(54) Title: USE OF PYRIDYMETHYLsULPHINYL-1H-BENZIMIDAZOLE DERIVATIVES IN THE TREATMENT OF ILLNESSES CAUSED BY HELICOBACTER BACTERIA

(57) Abstract:
The use of compounds of the formula 1 (see formula I) wherein the substituents and symbols have the meanings given in the description, for combating Helicobacter bacteria is described.
The use of compounds of the formula 1

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wherein the substituents and symbols have the meanings given in the description, for combating Helicobacter bacteria is described.
Use of pyridylmethysulphynyl-1H-benzimidazole derivates in the treatment of illnesses caused by helicobacter bacteria

Scope of application of the invention

The invention relates to new oral drug forms. The new drug forms are employed for the treatment of diseases of the stomach and/or intestine caused by Helicobacter bacteria.

Prior art

Pyridylmethysulphynyl-1H-benzimidazoles which have gastric acid secretion-inhibiting properties are described in a large number of patent applications. The following patent applications and patents may be mentioned in particular here in connection with the present invention: EP-A-134 400 (= USP 4,555,518), EP-A-127 763 (= USP 4,560,693), EP-B-166 287 (= USP 4,758,579), EP-A-201 575 (= USP 4,686,230), WO89/05299 and WO89/11479. - European Patent Application EP-A-382 489 describes and claims the suitability of certain pyridylmethysulphynyl-1H-benzimidazoles, which are substituted in the benzimidazole part, if desired, by methoxy or trifluoromethyl, for the treatment of infectious diseases caused by bacteria of the Campylobacter (= Helicobacter) strain. International Patent Application WO90/09175 discloses the use of omeprazole in the treatment of infectious diseases, in particular those caused by Campylobacter pylori. - Because the pyridylmethysulphynyl-1H-benzimidazoles have a low stability and are easily decomposed by acid, various patent applications (e.g. EP-A-244 380 or EP-A-247 983) refer to the need to administer these active compounds in a form which is resistant to gastric juice in the case of oral administration. An "enteric coated" formulation is also used in the abovementioned EP-A-382 489 as the oral presentation form for combating Campylobacter.

Description of the invention

The invention relates to the use of compounds of the formula I
wherein

R1 denotes hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

R2 denotes hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy which is substituted completely or predominantly by fluorine, chlorodifluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R3, 1-2C-alkylenedioxy which is substituted completely or partly by fluorine, or chlorotrifluoroethylenedioxy,

R3 denotes 1-4C-alkoxy which is substituted completely or predominantly by fluorine, chlorodifluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R2, 1-2C-alkylenedioxy which is substituted completely or partly by fluorine, or chlorotrifluoroethylenedioxy,

R4 denotes hydrogen or a group which can easily be split off under physiological conditions,

R5 denotes hydrogen or 1-4C-alkyl,

R6 denotes hydrogen or 1-4C-alkyl,

R7 denotes hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

R8 denotes 1-4C-alkoxy, 1-4C-alkoxy which is substituted completely or predominantly by fluorine, or benzyloxy and

n represents the number 0 or 1,

and their pharmacologically tolerated salts, for the preparation of medicaments to be administered orally for combating Helicobacter bacteria.

1-4C-Alkyl represents straight-chain or branched alkyl radicals; examples which may be mentioned are the butyl, i-butyl, sec.-butyl, t-butyl, propyl, isopropyl, ethyl and in particular the methyl radical.

1-4C-Alk oxy represents straight-chain or branched alkoxy radicals; examples which may be mentioned are the butoxy, i-butoxy, sec.-butoxy, t-butoxy, propoxy, isoproxy, ethoxy and in particular the methoxy radical.
Examples which may be mentioned of 1-4C-alkoxy which is substituted completely or predominantly by fluorine are the 1,2,2-trifluoroethoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the trifluoromethoxy, the 2,2,2-trifluoroethoxy and the difluoromethoxy radical.

Examples which may be mentioned of 1-2C-alkylenedioxy which is substituted completely or partly by fluorine are the 1,1-difluoroethylenedioxy (−O−CF₂−CH₂−O−), the 1,1,2,2-tetrafluoroethylenedioxy (−O−CF₂−CF₂−O−) and in particular the difluoromethylenedioxy (−O−CF₂−O−) and the 1,1,2-trifluoroethylenedioxy radical (−O−CF₂−CFH−O−).

If R² and R³ together denote 1-2C-alkylenedioxy which is substituted completely or partly by fluorine, or chlorotrifluoroethylenedioxy, the substituents R² and R³ are bonded in adjacent positions to the benzo part of the benzimidazole ring.

A group R⁴ which can easily be split off under physiological conditions is a substituent which is separated off from the nitrogen atom by hydrolysis - if appropriate under enzymatic catalysis - to form an N-H bond, the group itself bonding a hydroxyl group - being converted into a physiologically acceptable and in particular pharmacologically tolerated compound. Groups R⁴ which can be split off and which may be mentioned are, in particular, all types of substituted carbonyl groups, such as the alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkoxy carbonyl, aryloxy carbonyl or aralkoxy carbonyl group, or the optionally substituted carbamoyl group. Examples which may be mentioned are the methoxycarbonyl, t-butoxycarbonyl, benzoyl, phenyl carbamoyl and the dimethyl carbamoyl group.

Preferred possible salts for compounds of the formula I in which n denotes the number 0 (sulphides) are all the pharmacologically tolerated acid addition salts. Salts which may be mentioned in particular are the pharmacologically tolerated salts of the inorganic and organic acids usually used in galenics. Examples of such suitable salts are water-soluble and water-insoluble acid addition salts, such as the hydrochloride, hydrobromide, hydriodide, phosphate, nitrate, sulphate, acetate, citrate, gluconate, benzoate, hibenzate, fendizolate, butyrate, sulphosalicylate, maleate, laurate, malate, fumarate, succinate,
oxalate, tartrate, ammonate, embonate, metembonate, stearate, tosylate, 2-
hydroxy-3-naphthoate, 3-hydroxy-2-naphthoate or mesylate.

Preferred possible salts for compounds of the formula I in which n denotes the
number 1 (sulphoxides) are pharmacologically tolerated basic salts, in
particular pharmacologically tolerated salts with the inorganic and organic
bases usually used in galenics. Examples of basic salts which may be mentioned
are the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium,
ammonium or guanidinium salts.

Of the Helicobacter strains against which the compounds of the formula I have
proved to be active, the Helicobacter pylori strain may be mentioned in
particular.

Examples which may be mentioned of medicaments to be administered orally are
tablets, coated tablets, hard and soft capsules, for example of gelatine,
dispersible powders, granules, aqueous and oily suspensions, emulsions,
solutions or syrups, it being advantageous for the tablets, coated tablets,
capsules or granules to be such that they readily dissolve in gastric juice and
release the active compound in the stomach.

For combined treatment of gastric diseases which are based both on an increased
secretion of gastric acid and on damage to the stomach by Helicobacter pylori,
there may also be mentioned those drug formulations to be administered orally
which contain active compounds of the formula I both in a form which is
resistant to gastric juice and in a form which is not resistant to gastric juice
simultaneously in an individual dose. Examples which may be mentioned are
tablets which contain the active compound both in a core which is resistant to
gastric juice and in a shell which is not resistant to gastric juice, or
capsules filled with pellets or (mini)tablets which are resistant to gastric
juice and those which are not resistant to gastric juice.

In human medicine, the active compounds are in general administered in a daily
dose of about 0.05 to about 5, preferably 0.1 to 2.5 mg/kg of body weight, if
appropriate in the form of several, preferably 2 to 6, individual doses, to
achieve the desired result.
If the compounds of the formula I and/or their salts are to be employed for the treatment of diseases of the stomach based on the presence of Helicobacter pylori, the medicaments to be administered can also contain one or more pharmacologically active constituents of other groups of medicaments. Combination of compounds of the formula I and/or their salts with antimicrobial substances which have an action against Helicobacter pylori, such as, for example, penicillin G, gentamycin, erythromycin, nitrofurazone, nitrofurantoin, furazolidone, metronidazole and in particular amoxycillin, with the aim of intensifying the main action in the super-additive sense, is to be emphasized in particular in this connection. Combination of the active compound 5-difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole [= pantoprazole (INN)] and its salts with substances having an antimicrobial action, in particular with amoxycillin, is particularly preferred in this connection and the invention therefore furthermore relates to this combination.

It has been found, surprisingly, that the compounds of the formula I are considerably more active against Helicobacter bacteria in an acid medium than in a neutral medium, and that they accordingly - in contrast to the doctrine to be found in the prior art - should appropriately not be administered in a form which is resistant to gastric juice.

The invention thus preferably relates to the use of compounds of the formula I and their pharmacologically tolerated salts for the preparation of medicaments which are not in a formulation which is resistant to gastric juice and are to be administered orally for combating Helicobacter bacteria.

One embodiment of the invention which is worth mentioning (embodiment a) comprises the use, according to the invention, of compounds of the formula Ia

![Chemical structure](image)
wherein

R1 denotes hydrogen or methyl,
R2 denotes hydrogen, methyl, ethyl, methoxy, ethoxy, 1,1,2,2-tetrafluorooethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R3, difluoromethylenedioxy, 1,1,2-trifluoroethylenedioxy or 1-chloro-1,2,2-trifluoroethylenedioxy,
R3 denotes 1,1,2,2-tetrafluoroethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R2, difluoromethylenedioxy, 1,1,2-trifluoroethylenedioxy or 1-chloro-1,2,2-trifluoroethylenedioxy,
R4 denotes hydrogen,
R5 denotes hydrogen, methyl or ethyl,
R6 denotes hydrogen or 1-4C-alkyl,
R7 denotes hydrogen or 1-4C-alkyl,
R8 denotes 1-4C-alkoxy and
n represents the number 0 or 1,
and their pharmacologically tolerated salts.

The use, according to the invention, of the following compounds of embodiment a
and their pharmacologically tolerated salts is particularly worth mentioning:

2-[(4-methoxy-2-pyridyl)methylsulphinyl]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4-methoxy-5-methyl-2-pyridyl)methylsulphinyl]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4-methoxy-2-pyridyl)methylsulphinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulphinyl]-5-trifluoromethoxy-1H-benzimidazole
2-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
5-difluoromethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(4-methoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-1H-benzimidazole,
5-chlorodifluoromethoxy-2-[(4-methoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole,
2,2-difluoro-6-[(4-methoxy-2-pyridyl)methylsulphinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
2,2-difluoro-6-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4-methoxy-2-pyridyl)methylsulphinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2,2-difluoro-6-[(4-methoxy-5-methyl-2-pyridyl)methylsulphinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulphinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
5-difluoromethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-4,6-dimethyl-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[[1-(4-methoxy-2-pyridyl)ethyl]sulphinyl]-1H-benzimidazole,
5-(1,1,2,2-tetrafluoroethoxy)-2-[[1-(4-methoxy-2-pyridyl)ethyl]sulphinyl]-1H-benzimidazole,
2,2-difluoro-6-[[1-(4-methoxy-2-pyridyl)ethyl]sulphinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
5-(2-chloro-1,1,2-trifluoroethoxy)-2-[[4-methoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole,
5-(2-chloro-1,1,2-trifluoroethoxy)-2-[[1-(4-methoxy-2-pyridyl)ethyl]sulphinyl]-1H-benzimidazole,
5-(2-chloro-1,1,2-trifluoroethoxy)-2-[[4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-1H-benzimidazole,
2[[4-methoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4-methoxy-5-methyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4-methoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
5-difluoromethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(4-methoxy-2-pyridyl)methylthio]-1H-benzimidazole,
5,6-bis(difluoromethoxy)-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
5-chlorodifluoromethoxy-2-[(4-methoxy-2-pyridyl)methylthio]-1H-benzimidazole,
2,2-difluoro-6-[(4-methoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
2,2-difluoro-6-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4-methoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2,2-difluoro-6-[(4-methoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
5-difluoromethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-4,6-dimethyl-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[[1-(4-methoxy-2-pyridyl)ethyl]sulphinyl]-1H-benzimidazole,
5-(1,1,2,2-tetrafluoroethoxy)-2-[[1-(4-methoxy-2-pyridyl)ethyl]sulphinyl]-1H-benzimidazole,
2,2-difluoro-6-[[1-(4-methoxy-2-pyridyl)ethyl]sulphinyl]-5H-[1,3]-dioxole[4,5-f]benzimidazole,
5-(2-chloro-1,1,2-trifluoroethoxy)-2-[[4-methoxy-2-pyridyl]methylthio]-1H-benzimidazole,
5-(2-chloro-1,1,1-trifluoroethoxy)-2-[[1-(4-methoxy-2-pyridyl)ethyl]-sulphinyl]-1H-benzimidazole,
5-(2-chloro-1,1,2-trifluoroethoxy)-2-[[4-methoxy-3-methyl-2-pyridyl]methylthio]-1H-benzimidazole.

Another embodiment of the invention which is worth mentioning (embodiment b) comprises the use, according to the invention, of compounds of the formula Ib,

![Chemical Structure](image)

wherein
- R1 denotes hydrogen or methyl,
- R2 denotes hydrogen, methyl, ethyl, methoxy, ethoxy, 1,1,2,2-tetrafluoroethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R3, difluoromethylenedioxy, 1,1,2-trifluoroethylenedioxy or 1-chloro-1,2,2-trifluoroethylenedioxy,
- R3 denotes 1,1,2,2-tetrafluoroethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R2, difluoromethylenedioxy, 1,1,2-trifluoroethylenedioxy or 1-chloro-1,2,2-trifluoroethylenedioxy,
- R4 denotes hydrogen,
- R5 denotes hydrogen, methyl or ethyl,
- R6 denotes hydrogen or 1-4c-alkyl,
R7 denotes 1-4C-alkoxy,
R8 denotes 1-4C-alkoxy and
n represents the number 0 or 1,
and their pharmacologically tolerated salts.

The use, according to the invention, of the following compounds of embodiment b
and their pharmacologically tolerated salts is particularly worth mentioning:

5-difluoromethoxy-2-{[3,4-dimethoxy-2-pyridyl)methylsulphonyl]-4,6-dimethyl-1H-benzimidazole,
5-difluoromethoxy-2-{[3,4-dimethoxy-2-pyridyl)methylsulphonyl]-1H-benzimidazole,
5-difluoromethoxy-2-{[4,5-dimethoxy-3-methyl-2-pyridyl)methylsulphonyl]-1H-benzimidazole,
2-{[4,5-dimethoxy-3-methyl-2-pyridyl)methylsulphonyl]-5-trifluoromethoxy-1H-benzimidazole,
2-{[3,4-dimethoxy-2-pyridyl)methylsulphonyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-{[3,4-dimethoxy-2-pyridyl)methylsulphonyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-{[3,4-dimethoxy-2-pyridyl)methylsulphonyl]-1H-benzimidazole,
2,2-difluoro-6-{[3,4-dimethoxy-2-pyridyl)methylsulphonyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-{[3,4-dimethoxy-2-pyridyl)methylsulphonyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-{[4,5-dimethoxy-2-pyridyl)methylsulphonyl]-5-trifluoromethoxy-1H-benzimidazole,
2-{[4,5-dimethoxy-2-pyridyl)methylsulphonyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2,2-difluoro-6-{[4,5-dimethoxy-2-pyridyl)methylsulphonyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
5-difluoromethoxy-2-{[3,4-dimethoxy-2-pyridyl)methylthio]-4,6-dimethyl-1H-benzimidazole,
5-difluoromethoxy-2-{[3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole,
5-difluoromethoxy-2-{[4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole,
2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2-[(3,4-dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(3,4-dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2-[(3,4-dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,
5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole,
2,2-difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
6,6,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,
2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole,
2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole,
2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole.

Another embodiment of the invention which is worth mentioning (embodiment c) comprises the use, according to the invention, of compounds of the formula Ic

wherein

R1 denotes hydrogen,
R2 denotes hydrogen, methyl, ethyl, methoxy, ethoxy, 1,1,2,2-tetrafluoroethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R3, difluoromethylenedioxy, 1,1,2-trifluoroethylenedioxy or 1-chloro-1,2,2-trifluoroethylenedioxy,
R3 denotes 1,1,2,2-tetrafluoroethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R2, difluoromethylenedioxy, 1,1,2-trifluoromethylenedioxy or 1-chloro-1,2,2-trifluoromethylenedioxy,
R4 denotes hydrogen,
R5 denotes hydrogen, methyl or ethyl,
R6 denotes hydrogen or 1-4C-alkyl,
R7 denotes 1-4C-alkoxy,
R8 denotes benzyloxy and
n represents the number 0 or 1,
and their pharmacologically tolerated salts.

The use, according to the invention, of the following compounds of embodiment c and their pharmacologically tolerated salts is particularly worth mentioning:

2,2-difluoro-6-[(5-benzyloxy-4-methoxy-2-pyridyl)methylsulphinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
2-[(4-benzyloxy-3-methoxy-2-pyridyl)methylsulphinyl]-5-difluoromethoxy-1H-benzimidazole,
2-[(3-benzyloxy-4-methoxy-2-pyridyl)methylsulphinyl]-5-difluoromethoxy-1H-benzimidazole,
2-[(5-benzyloxy-4-methoxy-3-methyl-2-pyridyl)methylsulphinyl]-5-difluoromethoxy-1H-benzimidazole,
2-[(5-benzyloxy-4-methoxy-2-pyridyl)methylsulphinyl]-5-trifluoromethoxy-1H-benzimidazole,
2,2-difluoro-6-[(5-benzyloxy-4-methoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole,
2-[(4-benzyloxy-3-methoxy-2-pyridyl)methylthio]-5-difluoromethoxy-1H-benzimidazole,
2-[(3-benzyloxy-4-methoxy-2-pyridyl)methylthio]-5-difluoromethoxy-1H-benzimidazole,
2-[(5-benzyloxy-4-methoxy-3-methyl-2-pyridyl)methylthio]-5-difluoromethoxy-1H-benzimidazole,
2-[(5-benzyloxy-4-methoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole.
Another embodiment of the invention which is worth mentioning (embodiment d) is the use, according to the invention, of compounds of the formula I d

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wherein

- **R1** denotes hydrogen,
- **R2** denotes hydrogen, methyl, ethyl, methoxy, ethoxy, 1,1,2,2-tetrafluorooethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R3, difluoromethyleneoxy, 1,1,2-trifluoroethylenedioxy or 1-chloro-1,2,2-trifluoroethylenedioxy,
- **R3** denotes 1,1,2,2-tetrafluoroethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, together with R2, difluoromethyleneoxy, 1,1,2-trifluoroethylenedioxy or 1-chloro-1,2,2-trifluoroethylenedioxy,
- **R4** denotes hydrogen,
- **R5** denotes hydrogen, methyl or ethyl,
- **R6** denotes hydrogen or 1-4C-alkyl,
- **R7** denotes hydrogen, 1-4C-alkyl or 1-4C-alkoxy,
- **R8** denotes 1,1,2,2-tetrafluoroethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy or difluoromethoxy and
- **n** represents the number 0 or 1,

and their pharmacologically tolerated salts.

The use, according to the invention, of the following compounds of embodiment d and their pharmacologically tolerated salts is particularly worth mentioning:

- 5-difluoromethoxy-2-[[3-methoxy-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methylsulphinyl]-1H-benzimidazole,
- 5-difluoromethoxy-2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridyl] methylsulphinyl]-1H-benzimidazole,
2-\{(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylsulphinyl\}-5-\{(2,2,2-trifluoroethoxy)-1H-benzimidazole, 
2,2-difluoro-6-\{(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylsulphinyl\}-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 
5-difluoromethoxy-2-\{(3-methoxy-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylthio\}-1H-benzimidazole, 
5-difluoromethoxy-2-\{(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylthio\}-1H-benzimidazole, 
2-\{(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylthio\}-5-\{(2,2,2-trifluoroethoxy)-1H-benzimidazole, 
2,2-difluoro-6-\{(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylthio\}-5H-[1,3]-dioxolo[4,5-f]benzimidazole. 


The medicaments to be administered orally are prepared using the active compounds of the formula I in a manner which is known per se to the expert.
WHAT IS CLAIMED IS:

1. Use of 5-difluoromethoxy-2-[3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole and its pharmaceutically tolerated salts for the preparation of oral medicaments for combating Helicobacter bacteria.

2. Use of 5-difluoromethoxy-2-[3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole sodium for the preparation of oral medicaments which are not in a formulation which is resistant to gastric juice and are for combating Helicobacter bacteria of the species Helicobacter pylori.

3. Drug formulation containing 5-difluoromethoxy-2-[3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole or a pharmaceutically tolerated salt thereof simultaneously in a form which is resistant to gastric juice and in a form which is not resistant to gastric juice.

4. Drug formulation according to claim 3 in the form of tablets which contain 5-difluoromethoxy-2-[3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole or a pharmaceutically tolerated salt thereof both in a core which is resistant to gastric juice and in a shell which is not resistant to gastric juice.

5. Drug formulation according to claim 3 in the form of capsules which contain 5-difluoromethoxy-2-[3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole or a pharmaceutically tolerated salt thereof in pellets, mini tablets or tablets which are both resistant to gastric juice and not resistant to gastric juice.

6. A Helicobacter bacteria treatment oral composition comprising 5-difluoromethoxy-2-[3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole or a pharmaceutically tolerated salt thereof, together with a pharmaceutically acceptable carrier.
7. A Helicobacter bacteria treatment oral composition comprising 5-difluoromethoxy-2-[3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole or a pharmaceutically tolerated salt thereof, together with a pharmaceutically acceptable carrier, the composition comprising a first formulation which is substantially resistant to gastric juice and a second formulation which is substantially non-resistant to gastric juice.

8. A tablet comprising the composition defined in claim 7.

9. The tablet defined in claim 8, having a core comprising the first formulation and a shell comprising the second formulation.

10. A capsule comprising the composition defined in claim 7.

11. The capsule defined in claim 10, wherein at least one of the first formulation and the second formulation comprise pellets, mini tablets or tablets.

12. The capsule defined in claim 10, wherein both of the first formulation and the second formulation comprise pellets, mini tablets or tablets.


14. A Helicobacter pylori treatment oral composition comprising 5-difluoromethoxy-2-[3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole sodium, together with a pharmaceutically acceptable carrier, the composition comprising a first formulation which is substantially resistant to gastric juice and a second formulation which is substantially non-resistant to gastric juice.

15. A tablet comprising the composition defined in claim 14.
16. The tablet defined in claim 15, having a core comprising the first formulation and a shell comprising the second formulation.

17. A capsule comprising the composition defined in claim 14.

18. The capsule defined in claim 17, wherein at least one of the first formulation and the second formulation comprise pellets, mini tablets or tablets.

19. The capsule defined in claim 17, wherein both of the first formulation and the second formulation comprise pellets, mini tablets or tablets.

20. A oral composition comprising 5-difluoromethoxy-2-[3,4-dimethoxy-2-pyridyl]methylsulphinyl]-1H-benzimidazole or a pharmaceutically tolerated salt thereof, together with a pharmaceutically acceptable carrier, the composition comprising a first formulation which is substantially resistant to gastric juice and a second formulation which is substantially non-resistant to gastric juice.

21. A tablet comprising the composition defined in claim 20.

22. The tablet defined in claim 21, having a core comprising the first formulation and a shell comprising the second formulation.

23. A capsule comprising the composition defined in claim 20.

24. The capsule defined in claim 23, wherein at least one of the first formulation and the second formulation comprise pellets, mini tablets or tablets.

25. The capsule defined in claim 23, wherein both of the first formulation and the second formulation comprise pellets, mini tablets or tablets.

26. The composition defined in claim 20 for the use of treating Helicobacter bacteria.

27. The composition defined in claim 20 for the use of treating Helicobacter pylori.
28. The tablet defined in any one of claims 21-22 for the use of treating Helicobacter bacteria.

29. The tablet defined in any one of claims 21-22 for the use of treating Helicobacter pylori.

30. The capsule defined in any one of claims 23-25 for the use of treating Helicobacter bacteria.

31. The capsule defined in any one of claims 23-25 for the use of treating Helicobacter pylori.