(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 November 2005 (24.11.2005)

PCT

(10) International Publication Number
WO 2005/111000 A1

(51) International Patent Classification[7]: C07D 235/08, A61K 31/4184, A61P 1/04

(21) International Application Number: PCT/EP2005/052196

(22) International Filing Date: 13 May 2005 (13.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04102191.6 18 May 2004 (18.05.2004) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

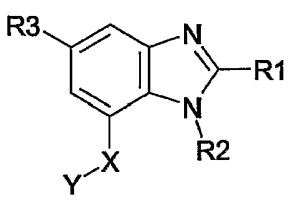
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 7-SUBSTITUTED BENZIMIDAZOLES AND THEIR USE AS INHIBITORS OF GASTRIC ACID SECRETION



(1)

(57) Abstract: The invention provides compounds of the formula (1), in which the substituents and symbols are as defined in the description. The compounds inhibit the secretion of gastric acid.

WO 2005/111000 A1

Description

Title

7-SUBSTITUTED BENZIMIDAZOLES AND THEIR USE AS INHIBITORS OF GASTRIC ACID SECRETION

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

In the European patent application EP 0266326 (which corresponds to US Patent 5,106,862), benzimidazole derivatives having a broad variety of substituents are disclosed which are said to be active as anti-ulcer agents. 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.

Torigoe et al. describe in Phytochemistry, 1972, 11, 1623 the cytokinin activity of azaindene, azanaphtalene, naphtalene and indole derivatives in the tobacco pith callus bioassay.

Dincer et al. describe in Indian Journal of Chemistry, Section B, 1995, 34 (11), 982 the synthesis of 4-(substituted benzylamino)benzimidazole derivatives which compounds are expected to give an insight into the relationship between their structures and cytokinin activity.

The US Patent 6,083,961 describes benzimidazole compounds which have activities as bradykinin antagonists and are said to be useful for treating several diseases such as allergy, inflammation, autoimmune disease, shock, pain or the like.

Bräuninger et al. describe in Archiv der Pharmazie, 1966, 299 (3), the synthesis of some benzimidazole derivatives and their kinetin activity.

In the International patent application WO 04/054984, 4-substituted benzimidazole derivatives having a broad variety of substituents are disclosed, which compounds are useful in the prevention and treatment of gastrointestinal disorders.

In the international patent application WO 94/18199 (which corresponds to US Patent 5,665730), imidazopyridine derivatives and their use in treating gastrointestinal diseases is disclosed.

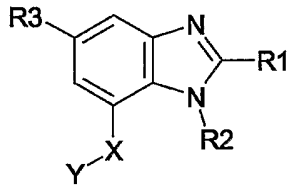
Disclosure of Invention

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) or as acid pump antagonists (APA's) bind reversibly to the H+/K+-ATPase. Although rPPI's or APA's are known for more than 20 years and many companies are engaged in their development, no rPPI or APA 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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

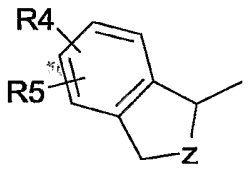
X is O (oxygen) or NH and

Y has either the meaning $-CH_2$-Ar

wherein

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

or Y denotes the group gp



(gp)

wherein

Z has the meaning –CHR8- or –CHR8-CHR9-

where in, Ar and/or in the group gp

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-

alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy,

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.

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, the methoxyethyl group and the 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. An example which may be mentioned is the trifluoromethyl group.

Hydroxy-1-4C-alkyl represents aforementioned 1-4C-alkyl groups, which are substituted by a hydroxy group. Examples which may be mentioned are the hydroxymethyl, the 2-hydroxyethyl and the 3-hydroxypropyl 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.

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 groups. Examples, which may be mentioned, are the dimethylamino-methylcarbonyl and the dimethylamino-ethylcarbonyl group.

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

Aryl-1-4C-alkoxy denotes an aryl-substituted 1-4C-alkoxy radical. An example which may be mentioned is the benzyloxy radical.

Aryl-1-4C-alkoxy-1-4C-alkyl denotes one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned aryl-1-4C-alkoxy radicals. An example which may be mentioned is the benzyloxymethyl radical.

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

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-O-CH_2-CH_2-O-) and 2-(ethoxy)ethoxy (CH_3-CH_2-O-CH_2-CH_2-O-).

1-4C-Alkoxy-1-4C-alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkoxy-1-4C-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-O-CH_2-CH_2-O-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 is completely or mainly substituted by fluorine. Examples of completely or mainly fluoro-substituted 1-4C-alkoxy groups which may be mentioned are 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-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably 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, the 1,1,2,2-tetrafluoroethoxyethyl, the 2,2,2-trifluoroethoxyethyl, the trifluoromethoxyethyl and preferably the difluoromethoxymethyl and the difluoromethoxyethyl radicals.

1-7C-Alkyl represents straight-chain or branched alkyl groups 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.

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.

Aryl-1-4C-alkyl denotes an aryl-substituted 1-4C-alkyl radical. An example which may be mentioned is the benzyl radical.

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.

2-7C-Alkenyl represents straight-chain or branched alkenyl groups having 2 to 7 carbon atoms. Examples which may be mentioned are the 2-butenyl, 3-butenyl, 1-propenyl, the 2-propenyl (allyl) and the vinyl group. The aforementioned 2-4C-alkenyl groups are preferred.

2-7C-Alkenyl represents straight-chain or branched alkenyl groups having 2 to 7 carbon atoms. Examples which may be mentioned are the 2-butenyl, 3-butenyl, 1-propenyl, the 2-propenyl (allyl) and the vinyl group. The aforementioned 2-4C-alkenyl groups are preferred.

Oxo-substituted 1-4C-alkoxy represents a 1-4C-alkoxy group, which instead of a methylene group contains a carbonyl group. An example which may be mentioned is the 2-oxopropoxy group.

3-7C-Cycloalkoxy represents cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkyl-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the aforementioned 3-7C-cycloalkyl groups. Examples which may be mentioned are the cyclopropylmethoxy, the cyclobutylmethoxy and the cyclohexylethoxy group.

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.

1-4C-Alkoxy-1-4C-alkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the aforementioned 1-4C-alkoxy-1-4C-alkoxy groups. A preferred example which may be mentioned is the methoxyethoxyethoxy group.

3-7C-Cycloalkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the aforementioned 3-7C-cycloalkoxy groups. Examples which may be mentioned are the cyclopropoxymethoxy, the cyclobutoxymethoxy and the cyclohexyloxyethoxy group.

3-7C-Cycloalkyl-1-4C-alkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the aforementioned 3-7C-cycloalkyl-1-4C-alkoxy groups. Examples which may be mentioned are the cyclopropylmethoxyethoxy, the cyclobutylmethoxyethoxy and the cyclohexylethoxyethoxy group.

1-4C-Alkylcarbonyloxy represents a 1-4C-alkylcarbonyl group which is bonded to an oxygen atom. An example which may be mentioned is the acetoxy group (CH_3CO-O-).

1-4C-Alkylcarbonyloxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned 1-4C-alkylcarbonyloxy groups. An example which may be mentioned is the acetoxymethyl group (CH_3CO-O-CH_2).

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-trifluoroethoxy, 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-1-4C-alkylcarbonyloxy represents a 1-4C-alkylcarbonyloxy group, which is substituted by one of the aforementioned mono- or di-1-4C-alkylamino groups. Examples, which may be mentioned, are the dimethylamino-methylcarbonyloxy and the dimethylamino-ethylcarbonyloxy group.

1-4C-Alkoxy-1-4C-alkylcarbonyloxy represents one of the aforementioned 1-4C-alkylcarbonyloxy radicals which is substituted by one of the aforementioned 1-4C-alkoxy groups. An example, which may be mentioned, is the methoxymethylcarbonyloxy group.

Suitable salts of compounds of the formula 1 are - depending on the substitution - in particular all acid addition salts. Particular mention may be made of the pharmacologically acceptable 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 employed in the salt preparation in an equimolar ratio or in a ratio differing therefrom, depending on whether the acid is a mono- or polybasic acid and on which salt is desired.

Pharmacologically unacceptable salts, which can be initially obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically acceptable 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 can, for example when they are isolated in crystalline form, comprise varying amounts of solvents. The invention therefore also embraces all solvates and, in particular, all hydrates of the compounds of the formula 1, and all solvates and, in particular, all hydrates of the salts of the compounds of the formula 1.

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

X is O (oxygen)
R1, R2, R3 and Y have the meanings as indicated in the outset,
and the salts of these compounds.
Another embodiment (embodiment 2) of the invention relates to compounds of the formula 1, in which
X is NH,
R1, R2, R3 and Y have the meanings as indicated in the outset,
and the salts of these compounds.

Another embodiment (embodiment 3) of the invention relates to compounds of the formula 1, in which
R3 is hydrogen,
R1, R2, X and Y have the meanings as indicated in the outset,
and the salts of these compounds.

Still another embodiment (embodiment 4) of the invention relates to compounds of the formula 1, in which R3 does not have the meaning hydrogen,
R1, R2, X and Y have the meanings as indicated in the outset,
and the salts of these compounds.

Still another embodiment (embodiment 5) of the invention relates to compounds of the formula 1, in which
R3 is halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and
Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol
where
R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R1, R2, X and Y have the meanings as indicated in the outset,

and the salts of these compounds

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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

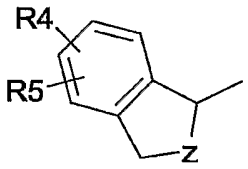
X is O (oxygen) or NH and

Y has either the meaning $-CH_2$-Ar

wherein

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

or Y denotes the group gp



(gp)

wherein

Z has the meaning –CHR8- or –CHR8-CHR9-

where in, Ar and/or in the group gp

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-

alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy,

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,

with the proviso that R3 does not have the meaning hydrogen when R1 and R2 have the meanings hydrogen or 1-4C-alkyl and Y denotes CH_2-phenyl or a CH_2-phenyl substituted by a 1-4C-alkoxy radical,

and the salts of these compounds.

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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

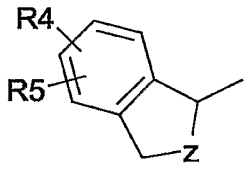
X is O (oxygen) or NH and

Y has either the meaning $-CH_2$-Ar

wherein

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

or Y denotes the group gp



(gp)

wherein

Z has the meaning –CHR8- or –CHR8-CHR9-

where in, Ar and/or in the group gp

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-

4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy,

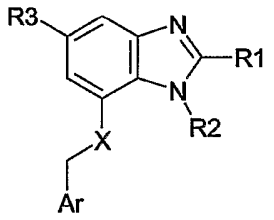
and wherein

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,

with the proviso that R3 does not have the meaning hydrogen or halogen when R1 denotes hydrogen, 1-4C-alkyl, or hydroxy-1-4C-alkyl, R2 denotes hydrogen, 1-4C-alkyl or 3-7C-cycloalkyl-1-4C-alkyl and Y denotes CH_2-Ar,

and the salts of these compounds.

In one aspect, the invention relates to compounds of the formula 1a



(1a)

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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

X is O (oxygen) or NH,

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

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.

In a further aspect, the invention relates to compounds of the formula 1a, 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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

X is O (oxygen) or NH,

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

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,

with the proviso that R3 does not have the meaning hydrogen when R1 and R2 have the meanings hydrogen or 1-4C-alkyl and Ar is phenyl or a phenyl substituted by a 1-4C-alkoxy radical,

and the salts of these compounds.

In a further aspect, the invention relates to compounds of the formula 1a, 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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

X is O (oxygen) or NH,

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

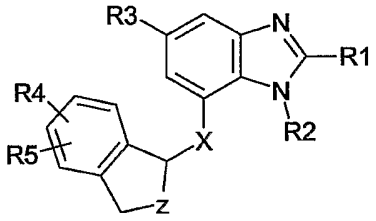
R7 is hydrogen, 1-4C-alkyl or halogen,

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,

with the proviso that R3 does not have the meaning hydrogen or halogen when R1 denotes hydrogen, 1-4C-alkyl, or hydroxy-1-4C-alkyl and R2 denotes hydrogen, 1-4C-alkyl or 3-7C-cycloalkyl-1-4C-alkyl,

and the salts of these compounds.

In another aspect, the invention relates to compounds of the formula 1b



(1b)

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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

X is O (oxygen) or NH and

Z has the meaning –CHR8- or –CHR8-CHR9-

where

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy,

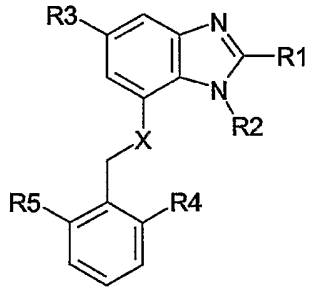
and wherein

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.

The compounds of the formula 1b have up to three chiral centers in the parent structure. The invention thus relates to all conceivable stereoisomers in any desired mixing ration to one another, including the pure enantiomers, which are a preferred subject of the invention.

Among the compounds of the formula 1a, preferred compounds are those of the formula 1a-1



(1a-1)

in which

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

R2 is hydrogen,1-4C-alkyl, hydroxy, 1-4C-alkoxy or aryl-1-4C-alkoxy-1-4C-alkyl

R3 is carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 3-7C-cycloalkyl or amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol and dihydroimidazol,

where

R33 is hydrogen or 1-4C-alkyl,

R34 is hydrogen or 1-4C-alkyl

R35 is hydrogen or 1-4C-alkyl

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, trifluoromethyl, fluoro-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

R5 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy and

X is O (oxygen) or NH,

and the salts of these compounds.

Among the compounds of the formula 1a, particularly preferred compounds are those of the formula 1a-1

where

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

R2 is hydrogen or 1-4C-alkyl,

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

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group,

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, trifluoromethyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

R5 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy and

X is O (oxygen) or NH,

and the salts of these compounds.

Emphasis is given to those compounds of the formula 1a-1, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

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

where

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

R32 is hydrogen or 1-4C-alkyl,

or where

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

R4 is 1-4C-alkyl or 1-4C-alkylcarbonylamino,

R5 is 1-4C-alkyl,

X is O (oxygen) or NH,
and their salts.

Emphasis is also given to those compounds of the formula 1a-1, in which
R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,
R3 is carboxyl, -CO-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl and
R32 is hydrogen or 1-4C-alkyl,
R4 is 1-4C-alkyl or 1-4C-alkylcarbonylamino,
R5 is 1-4C-alkyl,
X is O (oxygen) or NH,
and their salts.

Particular emphasis also given to compounds of the formula 1a-1, in which
R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,
R3 the group -CO-NR31R32,
where
R31 is 1-4C-alkyl and
R32 is 1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino group,
R4 is 1-4C-alkyl
R5 is 1-4C-alkyl,
X is NH,
and their salts.

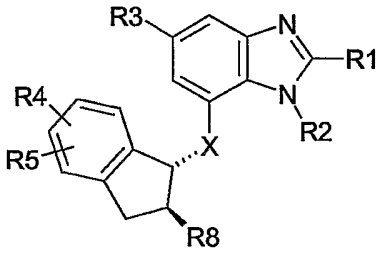
Particular emphasis is also given to compounds of the formula 1a-1, in which
R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,
R3 the group -CO-NR31R32,
where
R31 is 1-4C-alkyl and
R32 is 1-4C-alkyl,
R4 is 1-4C-alkyl

R5 is 1-4C-alkyl,

X is NH,

and their salts.

Among the compounds of the formula 1b, preferred compounds are those of the formula 1b-1



(1b-1)

in which

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

R2 is hydrogen,1-4C-alkyl, hydroxy, 1-4C-alkoxy or aryl-1-4C-alkoxy-1-4C-alkyl

R3 is carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 3-7C-cycloalkyl or amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol and dihydroimidazol,

where

R33 is hydrogen or 1-4C-alkyl,

R34 is hydrogen or 1-4C-alkyl

R35 is hydrogen or 1-4C-alkyl

R4 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

R5 is hydrogen or 1-4C-alkyl,

R8 is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

X is O (oxygen) or NH,

and their salts.

Particularly preferred compounds of the formula 1b-1 are those, in which

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

R2 is hydrogen or 1-4C-alkyl,

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

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group,

R4 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

R5 is hydrogen or alkyl,

R8 is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

X is O (oxygen) or NH,

and their salts.

Still particularly preferred compounds of the formula 1b-1 are those, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

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

where

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

R32 is hydrogen or 1-4C-alkyl,

R4 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

R5 is hydrogen,

R8 is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-

4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

X is O (oxygen) or NH,

and their salts.

Still particularly preferred compounds of the formula 1b-1 are those, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

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

where

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

R32 is hydrogen or 1-4C-alkyl,

R4 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

R5 is hydrogen,

R8 is hydroxyl or 1-4C-alkoxy

X is O (oxygen) or NH,

and their salts.

Emphasis is given to compounds of the 1b-1, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is the group -CO-NR31R32,

where

R31 is 1-4C-alkyl,

R32 is 1-4C-alkyl

R4 is hydrogen

R5 is hydrogen,

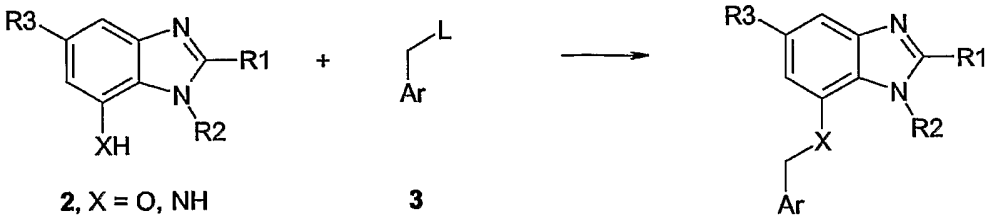
R8 is hydroxyl

X is O (oxygen)

and their salts.

The compounds of the general formula 1a can be obtained as depicted in scheme 1 by reacting substituted benzimidazole compounds of formula 2 with compounds of formula 3, wherein L is a suitable leaving group like for example a suitable halogen atom, like for example chlorine.

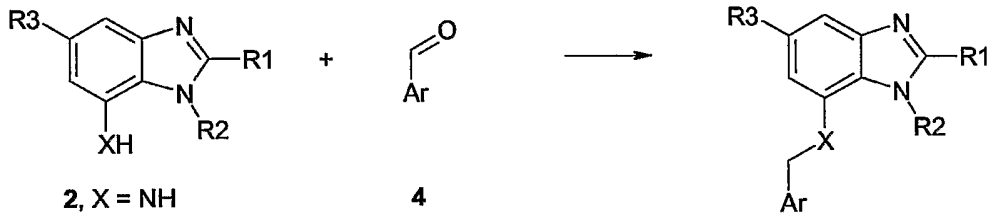
Scheme 1:



2, X = O, NH **3** **1a**, X = O, NH

Another method for the preparation of compounds of the formula 1a where X = NH consists of reacting substituted benzimidazole compounds of the general formula 2 where X = NH with substituted ketones of the formula 4 and subsequent reduction of the resulting imine intermediate by suitable reducing agents, like for example sodium borohydride (reductive amination, scheme 2).

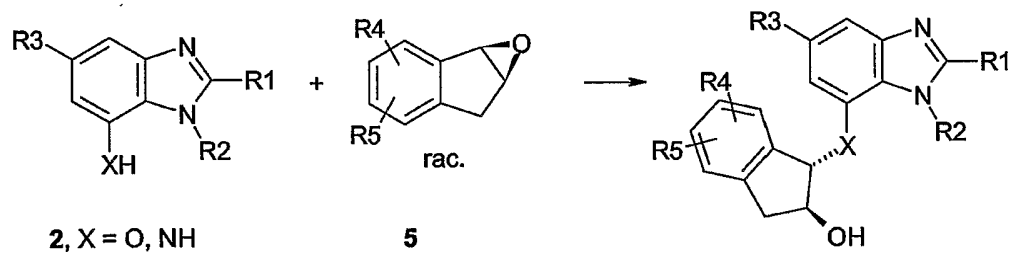
Scheme 2:



2, X = NH **4** **1a**, X = NH

Analogously, compounds of the general formula 1b are obtained by reacting substituted benzimidazoles of formula 2 with 1,2-epoxyindanes of the formula 5, carrying any desired substituent R4 and R5 (cf. scheme 3 for a compound 1b-1). 1,2-Epoxyindan is described for example in W. F. Whitmore; A. I. Gebhart, J. Am. Chem. Soc. 1942, 64, 912. In general, substituted alkyl-, alkoxy- or halogeno-epoxyindanes can be prepared from the corresponding substituted indenes by methods known from literature (e.g. epoxidation).

Scheme 3:

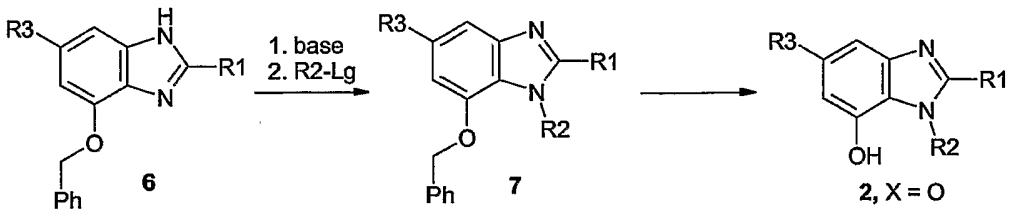


2, X = O, NH **5** **1b-1**, X = O, NH

The starting compounds of the formula 2 where X = O can be obtained for example according to the reaction sequence as shown in scheme 4. Compounds of the formula 6 can be deprotonated using a suitable base, like for example n-butyllithium, followed by reaction with a

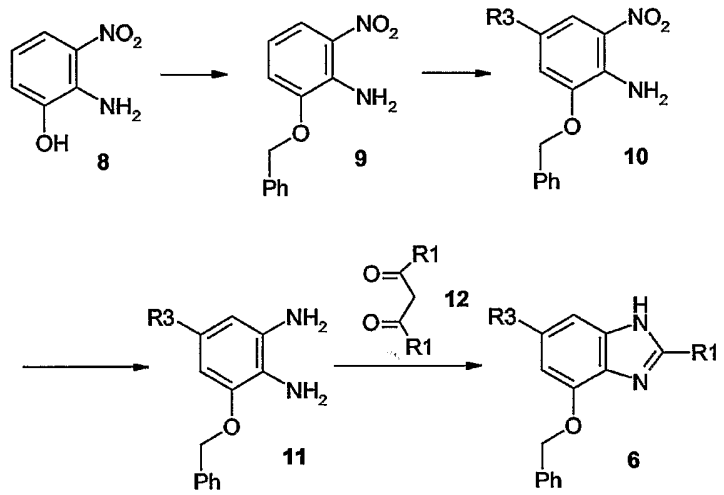
suitable R2 precursor R2-Lg, whereby that precursor R2-Lg is a R2 group substituted with a suitable leaving group Lg, like a halogen atom, for example an iodine atom. This reaction leads to compounds of the formula 7 which can be converted by methods known to the expert to the desired compounds of the formula 2 with X = O (oxygen).

Scheme 4:



Compounds of the formula 6 can be prepared from compounds of the formula 8 for example following the reaction sequence shown in scheme 5.

Scheme 5:

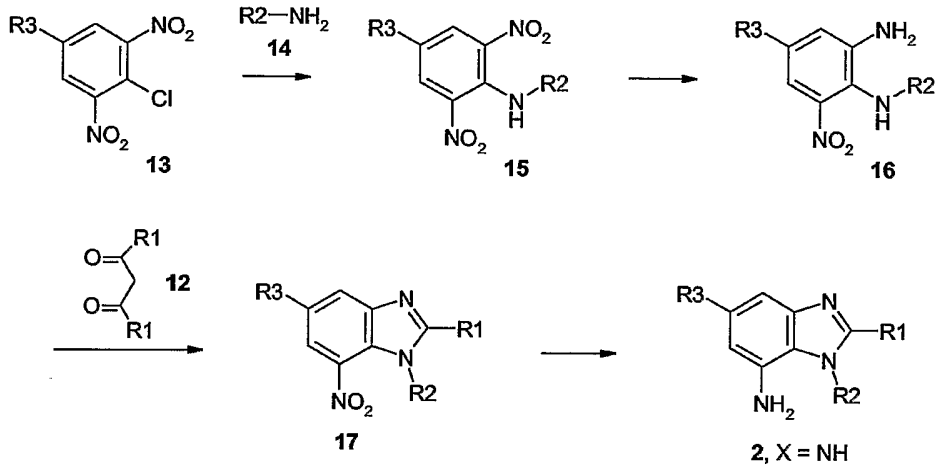


3-Nitro-2-aminophenol can be reacted in a first step with a suitable benzyl derivative, for example benzylchloride, to form the reaction product of the formula 9 which is known for example from J. Heterocyclic Chem. (1983), 20, 1525). Into the compound of the formula 9 a substituent R3 can be introduced, for example a bromine substituent can be introduced by a bromination reaction using a suitable bromination reagent, like for example N-bromosuccinimide. Subsequent reduction of the compound of the formula 10 under standard conditions, for example using hydrazine N_2H_4 in the presence of $FeCl_3$, leads to the formation of compounds of the formula 11 which can be transformed to the benzimidazole derivatives of the formula 6 by methods known to the expert, for example by a cyclization reaction with a diketone of the formula 12.

The starting compounds of the formula 2 where X = NH can be obtained for example according to the reaction sequence as shown in scheme 6. Starting from substituted dinitrochlorbenzenes of the formula 13, reaction with primary amines of the formula 14 leads to compounds

of the formula 15 (L. A. Summers, Austr. J. Chem. 1965, 18, 1695-1698) that are reduced to phenylenediamines of the formula 16 by methods known to the expert. The benzimidazoles of the formula 2 are then obtained by a cyclization reaction of compounds of the formula 16, for example with a diketone of the formula 12 to give compounds of the formula 17, and subsequent reduction of the NO_2-group by catalytic hydrogenation or any other method known from literature (scheme 6).

Scheme 6:



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 derivatization, if any, of the compounds obtained according to the above Scheme 1, 2 and 3 (e.g. conversion of a group R3 into another group R3, or of R2 = H into another group R2, or conversion of a hydroxyl group into an alkoxy or ester group) is likewise carried out in a manner known per se. If compounds where R3 = -CO-1-4C-alkoxy or R3 = -CO-NR31R32 are desired, an appropriate derivatization can be performed in a manner known per se (e. g. metal catalysed carbonylation of the corresponding bromo compound or conversion of an ester into an amide) at the stage of the benzimidazoles of the formula 2 (scheme 1, 2 and 3), or at a later point in time.

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	> 50
2	1	> 50
3	1	> 50

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 determi-

nation 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 examples below serve to illustrate the invention in more detail without limiting it. Further compounds of the formula 1 whose preparation is not described explicitly can likewise be prepared in an analogous manner or in a manner known per se to the person skilled in the art, using customary process techniques. The compounds named expressly as examples, and the salts of these compounds, are preferred subject matter of the invention. The abbreviation min stands for minute(s), h stands for hour(s), m.p. stands for melting point and ee for enantiomeric excess.

I. Final Compounds of the formula 1

1. 7-(*trans*-2,3-Dihydro-2-hydroxy-1-indenyloxy)-5-(N,N-dimethylaminocarbonyl)-1,2-dimethyl-1*H*-benzimidazole

To a suspension of 0.38 g (1.63 mmol) 7-hydroxy-1,2-dimethyl-1*H*-benzimidazole-5-carboxylic acid dimethylamide and 0.8 g (6.1 mmol) 1,2-epoxyindane in 4 ml methanol and 1 ml water were added 0.45 ml triethylamine and the mixture was heated to 70 °C for 1 h. The cooled solution was partitioned between dichloromethane and water. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by column chromatography on silica gel using dichloromethane:methanol (13:1) and crystallization from ethyl acetate yielded 0.45 g (76 %) of the title compound as a colourless solid (m.p. 230 °C).

2. 6-(N,N-dimethylaminocarbonyl)-4-(2,6-dimethyl-benzylamino)-2,3-dimethyl-3*H*-benzimidazole

To a solution of 0.54 g (1.56 mmol) 6-(N,N-dimethylaminocarbonyl)-4-(2,6-dimethyl-benzylideneamino)-2,3-dimethyl-3*H*-benzimidazole in 10 ml methanol were slowly added 0.09 g (2.38 mmol) sodium borohydride. After 10 min, the reaction mixture was partitioned between saturated aqueous ammonium chloride and dichloromethane. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by crystallization from ethyl acetate/n-heptane yielded 0.52 g (95 %) of the title compound as a colourless solid (m.p. 187-188 °C).

3. 4-(2,6-Dimethyl-benzylamino)-2,3-dimethyl-6-(N-pyrrolidinocarbonyl)-3*H*-benzimidazole

To a solution of 0.5 g (1.94 mmol) 4-amino-2,3-dimethyl-6-(N-pyrrolidinocarbonyl)-3*H*-benzimidazole and 0.39 g (2.9 mmol) 2,6-dimethylbenzaldehyd in 15 ml dichloromethane and 5 ml acetic acid were added 0.82 mg (3.9 mmol) sodium triacetoxyborohydride. After 2 h, TLC indicated incomplete reaction and the mixture was evaporated to dryness. The residue was diisolved in 20 ml methanol and treated with excess sodium borohydride. After complete reaction, mixture was partitioned between saturated aqueous ammonium chloride and dichloromethane. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by column chromatography on silica gel using dichloromethane:methanol (20:1) and crystallization from ethyl acetate/n-heptane yielded 0.41 g (56 %) of the title compound as a colourless solid (m.p. 188-189 °C).

II. Starting Compounds

A. 2-Benzyloxy-4-bromo-6-nitro-aniline

To a suspension of 50 g (325 mmol) 2-amino-3-nitrophenol, 45 g (325 mmol) potassium carbonate and 2 g (13 mmol) sodium iodide in 400 ml ethanol were added 47 ml (408 mmol) benzyl chloride and the mixture was heated to 80 °C. After 2 h, the reaction mixture was cooled down and the solvent was evaporated. The residue was dissolved in ethyl acetate and extracted with water. The organic layer was dried over anhydrous magnesium sulphate and evaporated. Coevaporation with dichloromethane led to a dark brown oily residue which was dissolved in 400 ml acetonitrile. After addition of 63.4 g (356 mmol) N-bromosuccinimide, the reaction mixture was refluxed for 1 h. After cooling down, 400 g silica gel were added and the mixture was evaporated to dryness. The resulting solid was put on a column and the product was eluted with ethyl acetate:light petroleum ether (4:1). Evaporation of the eluent left a solid which was recrystallized from ethyl acetate/n-heptane to give 62 g (59 %) of the title compound as a red solid (m.p. 90 °C).

B. 2-Amino-3-benzyloxy-5-bromo-aniline

To a suspension of 3.23 g (10 mmol) 2-benzyloxy-4-bromo-6-nitro-aniline in 60 ml methanol and 15 ml concentrated hydrochloric acid were added 2.23 g (40 mmol) iron filings in small portions at 60 °C. After 10 min, the mixture was cooled down and neutralized with 6N aqueous sodium hydroxide. Activated charcoal was added and the suspension was filtered. The filtrate was partitioned between dichloromethane and water. The organic layer was dried over anhydrous magnesium sulphate and evaporated. Crystallization of the residue from ethyl acetate/n-heptane yielded 2.05 g (70 %) of the title compound as a colourless solid (m.p. 108 °C).

C. 4-Benzyloxy-6-bromo-2-methyl-1*H*-benzimidazole

To a suspension of 2.0 g (6.82 mol) 2-amino-3-benzyloxy-5-bromo-aniline in 20 ml ethanol were added 5 ml 5N hydrochloric acid. The reaction mixture was hetaed to 60 °C and 1.41 ml (13.6 mol)

2,4-pentanedione were added in one portion. After refluxing 1 h, the mixture was cooled down and neutralized with 6N aqueous sodium hydroxide. The mixture was partitioned between dichloromethane and water. The organic layer was dried over anhydrous magnesium sulphate and evaporated. Crystallization of the residue from ethyl acetate/n-heptane yielded 2.12 g (98 %) of the title compound as a colourless solid (m.p. 174 °C).

D. 7-Benzyloxy-2-methyl-3*H*-benzimidazole-5-carboxylic acid dimethylamide

To a suspension of 2.0 g (6.3 mmol) 4-benzyloxy-6-bromo-2-methyl-1*H*-benzimidazole in 30 ml dimethylamine (3.2M solution in tetrahydrofuran) were added 210 mg (0.95 mmol) palladium(II) acetate and 495 mg (1.9 mmol) triphenylphosphine. The mixture was transferred to an autoclave and carbonylated (5 bar carbon monoxide pressure, 120 °C) for 16 h. The reaction mixture was cooled down and evaporated. Purification of the residue by column chromatography on silica gel using dichloromethane/methanol (13:1) yielded 1.53 g (79 %) of the title compound as a a light brown oil, which was used without further purification in the next step.

E. 7-Benzyloxy-1,2-dimethyl-1*H*-benzimidazole-5-carboxylic acid dimethylamide

To a solution of 1.53 g (4.7 mmol) 7-benzyloxy-2-methyl-3*H*-benzimidazole-5-carboxylic acid dimethylamide in 25 ml dried tetrahydrofuran were slowly added 3.1 ml (5 mmol) n-butyllithium (1.6M in hexanes) at -78 °C. After adding 0.32 ml (5.1 mmol) methyl iodide, the reaction mixture was allowed to warm to room temperature. After 16 h, the mixture was partitioned between dichloromethane and water. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by column chromatography on silica gel using dichloromethane/methanol (13:1) and crystallization of the residue from ethyl acetate/n-heptane yielded 0.79 g (52 %) of the title compound as a colourless solid (m.p. 117-118 °C).

F. 7-Hydroxy-1,2-dimethyl-1*H*-benzimidazole-5-carboxylic acid dimethylamide

A solution of 0.7 g (2.2 mmol) 7-benzyloxy-1,2-dimethyl-1*H*-benzimidazole-5-carboxylic acid dimethylamide in 25 ml methanol and 0.1 ml acetic acid was hydrogenated over 0.25 g 10% Pd/C (25 °C, 1 bar H_2) for 16 h. The catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from ethyl acetate to give 0.44 g (87 %) of the title compound as a colourless solid (m.p. 209 °C).

G. 4-Methylamino-3,5-dinitrobenzene-carboxylic acid

25.0 g (101 mmol) 4-chloro-3,5-dinitrobenzene-carboxylic acid were slowly added to 120 ml aqueous methylamine (40 %) and the mixture was heated to reflux. After 1 h, the mixture was cooled down and evaporated to dryness. The residue was dissolved in water and the pH was adjusted to pH ~ 5 by add-

ing 6N hydrochloric acid. The precipitate was collected, washed with water and dried to yield 21.6 g (90 %) of the title compound as a yellow solid (m.p. 184-188 °C).

H. 1,2-Dimethyl-7-nitro-1H-benzimidazole-5-carboxylic acid

To a suspension of 4.0 g (16.6 mmol) 4-methylamino-3,5-dinitrobenzene-carboxylic acid in 50 ml ethanol were added 40 ml 2N aqueous ammonium polysulfide. After 1 h, excess ethanol was evaporated and the residue was neutralized with 6N hydrochloric acid. The solids were filtered off and the filtrate was evaporated to dryness. The residue was suspended in 100 ml ethanol and 20 ml 5N hydrochloric acid. To the boiling mixture were added 4.1 ml (40 mmol) 2,5-pentanedione. After 4 h, the solvent was removed and the residue was diluted with water and neutralized with 40% aqueous sodium hydroxide. The precipitate was collected and suspended in 30 ml methanol and 10 ml water. To the mixture were added 0.96 g (40 mmol) lithium hydroxide and the suspension was heated to 70 °C. After 30 min, the pH of the reaction mixture was adjusted to pH ~ 6 by adding 4N hydrochloric acid. Excess methanol was removed and the precipitate was collected and washed with water to yield 0.8 g (21 %) of the title compound as a colourless solid (m.p. 303-305 °C).

I. 6-(N,N-Dimethylaminocarbonyl)-4-(2,6-dimethyl-benzylidene-amino)-2,3-dimethyl-3*H*-benzimidazole

A suspension of 0.8 g (3.4 mmol) 1,2-dimethyl-7-nitro-1H-benzimidazole-5-carboxylic acid in 10 ml methanol and 1 ml acetic acid was hydrogenated over palladium on charcoal (3 h, 80 °C). The reaction mixture was neutralized with 40% aqueous sodium hydroxide and the catalyst was filtered off. The filtrate was evaporated and the residue was redissolved in 15 ml methanol and 10 ml acetic acid and treated with 2,6-dimethylbenzaldehyd to yield the corresponding imine, which was dissolved in 10 ml dimethylformamide and 10 ml dichloromethane. To this solution were added 1.5 g (4.7 mmol) O-(1*H*-benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate (TBTU) and the mixture was heated to 50 °C. After 20 min, 5 ml (10 mmol) dimethylamine (2M in tetrahydrofuran) were added at ambient temperature. After 30 min, the reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and dichloromethane. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by column chromatography on silica gel using dichloromethane:methanol (10:1) and crystallization from ethyl acetate/n-heptane yielded 0.6 g (51 %) of the title compound as a light yellow solid (m.p. 165-166 °C).

J. 4-Methylamino-3,5-dinitro-N-pyrrolidinyl-benzamide

To a suspension of 2.0 g (8.3 mmol) 4-methylamino-3,5-dinitrobenzene-carboxylic acid and 4.0 g (12.4 mmol) O-(1*H*-benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate (TBTU) in 25 ml chloroform were added 2.5 ml (30 mmol) pyrrolidine at 45 °C. After 30 min, a further amount of 4.0 g TBTU and 2.5 ml pyrrolidine were added and stirring was continued for 45 min. The reaction mixture

was partitioned between saturated aqueous sodium hydrogen carbonate and dichloromethane. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by column chromatography on silica gel using dichloromethane:methanol (100:1) and crystallization from ethyl acetate/n-heptane yielded 1.72 g (70 %) of the title compound as an orange solid (m.p. 148-150 °C).

K. 2,3-Dimethyl-4-nitro-6-(N-pyrrolidinocarbonyl)-3*H*-benzimidazole

To a mixture of 1.65 g (5.6 mmol) 4-methylamino-3,5-dinitro-N-pyrrolidinyl-benzamide and 330 mg ruthenium on charcoal (5 %) in 30 ml ethanol were slowly added 0.55 ml (11.2 mmol) hydrazine hydrate at 75 °C. After 1.5 h, the catalyst was filtered off and the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel using dichloromethane:methanol (20:1). The intermediate product was suspended in 25 ml methanol and 5 ml 5N hydrochloric acid. To this suspension were added 1.15 ml (11.2 mmol) 2,4-pentanedione at 80 °C. After 30 min, the reaction mixture was cooled down, neutralized with 40% aqueous sodium hydroxide and extracted with dichloromethane. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by column chromatography on silica gel using dichloromethane:methanol (20:1) and crystallization from ethyl acetate/n-heptane yielded 0.91 g (56 %) of the title compound as an orange solid (m.p. 114-117 °C).

L. 4-Amino-2,3-dimethyl-6-(N-pyrrolidinocarbonyl)-3*H*-benzimidazole

A solution of 0.82 g (2.84 mmol) 2,3-dimethyl-4-nitro-6-(N-pyrrolidinocarbonyl)-3*H*-benzimidazole in 20 ml methanol and 1 ml acetic acid was hydrogenated over 300 mg palladium on charcoal (10 %, 2.5 h, 50 °C). The catalyst was filtered off and the reaction mixture was evaporated to dryness. The residue was crystallized with ethyl acetate/n-heptane to give 0.61 g (83 %) of a beige solid (m.p. 250-251 °C).

Industrial applicability

The compounds of the formula 1 and their salts 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 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 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 compounds of the formula 1 and their pharmacologically acceptable salts 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 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 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 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 compounds of the formula 1 and/or their pharmacologically acceptable salts.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the pharmacologically 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 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 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 antago-

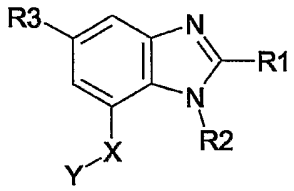
nists with the aim of increasing the principal action in an additive or super-additive sense and/or of eliminating or of decreasing the side effects, or further the combination with antibacterially active substances (such as, for example, cephalosporins, tetracyclines, penicillins, macrolides, nitroimidazoles 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 compounds of formula 1 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.

Claims

We claim:

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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

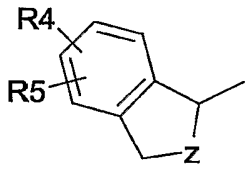
X is O (oxygen) or NH and

Y has either the meaning $-CH_2$-Ar

wherein

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

or Y denotes the group gp



(gp)

wherein

Z has the meaning –CHR8- or –CHR8-CHR9-

where in, Ar and/or in the group gp

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-

alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy,

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 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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

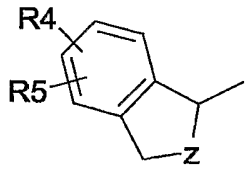
X is O (oxygen) or NH and

Y has either the meaning $-CH_2$-Ar

wherein

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

or Y denotes the group gp



(gp)

wherein

Z has the meaning –CHR8- or –CHR8-CHR9-

where in, Ar and/or in the group gp

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy,

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,

with the proviso that R3 does not have the meaning hydrogen when R1 and R2 have the meanings hydrogen or 1-4C-alkyl and Y denotes CH_2-phenyl or a CH_2-phenyl substituted by a 1-4C-alkoxy radical,

and its salts.

3. A compound of the formula 1 as claimed in claim 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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

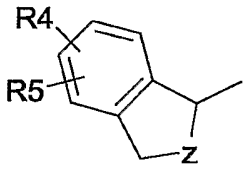
X is O (oxygen) or NH and

Y has either the meaning $-CH_2$-Ar

wherein

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

or Y denotes the group gp



(gp)

wherein

Z has the meaning –CHR8- or –CHR8-CHR9-

where in, Ar and/or in the group gp

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy,

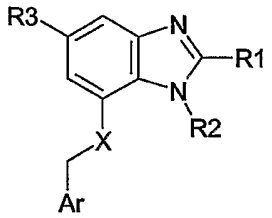
and wherein

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,

with the proviso that R3 does not have the meaning hydrogen or halogen when R1 denotes hydrogen, 1-4C-alkyl, or hydroxy-1-4C-alkyl, R2 denotes hydrogen, 1-4C-alkyl or 3-7C-cycloalkyl-1-4C-alkyl and Y denotes CH_2-Ar,

and its salts.

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



(1a)

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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

X is O (oxygen) or NH,

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

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.

5. A compound of the formula 1a as claimed in claim 4,

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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

X is O (oxygen) or NH,

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

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

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,

with the proviso that R3 does not have the meaning hydrogen when R1 and R2 have the meanings hydrogen or 1-4C-alkyl and Ar is phenyl or a phenyl substituted by a 1-4C-alkoxy radical,

and the salts of these compounds.

6. A compound of the formula 1a as claimed in claim 4,

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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

X is O (oxygen) or NH,

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, 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,

R4 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,

fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

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

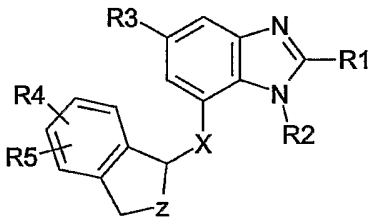
R7 is hydrogen, 1-4C-alkyl or halogen,

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,

with the proviso that R3 does not have the meaning hydrogen or halogen when R1 denotes hydrogen, 1-4C-alkyl, or hydroxy-1-4C-alkyl and R2 denotes hydrogen, 1-4C-alkyl or 3-7C-cycloalkyl-1-4C-alkyl,

and its salts

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



(1b)

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, hydroxy-1-4C-alkyl, mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonyloxy-1-4C-alkyl

R2 is hydrogen, 1-4C-alkyl, 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, aryl-1-4C-alkoxy-1-4C-alkyl, hydroxy or 1-4C-alkoxy

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, 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, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or 3-7C-cycloalkyl, amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol, dihydroimidazol, oxazol, imidazol, isoxazol, dihydroisoxazol, pyrazol and tetrazol

where

R33 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,

R34 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R35 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

X is O (oxygen) or NH and

Z has the meaning –CHR8- or –CHR8-CHR9-

where

R4 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, fluoro-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,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

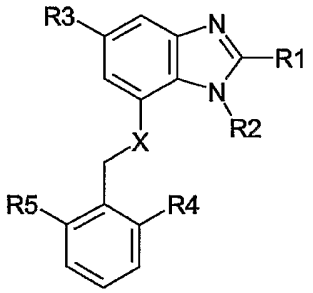
R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy,

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.

8. A compound of the formula 1a as claimed in claim 4, characterized by the formula 1a-1



(1a-1)

in which

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

R2 is hydrogen,1-4C-alkyl, hydroxy, 1-4C-alkoxy or aryl-1-4C-alkoxy-1-4C-alkyl

R3 is carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 3-7C-cycloalkyl or amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol and dihydroimidazol,

where

R33 is hydrogen or 1-4C-alkyl,

R34 is hydrogen or 1-4C-alkyl

R35 is hydrogen or 1-4C-alkyl

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, trifluoromethyl, fluoro-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

R5 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy and

X is O (oxygen) or NH,

and its salts.

9. A compound of the formula 1a-1 as claimed in claim 8, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 the group -CO-NR31R32,

where

R31 is 1-4C-alkyl and

R32 is 1-4C-alkyl,

or where

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

R4 is 1-4C-alkyl

R5 is 1-4C-alkyl,

X is NH,

and their salts.

10. A compound of the formula 1a-1 as claimed in claim 8, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 the group -CO-NR31R32,

where

R31 is 1-4C-alkyl and

R32 is 1-4C-alkyl,

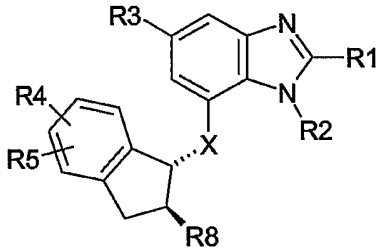
R4 is 1-4C-alkyl

R5 is 1-4C-alkyl,

X is NH,

and its salts.

11. A compound of the formula 1b as claimed in claim 7, characterized by the formula 1b-1



(1b-1)

in which

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

R2 is hydrogen,1-4C-alkyl, hydroxy, 1-4C-alkoxy or aryl-1-4C-alkoxy-1-4C-alkyl

R3 is carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano, the group -CO-NR31R32, the group SO_2-NR31R32 or the group Het,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 3-7C-cycloalkyl or amino 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, piperidino, piperazino, N-1-4C-alkylpiperazino, morpholino, aziridino or azetidino group and

Het is a heterocyclic residue, substituted by R33, R34 and R35, selected from the group consisting of oxadiazol, dihydrooxazol and dihydroimidazol,

where

R33 is hydrogen or 1-4C-alkyl,

R34 is hydrogen or 1-4C-alkyl

R35 is hydrogen or 1-4C-alkyl

R4 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

R5 is hydrogen or 1-4C-alkyl,

R8 is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkylcarbonyloxy

X is O (oxygen) or NH,

and its salts.

12. A compound of the formula 1b-1 as claimed in claim 11, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is the group -CO-NR31R32,

where

R31 is 1-4C-alkyl,

R32 is 1-4C-alkyl

R4 is hydrogen

R5 is hydrogen,

R8 is hydroxyl

X is O (oxygen)

and its salts.

13. 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.

14. 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

Inte I Application No
PC I/EP 2005/052196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/08 A61K31/4184 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)
IPC 7 C07D A61K A61P

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.
X	EP 0 266 326 A (AKTIEBOLAGET HÄSSLE) 4 May 1988 (1988-05-04) cited in the application the whole document	1-6, 8-10,13, 14
X	WO 97/47603 A (ASTRA AKTIEBOLAG) 18 December 1997 (1997-12-18) cited in the application the whole document	1-6, 8-10,13, 14

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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"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.

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Date of the actual completion of the international search	Date of mailing of the international search report
1 August 2005	11/08/2005

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	Allard, M

INTERNATIONAL SEARCH REPORT

Int ial Application No
PCT/EP2005/052196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TORIGOE Y ET AL: "Cytokinin activity of azaindene, azanaphthalene, naphthalene, and indole derivatives" PHYTOCHEMISTRY, vol. 11, 1972, pages 1623-1631, XP002936901 cited in the application the whole document, particularly page 1624, compound (VIII)	1,4
X	DINCER S ET AL: "Synthesis of new 4-(substituted benzylamino)benzimidazole derivatives" INDIAN JOURNAL OF CHEMISTRY, SECTION B, vol. 34, no. 11, November 1995 (1995-11), pages 982-984, XP002298063 cited in the application the whole document	1,2,4,5
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INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP2005/052196

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 14 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), 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.

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