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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA AB; AKTIEBOLAGET HÄSSLE; ASTRAZENECA LP; KBI INC.; and KBI-E INC.,	Civil Action No. _____
Plaintiffs,	COMPLAINT FOR PATENT INFRINGEMENT AND CERTIFICATION PURSUANT TO LOCAL RULE 11.2
v.	
SANDOZ, INC.	
Defendants.	

JURISDICTION AND VENUE

1. This is an action for patent infringement arising under the Patent and Food and Drug laws of the United States, Titles 35 and 21, United States Code. Jurisdiction and venue are based on 28 U.S.C. §§ 1331, 1338(a), 1391(b), 1391(c), 1400(b), 2201, 2202 and 35 U.S.C. § 271.

2. On information and belief, Sandoz, Inc. ("Sandoz") has been and is engaging in activities directed toward infringement of United States Patent Nos. 5,714,504 (the "'504 patent"), 5,877,192 (the "'192 patent"), 6,875,872 (the "'872 patent"), 6,369,085 (the "'085 patent"), and 7,411,070 (the "'070 patent"), by, *inter alia*, submitting an abbreviated new drug application designated ANDA No. 90-841 and by submitting Drug Master Files (DMF) seeking FDA's approval to manufacture commercially its proposed 20 mg and 40 mg product called "Esomeprazole Magnesium Delayed Release Capsules, 20 mg Base, and 40 mg Base" (hereinafter referred to as "Esomeprazole Magnesium Capsules") containing the active ingredient esomeprazole magnesium.

3. In Sandoz's notice letter entitled "Notice of Certification Under 21 U.S.C. § 355(j)(2)(B) (§ 505(j)(2)(B)) of Federal Food, Drug and Cosmetic Act) and 21 C.F.R. § 314.95 Sandoz Inc.'s Esomeprazole Magnesium Delayed Release Capsules, 20 mg Base, and 40 mg Base Sandoz Inc.'s ANDA 90-841" (hereinafter referred to as the "Notice of Certification"), Sandoz has indicated that it intends to market its Esomeprazole Magnesium Capsules before the expiration of the '504, '192, '872, '085 and '070 patents.

4. Sandoz's submission of ANDA No. 90-841 and the DMF, in addition to service of its Notice of Certification, indicates a refusal to change its current course of action.

5. There has been and is now an actual controversy between Sandoz and Plaintiffs as to whether Sandoz infringes the '504, '192, '872, '085 and '070 patents.

THE PARTIES

6. Plaintiff AstraZeneca AB is a company organized and existing under the laws of Sweden, having its principal place of business at Södertälje, Sweden. AstraZeneca AB was a corporate name change from Astra Aktiebolaget.

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

8. Plaintiff AstraZeneca LP is a limited partnership organized under the laws of Delaware having its principal place of business at Wilmington, Delaware. AstraZeneca LP holds an approved New Drug Application from the United States Food and Drug Administration ("FDA") for an esomeprazole magnesium formulation which it sells under the name NEXIUM®.

9. Plaintiff KBI Inc. ("KBI") is a Delaware corporation having its principal place of business at Whitehouse Station, New Jersey.

10. Plaintiff KBI-E Inc. ("KBI-E") is a Delaware corporation, having its principal place of business at Wilmington, Delaware. KBI and KBI-E have exclusive rights in the United States to patents-in-suit.

11. On information and belief, defendant Sandoz, Inc. is a company incorporated under the laws of the state of Colorado, having a principal place of business at 506 Carnegie Center, Suite 400, Princeton, NJ 08540.

12. On information and belief, Sandoz is doing business in New Jersey, has continuous and systematic contacts with New Jersey, has engaged in activities related to the subject matter of this action and is subject to personal jurisdiction in this judicial district.

FIRST CLAIM FOR RELIEF: '504 PATENT

13. AstraZeneca AB, Hässle, AstraZeneca LP, KBI and KBI-E (collectively, "Plaintiffs") reallege paragraphs 1-12, above, as if set forth specifically here.

14. The '504 patent (copy attached as Exhibit "A"), entitled "Compositions," was issued on February 3, 1998 to Astra Aktiebolag upon assignment from the inventors Per Lennart Lindberg and Sverker Von Unge. The patent was subsequently assigned to AstraZeneca AB. The '504 patent claims, *inter alia*, pharmaceutical formulations comprising alkaline salts of esomeprazole (including esomeprazole magnesium) and methods of using esomeprazole magnesium.

15. Plaintiff AstraZeneca AB has been and is still the owner of the '504 patent. The '504 patent will expire on February 3, 2015 and pediatric exclusivity relating to the '504 patent expires on August 3, 2015.

16. Sandoz's Notice of Certification notified Plaintiffs that it had submitted an Abbreviated New Drug Application ("ANDA") to the FDA under 21 U.S.C. § 355(j), seeking the FDA's approval to manufacture, use, offer to sell and sell Sandoz's Esomeprazole Magnesium Capsules as a generic version of the NEXIUM® product.

17. In the Notice of Certification, Sandoz notified Plaintiffs that as part of its ANDA it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") with respect to the '504 patent. This statutory section requires, *inter alia*,

certification by the ANDA applicant that the subject patent, here the '504 patent, "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted . . . ." The statute (21 U.S.C. § 355(j)(2)(B)(iv)) also requires a Paragraph IV notice to "include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." The FDA Rules and Regulations (21 C.F.R. § 314.95(c)) specify, *inter alia*, that a Paragraph IV notification must include "[a] detailed statement of the factual and legal basis of applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement is to include "(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation."

18. On information and belief, at the time Sandoz's Notice of Certification was served, Sandoz was aware of the statutory provisions and regulations referred to in paragraph 17, above.

19. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding non-infringement (see paragraph 17 above), does not allege non-infringement of any of the claims of the '504 patent.

20. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding unenforceability (see paragraph 17 above), does not address unenforceability or inequitable conduct of the '504 patent.

21. In the Notice of Certification, Sandoz did not provide the full and detailed statement required by, and therefore fails to comply with, the statutory and regulatory provisions set forth in paragraph 17, above, as to the '504 patent.

22. Sandoz's Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(j), and FDA rules and regulations, as specified in 21 C.F.R. § 314.95.

23. Sandoz has infringed the '504 patent under 35 U.S.C. § 271(e)(2) by filing its ANDA seeking approval from the FDA to engage in the commercial manufacture, use or sale of a drug claimed in this patent, or the use of which is claimed in this patent, prior to the expiration of the '504 patent.

24. On information and belief, Sandoz's Esomeprazole Magnesium Capsules, if approved, will be 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 Sandoz's active behest and with its intent, knowledge and encouragement. On information and belief, Sandoz will actively encourage, aid and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '504 patent.

25. On information and belief, Sandoz's Esomeprazole Magnesium Capsules are especially made or especially adapted to inhibit gastric acid secretion and for use in the treatment of gastrointestinal inflammatory disease via the administration of a therapeutically effective amount of a pharmaceutical formulation containing the claimed esomeprazole magnesium and a pharmaceutically acceptable carrier. On information and belief, Sandoz is aware that its Esomeprazole Magnesium Capsules are so made or so adapted. On information and belief, Sandoz is aware that its Esomeprazole Magnesium Capsules, if approved, will be used in contravention of Plaintiffs' rights under the '504 patent.

26. Sandoz's Notice of Certification does not allege and does not address non-infringement of any claims of the '504 patent. By not addressing non-infringement of any claims of the '504 patent in its Notice of Certification, Sandoz admits that its Esomeprazole Magnesium Capsules meet all limitations of all claims of the '504 patent.

27. On information and belief, the manufacture, use and sale of Sandoz's Esomeprazole Magnesium Capsules infringe the '504 patent claims.

SECOND CLAIM FOR RELIEF: '192 PATENT

28. AstraZeneca AB, Hässle, AstraZeneca LP, KBI and KBI-E (collectively, "Plaintiffs") reallege paragraphs 1-12 and 16, above, as if set forth specifically here.

29. The '192 patent, (copy attached as Exhibit "B"), entitled "Method For The Treatment Of Gastric Acid-Related Diseases And Production Of Medication Using (-)Enantiomer Of Omeprazole," was issued on March 2, 1999 to Astra Aktiebolag, upon assignment from the inventors Per Lindberg and Lars Weidolf. The patent was subsequently assigned to AstraZeneca AB. The '192 patent claims, *inter alia*, methods for treatment of gastric acid related diseases by administering a therapeutically effective amount of esomeprazole and pharmaceutically acceptable salts thereof and methods for producing a medicament for such treatment.

30. Plaintiff AstraZeneca AB has been and still is the owner of the '192 patent. The '192 patent will expire on May 27, 2014 and pediatric exclusivity relating to the '192 patent expires on November 27, 2014.

31. In the Notice of Certification, Sandoz notified Plaintiffs that as part of its ANDA it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") with respect to the '192 patent. This statutory section requires, *inter alia*, certification by the ANDA applicant that the subject patent, here the '192 patent, "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted . . . ." The statute (21 U.S.C. § 355(j)(2)(B)(iv)) also requires a Paragraph IV notice to "include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." The FDA Rules and Regulations (21 C.F.R. § 314.95(c)) specify, *inter alia*, that a Paragraph IV notification must include "[a] detailed statement of the factual and legal basis of applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement is to include "(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation."

32. On information and belief, at the time Sandoz's Notice of Certification was served, Sandoz was aware of the statutory provisions and regulations referred to in paragraph 31, above.

33. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding non-infringement (see paragraph 31 above), does not allege non-infringement of any of the claims of the '192 patent.

34. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding unenforceability (see paragraph 31 above), does not address unenforceability or inequitable conduct of the '192 patent.

35. In the Notice of Certification, Sandoz did not provide the full and detailed statement required by, and therefore fails to comply with, the statutory and regulatory provisions set forth in paragraph 31, above, as to the '192 patent.

36. Sandoz's Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(j), and FDA rules and regulations, as specified in 21 C.F.R. § 314.95.

37. Sandoz has infringed the '192 patent under 35 U.S.C. § 271(e)(2) by filing its ANDA seeking approval from the FDA to engage in the commercial manufacture, use or sale of a drug claimed in this patent, or the use of which is claimed in this patent, prior to the expiration of the '192 patent.

38. On information and belief, Sandoz's Esomeprazole Magnesium Capsules, if approved, will be administered to human patients in a therapeutically effective amount to treat gastric acid related diseases by inhibiting gastric acid secretion. On information and belief, such administration will decrease interindividual variation in plasma levels (AUC) during such treatment. On information and belief, such treatment will increase average plasma levels (AUC) per dosage unit. On information and belief, such treatment will effect a pronounced increase in gastrin levels in slow metabolizers during such treatment. On information and belief, such treatment will effect decreased CYP1A induction in slow metabolizers during such treatment. On information and belief, such treatment will elicit an improved antisecretory effect during such treatment. On information and belief, such treatment will elicit an improved clinical effect comprising accelerated rate of healing and accelerated rate of symptom relief during such treatment. On information and belief the amount to be administered will be between about 20 mg and about 40 mg total daily dose during such

treatment. On information and belief, this administration will occur at Sandoz's active behest and with its intent, knowledge and encouragement. On information and belief, Sandoz will actively encourage, aid and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '192 patent.

39. On information and belief, Sandoz's Esomeprazole Magnesium Capsules are especially made or especially adapted to inhibit gastric acid secretion and for use in the treatment of gastrointestinal inflammatory disease via the administration of a therapeutically effective amount of a pharmaceutical formulation containing the magnesium salt of esomeprazole. On information and belief, Sandoz is aware that its Esomeprazole Magnesium Capsules are so made or so adapted. On information and belief, Sandoz is aware that its Esomeprazole Magnesium Capsules, if approved, will be used in contravention of Plaintiffs' rights under the '192 patent.

40. Sandoz's Notice of Certification does not allege and does not address non-infringement of any claims of the '192 patent. By not addressing non-infringement of any claims of the '192 patent in its Notice of Certification, Sandoz admits that its Esomeprazole Magnesium Capsules meet all limitations of all claims of the '192 patent.

41. On information and belief, the manufacture, use and sale of Sandoz's Esomeprazole Magnesium Capsules infringe the '192 patent claims.

THIRD CLAIM FOR RELIEF: '872 PATENT

42. Plaintiffs reallege paragraphs 1-12 and 16, above, as if set forth specifically here.

43. The '872 patent, (copy attached as Exhibit "C"), entitled "Compounds," was issued on April 5, 2005 to AstraZeneca AB, upon assignment from the inventors Per Lennart Lindberg and Sverker Von Unge. The '872 patent claims, *inter alia*, esomeprazole magnesium salts.

44. Plaintiff AstraZeneca AB has been and still is the owner of the '872 patent. The '872 patent will expire on May 27, 2014 and pediatric exclusivity relating to the '872 patent expires on November 27, 2014.

45. In the Notice of Certification, Sandoz notified Plaintiffs that as part of its ANDA it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") with respect to the '872 patent. This statutory section requires, *inter alia*, certification by the ANDA applicant that the subject patent, here the '872 patent, "is invalid or will not be infringed by the manufacture, use, offer to sale or sale of the new drug for which the application is submitted . . . ." The statute (21 U.S.C. § 355(j)(2)(B)(iv)) also requires a Paragraph IV notice to "include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." The FDA Rules and Regulations (21 C.F.R. § 314.95(c)) specify, *inter alia*, that a Paragraph IV notification must include "[a] detailed statement of the factual and legal basis of applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement is to include "(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds of supporting the allegation."

46. On information and belief, at the time Sandoz's Notice of Certification was served, Sandoz was aware of the statutory provisions and regulations referred to in paragraph 45, above.

47. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding non-infringement (see paragraph 45 above), does not allege non-infringement of any of the claims of the '872 patent.

48. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding unenforceability (see paragraph 45 above), does not address unenforceability or inequitable conduct of the '872 patent.

49. In the Notice of Certification, Sandoz did not provide the full and detailed statement required by, and therefore fails to comply with, the statutory and regulatory provisions set forth in paragraph 45, above, as to the '872 patent.

50. Sandoz's Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(j), and FDA rules and regulations, as specified in 21 C.F.R. § 314.95.

51. Sandoz has infringed the '872 patent under 35 U.S.C. § 271(e)(2) by filing its ANDA seeking approval from the FDA to engage in the commercial manufacture, use or sale of a drug claimed in this patent, prior to the expiration of the '872 patent.

52. On information and belief, Sandoz's Esomeprazole Magnesium Capsules, if approved, will be administered to human patients at Sandoz's active behest and with its intent, knowledge and encouragement. On information and belief, Sandoz will actively encourage, aid and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '872 patent.

53. On information and belief, Sandoz's Esomeprazole Magnesium Capsules are especially made or especially adapted for treatment of humans. On information and belief, Sandoz is aware that its Esomeprazole Magnesium Capsules are so made or so adapted. On information and belief, Sandoz is aware that its Esomeprazole Magnesium Capsules, if approved, will be used in contravention of Plaintiffs' rights under the '872 patent.

54. Sandoz's Notice of Certification does not allege and does not address non-infringement of any claims of the '872 patent. By not addressing non-infringement of any claims of the '872 patent in its Notice of Certification, Sandoz admits that its Esomeprazole Magnesium Capsules meet all limitations in all claims of the '872 patent.

55. On information and belief, the manufacture, use and sale of Sandoz's Esomeprazole Magnesium Capsules infringe the '872 patent claims.

FOURTH CLAIM FOR RELIEF: '085 PATENT

56. Plaintiffs reallege paragraphs 1-12 and 16, above, as if set forth specifically here.

57. The '085 patent, (copy attached as Exhibit "D"), entitled "Form of S-Omeprazole," was issued on April 9, 2002 to AstraZeneca AB, upon assignment from the inventors Hanna Cotton, Anders Kronström, 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.

58. Plaintiff AstraZeneca 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.

59. In the Notice of Certification, Sandoz notified Plaintiffs that as part of its ANDA it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") with respect to the '085 patent. This statutory section requires, *inter alia*, certification by the ANDA applicant that the subject patent, here the '085 patent, "is invalid or will not be infringed by the manufacture, use, offer to sale or sale of the new drug for which the application is submitted . . . ." The statute (21 U.S.C. § 355(j)(2)(B)(iv)) also requires a Paragraph IV notice to "include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." The FDA Rules and Regulations (21 C.F.R. § 314.95(c)) specify, *inter alia*, that a Paragraph IV notification must include "[a] detailed statement of the factual and legal basis of applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement is to include "(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds of supporting the allegation."

60. On information and belief, at the time Sandoz's Notice of Certification was served, Sandoz was aware of the statutory provisions and regulations referred to in paragraph 59, above.

61. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding invalidity (see paragraph 59 above), does not allege invalidity of any claims of the '085 patent.

62. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding unenforceability (see paragraph 59 above), does not address unenforceability or inequitable conduct of the '085 patent.

63. In the Notice of Certification, Sandoz did not provide the full and detailed statement required by, and therefore fails to comply with, the statutory and regulatory provisions set forth in paragraph 59, above, as to the '085 patent.

64. Sandoz's Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(j), and FDA rules and regulations, as specified in 21 C.F.R. § 314.95.

65. Sandoz has infringed the '085 patent under 35 U.S.C. § 271(e)(2) by filing its ANDA seeking approval from the FDA to engage in the commercial manufacture, use or sale of a drug claimed in this patent, prior to the expiration of the '085 patent.

66. On information and belief, Sandoz's Esomeprazole Magnesium Capsules, if approved, will be administered to human patients in a therapeutically effective amount to treat gastric acid related conditions. On information and belief, this administration will occur at Sandoz's active behest and with its intent, knowledge and encouragement. On information and belief, Sandoz will actively encourage, aid and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '085 patent.

67. On information and belief, Sandoz's Esomeprazole Magnesium Capsules are especially made or especially adapted to treat gastric acid related diseases via the administration of a therapeutically effective amount of a pharmaceutical formulation containing esomeprazole magnesium. On information and belief, Sandoz is aware that its Esomeprazole Magnesium Capsules are so made or so adapted. On information and belief, Sandoz is aware

that its Esomeprazole Magnesium Capsules, if approved, will be used in contravention of Plaintiffs' rights under the '085 patent.

68. On information and belief, the manufacture, use and sale of Sandoz's Esomeprazole Magnesium Capsules infringe the '085 patent claims.

69. To further investigate whether Sandoz will infringe AstraZeneca's patents, in a letter dated December 30, 2008, AstraZeneca requested access to certain documents, information and samples, as well as access to Sandoz's ANDA No. 90-841 and the DMF.

70. On January 7, 2009, Sandoz' outside attorney responded that it was still considering AstraZeneca requests. By the date of this Complaint, Sandoz had still not agreed to provide AstraZeneca access to any of the requested documents, information and samples.

71. Plaintiffs bring this suit, in part, to employ the judicial process and the aid of discovery to obtain under appropriate judicial safeguards information to confirm that Sandoz's Esomeprazole Magnesium Capsules infringe the '085 patent claims.

FIFTH CLAIM FOR RELIEF: '070 PATENT

72. Plaintiffs reallege paragraphs 1-12 and 16, above, as if set forth specifically here.

73. The '070 patent (copy attached as Exhibit "E"), entitled "Form of S-omeprazole," was issued on August 12, 2008 to AstraZeneca AB upon assignment from the inventors Hanna Cotton, Anders Kronstrom, Anders Mattson and Eva Moller. The '070 patent is directed to, *inter alia*, magnesium salts of esomeprazole trihydrate and processes for preparing the claimed salts.

74. Plaintiff AstraZeneca AB has been and is still 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.

75. In the Notice of Certification, Sandoz notified Plaintiffs that as part of its ANDA it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") with respect to the '070 patent. This statutory section requires, *inter alia*, certification by the ANDA applicant that the subject patent, here the '070 patent, "is invalid or will not be infringed by the manufacture, use, offer to sale or sale of the new drug for which the application is submitted . . . ." The statute (21 U.S.C. § 355(j)(2)(B)(iv)) also requires a Paragraph IV notice to "include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." The FDA Rules and Regulations (21 C.F.R. § 314.95(c)) specify, *inter alia*, that a Paragraph IV notification must include "[a] detailed statement of the factual and legal basis of applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement is to include "(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds of supporting the allegation."

76. On information and belief, at the time Sandoz's Notice of Certification was served, Sandoz was aware of the statutory provisions and regulations referred to in paragraph 75, above.

77. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding invalidity (see paragraph 75 above), does not allege invalidity of any claims of the '070 patent.

78. Sandoz's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding unenforceability (see paragraph 75 above), does not address unenforceability or inequitable conduct of the '070 patent.

79. In the Notice of Certification, Sandoz did not provide the full and detailed statement required by, and therefore fails to comply with, the statutory and regulatory provisions set forth in paragraph 75, above, as to the '070 patent.

80. Sandoz's Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(j), and FDA rules and regulations, as specified in 21 C.F.R. § 314.95.

81. Sandoz has infringed the '070 patent under 35 U.S.C. § 271(e)(2) by filing its ANDA seeking approval from the FDA to engage in the commercial manufacture, use or sale of a drug claimed in this patent, prior to the expiration of the '070 patent.

82. On information and belief, Teva's Esomeprazole Magnesium Capsules contain a magnesium salt of esomeprazole trihydrate as claimed by the '070 patent.

83. On information and belief, Teva's Esomeprazole Magnesium Capsules are manufactured by a process comprised of treating a magnesium salt of esomeprazole of any form with water as claimed by the '070 patent.

84. On information and belief, the manufacture, use and sale of Sandoz's Esomeprazole Magnesium Capsules infringe the '070 patent claims.

85. To further investigate whether Sandoz will infringe AstraZeneca's patents, in a letter dated December 30, 2008, AstraZeneca requested access to certain documents, information and samples, as well as access to Sandoz's ANDA No. 90-841 and the DMF.

86. On January 7, 2009, Sandoz' outside attorney responded that it was still considering AstraZeneca requests. By the date of this Complaint, Sandoz had still not agreed to provide AstraZeneca access to any of the requested documents, information and samples.

87. Plaintiffs bring this suit, in part, to employ the judicial process and the aid of discovery to obtain under appropriate judicial safeguards information to confirm that Sandoz's Esomeprazole Magnesium Capsules infringe the '070 patent claims.

WHEREFORE, Plaintiffs respectfully request the following relief:

(a) A judgment declaring that the effective date of any approval of Sandoz's ANDA under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) for the drug product "Esomeprazole magnesium" must be later than November 25, 2018, the expiration date of the last patent in suit, including pediatric exclusivity relating to the patent, that is infringed;

(b) A judgment declaring that the '504, '192, '872, '085 and '070 patents remain valid, remain enforceable and have been infringed by defendant Sandoz;

(c) A judgment declaring that Sandoz has not complied with the requirements of 35 U.S.C. § 271(e)(2), 21 U.S.C. § 355(j)(2)(A)(vii)(IV), 21 U.S.C. § 355(j)(2)(B)(iv), 21 C.F.R. § 314.94 and 21 U.S.C. § 314.95;

(d) A permanent injunction against any infringement by Sandoz of the '504, '192, '872, '085 and '070 patents;

(e) A judgment that Sandoz's conduct is exceptional;

(f) Attorneys' fees in this action under 35 U.S.C. § 285;

(g) Costs and expenses in this action; and

(h) Such other relief as this Court may deem proper.

Respectfully Submitted,

Dated: January 14, 2009

By: s/ Andrew T. Berry

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

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

ASTRAZENECA AB; AKTIEBOLAGET HÄSSLE; ASTRAZENECA LP; KBI INC.; and KBI-E INC. v. IVAX CORPORATION, IVAX PHARMACEUTICALS, INC., IVAX PHARMACEUTICALS NV, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC., and CIPLA, LTD., 3:05-cv-05553-JAP-TJB (Consolidated) (District of New Jersey).

ASTRAZENECA AB; AKTIEBOLAGET HÄSSLE; ASTRAZENECA LP; KBI INC.; and KBI-E INC. v. DR. REDDY'S LABORATORIES, LTD.; and DR. REDDY'S LABORATORIES, INC., 3:08-cv-00328-JAP-TJB (District of New Jersey).

IVAX PHARMACEUTICALS, INC. v. ASTRAZENECA AB; and MERCK & CO., INC., 3:08-cv-02165-JAP-TJB (District of New Jersey).

DR. REDDY'S LABORATORIES, LTD.; and DR. REDDY'S LABORATORIES, INC. v. ASTRAZENECA AB; AKTIEBOLAGET HÄSSLE; ASTRAZENECA LP; and MERCK & CO., INC. 3:08-vc-02496-JAP-TJB (District of New Jersey).

ASTRAZENECA AB; AKTIEBOLAGET HÄSSLE; ASTRAZENECA LP; KBI INC.; and KBI-E INC. v. IVAX CORPORATION, IVAX PHARMACEUTICALS NV, INC., IVAX PHARMACEUTICALS, INC., TEVA PHARMACEUTICALS INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, CIPLA, LTD., 3:08-cv-4993-JAP-TJB (District of New Jersey).

Dated: January 14, 2009

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EXHIBIT A

US005714504A

United States Patent [19]

Lindberg et al.

[11] Patent Number: 5,714,504

[45] Date of Patent: Feb. 3, 1998

[54] **COMPOSITIONS**

[75] Inventors: **Per Lennart Lindberg**, Mölndal; **Sverker Von Unge**, Fjärås, both of Sweden

[73] Assignee: **Astra Aktiebolag**, Sodertalje, Sweden

[21] Appl. No.: **376,512**

[22] Filed: **Jan. 23, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 256,174, filed as PCT/SE94/00509, May 27, 1994.

[30] **Foreign Application Priority Data**

May 28, 1993 [SE] Sweden 9301830

[51] **Int. Cl.**^{6} **C07D 401/12**; A61K 31/44

[52] **U.S. Cl.** **514/338**; 546/273.7

[58] **Field of Search** 546/273.7; 514/338

[56] **References Cited**

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Primary Examiner—Jane Fan

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[57] **ABSTRACT**

The novel optically pure compounds Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (–)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, in particular sodium and magnesium salt form thereof, where R is an alkyl with 1–4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.

10 Claims, No Drawings

COMPOSITIONS

This application is a continuation-in-part of application Ser. No. 08/256,174, filed as PCT/SE94/00509, May 27, 1994.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in U.S. Pat. No. 4,255,431 to Junggren et al., EP 5129 and EP 124 495, respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers).

The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305–19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application (DE 4035455) this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because them is a great risk of locally reaching pH values between 1–6, which would be devastating for the substance. Moreover, instantaneous neutralization will create heat which will be difficult to handle in large scale production.

There is no example in the known prior art of any isolated or characterized salt of optically pure omeprazole, i.e. of single enantiomers of omeprazole or of any isolated or characterized salt of any optically pure omeprazole analogue.

SUMMARY OF THE INVENTION

It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

A preferred embodiment of the present invention provides pure crystalline enantiomeric salts of omeprazole and methods for the preparation thereof.

A more preferred embodiment of the present invention is directed to an optically pure crystalline enantiomeric magnesium salt of omeprazole and method for the preparation thereof.

A nonaqueous process according to the present invention is directed to the preparation of crystalline forms of an optically pure enantiomer of omeprazole magnesium salt or analogues thereof which includes steps of stirring a crude

preparation of the omeprazole enantiomer under nitrogen into a methanolic magnesium methoxide solution, precipitating inorganic magnesium salt with addition of a small amount of water, removing any precipitated inorganic magnesium salts, concentrating the residual methanolic solution, precipitating the omeprazole enantiomer by adding acetone to the residual solution, and filtering off the optically pure enantiomer crystals of magnesium omeprazole or analogues thereof.

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

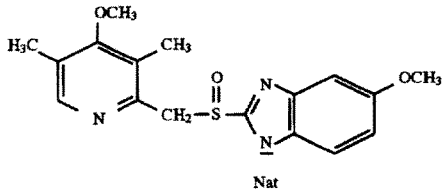
The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as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

DETAILED DESCRIPTION OF THE INVENTION

The present invention refers to the new Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of the single enantiomers of omeprazole, where R is an alkyl with 1–4 carbon atoms, i.e. Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1–4 carbon atoms.

Particularly preferred salts according to the invention are the Na^+, Ca^{2+} and Mg^{2+} salts, i.e (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt.

Most preferred salts according to the invention are the optically pure Na^+ salts of omeprazole according to compounds Ia and Ib

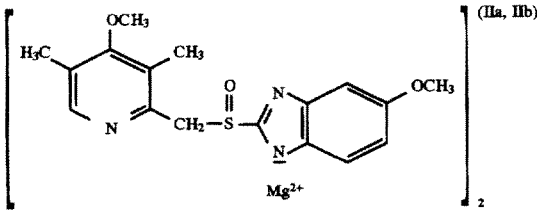


(Ia, Ib)

Nat

Ia (+)-enantiomer
Ib (−)-enantiomer

and the optically pure magnesium salts of omeprazole according to compounds IIa and IIb



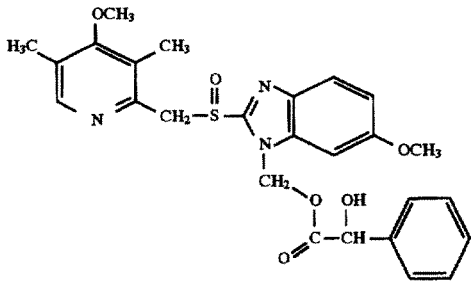
(IIa, IIb)

IIa (+)-enantiomer
IIb (−)-enantiomer

With the expression "optically pure Na^+ salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (−)-enantiomer of omeprazole Na-salt and the (−)-enantiomer essentially free of the (+)-enantiomer, respectively. Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. The salts defined by the present invention are easy to obtain by means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole. In contrast to the neutral forms the salts can be obtained as crystalline products. Because it is possible to purify optically impure or partially pure salts of the enantiomers of omeprazole by crystallization, they can be obtained in very high optical purity, namely ≧99.8% enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy.

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

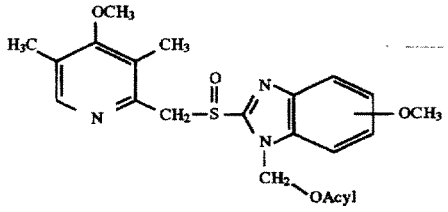
Yet a further aspect of the invention is the compound III, which is an intermediate used in the specific method of preparation.



(III)

Preparation

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV



(IV)

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

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

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

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

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

To obtain the optically pure Mg^{2+} salts of the invention, optically pure enantiomeric Na^+ salts may be treated with an aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomers of omeprazole with a base, such as

$Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1–4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

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

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1–95% by weight of the preparation, between 0.2–20% by weight in preparations for parenteral use and between 1–50% by weight in preparations for oral administration.

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

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

Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

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

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

Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

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

The invention is illustrated by the following examples using preferred procedures for the preparation of optically pure sodium salts and magnesium salts.

The processes described below for optically pure enantiomeric sodium salts of omeprazole result in change of directions from (−) to (+) optical rotation and, vice versa, from (+) to (−) optical rotation when preparing the sodium salt from the neutral form of omeprazole and again, when preparing the magnesium salt from the sodium salt of omeprazole.

EXAMPLE 1

Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole Sodium Salt

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

NMR data are given below.

EXAMPLE 2

Preparation of (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole Sodium Salt

100 mg-(0.3 mmol) of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (−)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of

an aqueous solution of 5.0M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 56 mg (51%) of the title compound as white crystals m.p. (decomposition) 247°–249° C. The optical purity (e.e.) which was analyzed by chiral column chromatography was ≧99.8%. $[\alpha]_D^{20}$=–44.1° (c=0.5%, water).

NMR data are given below.

EXAMPLE 3

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

2.9 ml of a 0.1M solution of NaOH was added to 0.10 g (0.29 mmol) (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. To this mixture 2 ml methylene chloride was added, and after mixing in a separatory funnel the aqueous solution was separated off. A solution of 14 mg (0.145 mmol) $MgCl_2$ in water was added dropwise. The formed precipitate was isolated by centrifugation, and 52 mg (50%) of the product was isolated as an amorphous powder. The optical purity (e.e.) was 98%, and thus the same as the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=+101.2° (c=1%, methanol). The Mg content of the sample was found to be 3.0%, shown by atomic absorption spectroscopy.

EXAMPLE 4

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

(–)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (0.500 g, 1.36 mmol) was dissolved in water (10 ml). To this mixture 10 ml of an aqueous solution of $MgCl_2 \times H_2O$ (138 mg, 0.68 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 418 mg (86%) of the product as a white powder. The optical purity (ee) of the product was 99.8% which was the same as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=+129.9° (c=1%, methanol).

EXAMPLE 5

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

(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $MgCl_2 \times H_2O$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 85 mg (51%) of the product as a white powder. The optical purity (ee) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=–128.2° (c=1%, methanol).

TABLE 1

Ex.	Solvent	NMR data δ ppm
1.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
2.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).

A preferred method for preparing optically pure omeprazole enantiomer crystal salts of magnesium is described in Examples 6 and 7.

EXAMPLE 6

Enhancement of the Optical Purity by Preparing the Magnesium Salt of (–)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in Nonaqueous Solution Followed by Crystallization of Said Salt

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 mintues 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).

EXAMPLE 7

Enhancement of the Optical Purity by Preparing the Magnesium Salt of (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in Nonaqueous Solution Followed by Crystallization of Said Salt

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 (e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for one hour, a white precipitate was obtained. Additonal stirring for 30 minutes and thereafter filtration afforded 0.35 g of the title compound as white crystals. Additional stirring of the mother liquor for 24 hours at room temperature afforded another 1.0 g (total yield=52%). Chiral analyses of the crystals and the second mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the two crystal fractions was 98.8% e.e. and 99.5% e.e., respectively. The optical purity of the mother liquor was found to be 57% e.e. Thus, the optical purity (e.e.) has been enhanced from 80% to approximately 99% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The first precipitation was crystalline as shown by powder X-ray diffraction and the magnesium content of the same fraction was 3.49% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20}$=+135.6° (c=0.5%, methanol).

The crystalline salt according to Example 6 is most preferred.

Preparation of the synthetic intermediates according to the invention is described in the following examples.

EXAMPLE 8

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

A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulfate and 6.4 g (42 mmol) (R)-(−)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3×200 ml water and the organic solution was dried over $MgSO_4$ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

NMR data are given below.

EXAMPLE 9

Separation of the More Hydrophilic Diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1[(R) mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 8 were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5% sodium hydrogen carbonate solution, drying over Na_2SO_4 and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colorless syrup.

NMR data are given below.

EXAMPLE 10

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

The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 8. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

NMR data are given below.

EXAMPLE 11

Separation of the More Hydrophilic Diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 10 were separated using reversed phase chromatography (HPLC) in the same way as in Example 7, but using the diasteromeric mixture of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 9. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colorless syrup.

NMR data are given below.

EXAMPLE 12

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

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxide in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 µl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3×10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.12 g (77%) of the title compound as a colorless syrup. The optical purity (e.e.)

which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20}$=−155° (c=0.5% chloroform).

NMR data are given below

EXAMPLE 13

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

0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxide in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and 25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 µl (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3×25 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colorless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]_D^{20}$=+157° (c=0.5%. chloroform).

NMR data are given below

TABLE 2

Ex.	Solvent	NMR data δ ppm
8.	$CDCl_3$ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6–6.7 (m, 2H), 6.90 (d, 1H), 6.95–6.98 (m, 2H), 7.01 (d, 1H), 7.2–7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
9.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2–7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
10.	$CDCl_3$ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6–6.7 (m, 2H), 6.90 (d, 1H), 6.96–6.98 (m, 2H), 7.01 (d, 1H), 7.2–7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
11.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2–7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
12.	$CDCl_3$ 300 MHz	2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77 (m, 2H), 6.93 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.19 (s, 1H).
13.	$CDCl_3$	2.21 (s, 3H), 2.23 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.76 (m, 2H), 6.94 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.20 (s, 1H).

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

Syrup

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

Compound according to Example 1	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavoring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar, solution and glycerol and a solution of flavoring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated Tablets

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

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

I Compound according to Example 6, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

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

Solution for Intravenous Administration

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

Compound according to Example 2	4 g
Sterile water to a final volume of	1000 ml

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

Capsules

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

Compound according to Example 6	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phos-

phate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

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

The final coated pellets were filled into capsules.

Suppositories

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

Compound according to Example 1	4 g
Witepsol H-15	180 g

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

Stability Towards Racemization at Different pH Values

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

In another racemization experiment with the optically pure compounds of the invention, an aqueous phosphate buffer solution (pH=11) of the (+)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt ($c=10^{-5}$M) was warmed for 26 hours at 37° C. without any racemization at all being observed.

What is claimed is:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of the (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier.

2. The pharmaceutical formulation according to claim **1** wherein the solid state salt is optically pure.

3. The pharmaceutical formulation according to claim **1**, wherein the alkaline salt is a Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt.

4. The pharmaceutical formulation according to claim **1**, wherein the solid state salt is in substantially crystalline form.

5. The pharmaceutical formulation according to claim **1** wherein the alkaline salt is a sodium or magnesium salt.

6. A method of inhibiting gastric acid secretion comprising the oral administration of a pharmaceutical formulation comprising a therapeutically effective amount of a pure solid state alkaline salt of the (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier.

7. A method for the treatment of gastrointestinal inflammatory disease comprising the oral administration to a mammal including man in need of such treatment of a pharmaceutical formulation comprising a therapeutically effective amount of a pure solid state alkaline salt of the (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier.

8. A method for the treatment of gastrointestinal inflammatory diseases comprising the oral administration to a mammal including man in need of such treatment a composition comprising an effective amount of the pure (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier.

9. A method of inhibiting gastric acid secretion comprising the oral administration of a pharmaceutical composition comprising an effective amount of the pure (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier.

10. The method of claim **6** or **7** wherein the alkaline salt is a Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt.

* * * * *

EXHIBIT B

US005877192A

United States Patent [19]

Lindberg et al.

[11] Patent Number: 5,877,192

[45] Date of Patent: *Mar. 2, 1999

[54] **METHOD FOR THE TREATMENT OF GASTRIC ACID-RELATED DISEASES AND PRODUCTION OF MEDICATION USING (-) ENANTIOMER OF OMEPRAZOLE**

[75] Inventors: **Per Lindberg**, Mölndal; **Lars Weidolf**, Västra Frölunda, both of Sweden

[73] Assignee: **Astra Aktiebolag**, Sodertalje, Sweden

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,714,504.

[21] Appl. No.: **833,962**

[22] Filed: **Apr. 11, 1997**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 376,512, Jan. 23, 1995, Pat. No. 5,714,504, which is a continuation-in-part of Ser. No. 256,174, Jun. 28, 1994, Pat. No. 5,693,818.

[30] **Foreign Application Priority Data**

May 28, 1993 [SE] Sweden 9301830
Apr. 11, 1996 [SE] Sweden 9601383

[51] **Int. Cl.**[6] **A61K 31/44**

[52] **U.S. Cl.** **514/338**; 514/819; 514/927

[58] **Field of Search** 514/338, 819, 514/927

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,714,504 2/1998 Linberg et al. 514/338

Primary Examiner—Kimberly Jordan
Attorney, Agent, or Firm—White & Case LLP

[57] **ABSTRACT**

A method for treatment of gastric acid related diseases by inhibition of gastric acid secretion comprising administering to a mammal in need of treatment a therapeutically effective amount of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, so as to effect decreased interindividual variation in plasma levels upon administration. The use of the (−)-enantiomer of omeprazole to receive increased average plasma levels (AUC) upon administration of the same doses of the (−)-enantiomer of omeprazole compared to those of racemic omeprazole is also claimed, as well as an improved anti-secretory effect and a better clinical effect.

23 Claims, 3 Drawing Sheets

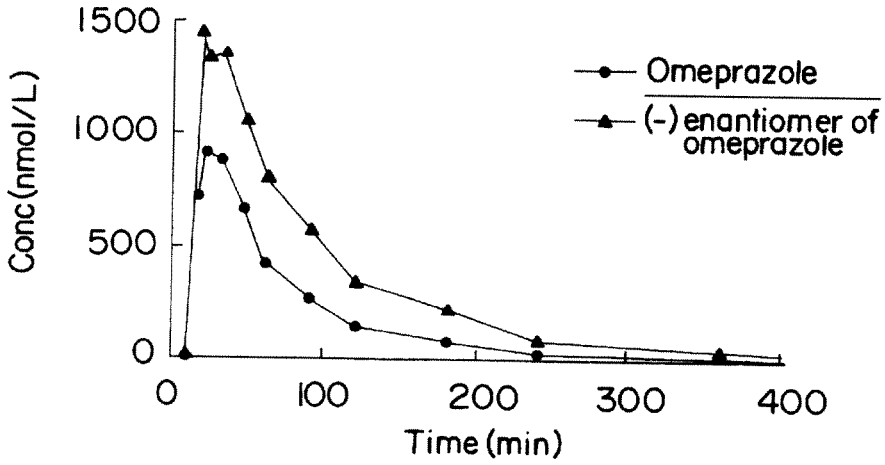

1500
1000
500
0
Conc(nmol/L)
0
100
200
300
400
Time (min)
Omeprazole
(-) enantiomer of omeprazole

FIG. 1

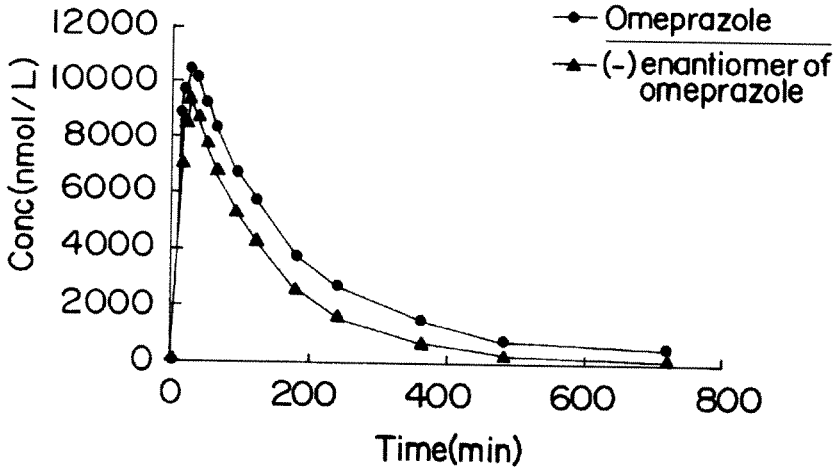

12000
10000
8000
6000
4000
2000
0
Conc(nmol/L)
0
200
400
600
800
Time(min)
Omeprazole
(-) enantiomer of omeprazole

FIG. 2

Mean plasma concentration (day 7)

AUC slow/AUC rapid		
(±)-omeprazole	(−)-omeprazole	(+)-omeprazole
10	3	30

AUC: area under the plasma concentration vs. time curve

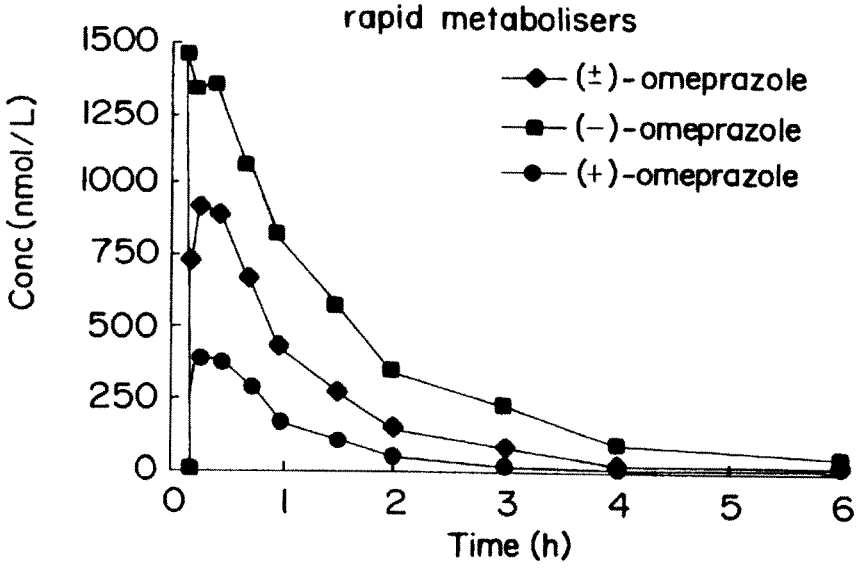


FIG.3A

Mean plasma concentration (day 7)

AUC slow/AUC rapid		
(±)-omeprazole	(−)-omeprazole	(+)-omeprazole
10	3	30

AUC: area under the plasma concentration vs. time curve

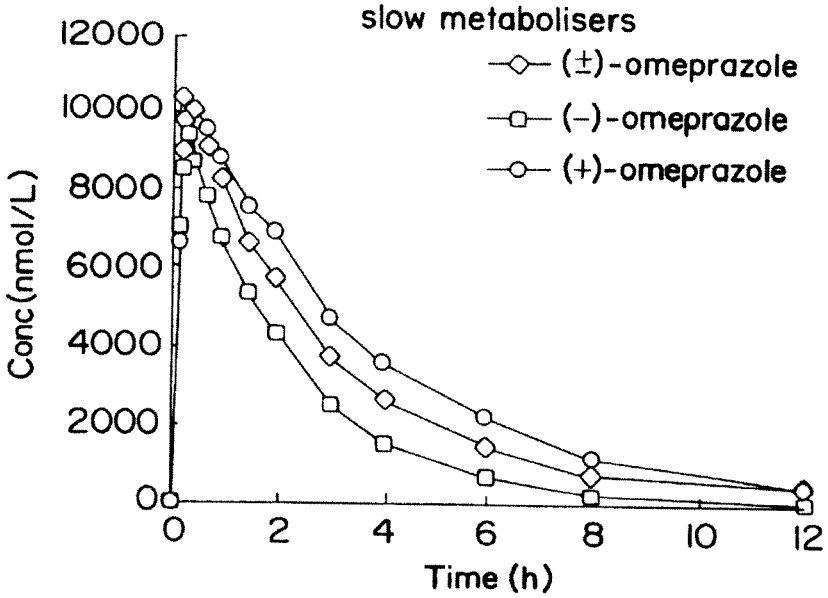


FIG.3B

METHOD FOR THE TREATMENT OF GASTRIC ACID-RELATED DISEASES AND PRODUCTION OF MEDICATION USING (-) ENANTIOMER OF OMEPRAZOLE

This application is a continuation-in-part of Ser. No. 08/376,512 filed on Jan. 23, 1995 now U.S. Pat. No. 5,714,504, which is a continuation-in-part of Ser. No. 08/256,174 filed Jun. 28, 1994, now U.S. Pat. No. 5,693,818.

The description of the salt forms of the single enantiomers of omeprazole and the process of making the same is herein incorporated by reference to copending Ser. No. 08/376,512.

FIELD OF THE INVENTION

The present invention is related to the use of one of the single enantiomers of omeprazole, i.e. the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, in the treatment of gastric acid related diseases. The expression single enantiomer refers to the fact that the (−)-enantiomer is substantially free from its (+)-enantiomeric contaminant.

BACKGROUND OF THE INVENTION

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 described in EP 124 495. Omeprazole is effective as a gastric acid secretion inhibitor, 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, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, omeprazole 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 (GERD), and in patients with gastrinomas. Omeprazole 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, omeprazole may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these.

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 (+)-enantiomer of omeprazole and the (−)-enantiomer of 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 neutral form. The (+)-enantiomer of the neutral form and the (−)-enantiomer of the neutral form were found to have the R and S configuration, respectively. The conditions for the optical rotation measurement for each of the compounds mentioned above are described in WO 94/27988.

Different salts of the single enantiomers of omeprazole are also described in WO 94/27988. Specific processes for the preparation of the single enantiomers of substituted benzimidazoles are described in WO 96/02535. An oral pharmaceutical dosage form of omeprazole or one of its

single enantiomers is described in WO 96/01623. Other oral dosage forms for the (−)-enantiomer of omeprazole can be found in EP 247 983.

There are few studies on the single enantiomers of omeprazole. One previous in vitro study on inhibition of acid secretion in isolated gastric glands showed no significant difference in effect between the two single enantiomers of omeprazole and the racemic mixture, see Erlandsson P. et al, Journal of Chromatography 1990; 532: 305–319. It has also been shown that, when omeprazole was administered intravenously to one subject, the plasma levels of the two enantiomers were similar, see Cairns A. M. et al, Journal of Chromatography B, 1995; 666: 323–328.

More than 135 million prescriptions by doctors indicate that omeprazole is an effective and safe drug. Notwithstanding, omeprazole exhibits polymorphic metabolism, i.e. a few individuals (3% among the Caucasian populations and 15–20% among Orientals) metabolise omeprazole slowly (slow metabolisers) compared to the rest of the population (rapid metabolisers). Slow metabolisers of omeprazole will obtain higher than the average plasma concentrations of the drug. Since the inhibition of gastric acid secretion is correlated to the area under the plasma concentration versus time curve (AUC), a more pronounced effect from omeprazole is expected in these slow metabolising individuals. A less interindividual variation, i.e. especially slow versus rapid metabolisers, and on the average higher plasma levels, giving higher dose efficiency in patients, could be of therapeutic benefit. Thus, one of the enantiomers of omeprazole, referred to as the (−)-enantiomer of omeprazole, or a pharmaceutically acceptable salt thereof, is hereby claimed to be an improved alternative to omeprazole in the treatment of gastric acid related diseases resulting in higher dose efficiency and in less interindividual variation in plasma levels (AUC), both between rapid and slow metabolisers and within the group of rapid metabolisers.

SUMMARY OF THE INVENTION

The use of the (−)-enantiomer of omeprazole, or a pharmaceutically acceptable salt thereof, in the treatment of gastric acid related diseases as a mean to decrease interindividual variation in plasma levels compared to omeprazole is claimed. The use of the (−)-enantiomer of omeprazole to receive increased average plasma levels (AUC) of the substance compared to those of racemic omeprazole and thereby a higher dose efficiency is also claimed.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the mean plasma levels of racemic omeprazole and the (−)-enantiomer of omeprazole at steady state (Day 7) in rapid metabolisers following administration of 15 mg doses of each substance.

FIG. **2** shows the mean plasma levels of racemic omeprazole and the (−)-enantiomer of omeprazole at steady state (Day 7) in slow metabolisers following administration of 60 mg doses of each substance.

FIGS. **3***a* and **3***b* show the mean plasma levels of racemic omeprazole, the single (−)-enantiomer of omeprazole and the single (+)-enantiomer of omeprazole at steady state in rapid and slow metabolisers following administration of 15 mg and 60 mg doses of each substance, respectively. The figure sheet also comprises the ratios between the mean AUCs at steady state of slow and rapid metabolisers.

DETAILED DESCRIPTION OF THE INVENTION

Omeprazole is metabolised mainly in the liver by the cytochrome P450 system (CYP). Metabolism can be defined

as the property of the body to transform lipophilic compounds into hydrophilic derivatives, which more easily can be excreted from the body. The metabolism can generally be divided into phase I and phase II reactions. During a phase I reaction, polar groups are formed via oxidation, hydroxylation, or hydrolysis. These reactions are mainly associated with the CYP enzymes. Phase II reactions are conjugation reactions, in which even further hydrophilic moities are attached to the drug or to its metabolites.

CYP is a superfamily of enzymes. Each family consists of one or more subfamilies and each subfamily contains one or more specific CYP isoforms. Apart from metabolising drugs, the CYP isoforms also have the property to metabolise endogenous compounds, such as steroids, fatty acids, and prostaglandins.

With respect to drug metabolism in man, three families, CYP1, CYP2, and CYP3 or, more specifically, six different CYP isoforms within these families are of particular importance. Each isoform demonstrates a certain substrate specificity. The expression of these enzymes is under genetic control, which is one of the reasons for the interindividual variation in rate and extent of metabolism demonstrated for most drugs. Moreover, at least two of the CYP isoforms, CYP2C19 and CYP2D6, are polymorphically expressed. Thus, a few individuals among the population, i.e. the slow metabolisers, lack or express a mutated form of the relevant CYP isoform, and consequently metabolise substrates for this isoform slowly. Metabolism still occurs in these slow metabolisers, although at a lower rate, because it is switched to other CYP isoforms which are less important for the metabolism of the substrate in the rest of the population.

Omeprazole is known to be a substrate for the polymorphically expressed CYP2C19. In vitro studies in human liver microsomes have surprisingly indicated that the (−)-enantiomer of omeprazole is less metabolised by CYP2C19 than omeprazole. In agreement with this, it has also been found, according to the present invention, that administration of the (−)-enantiomer of omeprazole or an acceptable therapeutical salt thereof results in a less pronounced difference in plasma levels between slow and rapid metabolisers.

Some studies have been published indicating that slow metabolisers, with higher than average plasma concentrations of omeprazole, are more prone to develop hypergastrinemia (Chang M. et al. Br J Clin Pharmacol 995; 39: 511–518, Caraco Y. et al. Clin Pharmacol Ther 1996; 59, 2: 216) as well as to slightly induce the levels of CYP1A2 (Rost KL et al. Clin Pharmacol Ther 1992; 52: 170–180, Rost KL et al. Clin Pharmacol Ther 1994; 55: 402–411), a CYP isoform distinct from CYP2C19. Some authors have therefore suggested that there might be a need for dosage adjustment in these individuals. The use of the (−)-enantiomer of omeprazole would decrease the potential for CYP1A2 induction in slow metabolisers as a result of the lower plasma levels (AUC) of this compound obtained in these individuals. Since the gastrin levels obtained simply are a result of a natural feedback mechanism determined by the degree of inhibition of gastric acid secretion, the use of the (−)-enantiomer of omeprazole may also potentially result in a less pronounced increase in gastrin in slow metabolisers.

The clinical study reported below supports the claimed invention and discusses the results more in detail.

The (−)-enantiomer of omeprazole is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, the (−)-enantiomer of omeprazole can be used for prevention and treatment of the same gastric-acid related diseases in mammals and especially in man as omeprazole, see above.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the (−)-enantiomer of omeprazole. For example, oral, parenteral, subcutaneous, intramuscular, rectal, transdermal and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions, solutions and the like.

The pharmaceutical compositions of the present invention comprise the (−)-enantiomer of omeprazole as active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salt" refers to both acid and alkaline pharmaceutically acceptable non-toxic salts. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections.

The compositions include compositions suitable for oral, rectal or parenteral such as subcutaneous, intramuscular, and intravenous administration. The most preferred route of the present invention is the oral route. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods well known in the art of pharmacy.

The most suitable route of administration as well as the magnitude of a therapeutic dose of the (−)-enantiomer of omeprazole or a pharmaceutically acceptable salt thereof 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. Such higher and lower doses of the (−)-enantiomer of omeprazole are within the scope of the present invention.

In general, a suitable oral dosage form may cover a dose range from 5 mg to 80 mg total daily dose, administered in one single dose or equally divided doses. A preferred dose range is from 20 mg to 60 mg total daily dose. For a parenteral dosage form the same dose ranges may apply.

The (−)-enantiomer of omeprazole 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 in a whole by reference.

Different routes of preparation of the (−)-enantiomer of omeprazole and pharmaceutically acceptable salts thereof are described in WO 94/ 27988 and WO 96/ 02535, the disclosures of which are hereby incorporated in a whole by reference.

The invention is further defined by reference to the following experimental work describing in detail the study and results as well as the clinical relevance of the findings.

EXPERIMENTAL STUDY

Methods:

In an open, randomised, three way cross-over designed study, consisting of three treatment periods, each with a duration of 7 days and each separated by a washout period of two weeks, the sodium salt of the (−)-enantiomer of omeprazole, the sodium salt of the (+)-enantiomer of ome-

prazole and omeprazole sodium salt were investigated. Nine healthy subjects, classified according to the urinary S/R mephenytoin ratio as five slow metabolisers and four rapid metabolisers of omeprazole, completed the study (Sanz E. J. et al, Clin Pharmacol Ther 1989; 45:495–499).

In slow metabolisers 60 mg doses of each compound were given once daily, while the rapid metabolisers were given once daily doses of 15 mg. The pharmacokinetics were studied in all subjects on days 1 and 7. The reason for using different doses was to optimise the conditions to explore the secondary aims of the study, to measure the effect on gastric acid secretion in rapid metabolisers and to measure the potential effect on caffeine metabolism in slow metabolisers.

Results and discussion:

In rapid metabolisers the mean AUC at steady state (Day 7) of the (−)-enantiomer of omeprazole was almost 90% higher than that of omeprazole. (FIG. **1**). This resulted in a more pronounced gastric acid antisecretory effect for the (−)-enantiomer of omeprazole compared to that of omeprazole. The inhibition of pentagastrin stimulated gastric acid secretion was 62% for omeprazole and 79% for the (−)-enantiomer of omeprazole following administration of 15 mg doses of each substance.

In slow metabolisers the mean AUC at steady state (Day 7) of the (−)-enantiomer of omeprazole was about 30% lower than that of omeprazole. (FIG. **2**). Thus, after correction for different dose levels, the resulting difference in AUC between slow and rapid metabolisers was almost 10-fold for omeprazole and only 3-fold for the (−)-enantiomer of omeprazole. With the (+)-enantiomer of omeprazole, on the other hand, the difference in AUC was much greater, approximately 30-fold (FIG. **3**).

In conclusion, the interindividual variation in plasma levels upon administration of the (−)-enantiomer of omeprazole will be less than for omeprazole and more patients will get optimal plasma concentrations with respect to gastric acid antisecretory effect and potentially also a better clinical effect following administration of the same doses.

Another study was conducted in 38 patients with symptomatic gastroesophageal reflux disease in which the effects on 24 hour intragastric acidity by oral treatment with 20 mg omeprazole racemate (capsules) and the magnesium salt of (−)-omeprazole (corresponding to 20 mg or 40 mg of the neutral compound) were compared. In addition, the plasma concentrations of (−)-omeprazole and omeprazole racemate were determined on the last treatment day (day 5).

The study was conducted as a double-blind, randomized, three-way cross-over trial consisting of three study periods, each with five days of daily oral administration of formulations containing the magnesium salt of (−)-omeprazole or omeprazole racemate separated by a wash-out period of at least two weeks. The 38 patients (22 females) ranged in age from 29–58 years. 32 of the patients were *Helicobacter pylori* negative.

Enteric coated pellets comprising the magnesium salt of (−)-omeprazole were filled in hard gelatin capsules calculated to correspond to either 20 mg or 40 mg of neutral (−)-omeprazole compound.

These formulations were compared with an identical treatment except for using enteric coated pellets comprising omeprazole filled in a hard gelatin capsule containing 20 mg racemic omeprazole in the non-salt form (Prilosec®).

The intragastric pH was recorded over 24 hours on day five of each study period upon administering the fifth dose.

The study was completed by 36 patients and the results therefrom were statistically evaluated. The effects of the treatments on intragastric pH are summarized in Table 1 and the AUC values are shown in Table 2.

As shown in Table 1 the percentage of time (of the 24-hour period assessed) with pH above 4 (a direct measure of inhibitory effect on gastric acid secretion) was 44% for 20 mg omeprazole racemate and 53% for 20 mg (−)-omeprazole ($p<0.0001$), which means that patients treated with (−)-omeprazole will have 2.2 hours longer time with pH above 4 than those treated with omeprazole racemate in corresponding doses.

TABLE 1

Least square estimates and 95% confidence intervals for the true mean treatment effects, regarding percentage of time with pH > 4 during 24 hours.

Treatment		Estimate	Lower	Upper
Omeprazole	20 mg	43.7	36.7	50.7
(−)ome	20 mg	53.0	46.0	60.0
(−)ome	40 mg	69.8	62.8	76.8

The data of Table 2 shown below demonstrate that the AUC of (−)omeprazole is significantly higher than that of racemic omeprazole at the 20 mg dose, and the 40 mg dose of (−)omeprazole produced a significantly higher AUC than the 20 mg dose of (−)-omeprazole ($p<0.0001$).

The interindividual variation in AUC and thus the inhibitory effect is less pronounced following administration of (−)-omeprazole than following administration of omeprazole racemate. This was judged by the coefficient of variation for the mean AUC which was 59% for 20 mg of the magnesium salt of (−)-omeprazole and 88% for 20 mg of omeprazole racemate ($p<0.0001$).

TABLE 2

Least square estimates and 95% confidence intervals for the true mean treatment effects, regarding AUC (μmol × h/L).

Treatment		Estimate	Lower	Upper
Omeprazole	20 mg	2.3	1.8	3.0
(−)ome	20 mg	4.2	3.3	5.4
(−)ome	40 mg	12.6	9.9	16.2

As a consequence of the less pronounced difference in AUC between slow and rapid metabolizers, the interindividual variation in AUC of (−)-omeprazole is less than that of omeprazole. Furthermore, available data indicate that the interindividual variation in AUC of (−)omeprazole within the group of rapid metabolizers also is less than that observed for omeprazole racemate. These characteristics taken together may potentially result in a larger fraction of patients attaining plasma concentrations which would be optimal with respect to the desired gastric acid anti-secretory effect in the clinical situation.

It was observed that the steady-state AUC of (−)-omeprazole in an average population was significantly higher (2-fold) than that of omeprazole racemate when each compound was given repeatedly in 20 mg daily doses. Therefore, the anti-secretory effect, which is directly correlated to the AUC irrespective of compound, was higher for (−)-omeprazole than for omeprazole racemate following administration of identical doses. This is expected to give a clinical advantage for (−)-omeprazole, since the number of patients healed from the acid-related disease is expected to be higher, and healing is also expected to be achieved within

a shorter time frame. It might also be expected that a more rapid symptom relief will be obtained.

The clinical studies outlined above demonstrate that the alkali metal salts of (−)-omeprazole have unexpected pharmacokinetic advantages over the omeprazole racemate, such as less interindividual variation in plasma levels (AUC) both between rapid and slow metabolizers and within the group of rapid metabolizers. The alkali metal salts of (−)-omeprazole provide for a larger fraction of patients with optimal plasma concentrations with respect to desired antisecretory effect. Higher average AUC results in a more pronounced inhibitory effect on gastric-acid secretion and is expected to result in a better overall clinical effect. Thus, the alkaline salts of (−)-omeprazole can provide an improved, alternative pharmaceutical formulation and method for the treatment of gastric acid-related diseases.

What is claimed is:

1. A method for treatment of gastric acid related diseases by inhibition of gastric acid secretion comprising administering to a mammal in need of treatment a therapeutically effective amount of a proton pump inhibitor consisting essentially of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)meth~~yl~~]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, so as to effect decreased interindividual variation in plasma levels (AUC) during treatment of gastric acid related diseases.

2. A method for treatment of gastric acid related diseases by inhibition of gastric acid secretion comprising administering to a mammal in need of treatment a therapeutically effective amount of a proton pump inhibitor consisting essentially of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, so as to effect an increased average plasma levels (AUC) per dosage unit.

3. The method according to claim **1** or **2** so as to effect a less pronounced increase in gastrin levels in slow metabolisers during treatment of gastric acid related diseases.

4. The method according to claim **1** or **2** so as to effect a decreased CYP1A induction in slow metabolisers during treatment of gastric acid related diseases.

5. The method according to claim **1** or **2** so as to elicit an improved antisecretory effect during the treatment of gastric acid related diseases.

6. The method according to claim **1** or **2** so as to elicit an improved clinical effect comprising accelerated rate of healing and accelerated rate of symptom relief during the treatment of gastric related diseases.

7. The method according to claim **1** or **2**, wherein the (−)-enantiomer of omeprazole or a pharmaceutically acceptable salt thereof, is administered orally in the form of a tablet or a capsule.

8. The method according to claim **1** or **2**, wherein the (−)-enantiomer of omeprazole or a pharmaceutically acceptable salt thereof, is administered parenterally.

9. The method according to claim **1** or **2**, wherein the (−)-enantiomer of omeprazole or a pharmaceutically acceptable salt thereof, is administered by intravenous infusion.

10. The method according to claim **1** or **2**, wherein the amount administered is about 5–80 mg total daily dose.

11. The method according to claim **1** or **2**, wherein the amount administered is about 20–60 mg total daily dose.

12. A method for the production of a medicament for treating gastric acid related diseases, which comprises: combining a therapeutically effective amount of a proton pump inhibitor consisting essentially of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.

13. The method according to claim **12**, wherein the medicament causes a decreased interindividual variation in plasma levels (AUC) per unit dosage during the treatment of gastric acid related diseases.

14. The method according to claim **12**, wherein the medicament causes an increased average plasma level (AUC) per unit dosage during the treatment of gastric acid related diseases.

15. The method according to claim **12**, wherein the medicament causes a less pronounced increase in gastrin levels in slow metabolisers during treatment of gastric acid related diseases.

16. The method according to claim **12**, wherein the medicament causes a decreased CYP1A induction in slow metabolisers during treatment of gastric acid related diseases.

17. The method according to claim **12**, wherein the medicament causes an improved antisecretory effect during the treatment of gastric acid related diseases.

18. The method according to claim **12**, wherein the medicament causes an improved clinical effect comprising accelerated rate of healing and accelerated rate of symptom relief during the treatment of gastric related diseases.

19. The method according to claim **12**, wherein the medicament produced for oral administration is in the form of a tablet or capsule.

20. The method according to claim **12**, wherein the medicament is administered parentally, by intravenous infusion.

21. The method according to any of claims **12–20**, wherein the medicament is administered in the amount of about 5 mg to 80 mg total daily dose.

22. The method according to any of claims **12–20**, wherein the medicament is administered in the amount of about 20 mg to 60 mg total daily dose.

23. The method according to claim **1** or **2** wherein the (−)-enantiomer of the proton pump inhibitor is essentially devoid of its (+)-enantiomeric contaminant.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRRECTION

PATENT NO. : 5,877,192
DATED : March 2, 1999
INVENTOR(S) : Per Lindberg, et al.

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

On the title page insert the following under item [56]:

U. S. PATENT DOCUMENTS

EXAMINER INITIAL		PATENT NUMBER	ISSUE DATE	PATENTEE	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
		4 6 3 6 4 9 9	1/13/96	Brandstrom et al			
		5 0 4 5 3 2 1	9/3/91	Makino et al			
		4 7 3 8 9 7 4	4/19/88	Brandstrom et al			
		4 8 5 3 2 3 0	8/1/89	Lovgren et al			
		4 7 8 6 5 0 5	11/22/88	Lovgren et al			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	PUBLICATION DATE	COUNTRY OR PATENT OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
		4 0 3 5 4 5 5	11/90	DE				
		0 1 2 4 4 9 5	1/14/87	EP				

UNITED STATES PATENT AND TRADEMARK OFFICE

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FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER							PUBLICATION DATE	COUNTRY OR PATENT OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
		9	6	0	1	6	2	3	1/25/96	WIPO				
		0	0	0	5	1	2	9	4/29/81	EP				
		0	3	6	5	9	4	7	5/2/90	EP				
		9	5	0	1	7	8	3	1/19/95	WIPO				
		9	2	2	2	2	8	4	12/23/92	WIPO				
		9	6	0	2	5	3	5	2/1/96	WIPO				
		9	4	2	7	9	8	8	12/8/94	WIPO				
		6	2	4	7	9	8	3	4/16/87	EP				

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRRECTION

PATENT NO. : 5,877,192
DATED : March 2, 1999
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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRRECTION

PATENT NO. : 5,877,192
DATED : March 2, 1999
INVENTOR(S) : Per Lindberg, et al.

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

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Signed and Sealed this

Twenty-seventh Day of April, 1999

Attest:

Attesting Officer

Q. TODD DICKINSON

Acting Commissioner of Patents and Trademarks

EXHIBIT C

US006875872B1

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

(10) **Patent No.: US 6,875,872 B1**
(45) **Date of Patent: Apr. 5, 2005**

(54) **COMPOUNDS**

(75) Inventors: **Per Lennart Lindberg**, Mölndal (SE); **Sverker Von Unge**, Fjärås (SE)

(73) Assignee: **AstraZeneca**, 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.: **09/690,044**

(22) Filed: **Oct. 16, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/187,277, filed on Nov. 6, 1998, which is a continuation of application No. 08/899,931, filed on Jul. 24, 1997, now abandoned, which is a continuation of application No. 08/376,512, filed on Jan. 23, 1995, now Pat. No. 5,714,504, which is a continuation-in-part of application No. 08/256,174, filed on Jun. 28, 1994, now Pat. No. 5,693,818.

(30) **Foreign Application Priority Data**

May 28, 1993 (SE) 9301830

(51) **Int. Cl.**[7] **C07D 401/12**

(52) **U.S. Cl.** **546/273.7**; 514/338
(58) **Field of Search** 514/338; 546/273.7

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

(57) **ABSTRACT**

The novel optically pure compounds Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, in particular sodium and magnesium salt form thereof, where R is an alkyl with 1–4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.

12 Claims, No Drawings

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COMPOUNDS

This is a continuation of pending U.S. patent application Ser. No. 09/187,277, filed Nov. 6, 1998, which is a continuation of U.S. patent application Ser. No. 08/899,931, filed Jul. 24, 1997, abandoned, which is a continuation application of U.S. patent application Ser. No. 08/376,512, filed Jan. 23, 1995, now U.S. Pat. No. 5,714,504, which is a continuation-in-part application of U.S. patent application Ser. No. 08/256,174, filed Jun. 28, 1994, now U.S. Pat. No. 5,693,818.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in U.S. Pat. No. 4,255,431 to Junggren et al., EP 5129 and EP 124 495, respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers).

The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application (DE 4035455) this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because here is a great risk of locally reaching pH values between 1–6, which would be devastating for the substance. Moreover, instantaneous neutralization will create heat which will be difficult to handle in large scale production.

There is no example in the known prior art of any isolated or characterized salt of optically pure omeprazole, i.e. of single enantiomers of omeprazole or of any isolated or characterized salt of any optically pure omeprazole analogue.

SUMMARY OF THE INVENTION

It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

A preferred embodiment of the present invention provides pure crystalline enantiomeric salts of omeprazole and methods for the preparation thereof.

A more preferred embodiment of the present invention is directed to an optically pure crystalline enantiomeric magnesium salt of omeprazole and method for the preparation thereof.

A nonaqueous process according to the present invention is directed to the preparation of crystalline forms of an optically pure enantiomer of omeprazole magnesium salt or analogues thereof which includes steps of stirring a crude preparation of the omeprazole enantiomer under nitrogen into a methanolic magnesium methoxide solution, precipitating inorganic magnesium salt with addition of a small amount of water, removing any precipitated inorganic magnesium salts, concentrating the residual methanolic solution, precipitating the omeprazole enantiomer by adding acetone to the residual solution, and filtering off the optically pure enantiomer crystals of magnesium omeprazole or analogues thereof.

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

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

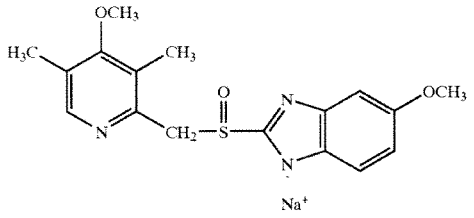
DETAILED DESCRIPTION OF THE INVENTION

The present invention refers to the new Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N+(R)_4$ salts of the single enantiomers of omeprazole, where R is an alkyl with 1–4 carbon atoms, i.e. Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1–4 carbon atoms.

Particularly preferred salts according to the invention are the Na^+, Ca^{2+} and Mg^{2+} salts, i.e (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt.

Most preferred salts according to the invention are the optically pure Na^+ salts of omeprazole according to compounds Ia and Ib

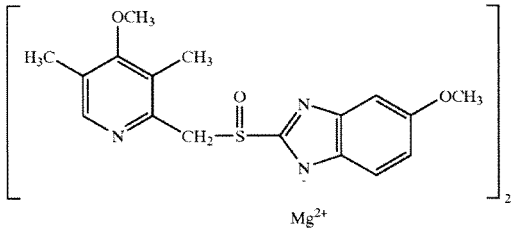
(Ia, Ib)



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

and the optically pure magnesium salts of omeprazole according to compounds IIa and IIb

(IIa, IIb)



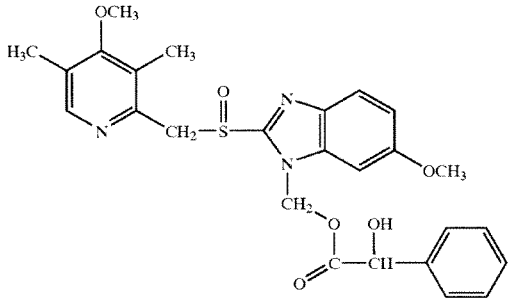
IIa (+)-enantiomer
IIb (-)-enantiomer

With the expression "optically pure Na^+ salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (−)-enantiomer of omeprazole Na-salt and the (−)-enantiomer essentially free of the (+)-enantiomer, respectively. Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. The salts defined by the present invention are easy to obtain by means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole. In contrast to the neutral forms the salts can be obtained as crystalline products. Because it is possible to purify optically impure or partially pure salts of the enantiomers of omeprazole by crystallization, they can be obtained in very high optical purity, namely ≧99.8% enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy.

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

Yet a further aspect of the invention is the compound m, which is an intermediate used in the specific method of preparation.

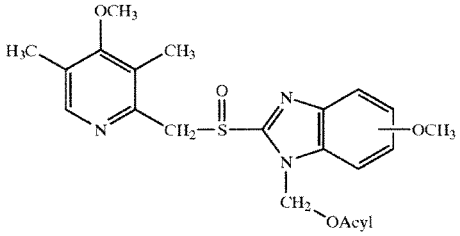
(III)



Preparation

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV

(IV)



wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

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

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

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

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

To obtain the optically pure Mg^{2+} salts of the invention, optically pure enantiomeric Na^+ salts may be treated with an

aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomers of omeprazole with a base, such as $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1–4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

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

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1–95% by weight of the preparation, between 0.2–20% by weight in preparations for parenteral use and between 1–50% by weight in preparations for oral administration.

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

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

Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

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

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

Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

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

The invention is illustrated by the following examples using preferred procedures for the preparation of optically pure sodium salts and magnesium salts.

The processes described below for optically pure enantiomeric sodium salts of omeprazole result in change of directions from (−) to (+) optical rotation and, vice versa, from (+) to (−) optical rotation when preparing the sodium salt from the neutral form of omeprazole and again, when preparing the magnesium salt from the sodium salt of omeprazole.

EXAMPLE 1

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

100 mg (0.3 mmol) of (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246–248° C. The optical purity (e.e.) which was analyzed by chiral column chromatography was >99.8%. $[\alpha]_D^{20}$=+42,8' (concentration, c=0.5%, water).

NMR data are given below.

EXAMPLE 2

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

100 mg-(0.3 mmol) of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-

benzimidazole (contaminated with 3% of the (−)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 56 mg (51%) of the title compound as white crystals m.p. (decomposition) 247–249° C. The optical purity (e.e.) which was analyzed by chiral column chromatography was >99.8%. $[\alpha]_D^{20}$=−44.1° (c=0.5%, water).

NMR data are given below.

EXAMPLE 3

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

2.9 ml of a 0.1 M solution of NaOH was added to 0.10 g (0.29 mmol) (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. To this mixture 2 ml methylene chloride was added, and after mixing in a separatory funnel the aqueous solution was separated off. A solution of 14 mg (0.145 mmol) $MgCl_2$ in water was added dropwise. The formed precipitate was isolated by centrifugation, and 52 mg (50%) of the product was isolated as an amorphous powder. The optical purity (e.e) was 98%, and thus the same as the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=+101.20 (c=1%, methanol). The Mg content of the sample was found to be 3.0%, shown by atomic absorption spectroscopy.

EXAMPLE 4

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

(−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (0.500 g, 1.36 mmol) was dissolved in water (10 ml). To this mixture 10 ml of an aqueous solution of $MgCl_2xH_2O$ (138 mg, 0.68 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 418 mg (86%) of the product as a white powder. The optical purity (ee) of the product was 99.8% which was the same as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=+129.9° (c=1%, methanol).

EXAMPLE 5

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

(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $MgCl_2xH_2O$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 85 mg (51%) of the product as a white powder. The optical purity (ee) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=−128.2° (c=1%, methanol).

TABLE 1

Ex.	Solvent	NMR data δ ppm
1.	DMSO-d_6 500 MHz	2.20(s, 3H), 2.22(s, 3H), 3.69(s, 3H), 3.72(s, 3H), 4.37(d, 1H), 4.75(d, 1H), 6.54(dd, 1H), 6.96(d, 1H) 7.30(d, 1H), 8.21(s, 1H).
2.	DMSO-d_6 500 MHz	2.20(s, 3H), 2.22(s, 3H), 3.69(s, 3H), 3.72(s, 3H), 4.38(d, 1H), 4.73(d, 1H), 6.54(dd, 1H), 6.96(d, 1H), 7.31(d, 1H), 8.21(s, 1H).

A preferred method for preparing optically pure omeprazole enantiomer crystal salts of magnesium is described in Examples 6 and 7.

EXAMPLE 6

Enhancement of the Optical Purity by Preparing the Magnesium Salt of (−)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in Nonaqueous Solution Followed by Crystallization of said Salt

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 mintues 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).

EXAMPLE 7

Enhancement of the Optical Purity by Preparing the Magnesium Salt of (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in Nonaqueous Solution Followed by Crystallization of said Salt

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 (e.e) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for one hour, a white precipitate was obtained. Additonal stirring for 30 minutes and thereafter filtration afforded 0.35 g of the title compound as white crystals. Additional stirring of the mother liquor for 24 hours at room temperature afforded another 1.0 g (total yield=52%). Chiral analyses of the crystals and the second mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the two crystal fractions was 98.8% e.e. and 99.5% e.e., respectively. The optical purity of the mother liquor was found to be 57% e.e. Thus, the optical purity (e.e.) has been enhanced from 80% to approximately 99% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The first precipitation was crystalline as shown by powder X-ray diffraction and the magnesium content of the same fraction was 3.49% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20}$=−135.60° (c=0.5%, methanol).

The crystalline salt according to Example 6 is most preferred.

Preparation of the synthetic intermediates according to the invention is described in the following examples.

EXAMPLE 8

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

A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulfate and 6.4 g (42 mmol) (R)-(−)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3×200 ml water and the organic solution was dried over $MgSO_4$ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

NMR data are given below.

EXAMPLE 9

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

The diastereomers of the title compound in Example 8 were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5% sodium hydrogen carbonate solution, drying over Na_2SO_4 and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colorless syrup.

NMR data are given below.

EXAMPLE 10

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

The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 8. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

NMR data are given below.

EXAMPLE 11

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

The diastereomers of the title compound in Example 10 were separated using reversed phase chromatography (HPLC) in the same way as in Example 7, but using the diasteromeric mixture of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 9. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colorless syrup.

NMR data are given below.

EXAMPLE 12

Preparation of (−)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1II-benzimidazole

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxide in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 μL (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3×10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.12 g (77%) of the

title compound as a colorless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20}$=−155° (c=0.5%, chloroform).
NMR data are given below

EXAMPLE 13

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

0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxide in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and 25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 μl (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3×25 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colorless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]_D^{20}$=+157° (c=0.5%, chloroform).
NMR data are given below

TABLE 2

Ex.	Solvent	NMR data δ ppm
8.	$CDCl_3$ 500 MHz	2.18(s, 3H), 2.20(s, 3H), 2.36(s, 3H), 2.39(s, 3H), 3.77(s, 3H), 3.78(s, 3H), 3.82(s, 3H), 3.87(s, 3H), 4.80(d, 1H), 4.88(d, 1H), 5.0(m, 2H), 5.34(s, 2H), 6.43(d, 1H), 6.54(d, 1H), 6.6–6.7(m, 2H), 6.90(d, 1H), 6.95–6.98(m, 2H), 7.01(d, 1H), 7.2–7.3(m, 6H), 7.37(m, 2H), 7.44(m, 2H), 7.58(d, 1H), 7.62(d, 1H), 7.95(s, 1H), 7.97(s, 1H).
9.	$CDCl_3$ 500 MHz	2.20(s, 3H), 2.36(s, 3H), 3.78(s, 3H), 3.82(s, 3H), 4.80(d, 1H), 5.00(d, 1H), 5.35(d, 1H), 6.43(d, 1H), 6.63(d, 1H), 6.90(d, 1H), 6.97(dd, 1H), 7.2–7.3(m, 3H), 7.37(m, 2H), 7.62(d, 1H), 7.97(s, 1H).
10.	$CDCl_3$ 500 MHz	2.19(s, 3H), 2.20(s, 3H), 2.36(s, 3H), 2.39(s, 3H), 3.77(s, 3H), 3.78(s, 3H), 3.83(s, 3H), 3.87(s, 3H), 4.80(d, 1H), 4.88(d, 1H), 5.0(m, 2H), 5.34(s, 2H), 6.43(d, 1H), 6.54(d, 1H), 6.6–6.7(m, 2H), 6.90(d, 1H), 6.96–6.98(m, 2H), 7.01(d, 1H), 7.2–7.3(m, 6H), 7.37(m, 2H), 7.44(m, 2H), 7.58(d, 1H), 7.62(d, 1H), 7.95(s, 1H), 7.97(s, 1H).
11.	$CDCl_3$ 500 MHz	2.20(s, 3H), 2.36(s, 3H), 3.78(s, 3H), 3.82(s, 3H), 4.80(d, 1H), 5.00(d, 1H), 5.35(d, 1H), 6.43(d, 1H), 6.63(d, 1H), 6.90(d, 1H), 6.97(dd, 1H), 7.2–7.3(m, 3H), 7.37(m, 2H), 7.62(d, 1H), 7.97(s, 1H).
12.	$CDCl_3$ 300 MHz	2.18, (s, 3H), 2.22(s, 3H), 3.68(s, 3H), 3.83(s, 3H), 4.77(m, 2H), 6.93(dd, 1H), ≈7.0(b, 1H), ≈7.5(b, 1H), 8.19(s, 1H).
13.	$CDCl_3$	2.21(s, 3H), 2.23(s, 3H), 3.69(s, 3H), 3.84(s, 3H), 4.76(m, 2H), 6.94(dd, 1H), ≈7.0(b, 1H), ≈7.5(b, 1H), 8.20(s, 1H).

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

Syrup

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

Compound according to Example 1	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavoring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavoring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-Coated Tablets

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

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

Compound according to Example 6, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

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

Solution for Intravenous Administration

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

Compound according to Example 2	4 g
Sterile water to a final volume of	1000 ml

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

Capsules

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

Compound according to Example 6	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g

-continued

Disodium hydrogen phosphate	2 g
Purified water	q. s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating Solution:

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

The final coated pellets were filled into capsules.

Suppositories

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

Compound according to Example 1	4 g
Witepsol H-15	180 g

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

Stability Towards Racemization at Different pH Values

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

In another racemization experiment with the optically pure compounds of the invention, an aqueous phosphate buffer solution (pH=11) of the (+)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt ($c=10^{-5}$M) was warmed for 26 hours at 37° C. without any racemization at all being observed.

What is claimed is:

1. Magnesium salt of (−)-5-methoxy-2-[[(4-methoxy-3,5, dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole in an optical purity of at least about 94% enantiomeric excess.

2. The compound according to claim **1**, when the optical purity is at least 94% enantiomeric excess.

3. The compound according to claim **1** or **2**, wherein the compound is in crystaline form.

4. Magnesium salt of (−)-5-methoxy-2-[[(4-methoxy-3,5, dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole in an optical purity of at least about 98.4% enantiomeric excess.

5. The compound according to claim **4**, wherein the optical purity is at least 98.4% enantiomeric excess.

6. The compound according to claim **4** or **5**, wherein the compound is in crystaline form.

7. Magnesium salt of (−)-5-methoxy-2-[[(4-methoxy-3,5, dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole in an optical purity of at last about 99.8% enantiomeric excess.

8. The compound according to claim **7**, wherein the optical purity is at least 99.8% enantiomeric excess.

9. The compound according to claim **7** or **8**, wherein the compound is in crystalline form.

10. Magnesium salt of $(-)_S$-methoxy-2-[[(4-methoxy-3,5, dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole in an optical purity of at least about 99.9% enantiomeric excess.

11. The compound according to claim **10**, wherein the optical purity is at least 99.9% enantiomeric excess.

12. The compound according to claim **10**, wherein the compound is in crystalline form.

* * * * *

EXHIBIT D

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**

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(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.

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§ 102(e) Date: **Jun. 8, 1998**

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

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May 30, 1997 (SE) 9702065

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(52) **U.S. Cl.** **514/338**; 546/273.7
(58) **Field of Search** 514/338; 546/273.7

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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.

12 Claims, 5 Drawing Sheets

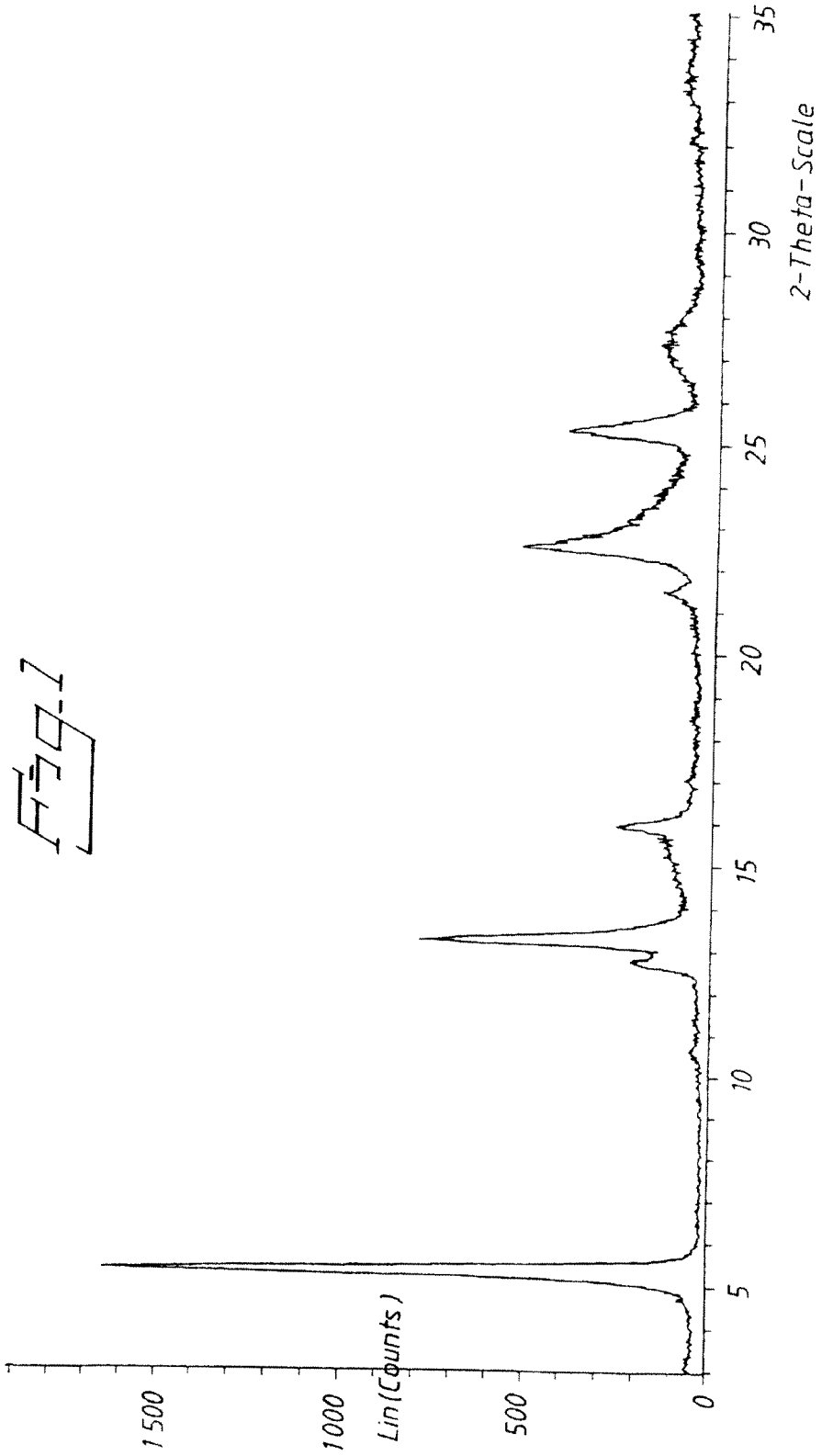


FIG. 1

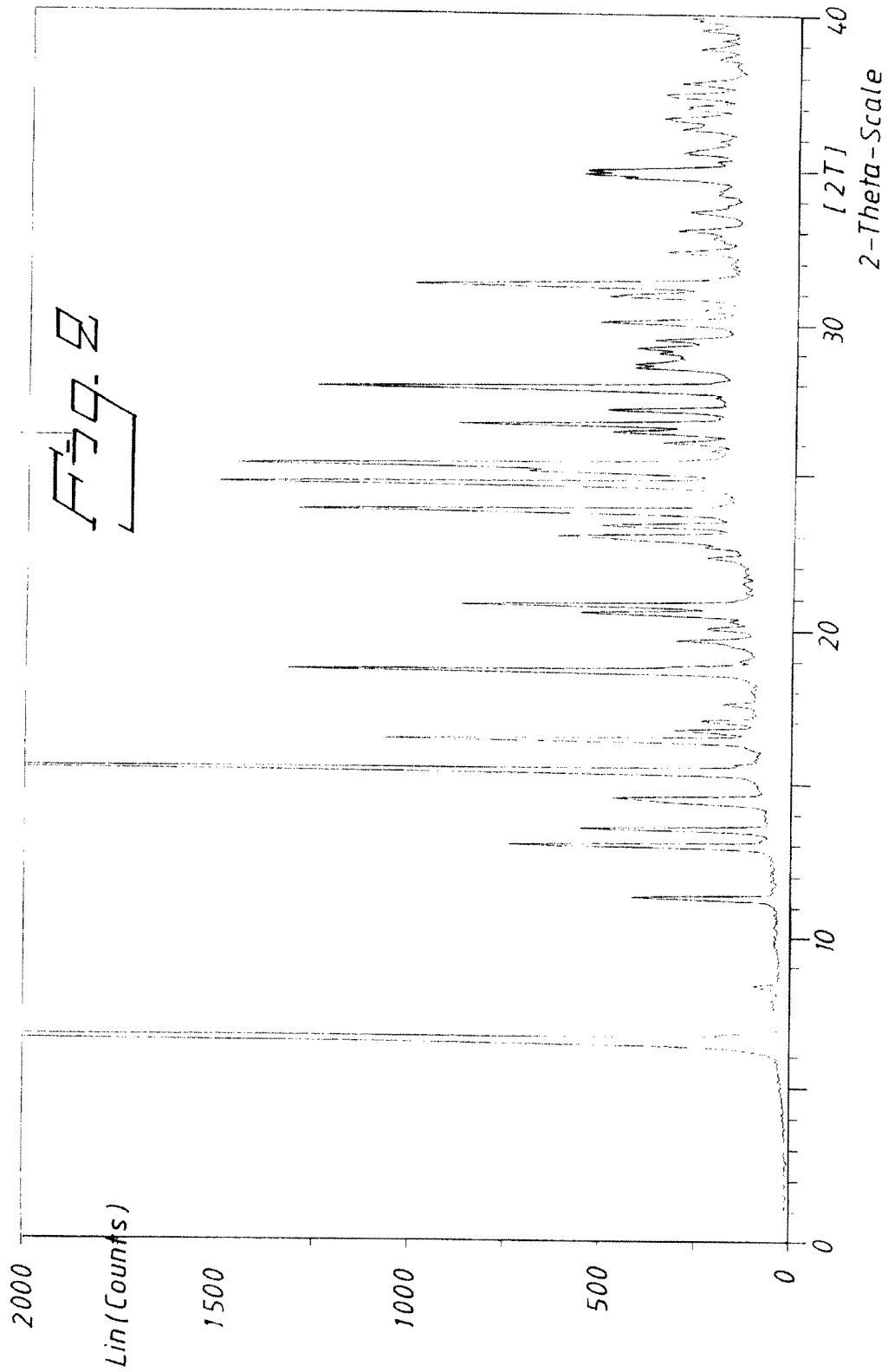
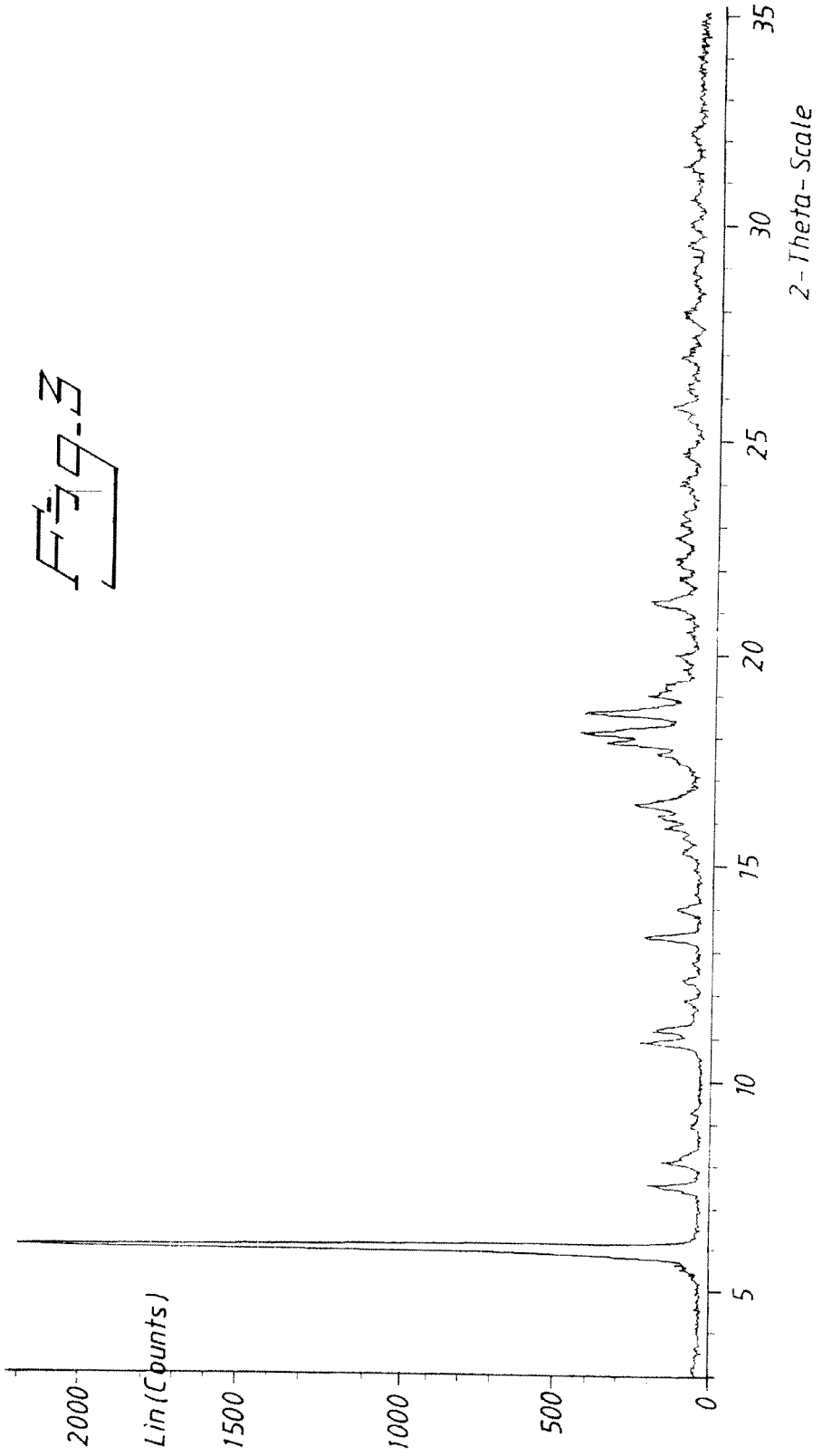


Fig. 2

Fig. 3



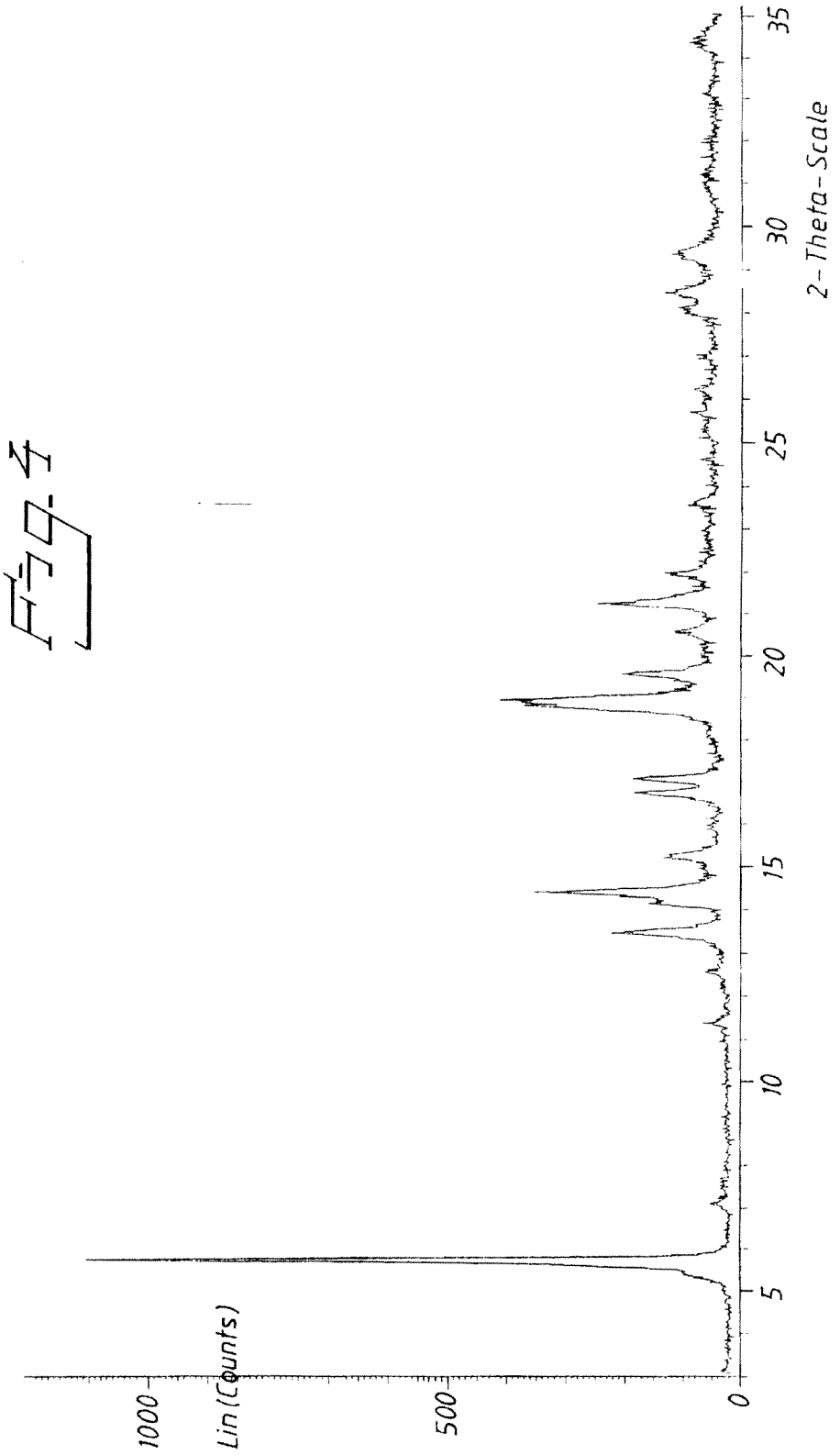
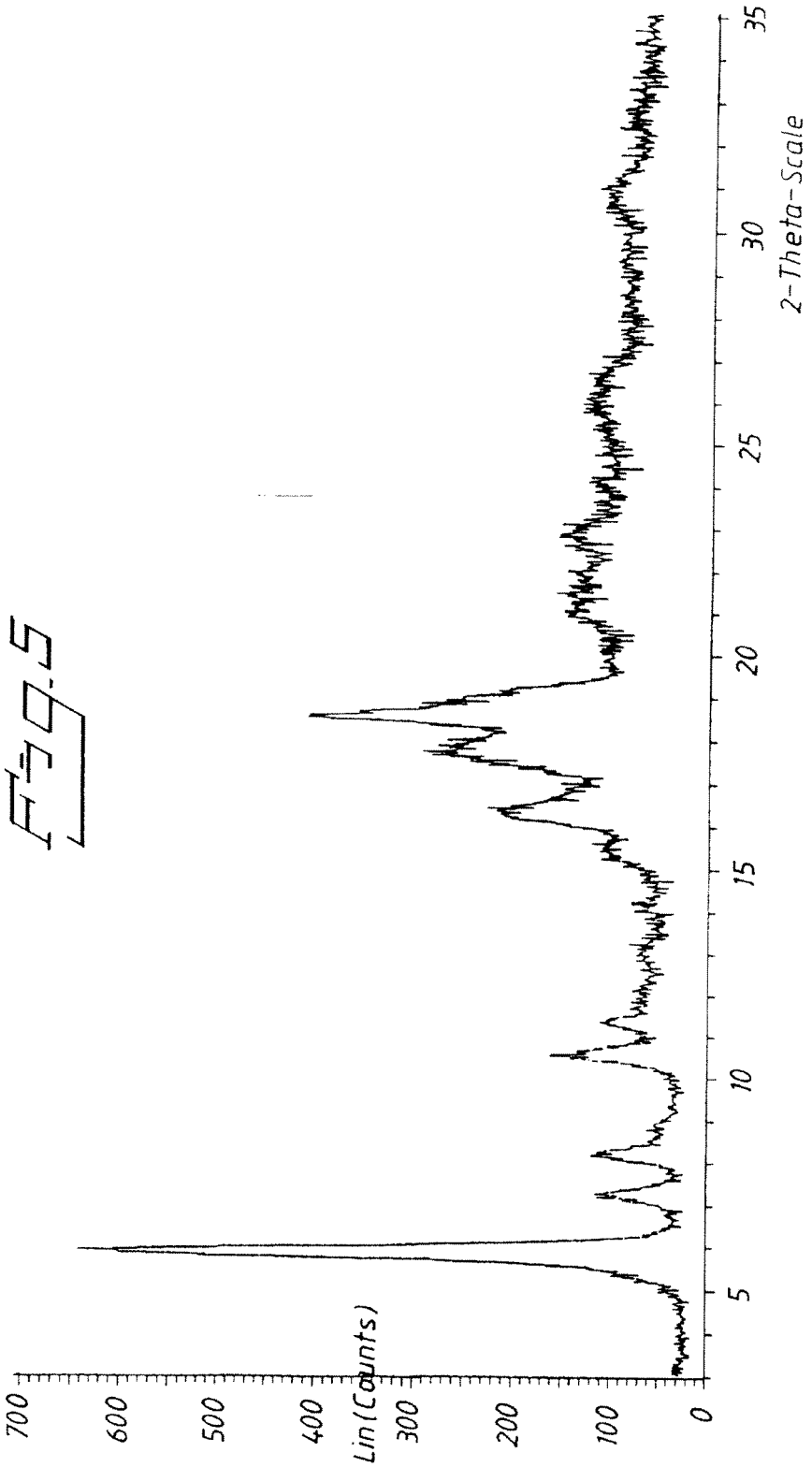


Fig. 4

FIG. 5


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

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 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 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
6.8	s
7.8	s
8.4	vs
10.8	s
12.2	s
15.1	vs

TABLE 5-continued

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

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 E

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**

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(*) 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**

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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.

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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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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.

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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

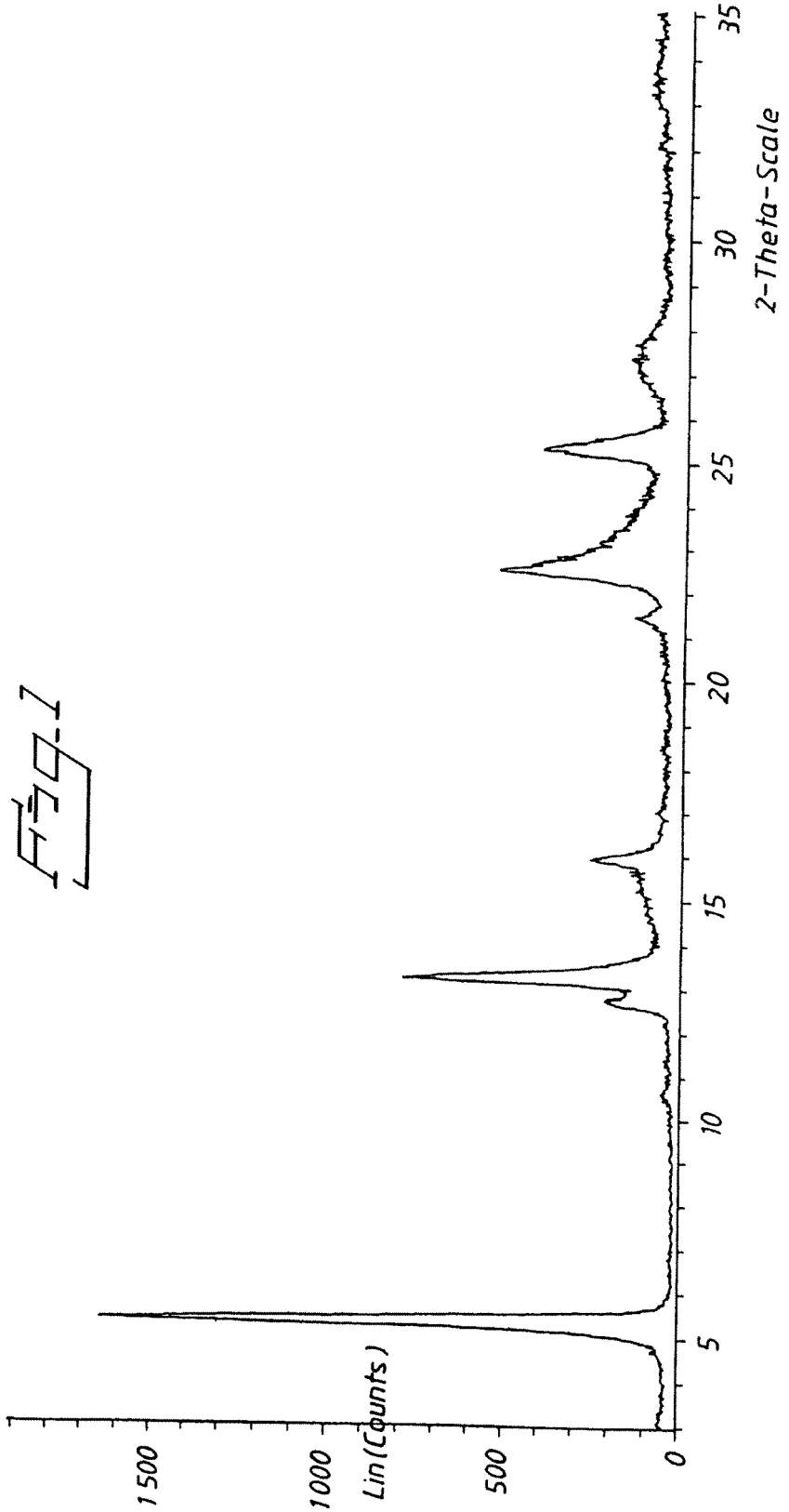

FIG. 1

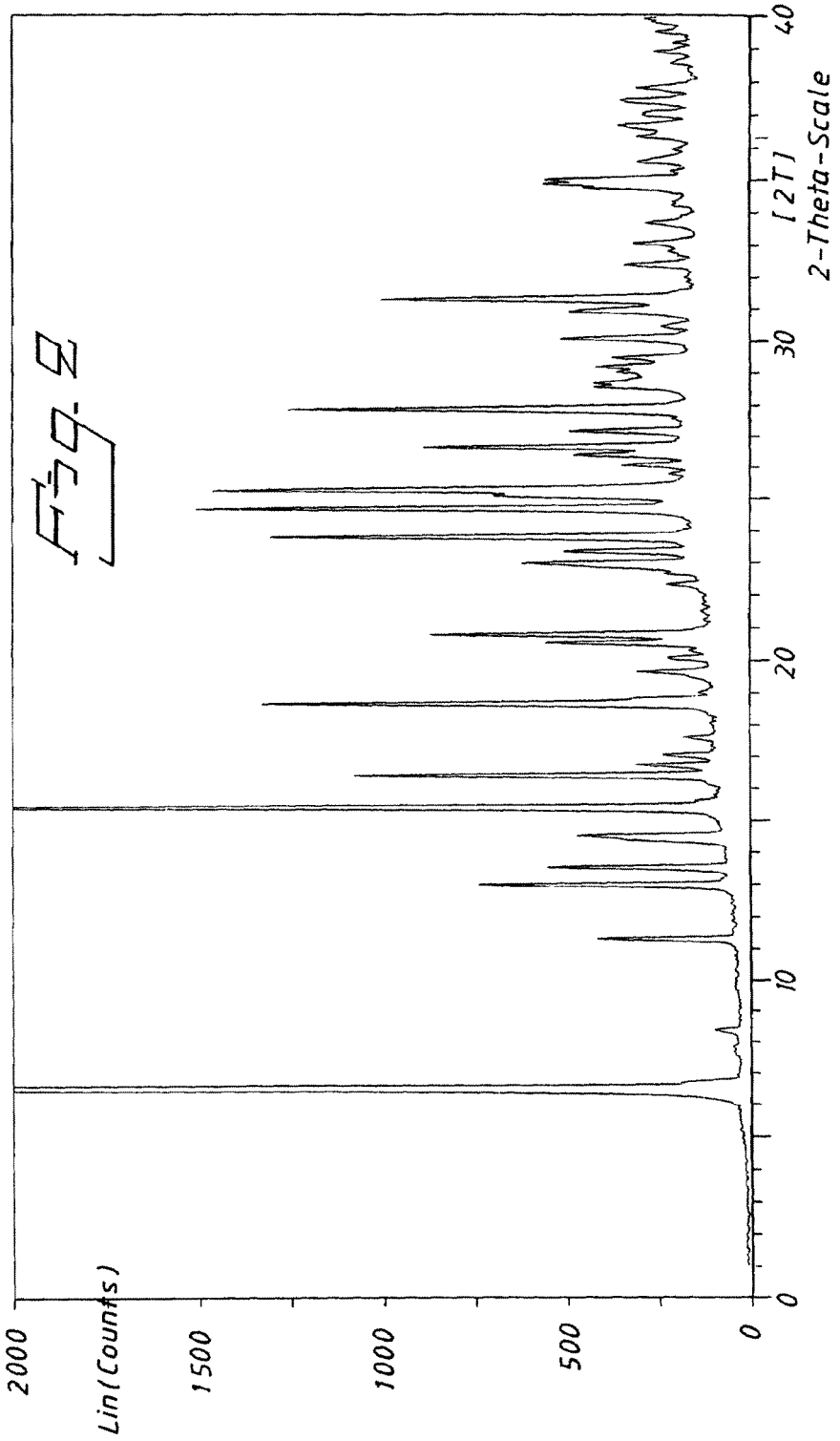
Fig. 2
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10
20
30
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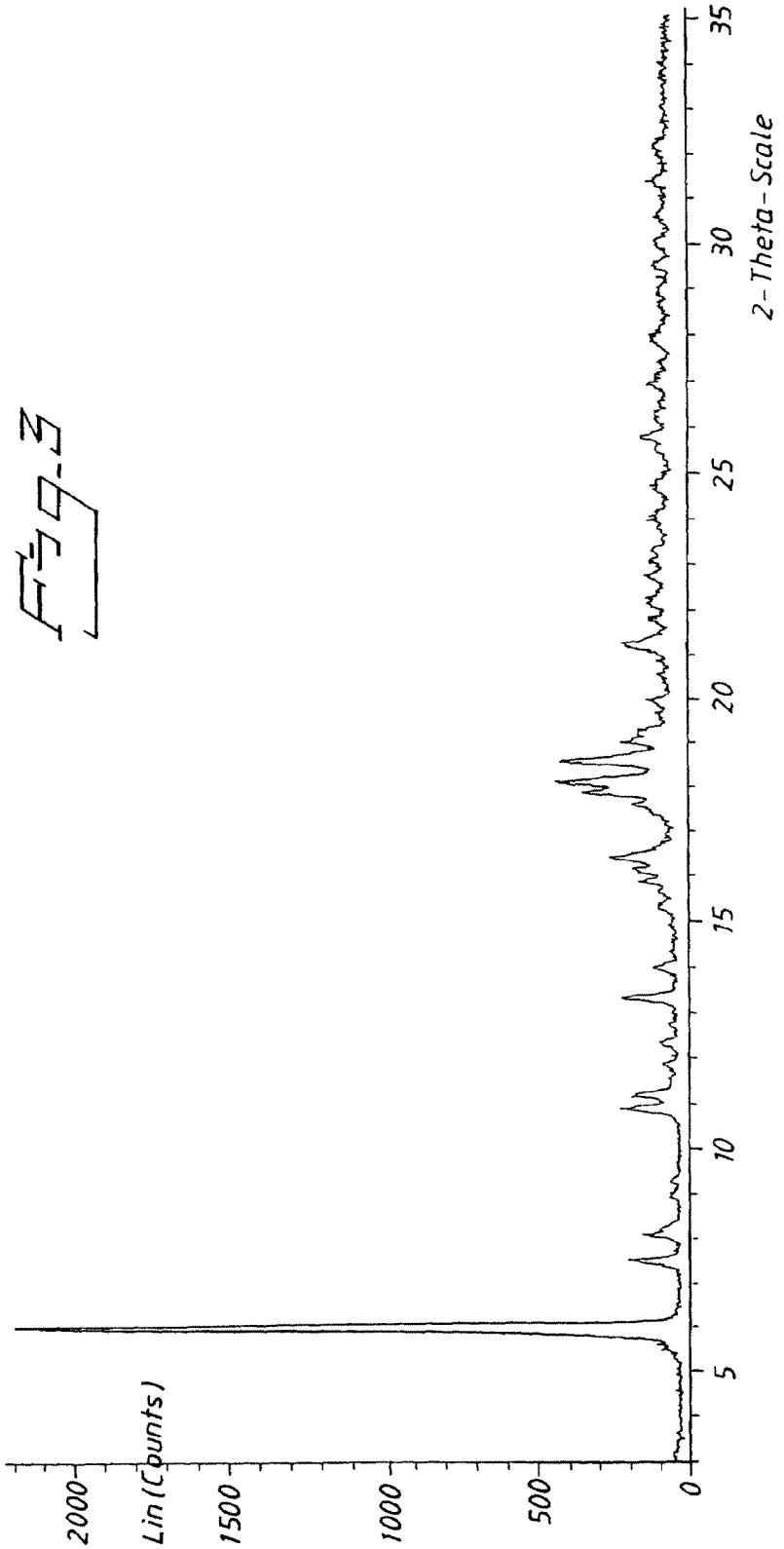
[2T]
2-Theta-Scale

Fig. 3



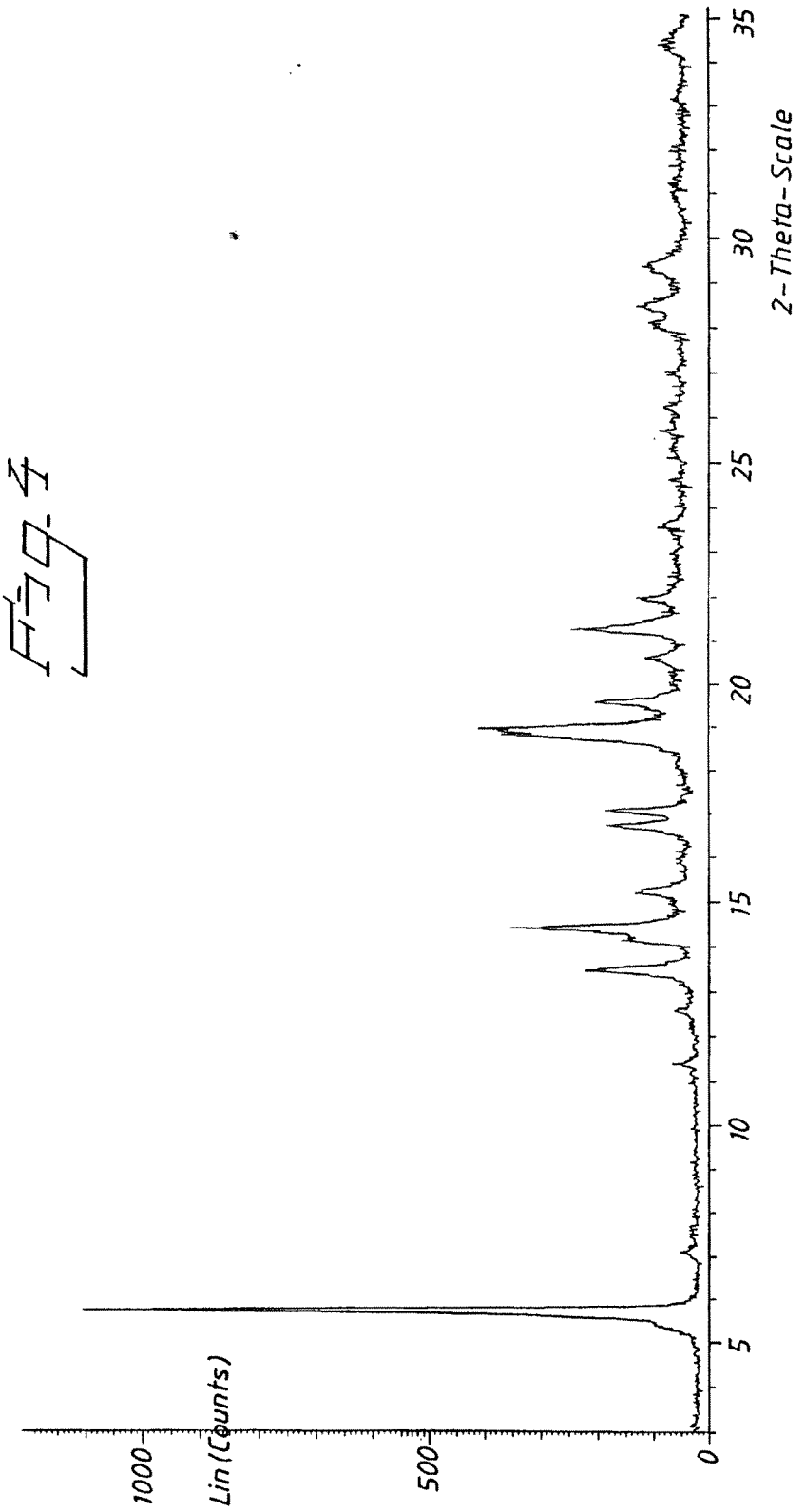
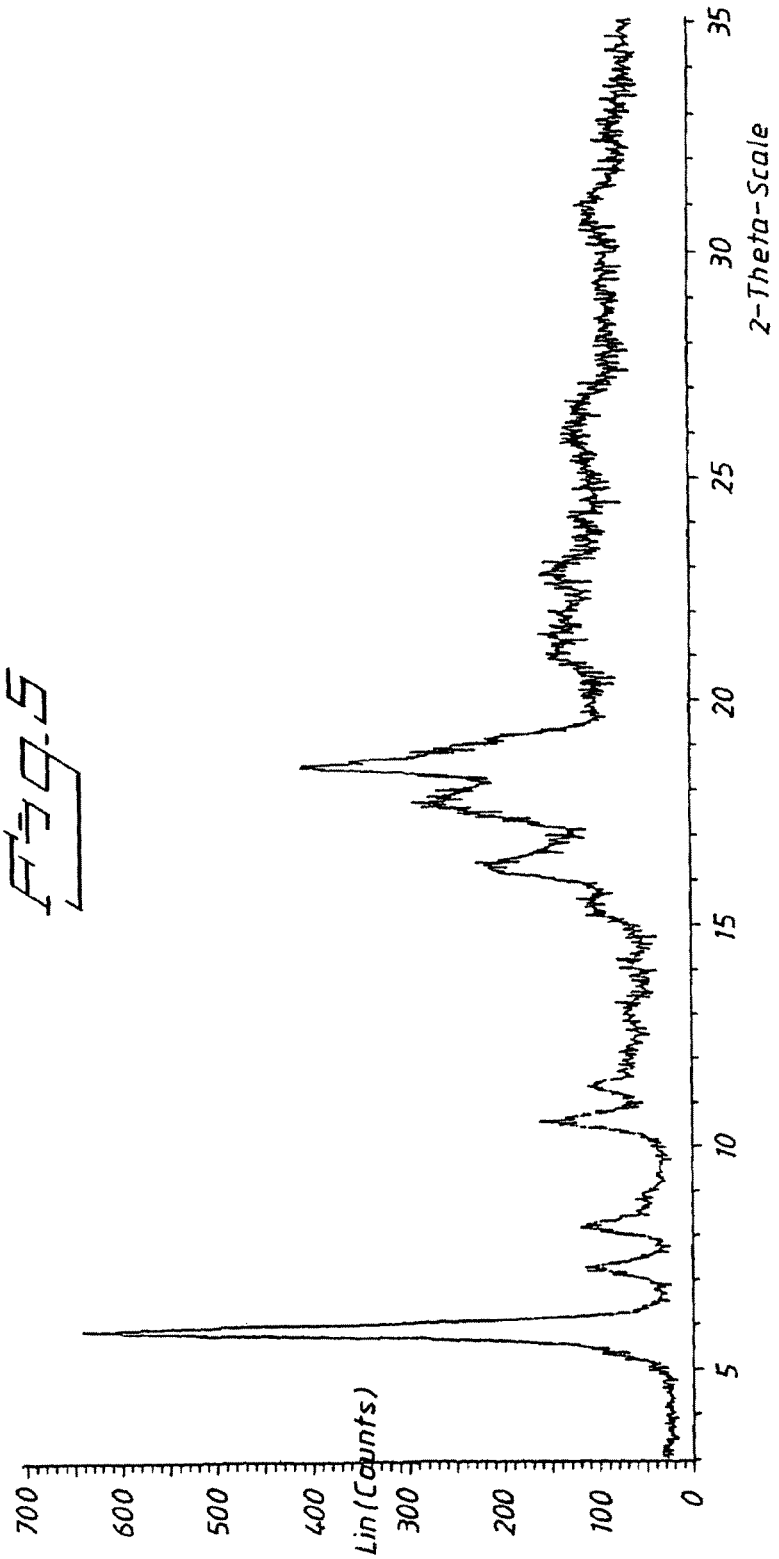


Fig. 4

FIG. 5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2-Theta-Scale

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 cc: 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.

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