates to all of the following stereoisomers of the formula 1:



The pure stereoisomers of the compounds of the formula 1 and salts according to the present invention can be obtained e.g. by asymmetric synthesis, by using chiral starting compounds in synthesis and by splitting up stereoisomeric mixtures obtained in synthesis. Preferably, the pure stereoisomers of the compounds of the formula 1 are obtained by using chiral starting compounds.

Stereoisomeric mixtures of compounds of the formula 1 can be split up into the pure stereoisomers by methods known to a person skilled in the art. Preferably, the mixtures are separated

by chromatography or (fractional) crystallization. For enantiomeric mixtures the split up is preferably done by forming diastereomeric salts by adding chiral additives like chiral acids, subsequent resolution of the salts and release of the desired compound from the salt. Alternatively, derivatization with chiral auxiliary reagents can be made, followed by diastereomer separation and removal of the chiral auxiliary group. Furthermore, enantiomeric mixtures can be separated using chiral separating columns in chromatography. Another suitable method for the separation of enantiomeric mixtures is the enzymatic separation.

One embodiment of the invention (embodiment 1) are compounds of the formula 1, in which

R3 is hydrogen,

and their salts.

Another embodiment of the invention (embodiment 2) are compounds of the formula 1, in which

R3 is the group -CO-NR31R32,

where

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

R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, fluoroazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

and their salts.

Another embodiment of the invention (embodiment 3) are compounds of the formula 1, in which

R3 is halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl

and their salts.

Another embodiment of the invention (embodiment 4) are compounds of the formula 1, in which

R4 and R5 are each hydrogen,

and their salts.

Another embodiment of the invention (embodiment 5) are compounds of the formula 1, in which
R1 is 1-4C-alkyl
and their salts.

Another embodiment of the invention (embodiment 6) are compounds of the formula 1, in which
R2 is hydrogen or 1-4C-alkyl,
and their salts.

Another embodiment of the invention (embodiment 7) are compounds of the formula 1, in which
R1 is methyl
and their salts.

Another embodiment of the invention (embodiment 8) are compounds of the formula 1, in which
R2 is hydrogen or methyl,
and their salts.

An embodiment of the invention (embodiment 9) to be emphasized are compounds of the formula 1, in which
R1 is methyl,
R2 is hydrogen or methyl,
and their salts.

The invention also relates to compounds of the formula 1, in which

R1 is hydrogen, 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 or hydroxy-1-4C-alkyl,

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

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl or 1-4C-alkoxycarbonyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, trifluoromethyl, halo-1-4C-alkoxy, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

and their salts.

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

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

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

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl or 1-4C-alkoxycarbonyl
and
R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, fluoroazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl or halogen,

and their salts.

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

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

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

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl or 1-4C-alkoxycarbonyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl or halogen,

and their salts.

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

R1 is hydrogen, 1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl or halogen,

R3 is hydrogen, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 1-4C-alkylcarbonyl-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, fluoroazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl or halogen,

and their salts.

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

R1 is hydrogen, 1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl or halogen,

R3 is hydrogen, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

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

R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl or halogen,

and their salts.

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

in which

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is hydrogen, carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

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

R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, fluoroazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are each hydrogen,

and their salts.

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

in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is hydrogen, carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32

where

R31 is 1-7C-alkyl and

R32 is hydrogen,

R4 and R5 are each hydrogen,

and their salts.

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

in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is hydrogen

R4 and R5 are each hydrogen,

and their salts.

Exemplary preferred compounds according to the invention are those compounds of the formula 1, wherein R1, R2, R3, R4 and R5 have the meanings as given in Table A (Me = CH_3, Et = C_2H_5), and the salts of these compounds. These compounds are either described by way of example as final products or can be prepared in an analogous manner using for example the process steps described below.

Table A:

R1	R2	R3	R4	R5
Me	Me	CH_2OH	H	H
Me	Me	CH_2OCH_3	H	H
Me	Me	C(O)NHMe	H	H
Me	Me	C(O)N-pyrrolidine	H	H
Me	Me	$C(O)NH(CH_2)_2OH$	H	H
Me	Me	$C(O)NH(CH_2)_2OMe$	H	H
Me	Me	$C(O)NH_2$	H	H
Me	Me	C(O)N-morpholine	H	H
Me	Me	$C(O)NMe_2$	H	H
Me	Me	C(O)N-aziridine	H	H
Me	Me	C(O)OEt	H	H
Me	Me	C(O)OH	H	H
Me	Me	C(O)N-azetidine	H	H
Me	Me	$C(O)NH(CH_2)_2Me$	H	H
Me	Me	$C(O)NHCH_2CH(OH)CH_2OH$	H	H
Me	Me	C(O)NH-cyclopropyl	H	H
Me	Me	H	H	H
Me	Me	C(O)NHEt	H	H
Me	Me	$C(O)NH(CH_2)_3OH$	H	H

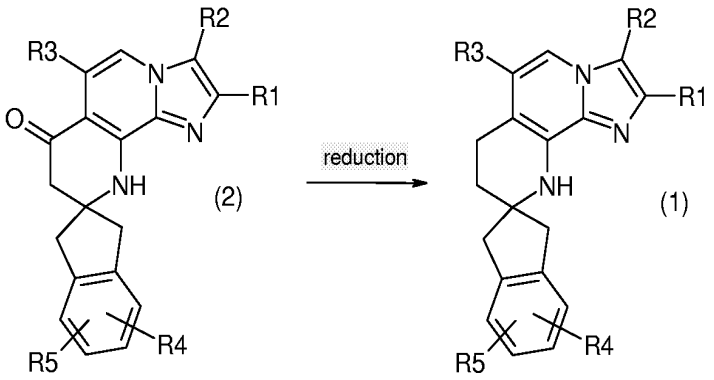
R1	R2	R3	R4	R5
Me	Me	$C(O)NH(CH_2)_3OMe$	H	H
Me	Me	$C(O)NHCH_2C(O)CH_3$	H	H
Me	Me	C(O)N-3-fluorazetidine	H	H
Me	Me	$C(O)N(CH_3)-(CH_2)_2OH$	H	H
Me	Me	$C(O)N(CH_3)-(CH_2)_2OMe$	H	H
Me	Me	$C(O)N(CH_3)-(CH_2)_3OH$	H	H
Me	Me	$C(O)N(CH_3)-(CH_2)_3OMe$	H	H
Me	H	CH_2OH	H	H
Me	H	CH_2OCH_3	H	H
Me	H	C(O)NHMe	H	H
Me	H	C(O)N-pyrrolidine	H	H
Me	H	$C(O)NH(CH_2)_2OH$	H	H
Me	H	$C(O)NH(CH_2)_2OMe$	H	H
Me	H	$C(O)NH_2$	H	H
Me	H	C(O)N-morpholine	H	H
Me	H	$C(O)NMe_2$	H	H
Me	H	C(O)N-aziridine	H	H
Me	H	C(O)OEt	H	H
Me	H	C(O)OH	H	H
Me	H	C(O)N-azetidine	H	H
Me	H	$C(O)NH(CH_2)_2Me$	H	H
Me	H	$C(O)NHCH_2CH(OH)CH_2OH$	H	H
Me	H	C(O)NH-cyclopropyl	H	H
Me	H	H	H	H
Me	H	C(O)NHEt	H	H
Me	H	$C(O)NH(CH_2)_3OH$	H	H
Me	H	$C(O)NH(CH_2)_3OMe$	H	H
Me	H	$C(O)NHCH_2C(O)CH_3$	H	H
Me	H	C(O)N-3-fluorazetidine	H	H
Me	H	$C(O)N(CH_3)-(CH_2)_2OH$	H	H
Me	H	$C(O)N(CH_3)-(CH_2)_2OMe$	H	H
Me	H	$C(O)N(CH_3)-(CH_2)_3OH$	H	H
Me	H	$C(O)N(CH_3)-(CH_2)_3OMe$	H	H

Exemplary particularly preferred compounds according to the invention are those described by way of example and the salts of these compounds.

The compounds according to the invention can be synthesized 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 following examples.

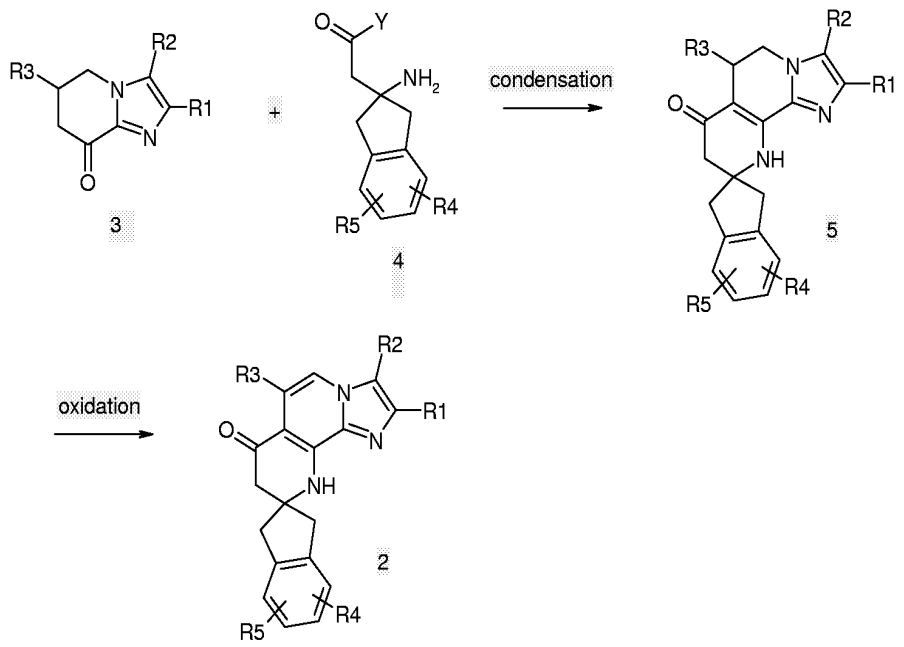
As outlined in scheme 1, the compounds of the formula 1 can be obtained by reduction of the carbonyl group in the corresponding compounds of the formula 2 by methods which are familiar to a person skilled in the art, for example using triethylsilane / trifluoroacetic acid (West et al., J. Org. Chem. 1973, 38, 2675-2681) or, for example using lithium aluminium hydride in the case when R3 is a group which can not be reduced under these conditions like for example R3 = hydrogen.

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 3 are reacted with spiro-amino acid derivatives of the formula 4 (wherein Y is a suitable leaving group, for example an 1-4C-alkoxy group, e.g. an ethoxy group) to give compounds of the formula 5. In a second step, compounds of the formula 5 are oxidized by standard procedures using a suitable oxidizing agent (e.g. chloranil or 2,3-dichloro-5,6-dicyanobenzoquinone) to give compounds of the formula 2.

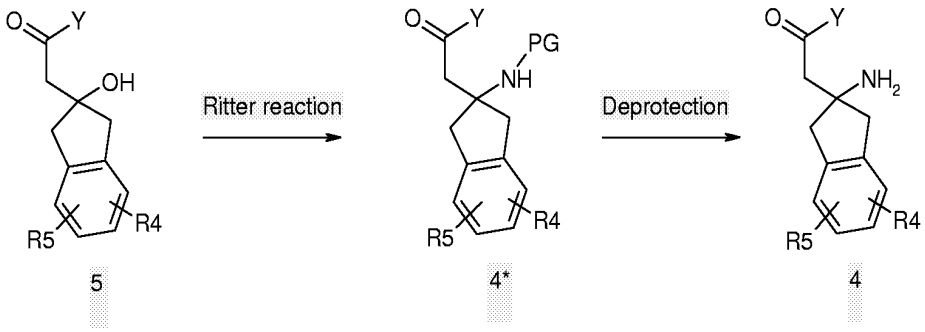
Scheme 2.



Ketones of the formula 3 are known to a person skilled in the art (inter alia from the International Patent Applications WO 02/34749, WO 01/72748, WO 01/72757 or from Angew. Chem. Int. Ed. Engl. 1996, 35, 545), or they can be prepared using analogous process steps which are known to a person skilled in the art.

As outlined in scheme 3, the required ß-amino acid derivatives of the general formula 4 can be prepared from the corresponding ß-hydroxy acids of the formula 5, wherein Y is a suitable leaving group, for example an 1-4C-alkoxy group, e.g. an ethoxy group, by methods familiar to a person skilled in the art, like for example the Ritter reaction in analogy to the procedure described for example in Org. React. 1969, 17, 213. Compounds of the formula 5 are known to a person skilled in the art, for example from J. Chem. Soc. 1960, 4115, or they can be prepared using analogous process steps. If acetonitrile is used for the Ritter reaction, ß-amino acids of the formula 4* with PG = acetyl are obtained. The protecting group PG in compounds of the formula 4* can then be cleaved from the amino functionality by methods known to the expert, for example if PG is an acetyl group, it can be cleaved by acidic hydrolysis to give compounds of the formula 4. The group Y can be transformed into any other group Y by standard procedures known to the expert, for example by esterification.

Scheme 4:



5 4* 4

The derivatization, if any, of the compounds obtained according to the schemes above (e.g. conversion of a group R3 into another group R3 or conversion of a hydroxyl group into an alkoxy or ester group) is likewise carried out in a manner known per se. If, for example, compounds of the formula 1 where R3 = -CO-NR31R32 are desired, an appropriate derivatization can be performed in a manner known per se (e. g. conversion of an ester or a carboxylic acid into an amide), preferably at the stage of compounds of the formula 1 or at the stage of any intermediate thereof.

The reaction steps outlined above are carried out in a manner known per se, e.g. as described in more detail in the examples.

The present invention further relates to compounds of the formula 2 and 5 shown above, which are intermediates in the process of producing the compounds of the formula 1 according to the present invention. R1, R2, R3, R4, R5 are thereby defined as for compounds of the formula 1.

The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for compounds according to this invention. All synthesis routes described herein as well as all other possible synthesis routes are also part of this invention.

Advantageous effects

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 of the formula 1 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	1	> 40

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).

Mode(s) for Carrying Out the Invention

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.

I. Final Compounds of the formula 1

1. 2,3-Dimethyl-1',3',7,10-tetrahydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]

To a suspension of 0.7 g (2.2 mmol) 2,3-dimethyl-1',3'-dihydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-inden]-7(10*H*)-one in 12 ml tetrahydrofuran were slowly added 4.4 ml (4.4 mmol) lithium aluminium hydride (1M in diethyl ether) at 0 °C. After 2 h, the reaction mixture was hydrolyzed with 0.17 ml water, 0.2 ml aqueous sodium hydroxide (10 %) and 0.5 ml water. Anhydrous magnesium sulphate was added and the mixture was filtered. The filtrate was evaporated and the residue purified by column chromatography (silica gel, ethyl acetate). Crystallization from ethyl acetate/diethyl ether yielded 270 mg (40 %) of the title compound as a colourless solid. m.p. 175-176 °C.

2. Methyl 2,3-dimethyl-1',3',7,10-tetrahydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]-6-carboxylate

To a solution of 0.42 g (1.12 mmol) methyl 2,3-dimethyl-7-oxo-1',3',7,10-tetrahydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]-6-carboxylate in 5.5 ml trifluoroacetic acid were added 1.1 ml (6.9 mmol) triethylsilane and the mixture was stirred overnight at 40 °C. A further amount of 0.3 ml triethylsilane was added and stirring was continued for 24 h at 40 °C. The reaction mixture was evaporated, neutralized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulphate and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, ethyl acetate/petroleum ether/triethylamine 2:8:1) and crystallization from ethyl acetate/n-heptane yielded 0.34 g (84 %) of the title compound as a near colourless solid. m.p. 188-189 °C.

3. 2,3-Dimethyl-1',3',7,10-tetrahydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]-6-carboxylic acid

A solution of 150 mg (0.42 mmol) methyl 2,3-dimethyl-1',3',7,10-tetrahydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]-6-carboxylate and 415 mg (3.7 mmol) potassium tert-butoxide in 15 ml

tert-butanol was heated to 50 °C. After 1 h, the mixture was evaporated to dryness, dissolved in 2 ml water and neutralized with 10% hydrochloric acid. The precipitate was collected and dried in vacuo over phosphorus pentoxide to yield 105 mg (72 %) of the title compound as a beige solid. m.p. >300 °C.

4. *N*,2,3-Trimethyl-1',3',7,10-tetrahydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]-6-carboxamide

To a suspension of 90 mg (0.26 mmol) 2,3-dimethyl-1',3',7,10-tetrahydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]-6-carboxylic acid in 4 ml tetrahydrofuran were added 1.04 g (6.4 mmol) N,N'-carbonyldiimidazole and the mixture was heated to reflux. After 6 h, 0.5 ml (3.5 mmol) methylamine (7M in N,N-dimethylformamide) were added at 0 °C. After 30 min, the reaction mixture was partitioned between saturated aqueous ammonium chloride and dichloromethane. The organic layer was washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulphate and evaporated. The residue was crystallized from ethyl acetate/heptane to yield 39 mg (42 %) of the title compound as a colourless solid. m.p. 157-158 °C.

II. Starting Compounds

A. 2,3-Dimethyl-1',3',6,10-tetrahydro-5*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-inden]-7(8*H*)-one

A mixture of 3.8 g (17 mmol) ethyl (2-amino-2,3-dihydro-1*H*-inden-2-yl)acetate, [liberated from its hydrochloride salt, ethyl (2-amino-2,3-dihydro-1*H*-inden-2-yl)acetate hydrochloride, example K, by treatment with triethylamine], 3.2 g (20 mmol) 2,3-dimethyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine and 200 mg p-toluenesulphonic acid monohydrate in 80 ml xylene was heated under reflux for 16 h while water was removed with a Dean-Stark trap. The reaction mixture was cooled to room temperature and diluted with 80 ml tetrahydrofuran. At -40 °C, 25 ml (25 mmol) of lithium bis(trimethylsilylamide) (1M in tetrahydrofuran) were added dropwise during 5 min and the mixture was allowed to warm to room temperature. The reaction mixture was hydrolyzed with 60 ml saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layer was separated and dried over anhydrous sodium sulphate. On concentration in vacuo, a precipitate formed which was collected and rinsed with xylene and heptane to yield 3.0 g (55 %) of the title compound as a yellow solid. m.p. 232-233 °C.

B. 2,3-Dimethyl-1',3'-dihydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-inden]-7(10*H*)-one

To a solution of 3.0 g (9.4 mmol) 2,3-dimethyl-1',3',6,10-tetrahydro-5*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-inden]-7(8*H*)-one in 50 ml dichloromethane were added 2.56 g (11.3 mmol) 2,3-dichloro-5,6-dicyanobenzoquinone at 0 °C and the mixture was allowed to warm to room temperature. After 2 h, additional 2,3-dichloro-5,6-dicyanobenzoquinone (0.3 g, 1.4 mmol) was added and the mixture was stirred overnight. The mixture was diluted with 500 ml dichloromethane and washed with 1N aqueous sodium hydroxide (3 x 500 ml). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, ethyl acetate) yielded 0.9 g (30 %) of the title compound as a yellow solid. m.p. 288-290 °C.

C. Methyl 2,3-dimethyl-7-oxo-1',3',6,7,8,10-hexahydro-5*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]-6-carboxylate

A mixture of 9.0 g (41 mmol) ethyl (2-amino-2,3-dihydro-1*H*-inden-2-yl)acetate, [liberated from its hydrochloride salt, ethyl (2-amino-2,3-dihydro-1*H*-inden-2-yl)acetate hydrochloride, example K, by treatment with triethylamine], 7.63 g (34.3 mmol) methyl 2,3-dimethyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate and 250 mg p-toluenesulphonic acid monohydrate in 250 ml degassed xylene was heated under reflux for 3 d while water was removed with a Dean-Stark trap. The reaction mixture was cooled to room temperature and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate) and crystallized from ethyl acetate/n-heptane to yield 1.3 g (10 %) of the title compound as a yellow solid. m.p. 185-186 °C.

D. Methyl 2,3-dimethyl-7-oxo-1',3',7,10-tetrahydro-8*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]-6-carboxylate

1.3 g (3.44 mmol) methyl 2,3-dimethyl-7-oxo-1',3',6,7,8,10-hexahydro-5*H*-spiro[imidazo[1,2-*h*]-1,7-naphthyridine-9,2'-indene]-6-carboxylate were dissolved in 100 ml ethyl acetate at 45-50 °C. To this solution were added 7.8 g (34.4 mmol) 2,3-dichloro-5,6-dicyanobenzoquinone portionwise over a period of 6 h at room temperature. To the reaction mixture were added 200 ml water and 50 ml 2N aqueous potassium hydroxide. The mixture was extracted with ethyl acetate and the organic layer was washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous magnesium sulphate and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, ethyl acetate) and crystallization from ethyl acetate/n-heptane yielded 0.49 g (38 %) of the title compound as a light green solid. ^{1}H-NMR ($CDCl_3$): 2.34 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 2.92 (m, 2 H), 3.24 (s, 4 H), 3.95 (s, 3 H, OCH_3), 6.22 (bs, 1 H, NH), 7.19 (m, 4 H), 7.31 (s, 1 H).

E. 8-(Benzyloxy)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic acid

To a solution of 6.5 g ethyl 8-(benzyloxy)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylate in 200 ml dioxane are added 15 ml 6N aqueous sodium hydroxide and the mixture is heated to 100 °C. After 20 min, 200 ml water and 35 ml 4N hydrochloric acid are added to give a suspension which is stirred for 15 min. The precipitate is collected, washed with water and dried in vacuo to give 5.47 g (92 %) of the title compound as a colourless solid of melting point 191-193 °C.

F. Methyl 8-hydroxy-2,3-dimethyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate

A solution of 139.6 g 8-(benzyloxy)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic acid is hydrogenated over 20 g palladium on charcoal (80-100 bar, 80 °C). After complete reaction, the catalyst is filtered off and the filtrate is evaporated to give a solid which is suspended in 500 ml methanol. This suspension is added to a solution of 41 ml thionyl chloride in 500 ml methanol at 0 °C. After 30 min at room temperature, the mixture is heated to 60 °C for 4 h. The solvent is evaporated and the residue partitioned between dichloromethane and saturated aqueous sodium hydrogencarbonate. The organic layer is separated, dried over anhydrous magnesium sulphate and evaporated to give 71.4 g (78 %) of the title compound as a colourless solid (95 % purity, melting point 186-187 °C).

G. Methyl 2,3-dimethyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate

To a solution of 0.22 g methyl 8-hydroxy-2,3-dimethyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate in 10 ml chloroform are added 0.9 g manganese(IV) oxide. After 9 h, the mixture is filtered through celite and the filtrate is evaporated. The residue is triturated with diisopropyl ether to give 0.16 g (72 %) of the title compound of melting point 156-157 °C.

H. Ethyl (2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)acetate

A solution of lithium diisopropylamide in heptane/tetrahydrofuran (305 ml, 0.55 mol) was cooled to -75 °C and 55 ml (0.56 mol) ethyl acetate were added dropwise while the temperature was kept below -75 °C. After addition was complete, the mixture was stirred at -75 °C for 30 min. A solution of 36.5 g (0.27 mol) 2-indanone in 90 ml tetrahydrofuran was added dropwise while the temperature was kept below -75 °C. The mixture was stirred for 60 min while the temperature was allowed to rise to -12 °C. The mixture was quenched with 200 ml tetrahydrofuran/water (1:1) and 500 ml saturated aqueous ammonium chloride solution were added. The mixture was acidified with 5N hydrochloric acid and extracted with tert-butyl methyl ether (2 x 500 ml). The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was purified by distillation at 123-130 °C and 0.5 mm Hg, affording 31.2 g (52 %) of the title compound. ^{1}H-NMR ($CDCl_3$): 1.30 (t, J = 7.1 Hz, 3 H), 2.76 (s, 2 H),

3.02 (d, J = 16.1 Hz, 2 H), 3.15 (d, J = 16.1 Hz, 2 H), 3.71 (s, 1 H, OH), 4.21 (q, J = 7.1 Hz, 2 H), 7.18 (m, 4 H).

I. Ethyl [2-(acetylamino)-2,3-dihydro-1*H*-inden-2-yl]-acetate

A solution of 75 g (0.34 mol) ethyl (2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)acetate in 1.5 L acetonitrile was cooled to 5 °C. 67 ml chlorosulphonic acid were added dropwise while the temperature was allowed to rise to 14 °C. The reaction mixture was then stirred for 5 h at ambient temperature. The mixture was poured into water (10 L) and extracted with ethyl acetate. The organic layer was concentrated in vacuo affording 47.7 g (54 %) of the title compound. m.p. 72-73 °C.

J. (2-Amino-2,3-dihydro-1*H*-inden-2-yl)acetic acid hydrochloride

A solution of 23.5 g (90 mmol) ethyl [2-(acetylamino)-2,3-dihydro-1*H*-inden-2-yl]-acetate in 200 ml 5N hydrochloric acid was refluxed overnight. The mixture was evaporated to dryness and the residue was mixed with ethyl acetate. The obtained solid was collected by filtration affording 12.4 g (61 %) of the title compound. m.p. 176-178 °C.

K. Ethyl (2-amino-2,3-dihydro-1*H*-inden-2-yl)acetate hydrochloride

A solution of 12.4 g (55 mmol) (2-amino-2,3-dihydro-1*H*-inden-2-yl)acetic acid hydrochloride in 250 ml ethanol was cooled to 0-5 °C and 7.5 ml thionylchloride were added dropwise during 20 min. The mixture was refluxed for 3 h and concentrated in vacuo affording 17 g (quant.) of the title compound. m.p. 188-190 °C.

Industrial applicability

The compounds of the formula 1 and their pharmaceutically 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 or curative 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, a fast onset of action, an advantageous duration of action, efficient control of the duration of action by the dosage, a particularly good antisecretory efficacy, the absence of significant side effects and a large therapeutic range.

"Gastric and intestinal protection or cure" in this connection is understood to include, according to general knowledge, the prevention, the treatment and the maintenance treatment of gastrointestinal diseases, in particular of gastrointestinal inflammatory diseases and lesions (such as, for example, reflux esophagitis, gastritis, hyperacidic or drug-related functional dyspepsia, and peptic ulcer disease [including peptic ulcer bleeding, gastric ulcer, duodenal ulcer]), which can be caused, for example, by microorganisms (e.g. Helicobacter pylori), bacterial toxins, drugs (e.g. certain antiinflammatories and antirheumatics, such as NSAIDs and COX-inhibitors), chemicals (e.g. ethanol), gastric acid or stress situations.

The term "gastrointestinal diseases" is understood to include, according to general knowledge,
A) gastroesophageal reflux disease (GERD), the symptoms of which include, but are not limited to, heartburn and/or acid regurgitation and/or non-acid regurgitation.
B) other extra-esophageal manifestations of GERD that include, but are not limited to, acid-related asthma, bronchitis, laryngitis and sleep disorders.
C) other diseases that can be connected to undiagnosed reflux and/or aspiration include, but are not limited to, airway disorders such as asthma, bronchitis, COPD (chronic obstructive pulmonary disease).
D) Helicobacter pylori infection whose eradication is playing a key role in the treatment of gastrointestinal diseases.
E) Furthermore, "gastrointestinal diseases" comprise other gastrointestinal conditions that might be related to acid secretion, such as Zollinger-Ellison syndrome, acute upper gastrointestinal bleeding, nausea, vomiting due to chemotherapy or post-operative conditions, stress ulceration, IBD (inflammatory bowel disease) and particularly IBS (irritable bowel syndrome).

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 and/or upper digestive tract, particularly of the abovementioned diseases.

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.

As medicaments, the active compounds according to the invention are either employed as such, or preferably in combination with suitable pharmaceutical excipients in the form of tablets, coated tablets (e.g. film-coated tablets), multi unit particulate system tablets, capsules, suppositories, granules, powders (e.g. lyophilized compounds), pellets, patches (e.g. as TTS [transdermal therapeutic system]), emulsions, suspensions or solutions. The content of the active compound is advantageously being between 0.1 and 95wt% (weight percent in the final dosage form), preferably between 1 and 60wt%. By means of the appropriate selection of the excipients, it is possible to obtain a pharmaceutical administration form adapted to the active compound and/or to the desired onset and/or duration of action (e.g. a sustained release form or a delayed release form).

The active compounds according to the invention can be administered orally, parenterally (e.g. intravenously), rectally or percutaneously. Oral or intravenous administration is preferred.

The excipients or combinations of 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 and are composed of one or more accessory ingredients. In addition to solvents, antioxidants, stabilizers, surfactants, complexing agents (e.g. cyclodextrins), the following excipients may be mentioned as examples: For oral administration, gelling agents, antifoams, plasticizer, adsorbent agents, wetting agents, colorants, flavorings, sweeteners and/or tabletting excipients (e.g. carriers, fillers, binders, disintegrating agents, lubricants, coating agents); for intravenous administration, dispersants, emulsifiers, preservatives, solubilizers, buffer substances and/or isotonic adjusting substances. For percutaneous administration, the person skilled in the art may choose as excipients, for example: solvents, gelling agents, polymers, permeation promoters, adhesives, matrix substances and/or wetting agents.

In general, it has been proven advantageous in human medicine to administer the active compound(s) in the case of oral administration in a daily dose (given continuously or on-demand) of approximately 0.01 to approximately 20, preferably 0.02 to 5, in particular 0.02 to 1.5, mg/kg of body weight, if appropriate in the form of several, preferably 1 to 2, 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. Furthermore, the frequency of administration can be adapted to intermittent, weekly, monthly, even more infrequent (e.g. implant) dosing. 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.

The medicaments may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmaceutical science. All methods include the step of bringing the active compounds according to the invention into association with the excipients or a combination of excipients. In general the formulations are prepared by uniformly and intimately bringing into association the active compounds according to the invention with liquid excipients or finely divided solid excipients or both and then, if necessary, formulating the product into the desired medicament.

The active compounds according to the invention or their pharmaceutical preparations can also be used in combination with one or more pharmacologically active constituents from other groups of drugs [combination partner(s)]. “Combination” is understood to be the supply of both the active compound(s) according to the invention and the combination partner(s) for separate, sequential, simultaneous or chronologically staggered use. A combination is usually designed with the aim of increasing the principal action in an additive or super-additive sense and/or of eliminating or decreasing the side effects of the combination partner(s), or with the aim to obtain a more rapid onset of action and a fast symptom relief. By choosing the appropriate pharmaceutical formulation of the drugs contained in the combination, the drug release profile of the components can be exactly adapted to the desired effect, e.g. the release of one compound and its onset of action is chronologically previous to the release of the other compound.

A combination can be, for example, a composition containing all active compounds (for example a fixed combination) or a kit-of-parts comprising separate preparations of all active compounds.

A “fixed combination” is defined as a combination wherein a first active ingredient and a second active ingredient are present together in one unit dosage or in a single entity. One example of a “fixed combination” is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture of simultaneous administration, such as in a formulation. Another example of a “fixed combination” is a pharmaceutical composition wherein the

said first active ingredient and the said second active ingredient are present in one unit without being in admixture.

A "kit-of-parts" is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One example of a "kit-of-parts" is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the kit-of-parts may be administered separately, sequentially, simultaneously or chronologically staggered.

"Other groups of drugs" are understood to include, for example: tranquillizers (for example from the group of the benzodiazepines, like diazepam), spasmolytics (for example butylscopolaminium bromide [Buscopan®]), anticholinergics (for example atropine sulfate, pirenzepine, tolterodine), pain perception reducing or normalizing agents (for example, paracetamol, tetracaine or procaine or especially oxetacain), and, if appropriate, also enzymes, vitamins, trace elements 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 buffer or neutralize gastric acid (such as, for example, magaldrat, aluminium hydroxide, magnesium carbonate, magnesium hydroxide or other antacids), or especially with pharmaceuticals which inhibit or reduce acid secretion, such as, for example:
(I) histamine-H2 blockers [e.g. cimetidine, ranitidine], or
(II) proton pump inhibitors [e.g. omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, tenatoprazole, ilaprazole, leminoprazole, all including their salts and enantiomers] or
(III) other potassium-competitive acid blockers [e.g. soraprazan and its stereoisomers, linaprazan, revaprazan, all including their salts]), or
(IV) so-called peripheral anticholinergics (e.g. pirenzepine), with gastrin antagonists such as CCK2 antagonists (cholestocystokinin 2 receptor antagonists).

An important combination to be mentioned is the combination with antibacterially active substances, and especially substances with a bactericidal effect, or combinations thereof. These combination partner(s) are especially useful for the control of Helicobacter pylori infection whose eradication is playing a key role in the treatment of gastrointestinal diseases. As suitable antibacterially active combination partner(s) may be mentioned, for example:
(A) cephalosporins, such as, for example, cifuroximaxetil
(B) penicillines, such as, for example, amoxicillin, ampicillin
(C) tetracyclines, such as, for example, tetracyline itself, doxycycline
(D) β-lactamase inhibitors, such as, for example, clavulanic acid
(E) macrolide antibiotics, such as, for example, erythromycin, clarithromycin, azithromycin
(F) rifamycines, such as, for example, rifamycine itself
(G) glycoside antibiotics, such as, for example, gentamicin, streptomycin

(H) gyrase inhibitors, such as, for example, ciprofloxaxin, gatifloxacin, moxifloxacin
(I) oxazolidines, such as, for example, linezolid
(J) nitrofuranes or nitroimidazoles, such as, for example, metronidazole, tinidazole, nitrofurantoin
(K) bismuth salts, such as, for example, bismuth subcitrat
(L) other antibacterially active substances
and combinations of substances selected from (A) to (L), for example clarithromycin + metronidazole. Preferred is the use of two combination partners. Preferred is the use of two combination partners selected from amoxicillin, clarithromycin and metronidazole. A preferred example is the use of amoxicillin and clarithromycin.

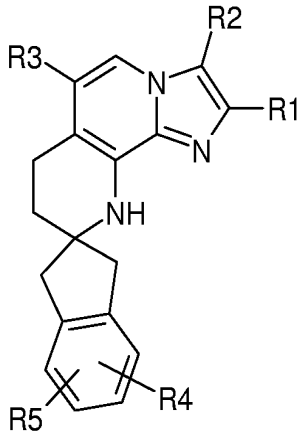
In view of their excellent activity regarding gastric and intestinal protection or cure, the active compounds according to the invention are especially suited for a free or fixed combination with drugs, which are known to cause "drug-induced dyspepsia" or are known to have a certain ulcerogenic potency, such as, for example, acetylsalicylic acid, certain antiinflammatories and antirheumatics, such as NSAIDs (non-steroidal antiinflammatory drugs, e.g. etofenamate, diclofenac, indometacin, ibuprofen, piroxicam, naproxen, meloxicam), oral steroids, bisphosponates (e.g. alendronate), or even NO-releasing NSAIDs, COX-2 inhibitors (e.g. celecoxib, lumiracoxib).

In addition, the active compounds according to the invention are suited for a free or fixed combination with motility-modifying or -regulating drugs (e.g. gastroprokinetics like mosapride, tegaserod, itopride, metoclopramid), and especially with pharmaceuticals which reduce or normalize the incidence of transient lower esophageal sphincter relaxation (TLESR), such as, for example, GABA-B agonists (e.g. baclofen, (2R)-3-amino-2-fluoropropylphosphinic acid) or allosteric GABA-B agonists (e.g. 3,5-bis(1,1-dimethylethyl)-4-hydroxy-β,β-dimethylbenzenepropanol), GABA-B re-uptake inhibitors (e.g. tiagabine), metabotropic glutamate receptor type 5 (mGluR5) antagonists (e.g. 2-methyl-6-(phenylethynyl)pyridine hydrochloride), CB2 (cannabinoid receptor) agonists (e.g. [(3R)-2,3-dihydro-5-methyl-3-(4-morpholinyl-methyl)pyrrolo[1,2,3,de]-1,4-benzoxazin-6-yl]-1-naphthalenyl-methanone mesylate). Pharmaceuticals used for the treatment of IBS or IBD are also suitable combination partner(s), such as, for example: 5-HT4 receptor agonists like mosapride, tegaserod; 5-HT3 receptor antagonists like alosetron, cilansetron; NK2 antagonists like saredutant, nepadutant; κ-opiate agonists like fedotozine.

Suitable combination partner(s) also comprise airway therapeutica, for example for the treatment of acid-related asthma and bronchitis. In some cases, the use of a hypnotic aid (such as, for example, Zolpidem [Bikalm®]) as combination partner(s) may be rational, for example for the treatment of GERD-induced sleep disorders.

Claims

1. A compound of the formula 1



(1)

in which

R1 is hydrogen, 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 or hydroxy-1-4C-alkyl,

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

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, 3-7C-cycloalkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 1-4C-alkylcarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyl or 1-4C-alkoxycarbonyl
and
R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, fluoroazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, trifluoromethyl, halo-1-4C-alkoxy, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkyl-

carbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

and its salts.

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

R1 is hydrogen, 1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl or halogen,

R3 is hydrogen, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

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

R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, fluorazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are identical or different substituents selected from the group consisting of hydrogen, 1-4C-alkyl or halogen,

and its salts.

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

in which

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is hydrogen, carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32,

where

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

R32 is hydrogen, 1-7C-alkyl, hydroxy-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, hydroxypyrrolidino, piperidino, piperazino, azetidino, hydroxyazetidino, fluorazetidino, aziridino, N-1-4C-alkylpiperazino or morpholino group,

R4 and R5 are each hydrogen,

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 hydrogen, carboxyl, 1-4C-alkoxycarbonyl or the group -CO-NR31R32
where
R31 is 1-7C-alkyl and
R32 is hydrogen,

R4 and R5 are each hydrogen,

and its salts.

5. 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

R4 and R5 are each hydrogen,

and its salts.

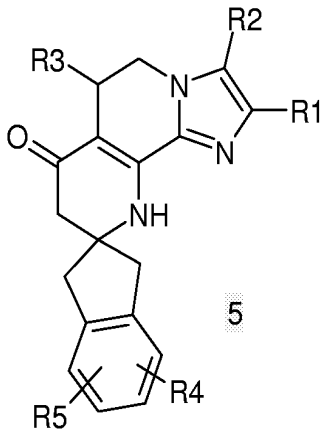
6. A compound of the formula 1 as claimed in claim 1, in which the substituents R1, R2, R3, R4 and R5 have the meanings given in the following table, whereby Me is CH_3 and Et is C_2H_5

R1	R2	R3	R4	R5
Me	Me	CH_2OH	H	H
Me	Me	CH_2OCH_3	H	H
Me	Me	C(O)NHMe	H	H
Me	Me	C(O)N-pyrrolidine	H	H
Me	Me	$C(O)NH(CH_2)_2OH$	H	H
Me	Me	$C(O)NH(CH_2)_2OMe$	H	H
Me	Me	$C(O)NH_2$	H	H
Me	Me	C(O)N-morpholine	H	H
Me	Me	$C(O)NMe_2$	H	H
Me	Me	C(O)N-aziridine	H	H
Me	Me	C(O)OEt	H	H
Me	Me	C(O)OH	H	H
Me	Me	C(O)N-azetidine	H	H
Me	Me	$C(O)NH(CH_2)_2Me$	H	H
Me	Me	$C(O)NHCH_2CH(OH)CH_2OH$	H	H
Me	Me	C(O)NH-cyclopropyl	H	H
Me	Me	H	H	H

R1	R2	R3	R4	R5
Me	Me	C(O)NHEt	H	H
Me	Me	$C(O)NH(CH_2)_3OH$	H	H
Me	Me	$C(O)NH(CH_2)_3OMe$	H	H
Me	Me	$C(O)NHCH_2C(O)CH_3$	H	H
Me	Me	C(O)N-3-fluorazetidine	H	H
Me	Me	$C(O)N(CH_3)-(CH_2)_2OH$	H	H
Me	Me	$C(O)N(CH_3)-(CH_2)_2OMe$	H	H
Me	Me	$C(O)N(CH_3)-(CH_2)_3OH$	H	H
Me	Me	$C(O)N(CH_3)-(CH_2)_3OMe$	H	H
Me	H	CH_2OH	H	H
Me	H	CH_2OCH_3	H	H
Me	H	C(O)NHMe	H	H
Me	H	C(O)N-pyrrolidine	H	H
Me	H	$C(O)NH(CH_2)_2OH$	H	H
Me	H	$C(O)NH(CH_2)_2OMe$	H	H
Me	H	$C(O)NH_2$	H	H
Me	H	C(O)N-morpholine	H	H
Me	H	$C(O)NMe_2$	H	H
Me	H	C(O)N-aziridine	H	H
Me	H	C(O)OEt	H	H
Me	H	C(O)OH	H	H
Me	H	C(O)N-azetidine	H	H
Me	H	$C(O)NH(CH_2)_2Me$	H	H
Me	H	$C(O)NHCH_2CH(OH)CH_2OH$	H	H
Me	H	C(O)NH-cyclopropyl	H	H
Me	H	H	H	H
Me	H	C(O)NHEt	H	H
Me	H	$C(O)NH(CH_2)_3OH$	H	H
Me	H	$C(O)NH(CH_2)_3OMe$	H	H
Me	H	$C(O)NHCH_2C(O)CH_3$	H	H
Me	H	C(O)N-3-fluorazetidine	H	H
Me	H	$C(O)N(CH_3)-(CH_2)_2OH$	H	H
Me	H	$C(O)N(CH_3)-(CH_2)_2OMe$	H	H
Me	H	$C(O)N(CH_3)-(CH_2)_3OH$	H	H
Me	H	$C(O)N(CH_3)-(CH_2)_3OMe$	H	H

and its salts.

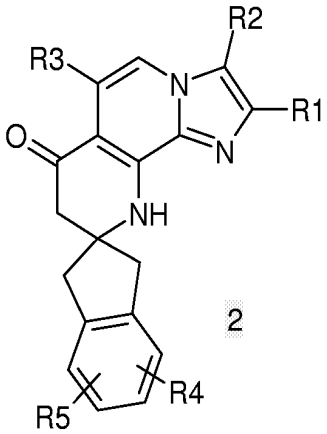
7. A compound of the formula 5,



5

in which R1, R2, R3, R4 and R5 are defined as in claim 1 for compounds of the formula 1.

8. A compound of the formula 2,



2

in which R1, R2, R3, R4 and R5 are defined as in claim 1 for compounds of the formula 1.

9. Use of a compound according to any of claims 1 to 6 for the production of medicaments which are employed for the treatment and/or prophylaxis of gastrointestinal disorders.

10. A medicament comprising one or more compounds according to any of claims 1 to 6 and/or a pharmaceutically acceptable salt thereof together with customary pharmaceutical auxiliaries and/or excipients.

11. The use of a compound according to any of claims 1 to 6 and its pharmaceutically acceptable salts for the prevention and/or treatment of gastrointestinal disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/063164

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/20 A61K31/438 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, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/014123 A (ALTANA PHARMA AG [DE]; BUHR WILM [DE]; SENN-BILFINGER JOERG [DE]) 20 February 2003 (2003-02-20) see structure of compounds of claim 1 and their pharmaceutical activity	1-11
A	WO 98/42707 A (BYK GULDEN LOMBERG CHEM FAB [DE]; SENN BILFINGER JOERG [DE]; GRUNDLER) 1 October 1998 (1998-10-01) see structure of compounds of claim 1 and their pharmaceutical activity	1-11

☐ Further documents are listed in the continuation of Box C.

☒ 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 October 2006	20/10/2006

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	TRAEGLER-GOELDEL, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/063164

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:

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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/EP2006/063164

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03014123 A	20-02-2003	AT	297931 T	15-07-2005
		BR	0211826 A	28-06-2005
		CA	2452803 A1	20-02-2003
		CN	1541219 A	27-10-2004
		DE	60204701 D1	21-07-2005
		DE	60204701 T2	03-08-2006
		ES	2243788 T3	01-12-2005
		HK	1066213 A1	25-11-2005
		HR	20040229 A2	28-02-2005
		HU	0500330 A2	28-07-2005
		JP	2005504761 T	17-02-2005
		MX	PA04001277 A	27-05-2004
		NO	20040604 A	10-02-2004
		NZ	531520 A	28-10-2005
		PT	1419163 T	31-10-2005
		US	2005049272 A1	03-03-2005
		ZA	200400918 A	20-04-2005
WO 9842707 A	01-10-1998	AU	7520898 A	20-10-1998
		HU	0001555 A2	28-11-2000