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Of Counsel for Plaintiffs

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC.,

Plaintiffs,

v.

MACLEODS PHARMACEUTICALS LTD. and MACLEODS PHARMA USA, INC.,

Defendants.

Civil Action No. _____

COMPLAINT FOR PATENT INFRINGEMENT AND CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 11.2

Plaintiffs AstraZeneca AB, Aktiebolaget Hassle, AstraZeneca LP, and Zeneca Inc. (collectively, "Plaintiffs"), by their attorneys, for their Complaint against Macleods Pharmaceuticals Ltd. ("Macleods") and Macleods Pharma USA, Inc. ("Macleods USA"), allege as follows:

NATURE OF THE ACTION

1. This is a civil action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 100 *et seq.*, and in particular under 35 U.S.C. § 271(e). This action relates to Abbreviated New Drug Application ("ANDA") No. 208511 filed by or for the benefit of Macleods and Macleods USA (collectively, "Defendants") with the United States Food and Drug Administration ("FDA") for approval to market generic versions of Plaintiffs' NEXIUM® pharmaceutical products that are sold in the United States.

THE PARTIES

2. Plaintiff AstraZeneca AB ("AZ AB") is a corporation operating and existing under the laws of the Sweden, with its principal place of business at S-151 85 Södertälje, Sweden.

3. Plaintiff Aktiebolaget Hässle ("Hässle") is a corporation organized and existing under the laws of Sweden, having its principal place of business at Mölndal, Sweden.

4. Plaintiff AstraZeneca LP ("AZ LP") is a limited partnership operating and existing under the laws of the State of Delaware, with its principal place of business at 1800 Concord Pike, Wilmington, Delaware 19803. AZ LP holds an approved New Drug Application from the FDA for an esomeprazole magnesium formulation which it sells under the name NEXIUM®.

5. Plaintiff Zeneca Inc. ("Zeneca") is a Delaware corporation having its principal place of business at Wilmington, Delaware. Zeneca has exclusive rights in the United States to market and sell products covered by United States Patent Nos. 6,369,085; 7,411,070; and 8,466,175.

6. Upon information and belief, Macleods is an Indian company having its principal place of business at Atlanta Arcade, Marol Church Road, Andheri (East), Mumbai, India 400059. Upon information and belief, Macleods is in the business of developing, manufacturing, marketing, and selling generic drugs.

7. Upon information and belief, Macleods USA is a wholly-owned subsidiary of Macleods.

8. Upon information and belief, Macleods USA is a corporation organized under the laws of the State of Delaware, with its principal place of business at 666 Plainsboro Road, Building 200, Suite 230, Plainsboro, New Jersey 08536. Upon information and belief, Macleods USA is in the business of marketing, distributing, and selling, in the State of New Jersey and throughout the United States, pharmaceutical drugs, including generic pharmaceutical drugs manufactured by Macleods.

9. Upon information and belief, Defendants collaborate to manufacture, import, market, distribute, and sell generic pharmaceutical products in the State of New Jersey and the throughout the United States.

10. Upon information and belief, following any FDA approval of ANDA No. 208511, Macleods itself and through its U.S. agent, Macleods USA, will make, use, offer to sell, and/or sell the generic drug products that are the subject of ANDA No. 208511 throughout the United States, and/or import such generic drug products into the United States.

BACKGROUND

The NDA

11. AZ LP is the holder of New Drug Application ("NDA") No. 21153 for NEXIUM® Esomeprazole Magnesium Delayed-Release Capsules, in 20 mg and 40 mg dosage forms. NEXIUM® is a prescription drug approved for use to relieve the symptoms of acid reflux disease and treat erosive esophagitis. Esomeprazole magnesium trihydrate is the active ingredient in NEXIUM®.

The Patents-in-Suit

12. United States Patent No. 6,369,085 ("the '085 patent"), entitled "Form of S-Omeprazole," was duly and legally issued by the United States Patent and Trademark Office ("the USPTO") on April 9, 2002 to AZ AB, upon assignment from the inventors Hanna Cotton, Anders Kronstrom, Anders Mattson, and Eva Möller. The '085 patent claims, *inter alia*, magnesium salts of esomeprazole trihydrate, pharmaceutical compositions comprising the claimed salts, methods of treatment using the claimed salts, and processes for preparing the claimed salts. A true and correct copy of the '085 patent is attached as Exhibit A.

13. Plaintiff AZ AB has been and still is the owner of the '085 patent. The '085 patent will expire on May 25, 2018, and pediatric exclusivity relating to the '085 patent expires on November 25, 2018.

14. United States Patent No. 7,411,070 ("the '070 patent"), entitled "Form of S-omeprazole," was duly and legally issued by the USPTO on August 12, 2008 to AZ AB upon assignment from inventors Hanna Cotton, Anders Kronstrom, Anders Mattson, and Eva Moller. The claims of the '070 patent are directed to, *inter alia*, magnesium salts of esomeprazole

trihydrate and processes for preparing the claimed salts. A true and correct copy of the '070 patent is attached as Exhibit B.

15. Plaintiff AZ AB has been and still is the owner of the '070 patent. The '070 patent will expire on May 25, 2018, and pediatric exclusivity relating to the '070 patent expires on November 25, 2018.

16. United States Patent No. 8,466, 175 ("the '175 patent"), entitled "Form of S-omeprazole," was duly and legally issued by the USPTO on June 18, 2013 to AZ AB upon assignment from inventors Hanna Cotton, Anders Kronstrom, Anders Mattson, and Eva Moller. The claims of the '175 patent are directed to, *inter alia*, methods of treating Heliobacter infections comprising administration of magnesium salts of esomeprazole trihydrate. A true and correct copy of the '175 patent is attached as Exhibit C.

17. Plaintiff AZ AB has been and still is the owner of the '175 patent. The '175 patent will expire on May 25, 2018, and pediatric exclusivity relating to the '175 patent expires on November 25, 2018.

The ANDA

18. On information and belief, Macleods filed ANDA No. 208511 with the FDA under 21 U.S.C. § 355(j) to obtain FDA approval for the commercial manufacture, use, importation, offer for sale, and sale in the United States of esomeprazole magnesium delayed-release pellets, 20 mg and 40 mg ("Macleods's Esomeprazole Magnesium Delayed-Release Pellets"), which are generic versions of Plaintiffs' NEXIUM® Esomeprazole Magnesium Delayed-Release Capsules, in 20 mg and 40 mg dosage forms.

19. By letter dated February 8, 2016 (the "ANDA Notice Letter"), Macleods notified Plaintiffs that Macleods had filed ANDA No. 208511 seeking approval to market Macleods's

Esomeprazole Magnesium Delayed-Release Pellets and that Macleods was providing information to Plaintiffs pursuant to 21 U.S.C. § 355(j)(2)(B) and 21 C.F.R. § 314.95. Macleods's ANDA Notice Letter failed to provide "the name and address of an agent in the United States authorized to accept service of process" for applicants that, like Macleods, do not reside or have a place of business in the United States. *See* 21 C.F.R. § 314.95(c)(7).

JURISDICTION AND VENUE

20. Subject matter jurisdiction over this action is proper pursuant to the provisions of Title 28, United States Code, Sections 1331 and 1338(a).

21. Upon information and belief, Macleods is an Indian company having its principal place of business at Atlanta Arcade, Marol Church Road, Andheri (East), Mumbai, India 400059. Upon information and belief, Macleods is in the business of developing, manufacturing, marketing, and selling generic drugs.

22. On information and belief, Macleods, either directly or through one or more of its wholly owned subsidiaries and/or agents, develops, manufactures, distributes, markets, offers to sell, and sells generic drug products for sale and use throughout the United States, including within the judicial district.

23. Upon information and belief, Macleods purposefully has conducted and continues to conduct business, directly or indirectly, in this judicial district, and this judicial district is a likely destination of Macleods's generic products. Upon information and belief, Macleods is a "truly global pharmaceutical company" that has grown at an average rate of 22% over the last five years. *See* http://www.macleodspharma.com/default.asp. Upon information and belief, "Macleods has received FDA approval on 9 Abbreviated New Drug Applications and has

another 60 filed and awaiting approval." *See* http://www.macleodspharma.com/UnitedStates.asp.

24. On information and belief, Macleods USA is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 666 Plainsboro Road, Building 200, Suite 230, Plainsboro, New Jersey 08536. Macleods has designated Macleods Pharma USA, Inc., located in New Jersey, to accept service of process for this matter.

25. On information and belief, Macleods USA is in the business of marketing, distributing, and selling, in the State of New Jersey and throughout the United States, pharmaceutical drugs, including generic pharmaceutical drugs manufactured by Macleods.

26. On information and belief, Defendants acted in concert to develop Macleods's Esomeprazole Magnesium Delayed-Release Pellets and to seek approval from the FDA to sell Macleods's Esomeprazole Magnesium Delayed-Release Pellets throughout the United States, including within this judicial district.

27. On information and belief, and as stated in the ANDA Notice Letter, Macleods prepared and filed ANDA No. 208511.

28. On information and belief, and as stated in the ANDA Notice Letter, the FDA received ANDA No. 208511 from Macleods.

29. On information and belief, by virtue of, *inter alia*, Macleods's preparation and/or filing of ANDA No. 208511 and sales-related activities in New Jersey, including but not limited to the substantial, continuous, and systematic distribution, marketing, and/or sales of pharmaceutical products to residents of New Jersey, this Court has personal jurisdiction over Macleods. *See, e.g.*, *Acorda Therapeutics Inc. v. Mylan Pharm. Inc.*, No. 15-1456, slip op. at 14 (Fed. Cir. Mar. 18, 2016) (holding that minimum-contacts requirement for specific personal

jurisdiction is established where Defendant's "ANDA filings and its distribution channels establish that [the Defendant] plans to market its proposed drugs in [the State where the complaint was filed] and the lawsuit is about patent constraints on such in-State marketing.")

30. On information and belief, Macleods has previously been sued in this district and has not challenged personal jurisdiction. *See, e.g., AstraZeneca Pharmaceuticals LP et al. v. Macleods Pharmaceuticals, Ltd. et al.*, Civ. Action No. 2:15-cv-01513-CCC-MF (D.N.J.); *Otsuka Pharmaceutical Co., Ltd. v. Macleods Pharmaceuticals, Ltd. et al.*, Civ. Action No. 1:15-cv-5109-JBS-KMW (D.N.J.).

31. On information and belief, Macleods has availed itself of the jurisdiction of this court by asserting counterclaims in this district. *See, e.g., Otsuka Pharmaceutical Co., Ltd. v. Macleods Pharmaceuticals, Ltd. et al.*, Civ. Action No. 1:15-cv-5109-JBS-KMW (D.N.J.).

32. Venue is proper in this District pursuant to the provisions of Title 28, United States Code, Sections 1391(c) and (d), and 1400 (b).

COUNT 1: INFRINGEMENT OF THE '085 PATENT

33. Plaintiffs incorporate by reference paragraphs 1-32 of this Complaint as if fully set forth herein.

34. On information and belief, Defendants submitted ANDA No. 208511 to the FDA under 21 U.S.C. § 355(j) in order to obtain approval to market their Esomeprazole Magnesium Delayed-Release Pellets in the United States before the expiration of the '085 patent.

35. By their ANDA Notice Letter, Defendants informed Plaintiffs that they had submitted to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the '085 patent is invalid, unenforceable, or will not be infringed by the commercial

manufacture, use, sale, offer for sale, or importation into the United States of Macleods's Esomeprazole Magnesium Delayed-Release Pellets.

36. Under 35 U.S.C. § 271(e)(2)(A), the submission by Defendants to the FDA of ANDA No. 208511 to obtain approval for the commercial manufacture, use, sale, offer for sale, or importation into the United States of Macleods's Esomeprazole Magnesium Delayed-Release Pellets before the expiration of the '085 patent constitutes infringement of one or more claims of the '085 patent, either literally or under the doctrine of equivalents.

37. On information and belief, Macleods's Esomeprazole Magnesium Delayed-Release Pellets, if approved by the FDA, will be prescribed and administered to human patients in a therapeutically effective amount to inhibit gastric acid secretion and for the treatment of gastrointestinal inflammatory disease. On information and belief, this administration will occur at Defendants' active behest and with their intent, knowledge, and encouragement. On information and belief, Defendants will actively encourage, aid and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '085 patent.

38. The ANDA Notice Letter, which is required by statute and regulation to provide a full and detailed explanation regarding all defenses, provides only a bare allegation of invalidity and unenforceability of the '085 patent's claims without any explanation or identifying any legal basis or supporting facts. Because Defendants allege that the '085 patent is invalid or unenforceable without any explanation or identifying any legal basis or supporting facts, Defendants effectively admit that the '085 patent is both valid and enforceable.

39. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

COUNT 2: INFRINGEMENT OF THE '070 PATENT

40. Plaintiffs incorporate by reference paragraphs 1-39 of this Complaint as if fully set forth herein.

41. On information and belief, Defendants submitted ANDA No. 208511 to the FDA under 21 U.S.C. § 355(j) in order to obtain approval to market Macleods's Esomeprazole Magnesium Delayed-Release Pellets in the United States before the expiration of the '070 patent.

42. By their ANDA Notice Letter, Defendants informed Plaintiffs that they had submitted to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the '070 patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, sale, offer for sale, or importation into the United States of Macleods's Esomeprazole Magnesium Delayed-Release Pellets.

43. Under 35 U.S.C. § 271(e)(2)(A), the submission by Defendants to the FDA of ANDA No. 208511 to obtain approval for the commercial manufacture, use, sale, offer for sale, or importation into the United States of Macleods's Esomeprazole Magnesium Delayed-Release Pellets before the expiration of the '070 patent constitutes infringement of one or more claims of the '070 patent, either literally or under the doctrine of equivalents.

44. On information and belief, Macleods's Esomeprazole Magnesium Delayed-Release Pellets, if approved by the FDA, will be prescribed and administered to human patients in a therapeutically effective amount to inhibit gastric acid secretion and for the treatment of gastrointestinal inflammatory disease. On information and belief, this administration will occur at Defendants' active behest and with their intent, knowledge, and encouragement. On information and belief, Defendants will actively encourage, aid and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '070 patent.

45. The ANDA Notice Letter, which is required by statute and regulation to provide a full and detailed explanation regarding all defenses, provides only a bare allegation of invalidity and unenforceability of the '070 patent's claims without any explanation or identifying any legal basis or supporting facts. Because Defendants allege that the '070 patent is invalid or unenforceable without any explanation or identifying any legal basis or supporting facts, Defendants effectively admit that the '070 patent is both valid and enforceable.

46. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

COUNT 3: INFRINGEMENT OF THE '175 PATENT

47. Plaintiffs incorporate by reference paragraphs 1-46 of this Complaint as if fully set forth herein.

48. On information and belief, Defendants submitted ANDA No. 208511 to the FDA under 21 U.S.C. § 355(j) in order to obtain approval to market Macleods's Esomeprazole Magnesium Delayed-Release Pellets in the United States before the expiration of the '175 patent.

49. By their ANDA Notice Letter, Defendants informed Plaintiffs that they had submitted to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the '175 patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, sale, offer for sale, or importation into the United States of Macleods's Esomeprazole Magnesium Delayed-Release Pellets.

50. Under 35 U.S.C. § 271(e)(2)(A), the submission by Defendants to the FDA of ANDA No. 208511 to obtain approval for the commercial manufacture, use, sale, offer for sale, or importation into the United States of Macleods's Esomeprazole Magnesium Delayed-Release

Pellets before the expiration of the '175 patent constitutes infringement of one or more claims of the '175 patent, either literally or under the doctrine of equivalents.

51. On information and belief, Macleods's Esomeprazole Magnesium Delayed-Release Pellets, if approved by the FDA, will be prescribed and administered to human patients in a therapeutically effective amount to inhibit gastric acid secretion and for the treatment of gastrointestinal inflammatory disease, including Heliobacter infection. On information and belief, this administration will occur at Defendants' active behest and with their intent, knowledge, and encouragement. On information and belief, Defendants will actively encourage, aid and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '175 patent.

52. The ANDA Notice Letter, which is required by statute and regulation to provide a full and detailed explanation regarding all defenses, provides only a bare allegation of invalidity and unenforceability of the '175 patent's claims without any explanation or identifying any legal basis or supporting facts. Because Defendants allege that the '175 patent is invalid or unenforceable without any explanation or identifying any legal basis or supporting facts, Defendants effectively admit that the '175 patent is both valid and enforceable.

53. Plaintiffs will be substantially and irreparably harmed by the infringing activities described above unless those activities are precluded by this Court. Plaintiffs have no adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that the claims of the '085, '070, and '175 patents are valid and enforceable;

B. A judgment that the submission of ANDA No. 208511 by Defendants infringes one or more claims of each of the '085, '070, and '175 patents under 35 U.S.C. § 271(e)(2);

C. A judgment providing that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any FDA approval of Macleods's ANDA No. 208511 shall be no earlier than the latest expiration date of the Patents-in-Suit and any additional periods of exclusivity;

D. A judgment pursuant to 35 U.S.C. § 271(e)(4)(B) permanently enjoining Defendants, and all persons acting in concert with Defendants, from making, using, selling, offering to sell, or importing the esomeprazole magnesium product described in Defendants' ANDA No. 208511 prior to the latest expiration of the Patents-in-Suit and any additional periods of exclusivity;

E. Attorneys' fees in this action pursuant to 35 U.S.C. § 285;

F. Costs and expenses in this action; and

G. Such further and other relief as this Court may deem just and proper.

Dated: March 24, 2016

Respectfully submitted,

s/ John E. Flaherty

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Of Counsel for Plaintiffs

CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Pursuant to Local Civil Rule 11.2, I hereby certify that the matter in controversy is related to the subject matter of the following actions:

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. MYLAN LABORATORIES LTD. and MYLAN, INC.*, C.A. No. 3:12-cv- 01378-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. WATSON LABORATORIES, INC. – FLORIDA*, C.A. No. 3:13-cv-01669- MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. WOCKHARDT LIMITED and WOCKHARDT USA LLC*, C.A. No. 3:13- cv-04854-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. AUROBINDO PHARMA LIMITED and AUROBINDO PHARMA USA Inc.*, C.A. No. 3:13-cv-7298-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. KREMERS URBAN PHARMACEUTICALS, KREMERS URBAN DEVELOPMENT CO., and KREMERS URBAN LLC*, C.A. No. 3:13-cv-7299-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. ZYDUS PHARMACEUTICALS (USA) INC., and CADILA HEALTHCARE LTD. (dba ZYDUS CADILA)*, C.A. No. 3:14-cv-4782-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. ACTAVIS LABORATORIES FL, INC., and ACTAVIS PHARMA, INC.*, C.A. No. 3:14-cv-7870-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. ANDRX LABS, LLC, ANDRX CORPORATION, and ACTAVIS, INC.*, C.A. No. 3:14-cv-8030-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. PERRIGO COMPANY PLC, PERRIGO COMPANY, L. PERRIGO COMPANY, and PADDOCK LABORATORIES, LLC*, C.A. No. 3:15-cv-1057-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. HEC PHARM CO., LTD., HEC PHARM GROUP, and HEC PHARM USA INC.*, C.A. No. 3:15-cv-06025-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. LUPIN LTD. and LUPIN PHARMACEUTICALS INC.,*, C.A. No. 3:15-cv-06092-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. ALKEM LABORATORIES LTD., and ASCEND LABORATORIES, LLC.*, C.A. No. 3:15-cv-06609-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. ZYDUS PHARMACEUTICALS (USA) INC., and CADILA HEALTHCARE LTD. (dba ZYDUS CADILA)*, C.A. 3:15-cv-07415-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC.*, C.A. No. 3:15-cv-08267-MLC-TJB (District of New Jersey)

Date: March 24, 2016

By: *s/ John E. Flaherty*

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Of Counsel for Plaintiffs

JS 44 (Rev. 12/12)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC.

(b) County of Residence of First Listed Plaintiff Sweden
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, Email and Telephone Number)*
John E. Flaherty, Esq.
McCarter & English, LLP, Four Gateway Center, 100 Mulberry Street, Newark, NJ, 07102. Tel: 973-622-4444 Email: jflaherty@mccarter.com

DEFENDANTS

MACLEODS PHARMACEUTICALS LTD. and MACLEODS PHARMA USA, INC.

County of Residence of First Listed Defendant Mumbai, India
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	❒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	❒ 4
Citizen of Another State	❒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	❒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
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FORFEITURE/PENALTY
- ❒ 625 Drug Related Seizure of Property 21 USC 881
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- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Management Relations
- ❒ 740 Railway Labor Act
- ❒ 751 Family and Medical Leave Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Employee Retirement Income Security Act

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- ❒ 462 Naturalization Application
- ❒ 465 Other Immigration Actions

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ☒ 830 Patent
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

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- ❒ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from Another District *(specify)* ❒ 6 Multidistrict Litigation

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 U.S.C. §271

Brief description of cause:
Patent Infringement (ANDA)

VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ❒ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE Hon. Mary L. Cooper, U.S.D.J. / Hon. Tonianne J. Bongiovanni, U.S.M.J. DOCKET NUMBER Please see attached

DATE
03/24/2016

SIGNATURE OF ATTORNEY OF RECORD
s/ John E. Flaherty

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CIVIL COVER SHEET ATTACHMENT

Related Cases

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. MYLAN LABORATORIES LTD. and MYLAN, INC.*, C.A. No. 3:12-cv-01378-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. WATSON LABORATORIES, INC. – FLORIDA*, C.A. No. 3:13-cv-01669-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. WOCKHARDT LIMITED and WOCKHARDT USA LLC*, C.A. No. 3:13-cv-04854-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. AUROBINDO PHARMA LIMITED and AUROBINDO PHARMA USA Inc.*, C.A. No. 3:13-cv-7298-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. KREMERS URBAN PHARMACEUTICALS, KREMERS URBAN DEVELOPMENT CO., and KREMERS URBAN LLC*, C.A. No. 3:13-cv-7299-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC. v. ZYDUS PHARMACEUTICALS (USA) INC., and CADILA HEALTHCARE LTD. (dba ZYDUS CADILA)*, C.A. No. 3:14-cv-4782-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. ACTAVIS LABORATORIES FL, INC., and ACTAVIS PHARMA, INC.*, C.A. No. 3:14-cv-7870-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. ANDRX LABS, LLC, ANDRX CORPORATION, and ACTAVIS, INC.*, C.A. No. 3:14-cv-8030-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. PERRIGO COMPANY PLC, PERRIGO COMPANY, L. PERRIGO COMPANY, and PADDOCK LABORATORIES, LLC*, C.A. No. 3:15-cv-1057-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. HEC PHARM CO., LTD., HEC PHARM GROUP, and HEC PHARM USA INC.*, C.A. No. 3:15-cv-06025-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. LUPIN LTD. and LUPIN PHARMACEUTICALS INC.*,, C.A. No. 3:15-cv-06092-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. ALKEM LABORATORIES LTD., and ASCEND LABORATORIES, LLC.*, C.A. No. 3:15-cv-06609-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. ZYDUS PHARMACEUTICALS (USA) INC., and CADILA HEALTHCARE LTD. (dba ZYDUS CADILA)*, C.A. 3:15-cv-07415-MLC-TJB (District of New Jersey)

- *ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and ZENECA INC. v. DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC.*, C.A. No. 3:15-cv-08267-MLC-TJB (District of New Jersey)

EXHIBIT A

US006369085B1

(12) **United States Patent**
Cotton et al.

(10) **Patent No.: US 6,369,085 B1**
(45) **Date of Patent: Apr. 9, 2002**

(54) **FORM OF S-OMEPRAZOLE**

(75) Inventors: **Hanna Cotton**; **Anders Kronström**; **Anders Mattson**; **Eva Möller**, all of Södertälje (SE)

(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/077,719**

(22) PCT Filed: **May 5, 1998**

(86) PCT No.: **PCT/SE98/00974**

§ 371 Date: **Jun. 8, 1998**

§ 102(e) Date: **Jun. 8, 1998**

(87) PCT Pub. No.: **WO98/54171**

PCT Pub. Date: **Dec. 3, 1998**

(30) **Foreign Application Priority Data**

May 30, 1997 (SE) 9702065

(51) **Int. Cl.**[7] **A61K 31/4439**; C07D 401/12
(52) **U.S. Cl.** **514/338**; 546/273.7
(58) **Field of Search** 514/338; 546/273.7

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Primary Examiner—Jane Fan
(74) *Attorney, Agent, or Firm*—White & Case LLP

(57) **ABSTRACT**

The present invention relates to a novel form of the (–)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. S-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

12 Claims, 5 Drawing Sheets

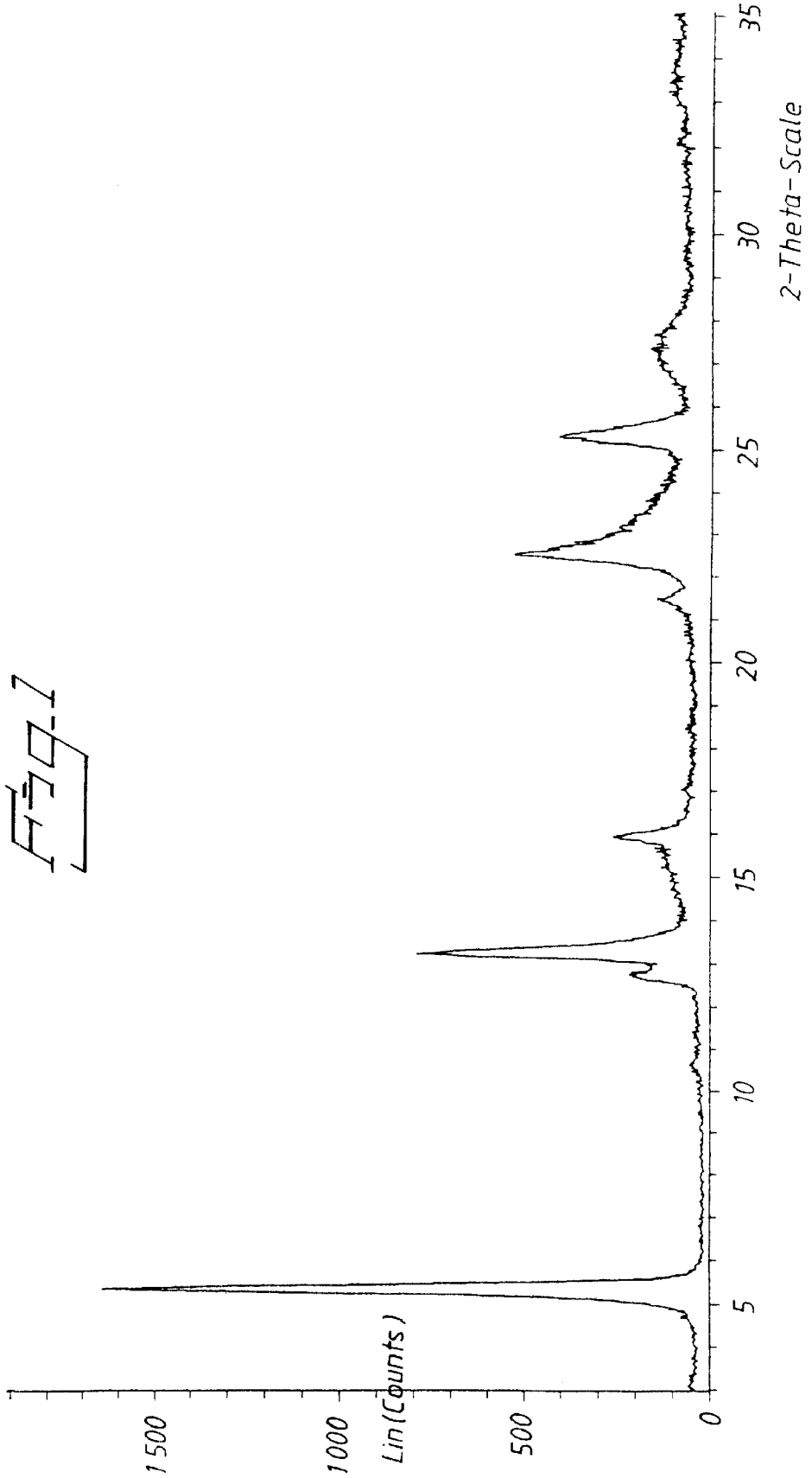


Fig. 1

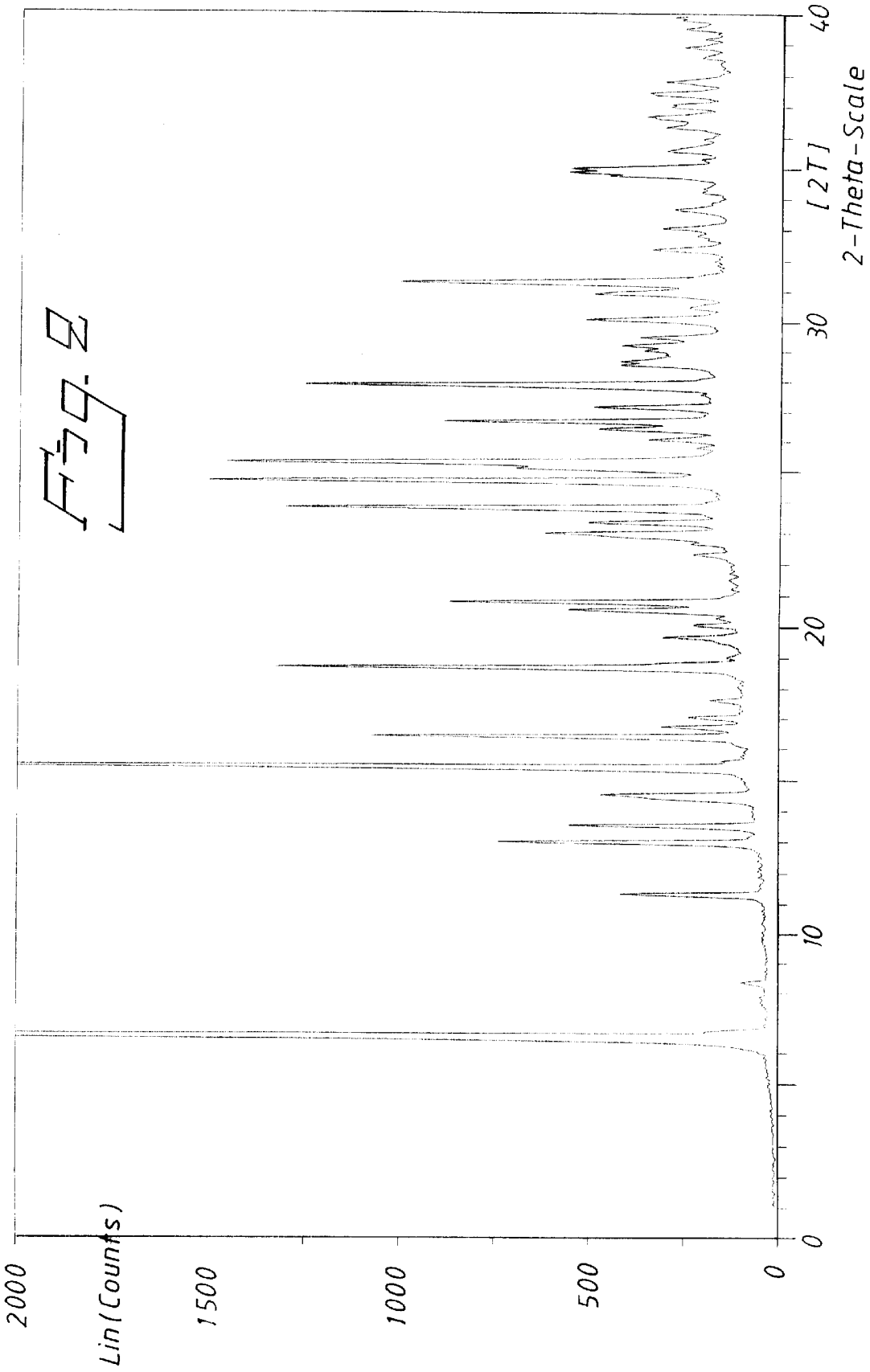


Fig. 2

Fig. 3

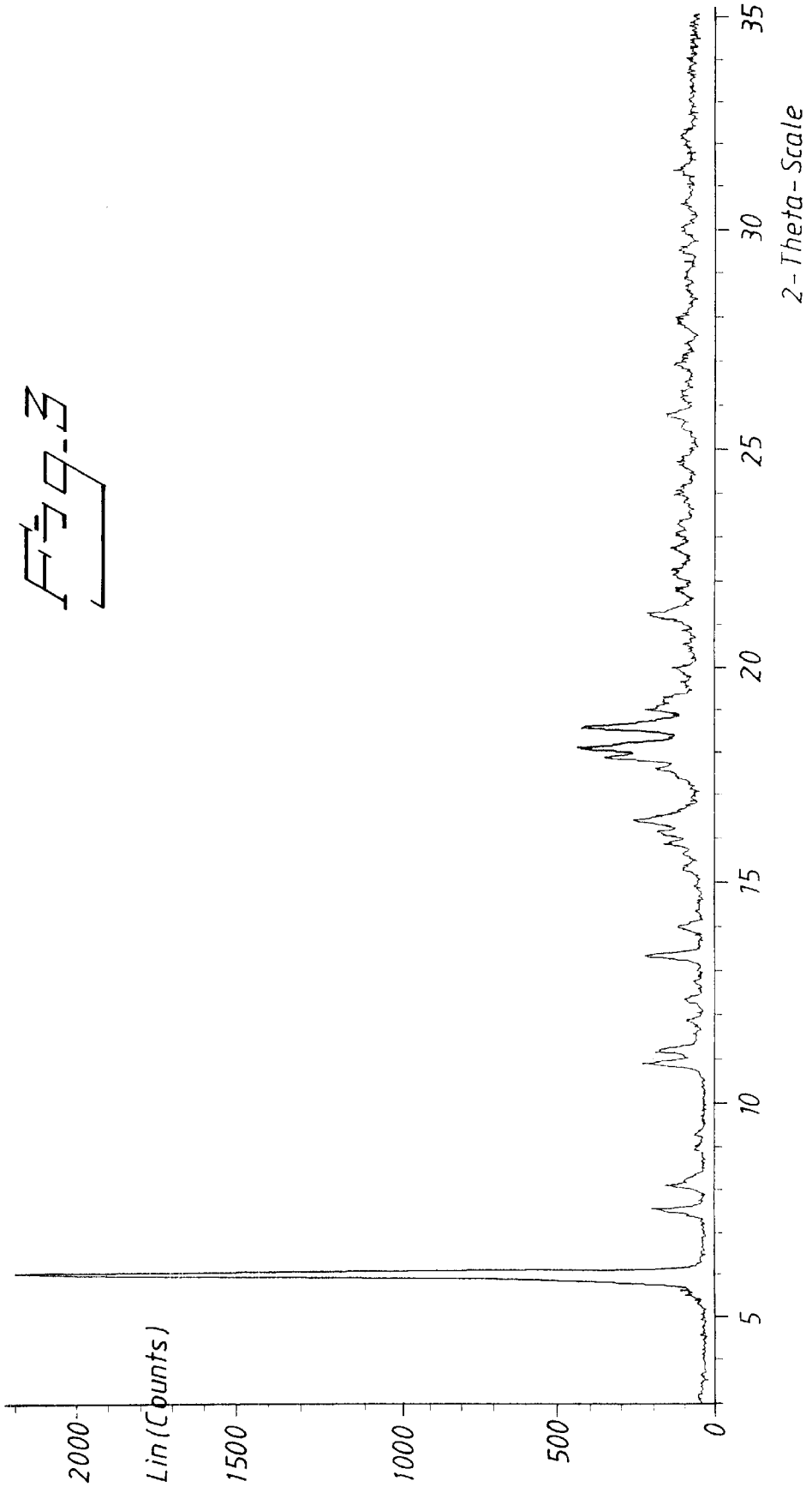
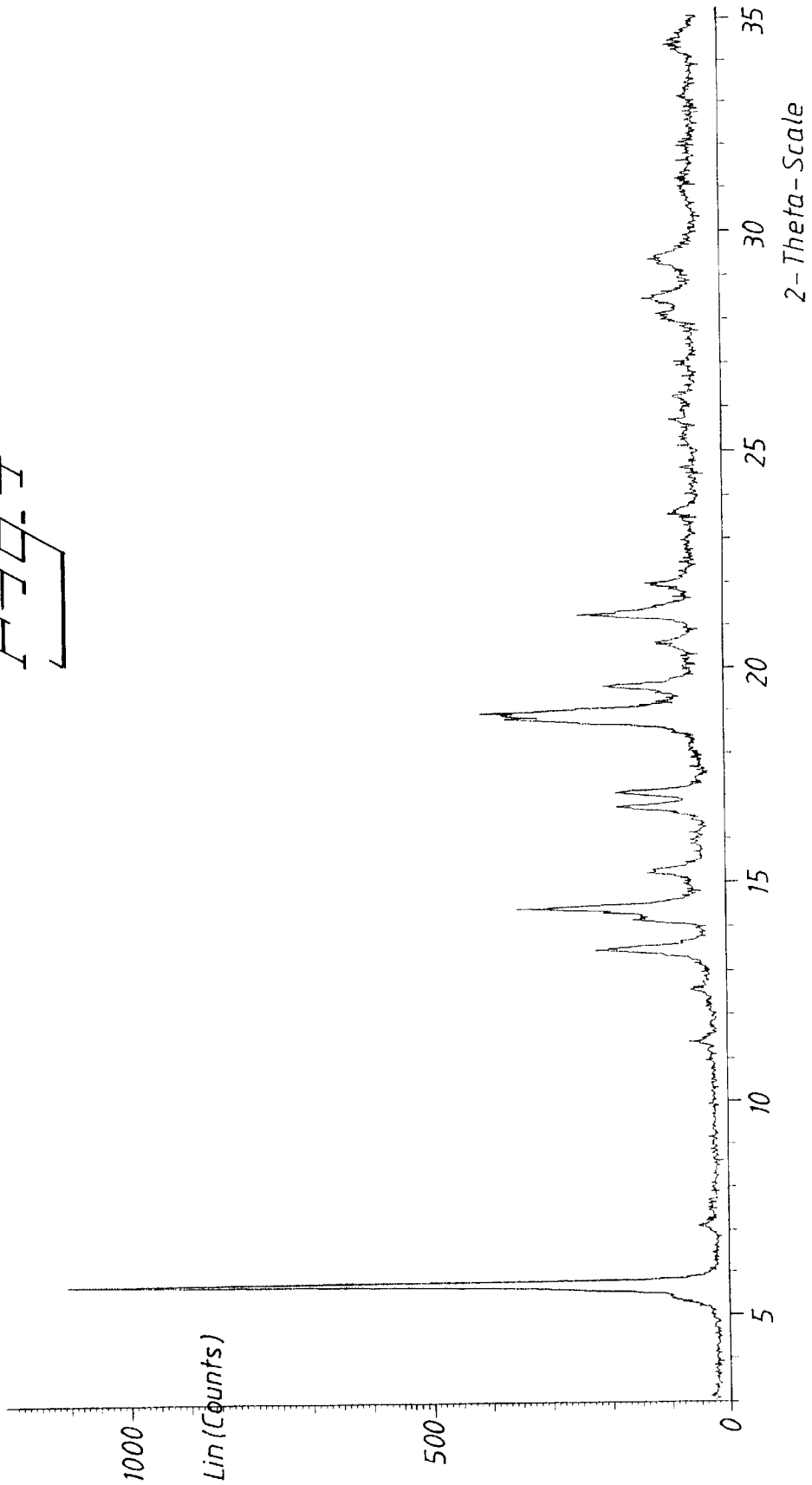


Fig. 4



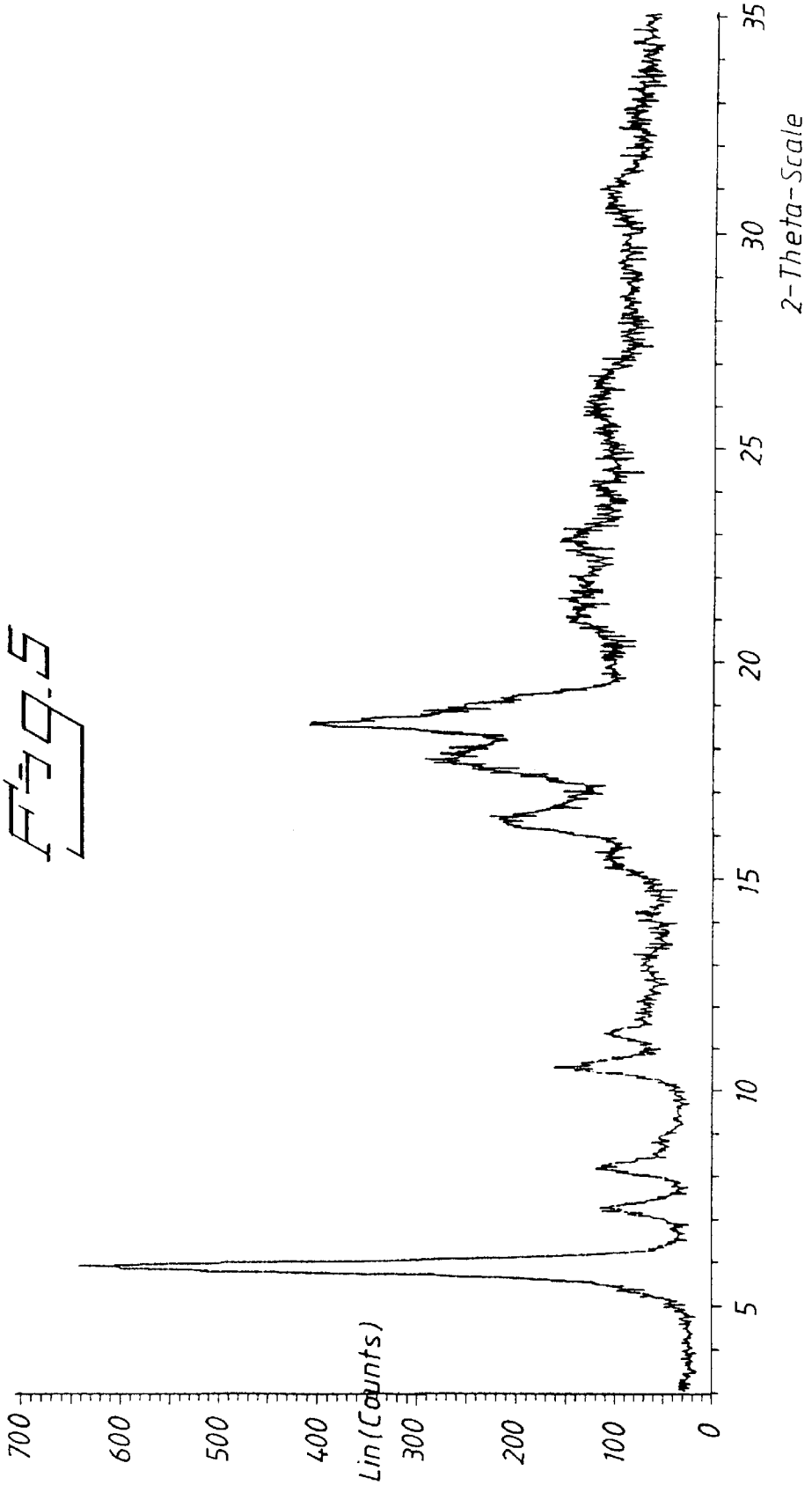

Lin(Counts)
0
100
200
300
400
500
600
700
5
10
15
20
25
30
35
2-Theta-Scale

Fig. 5

FORM OF S-OMEPRAZOLE

This application is a 371 of PCT/SE98/00974, May 5, 1998 now WO 9854171 Dec. 3, 1998.

FIELD OF THE INVENTION

The present invention relates to a novel form of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. S-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to intermediates used in the process, and their preparation.

BACKGROUND OF THE INVENTION AND PRIOR ART

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are disclosed in EP 124 495. Omeprazole is a proton pump inhibitor, i.e. effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R and S-enantiomer of omeprazole, herein referred to as R-omeprazole and S-omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (−)-enantiomer of the non-salt form were found to have R and S configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (−)-enantiomer of the magnesium salt were also found to have R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

Certain salts of single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988. These compounds have improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.

WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts of R- and S-omeprazole.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a X-ray powder diffractogram of the magnesium salt of S-omeprazole trihydrate prepared according to the present invention.

FIG. **2** shows a X-ray powder diffractogram of the potassium salt of S-omeprazole prepared and used in the present application (See examples 2 and 3)

FIG. **3** shows a X-ray powder diffractogram of a magnesium salt of S-omeprazole dihyclrate prepared and used in the present application (See example 5)

FIG. **4** shows a X-ray powder diffractogram of a magnesium salt of S-omeprazole dihyclrate which is a polymorph of the dihydrate shown in FIG. **3** (See Example 6). This magnesium salt of S-omeprazole dihydrate has been prepared and can be used in the preparation of the magnesium salt of S-omeprazole trihydrate according to the present invention.

FIG. **5** shows X-ray powder diffractogram of the magnesium salt of S-omeprazole prepared according to example A in WO 96/01623.

DESCRIPTION OF THE INVENTION

It has surprisingly been found that the magnesium salt of S-omeprazole occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of S-omeprazole trihydrate, hereinafter referred to as the compound of the invention. This trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of S-omeprazole trihydrate from other forms of magnesium salts of S-omeprazole.

The compound of the invention is advantageous because it is more stable than the corresponding magnesium salt compounds in prior art and is therefore easier to handle and store. The compound of the invention is also easier to characterize because it exists in a well defined state. Additionally, the compound of the invention is easier to synthesize in a reproducible manner and thereby easier to handle in a full scale production.

The magnesium salt of S-omeprazole trihydrate obtained according to the present invention is substantially free from magnesium salts of R-omeprazole. The magnesium salt of S-omeprazole trihydrate obtained according to the present invention is also substantially free from other forms of magnesium salts of S-omeprazole, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of S-omeprazole and accordingly, the magnesium salt of S-omeprazole trihydrate is easily distinguishable from any other crystal form of the magnesium salt of S-omeprazole disclosed in prior art. The compound of the invention is characterized by being highly crystalline, i.e. having a higher crystallinity than any other form of magnesium salt of S-omeprazole disclosed in the prior art. With the expression "any other form" is meant anhydrates, hydrates, solvates, and polymorphs or amorphous forms thereof disclosed in the prior art. Examples of any other forms of magnesium salt of S-omeprazole includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, and polymorphs or amorphous forms thereof.

The compound of the invention may also be characterized by its unit cell.

In a further aspect, the present invention provides processes for the preparation of the magnesium salt of S-omeprazole trihydrate which comprises;

a) treating a magnesium salt of S-omeprazole of any form, for example prepared according to procedures known in the art such as Example A in WO 96/01623 which is incorporated herein by reference, with water at a suitable temperature for a suitable time. By a suitable

temperature is meant a temperature which induces the transformation of starting material to product without decomposing any of these compounds. Examples of such suitable temperatures include, but are not limited to, room temperature and above. By a suitable time is meant a time that results in high conversion of the starting material into product without causing any decomposition of either compounds, i.e. results in a good yield. This suitable time will vary depending on the temperature used in a way well known to people in the art. The higher the temperature, the shorter time is needed to give the desired conversion. The amount of water is not crucial and will depend on the process conditions used. The magnesium salt of S-omeprazole trihydrate is thereafter separated from the aqueous slurry, for example by filtration or centrifugation and thereafter dried to constant weight; or

b) oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base. The oxidation is carried out in an organic solvent, for example toluene or dichlromethane.

The crude product is converted to the corresponding potassium salt by treatment with a potassium source, such as methanolic potassium hydroxide or methanolic potassium methylate, followed by isolation of the formed salt.

The resulting potassium salt of S-omeprazole is thereafter converted to the corresponding magnesium salt by treatment with a magnesium source, such as magnesium sulfate in a lower alcohol, such as methanol. The solution is optionally filtered and the precipitation is initialized by addition of a non-solvent such as acetone. The product is filtered off and optionally washed with water and further processed as is described in a) above. Alternatively, the potassium salt may be treated with a magnesium source, such as magnesium sulfate in water, and isolation of the magnesium salt of S-omeprazole trihydrate, or any other conventional technique for transforming a potassium salt to the corresponding magnesium salt can be used and is within the scope of the present invention.

Yet a further aspect of the present invention is to provide a suitable intermediate used in the preparation of the compound of the invention, as well as a process for its preparation. The potassium salt of S-omeprazole is found to be such a suitable intermediate. The potassium salt of S-omeprazole may also be used as an active component of a pharmaceutical formulation to be used in the treatment of gastrointestinal diseases.

The compound of the invention, i.e. the magnesium salt of S-omeprazole trihydrate, prepared according to the present invention may be analyzed by XRPD, a technique which is known per se.

The amount of water in the magnesium salt of S-omeprazole trihydrate is determined by thermogravimetric analysis, a technique which is known per se.

The compound of the invention is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for prevention and treatment of gastric-acid related conditions in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these. The compound of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the magnesium salt of S-omeprazole trihydrate, according to the invention. For example, peroral or parental 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 magnesium salt of S-omeprazole trihydrate 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 magnesium salt of S-omeprazole trihydrate of the invention 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 magnesium salt of S-omeprazole trihydrate according to the invention.

The compositions of the invention include compositions suitable for peroral or parental 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 magnesium salt of S-omeprazole trihydrate according to the invention in any given 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 the 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.

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 247 983, the disclosures of which are hereby incorporated as a whole by reference.

Combination preparations comprising the magnesium salt of S-omeprazole trihydrate 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, antacid agents, alginates and prokinetic agents.

The examples which follow 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 claimed below.

EXAMPLES

Example 1

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

Water (157 kg) was added to the wet crystals of the magnesium salt of S-omeprazole, prepared according to Example 4, below. The mixture was heated to 38° C. with stirring and left for 3 hours. The crystals were filtered off and dried in vacuo. Yield: 31.6 kg

X-ray powder diffraction analysis was performed on a sample of the crystals prepared above according to standard methods, which can be found in e.g. Kitaigorodsky, A. I. (1973), Molecular Crystals and Molecules, Academic Press, 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 York. The analysis gave the diffractogram depicted in FIG. **1**. The main peaks, with positions and relative intensities, have been extracted from the diffractogram in FIG. **1** and is given below in table 1. The relative intensities are less reliable and instead of numerical values the following definitions are used.

% Relative Intensity	Definition
25–100	vs (very strong)
10–25	s (strong)
3–10	m (medium)
1–3	w (weak)
<1	vw (very weak)

Some additional very weak peaks found in the diffractogram have been omitted from table 1.

TABLE 1

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole trihydrate.

d-value / Å	Relative Intensity
2.67	m
2.79	m
3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s
8.3	w
16.6	vs

Example 2

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole potassium salt

A solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (15.4 g, 46.8 mmol) in toluene (70 ml) was heated to 50° C. and water (0.05 ml, 2,8 mmol) and D-(−)-diethyl tartrate (2.02 g, 9.82 mmol) were added. The reaction mixture was stirred for 20 minutes. Titanium(IV)isopropoxide (1.34 g, 4.68 mmol) was added and the reaction mixture was stirred for 45 minutes. The mixture was cooled to 30° C. and diisopropylethylamine (0.91 g, 7.01 mmol) was added followed by cumene hydroperoxide (9.52 g, 51.89 mmol). The resultant mixture was stirred at 30° C. for 3 hours. Methanol (40 ml) was added followed by potassium hydroxide (3.05 g, 46.8 mmol) in methanol (30 ml). Seed crystals were added and the reaction mixture was stirred at 35° C. overnight. The precipitated product was filtered off, washed with methanol and toluene and dried in vacuo. Yield: 9.74 g (54%).

Example 3

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt

Water (157.6 gl) was added to a solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole in toluene (370 ml; 211.5 g/l) with a water content of 0.031% (w/w), followed by addition of D-(−)-diethyl tartrate (8.55 ml). The solution was heated to 50° C. and stirred at this temperature for 20 minutes. Titanium(IV) isopropoxide (7.15 ml) was added and reaction was left at 50° C. for 45 minutes. The temperature was lowered to 30° C. and diisopropylethylamine (6.2 ml) was added. Cumene hydroperoxide was added at an appropriate speed to maintain the temperature from 28° C. to 34° C. The temperature was raised to 35° C. after 2 hours and potassium methoxide (24.55 g) in methanol (222 ml) was added. The mixture was filtered after 14 hours and the crystals were washed with methanol:toluene (240 ml; 1:1) and methanol (120 ml) and dried. Yield: 79 g (74%), ee>99.9%. $[\alpha]_D^{20}$=+28.7° (c=1%, water); Assay: 89% is S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt (11% is methanol).

1H-NMR (200 MHz, DMSO-d6, δ ppm): 2.23 (s, 3H), 2.24 (s, 3H), 3.71 (s, 3H), 3.75 (s 3H), 4.40 (d, 1H), 4.78 (d, 1H), 6.58 (dd, 1H), 7.00 (d, 1H), 7.35 (d, 1H), 8.25 (s, 1H.

The products from Examples 2 and 3 were analysed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. **2** and given below in

Table 2. Some additional very weak peaks found in the diffractogram have been omitted from Table 2.

TABLE 2

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of S-omeprazole.

d-value/Å	Relative intensity	d-value/ (Å)	Relative intensity	
13.6	vs	3.52	m	
10.6	vw	3.42	w	
7.8	m	3.38	w	
6.8	m	3.34	m	
6.5	m	3.28	w	
6.2	w	3.20	m	
6.1	m	3.12	w	
5.8	s	3.06	w	
5.4	m	3.03	w	
5.3	w	2.97	w	α1 = 1.54060 Å
5.2	w	2.93	vw	
5.0	vw	2.89	w	
4.75	m	2.85	m	
4.71	w	2.76	w	
4.52	w	2.71	vw	
4.42	w	2.66	vw	

TABLE 2-continued

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of S-omeprazole.

d-value/Å	Relative intensity	d-value/ (Å)	Relative intensity
4.32	w	2.58	w
4.27	m	2.57	w
3.98	vw	2.56	w
3.92	w	2.52	vw
3.89	w	2.47	vw
3.87	w	2.45	vw
3.81	w	2.43	vw
3.74	m	2.40	vw
3.60	m	2.38	vw
3.55	m	2.31	vw

Example 4

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

Methanol (148 kg) was added to S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt (71 kg, methanol content= 13%). $MgSO_4 \times 7\ H_2O$ (40 kg) was added to the mixture while stirring. After 70 minutes the mixture was filtered and the filtrate was washed with methanol (46 kg). The solution was concentrated to a volume of 100 liter, acetone (253 kg) was added and the resulting mixture was left for 4 hours. The precipitated product was filtered off, washed with acetone and water. The wet crystals were immediately used as is described in Example 1.

Example 5

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate

5.0 g of the moist product from Example 4 with an approximate dry content of 74%, was dried in vacuum at 35° C. over night to yield 3.58 g (2.68 mmol) of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named Form B.

The product was analyzed using X-ray powder diffraction as described in Example 1, and the analyze gave the diffractogram depicted in FIG. **3** and given below in Table 3. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 3.

TABLE 3

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form B.

d-value/Å	Relative Intensity
4.19	m
4.45	m
4.68	m
4.79	s
4.91	s
4.98	s
5.1	m
5.4	s
5.5	m
5.6	m
5.8	m
6.3	m
6.7	s
7.9	m

TABLE 3-continued

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form B.

d-value/Å	Relative Intensity
8.1	s
11.0	m
11.8	m
14.9	vs

Convertion of magnesium salt of S-omeprazole dihydrate to trihydrate

This material was subsequently processed to S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate according to the procedure described for the moist substance in Example 1.

Example 6

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate

A methanolic solution of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt was prepared as is described in Example 4. Such a solution of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt (1.86 g) in 5 ml methanol was concentrated by evaporation until 1.58 ml methanol remained. Then, a mixture of 1.6 ml water and 6.32 ml aceton was added. The solution was allowed to crystallize during 26 h at room temperature. The resulting crystals were filtered off and dried at 40 ° C. under reduced pressure giving 1.17 g of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named form A.

The product was analyzed using X-ray powder diffration as described in Example 1 and gave the diffractogram depicted in FIG. **4** and given below in Table 4. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 4.

TABLE 4

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form A.

d-value/Å	Relative Intensity
3.04	s
3.14	s
3.18	m
4.05	s
4.19	s
4.32	m
4.54	s
4.69	vs
5.2	s
5.3	s
5.8	s
6.2	vs
6.6	s
15.5	vs

Example 7

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

22,0 g (29,1 mmol) of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

potassium salt was dissolved in 40 mL of water. The solution was seeded with 0,11 g (0,1 mmol) S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate. 22 mL (69,6 mmol) of $MgSO_4$ (aq) was added under a 3 h period. The slurry was filtered off and the precipitate was elutriated in water for approximately 30 minutes and the crystals were filtered off and dried (35° C., vacuum).

Yield: 9,15 g (11,6 mmol; 80%). The substance had a purity (HPLC):99,8 area %, Mg content: 3,40% (w/w) and ee: 99,8%.

The product was analyzed using X-ray powder diffraction and the result complies with s FIG. **1** and Table 1.

Reference Example A

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

(The method used is in accordance with the method described in Example A in WO 96/01623)

Magnesium (0.11 g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40° C. with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(−)-isomer and 10%(+)-isomer] of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole (2.84 g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (+)-isomer), with an optical purity (enantiomeric excess, e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for 15 minutes, a white precipitate was obtained. Additional stirring for 15 minutes and thereafter filtration afforded 1.3 g (50%) of the title compound as white crystals. Chiral analyses of the crystals and mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the crystals and mother liquor was found to be 98.4 e.e. and 64.4% e.e., respectively. Thus, the optical purity (ee.) has been enhanced from 80% to 98.4% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The product was crystalline as shown by powder X-ray diffraction and the magnesium content was 3.44% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20}=-131.5°$ (c=0.5%, methanol).

The product was analyzed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. **5** and given below in Table 5. Some additional very weak peaks found in the diffractograms have been omitted from Table 5.

TABLE 5

Positions and intensities of the major peaks in the XRP-diffractogram shown in FIG. 5.

d-value/Å	Relative Intensity
2.90	s
3.41	s
3.90	s
4.13	s
4.79	vs
5.00	vs
5.4	vs
5.7	s
6.3	s

TABLE 5-continued

Positions and intensities of the major peaks in the XRP-diffractogram shown in FIG. 5.

d-value/Å	Relative Intensity
6.8	s
7.8	s
8.4	vs
10.8	s
12.2	s
15.1	vs

What is claimed is:

1. The magnesium salt of S-omeprazole trihydrate, wherein the compound is characterized by the following major peaks in its X-ray diffractogram:

d-value / Å	Relative Intensity
2.67	m
2.79	m
3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s
8.3	w
16.6	vs

2. The magnesium salt of S-omeprazole trihydrate according to claim **1**, wherein the compound is in a highly crystalline form.

3. The magnesium salt of S-omeprazole trihydrate according to claim **1**, wherein the compound is in a stable form.

4. A process for the preparation of the magnesium salt of S-omeprazole trihydrate according to any of claims **1**, **2** or **3** which comprises treating a magnesium salt of S-omeprazole any other form with water.

5. A process for the preparation of the magnesium salt of S-omeprazole trihydrate according to any of claims **1**, **2** or **3** which comprises the following steps:

a) mixing a potassium salt of S-omeprazole with an organic solvent;

b) converting the potassium salt of S-omeprazole into a corresponding magnesium salt of S-omeprazole by treating the potassium salt with a magnesium source;

c) precipitating the magnesium salt of S-omeprazole by addition of a non-solvent;

d) isolating the obtained magnesium salt of S-omeprazole;

e) treating the obtained magnesium salt of S-omeprazole with water, and

f) isolating and drying the obtained magnesium salt of S-omeprazole trihydrate.

6. The process according to claim **5**, wherein the organic solvent of step a) is methanol.

7. The process according to claim **5**, wherein the non-solvent of step c) is acetone.

8. The process according to claim **5** wherein steps a) to e) are replaced by the following single step: converting the potassium salt of S-omeprazole into a corresponding magnesium salt of S-omeprazole by treating the potassium salt with a magnesium source in water.

9. The process according to claim **5**, wherein the magnesium source is magnesium sulfate.

10. The process according to claim **8**, wherein the magnesium source is magnesium sulfate.

11. A pharmaceutical composition comprising the magnesium salt of S-omeprazole trihydrate according to any of claims **1**, **2** or **3** as active ingredient and a pharmaceutically acceptable carrier.

12. 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 magnesium salt of S-omeprazole trihydrate according to any of claims **1**, **2** or **3**.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,369,085 B1
DATED : April 9, 2002
INVENTOR(S) : Cotton et al.

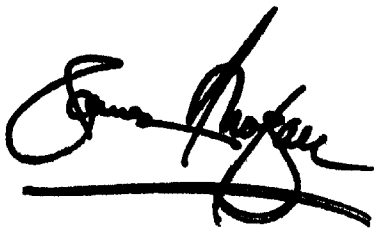
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [22] PCT Filed, delete "**May 5, 1998**" and insert therefor -- **May 25, 1998** --.

Column 10,
Line 42, insert -- of -- after "S-omeprazole".

Signed and Sealed this

Eighth Day of April, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT B

US007411070B2

(12) United States Patent
Cotton et al.

(10) Patent No.: US 7,411,070 B2
(45) Date of Patent: *Aug. 12, 2008

(54) **FORM OF S-OMEPRAZOLE**

(75) Inventors: **Hanna Cotton**, Södertälje (SE); **Anders Kronström**, Södertälje (SE); **Anders Mattson**, Södertälje (SE); **Eva Möller**, Södertälje (SE)

(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/672,936**

(22) Filed: **Sep. 25, 2003**

(65) **Prior Publication Data**

US 2005/0075369 A1 Apr. 7, 2005

Related U.S. Application Data

(60) Continuation of application No. 10/076,711, filed on Feb. 14, 2002, now Pat. No. 6,677,455, which is a division of application No. 09/077,719, filed as application No. PCT/SE98/00974 on May 25, 1998, now Pat. No. 6,369,085.

(30) **Foreign Application Priority Data**

May 30, 1997 (SE) 9702065

(51) **Int. Cl.**
C07D 401/12 (2006.01)
A61K 31/4439 (2006.01)

(52) **U.S. Cl.** **546/273.7**; 514/338

(58) **Field of Classification Search** 514/338; 546/273.7

See application file for complete search history.

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Opposition filed by Torrent Pharmaceuticals Limited against Indian Patent Application No. 1344/DEL/98.

X-ray powder diffraction pattern of Mg-salt of S-omeprazole trihydrate depicted by Torrent obtained by method of WO 94/27988.

NDA 21-153/S-020 for Nexium® (esomeprazole magnesium) Delayed Release Capsule.

NDA 21-153/21-154 entitled "Medical Review(s)".

Statement with Exhibits A-C on Behalf of the Applicant, AstraZeneca AB, to the Opposition filed by Ranbaxy Laboratories Limited against Indian Patent Application No. 1344/DEL/98.

Statement with Exhibits A-D on Behalf of the Applicant, AstraZeneca AB, to the Opposition filed by Torrent Pharmaceuticals Limited against Indian Patent Application No. 1344/DEL/98.

Decision of the Pre-grant Opposition filed by Ranbaxy Laboratories Limited against Indian Patent Application No. 1344/DEL/98.

Decision of the Pre-grant Opposition filed by Torrent Pharmaceuticals Limited against Indian Patent Application No. 1344/DEL/98.

Notice of Allegation, dated Nov. 13, 2007, pursuant to the *Patented Medicines* (*Notice of Compliance*) *Regulations* with respect to Canadian Letters Patent No. 2,290,963.

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Primary Examiner—Charanjit S Aulakh
(74) *Attorney, Agent, or Firm*—White & Case LLP

(57) **ABSTRACT**

The present invention relates to a novel form of the (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. S-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

4 Claims, 5 Drawing Sheets

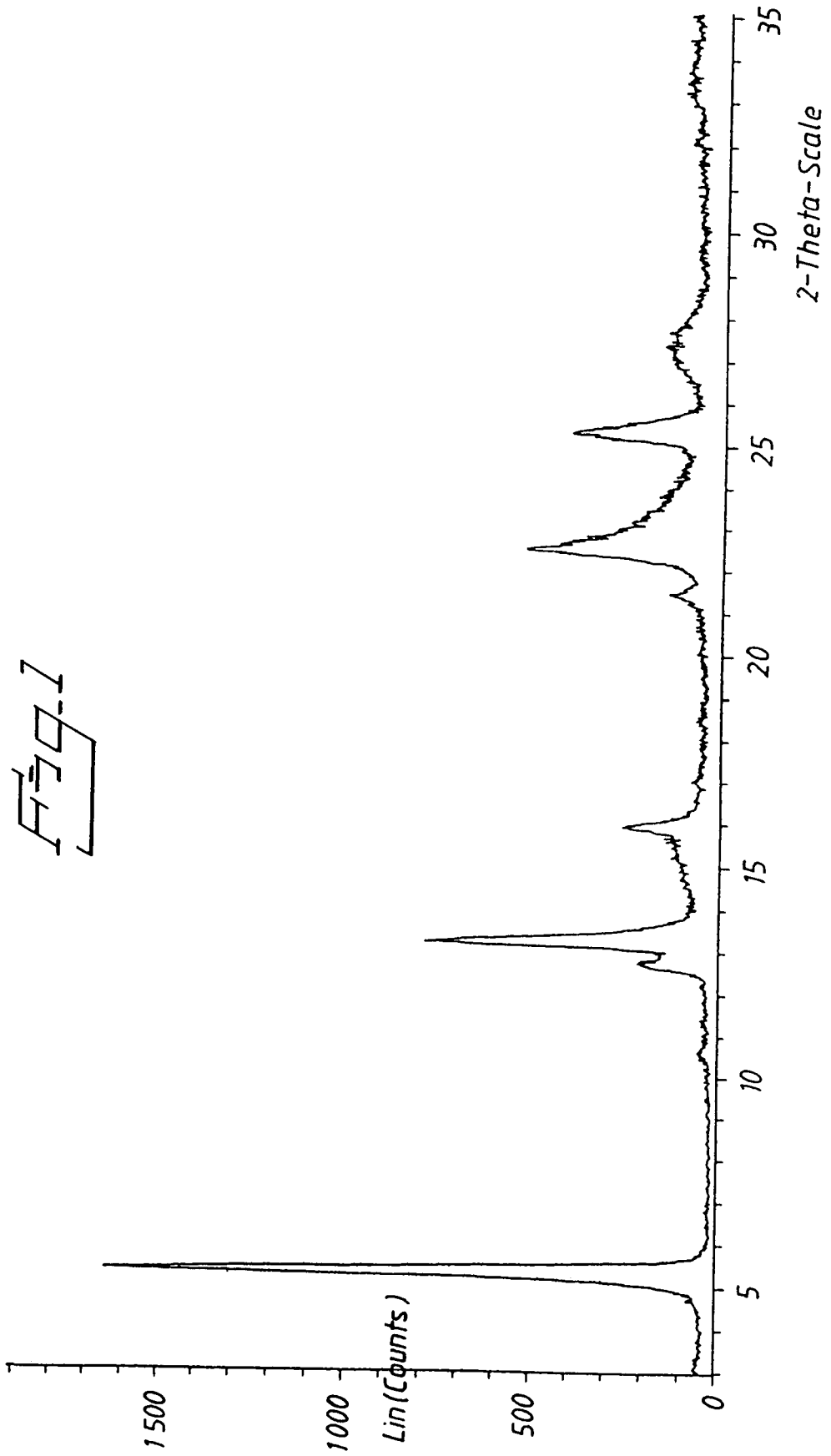


FIG. 1

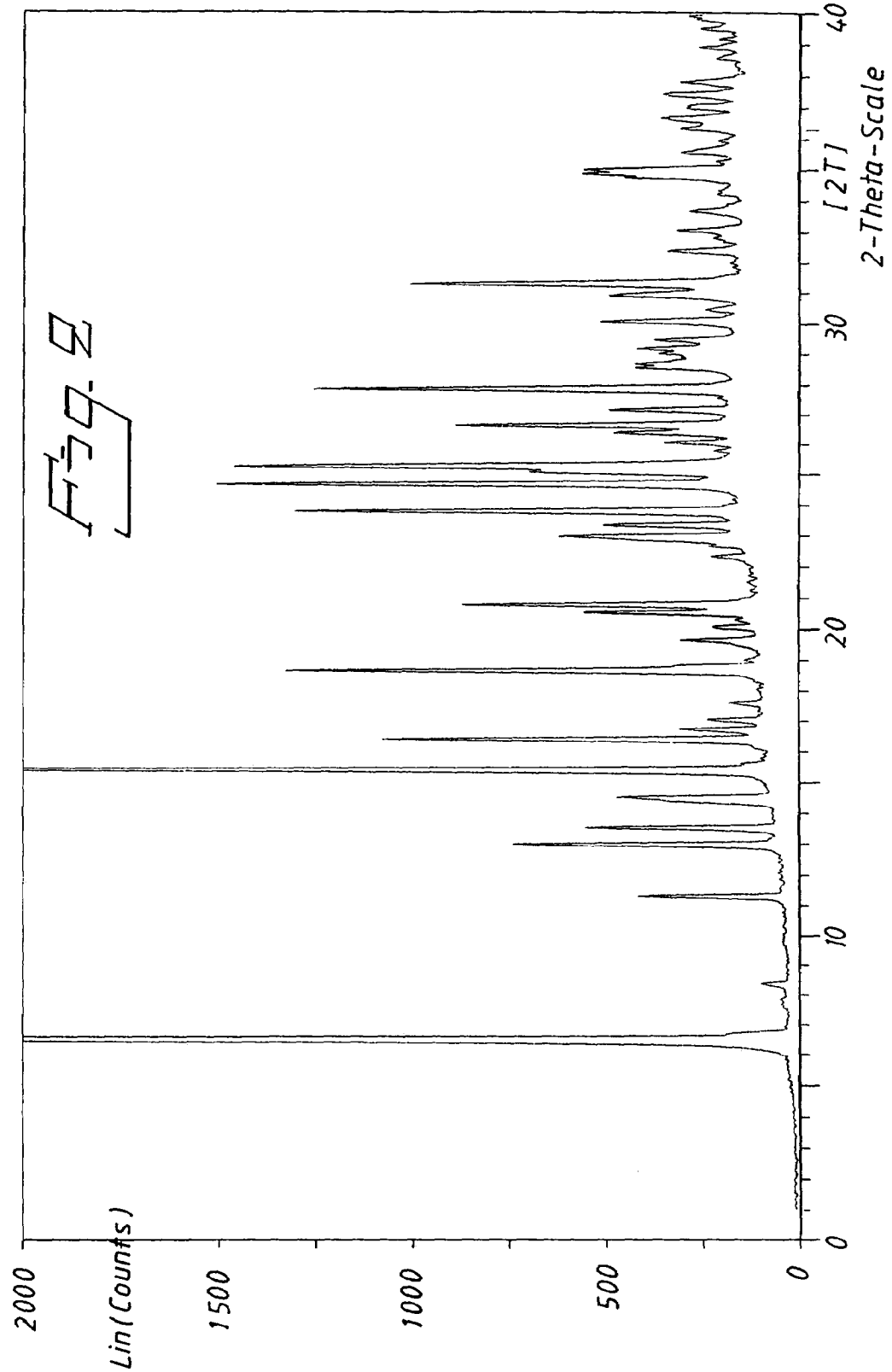


Fig. 2

Fig. 3

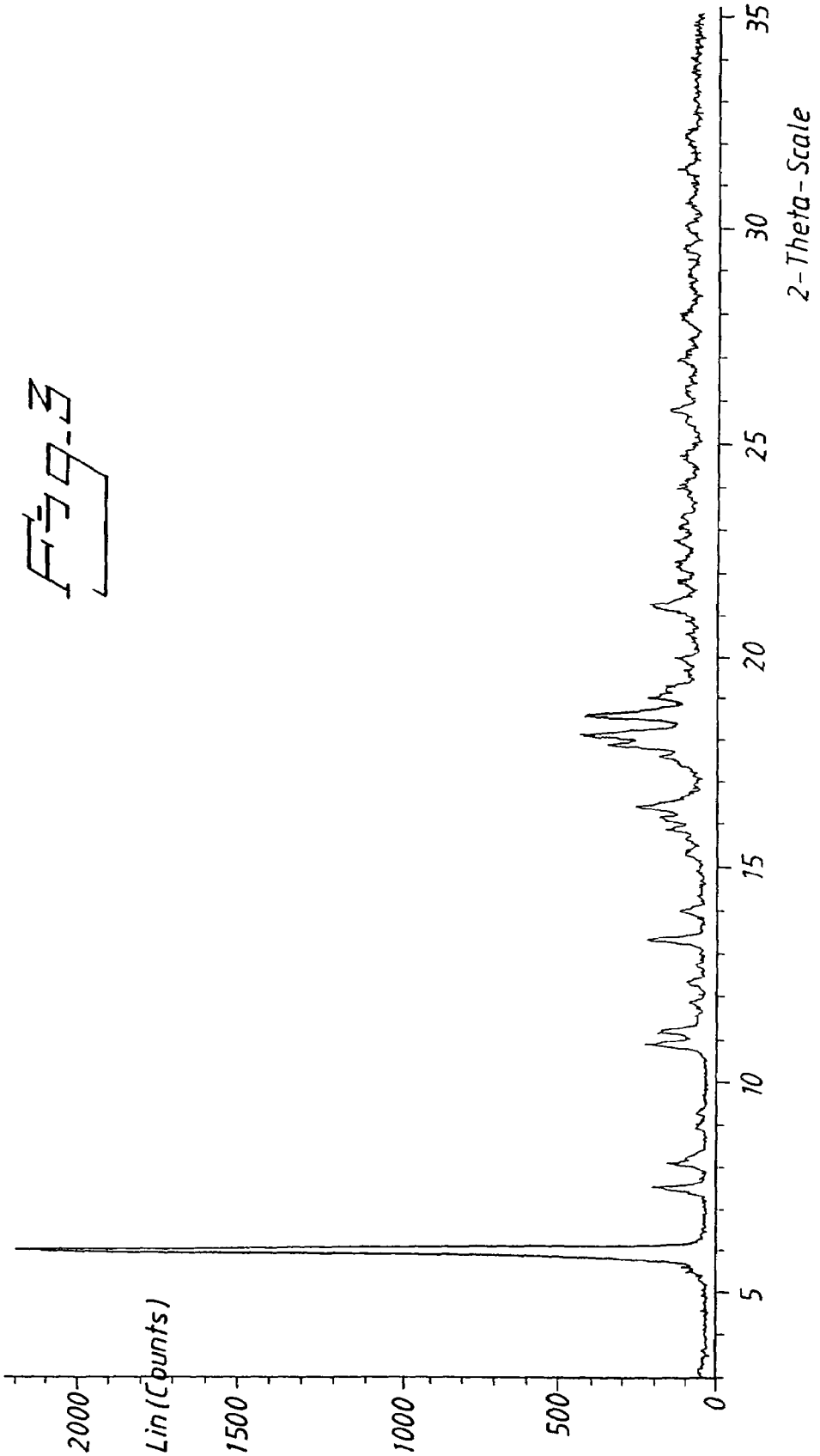
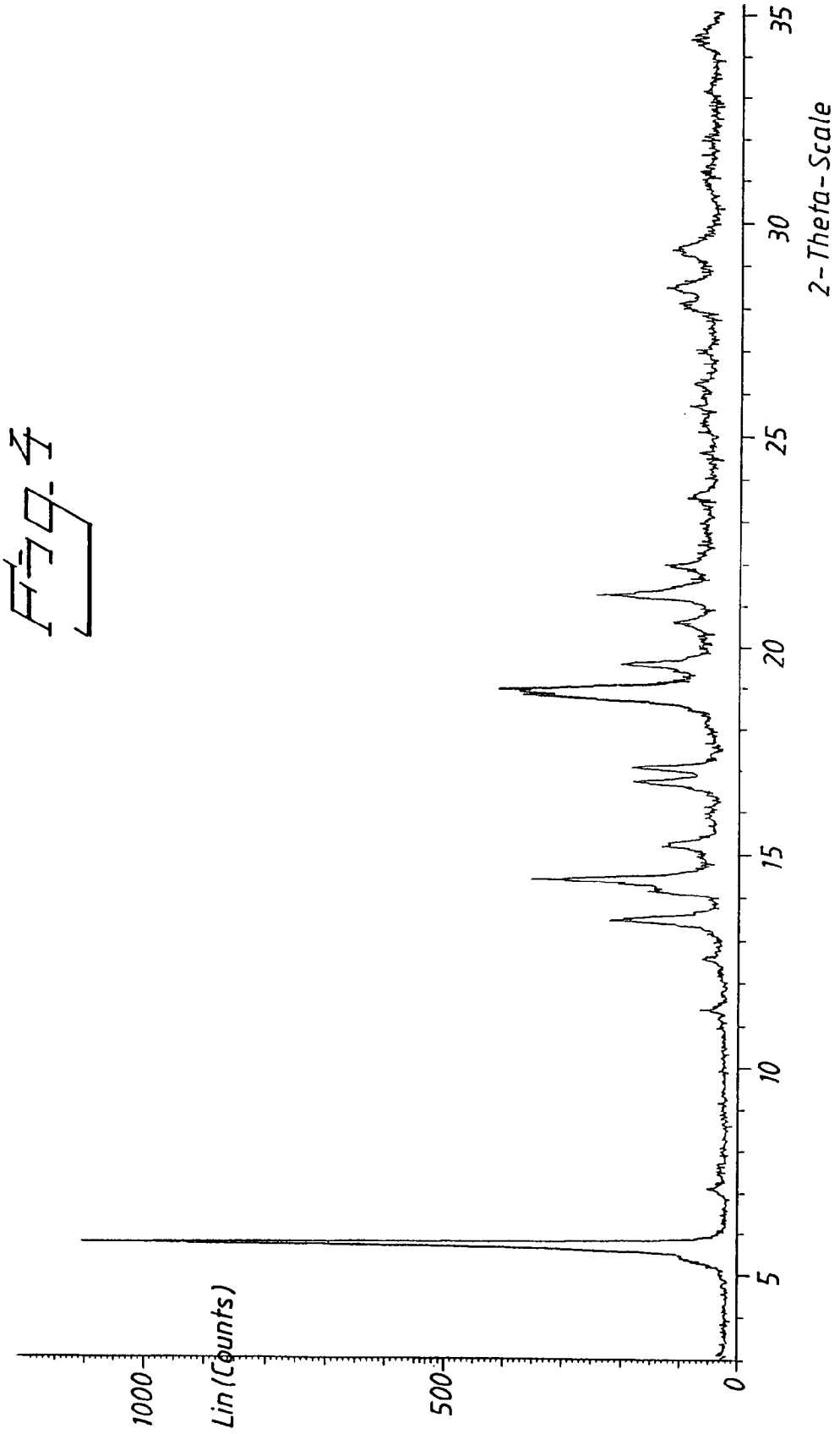


Fig. 4



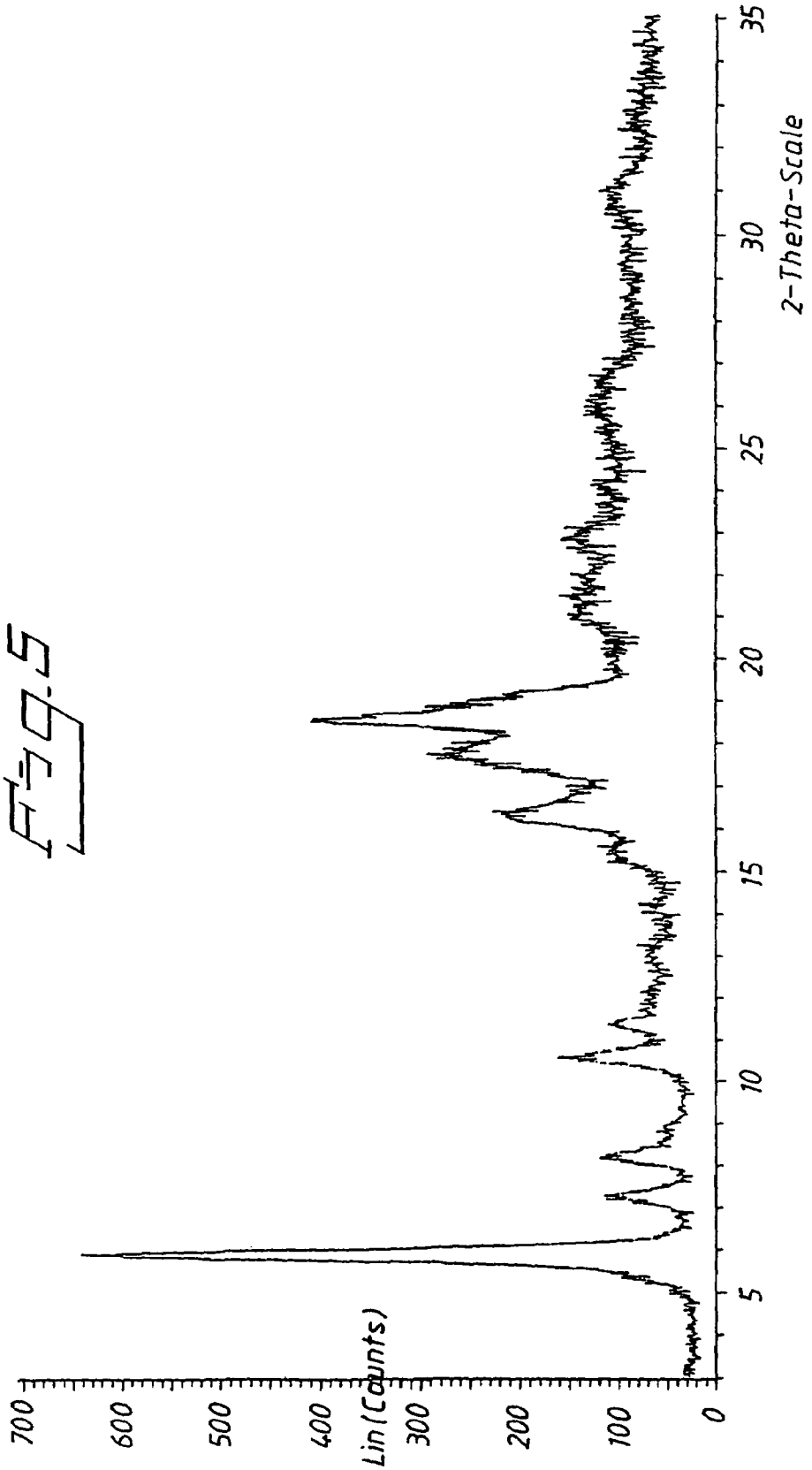

Lin (Counts)
0
100
200
300
400
500
600
700
5
10
15
20
25
30
35
2-Theta-Scale

Fig. 5

FORM OF S-OMEPRAZOLE

This application is a continuation of U.S. patent application Ser. No. 10/076,711, filed Feb. 14, 2002, now U.S. Pat. No. 6,667,455 which is a divisional of U.S. patent application Ser. No. 09/077,719, filed Jun. 8, 1998, now U.S. Pat. No. 6,369,085, which was the National Stage of International Application No. PCT/SE98/00974, filed May 25, 1998.

FIELD OF THE INVENTION

The present invention relates to a novel form of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. S-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to intermediates used in the process, and their preparation.

BACKGROUND OF THE INVENTION AND PRIOR ART

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are disclosed in EP 124 495. Omeprazole is a proton pump inhibitor, i.e. effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R and S-enantiomer of omeprazole, herein referred to as R-omeprazole and S-omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (−)-enantiomer of the non-salt form were found to have R and S configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (−)-enantiomer of the magnesium salt were also found to have R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

Certain salts of single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988. These compounds have improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.

WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts of R- and S-omeprazole.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a X-ray powder diffractogram of the magnesium salt of S-omeprazole trihydrate prepared according to the present invention.

FIG. **2** shows a X-ray powder diffractogram of the potassium salt of S-omeprazole prepared and used in the present application (See examples 2 and 3)

FIG. **3** shows a X-ray powder diffractogram of a magnesium salt of S-omeprazole dihydrate prepared and used in the present application (See example 5)

FIG. **4** shows a X-ray powder diffractogram of a magnesium salt of S-omeprazole dihydrate which is a polymorph of the dihydrate shown in FIG. **3** (See Example 6). This magnesium salt of S-omeprazole dihydrate has been prepared and can be used in the preparation of the magnesium salt of S-omeprazole trihydrate according to the present invention.

FIG. **5** shows X-ray powder diffractogram of the magnesium salt of S-omeprazole prepared according to example A in WO 96/01623.

DESCRIPTION OF THE INVENTION

It has surprisingly been found that the magnesium salt of S-omeprazole occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of S-omeprazole trihydrate, hereinafter referred to as the compound of the invention. This trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of S-omeprazole trihydrate from other forms of magnesium salts of S-omeprazole.

The compound of the invention is advantageous because it is more stable than the corresponding magnesium salt compounds in prior art and is therefore easier to handle and store. The compound of the invention is also easier to characterize because it exists in a well defined state. Additionally, the compound of the invention is easier to synthesize in a reproducible manner and thereby easier to handle in a full scale production.

The magnesium salt of S-omeprazole trihydrate obtained according to the present invention is substantially free from magnesium salts of R-omeprazole. The magnesium salt of S-omeprazole trihydrate obtained according to the present invention is also substantially free from other forms of magnesium salts of S-omeprazole, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of S-omeprazole and accordingly, the magnesium salt of S-omeprazole trihydrate is easily distinguishable from any other crystal form of the magnesium salt of S-omeprazole disclosed in prior art. The compound of the invention is characterized by being highly crystalline, i.e. having a higher crystallinity than any other form of magnesium salt of S-omeprazole disclosed in the prior art. With the expression "any other form" is meant anhydrates, hydrates, solvates, and polymorphs or amorphous forms thereof disclosed in the prior art. Examples of any other forms of magnesium salt of S-omeprazole includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, and polymorphs or amorphous forms thereof.

The compound of the invention may also be characterized by its unit cell.

In a further aspect, the present invention provides processes for the preparation of the magnesium salt of S-omeprazole trihydrate which comprises;

a) treating a magnesium salt of S-omeprazole of any form, for example prepared according is to procedures known in the art such as Example A in WO 96/01623 which is incorporated herein by reference, with water at a suitable temperature for a suitable time. By a suitable temperature is meant a temperature which induces the transformation of starting material to product without decomposing any of these compounds. Examples of such suitable temperatures include, but are not limited to, room temperature and above. By a suitable time is meant a time that results in high conversion of the starting material into product without causing any decomposition of either compounds, i.e. results in a good yield. This suitable time will vary depending on the temperature used in a way well known to people in the art. The higher the temperature, the shorter time is needed to give the desired conversion. The amount of water is not crucial and will depend on the process conditions used. The magnesium salt of S-omeprazole trihydrate is thereafter separated from the aqueous slurry, for example by filtration or centrifugation and thereafter dried to constant weight; or

b) oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base. The oxidation is carried out in an organic solvent, for example toluene or dichloromethane.

The crude product is converted to the corresponding potassium salt by treatment with a potassium source, such as methanolic potassium hydroxide or methanolic potassium methylate, followed by isolation of the formed salt.

The resulting potassium salt of S-omeprazole is thereafter converted to the corresponding magnesium salt by treatment with a magnesium source, such as magnesium sulfate in a lower alcohol, such as methanol. The solution is optionally filtered and the precipitation is initialized by addition of a non-solvent such as acetone. The product is filtered off and optionally washed with water and further processed as is described in a) above. Alternatively, the potassium salt may be treated with a magnesium source, such as magnesium sulfate in water, and isolation of the magnesium salt of S-omeprazole trihydrate, or any other conventional technique for transforming a potassium salt to the corresponding magnesium salt can be used and is within the scope of the present invention.

Yet a further aspect of the present invention is to provide a suitable intermediate used in the preparation of the compound of the invention, as well as a process for its preparation. The potassium salt of S-omeprazole is found to be such a suitable intermediate. The potassium salt of S-omeprazole may also be used as an active component of a pharmaceutical formulation to be used in the treatment of gastrointestinal diseases.

The compound of the invention, i.e. the magnesium salt of S-omeprazole trihydrate, prepared according to the present invention may be analyzed by XRPD, a technique which is known per se.

The amount of water in the magnesium salt of S-omeprazole trihydrate is determined by thermogravimetric analysis, a technique which is known per se.

The compound of the invention is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for prevention and treatment of gastric-acid related conditions in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders

where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these. The compound of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the magnesium salt of S-omeprazole trihydrate, according to the invention. For example, peroral or parental 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 magnesium salt of S-omeprazole trihydrate 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 magnesium salt of S-omeprazole trihydrate of the invention 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 magnesium salt of S-omeprazole trihydrate according to the invention.

The compositions of the invention include compositions suitable for peroral or parental 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 magnesium salt of S-omeprazole trihydrate according to the invention in any given 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 the 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.

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 247 983, the disclosures of which are hereby incorporated as a whole by reference.

Combination preparations comprising the magnesium salt of S-omeprazole trihydrate 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, antacid agents, alginates and pro-kinetic agents.

The examples which follow 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 claimed below.

EXAMPLES

Example 1

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Magnesium Salt Trihydrate

Water (157 kg) was added to the wet crystals of the magnesium salt of S-omeprazole, prepared according to Example 4, below. The mixture was heated to 38° C. with stirring and left for 3 hours. The crystals were filtered off and dried in vacuo. Yield: 31.6 kg.

X-ray powder diffraction analysis was performed on a sample of the crystals prepared above according to standard methods, which can be found in e.g. Kitaigorodsky, A. I. (1973), Molecular Crystals and Molecules, Academic Press, 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 York. The analysis gave the diffractogram depicted in FIG. **1**. The main peaks, with positions and relative intensities, have been extracted from the diffractogram in FIG. **1** and is given below in table **1**. The relative intensities are less reliable and instead of numerical values the following definitions are used.

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3	w (weak)
<1	vw (very weak)

Some additional very weak peaks found in the diffractogram have been omitted from table **1**.

TABLE 1

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole trihydrate.

d-value/Å	Relative Intensity
2.67	m
2.79	m
3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s

TABLE 1-continued

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole trihydrate.

d-value/Å	Relative Intensity
8.3	w
16.6	vs

Example 2

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole Potassium Salt

A solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (15.4 g, 46.8 mmol) in toluene (70 ml) was heated to 50° C. and water (0.05 ml, 2.8 mmol) and D-(−)-diethyl tartrate (2.02 g, 9.82 mmol) were added. The reaction mixture was stirred for 20 minutes. Titanium(IV)isopropoxide (1.34 g, 4.68 mmol) was added and the reaction mixture was stirred for 45 minutes. The mixture was cooled to 30° C. and diisopropylethylamine (0.91 g, 7.01 mmol) was added followed by cumene hydroperoxide (9.52 g, 51.89 mmol). The resultant mixture was stirred at 30° C. for 3 hours. Methanol (40 ml) was added followed by potassium hydroxide (3.05 g, 46.8 mmol) in methanol (30 ml). Seed crystals were added and the reaction mixture was stirred at 35° C. overnight. The precipitated product was filtered off, washed with methanol and toluene and dried in vacuo. Yield: 9.74 g (54%).

Example 3

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Potassium Salt

Water (157.6 μl) was added to a solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole in toluene (370 ml; 211.5 g/l) with a water content of 0.031% (w/w), followed by addition of D-(−)-diethyl tartrate (8.55 ml). The solution was heated to 50° C. and stirred at this temperature for 20 minutes. Titanium(IV) isopropoxide (7.15 ml) was added and reaction was left at 50° C. for 45 minutes. The temperature was lowered to 30° C. and diisopropylethylamine (6.2 ml) was added. Cumene hydroperoxide was added at an appropriate speed to maintain the temperature from 28° C. to 34° C. The temperature was raised to 35° C. after 2 hours and potassium methoxide (24.55 g) in methanol (222 ml) was added. The mixture was filtered after 14 hours and the crystals were washed with methanol:toluene (240 ml; 1:1) and methanol (120 ml) and dried. Yield: 79 g (74%), ee>99.9%.

$[\alpha]_D^{20}$=+28.7° (c=1%, water); Assay: 89% is S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl] sulfinyl]-1H-benzimidazole potassium salt (11% is methanol).

1H-NMR (200 MHz, DMSO-d6, δ ppm): 2.23 (s, 3H), 2.24 (s, 3H), 3.71 (s, 3H), 3.75 (s, 3H), 4.40 (d, 1H), 4.78 (d, 1H), 6.58 (dd, 1H), 7.00 (d, 1H), 7.35 (d, 1H), 8.25 (s, 1H).

The products from Examples 2 and 3 were analysed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. **2** and given below in Table

2. Some additional very weak peaks found in the diffractogram have been omitted from Table 2.

TABLE 2

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of S-omeprazole.

d-value/Å	Relative intensity
13.6	vs
10.6	vw
7.8	m
6.8	m
6.5	m
6.2	w
6.1	m
5.8	s
5.4	m
5.3	w
5.2	w
5.0	vw
4.75	m
4.71	w
4.52	w
4.42	w
4.32	w
4.27	m
3.98	vw
3.92	w
3.89	w
3.87	w
3.81	w
3.74	m
3.60	m
3.55	m
3.52	m
3.42	w
3.38	w
3.34	m
3.28	w
3.20	m
3.12	w
3.06	w
3.03	w
2.97	w
2.93	vw
2.89	w
2.85	m
2.76	w
2.71	vw
2.66	vw
2.58	w
2.57	w
2.56	w
2.52	vw
2.47	vw
2.45	vw
2.43	vw
2.40	vw
2.38	vw
2.31	vw

$\alpha 1 = 1.54060$ Å

Example 4

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Magnesium Salt

Methanol (148 kg) was added to S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole potassium salt (71 kg, methanol content=13%). $MgSO_4 \times 7H_2O$ (40 kg) was added to the mixture while stirring. After 70 minutes the mixture was filtered and the filtrate was washed with methanol (46 kg). The solution was concentrated to a volume of 100 liter, acetone (253 kg) was added and the resulting mixture was left for 4 hours. The precipitated product was filtered off, washed with acetone and water. The wet crystals were immediately used as is described in Example 1.

Example 5

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Magnesium Salt Dihydrate

5.0 g of the moist product from Example 4 with an approximate dry content of 74%, was dried in vacuum at 35° C. over night to yield 3.58 g (2.68 mmol) of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named Form B.

The product was analyzed using X-ray powder diffraction as described in Example 1, and the analyze gave the diffractogram depicted in FIG. **3** and given below in Table 3. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 3.

TABLE 3

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form B.

d-value/Å	Relative Intensity
4.19	m
4.45	m
4.68	m
4.79	s
4.91	s
4.98	s
5.1	m
5.4	s
5.5	m
5.6	m
5.8	m
6.3	m
6.7	s
7.9	m
8.1	s
11.0	m
11.8	m
14.9	vs

Conversion of Magnesium Salt of S-omeprazole Dehydrate to Trihydrate

This material was subsequently processed to S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate according to the procedure described for the moist substance in Example 1.

Example 6

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Magnesium Salt Dihydrate

A methanolic solution of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt was prepared as is described in Example 4. Such a solution of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt (1.86 g) in 5 ml methanol was concentrated by evaporation until 1.58 ml methanol remained. Then, a mixture of 1.6 ml water and 6.32 ml aceton was added. The solution was allowed to crystallize during 26 h at room temperature. The resulting crystals were filtered off and dried at

40° C. under reduced pressure giving 1.17 g of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named form A.

The product was analyzed using X-ray powder diffration as described in Example 1 and gave the diffractogram depicted in FIG. **4** and given below in Table 4. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 4.

TABLE 4

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form A.

d-value/Å	Relative Intensity
3.04	s
3.14	s
3.18	m
4.05	s
4.19	s
4.32	m
4.54	s
4.69	vs
5.2	s
5.3	s
5.8	s
6.2	vs
6.6	s
15.5	vs

Example 7

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Magnesium Salt Trihydrate

22.0 g (29,1 mmol) of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole potassium salt was dissolved in 40 mL of water. The solution was seeded with 0.11 g (0,1 mmol) S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate. 22 mL (69,6 mmol) of $MgSO_4$ (aq) was added under a 3 h period. The slurry was filtered off and the precipitate was elutriated in water for approximately 30 minutes and the crystals were filtered off and dried (35° C., vacuum).

Yield: 9.15 g (11,6 mmol; 80%). The substance had a purity (HPLC):99.8 area %, Mg content: 3.40% (w/w) and ee: 99.8%.

The product was analyzed using X-ray powder diffraction and the result complies with FIG. **1** and Table 1.

Reference Example A

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Magnesium Salt

(The method used is in accordance with the method described in Example A in WO 96/01623)

Magnesium (0.1 μg, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40° C. with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(−)-isomer and 10%(+)-isomer] of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (2.84 g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (+)-isomer), with an optical purity (enantiomeric excess, e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for 15 minutes, a white precipitate was obtained. Additional stirring for 15 minutes and thereafter filtration afforded 1.3 g (50%) of the title compound as white crystals. Chiral analyses of the crystals and mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the crystals and mother liquor was found to be 98.4 e.e. and 64.4% e.e., respectively. Thus, the optical purity (e.e.) has been enhanced from 80% to 98.4% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The product was crystalline as shown by powder X-ray diffraction and the magnesium content was 3.44% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20}=-131.5°$ (c=0.5%, methanol).

The product was analyzed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. **5** and given below in Table 5. Some additional very weak peaks found in the diffractograms have been omitted from Table 5.

TABLE 5

Positions and intensities of the major peaks in the XRP-diffractogram shown in FIG. 5.

d-value/Å	Relative Intensity
2.90	s
3.41	s
3.90	s
4.13	s
4.79	vs
5.00	vs
5.4	vs
5.7	s
6.3	s
6.8	s
7.8	s
8.4	vs
10.8	s
12.2	s
15.1	vs

The invention claimed is:

1. The magnesium salt of S-omeprazole trihydrate.

2. The magnesium salt of S-omeprazole trihydrate according to claim **1** represented by FIG. **1**.

3. A process for the preparation of the magnesium salt of S-omeprazole trihydrate according to claim **1** which comprises treating a magnesium salt of S-omeprazole of any other form with water.

4. A process for the preparation of the magnesium salt of S-omeprazole trihydrate according to claim **2** which comprises treating a magnesium salt of S-omeprazole of any other form with water.

* * * * *

EXHIBIT C

US008466175B2

(12) **United States Patent**
Cotton et al.

(10) **Patent No.: US 8,466,175 B2**
(45) **Date of Patent: *Jun. 18, 2013**

(54) **FORM OF *S*-OMEPRAZOLE**

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This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(60) Continuation of application No. 12/784,881, filed on May 21, 2010, now Pat. No. 8,076,361, which is a continuation of application No. 11/853,323, filed on Sep. 11, 2007, now Pat. No. 7,745,466, which is a continuation of application No. 10/672,936, filed on Sep. 25, 2003, now Pat. No. 7,411,070, which is a continuation of application No. 10/076,711, filed on Feb. 14, 2002, now Pat. No. 6,677,455, which is a division of application No. 09/077,719, filed as application No. PCT/SE98/00974 on May 25, 1998, now Pat. No. 6,369,085.

(30) **Foreign Application Priority Data**

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to a novel form of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. S-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

14 Claims, 5 Drawing Sheets

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Notice of Allegation, filed Nov. 13, 2007, pursuant to the patented Medicines (Notice of Compliance) *Regulations* with respect to Canadian Letters Patent No. 2,290,963.

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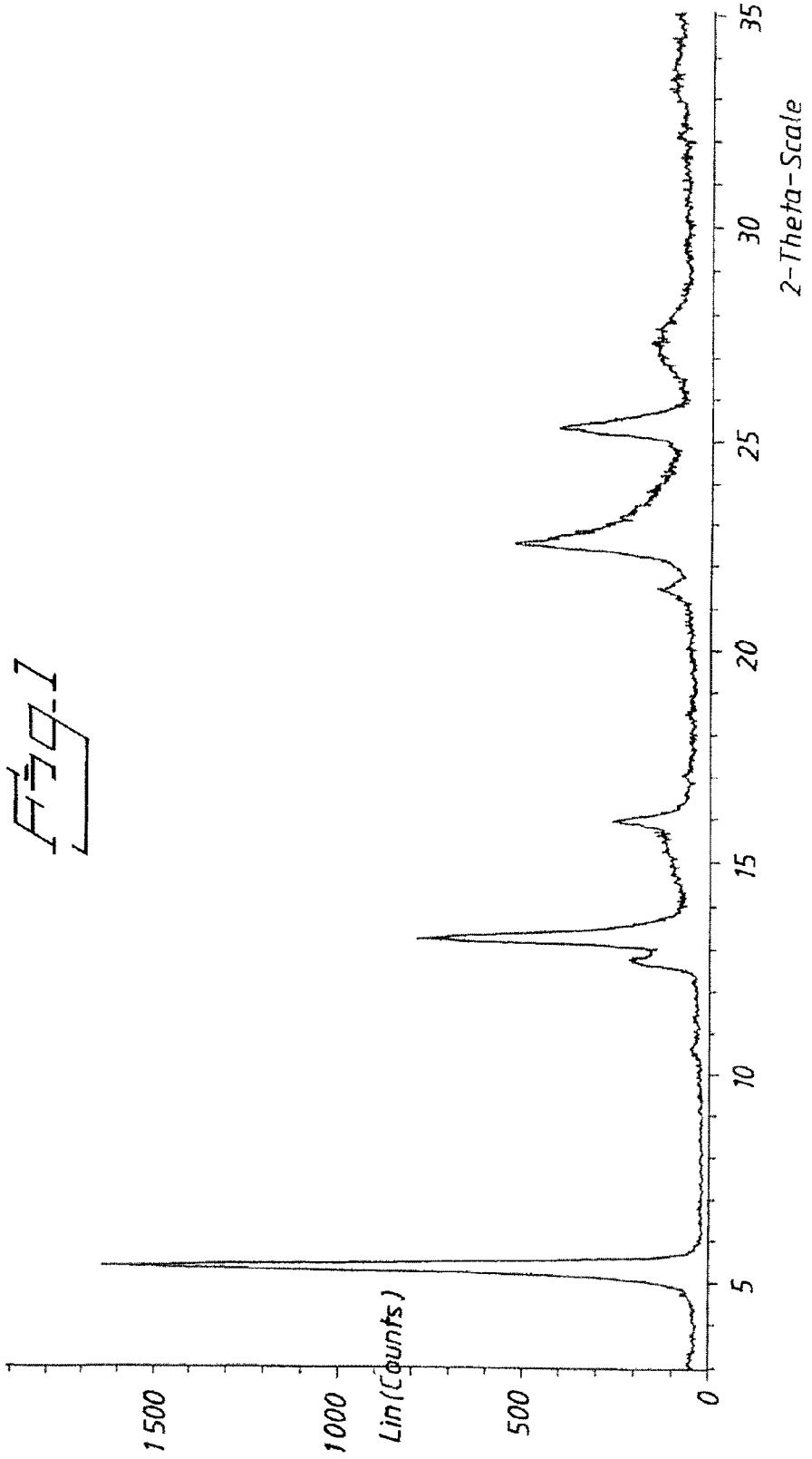

FIG. 1

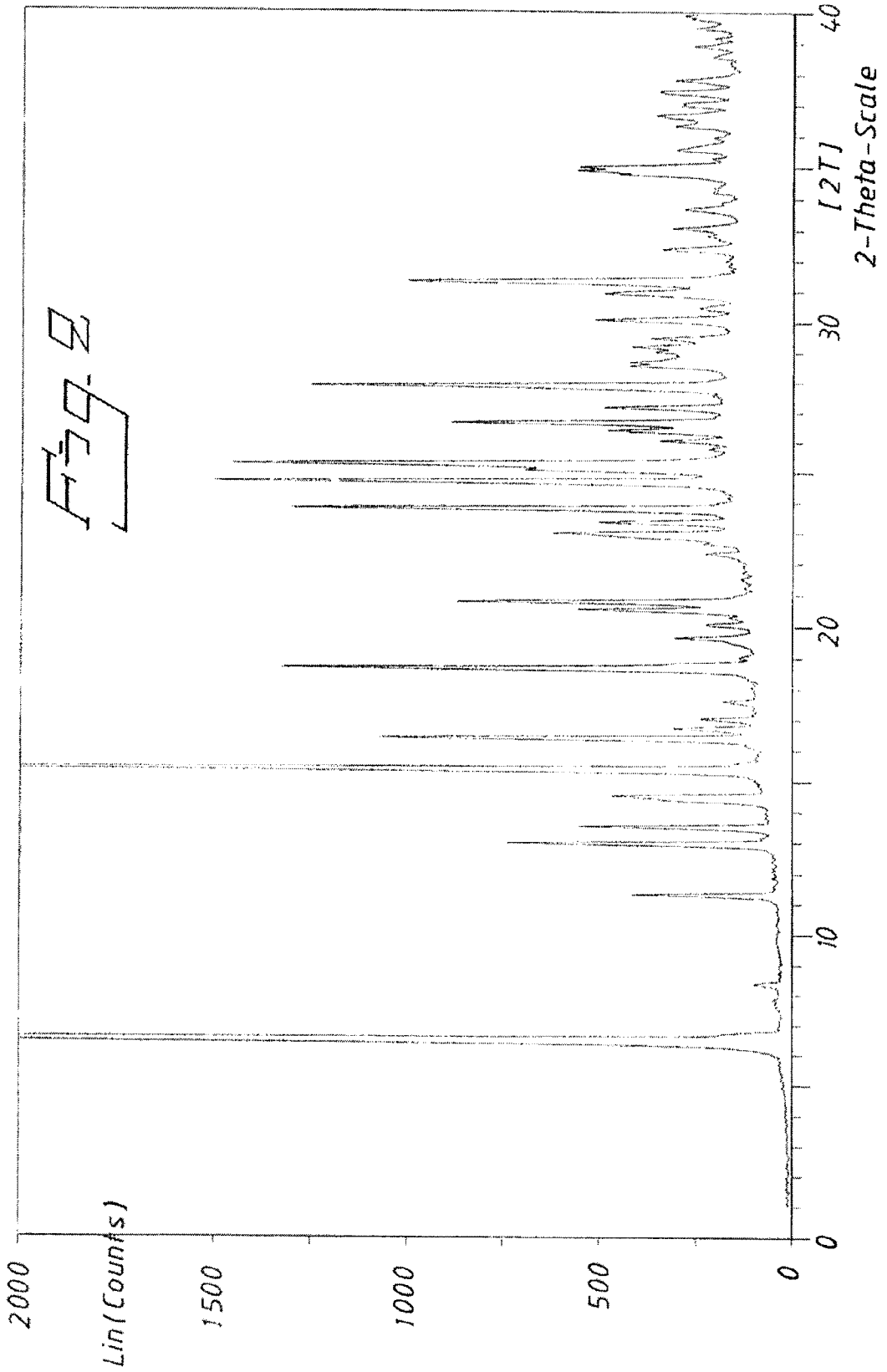
Fig. 2
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1500
1000
500
0
0
10
20
30
40
[2T]
2-Theta-Scale

Fig. 3

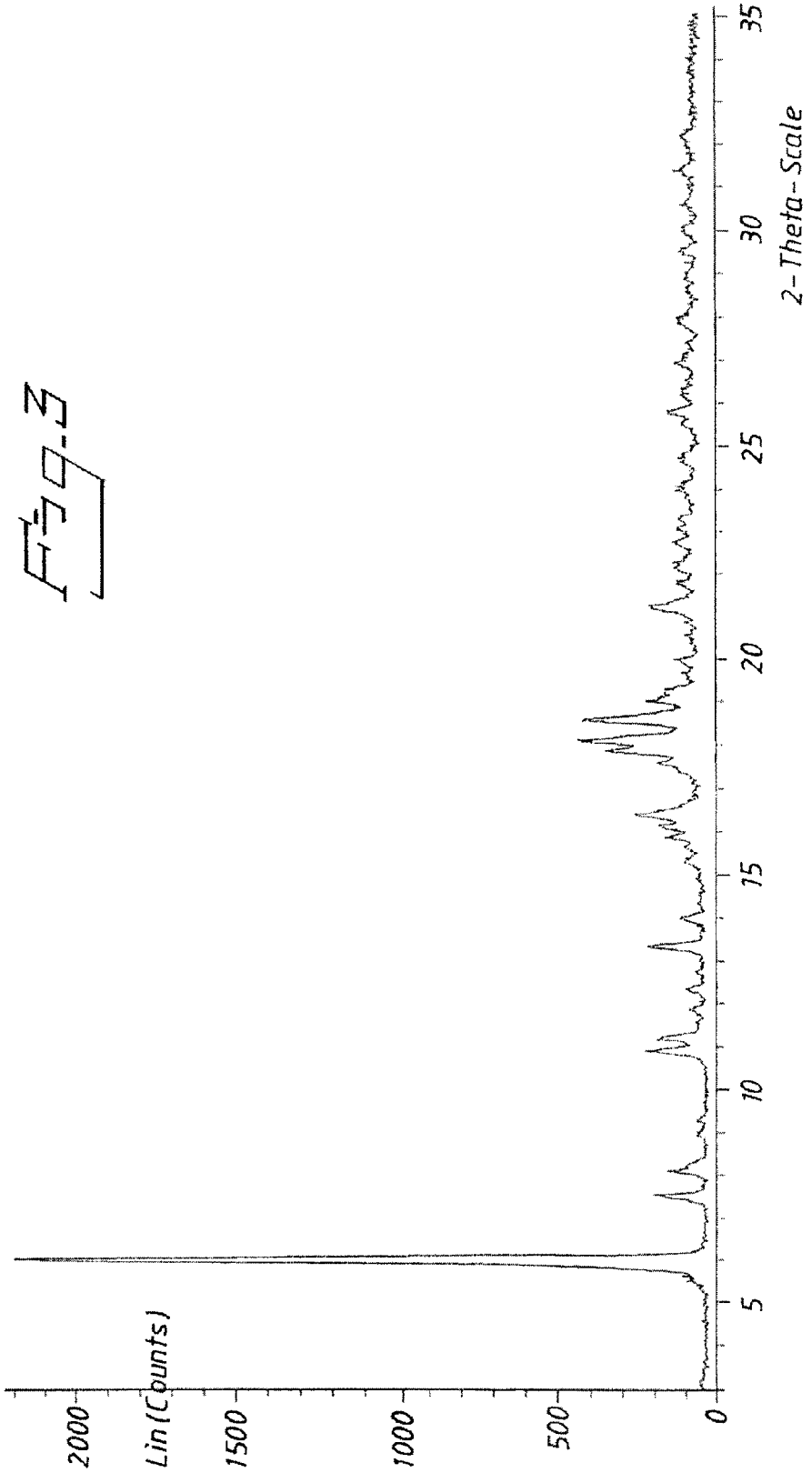
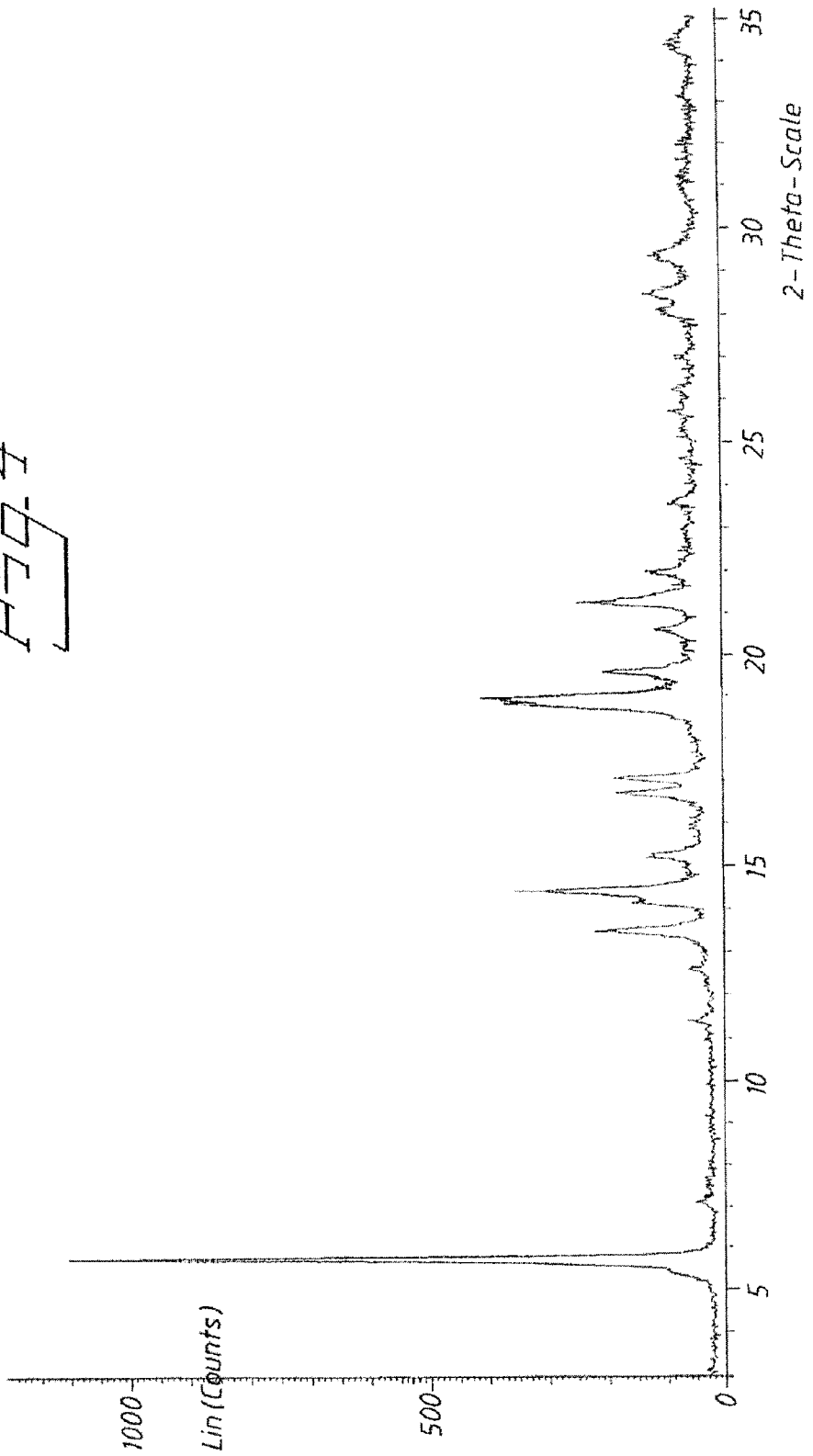
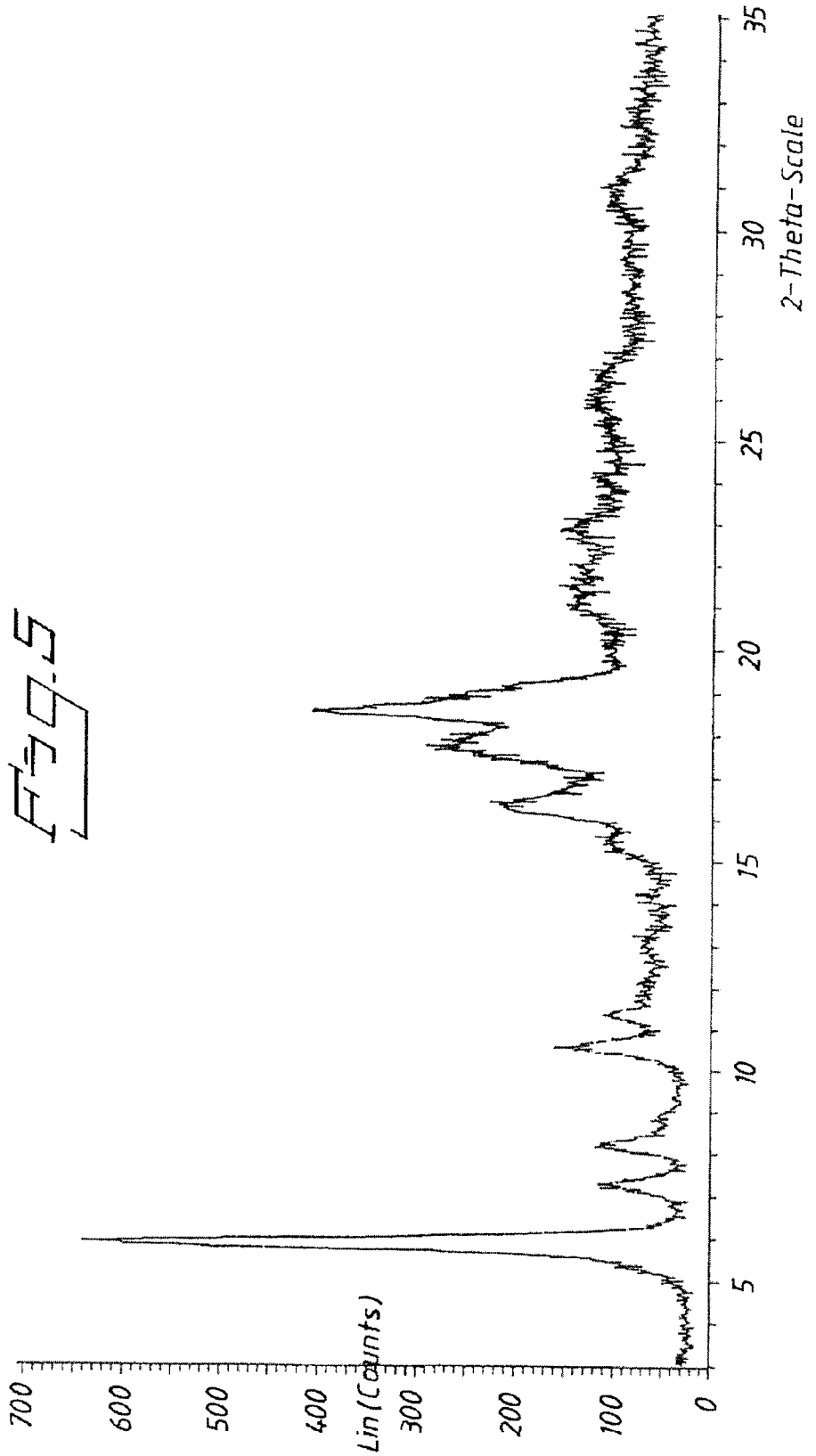


Fig. 4




Lin (Counts)
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100
200
300
400
500
600
700
5
10
15
20
25
30
35
2-Theta-Scale

FIG. 5

FORM OF *S*-OMEPRAZOLE

This application is a continuation of U.S. patent application Ser. No. 12/784,881, filed 21 May 2010 now U.S. Pat. No. 8,076,361, which is a continuation of U.S. patent application Ser. No. 11/853,323, filed 11 Sep. 2007, now U.S. Pat. No. 7,745,466, which is a continuation of U.S. patent application Ser. No. 10/672,936, filed 25 September 2003, now U.S. Pat. No. 7,411,070, which is a continuation of U.S. patent application Ser. No. 10/076,711, filed 14 Feb. 2002, now U.S. Pat. No. 6,677,455, which is a divisional of U.S, patent application Ser. No. 09/077,719, filed 8 Jun. 1998, now U.S. 6,369,085, which was the National Stage of International Application No. PCT/SE98/00974, tiled 25 May 1998.

FIELD OF THE INVENTION

The present invention relates to a novel form of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. S-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to intermediates used in the process, and their preparation.

BACKGROUND OF THE INVENTION AND PRIOR ART

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are disclosed in EP 124 495. Omeprazole is a proton pump inhibitor, i.e. effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole is a sulfoxide and achiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R and S-enantiomer of omeprazole, herein referred to as R-omeprazole and S-omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (−)-enantiomer of the non-salt form were found to have R and S configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (−)-enantiomer of the magnesium salt were also found to have R and S configuration respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

Certain salts of single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988. These compounds have improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.

WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts R- and S-omeprazole.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a X-ray powder diffractogram of the magnesium salt of S-omeprazole trihydrate prepared according to the present invention.

FIG. **2** shows a X-ray powder diffractogram of the potassium salt of S-omeprazole prepared and used in the present application (See examples 2 and 3)

FIG. **3** shows a X-ray powder diffractogram of a magnesium salt of S-omeprazole dihydrate prepared and used in the present application (See example 5)

FIG. **4** shows a X-ray powder diffractogram of a magnesium salt of S-omeprazole dihydrate which is a polymorph of the dihydrate shown in FIG. **3** (See Example 6). This magnesium salt of S-omeprazole dihydrate has been prepared and can be used in the preparation of the magnesium salt of S-omeprazole trihydrate according to the present invention.

FIG. **5** shows X-ray powder diffractogram of the magnesium salt of S-omeprazole prepared according to example A in WO 96/01623.

DESCRIPTION OF THE INVENTION

It has surprisingly been found that the magnesium salt of S-omeprazole occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of S-omeprazole trihydrate, hereinafter referred to as the compound of the invention. This trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of S-omeprazole trihydrate from other fauns of magnesium salts of S-omeprazole.

The compound of the invention is advantageous because it is more stable than the corresponding magnesium salt compounds in prior art and is therefore easier to handle and store. The compound of the invention is also easier to characterize because it exists in a well defined state. Additionally, the compound of the invention is easier to synthesize in a reproducible manner and thereby easier to handle in a full scale production.

The magnesium salt of S-omeprazole trihydrate obtained according to the present invention is substantially free from magnesium salts of R-omeprazole. The magnesium salt of S-omeprazole trihydrate obtained according to the present invention is also substantially free from other forms of magnesium salts of S-omeprazole, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of S-omeprazole and accordingly, the magnesium salt of S-omeprazole trihydrate is easily distinguishable from any other crystal form of the magnesium salt of S-omeprazole disclosed in prior art. The compound of the invention is characterized by being highly crystalline i.e. having a higher crystallinity than any other form of magnesium salt of S-omeprazole disclosed in the prior art. With the expression "any ether form" is meant anhydrates, hydrates, solvates, and polymorphs or amorphous forms thereof disclosed in the prior art. Examples of any other forms of magnesium salt of S-omeprazole includes, but are not limited to, anhydrates, monohydrates, dihydrates,

sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, and polymorphs or amorphous forms thereof.

The compound of the invention may also be characterized by its unit cell.

In a further aspect, the present invention provides processes for the preparation of the magnesium salt of S-omeprazole trihydrate which comprises;

a) treating a magnesium salt of S-omeprazole of any form, for example prepared according is to procedures known in the art such as Example A in WO 96/01623 which is incorporated herein by reference, with water at a suitable temperature for a suitable time. By a suitable temperature is meant a temperature which induces the transformation of starting material to product without decomposing any of these compounds. Examples of such suitable temperatures include, but are not limited to, room temperature and above. By a suitable time is meant a time that results in high conversion of the starting material into product without causing any decomposition of either compounds, i.e. results in a good yield. This suitable time will vary depending on the temperature used in a way well known to people in the art. The higher the temperature, the shorter time is needed to give the desired conversion. The amount of water is not crucial and will depend on the process conditions used. The magnesium salt of S-omeprazole trihydrate is thereafter separated from the aqueous slurry, for example by filtration or centrifugation and thereafter dried to constant weight; or

b) oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base. The oxidation is carried out in an organic solvent, for example toluene or dichloromethane.

The crude product is converted to the corresponding potassium salt by treatment with a potassium source, such as methanolic potassium hydroxide or methanolic potassium methylate, followed by isolation of the formed salt.

The resulting potassium salt of S-omeprazole is thereafter converted to the corresponding magnesium salt by treatment with a magnesium source, such as magnesium sulfate in a lower alcohol, such as methanol. The solution is optionally filtered and the precipitation is initialized by addition of a non-solvent such as acetone. The product is filtered off and optionally washed with water and further processed as is described in a) above. Alternatively, the potassium salt may be treated with a magnesium source, such as magnesium sulfate in water, and isolation of the magnesium salt of S-omeprazole trihydrate, or any other conventional technique for transforming a potassium salt to the corresponding magnesium salt can be used and is within the scope of the present invention.

Yet a further aspect of the present invention is to provide a suitable intermediate used in the preparation of the compound of the invention, as well as a process for its preparation. The potassium salt of S-omeprazole is found to be such a suitable intermediate. The potassium salt of S-omeprazole may also be used as an active component of a pharmaceutical formulation to be used in the treatment of gastrointestinal diseases.

The compound of the invention, i.e. the magnesium salt of S-omeprazole trihydrate, prepared according to the present invention may be analyzed by XRPD, a technique which is known per se.

The amount of water in the magnesium salt of S-omeprazole trihydrate is determined by thermogravimetric analysis, a technique which is known per se.

The compound of the invention is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for prevention and treatment of gastric-acid related conditions in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these. The compound of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the magnesium salt of S-omeprazole trihydrate, according to the invention. For example, peroral or parental formulations and the like may be employed. Dosage founts include capsules, tablets, dispersions, suspensions and the like.

It is further provided a pharmaceutical composition comprising the magnesium salt of S-omeprazole trihydrate 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 magnesium salt of S-omeprazole trihydrate of the invention 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 magnesium salt of S-omeprazole trihydrate according to the invention.

The compositions of the invention include compositions suitable for peroral or parental 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 magnesium salt of S-omeprazole trihydrate according to the invention in any given 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 patients. 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 the 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.

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 247 983, the disclosures of which are hereby incorporated as a whole by reference.

Combination preparations comprising the magnesium salt of S-omeprazole trihydrate 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, antacid agents, alginates and pro-kinetic agents.

The examples which follow 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 claimed below.

EXAMPLES

Example 1

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

Water (157 kg) was added to the wet crystals of the magnesium salt of S-omeprazole, prepared according to Example 4, below. The mixture was heated to 38° C. with stirring and left for 3 hours. The crystals were filtered off and dried in vacuo. Yield: 31.6 kg

X-ray powder diffraction analysis was performed on a sample of the crystals prepared above according to standard methods, which can be found in e.g. Kitaigorodsky, A. I. (1973), Molecular Crystals and Molecules, Academic Press, 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 York. The analysis gave the diffractogram depicted in FIG. **1**. The main peaks, with positions and relative intensities, have been extracted from the diffractogram in FIG. **1** and is given below in table 1. The relative intensities are less reliable and instead of numerical values the following definitions are used.

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3	w (weak)
<1	vw (very weak)

Some additional very weak peaks found in the diffractogram have been omitted from table 1.

TABLE 1

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole trihydrate.

d-value/Å	Relative Intensity
2.67	m
2.79	m
3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s
8.3	w
16.6	vs

Example 2

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole potassium salt

A solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (15.4 g, 46.8 mmol) in toluene (70 ml) was heated to 50° C. and water (0.05 ml, 2.8 mmol) and D-(−)-diethyl tartrate (2.02 g, 9.82 mmol) were added. The reaction mixture was stirred for 20 minutes. Titanium(IV)isopropoxide (1.34 g, 4.68 mmol) was added and the reaction mixture was stirred for 45 minutes. The mixture was cooled to 30° C. and diisopropylethylamine (0.91 g, 7.01 mmol) was added followed by cumene hydroperoxide (9.52 g, 51.89 mmol). The resultant mixture was stirred at 30° C. for 3 hours. Methanol (40 ml) was added followed by potassium hydroxide (3.05 g, 46.8 mmol) in methanol (30 ml). Seed crystals were added and the reaction mixture was stirred at 35° C. overnight. The precipitated product was filtered off, washed with methanol and toluene and dried in vacuo. Yield: 9.74 g (54%).

Example 3

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt

Water (157.6 µl) was added to a solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole in toluene (370 ml; 211.5 g/l) with a water content of 0.031% (w/w), followed by addition of D-(−)-diethyl tartrate (8.55 ml). The solution was heated to 50° C. and stirred at this temperature for 20 minutes. Titanium(IV) isopropoxide (7.15 ml) was added and reaction was left at 50° C. for 45 minutes. The temperature was lowered to 30° C. and diisopropylethylamine (6.2 ml) was added. Cumene hydroperoxide was added at an appropriate speed to maintain the temperature from 28° C. to 34° C. The temperature was raised to 35° C. after 2 hours and potassium methoxide (24.55 g) in methanol (222 ml) was added. The mixture was filtered after 14 hours and the crystals were washed with methanol:toluene (240 ml; 1:1) and methanol (120 ml) and dried. Yield: 79 g (74%), ee >99.9%. $[\alpha]_D^{20}$=+28.7° (c=1%, water); Assay: 89% is S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt (11% is methanol).

^{1}H-NMR (200 MHz, DMSO-d6, δ ppm): 2.23 (s, 3H), 2.24 (s, 3H), 3.71 (s, 3H), 3.75 (s, 3H), 4.40 (d, 110, 4.78 (d, 1H), 6.58 (dd, 1H), 7.00 (d, 1H), 7.35 (d, 1H), 8.25 (s, 1H).

The products from Examples 2 and 3 were analysed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. **2** and given below in Table 2. Some additional very weak peaks found in the diffractogram have been omitted from Table 2.

TABLE 2

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of S-omeprazole.

d-value/Å	Relative intensity	d-value/(Å)	Relative intensity
13.6	vs	3.52	m
10.6	vw	3.42	w
7.8	m	3.38	w
6.8	m	3.34	m
6.5	m	3.28	w
6.2	w	3.20	m
6.1	m	3.12	w
5.8	s	3.06	w
5.4	m	3.03	w
5.3	w	2.97	w
5.2	w	2.93	vw
5.0	vw	2.89	w
4.75	m	2.85	m
4.71	w	2.76	w
4.52	w	2.71	vw
4.42	w	2.66	vw
4.32	w	2.58	w
4.27	m	2.57	w
3.98	vw	2.56	w
3.92	w	2.52	vw
3.89	w	2.47	vw
3.87	w	2.45	vw
3.81	w	2.43	vw
3.74	m	2.40	vw
3.60	m	2.38	vw
3.55	m	2.31	vw

$\alpha 1 = 1.54060$ Å

Example 4

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

Methanol (148 kg) was added to S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt (71 kg, methanol content 13%). $MgSO_4 \times 7H_2O$ (40 kg) was added to the mixture while stirring. After 70 minutes the mixture was filtered and the filtrate was washed with methanol (46 kg). The solution was concentrated to a volume of 100 liter, acetone (253 kg) was added and the resulting mixture was left for 4 hours. The precipitated product was filtered off, washed with acetone and water. The wet crystals were immediately used as is described in Example 1.

Example 5

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate

5.0 g of the moist product from Example 4 with an approximate dry content of 74%, was dried in vacuum at 35° C. over night to yield 3.58 g (2.68 mmol) of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named Form B.

The product was analyzed using X-ray powder diffraction as described in Example 1, and the analyze gave the diffractogram depicted in FIG. **3** and given below in Table 3. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 3.

TABLE 3

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form B.

d-value/Å	Relative Intensity
4.19	m
4.45	m
4.68	m
4.79	s
4.91	s
4.98	s
5.1	m
5.4	s
5.5	m
5.6	m
5.8	m
6.3	m
6.7	s
7.9	m
8.1	s
11.0	m
11.8	m
14.9	vs

Conversion of Magnesium Salt of S-Omeprazole Dihydrate to Trihydrate

This material was subsequently processed to S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate according to the procedure described for the moist substance in Example 1.

Example 6

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate

A methanolic solution of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt was prepared as is described in Example 4. Such a solution of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt (1.86 g) in 5 ml methanol was concentrated by evaporation until 1.58 ml methanol remained. Then, a mixture of 1.6 ml water and 6.32 ml aceton was added. The solution was allowed to crystallize during 26 h at room temperature. The resulting crystals were filtered off and dried at 40° C. under reduced pressure giving 1.17 g of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named form A.

The product was analyzed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. **4** and given below in Table 4. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 4.

TABLE 4

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form A.

d-value/Å	Relative Intensity
3.04	s
3.14	s
3.18	m
4.05	s
4.19	s
4.32	m
4.54	s
4.69	vs
5.2	s
5.3	s
5.8	s
6.2	vs
6.6	s
15.5	vs

Example 7

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

22.0 g (29.1 mmol) of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole potassium salt was dissolved in 40 mL of water. The solution was seeded with 0.11 g (0.1 mmol) S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate. 22 mL (69.6 mmol) of $MgSO_4$ (aq) was added under a 3 h period. The slurry was filtered off and the precipitate was elutriated in water for approximately 30 minutes and the crystals were filtered off and dried (35° C., vacuum).

Yield: 9.15 g (11.6 mmol; 80%). The substance had a purity (HPLC): 99.8 area %, Mg content: 3,40% (w/w) and ee: 99.8%.

The product was analyzed using X-ray powder diffraction and the result complies with FIG. **1** and Table 1.

Reference Example A

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

(The method used is in accordance method described in Example A in WO 96/01623)

Magnesium (0.11 g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40° C. with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90% (−)-isomer and 10% (+)-isomer] of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (2.84 g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (+)-isomer), with an optical purity (enantiomeric excess, e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for 15 minutes, a white precipitate was obtained. Additional stirring for 15 minutes and thereafter filtration afforded 1.3 g (50%) of the title compound as white crystals. Chiral analyses of the crystals and mother liquor were performed by chromatogaphy on an analytical chiral column. The optical purity of the crystals and mother liquor was found to be 98.4 e.e. and 64.4% e.e., respectively. Thus, the optical purity (e.e.) has been enhanced from 80% to 98.4% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The product was crystalline as shown by powder X-ray diffraction and the magnesium content was 144% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20}=-131.5°$ (c=0.5%, methanol).

The product was analyzed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. **5** and given below in Table 5. Some additional very weak peaks found in the diffractograms have been omitted from Table 5.

TABLE 5

Positions and intensities of the major peaks in the XRP-diffractogram shown in FIG. 5.

d-value/Å	Relative Intensity
2.90	s
3.41	s
3.90	s
4.13	s
4.79	vs
5.00	vs
5.4	vs
5.7	s
6.3	s
6.8	s
7.8	s
8.4	vs
10.8	s
12.2	s
15.1	vs

The invention claimed is:

1. A method of treating *Helicobacter* infections comprising the administration of an effective amount of the magnesium salt of S-omeprazole trihydrate and an antibacterial compound to a patient in need thereof.

2. The method according to claim **1**, wherein the magnesium salt of S-omeprazole trihydrate is represented by FIG. **1**.

3. The method according to claim **1**, wherein the magnesium salt of S-omeprazole trihydrate is characterized by the following peaks in its X-ray diffractogram:

d-value/Å	Relative Intensity
2.67	m
2.79	m
3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s
8.3	w
16.6	vs.

4. The method according to claim 1, wherein the magnesium salt of S-omeprazole trihydrate is in a highly crystalline form.

5. The method according to claim 1, wherein the magnesium salt of S-omeprazole trihydrate is in a stable form.

6. The method according to claim 1, wherein the magnesium salt of S-omeprazole trihydrate is suitable for oral administration.

7. The method according to claim 6, wherein the antibacterial compound is suitable for oral administration.

8. The method according to claim 6, wherein the antibacterial compound is suitable for parenteral administration.

9. The method according to claim 1, wherein the magnesium salt of S-omeprazole trihydrate is suitable for parenteral administration.

10. The method according to claim 9 wherein the antibacterial compound is suitable for oral administration.

11. The method according to claim 9, wherein the antibacterial compound is suitable for parenteral administration.

12. The method according to claim 1, wherein the antibacterial compound is suitable for oral administration.

13. The method according to claim 1, wherein the antibacterial compound is suitable for parenteral administration.

14. The method according to claim 1, wherein the total daily dose of the magnesium salt of S-omeprazole trihydrate is from 10 mg to 80 mg.

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