NOVEL SUBSTITUTED BENZIMIDAZOLES

27 May 1994

Field of the invention

The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

Background of the invention

The compound 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, and therapeutically acceptable salts thereof are described in US-A 5 008 278 corresponding to EP 90901079.5. This compound and its therapeutically acceptable salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile. The present invention provides such compounds, which are novel salts of single enantiomers of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as well as the novel single enantiomers of the neutral form of said compound.

The separation of the enantiomers of therapeutically active sulfoxides, such as substituted benzimidazoles, for example omeprazole (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole) in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19. The isolation of single enantiomers of the sulfoxide agent Ro 18-5364 is described in Euro. J. Biochem. 166 (1987) 453-459. Furthermore, separation of the enantiomers of omeprazole in a preparative scale is described in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, the active compound, omeprazole, is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values between 1-6, which would be devastating for the substance. Moreover, instantaneous

neutralization will create heat which will be difficult to handle in large scale production.

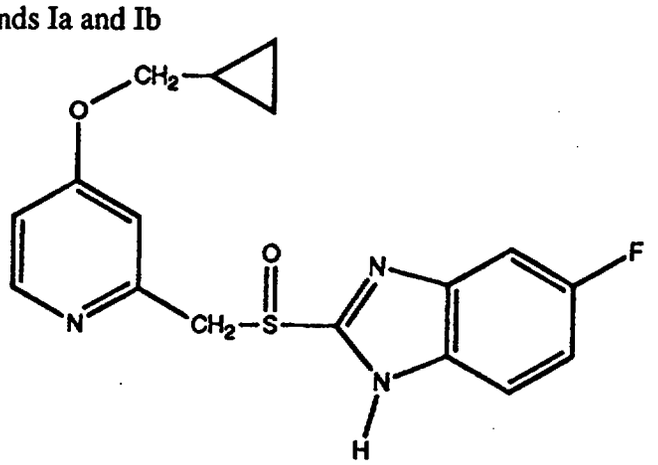
The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. Thus, this novel method can be used in large scale to obtain single enantiomers of the compound of the invention in neutral form, as well as in the form of the therapeutically active salts.

These novel compounds of the invention, being sulfoxides, could be expected to undergo racemization in neutral pH as well as basic pH. Surprisingly, the inventors now found that the novel single enantiomers of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as well as its therapeutically acceptable salts are stable towards racemization.

There is no example known in the prior art of any isolated or characterized single enantiomers of the compound of the invention. Furthermore, the inventors are not aware of any description in the scientific literature of any isolated salt of a single enantiomer of the claimed type.

Detailed description of the invention

The present invention refers to the new single enantiomers of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole according to compounds Ia and Ib



(Ia, Ib)

Ia (+)-enantiomer

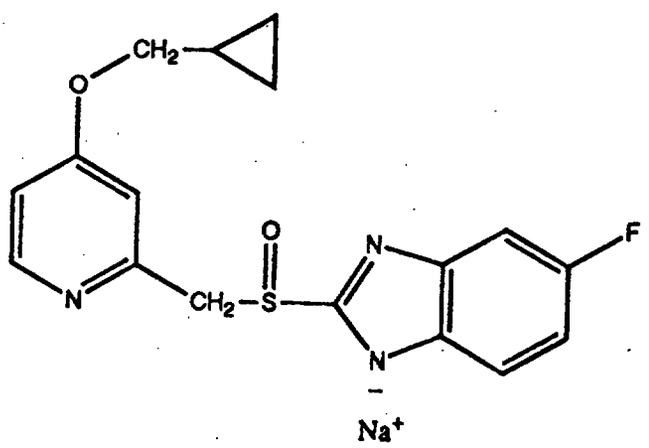
Ib (-)-enantiomer

as well as therapeutically acceptable salts therof. Such salts are for example the Na^+, Mg^{2+}, Ca^{2+}, Li^+, K^+ and $N^+(R)_4$ salts of the single enantiomers of said compound,

where R is an alkyl group with 1-4 carbon atoms, i.e. (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as well as Na^+, Mg^{2+}, Ca^{2+}, Li^+, K^+ and $N^+(R)_4$ salts of the single enantiomers, where R is an alkyl group with 1-4 carbon atoms.

Particularly preferred salts of the compound of the invention are the Na^+, Mg^{2+} and Ca^{2+} salts of the single enantiomers of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

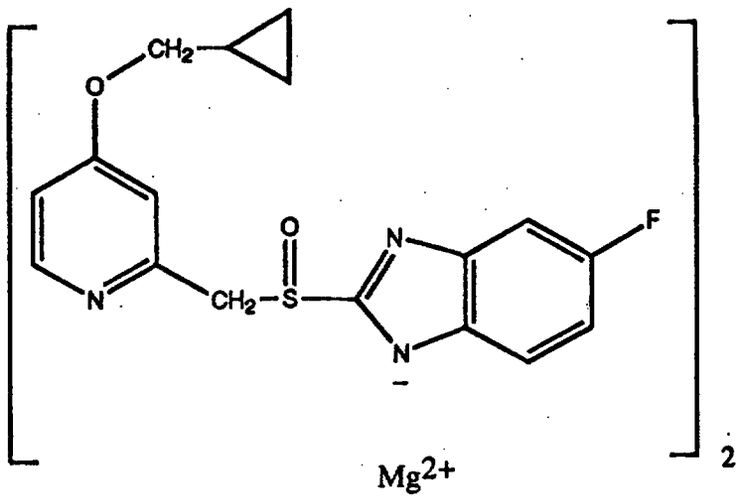
The most preferred compounds of the invention are the optically pure Na^+ salts of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole according to compounds IIa and IIb



(IIa, IIb)

IIa (+)-enantiomer
IIb (-)-enantiomer

and the optically pure magnesium salts of said compounds having the formulas IIIa and IIIb.



(IIIa, IIIb)

IIIa (+)-enantiomer

IIIb (-)-enantiomer

With the expression "optically pure compound of the invention" is meant the (+)-enantiomer of said compound essentially free from the corresponding (-)-enantiomer and the (-)-enantiomer essentially free from the corresponding (+)-enantiomer, respectively. Thus, every single compound of the invention is obtained in high optical purity. By means of the novel specific method according to one aspect of the invention of preparing the single enantiomers, the compounds of the invention are easy to obtain. Moreover, as mentioned above, the novel optically pure compounds are stable towards racemization in neutral pH as well as basic pH. The former was surprising since the mechanism of the degradation reactions at neutral pH of these kind of sulfoxides (omeprazole analogues) contains reversible reactions via achiral intermediates (see *e.g.* Brändström *et al.* Acta Chemica Scandinavica 43 (1989) 536). It is obvious that such reversible reactions from achiral intermediates back to a sulfoxide would cause a racemic product. Further, the novel optically pure compounds are stable towards racemization in basic pH, which was surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulphur atom was expected to cause racemization under alkaline conditions. This high stability towards racemization, both in neutral pH and basic pH, makes it possible to use a single enantiomeric compound of the invention in the neutral form as well as salts thereof in therapy.

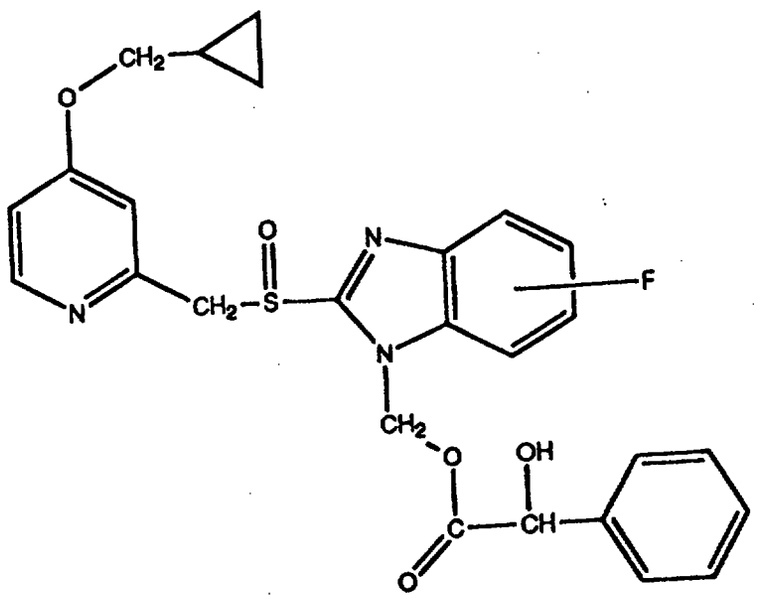
The specific method of preparation of the single enantiomers of the compound of the invention is a further aspect of the invention as mentioned above and it can be used to obtain the single enantiomeric compounds in the neutral form as well as the salts thereof.

The single enantiomeric compounds of the invention as well as the racemate show exceedingly high bioavailability, and still said compounds are very effective as inhibitors of gastric acid secretion and exhibit a high chemical stability in solution at a neutral pH.

Further, in aqueous solutions at neutral pH, the novel single enantiomers of the compounds of the invention in the neutral form as well as the sodium salts thereof have significantly lower solubility compared to the solubility of the racemate in the neutral form as well as the sodium salt thereof, respectively. This lower solubility in water is an important physicochemical property in that it potentially facilitates the manufacture of a well functioning enteric coated dosage form of the acid sensitive active compound.

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the single enantiomeric compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with accute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. Further, the compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may be also useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

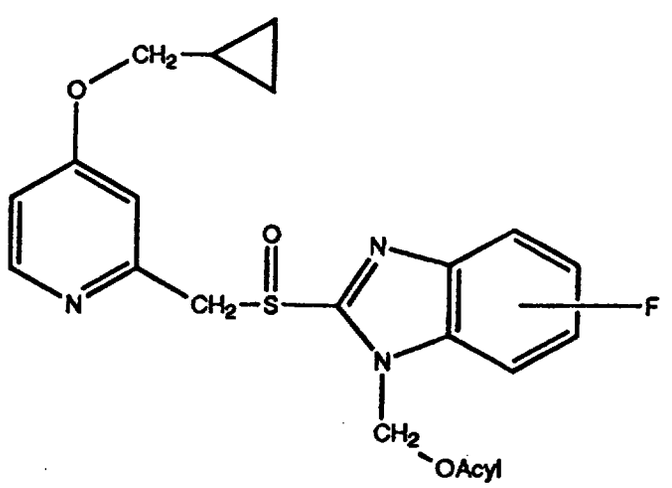
Yet a further aspect of the invention is the diasteromeric mixture of a regioisomeric mixture having the formula IV, which is an intermediate used in the specific method of preparation, wherein the fluoro substituent in the benzimidazole moiety is in position 5 or 6.



(IV)

Preparation

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the stereoisomers of a diastereomeric mixture of the regioisomeric mixture of the following type, 5- and 6-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-acyloxymethyl]-1H-benzimidazole, formula V



(V)

wherein the fluoro substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each

separated diastereomer in an alkaline solution. The formed single enantiomeric compounds of the invention in neutral form are then isolated by neutralizing aqueous solutions of the salts of said compounds with a neutralizing agent which can be an acid or an ester such as methyl formate.

The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

The diastereomeric esters can be separated either by chromatography or fractional crystallization.

The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water; or with a base in a mixture of acetonitrile and water, but the acyl group may also be hydrolysed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

To obtain the optically pure Na^+ salts of the invention, i.e. Na^+ salts of the single enantiomeric compound of the invention, the resulting compound in neutral form is treated with a base, such as NaOH, in an aqueous or nonaqueous medium, or with $NaOR^2$ wherein R^2 is an alkyl group containing 1-4 carbon atoms, or with $NaNH_2$. Also alkaline salts wherein the cation is Li^+ or K^+ may be prepared using lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the single enantiomers of the Na^+ salts, to the optically pure amorphous powder of the Na^+ salt are added a mixture of 2-butanone and toluene. The crystalline form of the single enantiomers of the Na^+ salt may also be prepared by adding NaOH to a mixture of the single enantiomeric compound of invention in neutral form and a non-aqueous medium, such as a mixture of 2-butanone and toluene.

To obtain the optically pure Mg^{2+} salts of the invention, the optically pure compound of the invention in the neutral form is treated with a base, such as $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomeric compound of the invention as a sodium salt with an aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. In an analogous way, also alkaline salts wherein the cation is Ca^{2+}

can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds IIa and IIb) and the magnesium salts (compound IIIa and IIIb), exemplified by their salts with Li^+, K^+, Ca^{2+} and $N^+(R)_4$, where R is an alkyl group with 1-4 C-atoms.

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the 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.

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the pure enantiomeric compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, 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 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 from acid catalysed 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 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 amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle 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 the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the 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 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 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, 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 dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a 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 vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconsituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound 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.

The invention is illustrated by the following examples.

Example 1. Preparation of (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (5.0 g, 9.8 mmol) were divided into five parts and each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The stereo isomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (67.5/32.5). However each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used directly in their solutions during the hydrolysis step. To the acetonitrile/aqueous solutions of the more lipophilic diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH_4Cl whereupon the solutions from each preparation were combined and extracted with methylene chloride. The organic phases were dried over Na_2SO_4 and the solvents were removed by film evaporation. Addition of 30 ml of acetonitrile afforded the product to crystallize and after filtration there was obtained 260 mg (16%) of the title compound as white crystals, m.p. 152°-154°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was 99.2%. $[\alpha]^{20}_D$= +208.6° (c=0.5%, chloroform).

NMR data are given below.

Example 2. Preparation of (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

To the acetonitrile/aqueous solutions of the less lipophilic diastereomer of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (obtained from the very same reversed phase chromatographic preparations described in Example 1) were added 1.0 M NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH_4Cl. The solutions from each preparation were combined and extracted with methylene

chloride. The organic phases were dried over Na_2SO_4 and the solvents were removed by film evaporation. Addition of 50 ml of acetonitrile afforded the product to crystallize and after filtration there was obtained 460 mg (28%) of the title compound as white crystals, m.p. 152°-154°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was 99.0%. $[\alpha]^{20}_D$= -208.7° (c=0.5%, chloroform).

NMR data are given below.

Example 3. Preparation of freeze-dried (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

To a methylene chloride solution (5 ml) of (-)-5-fluoro-2-[[(4-cyclopropyl-methoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (100 mg, 0.29 mmol) was added an aqueous solution of 0.2 M NaOH (1.4 ml, 0.28 mmol). The mixture was stirred for 30 minutes and then the layers were separated. The aqueous phase was freeze-dried which afforded 83 mg (78%) of the product as a white amorphous powder. $[\alpha]^{20}_D$= +47.2° (c=1.0%, water).

NMR data are given below

Example 4. Preparation of (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H -benzimidazole sodium salt in the crystalline form

Freeze-dried (+)-5-fluoro-2-[[(4-cyclopropyl-methoxy-2-pyridinyl)-methyl]sulfinyl]-1-H-benzimidazole sodium salt (61 mg) obtained in Example 3 was dissolved in 2-butanone (1 ml). Toluene (2 ml) was added slowly while stirring and white crystals were precipitated. The product was filtered off and washed with a small amount of diethyl ether. There was obtained 50 mg (82%) of the title compound as a crystalline product. m.p. (decomposition) 230°-240°C.

NMR data are given below

Example 5. Preparation of freeze-dried (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

To a methylene chloride solution (5 ml) of (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (100 mg, 0.29 mmol) was added an aqueous solution of 0.2 M NaOH (1.4 ml, 0.28 mmol). The mixture was stirred for 30 minutes and then the layers were separated. The aqueous phase was freeze-dried which afforded 89 mg (84%) of the product as a white amorphous powder. $[\alpha]^{20}_{D}$= -46.4° (c=1.0%, water).

NMR data are given below

Example 6. Preparation of (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H -benzimidazole sodium salt in the crystalline form

Freeze-dried (-)-5-fluoro-2-[[(4-cyclopropyl-methoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole sodium salt (75 mg) obtained in Example 5 was dissolved in 2-butanone (1 ml). Toluene (2 ml) was added slowly while stirring and white crystals were precipitated. The product was filtered off and washed with a small amount of diethyl ether. There was obtained 60 mg (82%) of the title compound as a crystalline product. m.p. (decomposition) 230°-240°C.

NMR data are given below

Example 7. Preparation of (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

Magnesium (7.1 mg, 0.29 mmol) was dissolved and reacted with methanol at 40°C with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after two hours. (+)-5-fluoro-2-[[(4-cyclo-propylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (200 mg, 0.58 mmol) was added after the magnesium methoxide solution had been chilled to room temperature. The mixture was stirred for two hours whereupon a small amount of water (0.05 ml) was added. After stirring another hour the small amount of inorganic salts were filtered off. The solution was concentrated on a rotavapor until two ml of the solution was left. While chilling and stirring, water was added dropwise which afforded the product to precipitate. After filtration the product was washed with a small amount of

water and then dried in vacuum. There was obtained 97 mg (47%) of the title compound as a white powder. $[\alpha]^{20}_{D}$= +191.3° (c=1.0%, DMSO).

Example 8. Preparation of (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

Magnesium (7.1 mg, 0.29 mmol) was dissolved and reacted with methanol at 40°C with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after two hours. (-)-5-fluoro-2-[[(4-cyclo-propylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (200 mg, 0.58 mmol) was added after the magnesium methoxide solution had been chilled to room temperature. The mixture was stirred for two hours whereupon a small amount of water (0.05 ml) was added. After stirring another hour the small amount of inorganic salts were filtered off. The solution was concentrated on a rotavapor until two ml of the solution was left. While chilling and stirring, water was added dropwise which afforded the product to precipitate. After filtration the product was washed with a small amount of water and then dried in vacuum. There was obtained 84 mg (41%) of the title compound as a white powder. The optical rotation was determined as (-). Due to difficulties of dissolving the compound in a number of solvents a representative value of optical rotation was not obtained.

Table 1.

Ex.	Solvent	NMR data δ ppm
1.	DMSO-d6 500 MHz	0.25 (m, 2H), 0.53 (m, 2H), 1.13 (m, 1H), 3.67 (m, 1H), 3.73 (m, 1H), 4.59 (d, 1H), 4.69 (d, 1H), 6.76 (d, 1H), 6.88 (dd, 1H), 7.17 (m, 1H), 7.43 (m, 1H), 7.65 (m, 1H), 8.28 (d, 1H), ≈13 (b, 1H).
2.	DMSO-d6 500 MHz	0.25 (m, 2H), 0.53 (m, 2H), 1.13 (m, 1H), 3.68 (m, 1H), 3.73 (m, 1H), 4.59 (d, 1H), 4.69 (d, 1H), 6.76 (d, 1H), 6.88 (dd, 1H), 7.17 (m, 1H), 7.43 (m, 1H), 7.64 (m, 1H), 8.28 (d, 1H). ≈13 (b, 1H).
3.	DMSO-d6 500 MHz	0.21 (m, 2H), 0.50 (m, 2H), 1.08 (m, 1H), 3.46 (m, 1H), 3.62 (m, 1H), 4.40 (d, 1H), 4.56 (d, 1H), 6.57 (d, 1H), 6.71 (m, 1H), 6.81 (m, 1H), 7.15 (dd, 1H), 7.41 (m, 1H),

8.30 (d, 1H).

4.	DMSO-d6 300 MHz	0.22 (m, 2H), 0.50 (m, 2H), 1.07 (m, 1H), 3.50 (m, 1H), 3.66 (m, 1H), 4.41 (d, 1H), 4.62 (d, 1H), 6.59 (d, 1H), 6.69 (m, 1H), 6.78 (m, 1H), 7.13 (dd, 1H), 7.39 (m, 1H), 8.29 (d, 1H).
5.	DMSO-d6 500 MHz	0.22 (m, 2H), 0.50 (m, 2H), 1.08 (m, 1H), 3.46 (m, 1H), 3.62 (m, 1H), 4.40 (d, 1H), 4.56 (d, 1H), 6.57 (d, 1H), 6.71 (m, 1H), 6.80 (m, 1H), 7.15 (dd, 1H), 7.40 (m, 1H), 8.30 (d, 1H).
6.	DMSO-d6 300 MHz	0.22 (m, 2H), 0.50 (m, 2H), 1.07 (m, 1H), 3.51 (m, 1H), 3.66 (m, 1H), 4.41 (d, 1H), 4.62 (d, 1H), 6.60 (d, 1H), 6.69 (m, 1H), 6.78 (m, 1H), 7.13 (dd, 1H), 7.39 (m, 1H), 8.29 (d, 1H).

Preparation of the synthetic intermediate according to the invention will be described in the following example.

Example 9. Preparation of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H -benzimidazole and 6-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

A solution of 1.6 g (40 mmol) sodium hydroxide in 8 ml water was added to a mixture of 6.8 g (20 mmol) tetrabutylammonium hydrogen sulfate and 3.0 g (20 mmol) of (R)-(-)-mandelic acid. Chloroform (200 ml) and a mixture of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1-(chloromethyl)-1H-benzimidazole and 6-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1-(chloromethyl)-1H-benzimidazole (as racemates) were added and the mixture was refluxed for one hour. The reaction mixture was chilled and then partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water and dried over Na_2SO_4. Removal of solvents yielded a diastereomeric mixture of the two regioisomeric mandelic esters. The crude

product was used directly in the chromatographic step where the diastereomers were separated (Example 1 and 2). Yield: 9.0 g, 88%.

NMR data are given below.

Table 2.

Ex.	Solvent	NMR data δ ppm
9.	$CDCl_3$	0.3-0.4 (m, 2H), 0.6-0.7 (m, 2H), 1.1-1.3 (m, 1H), 3.7-3.9 (m, 2H), 4.6-4.9 (m, 2H), 5.2-5.3 (m, 1H), 6.2-6.6 (m, 2H), ≈6.7 (m, 1H), 6.85 (m, 1H), 7.0-7.8 (m, 8H), 8.1-8.2 (m, 1H).

The best mode of carrying out the invention known at present is to use the sodium salts of the optically pure compounds of the invention, thus the compounds described in Example 3, 4, 5 and 6.

Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

Syrup

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

Compound according to Example 4	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
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. 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.

Enteric-coated tablets

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

I	Compound according to Example 7		500 g
	Lactose		700 g
	Methyl cellulose		6 g
	Polyvinylpyrrolidone cross-linked		50 g
	Magnesium stearate		15 g
	Sodium carbonate		6 g
	Distilled water	q.s.	
II	Cellulose acetate phthalate		200 g
	Cetyl alcohol		15 g
	Isopropanol		2000 g
	Methylene chloride		2000 g

I Compound according to Example 7, 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 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 tabletting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcolhol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota^{R}, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

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

Compound according to Example 6	4 g
Sterile water to a final volume of	1000 ml

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.

Capsules

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

Compound according to Example 4	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

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.

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:

Coating solution:

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

The final coated pellets were filled into capsules.

Suppositories

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

Compound according to Example 4	4 g
Witepsol 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 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.

Stability towards racemization at different pH:es

The stability of the optically pure compounds of the invention towards racemization has been measured at low concentrations (10^{-5} M) at 37°C in aqueous buffer solutions at pH 7 and pH 11. The stereo chemical stability was measured by comparing the optical purity for the (+)-isomer of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several hours. The surprising high stereo chemical stability in neutral as well as in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained neither at pH 7 nor at pH 11, even after 28 hours. At pH 7, however, the chemical degradation of the compounds are much apparent after 28 hours.

Solubility in aqueous solutions

The solubility of the optically pure compounds of the invention in aqueous solutions has been meassured at 22°C in buffer solutions at pH 7. The solubility was measured by adding the (+)-enantiomer, the (-)-enantiomer and the racemate of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole to separate buffer solutions in test tubes. The tubes were kept in an ultrasound bath for 10 minutes whereupon they were shaken for 30 minutes. The measurement was then

performed by analyzing the solution by chromatography on an analytical achiral column (Concentration A, in Table 3 below). Thereafter, the tubes were shaken for another 30 minutes and the solutions were re-analyzed by chromatography (Concentration B, in Table 3 below). The data of the solubility for each compound are given in Table 3 below.

Table 3.

Compound	Concentration A	Concentration B
(+)-isomer of the neutral form	0.042 mg/ml	0.045 mg/ml
(-)-isomer of the neutral form	0.047 mg/ml	0.046 mg/ml
racemate of the neutral form	0.062 mg/ml	0.068 mg/ml

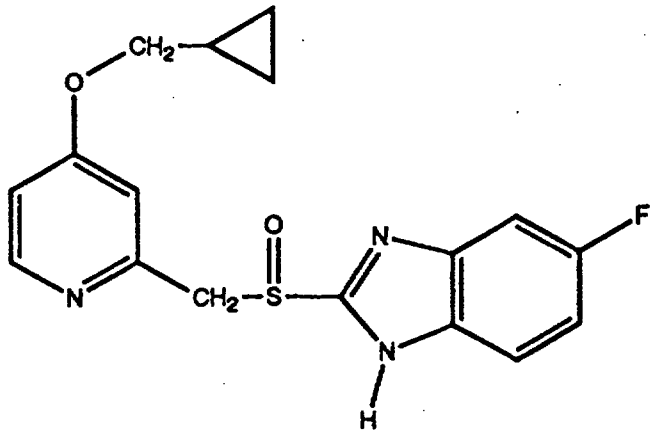
A comparison between the water solubility at 22°C of the sodium salts of the optically pure compounds of the invention and the water solubility of the racemate of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt has also been made. The solubility was measured by adding the (-)-enantiomer of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, the (+)-enantiomer and the racemate of said compound to separate tubes containing ultra-pure water (resistivity= 18MΩ). The tubes were kept in an ultrasound bath for 10 minutes whereupon they were shaken for 60 minutes. The measurement of the concentration of added compound was then performed by analyzing the solution by chromatography on an analytical achiral column. A surprisingly large difference in solubility between the single enantiomers and the racemate is exemplified by the following results.

When 40 mg of the sodium salt of the racemate was dissolved in 1 ml ultra-pure water, there was obtained a clear solution and the measured concentration was 40 mg/ml. In this solution, the pH was determined to be 10.2. However, when 1 mg of the (+)-enantiomer and the (-)-enantiomer, each, was dissolved in 1 ml of ultra-pure water, respectively, a suspension was obtained and the measured concentration was

<0.9 mg/ml. In this solution, the pH was determined to be 9.25. Further, when 4 mg of the (+)enantiomer and the (-)-enantiomer, each, was dissolved in 1 ml of ultra-pure water, respectively, a suspension was obtained and the measured concentration was 3.2 mg/ml. In this solution, the pH was determined to be 9.75.

Claims

1. Single enantiomeric compounds having the formula Ia and Ib



(Ia, Ib)

Ia (+)-enantiomer
Ib (-)-enantiomer

and the therapeutically acceptable salts thereof.

2. Compounds according to claim 1 c h a r a c t e r i z e d in that the compound is (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a therapeutically acceptable salt thereof, substantially free of its (-)-enantiomer.

3. Compounds according to to claim 1 c h a r a c t e r i z e d in that the compound is (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole, or a therapeutically acceptable salt thereof, substantially free of its (+)-enantiomer.

4. Compounds according to any of claims 1-3 c h a r a c t e r i z e d in that the therapeutically acceptable salts are Na^+, Mg^{2+}, Ca^{2+}, Li^+, K^+ and $N^+(R)_4$ salts wherein R is an alkyl group with 1-4 carbon atoms.

5. Compounds according to any of claims 1-4 c h a r a c t e r i z e d in that the compounds are (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole sodium salt, (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-fluoro-2-[[(4-

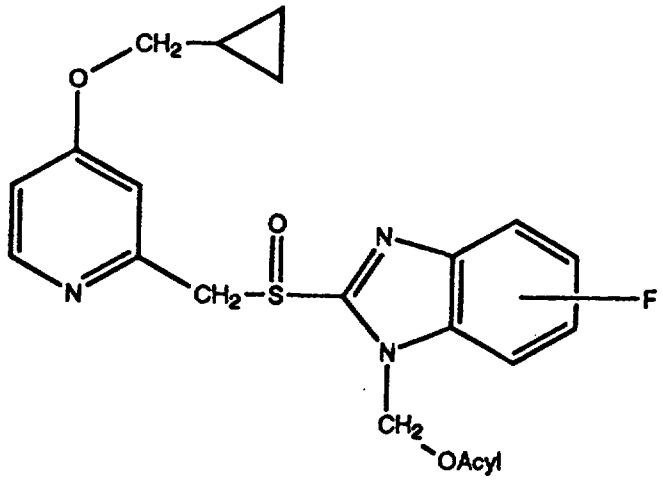
cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt and (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt.

6. Compounds according to any of claims 1-5 characterized in that the compounds are (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt and (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt in their crystalline forms.

7. Compounds according to claims 1 and 2 characterized in that the compound is (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt in its crystalline form substantially free of its (-)-enantiomer.

8. Compounds according to claims 1 and 3 characterized in that the compound is (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt in its crystalline form substantially free of its (+)-enantiomer.

9. Process for the preparation of a compound according to claim 1 characterized in that a diastereomeric ester of formula V



(V)

wherein the fluoro substituent in the benzimidazole moiety is in position 5 or 6, and wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, is separated, and each of the separated diastereomers is subjected to

* C L M S *

solvolysis with an alkaline solution where the acyloxymethyl group is hydrolyzed off giving the enantiomeric compound in neutral form after neutralization with a neutralizing agent whereupon the enantiomeric compound in neutral form optionally is converted to a therapeutically salt.

10. Process according to claim 9 c h a r a c t e r i z e d in that the diastereomers are separated by chromatography or fractional crystallization.

11. Process according to claim 9 c h a r a c t e r i z e d in that the solvolysis is performed in alkaline solution consisting of a base in a protic solvent, such as alcohols or water; or a base in an aprotic solvent, such as dimethylsulfoxide or dimethylformamide; or a base in a mixture of protic and aprotic solvents, such as water and acetonitrile.

12. Process for the preparation of a compound according to any of claims 1-4 in crystalline form c h a r a c t e r i z e d in that a product obtained in claim 9 either in neutral form or in the form of a therapeutically salt is treated with a non-aqueous solvent to precipate the product.

13. Process for preparation of (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt and (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt in their crystalline forms c h a r a c t e r i z e d in that (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt and (-)5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt crude product respectively is treated with a non-aqueous medium, such as 2-butanone and toluene.

14. Pharmaceutical preparation comprising a single enantiomeric compound according to any of claims 1-8 as active ingredient.

15. Single enantiomeric compounds according to any of claims 1-8 for use in therapy.

16. Use of a single enantiomeric compound according to any of claims 1-8 in the manufacture of a pharmaceutical formulation for inhibiting gastric acid secretion.

17. Use of a single enantiomeric compound according to any of claims 1-8 for the

manufacture of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.

18. A method for inhibiting gastric acid secretion comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.

19. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.

20. The compounds 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1-[mandeloyloxymethyl]-1H-benzimidazole and 6-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1-[mandeloyloxymethyl]-1H-benzimidazole.