

(19)



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(11)

EP 0 652 872 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:

08.11.2000 Bulletin 2000/45

(21) Application number: **94917244.9**

(22) Date of filing: **27.05.1994**

(51) Int. Cl.⁷: **C07D 401/12**, A61K 31/44

(86) International application number:
PCT/SE94/00509

(87) International publication number:
WO 94/27988 (08.12.1994 Gazette 1994/27)

(54) **OPTICALLY PURE MAGNESIUM -SALT OF PYRIDINYLMETHYL SULFINYL-1H-BENZIMIDAZOLE COMPOUND**

OPTISCH REINES MAGNESIUM-SALZ EINES PYRIDINYLMETHYLSULFINYL-1H-BENZIMIDAZOLE-DERIVATS

SEL DE MAGNESIUM OPTIQUEMENT PUR DE COMPOSE DE PYRIDINYLMETHYLE SULFINYL-1H-BENZIMIDAZOLE

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL
PT SE**
Designated Extension States:
SI

(30) Priority: **28.05.1993 SE 9301830**

(43) Date of publication of application:
17.05.1995 Bulletin 1995/20

(60) Divisional application:
00108480.5 / 1 020 461
00108479.7 / 1 020 460

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(56) References cited:
EP-A- 0 124 495 **DE-A- 4 035 455**

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EP 0 652 872 B1

Description

Field of the invention

- 5 [0001] The present invention is directed to magnesium salt of the (-)-enantiomer of omeprazole its use in medicine, a process for its preparation and its use in the manufacture of pharmaceutical preparations. The invention also relates to novel intermediates in the preparation of the compound of the invention.

Background of the invention

- 10 [0002] The compound 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in EP 5129 and EP 124 495, respectively. Omeprazole and its alkaline 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
15 optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such a compound, which is the magnesium salt of the (-)- enantiomer of omeprazole.

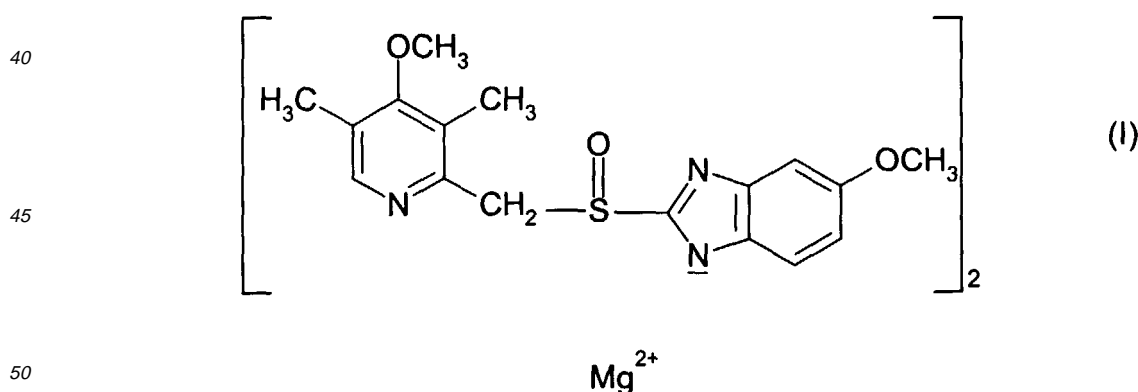
- [0003] The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, 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 neutralisation will create heat which will be difficult to handle in large scale production.
25

- [0004] The present invention in a further aspect provides a novel method for preparing the novel compound of the invention in large scale. This novel method can also be used in large scale to obtain single enantiomers of omeprazole in neutral form.

- [0005] There is no example known in the prior art of any isolated or characterized salt of optically pure omeprazole, i.e. single enantiomers of omeprazole neither of any isolated or characterized salt of any optically pure omeprazole analogue.
30

Detailed description of the invention

- 35 [0006] The present invention refers to the magnesium salt of the (-)-enantiomer of omeprazole. More preferred is the optically pure magnesium salt of the (-)-enantiomer of omeprazole according to formula I



hereinafter designated as Mg-salt of the (-)-enantiomer of omeprazole.

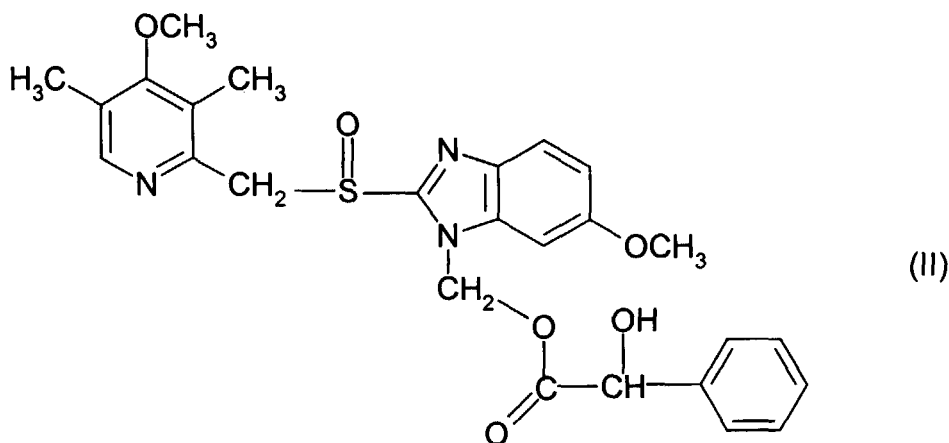
- 55 [0007] With the expression "optically pure Mg-salt of the (-)-enantiomer of omeprazole" is meant that said compound is essentially free of the Mg-salt of the (+)-enantiomer of omeprazole. Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. The Mg-salt of the (-)-enantiomer of omeprazole is easy to obtain from the (-)-enantiomer of omeprazole. In addition, the Mg-salt of the (-)-enantiomer of omeprazole,

however not the neutral form, is obtainable as a crystalline product. Because it is possible to purify optically impure salts of the enantiomers of omeprazole by crystallisation, the Mg-salt of the (-)-enantiomer of omeprazole can be obtained in very high optical purity, namely $\geq 99.8\%$ enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salt is stable towards racemization both in neutral pH and 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 makes it possible to use the Mg-salt of the (-)-enantiomer of omeprazole in therapy.

[0008] The specific method of preparation of the Mg-salt of the (-)-enantiomer of omeprazole is a further aspect of the invention as mentioned above and said method can be used to obtain the (-)-enantiomer of omeprazole in neutral form as well as the magnesium salt thereof.

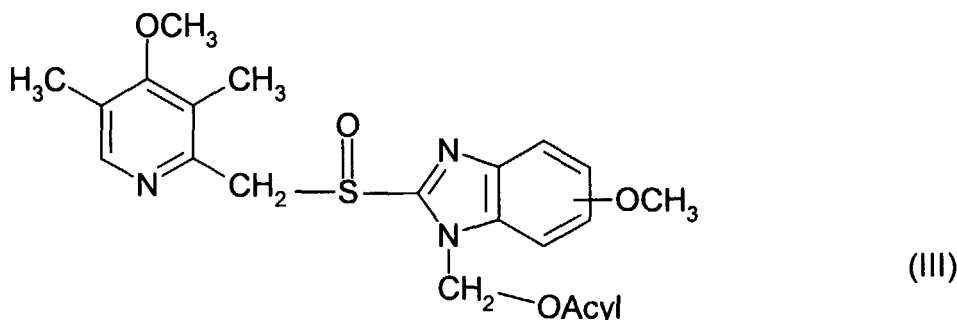
[0009] The Mg-salt of the (-)-enantiomer of omeprazole may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the Mg-salt of the (-)-enantiomer of omeprazole may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the Mg-salt of the (-)-enantiomer of omeprazole 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 acute upper gastrointestinal bleeding. It may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The Mg-salt of the (-)-enantiomer of omeprazole may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysosomal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

[0010] Yet a further aspect of the invention is the compound II, which is an intermediate used in the specific method of preparation of the Mg-salt of the (-)-enantiomer of omeprazole.



Preparation

[0011] The optically pure compound of the invention, i.e. the Mg-salt of the (-)-enantiomer of omeprazole is prepared by starting with separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula III



15 wherein the methoxy 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 comprising the (-)-enantiomer of omeprazole in an alkaline solution. The formed (-)-enantiomer of omeprazole is then isolated by neutralizing the aqueous solution of the formed salt of the (-)-enantiomer of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate, and then the magnesium salt is obtained.

20 **[0012]** 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.

[0013] The diastereomeric esters can be separated either by chromatography or fractional crystallization.

25 **[0014]** The solvolysis usually takes place together with a base in a protic solvent such as alcohols or 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.

30 **[0015]** To obtain the optically pure Mg^{2+} salt of the invention, the optically pure Na^+ salt is treated with an aqueous solution of an inorganic magnesium salt such as MgCl_2 , whereupon the Mg^{2+} salt of the (-)-enantiomer is precipitated. The optically pure Mg^{2+} salt may also be prepared by treating the (-)-enantiomer of omeprazole with a base, such as $\text{Mg}(\text{OR}^3)_2$, 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. To obtain the optically pure Na^+ salt, i.e. the sodium salt of the (-)-enantiomer of omeprazole, the (-)-enantiomer of omeprazole formed in the process described above 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 . In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

35 **[0016]** For clinical use the Mg -salt of the (-)-enantiomer of omeprazole, i.e. the optically pure compound of the invention is formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the Mg -salt of the (-)-enantiomer of omeprazole normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. 40 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.

45 **[0017]** In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as 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 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.

50 **[0018]** 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.

55 **[0019]** 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, sac-

charose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or gelatin. The capsules may be enteric-coated as described above.

[0020] 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.

[0021] 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.

[0022] 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 reconstituted with a suitable solvent extemporaneously before use.

[0023] 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.

[0024] The invention is illustrated by the following examples.

Example 1. Preparation of (-)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

[0025]

A. (+)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $\text{MgCl}_2 \cdot x\text{H}_2\text{O}$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 85 mg (51%) of the product as a white powder. The optical purity ($[\alpha]_D^{20}$) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20} = -128.2^\circ$ ($c=1\%$, methanol).

B. The starting compound of Example 1A, i.e. the (+)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, was prepared as follows.

100 mg (0.3 mmol) of (-)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical purity ($[\alpha]_D^{20}$) which was analyzed by chiral column chromatography was $\geq 99.8\%$. $[\alpha]_D^{20} = +42.8^\circ$ ($c=0.5\%$, water). NMR data are given below (1B).

C. The starting compound of Example 1B, i.e. the (-)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, was prepared as follows.

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxide in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 μl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.12 g (77%) of the title compound as a colourless syrup. The optical purity ($[\alpha]_D^{20}$) which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20} = -155^\circ$ ($c=0.5\%$, chloroform). NMR data are given below (1C). The preparation of the starting compound of Example 1C is described in Example 2B.

Ex.	Solvent	NMR data δ ppm
1B.	DMSO-d ₆ 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
1C.	CDCl ₃ 300 MHz	2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77 (m, 2H), 6.93 (dd, 1H), \approx 7.0 (b, 1H), \approx 7.5 (b, 1H), 8.19 (s, 1H).

[0026] Preparation of the synthetic intermediates according to the invention will be described in the following examples.

Example 2

[0027]

A. Preparation of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulphate and 6.4 g (42 mmol) (R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole.

Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3 x 200 ml water and the organic solution was dried over MgSO₄ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

NMR data are given below (2A).

B. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound of A above were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5 % sodium hydrogen carbonate solution, drying over Na₂SO₄ and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colourless syrup.

NMR data are given below (2B).

Example 3

[0028]

A. Preparation of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 2A. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

NMR data are given below (3A).

B. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound of A above were separated using reversed phase chromatography (HPLC) in the same way as in Example 2B, but using the diastereomeric mixture of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 2B. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colourless syrup.

NMR data are given below (3B).

Ex.	Solvent	NMR data δ ppm
2A.	CDCl ₃ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
2B.	CDCl ₃ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
3A.	CDCl ₃ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
3B.	CDCl ₃ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).

[0029] Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

Syrup

[0030] A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to the invention	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

[0031] 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

[0032] An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

5 10	I	Compound according to the invention as Mg salt	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.
15 20	II	Cellulose acetate phthalate	200 g
		Cetyl alcohol	15 g
		Isopropanol	2000 g
		Methylene chloride	2000 g

I Compound according to the invention, 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 tableting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol 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.

Capsules

[0033] Capsules containing 30 mg of active compound were prepared from the following ingredients:

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

[0034] 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.

[0035] 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:

[0036] Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g

(continued)

Acetone	200 g
Ethanol	600 g

[0037] The final coated pellets were filled into capsules.

Suppositories

[0038] Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to invention	4 g
Witepsol H-15	180 g

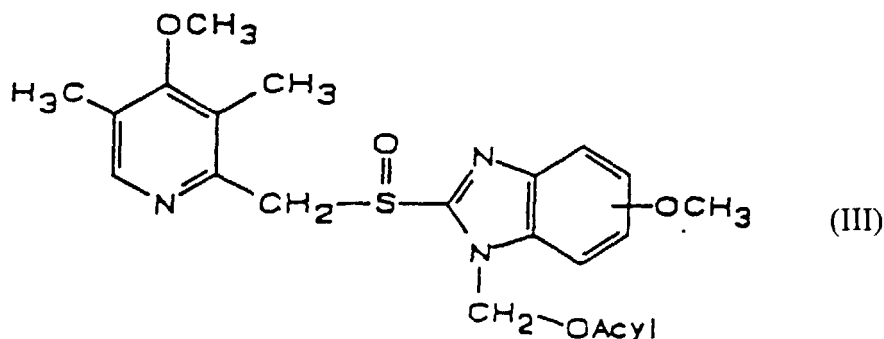
[0039] The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41°C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Stability towards racemization at different pH:es

[0040] The stability of the optically pure compound of the invention towards racemization has been measured at low concentrations in refrigerator in aqueous buffer solutions at pH 8, 9.3, 10 and 11.2. The stereochemical stability was measured by comparing the optical purity for the (-)-isomer of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several days. The measurement was performed by chromatography on an analytical chiral column. The surprising high stereochemical stability in alkaline conditions for the compound of the invention is exemplified by the fact that no racemization for the test compound was obtained at pH 11.2 even after 21 days. At pH 8, 9.3 and 10, the chemical degradation of the compound is more apparent which makes the racemization measurement more difficult to perform, however at none of these pH values a detectable racemization was obtained after 16 days.

Claims

1. The magnesium salt of (-)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Mg-salt of the (-)-enantiomer of omeprazole).
2. A process for the preparation of the Mg-salt of the (-)-enantiomer of omeprazole characterized in that a diastereomeric mixture of an ester of formula III



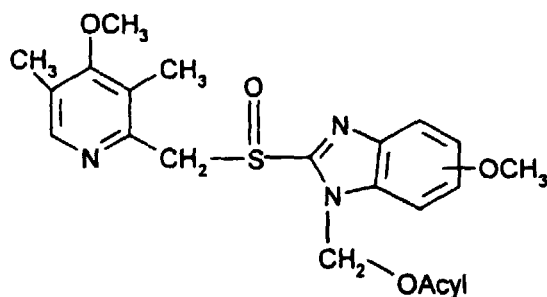
wherein Acyl designates a chiral acyl group having either R or S configuration, is separated, to obtain the separated diastereomers whereafter the diastereomer comprising the acyloxymethyl derivative of the (-)-enantiomer of ome-

prazole is dissolved in an alkaline solution wherein the acyloxymethyl group is hydrolyzed off to give the (-)-enantiomer of omeprazole which is converted to the magnesium salt.

3. A process according to claim 2 characterized in that the chiral acyl group is mandeloyl.
4. A process according to claim 2 characterized in that the diastereomers are separated by chromatography or fractional crystallization.
5. A process according to claim 2 characterized 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.
6. A process according to claim 2 characterized in that said magnesium salt is obtained by treatment of the (-)-enantiomer of omeprazole with a base comprising magnesium in non-aqueous solution.
7. A process according to claim 2, characterized in that said magnesium salt is obtained by first converting the (-)-enantiomer of omeprazole to the sodium salt which latter is treated with an aqueous solution of an inorganic magnesium salt to precipitate said magnesium salt.
8. A pharmaceutical preparation containing the Mg-salt of the (-)-enantiomer of omeprazole together with a pharmaceutically acceptable carrier.
9. The Mg-salt of the (-)-enantiomer of omeprazole for use in therapy.
10. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation for the treatment of gastric acid related diseases by inhibition of gastric acid secretion.
11. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.
12. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation having improved pharmacokinetic and metabolic properties.
13. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation with a lower degree of interindividual variation in plasma levels when treating gastric acid related diseases.
14. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation with an improved therapeutic profile when treating gastric acid related diseases.
15. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation for the treatment of reflux esophagitis.
16. 6-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole.
17. 6-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole.

Patentansprüche

1. Das Magnesiumsalz von (-)-5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol (Mg-Salz des (-)-Enantiomeren von Omeprazol).
2. Verfahren zur Herstellung des Mg-Salzes des (-)-Enantiomeren von Omeprazol, dadurch gekennzeichnet, daß man ein Diastereomerengemisch eines Esters der Formel III



(III)

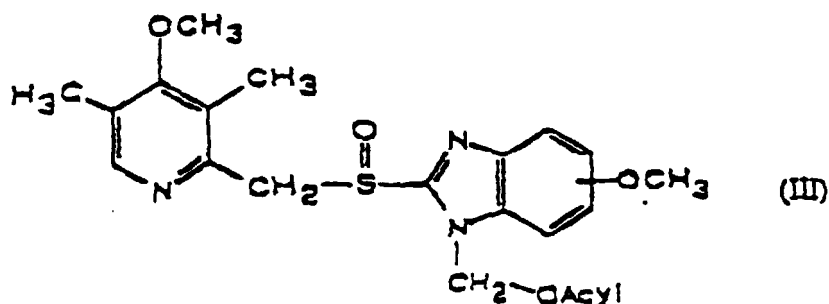
wobei Acyl eine chirale Acylgruppe in R- oder S-Konfiguration bedeutet, trennt unter Erhalt der getrennten Diastereomeren, worauf man das Diastereomere, das das Acyloxymethyl-Derivat des (-)-Enantiomeren von Omeprazole enthält, in einer alkalischen Lösung löst, wobei eine hydrolytische Abspaltung der Acyloxymethylgruppe erfolgt unter Erhalt des (-)-Enantiomeren von Omeprazol, das in das Magnesiumsalz überführt wird.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß die chirale Acylgruppe Mandeloyl darstellt.
4. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß die Diastereomeren mittels Chromatographie oder fraktionierter Kristallisation getrennt werden.
5. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß die Solvolyse in alkalischer Lösung einer Base in einem protischen Lösemittel, wie Alkohole oder Wasser; oder einer Base in einem aprotischen Lösungsmittel, wie Dimethylsulfoxid oder Dimethylformamid, erfolgt.
6. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das Magnesiumsalz erhalten wird durch Behandeln des (-)-Enantiomeren von Omeprazol mit einer Magnesium enthaltenden Base in nicht-wäßriger Lösung.
7. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das Magnesiumsalz erhalten wird, indem man zunächst das (-)-Enantiomere von Omeprazol in das Natriumsalz überführt, welches letzteres mit einer wäßrigen Lösung eines anorganischen Magnesiumsalzes zur Ausfällung des Magnesiumsalzes behandelt wird.
8. Pharmazeutische Zubereitung, enthaltend das Mg-Salz des (-)-Enantiomeren von Omeprazol zusammen mit einem pharmazeutisch verträglichen Träger.
9. Das Mg-Salz des (-)-Enantiomeren von Omeprazol zur Verwendung in der Therapie.
10. Verwendung des Mg-Salzes des (-)-Enantiomeren von Omeprazol zur Herstellung einer pharmazeutischen Zubereitung für die Behandlung Magensäure-bezogener Erkrankungen durch Inhibierung der Magensäuresekretion.
11. Verwendung des Mg-Salzes des (-)-Enantiomeren von Omeprazol zur Herstellung einer pharmazeutischen Zubereitung für die Behandlung gastrointestinaler Entzündungskrankheiten.
12. Verwendung des Mg-Salzes des (-)-Enantiomeren von Omeprazol zur Herstellung einer pharmazeutischen Zubereitung mit verbesserten pharmakokinetischen und Stoffwechsel-Eigenschaften.
13. Verwendung des Mg-Salzes des (-)-Enantiomeren von Omeprazol zur Herstellung einer pharmazeutischen Zubereitung mit einem geringeren Grad an interindividueller Abweichung der Plasmaspiegel bei der Behandlung Magensäure-bezogener Erkrankungen.
14. Verwendung des Mg-Salzes des (-)-Enantiomeren von Omeprazol zur Herstellung einer pharmazeutischen Zubereitung mit verbessertem therapeutischen Profil bei der Behandlung von Magensäure-bezogenen Erkrankungen.

15. Verwendung des Mg-Salzes des (-)-Enantiomeren von Omeprazol zur Herstellung einer pharmazeutischen Zubereitung für die Behandlung von Refluxösophagitis.
16. 6-Methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazol.
17. 6-Methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazol.

Revendications

- Sel de magnésium du (-)-5-méthoxy-2-[[[(4-méthoxy-3,5-diméthyl-2-pyridinyl)méthyl]sulfinyl]-1H-benzimidazole (sel de Mg de l'énantiomère (-) de l'oméprazole).
- Procédé pour la préparation du sel de Mg de l'énantiomère (-) de l'oméprazole, caractérisé en ce qu'un mélange diastéréomère d'un ester de formule III



dans laquelle Acyl désigne un groupe acyle chiral ayant une configuration R ou bien S, est séparé, pour obtenir les diastéréomères séparés, après quoi le diastéréomère comprenant le dérivé acyloxyméthyle de l'énantiomère (-) de l'oméprazole est dissous dans une solution alcaline dans laquelle le groupe acyloxyméthyle est éliminé par hydrolyse pour donner l'énantiomère (-) de l'oméprazole qui est converti en sel de magnésium.

- Procédé selon la revendication 2, caractérisé en ce que le groupe acyle chiral est un mandéyle.
- Procédé selon la revendication 2, caractérisé en ce que les diastéréomères sont séparés par chromatographie ou cristallisation fractionnée.
- Procédé selon la revendication 2, caractérisé en ce que la solvolysé s'effectue dans une solution alcaline constituée d'une base dans un solvant protique, tel que les alcools ou l'eau; ou d'une base dans un solvant aprotique, tel que le diméthylsulfoxyde ou le diméthylformamide.
- Procédé selon la revendication 2, caractérisé en ce que ledit sel de magnésium est obtenu par traitement de l'énantiomère (-) de l'oméprazole avec une base comprenant du magnésium en solution non aqueuse.
- Procédé selon la revendication 2, caractérisé en ce que ledit sel de magnésium est obtenu en convertissant tout d'abord l'énantiomère (-) de l'oméprazole en sel de sodium, lequel est traité avec une solution aqueuse d'un sel inorganique de magnésium pour précipiter ledit sel de magnésium.
- Préparation pharmaceutique contenant le sel de Mg de l'énantiomère (-) de l'oméprazole ainsi qu'un véhicule acceptable sur le plan pharmaceutique.
- Sel de Mg de l'énantiomère (-) de l'oméprazole, pour une utilisation en thérapie.
- Utilisation du sel de Mg de l'énantiomère (-) de l'oméprazole pour la préparation d'une formulation pharmaceutique destinée au traitement de maladies associées à l'acide gastrique par inhibition de la sécrétion d'acide gastrique.

11. Utilisation du sel de Mg de l'énantiomère (-) de l'oméprazole pour la préparation d'une formulation pharmaceutique destinée au traitement des maladies inflammatoires gastro-intestinales.

5 12. Utilisation du sel de Mg de l'énantiomère (-) de l'oméprazole pour la préparation d'une formulation pharmaceutique ayant des propriétés pharmacocinétiques et métaboliques améliorées.

10 13. Utilisation du sel de Mg de l'énantiomère (-) de l'oméprazole pour la préparation d'une formulation pharmaceutique présentant un degré inférieur d'écart des niveaux plasmatiques entre individus lors du traitement de maladies associées à l'acide gastrique.

14. Utilisation du sel de Mg de l'énantiomère (-) de l'oméprazole pour la préparation d'une formulation pharmaceutique présentant un profil thérapeutique amélioré lors du traitement de maladies associées à l'acide gastrique.

15 15. Utilisation du sel de Mg de l'énantiomère (-) de l'oméprazole pour la préparation d'une formulation pharmaceutique destinée au traitement d'une oesophagite par reflux.

16. 6-Méthoxy-2-[[[4-méthoxy-3,5-diméthyl-2-pyridinyl)méthyl]-(R/S)-sulfinyl]-1-[(R)-mandéloyloxyméthyl]-1H-benzimidazole.

20 17. 6-Méthoxy-2-[[[4-méthoxy-3,5-diméthyl-2-pyridinyl)méthyl]-(R/S)-sulfinyl]-1-[(S)-mandéloyloxyméthyl]-1H-benzimidazole.

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