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(54) Title: NEW SALTS OF OMERAZOLE AND ESOMERAZOLE I

(57) Abstract: The present invention relates to new salts of omeprazole and esomeprazole respectively, i.e. salts of 5-methoxy-2-
[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and the (S)-enantiomer thereof. More specifically, the
present invention relates to adamantan ammonium salt of the compounds, formed by a reaction of omeprazole and esomeprazole
respectively and adamantan amine. The present invention also relates to a process for preparing the compounds of the invention, a
pharmaceutical preparation and a method for treatment of gastric related disorders by administering the compounds of the invention.



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New salts of omerazole and esomerazole I.

Field of the Invention

5 The present invention relates to novel salts of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole or salts of the single enantiomers thereof in a pure and isolated form. Specifically, it relates to adamantan ammonium salts of the compounds. The present invention also relates to processes for preparing the adamantan ammonium salts of omeprazole and esomeprazole in a pure and isolated form and
10 pharmaceutical compositions containing them.

Background of the invention and prior art

The compound 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-
15 benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 0 005 129.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulphur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers,
20 the (*R*)- and (*S*)-enantiomer of omeprazole, herein referred to as (*R*)-omeprazole and (*S*)-omeprazole, the latter have the generic name esomeprazole. The absolute configuration of the enantiomers of omeprazole has been determined by an X-ray study of an N-alkylated derivative of the (*R*)-enantiomer.

25 Omeprazole and esomeprazole are proton pump inhibitors, and are useful as antiulcer agents. In a more general sense, omeprazole and esomeprazole may be used for prevention and treatment of gastric acid related diseases in mammals and especially in man. Specific alkaline salts of omeprazole are disclosed in EP 0 124 495. Herein, quaternary ammonium salts and guanidine salts of omeprazole are disclosed. Document WO 97/41114
30 discloses processes for preparing magnesium salt of benzimidazoles, including magnesium

salt of omeprazole. However, no salts of omeprazole prepared from primary amines are mentioned in these documents.

Certain salts of the single enantiomers of omeprazole and their preparation are disclosed in
5 WO 94/27988, for instance, quaternary ammonium salts of esomeprazole are mentioned.
However, no salts employing primary, secondary or tertiary amines are disclosed or
suggested. The described salts of esomeprazole have improved pharmacokinetic and
metabolic properties, which will give an improved therapeutic profile such as a lower
degree of interindividual variation. WO 96/02535 and WO 98/54171 disclose preferred
10 processes for preparing esomeprazole and salts thereof. Further, primary amine salts are
described in WO 03/074514.

In the formulation of drug compositions, it is important for the active pharmaceutical
ingredient to be in a form in which it can be conveniently handled and processed. This is of
15 importance, not only from the point of view of obtaining a commercially viable
manufacturing process, but also from the point of view of subsequent manufacture of
pharmaceutical formulations (e.g. oral dosage forms such as tablets) comprising the active
pharmaceutical ingredient.

20 Further, in the manufacture of oral pharmaceutical compositions, it is important that a
reliable, reproducible and constant plasma concentration profile of the active
pharmaceutical ingredient is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active pharmaceutical
25 ingredient are important properties for a pharmaceutical active compound. The active
pharmaceutical ingredient, and compositions containing it, should be capable of being
effectively stored over appreciable periods of time, without exhibiting a significant change
in the physico-chemical characteristics of the active pharmaceutical ingredient, e.g. its
chemical composition, density, hygroscopicity and solubility. Thus, in the manufacture of
30 commercially viable and pharmaceutically acceptable drug compositions, it is important,

wherever possible, to provide the active pharmaceutical ingredient in a crystalline and stable form.

Drawings

5 Figure 1 is an X-ray powder diffractogram of the 1-adamantan ammonium salt of omeprazole.

Figure 2 is an X-ray powder diffractogram of the 1-adamantan ammonium salt of esomeprazole.

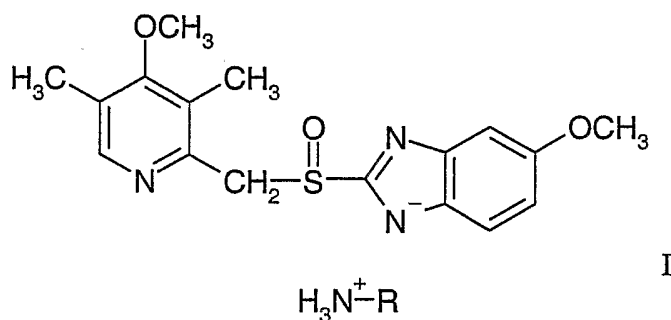
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Figure 3 is an X-ray powder diffractogram of the 2-adamantan ammonium salt of esomeprazole.

Description of the invention

15

The present invention refers to new adamantan ammonium salts having the following formula I including compounds Ia, Ib and Ic:



20 Formula Ia: adamantan ammonium salts of racemic omeprazole

Formula Ib: adamantan ammonium salts of the (*S*)-enantiomer of omeprazole

Formula Ic: adamantan ammonium salts of the (*R*)-enantiomer of omeprazole

wherein R is defined as the adamantan group. The adamantan amine, H₂N-R, is selected from tricyclo [3.3.1.1^{3,7}] decan-1-amine and tricyclo [3.3.1.1^{3,7}] decan-2-amine.

25

The compounds of the invention may be prepared in the form of solvates, hydrates, and anhydrides.

The chemical name 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole adamantan ammonium salt as well as the chemical name (*S*)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole adamantan ammonium salt; the chemical name 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole 1-adamantan ammonium salt as well as the chemical name (*S*)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole 1-adamantan ammonium; and the chemical name 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole 2-adamantan ammonium salt as well as the chemical name (*S*)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole 2-adamantan ammonium salt does not necessarily mean that the methoxy group of the benzimidazole moieties is in the 5-position but may as well be in the 6-position, or there may be mixtures thereof.

In a further aspect, the present invention provides processes for the preparation of adamantan ammonium salts of omeprazole and of esomeprazole. It has surprisingly been found that adamantan ammonium salts of omeprazole and adamantan ammonium salts of the (*R*)- and (*S*)-enantiomers thereof may be obtained in a well-defined crystalline state. More specifically, the compounds adamantan ammonium salt of omeprazole and adamantan ammonium salt of esomeprazole according to the present invention are characterized by being crystalline with a well-defined structure.

25

Another embodiment of the invention is the 1-adamantan ammonium salt of omeprazole. This compound of the invention is characterized in providing an X-ray powder diffraction pattern, as in figure 1, exhibiting substantially the following d-values and intensities:

30

d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
15.6	s	5.4	s	4.18	m
11.6	s	5.2	s	4.11	m
8.6	w	4.90	s	3.90	m
7.8	m	4.87	m	3.70	w
7.1	w	4.80	m	3.63	w
6.6	m	4.74	m	3.28	m
6.4	m	4.49	s	2.95	w
6.0	s	4.46	m	2.63	w
5.9	m	4.40	s	2.50	w
5.6	w	4.26	s		

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of the 1-adamantan ammonium salt of omeprazole.

The relative intensities are less reliable and instead of numerical values, the relative

intensities corresponding to the peaks are denoted being strong (s), medium (m), or weak (w).

In addition to the peaks indicated in the table the diffractogram contains a number of very weak peaks.

Another embodiment of the invention is the 1-adamantan ammonium salt of esomeprazole.

This compound of the invention is characterized in providing an X-ray powder diffraction pattern, as in figure 2, exhibiting substantially the following d-values and intensities:

d-value (Å)	Relative Intensity	d-value (Å)	Relative Intensity	d-value (Å)	Relative intensity
16.5	w	5.9	w	4.25	m
15.6	w	5.7	w	4.18	m
13.8	w	5.6	m	3.95	w
13.1	w	5.3	m	3.83	w
12.7	w	5.2	m	3.32	w
11.9	w	5.1	s	2.93	w
10.6	s	5.0	m	2.88	w
8.3	w	4.90	w	2.77	w
7.9	w	4.79	w	2.72	w
6.6	w	4.63	m	2.55	w
6.5	m	4.61	m		
6.3	w	4.45	m		
6.1	m	4.39	s		

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of the 1-adamantan ammonium salt of esomeprazole.

5

The relative intensities are less reliable and instead of numerical values, the relative intensities corresponding to the peaks are denoted being strong (s), medium (m), or weak (w).

10 In addition to the peaks indicated in the table the diffractogram contains a number of very weak peaks.

Another embodiment of the invention is the 2-adamantan ammonium salt of esomeprazole. This compound of the invention is characterized in providing an X-ray powder diffraction pattern, as in figure 3, exhibiting substantially the following d-values and intensities:

5

d-value (Å)	Relative Intensity	d-value (Å)	Relative Intensity	d-value (Å)	Relative intensity
15.8	m	5.0	m	3.49	w
11.1	s	4.93	s	3.28	m (broad)
7.9	m	4.82	s	3.21	w
7.8	w	4.66	m	3.14	w
7.0	w (broad)	4.39	s (broad)	3.05	w
6.3	w	4.27	w	2.98	w
6.1	s	4.19	w	2.97	w
5.9	w	4.12	w	2.93	m
5.7	w	3.96	m	2.87	w
5.5	w	3.77	w	2.83	w
5.3	w	3.58	w	2.78	w
5.2	w	3.53	m		

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of the 2-adamantan ammonium salt of esomeprazole.

10

The relative intensities are less reliable and instead of numerical values, the relative intensities corresponding to the peaks are denoted being strong (s), medium (m), or weak (w).

In addition to the peaks indicated in the table the diffractogram contains a number of very weak peaks.

The relative intensities are derived from the diffractograms measured with variable slits.

5 The XRPD distance values may vary in the range of ± 2 on the last decimal place.

X-ray powder diffraction (XRPD) analysis was performed on samples of 1-adamantan ammonium salt of omeprazole, on samples of 1-adamantan ammonium salt of esomeprazole, and on samples of 2-adamantan ammonium salt of esomeprazole according
10 to standard methods, for example, those described in Giacovazzo, C. et al. (1995), Fundamentals of Crystallography, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), Introduction to X-Ray Powder Diffractometry, John Wiley & Sons, New York; Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), X-ray Diffraction Procedures, John Wiley and Sons, New
15 York. X-ray analyses were performed using a Siemens D5000 diffractometer.

The compounds of the invention are characterized by the positions and intensities of the peaks in the X-ray powder diffractogram. Furthermore, the compounds of the invention could be characterized by ^1H -NMR, IR, FTIR and Raman spectroscopy.

20

In a further aspect, the present invention provides processes for the preparation of adamantan ammonium salts of omeprazole and of esomeprazole, respectively. Suitable processes for the salt formation are temperature induced crystallisation, fast crystallisation at elevated temperature, slow crystallisation at room temperature, thermal recrystallisation,
25 antisolvent induced crystallisation and crystallisation by evaporation.

In a further aspect, the present invention provides processes for the preparation of adamantan ammonium salts of omeprazole and of esomeprazole, which comprises the following steps: omeprazole or esomeprazole is either dissolved or formed *in situ* in a
30 suitable solvent, such as acetonitril, ethyl acetate, *tert*-butyl methyl ether and methanol, or

mixtures thereof. The adamantan amine is added during stirring. A precipitate of the salt compound is formed and the precipitate is separated by filtration. The obtained compound is washed with a solvent and the obtained crystals are dried.

5 Still a further aspect of the invention is that the novel compounds may be of interest as intermediates in the synthesis of other compounds such as magnesium salts of omeprazole and of esomeprazole, which are the pharmaceutically active components in products with the tradenames Losec[®] MUPS[®] and Nexium[®]. During the synthesis of the active component for Nexium[®] i.e. the magnesium salt of esomeprazole, a titanium catalyst may
10 be used in the oxidation step prior to the salt formation steps. The synthesis usually proceeds with the formation of monovalent salt of esomeprazole by adding a monovalent hydroxide or alkoxide. This monovalent salt of esomeprazole, such as sodium or potassium salt, is thereafter converted to the magnesium salt. Insoluble inorganic titanium salts, such as titanium oxid, are being formed when strong bases such as sodium or potassium
15 alkoxides are being added to a solution of titanium catalysts. Using adamantan amine as a salt forming agent rather than using a sodium- or potassium-containing base avoids the risk of inorganic titanium salts being co-precipitated with the desired salt. Even, if the titanium-catalyst may react with the adamantan amine, a soluble complex of the adamantane amine and titanium may be formed, which may stay in the solution while filtering off the desired
20 adamantane ammonium salt of the benzimidazole compound.

Solutions containing the dissolved and ionised alkylammonium salt of omeprazole or alkylammonium salt of esomeprazole have a lower pH than corresponding solutions made from the previously known sodium and potassium salts of omeprazole and of
25 esomeprazole. Less basic solutions are advantageous for intravenous administration.

The exemplified adamantan ammonium salts of omeprazole and esomeprazole, respectively, are in crystalline forms. They exhibit advantageous properties, such as convenient handling as well as chemical and solid-state stability. The products obtained
30 according to the present invention are well-defined crystalline products. Such crystalline

products give an easily processability during the manufacture of suitable dosage forms. A crystalline product is easy to handle during milling, filtering and tableting. The procedures have high reproducibility. Also, the stability is improved when a well-defined crystalline form of the compound is obtained. These properties are of great value considering dosage forms such as e.g. tablets.

These active substances are useful for inhibiting gastric acid secretion in mammals and man. In a more general sense, they may be used for prevention and treatment of gastric acid related diseases in mammals and man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID (nonsteroidal anti-inflammatory drug) therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic and non-symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent acid aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful for prevention and treatment of irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease, asthma, laryngitis, Barret's syndrome, sleep apnea, sleep disturbance, psoriasis as well as being useful for prevention and treatment of Helicobacter infections and diseases related to the above conditions.

For the avoidance of doubt, by "treatment" is meant to include the therapeutic treatment as well as the prophylaxis, of a condition.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the adamantan ammonium salt of omeprazole or esomeprazole, according to the invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

It is further provided a pharmaceutical composition comprising the compounds according to the invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of *Helicobacter* infections. The invention also provides the use of the compounds in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the compounds according to the invention.

The composition of the invention includes compositions suitable for peroral or parenteral administration. The most preferred route is the oral route. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the compounds according to the invention in any case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are somewhat lower than average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below, for example long-term treatments may request lower dosage. Such higher and lower doses are within the scope of the present invention. Such daily doses may vary between 5 mg to 300 mg.

In general, a suitable oral dosage form of the compound of the invention may cover a dose range from 5 mg to 300 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 10 mg to 80 mg.

- 5 The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/01623 and EP 0 247 983, the disclosures of which are hereby as a whole included by reference.
- 10 Combination preparations comprising the compounds of the invention and other active ingredients may also be used. Examples of such active ingredients include, but are not limited to anti-bacterial compounds, non-steroidal anti-inflammatory agents (including acetylsalicylic acid (ASA), antacid agents, alginates, prokinetic agents, histamine H₂-receptor antagonists, bisfosfonates, and GABA_B agonists such as baclofen and those
- 15 disclosed in WO 01/42252 and WO 01/41743.

The examples below will further illustrate the preparation of the compound of the invention, according to different process routes and including new intermediates. These examples are not intended to limit the scope of the invention as defined hereinabove or as

20 claimed below.

Examples

Example 1: 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole 1-adamantan ammonium salt.

5

Omeprazole (1.0 g, 2.9 mmol) was dissolved in acetonitril (10 ml) and methanol (2 ml) at 40-50 °C. 1-adamantan amine (0.86 g, 5.7 mmol) was added and the mixture was then cooled to room temperature. At these conditions, a slurry was achieved. The slurry was stirred for additional two hours whereupon the precipitate was filtered off, washed with
10 acetonitrile, and dried. 1 g (73 %) of the title compound was obtained.

¹H-NMR (400 MHz, CD₂Cl₂): 1.5 (bs, 18H), 2.12 (s, 3H), 2.17 (s, 3H), 3.63 (s, 3H), 3.77 (s, 3H), 4.49 (d, 1H), 4.65 (d, 1H), 6.84-6.91 (dd, 1H), 6.99 (bs, 1H), 7.47 (m, 1H), 8.14 (s, 1H)

15

The prepared compound was analysed by XRPD resulting in the diffractogram shown in Figure 1.

Example 2: (*S*)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-
20 1*H*-benzimidazole 1-adamantan ammonium salt.

Esomeprazole (1.0 g, 2.9 mmol) was dissolved in acetonitril (20 ml) at room temperature. 1-Adamantan amine (0.86 g, 5.7 mmol) was added to the solution whereupon a white solid precipitated. The reaction slurry was stirred at room temperature for additional two hours.
25 The formed precipitate was filtered off, washed with acetonitril (10 ml), and dried. 1.13 g (83 %) of the title compound was obtained.

¹H-NMR (400 MHz, CD₂Cl₂): 1.48 (bs, 18H), 2.14 (s, 3H), 2.18 (s, 3H), 3.66 (s, 3H), 3.78 (s, 3H), 4.46 (d, 1H), 4.66 (d, 1H), 6.88 (d, 1H), 6.95 (m, 1H), 7.52 (d, 1H), 8.15 (s, 1H)

30

The prepared compound was analysed by XRPD resulting in the diffractogram shown in Figure 2.

5 Example 3: (*S*)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole 2-adamantan ammonium salt.

Esomeprazole (0.5 g, 1.4 mmol) was dissolved in a solution of 2-Adamantanamine (0.44 g, 2.9 mmol) and ethyl acetate (10 ml). The obtained solution was concentrated to about 4 ml
10 and acetonitrile (10 ml) was added. The resulting mixture was concentrated once more to about half, whereupon a white solid started to precipitate. The reaction slurry was stirred at room temperature over night. The precipitated product was filtered off and washed with acetonitrile. 0.1 g of the title compound was obtained.

15 ¹H-NMR (400 MHz, CD₃OD): 1.64 (d, 2H), 1.77-1.88 (m, 8H), 1.93 (d, 2H), 2.02 (d, 2H), 2.16 (s, 3H), 2.25 (s, 3H), 3.10 (bs, 1H), 3.70 (s, 3H), 3.86 (s, 3H), 4.69 (d, 1H), 4.84 (d, 1H), 6.92 (dd, 1H), 7.11 (d, 1H), 7.52 (d, 1H), 8.15 (s, 1H)

The prepared compound was analysed by XRPD resulting in the diffractogram shown in
20 Figure 3.

25

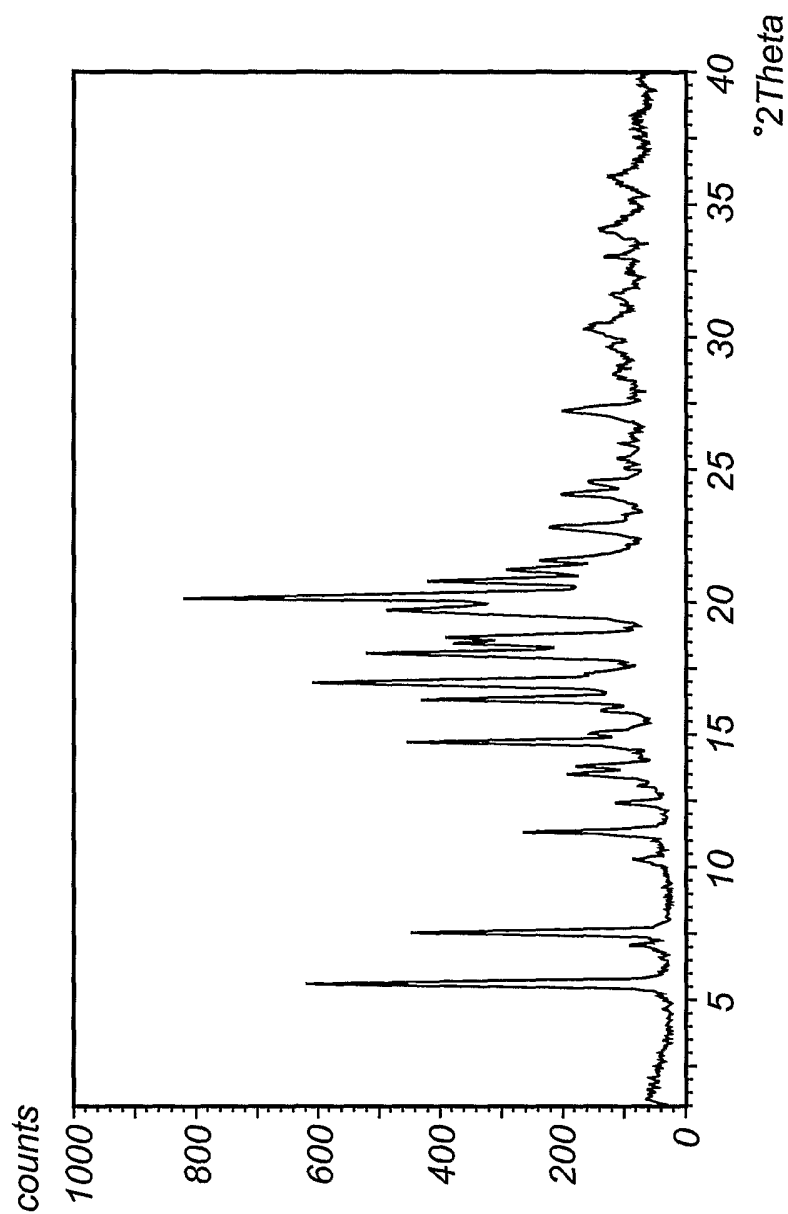
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Claims

1. Adamantan ammonium salts of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole (omeprazole) and of (*S*)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole (esomeprazole).
5
2. The adamantan ammonium salt according to claim 1 wherein the salt is 1-adamantan ammonium salt of omeprazole.
- 10 3. The adamantan ammonium salt according to claim 1 wherein the salt is 1-adamantan ammonium salt of esomeprazole.
4. The adamantan ammonium salt according to any of claims 1, wherein the salt is 2-adamantan ammonium salt of omeprazole.
- 15 5. The adamantan ammonium salt according to claim 1, wherein the salt is 2-adamantan ammonium salt of esomeprazole.
6. The adamantan ammonium salts according to any of claims 1 to 5 characterized in
20 that the compound is crystalline.
7. A process for preparation of an adamantan ammonium salt of omeprazole and of esomeprazole, according to any of claims 1 to 6, which comprises the following steps:
 - a) dissolving omeprazole or esomeprazole in an organic solvent;
 - 25 b) adding an adamantan amine and precipitating the desired salt;
 - c) isolating and drying of the obtained salt of omeprazole or esomeprazole.
8. The process according to claim 7 wherein the organic solvent is selected from acetonitril, ethylacetate, *tert*-butyl methyl ether and methanol, or a mixture thereof.

9. The process according to claim 7 wherein the organic solvent is selected from acetonitril, ethylacetate and methanol, or mixtures thereof.
10. The process according to any of claims 7 to 9 wherein an adamantan ammonium
5 salt of omeprazole is obtained.
11. The process according to any of claims 7 to 9 wherein an adamantan ammonium salt of esomeprazole is obtained.
- 10 12. A pharmaceutical composition comprising the adamantan ammonium salt of omeprazole or esomeprazole according to any of claims 1 to 6 as active ingredients in association with pharmaceutically acceptable excipients and optionally other therapeutic ingredients.
- 15 13. Use of the adamantan ammonium salt of omeprazole or esomeprazole according to any of claims 1 to 6 for the manufacture of a medicament for use in the treatment of gastric acid related condition.
14. A method for treatment of a gastric acid related condition which method
20 comprised administering to a subject suffering from said condition a therapeutically effective amount of the adamantan ammonium salt of omeprazole or esomeprazole according to any of claims 1 to 6.

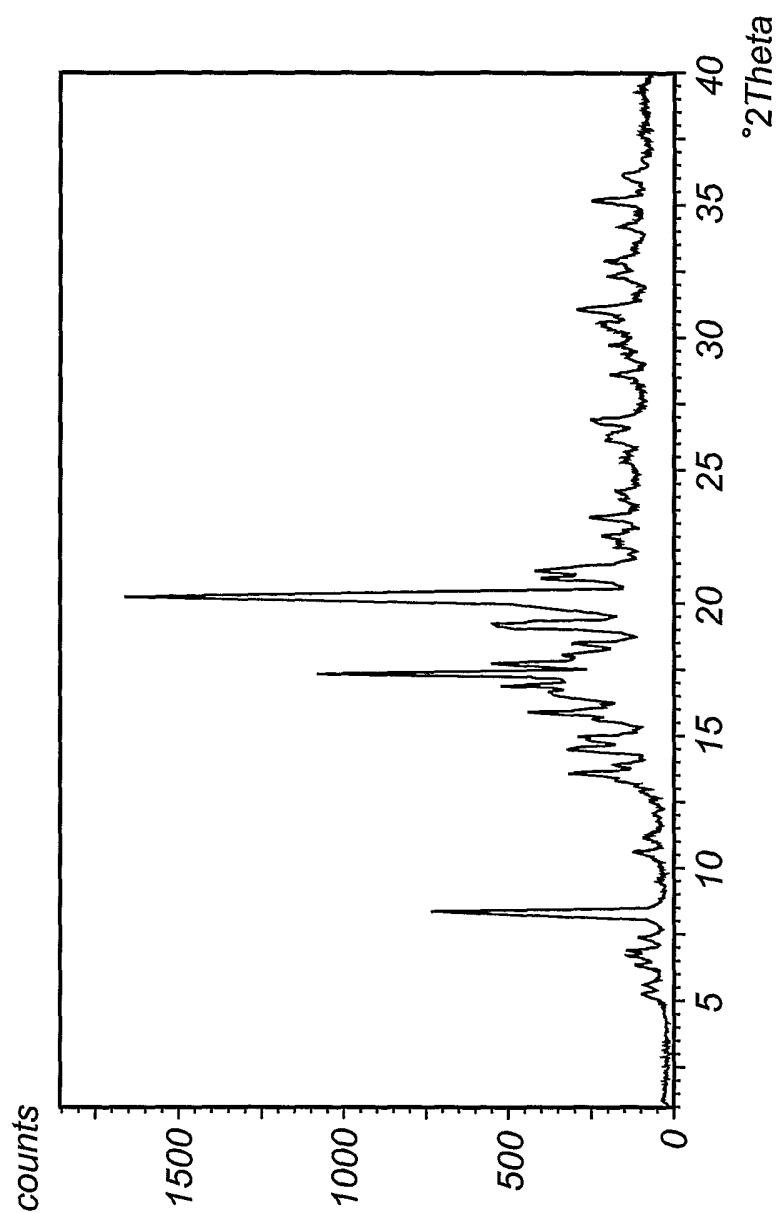
1/3



Omeprazol-adamantan ammonium salt

Figure 1

2/3



Esomeprazol-adamantanammoniumsalt,

Figure 2

3/3

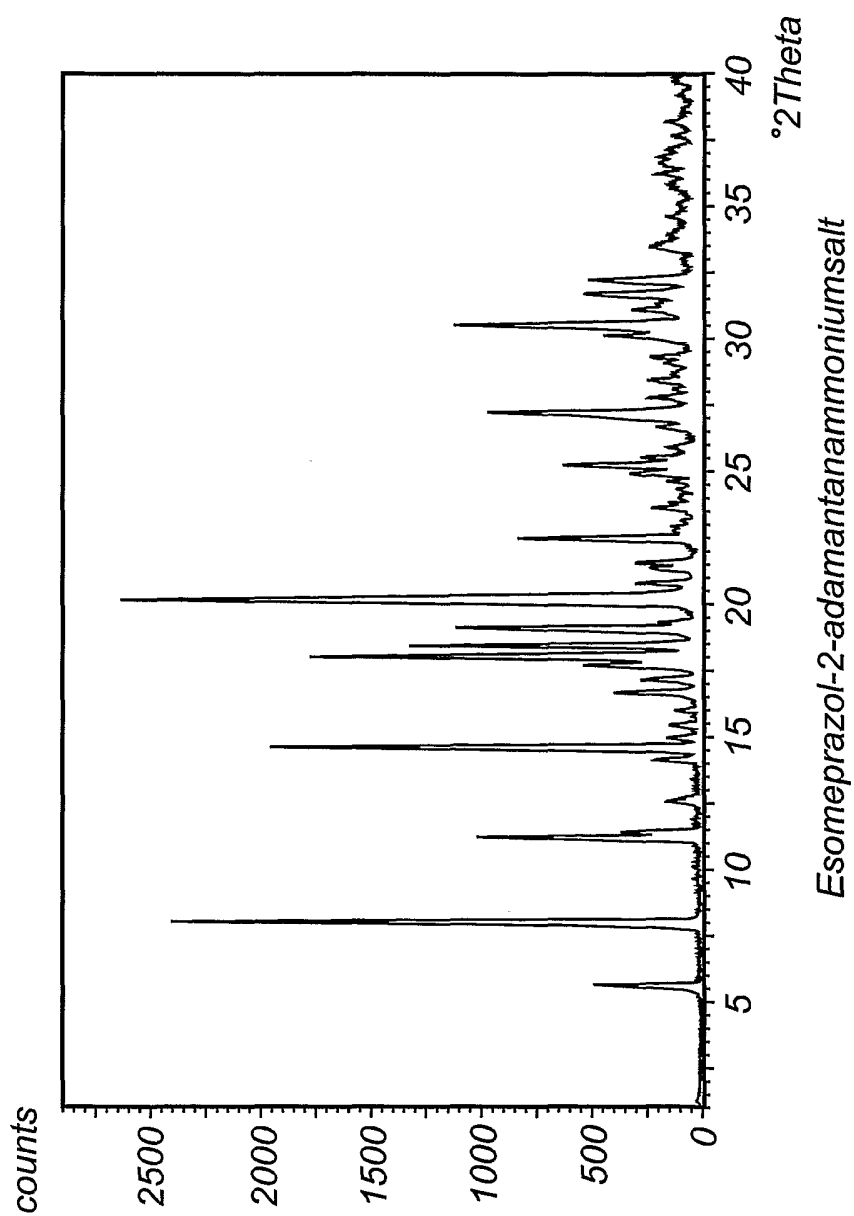


Figure 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/001258

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12, A61K 31/4439, C07C 211/38, A61P 1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0124495 A2 (AKTIEBOLAGET HÄSSLE), 7 November 1984 (07.11.1984) --	1-14
A	WO 9427988 A1 (ASTRA AKTIEBOLAG), 8 December 1994 (08.12.1994) -- -----	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

4 January 2005

Date of mailing of the international search report

05-01-2005

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

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Authorized officer

PER RENSTRÖM/BS

Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001258

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **14**
because they relate to subject matter not required to be searched by this Authority, namely:
see extra sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001258

Box II.1

Claim 14 relates to methods of treatment of the human or animal body by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/11/2004

International application No.

PCT/SE 2004/001258

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INTERNATIONAL SEARCH REPORT

Information on patent family members

27/11/2004

International application No.

PCT/SE 2004/001258

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