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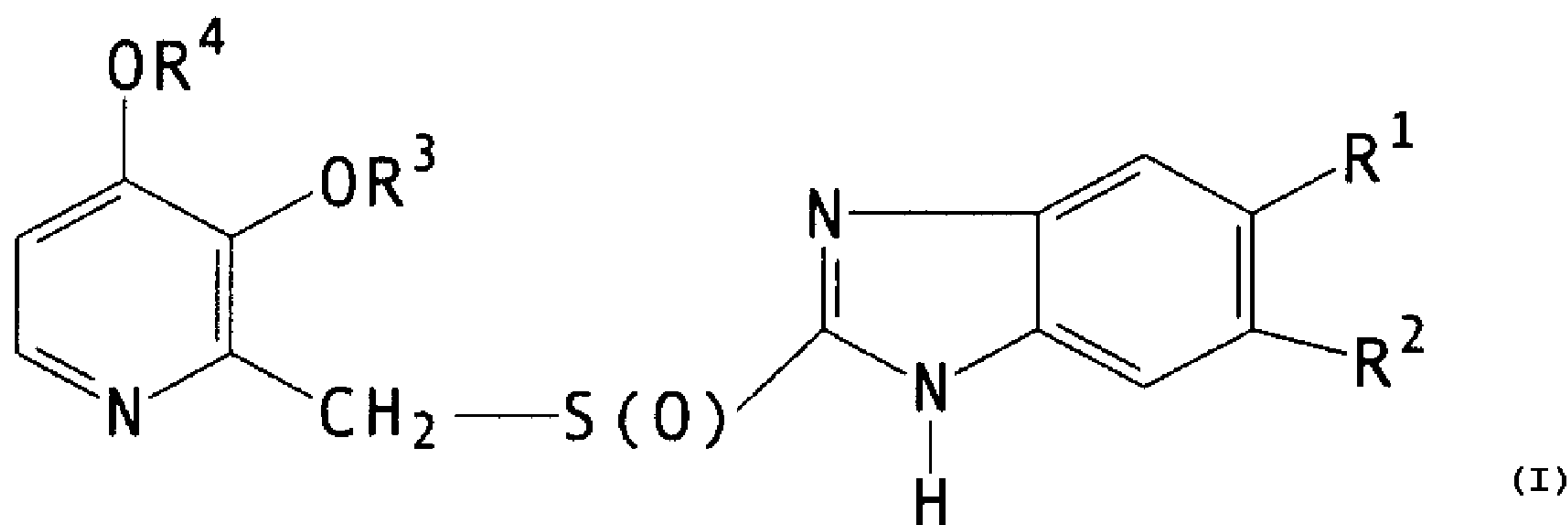
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(54) Titre : DERIVES DE DIALCOXYPYRIDINYLBENZIMIDAZOLE; METHODE DE PREPARATION ET UTILISATION EN PHARMACIE

(54) Title: DIALKOXY-PYRIDINYLBENZIMIDAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR PHARMACEUTICAL USE



(57) Abrégé/Abstract:

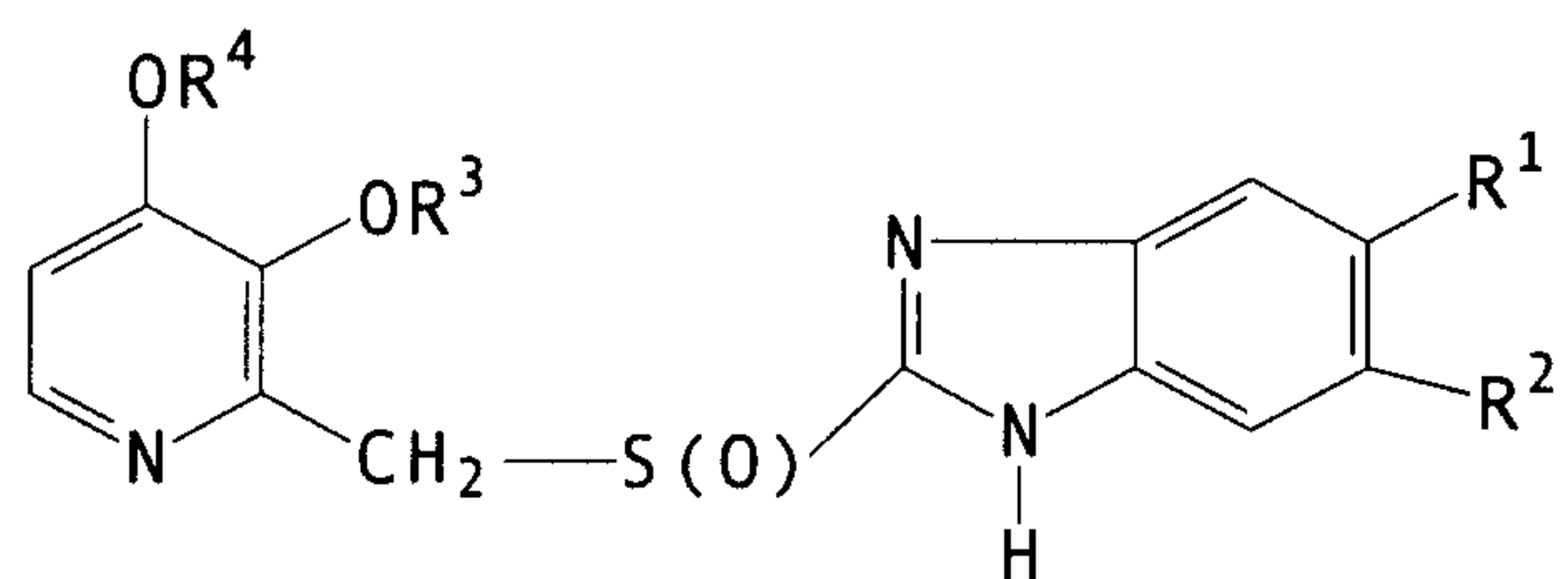
A compound of Formula I: (see formula I) and physiologically acceptable salts thereof wherein R¹ is -C(O)OCH₃, and R², R³, and R⁴ is each CH₃, as well as pharmaceutical compositions containing this compound, which can be used to inhibit gastric acid secretion or to treat gastrointestinal inflammatory diseases in a mammal.



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ABSTRACT

A compound of Formula I:



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and physiologically acceptable salts thereof wherein R^1 is $-C(O)OCH_3$, and R^2 , R^3 , and R^4 is each CH_3 , as well as pharmaceutical compositions containing this compound, which can be used to inhibit gastric acid secretion or to treat

10 gastrointestinal inflammatory diseases in a mammal.

Dialkoxy-pyridinyl-benzimidazole derivatives, process for their preparation and their pharmaceutical use

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DESCRIPTION

Field of the invention

10 The object of the present invention is to provide novel compounds, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer.

15

The present invention also relates to the use of the compounds of the invention, and therapeutically acceptable salts thereof, for inhibiting gastric acid secretion in mammals including man. In a more general sense, the

20 compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis, and Zollinger-Ellison syndrome. Furthermore,

25 the compound may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care

30 situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compounds of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions

35 that may be specifically mentioned are rheumatoid arthritis and gout. The compounds may also be useful in the treatment of diseases related to bone metabolism disorders as well as

2083606

2

the treatment of glaucoma. The invention also relates to pharmaceutical compositions containing the compounds of the invention, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention
5 relates to processes for preparation of such new compounds, to novel intermediates in the preparation of the compounds of the invention, and to the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

10

It is a specific primary object of the invention to provide compounds with a high level of bioavailability. The compounds of the invention will also exhibit high stability properties at neutral pH and a good potency in regard to
15 inhibition of gastric acid secretion. In addition the compounds of the invention will not block the uptake of iodine into the thyroid gland. It has earlier been disclosed in several lectures from the company, where the inventors are working that thyroid toxicity depends on if the
20 compounds are lipophilic or not. The inventors have now unexpectedly found that it is not the lipophilicity that is the critical parameter. The claimed compounds, which include rather hydrophilic compounds, do not give any thyroid toxic effect and have at the same time high acid
25 secretion inhibitory effect, good bioavailability and stability.

Prior art and background of the invention

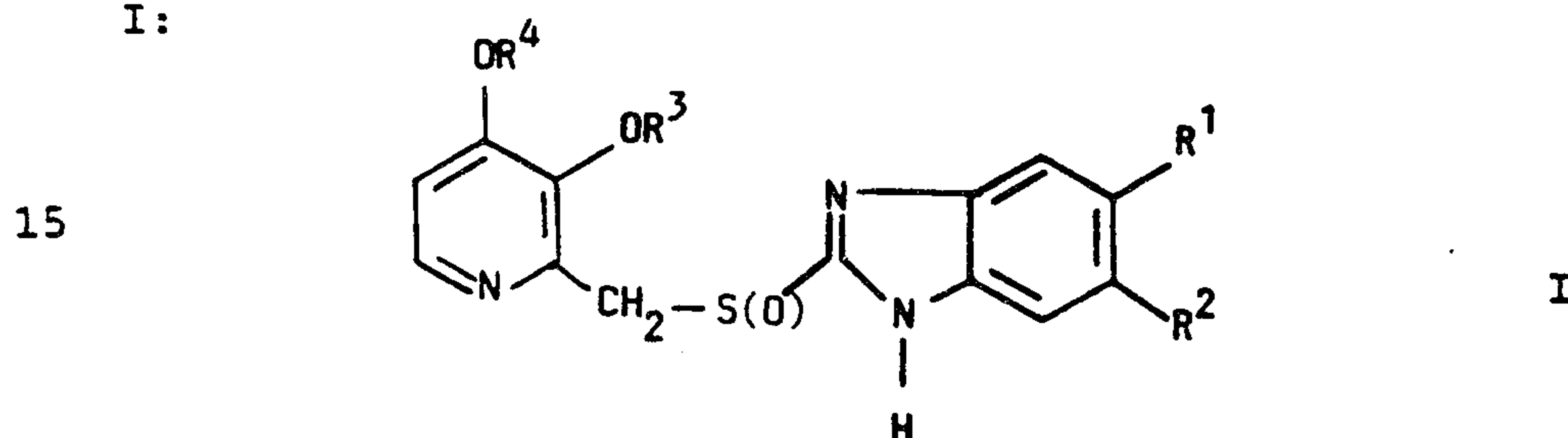
- 30 Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents. Among these can be mentioned GB 1 500 043, GB 1 525 958, US 4 182 766, US 4 255 431, US 4 599 347, EP 124 495, BE 898 880, EP 208 452 and Derwent abstract 87-294449/42.
- 35 Benzimidazole derivatives proposed for use in the treatment or prevention of special gastrointestinal inflammatory diseases are disclosed in US 4 359 465.

The invention

It has been found that the compounds of the following formula I show high bioavailability. The compounds of the formula I also are effective as inhibitors of gastric acid secretion in mammals and man and do not block the uptake of iodine into the thyroid gland. The compounds of the invention exhibit a high chemical stability in solution at neutral pH.

10

The compounds of the invention are of the following formula I:



20 and physiologically acceptable salts thereof

wherein R^1 and R^2 , which are different, is each H, alkyl containing 1-4 carbon atoms or $-C(O)-R^5$; wherein one of R^1 or R^2 is always selected from the group $-C(O)-R^5$; and
 25 wherein R^5 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms;

R^3 and R^4 are the same or different and selected from

30 $-CH_3$, $-C_2H_5$, $-CH_2-$ (cyclopropyl), $-CH_2-$ (4,4-dimethyl-1,3-dioxane), and $-CH_2CH_2OCH_3$ or R^3

and R^4 together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form a ring, wherein the part constituted by R^3 and R^4 is
 35 $-CH_2CH_2CH_2-$, $-CH_2CH_2-$ or $-CH_2-$.

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It should be understood that the expressions "alkyl" and "alkoxy" include straight and branched structures.

The compounds of the invention of the formula I have an asymmetric centre in the sulfur atom, i.e. exist as two optical isomers (enantiomers), or if they also contain one or more asymmetric carbon atoms the compounds have two or more diastereomeric forms, each existing in two enantiomeric forms.

10

Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are within the scope of the present invention. It should be understood that all the diastereomeric forms possible (pure enantiomers or racemic mixtures) are within the scope of the invention.

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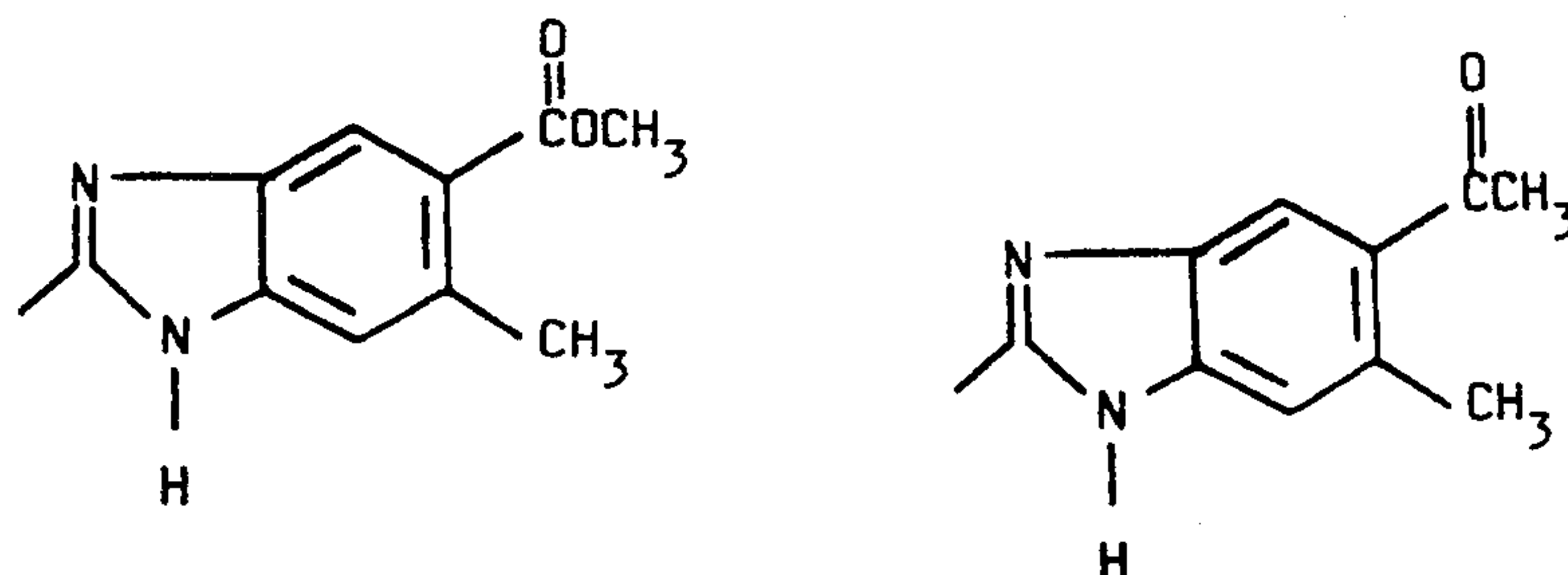
Preferred groups of compounds of the formula I are:

1. Compounds, wherein R^1 and R^2 are selected from H methyl or $-C(O)R^5$, wherein R^5 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms.

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2. Especially preferred benzimidazole structures are

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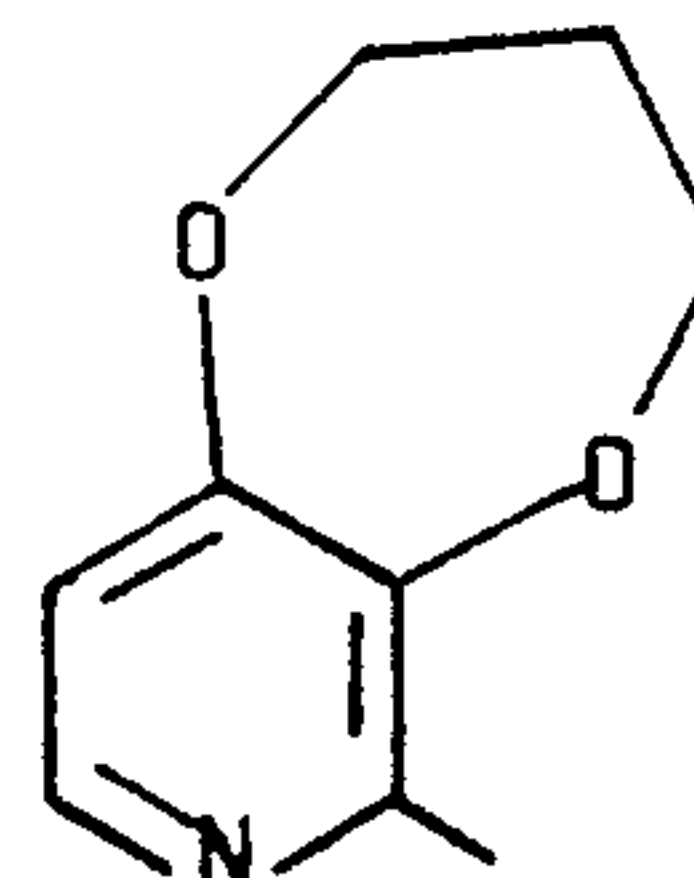
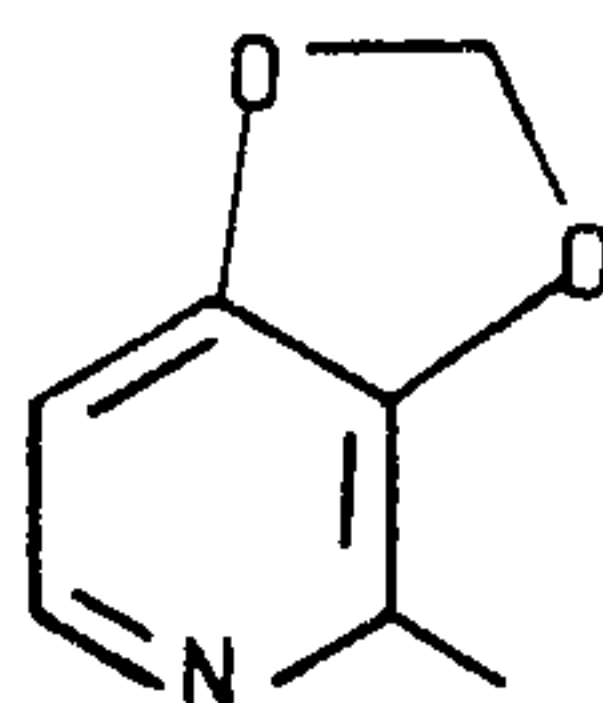
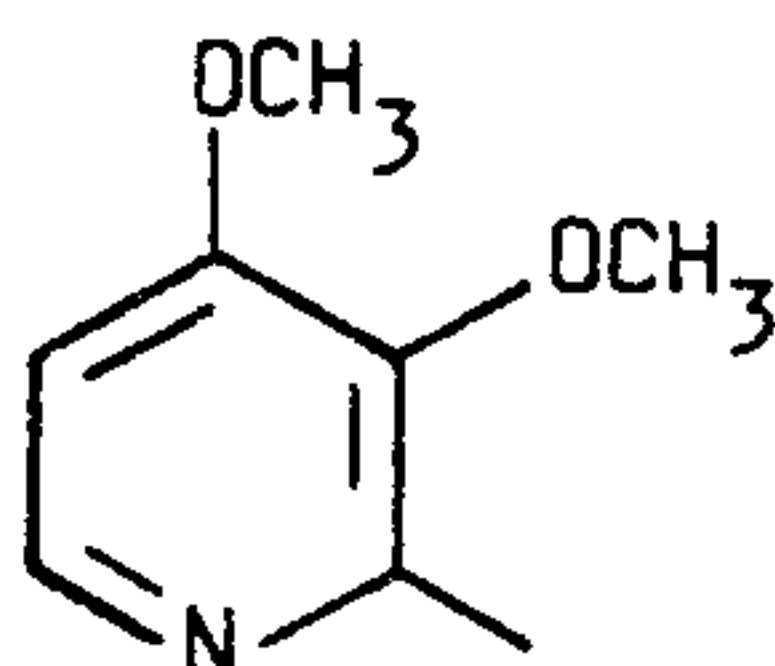
3. Compounds wherein R^3 and R^4 are CH_3 .

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4. Compounds wherein R^3 and R^4 together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form a ring wherein the part constituted by R^3 and R^4 is $-CH_2CH_2CH_2-$, $-CH_2CH_2-$ or $-CH_2-$.

5. Especially preferred pyridine structures are

5



10

6. Further especially preferred specific compounds of the invention are as listed in the following tabulation.

15

R^1	R^2	R^3	R^4
$C(O)OCH_3$	CH_3	CH_3	CH_3
$C(O)CH_3$	CH_3	CH_3	CH_3
20 $C(O)OCH_3$	CH_3		
$C(O)CH_3$	CH_3		
		$-CH_2-$	
		$-CH_2CH_2CH_2-$	

Preparation

25 The compounds of the invention may be prepared according to the following method:

Oxidizing a compound of the formula II

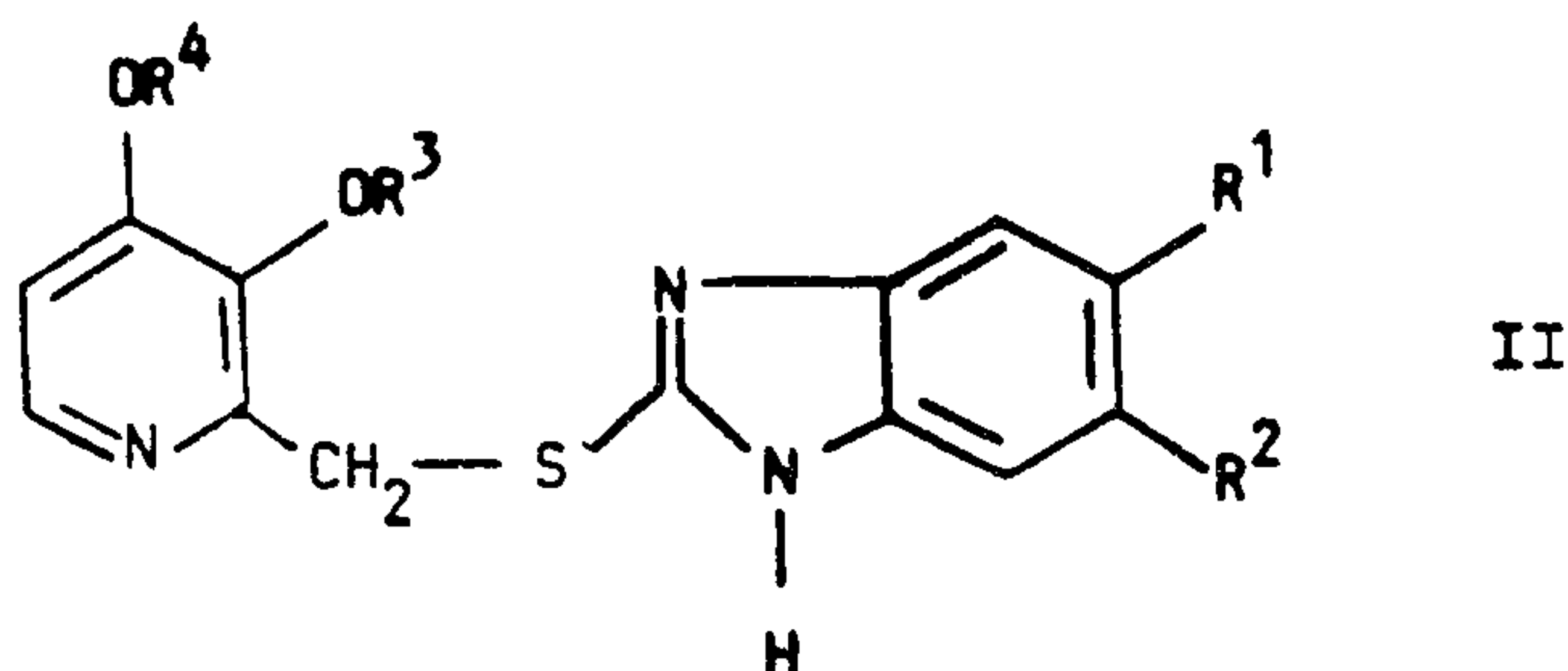
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wherein R^1 , R^2 , R^3 and R^4 are as defined under formula I.

- 10 This oxidation may be carried out by using an oxidizing agent such as nitric acid, hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, ozone, dinitrogen tetroxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite,
- 15 diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, ceric ammonium nitrate, bromine, chlorine, and sulfuric chloride. The oxidation usually takes place in a solvent such as halogenated hydrocarbons, alcohols, ethers,
- 20 ketones.

The oxidation may also be carried out enzymatically by using an oxidizing enzyme or microbiotically by using a suitable microorganism.

25

- Depending on the process conditions and the starting materials, the compounds of the invention are obtained either in neutral or salt form. Both the neutral compounds and the salts of these are included within the scope of the
- 30 invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates.

- Alkaline salts of the compounds, of the invention are exemplified by their salts with Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , and $N^+(R)_4$, where R is (1-4 C)alkyl. Particularly preferred
- 35 are the Na^+ , Ca^{2+} and Mg^{2+} salts. Especially preferred are the Na^+ and Mg^{2+} salts. Such salts may be prepared by

reacting a compound with a base capable of releasing the desired cation.

Examples of bases capable of releasing such cations, and
5 examples of reaction conditions are given below.

a) Salts wherein the cation is Li^+ , Na^+ or K^+ are prepared by treating a compound of the invention with LiOH , NaOH or KOH in an aqueous or nonaqueous medium or with LiOR , LiNH_2 ,
10 LiNR_2 , NaOR , NaNH_2 , NaNR_2 , KOR , KNH_2 or KNR_2 , wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous medium.

b) Salts wherein the cation is Mg^{2+} or Ca^{2+} , are prepared by
15 treating a compound of the invention with Mg(OR)_2 , Ca(OR)_2 or CaH_2 ; wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous solvent such as an alcohol (only for the alcoholates), e.g. ROH , or in an ether such as tetrahydrofuran.

20

Racemates obtained can be separated into the pure enantiomers. This may be done according to known methods, e.g. from racemic diastereomeric salts by means of chromatography or fractional crystallization.

25

The starting materials described in the intermediate examples may be obtained according to processes known per se.

30 For clinical use a compound of the invention is formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administration. The pharmaceutical formulation contains a compound of the invention normally in combination with a pharmaceutically
35 acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the

2083606

8

invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1-50% by weight in preparations for oral administration.

5

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration a compound selected may be mixed with a solid, powdered carrier, such as
10 lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with
15 lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound
20 from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose
25 phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts
30 of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of an active compound of the invention, vegetable oil, fat, or other suitable vehicle
35 for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of

an active compound. Hard gelatine capsules may also contain an active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or
5 gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain an active substance
10 mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains an active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro
15 enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared
20 in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired,
25 such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to
30 use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a
35 concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or

2083606

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vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

- 5 The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

10

The invention is illustrated by the following examples.

Example 1

- 15 Preparation of 5-carbomethoxy-6-methyl-2-[[[4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

- 20 5-Carbomethoxy-6-methyl-2-[[[4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]thio]]-1H-benzimidazole (0.42 g, 1.0 mmol) was dissolved in methylene chloride (30 ml). NaHCO₃ (0.17 g, 2.0 mmol) dissolved in water (5 ml) was added and the mixture was cooled to +2°C m-chloroperbenzoic acid, 71% (0.19, 0.80 mmol) dissolved in methylene chloride
25 (5 ml) was added dropwise with stirring. Stirring was continued at +2°C for 15 min. After separation the organic layer was washed with water, dried with Na₂SO₄ and evaporated. To the oily residue acetonitrile (1 ml) was added and after cooling the desired product was filtered off
30 as white crystals (0.15 g, 44%).

NMR data are given below.

- 35 Example 2

2083606

Preparation of 5-acetyl-6-methyl-2-[[[(3,4-ethylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

5-Acetyl-6-methyl-2-[[[(3,4-ethylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (0.17 g, 0.49 mmol) was dissolved in methylene chloride (5 ml). NaHCO₃ (0.082 g, 0.97 mmol) dissolved in water (2 ml) was added and the mixture was cooled to +2°C. m-Chloroperbenzoic acid, 69,5% (0.11 g, 0.44 mmol) dissolved in methylene chloride (2 ml) was added dropwise with stirring.

Stirring was continued at +2°C for 15 min. After separation the organic layer was extracted with an aqueous 0.20 M NaOH solution (3x2.5 ml, 1.5 mmol). Methyl formate (0.093 ml, 1.5 mmol) was added to the combined aqueous solutions and after 15 minutes the solution was extracted with methylene chloride. The organic solution was dried over Na₂SO₄ and evaporated leaving a white crystalline product which was washed with ether. In this way the desired compound was obtained (0.050 g, 30%).

NMR data are given below.

Example 3

Preparation of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-Carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (1.03 g, 0.00276 mol) was dissolved in CH₂Cl₂ (30 ml). NaHCO₃ (0.46 g, 0.0055 mol) in H₂O (10 ml) was added and the mixture was cooled to +2°C. m-chloroperbenzoic acid 69.5% (0.62 g, 0.0025 mol) dissolved in CH₂Cl₂ (5 ml) was added dropwise under stirring. Stirring was continued at +2°C for 15 min. After separation the organic layer was extracted with an aqueous 0.2 M NaOH solution (3x15 ml, 0.009 mol). After

2083606

12

separation the aqueous solutions were combined and neutralized with methyl formate (0.56 ml, 0.009 mol) in the presence of CH_2Cl_2 (25 ml). After separation the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN (10 ml) giving the title compound (0.68 g, 70 %).

NMR data are given below.

10 Example 4

Preparation of 5-acetyl-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

15 5-Acetyl-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.75 g, 10 mmol) was dissolved in CH_2Cl_2 (70 ml). NaHCO_3 (1.76 g, 21 mmol) in H_2O (25 ml) was added and the mixture was cooled to $+3^\circ\text{C}$. m-Chloroperbenzoic acid 69.5% (2.43 g, 9.8 mmol) dissolved in CH_2Cl_2 (20 ml) was added dropwise under stirring. 20 Stirring was continued for 10 min. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN giving the title compound (2.25 g, 60%).

25

NMR data are given below.

Example 5

30 **Preparation of 5-carbethoxy-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole**

5-Carbethoxy-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (95.2% pure) (1.4 g, 0.0036 mol) was 35 dissolved in CH_2Cl_2 (30 ml). NaHCO_3 (0.6 g, 0.0072 mol) in H_2O (10 ml) was added and the mixture was cooled to $+2^\circ\text{C}$. m-Chloroperbenzoic acid 69.5 % (0.87 g, 0.0035 mol)

dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring. Stirring was continued at $+2^\circ\text{C}$ for 10 min. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue
5 was crystallized from CH_3CN (15 ml) giving the title compound (0.76 g, 54 %).

NMR data are given below.

10 Example 6

Preparation of 5-acetyl-6-methyl-2-[[[3,4-propylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

15 The compound was prepared from 5-acetyl-6-methyl-2-[[[3,4-propylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole and m-chloroperbenzoic acid on a 0.01 mmol scale according to standard procedures.

20 NMR data are given below.

Example 7

5-Acetyl-6-methyl-2-[[[3,4-methylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.
25

5-Acetyl-6-methyl-2-[[[3,4-methylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (140 mg, 0.41 mmol) was dissolved in methylene chloride (20 ml) and sodium
30 hydrogen carbonate (5 ml, 1M). The mixture was stirred at ambient temperature and MCPBA (100 mg, 0.41 mmol, 70%) dissolved in methylene chloride (10 ml) was added portionwise. After 10 min sodium thiosulphate (100 mg) was added whereupon the phases were separated. The organic phase
35 was dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was chromatographed on

2083606

14

silica (CH₂Cl₂/MeOH/NH₃, 97.5:2.5:sat.) Yield: 90 mg (61%) of the title compound. Mp: 178-180°C (dec., uncorr.).

NMR data are given below.

5

Example 8

Preparation of 5-acetyl-6-methyl-2-[[[(3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

A stirred mixture of 5-acetyl-6-methyl-2-[[[(3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)methyl]thio]-1H-benzimidazole (87 mg, 0.19 mmol) in 20 ml CH₂Cl₂ and NaHCO₃ (32 mg, 0.38 mmol) in 5 ml H₂O was cooled to 0°C and treated with 3-chloro-perbenzoic acid (47 mg 70%, 0.19 mmol). After reacting for 10 min the layers were separated (the aqueous layer was washed once more with 5 ml CH₂Cl₂) and the organic layer extracted with 10 ml H₂O containing NaOH (15 mg, 38 mmol). The alkaline aqueous layer was collected and treated with several portions of methyl formate (each 23 µl, 38 mmol) until the solution turned opaque. The aqueous layer was extracted with 25 + 10 ml CH₂Cl₂. The two latter organic layers were combined, dried over MgSO₄ and evaporated. The residue was chromatographed (SiO₂, CH₂Cl₂/MeOH saturated with NH₃(g), 93/7) yielding 40 mg (44%) pure sulfoxide.

NMR data are given below.

30 Example 9

Preparation of 5-acetyl-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, sodium salt

35 5-Acetyl-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (0.50 g, 1.3 mmol) dissolved in dichloromethane and sodium hydroxide (51

mg, 1.3 mmol) dissolved in water (6 ml) were transferred to a separatory funnel. The mixture was shaken to equilibrium whereupon the solvent phases were separated. The aqueous solution was washed with dichloromethane and then freeze
5 dried.

NMR data are given below.

Example 10

10

Preparation of 5-acetyl-6-methyl-2-[[[4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-Acetyl-6-methyl-2-[[[4-cyclopropylmethoxy-3-methoxy-2-
15 pyridinyl)methyl]thio]-1H-benzimidazole (40 mg, 0.10 mmol) was dissolved in methylene chloride (10 ml) and sodium hydrogen carbonate (3 ml, 1M). The mixture was stirred at ambient temperature and MCPBA (25 mg, 0.10 mmol, 70 %) dissolved in methylene chloride (5 ml) was added
20 portionwise. After 10 min sodium thiosulphate (30 mg) was added whereupon the phases were separated. The organic phase was dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (CH₂Cl₂/MeOH/NH₃, 97.5:2.5:sat.) Yield 30 mg (73 %) of the title compound.
25

Table 1

Ex	Solvent	NMR data δ ppm
30		
1	CDCl ₃ (300 MHz)	0.30-0.35 (m, 2H), 0.60-0.67 (m, 2H), 1.2-1.3 (m, 1H) 2.67 (s, 3H), 3.83 (d, 2H), 3.86 (s, 3H), 3.90 (s, 3H), 35 4.72 (d, 1H), 4.86 (d, 1H), 6.71 (d, 1H), 7.35 (b, 1H), 8.09 (d, 1H), 8.24 (b, 1H),

2083606

2	CDCl ₃ (500 MHz)	2.65 (s, 3H), 2.66 (s, 3H), 3.9-4.2 (m, 4H), 4.70 (d, 1H), 4.82 (d, 1H), 6.75 (d, 1H), 7.3 (b, 1H), 7.92 (d, 1H), 8.2 (b, 1H),
5		
3	CDCl ₃ (500 MHz)	2.70 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.8 (d, 1H), 7.30 (b, 1H), 8.20 (d, 1H), 8.35 (b, 1H).
10		
4	CDCl ₃ (300 MHz)	2.60 (s, 6H), 3.85 (s, 3H), 3.85 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.80 (d, 1H), 7.30 (b, 1H), 8.15 (d, 1H), 8.20 (b, 1H)
15		
5	CDCl ₃ (300 MHz)	1.45 (t, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.40 (q, 2H), 4.65 (d, 1H), 4.40 (d, 1H), 6.80 (d, 1H), 7.50 7.80 (b, 1H) 8.05 (d, 1H), 8.20 (d, 1H), 8.25, 8.55 (b, 1H)
20		
25		
6	CDCl ₃ (500 MHz)	2.16 (m, 2H), 2.64 (s, 3H), 2.66 (s, 3H), 4.23 (t, 2H), 4.30 (t, 2H), 4.68 (d, 1H), 4.88 (d, 1H), 6.83 (d, 1H), 7.3-7.5 (b, 1H), 8.01 (d, 1H), 8.1-8.2 (b, 1H).
30		
7	CDCl ₃ (300 MHz)	2.66 (s, 6H), 4.54 (d, 1H), 4.75 (d, 1H), 5.80 (s, 1H), 5.87 (s, 1H), 6.77 (d, 1H), 7.93 (br. 1H), 8.07 (d, 1H), 8.12 (br. 1H)
35		

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8	CDCl ₃ (300 MHz)	0.91 (s, 3H), 2.63 (s, 3H), 2.64 (s, 3H), 3.49 (d, 2H), 3.84 (s, 3H), 3.94 (d, 2H), 4.15 (m, 2H), 4.66 (d, 1H), 4.73 (d, 1H), 4.86 (d, 1H), 5.02 (d, 1H), 6.89 (d, 1H), 7.33 (s, 1H), 8.08 (s, 1H), 8.14 (d, 1H)
5		
9	D ₂ O (protons in water were set to 4.82 ppm) (300 MHz)	2.66 (s, 3H), 2.81 (s, 3H), 3.81 (s, 3H), 4.02 (s, 3H), 4.73 (d, 1H), 4.91 (d, 1H), 7.16 (d, 1H), 7.62 (s, 1H), 8.23 (d, 1H), 8.30 (s, 1H)
10		
15	10 CDCl ₃ (300 MHz)	0.33 (m, 2H), 0.65 (m, 2H), 1.24 (m, 1H), 2.63 (s, 3H), 2.64 (s, 3H), 3.84 (d, 2H), 3.88 (s, 3H), 4.73 (d, 1H), 4.83 (d, 1H), 6.73 (d, 1H), 7.35 (s, 1H), 8.08 (s, 1H), 8.11 (d, 1H)
20		

Example of intermediates25 Example I 1

Preparation of 5-carbomethoxy-6-methyl-2-[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole.

30

To a solution of 5-carbomethoxy-6-methyl-2-mercapto-1H-benzimidazole (0.58 g, 2.6 mmol) in methanol (25 ml) aqueous NaOH (1.0 ml 5M, 5.0 mmol) and 4-cyclopropylmethoxy-3-methoxy-2-chloromethyl pyridine hydrochloride (prepared according to processes known per se.) (0.63 g, 2.4 mmol) dissolved in methanol (25 ml) were added in the given order. The mixture was refluxed for one hour whereupon the solution

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was evaporated. The residue was partitioned between methylene chloride and water. After separation the organic solution was dried over Na_2SO_4 and evaporated giving a yellow syrup (1.0 g, 100%).

5

NMR data are given below.

Example I 2

10 5-Acetyl-6-methyl-2-[[[3,4-ethylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

To a solution of 5-acetyl-6-methyl-2-mercapto-1H-benzimidazole (0.14 g, 0.66 mmol) in methanol (2 ml) aqueous NaOH (0.25 ml 5M, 1.25 mmol) and 3,4-ethylenedioxy-2-chloromethyl pyridine hydrochloride (0.13 g, 0.60 mmol) dissolved in methanol (2 ml) were added in the given order. The mixture was refluxed for one hour whereupon the solution was evaporated. The residue was partitioned between methylene chloride and water. After separation the organic solution was dried over Na_2SO_4 and evaporated giving a yellow syrup (0.17 g, 81%).

25 NMR data are given below.

Example I 3

Preparation of 5-carbomethoxy-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-Carbomethoxy-6-methyl-2-mercapto-1H-benzimidazole (0.67 g, 0.003 mol) and NaOH (0.12 g, 0.003 mol) in H_2O (0.6 ml) were dissolved in CH_3OH (15 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride, (≈ 0.0036 mol) as a crude material in CH_3OH (10 ml) and NaOH (0.144 g, 0.0036 mol) in H_2O (0.72 ml) were added. The mixture was heated to reflux

35

and the reflux was continued for 1 hour. CH₃OH was evaporated off and the crude material was purified by chromatography on a silica column using CH₂Cl₂-CH₃OH (98-2) as eluent, giving (1.03 g, 92%) of the pure title compound.

5 NMR data are given below.

Example I 4

10 Preparation of 5-acetyl-6-methyl-2-[[~~(3,4-dimethoxy-2-~~
pyridinyl)methyl]thio]-1H-benzimidazole

5-Acetyl-6-methyl-2-mercapto-1H-benzimidazole (4.2 g, 20 mmol) and NaOH (0.8 g, 20 mmol) in H₂O (1 ml) were dissolved in 60 ml ethanol. 3,4-dimethoxy-2-chloromethylpyridine
15 hydrochloride (=17 mmol) as a crude material was added and the mixture was heated to boiling. NaOH (0.7 g, 17 mmol) in H₂O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase
20 was dried over Na₂SO₄ and the solvent was removed under reduced pressure. Crystallizing from acetonitrile gave the title compound, (3.75 g, 62%).

NMR data are given below.

25 Example I 5

Preparation of 5-carbethoxy-2-[[~~(3,4-dimethoxy-2-~~
pyridinyl)methyl]thio]-1H-benzimidazole

30 5-Carbethoxy-2-mercapto-1H-benzimidazole (2.0 g, 9 mmol) and NaOH (0.36 g, 9 mmol) in H₂O (1 ml) were dissolved in ethanol (30 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (=6.6 mmol) as a crude material were added and the mixture was heated to boiling. NaOH (0.26 g, 6.6 mmol)
35 in H₂O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase

2083606

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was dried over Na_2SO_4 and the solvent removed under reduced pressure. Crystallizing from CH_3CN gave the desired product (1.75 g, 71%).

NMR data are given below.

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Example I 6

Preparation of 5-acetyl-6-methyl-2-[[(3,4-propylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

10

The compound was prepared from 5-acetyl-2-mercapto-6-methyl-1H-benzimidazole and 2-chloromethyl-3,4-propylenedioxy-pyridine on a 0.01 mmol scale according to standard procedures.

15 NMR data are given below.

Example I 7

Preparation of 5-acetyl-6-methyl-2-[[(3,4-methylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

20

2-Chloromethyl-3,4-methylenedioxy-pyridine (90 mg, 0.52 mmol) and 5-acetyl-6-methyl-2-mercaptobenzimidazole (214 mg, 1.04 mmol) were dissolved in ethanol (15 ml). The pH value of the solution was adjusted to 9 (0.2M NaOH) whereupon the solution was refluxed for 10 min. After concentration of the reaction mixture at reduced pressure the residue was taken up in methylene chloride (10 ml) and brine (2 ml). The phases were separated and the organic phase was dried over sodium sulphate, filtered and concentrated at reduced pressure. The residue was chromatographed on silica (ethyl acetate). Yield: 140 mg (79%) of the title compound. Mp: 141-143°C (uncorr.)

25

30

NMR data are given below.

35

Example I 8

Preparation of 5-acetyl-6-methyl-2-[[~~(3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)methyl~~]-thio]-1H-
5 benzimidazole

A solution of 2-(hydroxymethyl)-3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine (0.34 g, 1.3 mmol) in 10 ml CH_2Cl_2 was cooled to 0°C and treated with SOCl_2 (0.12 ml, 1.7 mmol). The solution was allowed to warm to room temperature and reacted for 1 h. Evaporation of the solvent furnished a quantitative yield of the corresponding chloromethyl derivative as the hydrochloride. DI-MS, m/z (%): 289 and 287 (11 and 38). A suspension of 5-acetyl-2-
15 mercapto-6-methyl-1H-benzimidazole (0.29 g, 1.4 mmol) in 10 ml MeOH was treated with a solution of NaOH (0.10 g, 2.6 mmol) in 1.5 ml H_2O . The formed solution was treated with the prepared chloromethyl compound and reacted for 21 h at room temperature. The solvent was evaporated and the residue
20 taken up in 20 ml 2.5% NaOH. The aqueous layer was extracted with 50 + 25 ml CH_2Cl_2 , the organic layers combined, dried over MgSO_4 , and evaporated leaving 0.49 g (82%) title compound as a tanned foam.
NMR data are given below.

25

Example I 9

Preparation of 5-acetyl-6-methyl-2-[[~~(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl~~]-thio]-1H-benzimidazole

30

2-Chloromethyl-4-cyclopropylmethoxy-3-methoxypyridine (50 mg, 0.22 mmol) and 5-acetyl-6-methyl-2-mercaptobenzimidazole (50 mg, 0.24 mmol) were dissolved in ethanol (15 ml). The pH value of the solution was adjusted to 9 (0.2M NaOH)
35 whereupon the solution was refluxed for 10 min. After concentration of the reaction mixture at reduced pressure the residue was taken up in methylene chloride (10 ml) and

2083606

22

brine (2 ml). The phases were separated and the organic phase was dried over sodium sulphate, filtered and concentrated at reduced pressure. The residue was chromatographed on silica (ethyl acetate). Yield: 40 mg (46%) of the title compound. NMR data are given below.

Example I 10

10 Preparation of 4-chloro-3-hydroxyethoxy-2-methylpyridine

A solution of 4-chloro-3-methoxyethoxy-2-methylpyridine (2.78 g, 0.014 mol) in dry CDCl_3 (≈ 14 ml) under Ar was treated with TMSI (5.10 ml, 0.036 mol) for 23 h at room temperature. The reaction mixture was partitioned between 100 ml CH_2Cl_2 and 100 ml 1M HCl. The aqueous layer was collected, washed once more with 50 ml CH_2Cl_2 , and then treated with Na_2CO_3 until the pH was ≈ 10 . The aqueous layer was extracted with 100 + 50 ml CH_2Cl_2 . The two latter organic layers were combined, dried over MgSO_4 and evaporated leaving 2.31 g enriched product.

Chromatography (silica gel, diethyl ether followed by diethyl ether/MeOH;95/5) afforded 1.06 g (40%) pure product. NMR data are given below.

Example I 11

Preparation of 3,4-ethylenedioxy-2-methylpyridine

30

A mixture of 4-chloro-3-hydroxyethoxy-2-methylpyridine (1.03g, 0.0055 mol) and NaH (55% in oil, 599 mg, 0.0138 mol) in 600 ml THF was refluxed for 15 h. Excess NaH was destroyed with 3 ml of H_2O . The solvent was evaporated and the residue partitioned between 100 ml 1M HCl and 100 ml CH_2Cl_2 . The aqueous layer was collected, washed once more with 100 ml CH_2Cl_2 and then treated with Na_2CO_3 until the pH

was ≈ 10 . The aqueous layer was extracted with 150 + 100 ml CH_2Cl_2 . The two latter organic layers were combined, dried over MgSO_4 , and evaporated leaving 720 mg enriched product. Chromatography (silica gel, diethyl ether) furnished 0.49 g
5 (59%) pure product.

NMR data are given below.

Example I 12

10 Preparation of 3,4-ethylenedioxy-2-hydroxymethyl-pyridine

The title compound was prepared on a 3.2 mmol scale according to standard procedures yielding 395 mg (77%) pure product.

15

NMR data for the intermediate are given below.

Example I 13

20 Preparation of 3-(3-hydroxy-1-propoxy)-2-methyl-4-pyrone

A suspension of 3-hydroxy-2-methyl-4-pyrone (25 g, 200 mmol), 3-bromo-1-propanol (70 g, 500 mmol) and K_2CO_3 (111 g 800 mmol) in 600 ml acetone was stirred for three days. The
25 solvent was evaporated and the residue partitioned between 300 ml methylene chloride and 500 ml 2.5% NaOH. The aqueous layer was separated and extracted with 2x300 ml methylene chloride. The organic phases were combined, dried over Na_2SO_4 and evaporated at 50°C. Eight grams of the residue
30 (24 g) was chromatographed on silica gel with methanol/methylene chloride (5:95) as eluent which afforded 2.7 g (22%) of the desired product as an oil.

NMR data are given below.

35 Example I 14

Preparation of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyrone

2083606

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A mixture of 3-(3-hydroxy-1-propoxy)-2-methyl-4-pyrone (1.4 g, 7.6 mmol), 85% KOH (0.55 g, 8.4 mmol) and methyl iodide (11 g, 76 mmol) was stirred at room temperature for one day. The red solution was partitioned between methylene chloride and half saturated aqueous ammonium chloride solution. The organic phase was washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel with methanol/methylene chloride (3:97) as eluent. Removing the eluent by film evaporation afforded 0.31 g (20%) of the desired product as an oil. NMR data are given below.

Example I 15

15

Preparation of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyridone

A solution of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyrone (0.31 g, 1.7 mmol) in 50 ml concentrated aqueous NH_3 was heated to 120°C for 2 h in an autoclave. The reaction mixture was transferred to a round bottomed flask and evaporation off the solvent afforded 0.32 g (100%) product as a yellow oil. NMR data are given below.

25

Example I 16

Preparation of 4-chloro-3-(3-methoxy-1-propoxy)-2-methyl-pyridine

30

A solution of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyridone (0.32 g, 1.6 mmol) in 50 ml POCl_3 was refluxed for 14 h. The POCl_3 was evaporated off and the residue was partitioned between methylene chloride and water. The aqueous layer was separated, treated with K_2CO_3 until pH=10 and extracted with methylene chloride. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by chromatography

on silica gel with methanol/methylene chloride (3:97) as eluent. Evaporation off the solvent afforded 0.12 g (34%) product as a red oil.

NMR data are given below.

5

Example I 17

Preparation of 4-chloro-3-(3-hydroxy-1-propoxy)-2-methylpyridine

10

To a solution of 4-chloro-3-(3-methoxy-1-propoxy)-2-methylpyridine (120 mg, 0.56 mmol) in 2 ml of CDCl_3 was added trimethylsilyl iodide (0.16 ml, 1.3 mmol), this was done in a NMR tube. The reaction was complete after four days as indicated by the absence of a signal for the OCH_3 protons at 3.3 ppm in the NMR spectrum. The solution was poured over 10 ml of 1 M HCl whereupon the mixture was stirred for 5 minutes with 10 ml of methylene chloride. The aqueous layer was separated, treated with K_2CO_3 until pH=10 and extracted with methylene chloride. The organic phase was dried over Na_2SO_4 and evaporated. This afforded 0.049 g (43%) of the desired product as a yellow oily film.

15

20

NMR data are given below.

25

Example I 18

Preparation of 2-methyl-3,4-propylenedioxy-pyridine

A solution of 4-chloro-3-(3-hydroxy-1-propoxy)-2-methylpyridine (49 mg, 0.24 mmol) in 3 ml of DMSO was heated for 2 h at 70°C with 55% NaH (32 mg, 0.73 mmol). The mixture was cooled, diluted with water and extracted with methylene chloride. The organic solution was evaporated and the residue was chromatographed on silica gel with methylene chloride as eluent. The solvent was evaporated which afforded 22 mg (55%) of a yellow oil.

30

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NMR data are given below.

2083606

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Example I 19**Preparation of 2-hydroxymethyl-3,4-propylene-dioxypyridine**

5

The title compound was prepared from 2-methyl-3,4-propylenedioxypyridine on a 0.01 mmol scale according to standard procedures yielding 3 mg (11%) product.

NMR data are given below.

10

Example I 20**Preparation of 2-chloromethyl-3,4-propylene-dioxypyridine**

15 The title compound was prepared from 2-hydroxymethyl-3,4-propylenedioxypyridine in a quantitative yield on a 0.01 mmol scale according to standard procedures. The compound was used in the synthesis without purification and characterisation.

20

Example I 21**Preparation of 2-methyl-3,4-methylenedioxypyridine**

25 2-Methyl-3-hydroxy-4-pyridone (1.25 g, 10 mmol) was dissolved in dry DMSO (20 ml). Dibromomethane (3.5 g, 20 mmol) was added followed by sodium hydride (1 g, >20 mmol, 50-60% in oil). The mixture was left at ambient temperature under stirring for 3 days whereupon it was poured into brine
30 (50 ml). The water-DMSO solution was extracted with methylene chloride (3x50 ml) and the collected extracts were used directly in the next step. A sample for NMR analysis was withdrawn.

35 NMR data are given below.

Example I 22**Preparation of 2-methyl-3,4-methylenedioxyppyridine-N-oxide**

5 To the methylene chloride solution of 2-methyl-3,4-methylenedioxyppyridine from example I 21 sodium hydrogen carbonate (1M, 50 ml) and MCPBA (4 g, 70%) were added. The mixture was stirred at ambient temperature for 15 min whereupon the excess of MCPBA was destroyed with addition of
10 sodium thiosulphate (1 g). The organic phase was separated and the aqueous phase was extracted with methylene chloride (3x50 ml). The collected organic phases were concentrated under reduced pressure and chromatographed on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 90:10). Yield: 120 mg (7,8%) of the title
15 compound.

NMR data are given below.

Example I 23**20 Preparation of 2-hydroxymethyl-3,4-methylenedioxyppyridine**

2-Methyl-3,4-methylenedioxyppyridine-N-oxide (120 mg, 0.78 mmol) was dissolved in acetic anhydride (10 ml) and the solution was heated at 110 °C for 15 min, whereupon the
25 mixture was concentrated under reduced pressure. The residue was dissolved in methanol (20 ml) and sodium hydroxide (3 drops, 6M) was added. After 30 min at ambient temperature the mixture was neutralised with acetic acid (pH 6) and concentrated under reduced pressure. The residue was
30 chromatographed on silica (hexane/ethyl acetate, 1:1). Yield: 90 mg (75%) of the title compound.

NMR data are given below.

35 Example I 24**Preparation of 2-chloromethyl-3,4-methylenedioxyppyridine**

2083606

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2-Hydroxymethyl-3,4-methylenedioxy pyridine (90 mg, 0.59 mmol) was dissolved in methylene chloride (10 ml) and thionyl chloride (240 mg, 2 mmol) was added. After 10 min at ambient temperature the mixture was hydrolysed with sodium hydrogen carbonate and the phases were separated. The organic phase was dried over sodium sulphate, filtered and concentrated under reduced pressure. Yield: 90 mg (88%) of the title compound (crude).

10

NMR data are given below.

Example I 25

15 Preparation of 3-methoxy-2-methyl-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine-N-oxide

A deareated solution of 5-(hydroxymethyl)-5-methyl-1,3-dioxane (1.19 g, 9 mmol) in 125 ml dry THF was treated with NaH (0.79 g 55% dispersion in oil, 18 mmol) for 20 min. 4-Chloro-3-methoxy-2-methylpyridine-N-oxide (1.04 g, 6 mmol) was added and the mixture was refluxed for 26 h. Excess NaH was quenched with 10 ml of H₂O and the solvent evaporated. The residue was partitioned between 150 ml CH₂Cl₂ and 50 ml 5% Na₂CO₃. The organic layer was passed through a phase separation paper and evaporated leaving 1.83 g enriched product. Chromatography (SiO₂CH₂Cl₂/MeOH, 95/5) afforded 0.39 g (24%) pure title compound as a tanned oil.

30 NMR data are given below.

Example I 26

35 Preparation of 2-(hydroxymethyl)-3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine

2083606

A solution of 3-methoxy-2-methyl-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine-N-oxide (0.39 g, 1.5 mmol) in 4.5 ml (CH₃CO)₂O was heated to 100°C for 4 h. Excess (CH₃CO)₂O was azeotroped off 4 times with 75 ml portions of abs. EtOH leaving 0.42 g (90%) crude 3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)-methyl acetate.

The crude acetate was treated with 20 ml 2M NaOH for 1 h at 100 °C. The aqueous layer was extracted with 75 + 50 + 25 ml CH₂Cl₂. The organic layers were combined, dried over MgSO₄, and evaporated leaving 0.34 g (97%) product pure enough for further use.

NMR data are given below.

Table 2

Ex	Solvent	NMR data δ ppm
20		
I 1	CDCl ₃ (300 MHz)	0.37-0.42 (m, 2H), 0.67-0.73 (m, 2H), 1.25-1.40 (m, 1H) 2.69 (s, 3H), 3.90 (s, 3H), 3.94 (d, 2H), 3.98 (s, 3H), 4.40 (s, 2H)
25		6.81 (d, 1H), 7.3 (b, 1H), 8.2 (b, 1H), 8.22 (d, 1H),
I 2	CDCl ₃ (500 MHz)	2.64 (s, 3H), 2.66 (s, 3H), 4.35 (s, 2H), 4.40 (s, 4H), 6.85 (d, 1H), 7.30 (s, 1H), 8.06 (d, 1H), 8.08 (s, 1H).
30		
I 3	CDCl ₃ (300 MHz)	2.70 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 4.40 (s, 2H), 6.90 (d, 1H), 7.35 (s, 1H), 8.20 (s, 1H), 8.25 (d, 1H)
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2083606

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5	I 4	CDCl ₃ (300 MHz)	2.60 (s, 3H), 2.65 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.35 (s, 2H), 6.85 (d, 1H), 7.25 (s, 0.6H), 7.40 (s, 0.4H), 7.85 (s, 0.4H), 8.05 (s, 0.6H), 8.30 (m, 1H)
10	I 5	CDCl ₃ (300 MHz)	1.40 (m, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.40 (m, 4H), 6.90 (dd, 1H), 7.45 (d, 0.4H), 7.60 (d, 0.6H), 7.90 (m, 1H), 8.20 (s, 0.6H), 8.25 (m, 1H), 8.25 (s, 0.4H)
15	I 6	CDCl ₃ (500 MHz)	2.32 (p, 2H), 2.64 (s, 3H), 2.66 (s, 3H), 4.37-4.43 (m, 4H), 4.39 (s, 2H), 6.88-6.90 (m, 1H), 7.29 (s, 0.6H), 7.42 (s, 0.4H), 7.85 (s, 0.4H), 8.07 (s, 0.6H), 8.11 (m, 1H)
20	I 7	CDCl ₃ (300 MHz)	2.648 (s, 3H), 2.652 (s, 3H), 4.32 (s, 2H), 6.14 (s, 2H), 6.85 (d, 1H), 7.34 (br. 1H), 8.00 (br. 1H), 8.20 (d, 1H)
30	I 8	CDCl ₃ (300 MHz)	0.98 (s, 3H), 2.65 (coinciding s, 6H), 3.53 (d, 2H), 3.95 (s, 3H), 4.00 (d, 2H), 4.25 (s, 2H), 4.39 (s, 2H), 4.69 (m, 1H), 5.06 (m, 1H), 6.9-7.0 (2 d, 1H), 7.3-7.5 (several b, 1H), 7.8-8.1 (several b, 1H), 8.2-8.3 (2 d, 1H), 13.2 (b, 1H)
35	I 9	CDCl ₃ (300 MHz)	0.38 (m, 2H), 0.69 (m, 2H), 1.31 (m, 1H), 2.63 (s, 3H), 2.636 (s, 3H), 3.93 (d, 2H), 3.98 (s, 3H),

			4.40 (s, 2H), 6.81 (d, 1H), 7.33 (s, 1H), 7.98 (s, 1H), 8.22 (d, 1H)
5	I 10	CDCl ₃ (500 MHz)	2.57 (s, 3H), 2.70 (t, 1H) 3.99 (dt, 2H), 4.09 (t, 2H), 7.19 (d, 1H), 8.16 (d, 1H)
10	I 11	CDCl ₃ (500 MHz)	2.41 (s, 3H), 4.30 (s, 4H), 6.65 (d, 1H), 7.90 (d, 1H),
	I 12	CDCl ₃ (500 MHz)	4.11 (b, 1H), 4.33 (m, 4H), 4.69 (b, 2H), 6.76 (d, 1H), 7.99 (d, 1H)
15	I 13	CDCl ₃ (300 MHz)	1.85 (p, 2H), 2.30 (s, 3H), 3.85 (q, 2H), 4.00 (t, 2H), 4.35 (t, 1H), 6.35 (d, 1H), 7.65 (d, 1H)
20	I 14	CDCl ₃ (300 MHz)	2.00 (p, 2H), 2.32 (s, 3H), 3.35 (s, 3H), 3.56 (t, 2H), 4.13 (t, 2H), 6.33 (d, 1H), 7.59 (d, 1H)
25	I 15	CDCl ₃ (300 MHz)	1.98 (p, 2H), 2.45 (s, 3H), 3.38 (s, 3H), 3.61 (t, 2H), 4.08 (t, 2H), 6.53 (d, 1H), 7.63 (d, 1H)
30	I 16	CDCl ₃ (300 MHz)	2.09 (p, 2H), 2.54 (s, 3H), 3.38 (s, 3H), 3.63 (t, 2H), 4.04 (t, 2H), 7.16 (d, 1H), 8.13 (d, 1H)
	I 17	CDCl ₃ (500 MHz)	2.10 (p, 2H), 2.56 (s, 3H), 3.96 (t, 2H), 4.10 (t, 2H), 7.18 (d, 1H), 8.15 (d, 1H)
35	I 18	CDCl ₃ (300 MHz)	2.25 (p, 2H), 2.45 (s, 3H), 4.28 (t, 2H), 4.34 (t, 2H), 6.70 (d, 1H), 7.96 (d, 1H)

2083606

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	I 19	CDCl ₃ (500 MHz)	2.27 (p, 2H), 4.30 (t, 2H), 4.37 (t, 2H), 4.71 (d, 2H), 6.80 (d, 2H), 8.05 (d, 1H)
5			
	I 21	CDCl ₃ (500 MHz)	2.34 (s, 3H), 5.92 (s, 2H), 6.61 (d, 1H), 7.93 (d, 1H)
	I 22	CDCl ₃ (500 MHz)	2.42 (s, 3H), 6.12 (s, 2H), 6.59 (d, 1H), 7.90 (d, 1H)
10			
	I 23	CDCl ₃ (300 MHz)	4.73 (s, 2H), 6.05 (s, 2H), 6.76 (d, 1H), 8.09 (d, 1H)
	I 24	CDCl ₃ (300 MHz)	4.65 (s, 2H), 6.10 (s, 2H), 6.78 (d, 1H), 8.13 (d, 1H)
15			
	I 25	CDCl ₃ (300 MHz)	0.97 (s, 3H), 2.50 (s, 3H), 3.52 (d, 2H), 3.85 (s, 3H), 3.98 (d, 2H), 4.18 (s, 2H), 4.67 (d, 1H), 5.02 (d, 1H), 6.77 (d, 1H), 8.08 (d, 1H)
20			
	I 26	CDCl ₃ (300 MHz)	0.98 (s, 3H), 3.52 (d, 2H), 3.86 (s, 3H), 4.00 (d, 2H), 4.09 (m, 1H), 4.20 (s, 2H), 4.68 (d, 1H), 4.75 (d, 2H), 5.02 (d, 1H), 6.88 (d, 1H), 8.20 (d, 1H)
25			

30 The best mode of carrying out the invention known at present is to use the compound according to Example 4 or its salt according to Example 9.

Table 3

Examples of compounds included in the formula I are given in the following table

Ex.	R ¹	R ²	R ³	R ⁴	Yield%	Ident.data
1	C(O)-OCH ₃	CH ₃	CH ₃	CH ₂	44	NMR
2	C(O)CH ₃	CH ₃	-CH ₂ CH ₂ -		30	NMR
3.	C(O)-OCH ₃	CH ₃	CH ₃	CH ₃	70	NMR
4.	C(O)CH ₃	CH ₃	CH ₃	CH ₃	60	NMR
5.	C(O)OCH ₂ CH ₃	H	CH ₃	CH ₃	54	NMR
6.	C(O)CH ₃	CH ₃	-CH ₂ CH ₂ CH ₂ -			NMR
7.	C(O)CH ₃	CH ₃	-CH ₂ -		61	NMR
8.	C(O)CH ₃	CH ₃	CH ₃	CH ₂	44	NMR
9.	C(O)CH ₃	CH ₃	CH ₃	CH ₃	sodium salt	NMR
10.	C(O)CH ₃	CH ₃	CH ₃	CH ₂	73	NMR

2083606

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

5		
	Compound according to Example 4	1.0 g
	Sugar, powder	30.0 g
	Saccharine	0.6 g
	Glycerol	15.0 g
10	Flavouring agent	0.05 g
	Ethanol 96%	5.0 g
	Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water.

15 After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

20 Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

	I	Compound according to Example 4	500 g
25		as Mg salt	
		Lactose	700 g
		Methyl cellulose	6 g
		Polyvinylpyrrolidone cross-linked	50 g
		Magnesium stearate15 g Sodium carbonate	6 g
30		Distilled water	q.s.
	II	Cellulose acetate phthalate	200 g
		Cetyl alcohol	15 g
		Isopropanol	2000 g
35		Methylene chloride	2000 g

I Compound according to example 1, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After
5 drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tableting machine using 7 mm diameter punches.

10

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota[®], Manesty coating equipment. A final tablet weight of 110 mg was obtained.

15

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the
20 following ingredients:

Compound according to Example 9	4 g
Sterile water to a final volume of	1000 ml

25 The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

30 Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

35 Compound according to Example 4	300 g
Lactose	700 g
Microcrystalline cellulose	40 g

36

Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

- 5 The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.
- 10 500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

15 Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
20 Ethanol	600 g

The final coated pellets were filled into capsules.

Suppositories

25

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

- 30 Compound according to Example 4 4 g
WitepsolTM H-15 180 g

- The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41°C. The molten mass was volume
35 filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat

sealed. Each suppository contained 40 mg of active compound.

5 Biological Effects

Bioavailability

Bioavailability is assessed by calculating the quotient between the area under plasma concentration (AUC) curve following intraduodenal (id) administration and intravenous (iv) administration from the rat.

Potency for inhibition of acid secretion

15 The potency for inhibition of acid secretion is measured in the dog, intravenously (iv) and in the female rat, intravenously (iv).

Effects on the uptake of iodine into the thyroid gland

20

The effect of a compound within the invention of the formula I on the uptake of iodine into the thyroid gland is measured as an effect on the accumulation of ^{125}I in the thyroid gland.

25

Biological tests

Inhibition of Gastric Acid Secretion in the Conscious Female Rat.

30

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen) for collection of gastric secretions. A fourteen days recovery period after surgery is allowed before testing is commenced.

35

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through

2083606

the gastric cannula, and 6 ml of Ringer-Glucose given s.c. Acid secretion is stimulated with infusion during 3.5 h (1.2 ml/h, s.c.) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric

5 secretions are collected in 30-min fractions. Test substances or vehicle are given iv at 90 min after starting the stimulation, in a volume of 1 ml/kg. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 mol/L, and acid output is calculated as the product of titrant volume

10 and concentration. Further calculations are based on group mean responses from 4-7 rats. The acid output during the periods after administration of test substances or vehicle are expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0.

15 Percentage inhibition is calculated from the fractional responses elicited by test compound and vehicle. ED₅₀-values are obtained from graphical interpolation on log dose-response curves, or estimated from single-dose experiments assuming a similar slope for all dose-response curves. The

20 results are based on gastric acid secretion during the second hour after drug/vehicle administration.

Bioavailability in the Male Rat.

25 Male adult rats of the Sprague-Dawley strain were used. One day, prior to the experiments, all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for the intravenous experiments, were also cannulated in the jugular vein. (Ref. V Popovic and P

30 Popovic, J Appl Physiol 1960;15,727-728). The rats used for the intraduodenal experiments, were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck. The rats were housed individually after surgery and were deprived of food, but not water,

35 before administration of the test substances. The same dose (4 µmol/kg) were given iv and id as a bolus for about one minute (2 ml/kg).

Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen as soon as possible until
5 analysis of the test compound.

The area under the blood concentration vs time curve, AUC, was determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined
10 blood concentration by the elimination rate constant in the terminal phase.

The systemic bioavailability (F%) following intraduodenal administration was calculated as

15

$$F(\%) = \frac{AUC_{id}}{AUC_{iv}} \times 100$$

20 Inhibition of Gastric Acid Secretion in the Conscious Dog.

Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a Heidenhain-pouch for the
25 collection of gastric secretions.

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated by a 4 h infusion of histamine dihydrochloride
30 (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle was given iv 1 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. The acidity of the gastric
35 juice samples were determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or

2083606

40

vehicle were expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition was calculated from fractional responses elicited by test compound and vehicle. ED_{50} -
5 values were obtained by graphical interpolation on log dose - response curves, or estimated from single-dose experiments under the assumption of the same slope of the dose-response curve for all test compounds. All results reported are based on acid output 2 h after dosing.

10

Effect on the accumulation of ^{125}I in the thyroid gland

The accumulation of ^{125}I in the thyroid gland was studied in male, Sprague-Dawley rats which were deprived of food for 24
15 hours before the test. The experimental protocol of Searle, CE et al. (Biochem J 1950, 47:77-81) was followed.

Test substances suspended in 0.5% buffered (pH 9) methocel, were administered by oral gavage in a volume of 5 ml/kg body
20 weight. After 1 hour, ^{125}I (300 kBq/kg, 3 ml/kg) was administered by intraperitoneal injection. Four hours after ^{125}I -administration, the animals were killed by CO_2 -asphyxiation and bled. The thyroid gland together with a
25 piece of the trachea was dissected out and placed in a small test tube for the assay of radioactivity in a gamma counter (LKB-Wallac model 1282 Compugamma). Percentage inhibition was calculated according to the formula $100 (1-T/P)$, where T and P is the mean radioactivity of thyroid glands from animals treated with test agent and placebo (buffered
30 methocel), respectively. The statistical significance for a difference between test agent- and placebo-treated animals was assessed with the Mann-Whitney U-test (two-tailed). $P < 0.05$ was accepted as significant.

35 Chemical Stability

The chemical stability of a compound of the invention is followed kinetically at low concentration at 37°C in aqueous buffer solution at different pH values. The results in Table 4 show the half life ($t_{1/2}$) at pH 7, that is the time period after which half the amount of the original compound remains unchanged.

Results of biological and stability tests

- 10 Table 4 gives a summary of the test data available for the compounds of the invention.

2083606

Table 4, Biological Test Data and Stability Data

Test compound Example No.	Inhibition of acid secretion iv administration ED ₅₀ µmol/kg	Bioavailability F%, Rat	Per cent inhibition of 400 µmol/kg on the uptake of ¹²⁵ I in the thyroid gland	Chemical stability pH 7 half-life (t 1/2) min
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	Dog	Rat
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2		a)
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42

3	0.5	
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0

480

4	0.74	0.9
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> 100

-7

470

5		
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-6

270

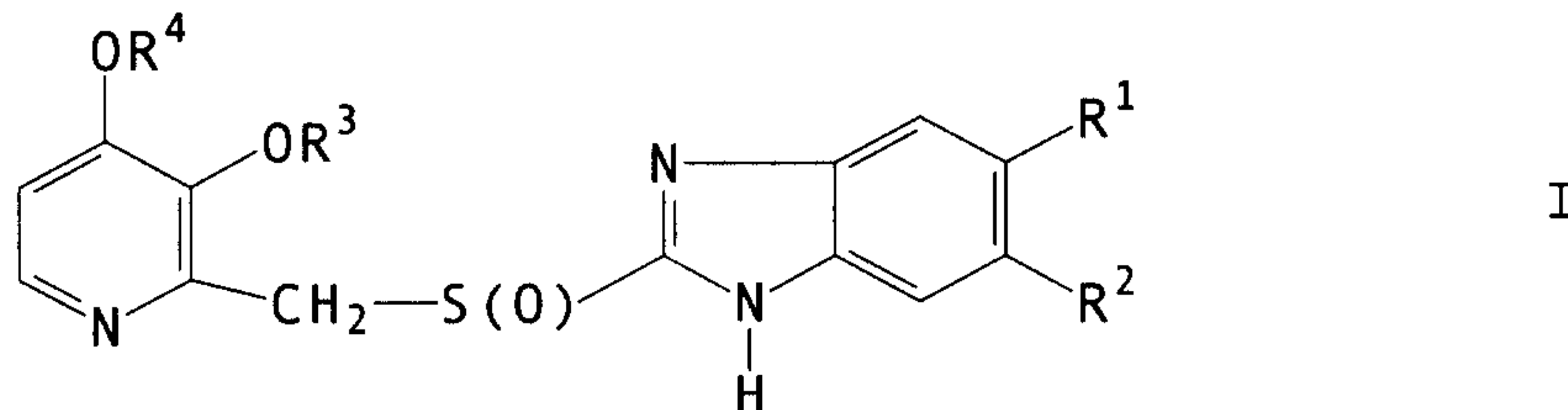
a) 1 µmol/kg gave 14% inhibition

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CLAIMS:

1. A compound of the formula I



and physiologically acceptable salts thereof wherein R^1 is $-C(O)OCH_3$ and R^2 is CH_3 and R^3 and R^4 are each $-CH_3$.

2. The sodium salt of the compound according to claim 1.

3. The magnesium salt of the compound according to claim

10 1.

4. A pharmaceutical composition comprising a compound or a salt according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier or diluent.

5. The pharmaceutical composition according to claim 4
15 for use in inhibiting gastric acid secretion in a mammal.

6. The pharmaceutical composition according to claim 4 for use in the treatment of gastrointestinal inflammatory diseases in a mammal.

7. The compound as defined in any one of claims 1 to 3
20 for use in inhibiting gastric acid secretion in a mammal.

8. The compound as defined in any one of claims 1 to 3 for use in the treatment of gastrointestinal inflammatory diseases in a mammal.

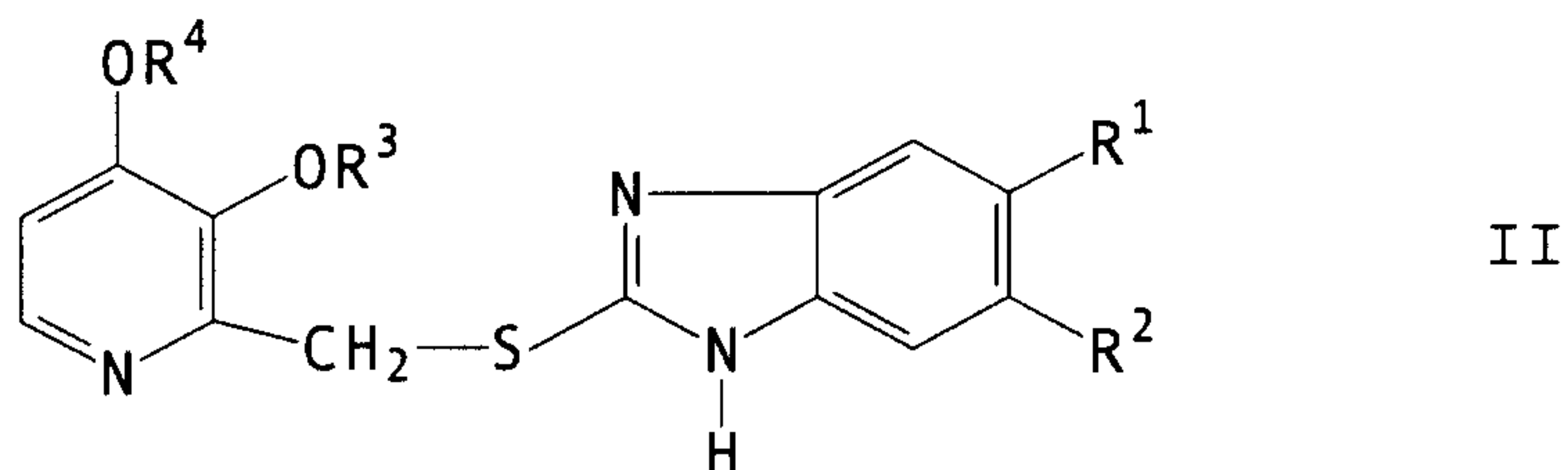
9. A use of a compound or a salt according to any one of
25 claims 1 to 3 for inhibiting gastric acid secretion in a mammal.

23940-746

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10. A use of a compound or a salt according to any one of claims 1 to 3 for treatment of gastrointestinal inflammatory diseases in a mammal.

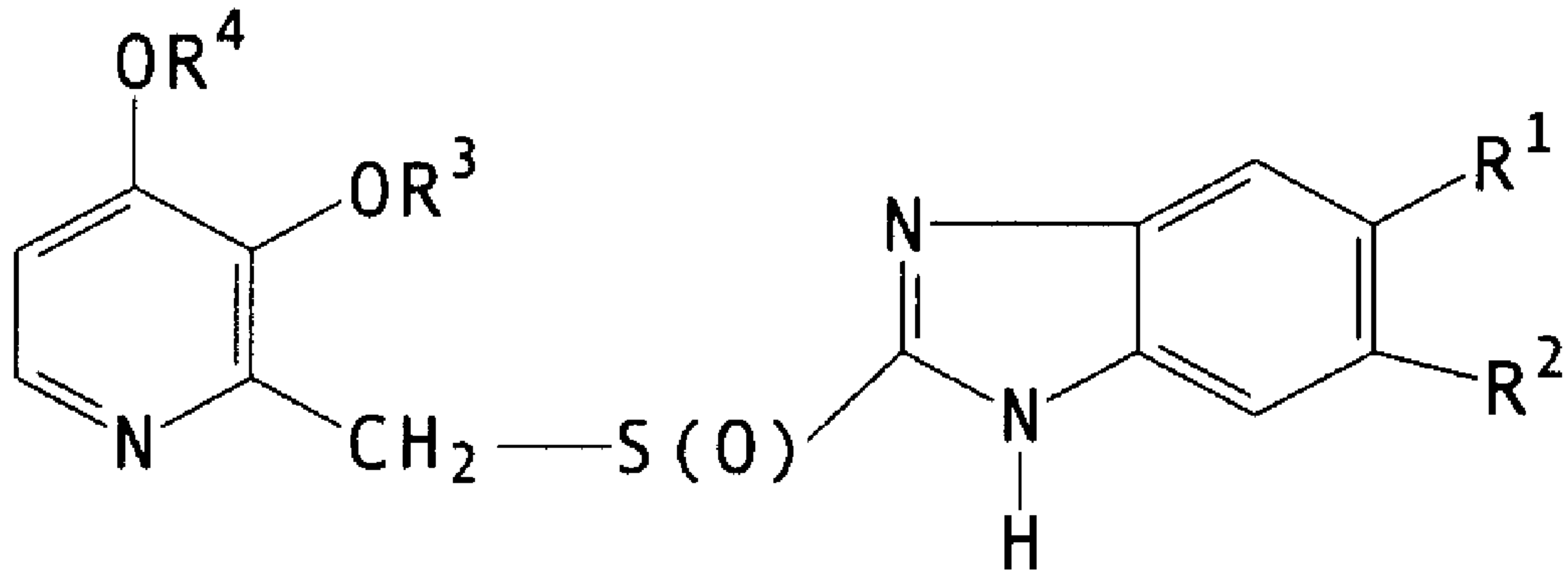
11. A process for the preparation of the compound of the formula I according to claim 1, by oxidizing a compound of the formula II,



10 wherein R^1 , R^2 , R^3 and R^4 are as defined under formula I.

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PATENT AGENTS



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